

Macrocycles as CFTR modulators

The present invention relates to novel macrocyclic compounds of formula (I) and their use as pharmaceuticals in the treatment of CFTR-related diseases and disorders such as especially cystic fibrosis. The invention also concerns
5 related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I), and their use as modulators of CFTR.

Cystic Fibrosis (CF; mucoviscidosis, sometimes also called fibrocystic disease of pancreas or pancreatic fibrosis) is an autosomal recessive genetic disease caused by a dysfunctional epithelial chloride/bicarbonate channel named Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). CFTR dysfunction leads to dysregulated chloride,
10 bicarbonate and water transport at the surface of secretory epithelia causing accumulation of sticky mucus in organs including lung, pancreas, liver and intestine and, as a consequence, multi-organ dysfunction. Most debilitating effects in CF are nowadays observed in the lung which - due to abnormal hydration of airway surface liquid, mucus plugging, impaired mucociliary clearance, chronic inflammation and infection - loses its functionality over time leading to death by respiratory failure (Elborn, 2016). Human CFTR is a multidomain protein of 1480 amino acids. Many different
15 mutations causing CFTR dysfunction have been discovered in CF patients leading e.g. to no functional CFTR proteins (class I mutations), CFTR trafficking defects (class II mutations), CFTR regulation defects (also known as gating defects; class III mutations), CFTR conductance defects (class IV mutations), less CFTR protein either due to splicing defects (class V mutations) or due to reduced CFTR stability (class VI mutations), no CFTR protein due to mRNA instability (class VII mutations) (de Boeck, Acta Paediatr. 2020, 109(5):893-895). The CFTR2 database
20 (<http://cftr2.org>; data retrieved 06.07.2021) currently contains information on 360 disease-causing mutations. By far the most common disease-causing mutation is the deletion of phenylalanine at position 508 (F508del; allele frequency 0.697 in the CFTR2 database), that leads to misfolding of the channel during synthesis at the endoplasmic reticulum, degradation of the misfolded protein and a resulting strongly reduced transport to the cell surface (class II mutation). The residual F508del-CFTR that is trafficked to the cell surface is functional, however less than wildtype CFTR, i.e.
25 F508del-CFTR also harbours a gating defect (Dalemans, 1991). Ca 40% of all CF patients are homozygous for the F508del mutation while another ~40% of patients are heterozygous for the F508del mutation and carry another disease-causing mutation from class I, II, III, IV, V, VI or VII. Such disease-causing mutations are considerably rarer with the class III G551D mutation (allele frequency 0.0210) and the class I G542X mutation (allele frequency 0.0254) and the class II N1303K mutation (allele frequency 0.0158) being the next most prevalent

30 CF is currently treated by a range of drugs addressing the various organ symptoms and dysfunctions. Intestinal and pancreatic dysfunction are treated from diagnosis by food supplementation with pancreatic digestive enzymes. Lung symptoms are mainly treated with hypertonic saline inhalation, mucolytics, anti-inflammatory drugs, bronchodilators and antibiotics (Elborn, 2016).

In addition to symptomatic treatments, CFTR modulators have been developed and approved for patients with certain
35 CFTR mutations. These compounds directly improve CFTR trafficking to the cell surface (CFTR correctors) or improve

CFTR function at the cell surface (CFTR potentiators). CFTR modulators can also enhance function of non-mutated (i.e. wildtype) CFTR and are therefore being studied in disorders where increasing wildtype CFTR function would have beneficial effects in non-CF disorders such as chronic bronchitis/COPD (Le Grand, J Med Chem. 2021, 64(11):7241-7260. Patel, Eur Respir Rev. 2020, 29(156):190068) and dry eye disease (Flores, FASEB J. 2016, 30(5):1789-1797).

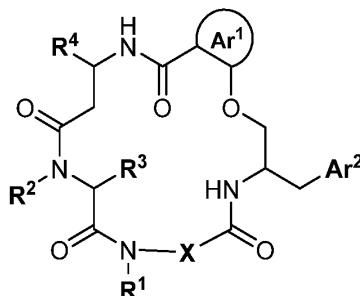
- 5 CFTR modulators and their combinations can be discovered and optimized by assessing their ability to promote trafficking and function of mutated CFTR in in vitro cultivated recombinant and primary cellular systems. Activity in such systems is predictive of activity in CF patients.

WO2019/161078 discloses macrocycles as modulators of cystic fibrosis, wherein said macrocycles generally are 15-membered macrocycles comprising a (pyridine-carbonyl)-sulfamoyl moiety that is linked to a further aromatic group.

- 10 Macrocytic tetrapeptides (12- or 13-membered) including the compound Apicidin (CAS: 183506-66-3) have been proposed as potential agents for treating CF (Hutt DM et al. ACS Med Chem Lett. 2011;2(9):703-707. doi:10.1021/ml200136e). WO2020/128925 discloses macrocycles capable of modulating the activity of CFTR, wherein said macrocycles comprise an optionally substituted divalent N-(pyridine-2-yl)pyridinyl-sulfonamide moiety. Non macrocyclic CFTR correctors and/or potentiators of CFTR have been disclosed for example in WO2011/119984, 15 WO2014/015841, WO2007/134279, WO2010/019239, WO2011/019413, WO2012/027731, WO2013/130669, WO2014/078842 and WO2018/227049, WO2010/037066, WO2011/127241, WO2013/112804, WO2014/071122, and WO2020/128768. Furthermore, particular macrocycles can be found as screening compounds, wherein the phenylene group which is part of said macrocycles is always unsubstituted (CAS registry number : CAS-2213100-89-9, CAS-2213100-96-8, CAS-2213100-99-1, CAS-2213101-02-9, CAS-2213101-04-1, CAS-2213101-06-3, CAS-2213101-08-5, CAS-2213101-09-6, CAS-2213101-19-8, CAS-2213101-24-5, CAS-2215788-95-5, CAS-2215788-98-8, CAS-2215789-01-6, CAS-2215789-02-7, CAS-2215789-09-4, CAS-2215789-15-2, CAS-2215789-20-9, CAS-2215789-24-3, CAS-2215789-35-6, CAS-2215789-37-8, CAS-2215946-94-2, CAS-2215947-04-7, CAS-2215947-13-8, CAS-2215947-24-1, CAS-2215947-34-3, CAS-2215947-44-5, CAS-2215947-51-4, CAS-2215947-64-9, CAS-2215947-68-3, CAS-2215947-78-5, CAS-2215947-91-2, CAS-2215954-57-5, CAS-2216342-34-4, CAS-2216342-78-6, CAS-2216342-86-6, CAS-2216343-03-0, CAS-2216343-09-6, CAS-2216343-14-3, CAS-2216343-18-7, CAS-2216343-24-5, CAS-2216343-32-5, CAS-2216343-38-1, CAS-2216343-45-0, CAS-2216343-53-0, CAS-2216343-59-6, CAS-2216343-64-3, CAS-2216343-74-5, CAS-2216343-76-7).

The present invention provides macrocyclic compounds which are modulators of CFTR. The present compounds may, thus, be useful for the treatment of cystic fibrosis.

1) A first aspect of the invention relates to compounds of the Formula (I)

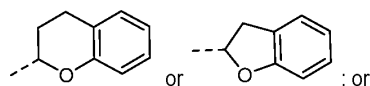


Formula (I)

wherein

- 5 ❖ X represents -CR^{X1}R^{X2}, wherein
- R^{X1} and R^{X2} together with the carbon atom to which they are attached form a ring which is:
 - C₃₋₆-cycloalkan-1,1-diyl (especially cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentane-1,1-diyl);
 - C₅₋₆-cycloalkan-1,1-diyl which is fused to a benzene ring (especially 1,3-dihydro-2H-indene-2,2-diyl);
 - C₃₋₆-cycloalkan-1,1-diyl, wherein said C₃₋₆-cycloalkan-1,1-diyl group independently is mono-substituted with C₁₋₃-alkoxy, fluoro, or hydroxy; or di-substituted with fluoro;
 - C₄₋₆-heterocycloalkan-diyl, wherein said C₄₋₆-heterocycloalkan-diyl contains one ring nitrogen atom, wherein said nitrogen when having a free valency is unsubstituted or mono-substituted wherein the substituents are independently selected from C₁₋₄-alkyl, and -COO-C₁₋₃-alkyl; or
 - C₄₋₆-heterocycloalkan-diyl, wherein said C₄₋₆-heterocycloalkan-diyl contains one ring oxygen atom;
 - R^{X1} and R^{X2} both independently represent C₁₋₄-alkyl (especially such group X is propan-2,2-diyl); or
 - R^{X1} represents hydrogen, and
 - 20 R^{X2} represents
 - hydrogen;
 - C₁₋₆-alkyl (especially C₁₋₄-alkyl);
 - C₁₋₄-fluoroalkyl;
 - C₃₋₆-cycloalkyl;
 - 25 ▪ C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with
 - hydroxy;
 - C₁₋₄-alkoxy;
 - -L^{X1}-C₃₋₆-cycloalkyl wherein said C₃₋₆-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein L^{X1} independently represents a direct bond or oxygen;

- C₄₋₆-heterocycloalkyl wherein said C₄₋₆-heterocycloalkyl contains one ring oxygen atom;
- -NR^{N1}R^{N2} wherein R^{N1} and R^{N2} together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom (i.e. an azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl ring), wherein said ring is mono- or di-substituted with fluoro;
- a partially aromatic bicyclic ring, which is



▪ -L^{X2}-Ar^{X2} wherein -

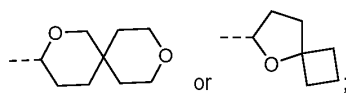
- L^{X2} independently represents a direct bond, C₁₋₃-alkylene, -C₁₋₃-alkylene-O*, or -C₁₋₃-alkylene-O-C₁₋₂-alkylene-*, wherein the asterisks indicate the bond that is attached to the group Ar^{X2}; and
- Ar^{X2} independently represents aryl (especially phenyl, or naphthyl), or 5- to 10-membered heteroaryl (especially oxadiazolyl, triazolyl, isoxazolyl, pyridinyl, or quinolinyl); wherein said group Ar^{X2} independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - C₃₋₆-cycloalkyl;
 - C₁₋₃-fluoroalkyl; and
 - Ar^{X3} wherein Ar^{X3} independently represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said group Ar^{X3} independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₂₋₃-alkyl, C₃₋₅-cycloalkyl, C₁₋₃-fluoroalkyl, and halogen; and

R¹ independently represents

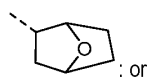
- hydrogen;
- -C₁₋₈-alkyl (especially methyl);
- -C₂₋₆-alkyl wherein said C₂₋₆-alkyl is mono-substituted with hydroxy, or C₁₋₄-alkoxy (especially methoxy, tert-butoxy);
- -C₁₋₆-alkyl (wherein especially said -C₁₋₆-alkyl is -(CH₂)_m- wherein m represents the integer 1 or 2) wherein said C₁₋₆-alkyl is mono-substituted with R¹¹; wherein R¹¹ independently represents
 - a saturated 5- or 6-membered heterocycloalkyl containing one or two ring heteroatoms wherein said heteroatoms are independently selected from nitrogen and oxygen, wherein

said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted, wherein the substituents independently are selected from C₁₋₄-alkyl (especially methyl), halogen, and benzyl;

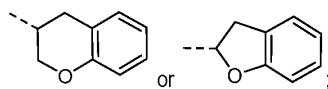
- C₃₋₆-cycloalkyl (especially cyclohexyl), wherein said C₃₋₆-cycloalkyl is unsubstituted or mono-substituted with C₁₋₄-alkoxy (especially methoxy);
- phenyl or 5- or 6-membered heteroaryl (especially pyridinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen, cyano, and morpholin-4-yl;
- benzyloxy;
- a spirocyclic fragment, which is



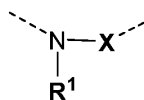
- a saturated bicyclic ring, which is



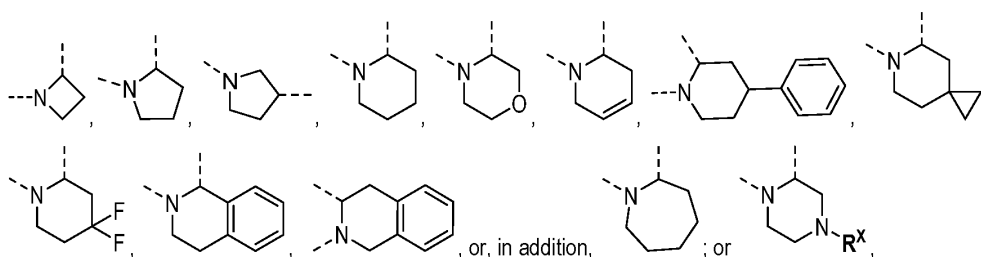
- a partially aromatic bicyclic ring, which is



❖ or the fragment



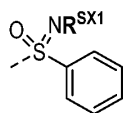
represents a heterocyclic ring which is



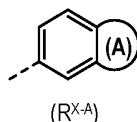
wherein R^x represents

- hydrogen;
- C₁₋₄-alkyl;
- C₃₋₆-cycloalkyl;
- C₁₋₄-alkyl, wherein said C₁₋₄-alkyl is mono-substituted with C₃₋₄-cycloalkyl;

- C₂₋₄-alkyl, wherein said C₂₋₄-alkyl is mono-substituted with hydroxy or C₁₋₃-alkoxy;
- phenyl or 5- or 6-membered heteroaryl (especially pyridinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₃-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen [especially such group is phenyl or pyridinyl; wherein said group is independently unsubstituted or substituted as defined before];



- , wherein R^{SX1} represents hydrogen or -CO-O-C₁₋₄-alkyl;
- -CO- R^{OX1} , or -SO₂- R^{OX1} ; wherein R^{OX1} independently represents
 - C₁₋₄-alkyl;
 - C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with C₁₋₃-alkoxy (especially methoxy), tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl (especially quinolinyl), or -NR^{ONX1}R^{ONX2} wherein R^{ONX1} and R^{ONX2} independently represent hydrogen or C₁₋₃-alkyl;
 - tetrahydropyranyl;
 - phenyl or 5- or 6-membered heteroaryl (especially pyridinyl or pyrazinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₃-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen; or
 - a group of the structure (R^{X-A}):



wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substituents independently are selected from oxo and C₁₋₃-alkyl; or

- -CO-O- R^{OX2} ; wherein R^{OX2} represents
 - C₁₋₄-alkyl;
 - 2,2,2-trichloroethyl; or
 - tetrahydropyranyl;

R^2 represents C₁₋₄-alkyl (especially methyl);

R^3 represents hydrogen; C₁₋₆-alkyl (especially methyl, isobutyl); -CH₂-C₃₋₆-cycloalkyl (especially -CH₂-cyclopropyl, -CH₂-cyclobutyl, -CH₂-cyclopentyl, -CH₂-cyclohexyl); or C₂₋₄-alkynyl (especially -CH₂-C≡CH);

R⁴ represents a group -CO-NH-**R⁴¹**; wherein **R⁴¹** represents

- C₂₋₆-alkyl, which is mono-substituted with C₁₋₄-alkoxy (especially methoxy), C₁₋₄-fluoroalkoxy (especially difluoromethoxy, or trifluoromethoxy), or hydroxy;
- C₁₋₃-alkoxy-C₂₋₃-alkylene-O-CH₂-CH₂-;
- 5 • -CH₂-CH₂-C₅₋₆-heterocycloalkyl, wherein said C₅₋₆-heterocycloalkyl contains one ring oxygen atom, wherein said C₅₋₆-heterocycloalkyl is unsubstituted, mono- or di-substituted with C₁₋₄-alkyl (especially methyl);
- -**L¹**-aryl; wherein **L¹** represents -CH₂-CH₂-, -CH₂-CH₂-O-*, -CH₂-CF₂*, -CH₂-(cyclopropan-1,1-diyl)-*, -CH(CH₂-OH)-CH₂*, or -CH₂-CH(OH)-*; wherein asterisks indicate the bond with which **L¹** is attached to the aryl; wherein aryl represents phenyl or naphthyl (especially phenyl); wherein said aryl is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C₁₋₄-alkyl (especially methyl, ethyl, tert-butyl), C₁₋₄-alkoxy (especially methoxy, ethoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen (especially fluoro, chloro, bromo), cyano, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-methyl, C₁₋₃-alkoxy-C₁₋₃-alkyl, hydroxy-C₁₋₃-alkyl, C₂₋₃-alkynyl, morpholin-4-yl, C₁₋₃-alkyl-SO₂-, 5- or 6-membered heteroaryl (especially pyrazolyl, triazolyl, pyrimidinyl, pyrazinyl), or -NR^{N41}R^{N42}, wherein independently **R^{N41}** is hydrogen or C₁₋₄-alkyl, and **R^{N42}** is hydrogen or C₁₋₄-alkyl;
- 15 • -**L²**-**HET**; wherein **L²** represents -CH₂-CH₂-, -CH₂-CH₂-O-*, -CH₂-CF₂*, -CH₂-(cyclopropan-1,1-diyl)-*, -CH(CH₂-OH)-CH₂*, or -CH₂-CH(OH)-*; wherein asterisks indicate the bond with which **L²** is attached to **HET** (especially **L²** represents -CH₂-CH₂-); wherein **HET** represents 5- to 10-membered heteroaryl, wherein said **HET** is independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C₁₋₄-alkyl (especially methyl, ethyl, isopropyl, tert-butyl); C₁₋₄-alkoxy (especially methoxy); C₁₋₃-fluoroalkyl; C₁₋₃-fluoroalkoxy; halogen; cyano; C₃₋₆-cycloalkyl; C₃₋₆-cycloalkyl-methyl; C₁₋₃-alkoxy-C₁₋₃-alkyl; hydroxy-C₁₋₃-alkyl; C₂₋₃-alkynyl; benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy), or C₁₋₄-fluoroalkoxy (especially trifluoromethoxy);
- 20 • -CH₂-CH₂-**HCy¹**, wherein **HCy¹** represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with C₁₋₄-alkyl (especially methyl); and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen (especially chloro), or cyano;
- -CH₂-CH₂-**HCy²**, wherein **HCy²** represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring; or
- -**L³**-**HCy³**, wherein **L³** represents a direct bond, or -CH₂-; wherein **HCy³** represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one oxygen atom; wherein **L³** is attached to said group **HCy³** at a carbon atom which is part of
- 35

said 5- to 7-membered saturated heterocyclic ring; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, or mono-substituted with C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen (especially chloro), or cyano;

Ar¹ represents

- 5 • 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted (especially pyridin-3,4-diyl, thiophen-2,3-diyl);
- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy, ethoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano, and halogen (especially fluoro, chloro);
- 10 • phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or
- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), C₁₋₃-fluoroalkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkoxy, cyano, and halogen (especially fluoro, chloro); or
- 15 • quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted, or said quinoline-diyl N-oxide is mono-substituted with methyl or fluoro;
- 20 [wherein it is understood that in the above groups **Ar¹** the -CO- group and the oxygen (i.e. the groups linking **Ar¹** to the rest of the molecule) are attached in ortho arrangement to aromatic ring carbon atoms of **Ar¹** as depicted in Formula (I)]; and

Ar² represents

- phenyl or naphthyl (especially phenyl), wherein said phenyl or naphthyl independently is unsubstituted, mono- or di-substituted wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₃-fluoroalkyl, halogen, cyano, C₁₋₆-alkoxy, and C₁₋₃-fluoroalkoxy;
- 25 • 5- or 6-membered heteroaryl (especially pyridinyl), wherein said 5- or 6-membered heteroaryl independently is unsubstituted or mono-substituted wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₃-fluoroalkyl, halogen, cyano, C₁₋₆-alkoxy, and C₁₋₃-fluoroalkoxy; or
- 30 • 9- or 10-membered heteroaryl (especially benzothiophenyl).

2) A further embodiment relates to compounds of the Formula (I) according to embodiment 1), wherein

❖ **X** represents $-\text{CR}^{\text{X1}}\text{R}^{\text{X2}}$, wherein

➤ **R^{X1}** and **R^{X2}** together with the carbon atom to which they are attached form a ring which is:

- C₃₋₆-cycloalkan-1,1-diyl- (especially cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentane-1,1-diyl);
- C₅₋₆-cycloalkan-1,1-diyl- which is fused to a benzene ring (especially 1,3-dihydro-2H-indene-2,2-diyl);
- C₃₋₆-cycloalkan-1,1-diyl-, wherein said C₃₋₆-cycloalkan-1,1-diyl group is mono-substituted with C₁₋₃-alkoxy, or di-substituted with fluoro (especially 3-methoxy-cyclobutan-1,1-diyl, 3,3-difluoro-cyclobutan-1,1-diyl); or

➤ **R^{X1}** and **R^{X2}** both independently represent C₁₋₄-alkyl (especially such group **X** is propan-2,2-diyl); or

➤ **R^{X1}** represents hydrogen, and

R^{X2} represents

- hydrogen;
- C₁₋₆-alkyl (especially C₁₋₄-alkyl);
- C₁₋₄-fluoroalkyl;
- C₃₋₆-cycloalkyl;
- C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with
 - hydroxy;
 - C₁₋₄-alkoxy;
 - $-\text{L}^{\text{X1}}\text{-C}_{3-6}\text{-cycloalkyl}$ wherein said C₃₋₆-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein **L^{X1}** independently represents a direct bond or oxygen;
 - C₄₋₆-heterocycloalkyl wherein said C₄₋₆-heterocycloalkyl contains one ring oxygen atom;
 - $-\text{NR}^{\text{N1}}\text{R}^{\text{N2}}$ wherein **R^{N1}** and **R^{N2}** together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom (i.e. an azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl ring), wherein said ring is mono- or di-substituted with fluoro; or
- $-\text{L}^{\text{X2}}\text{-Ar}^{\text{X2}}$ wherein -
 - **L^{X2}** independently represents a direct bond, C₁₋₃-alkylene, $-\text{C}_{1-3}\text{-alkylene-O-}^*$, or $-\text{C}_{1-3}\text{-alkylene-O-C}_{1-2}\text{-alkylene-}^*$; wherein the asterisks indicate the bond that is attached to the group **Ar^{X2}**; and
 - **Ar^{X2}** independently represents aryl (especially phenyl, or naphthyl), or 5- to 10-membered heteroaryl (especially oxadiazolyl, triazolyl, isoxazolyl, pyridinyl, or quinolinyl); wherein said group **Ar^{X2}** independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;

- halogen;
- C₃₋₆-cycloalkyl;
- C₁₋₃-fluoroalkyl; and
- **Ar^{x3}** wherein **Ar^{x3}** independently represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said group **Ar^{x3}** independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₂₋₃-alkyl, C₃₋₅-cycloalkyl, C₁₋₃-fluoroalkyl, and halogen; and

5

R¹ independently represents

10

- hydrogen;
- -C₁₋₆-alkyl (especially methyl);
- -C₂₋₆-alkyl, wherein said C₂₋₆-alkyl is mono-substituted with C₁₋₄-alkoxy (especially methoxy, tert-butoxy);
- -C₃₋₆-alkyl, wherein said C₃₋₆-alkyl is mono-substituted with phenyl, or benzyloxy;

15

- -(CH₂)_m-**R¹¹** wherein **m** represents the integer 1 or 2; and

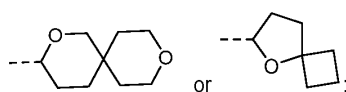
R¹¹ independently represents

20

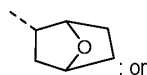
- a saturated 5- or 6-membered heterocycloalkyl containing one or two ring oxygen atoms, wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted with C₁₋₄-alkyl (especially methyl);
- C₃₋₆-cycloalkyl (especially cyclobutyl, cyclohexyl), wherein said C₃₋₆-cycloalkyl is unsubstituted or mono-substituted with C₁₋₄-alkoxy (especially methoxy);
- phenyl or 5- or 6-membered heteroaryl (especially pyridinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen [especially such group represents phenyl];

25

- a spirocyclic fragment, which is

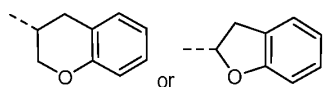


- a saturated bicyclic ring, which is

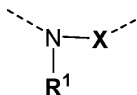


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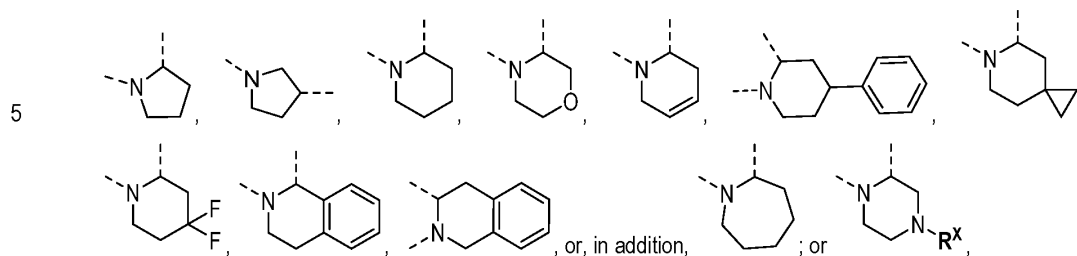
- a partially aromatic bicyclic ring, which is



❖ or the fragment

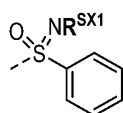


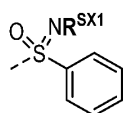
represents a heterocyclic ring which is



wherein R^X represents

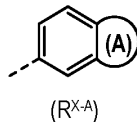
- hydrogen;
- C_{1-4} -alkyl;
- C_{3-6} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with C_{3-4} -cycloalkyl;
- C_{2-4} -alkyl, wherein said C_{2-4} -alkyl is mono-substituted with hydroxy or C_{1-3} -alkoxy;
- phenyl or 5- or 6-membered heteroaryl (especially pyridinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4} -alkyl, C_{1-3} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano or halogen [especially such group is phenyl];



- , wherein R^{SX1} represents hydrogen or $\text{---CO---O---C}_{1-4}\text{---alkyl}$;
- $\text{---CO---R}^{\text{OX1}}$, or $\text{---SO}_2\text{---R}^{\text{OX1}}$; wherein R^{OX1} independently represents
 - C_{1-4} -alkyl;
 - C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with C_{1-3} -alkoxy (especially methoxy), tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl (especially quinolinyl), or $\text{---NR}^{\text{ONX1}}\text{R}^{\text{ONX2}}$ wherein R^{ONX1} and R^{ONX2} independently represent hydrogen or C_{1-3} -alkyl;
 - tetrahydropyranyl;
 - phenyl or 5- or 6-membered heteroaryl (especially pyridinyl or pyrazinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4} -alkyl, C_{1-3} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano or halogen; or

12

- a group of the structure (R^{X-A}):



5 wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substituents independently are selected from oxo and C_{1-3} -alkyl; or

- $-CO-O-R^{OX2}$; wherein R^{OX2} represents
 - C_{1-4} -alkyl;
 - 10 ➤ 2,2,2-trichloroethyl; or
 - tetrahydropyranyl;

R^2 represents C_{1-4} -alkyl (especially methyl);

R^3 represents hydrogen; C_{1-6} -alkyl (especially methyl, isobutyl); $-CH_2-C_{3-6}$ -cycloalkyl (especially $-CH_2$ -cyclopropyl, $-CH_2$ -cyclobutyl, $-CH_2$ -cyclopentyl, $-CH_2$ -cyclohexyl); C_{2-4} -alkynyl (especially $-CH_2-C\equiv CH$);

15 R^4 represents a group $-CO-NH-R^{41}$; wherein R^{41} represents

- C_{2-6} -alkyl, which is mono-substituted with C_{1-4} -alkoxy (especially methoxy), C_{1-4} -fluoroalkoxy (especially difluoromethoxy), or hydroxy;
- C_{1-3} -alkoxy- C_{2-3} -alkylene- $O-CH_2-CH_2-$;
- $-CH_2-CH_2-C_{5-6}$ -heterocycloalkyl, wherein said C_{5-6} -heterocycloalkyl contains one ring oxygen atom, wherein said C_{5-6} -heterocyclyl is unsubstituted, mono- or di-substituted with C_{1-4} -alkyl (especially methyl);
- 20 • $-L^1$ -aryl; wherein L^1 represents $-CH_2-CH_2-$, $-CH_2-CH_2-O^*$, $-CH_2-CF_2^*$, $-CH_2-(cyclopropan-1,1-diyl)^*$, $-CH(CH_2-OH)-CH_2^*$, or $-CH_2-CH(OH)^*$; wherein asterisks indicate the bond with which L^1 is attached to the aryl; wherein aryl represents phenyl or naphthyl (especially phenyl); wherein said aryl is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C_{1-4} -alkyl (especially methyl, ethyl, tert-butyl), C_{1-4} -alkoxy (especially methoxy, ethoxy), C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, halogen (especially fluoro, chloro, bromo), cyano, hydroxy- C_{1-3} -alkyl, C_{2-3} -alkynyl, morpholin-4-yl, C_{1-3} -alkyl- SO_2 , 5- or 6-membered heteroaryl (especially pyrazolyl, triazolyl, pyrimidinyl, pyrazinyl), or $-NR^{N41}R^{N42}$, wherein independently R^{N41} is hydrogen or C_{1-4} -alkyl, and R^{N42} is hydrogen or C_{1-4} -alkyl;
- 25 • $-L^2-HET^1$; wherein L^2 represents $-CH_2-CH_2-$, $-CH_2-CF_2^*$, $-CH_2-(cyclopropan-1,1-diyl)^*$, or $-CH_2-CH(OH)^*$; wherein asterisks indicate the bond with which L^2 is attached to HET (especially L^2 represents $-CH_2-CH_2-$); wherein HET^1 represents 5- or 6-membered heteroaryl (especially thiophenyl, furanyl, thiazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, triazolyl, pyridinyl, pyrimidinyl, pyrazinyl), wherein said 5- or 6-membered heteroaryl is independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C_{1-4} -alkyl (especially methyl); C_{1-4} -alkoxy (especially methoxy); C_{1-3} -fluoroalkyl; C_{1-3} -
- 30

fluoroalkoxy; halogen; cyano; C₃₋₆-cycloalkyl (especially cyclopropyl); C₃₋₆-cycloalkyl-methyl; C₁₋₃-alkoxy-C₁₋₃-alkyl; C₂₋₃-alkynyl, benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy), or C₁₋₄-fluoroalkoxy (especially trifluoromethoxy);

- 5
 - -CH₂-CH₂-HET², wherein HET² represents 9- or 10-membered bicyclic heteroaryl (especially benzoxazolyl, benzisoxazolyl, benzofuranyl, benzo[d][1,2,3]triazolyl or [1,2,4]triazolo[1,5-a]pyrimidinyl), wherein said HET² is unsubstituted or mono-substituted with C₁₋₄-alkyl;
 - -CH₂-CH₂-HCy¹, wherein HCy¹ represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with C₁₋₄-alkyl (especially methyl); and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are indepently C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen (especially chloro), or cyano;
 - 10
 - -CH₂-CH₂-HCy², wherein HCy² represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring; or
 - HCy³; wherein HCy³ represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one oxygen atom; wherein said group HCy³ is bound to the nitrogen of the -CO-NH- group at a carbon atom which is part of said 5- to 7-membered saturated heterocyclic ring; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, or mono-substituted with C₁₋₄-alkyl (especially methyl), or C₁₋₄-alkoxy (especially methoxy);
 - 15
 - 20

Ar¹ represents

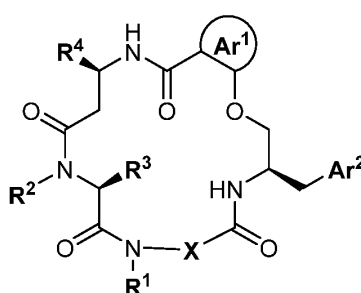
- 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted (especially pyridin-3,4-diyl, thiophen-2,3-diyl);
 - 25
 - phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy, ethoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano, and halogen (especially fluoro, chloro);
 - phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or
 - 30
 - a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl) and halogen (especially fluoro, chloro); or
 - 35
 - quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted, or said quinoline-diyl N-oxide is mono-substituted with methyl or fluoro;

[wherein it is understood that in the above groups **Ar**¹ the -CO- group and the oxygen (i.e. the groups linking **Ar**¹ to the rest of the molecule) are attached in ortho arrangement to aromatic ring carbon atoms of **Ar**¹ as depicted in Formula (I)]; and

Ar² represents

- 5 • phenyl or naphthyl (especially phenyl);
- 5- or 6-membered heteroaryl (especially pyridinyl); or
- 9- or 10-membered heteroaryl (especially benzothiophenyl).

3) A second aspect relates to compounds of Formula (I) according to embodiment 1) or 2), wherein the compounds are compounds of Formula (I_E):



Formula (I_E).

4) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein

❖ **X** represents -CR^{X1}R^{X2}, wherein

➤ **R**^{X1} and **R**^{X2} together with the carbon atom to which they are attached form a ring which is:

- 15 ▪ C₃₋₆-cycloalkan-1,1-diyl- (especially cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentane-1,1-diyl);
- C₅₋₆-cycloalkan-1,1-diyl- which is fused to a benzene ring (especially 1,3-dihydro-2H-indene-2,2-diyl); or
- C₃₋₆-cycloalkan-1,1-diyl-, wherein said C₃₋₆-cycloalkan-1,1-diyl group is mono-substituted with C₁₋₃-alkoxy, or di-substituted with fluoro (especially 3-methoxy-cyclobutan-1,1-diyl, 3,3-difluoro-cyclobutan-1,1-diyl);

➤ **R**^{X1} and **R**^{X2} both independently represent C₁₋₄-alkyl (especially such group **X** is propan-2,2-diyl); or

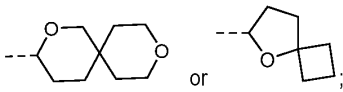
➤ **R**^{X1} represents hydrogen, and

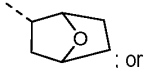
R^{X2} represents

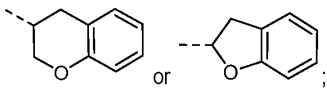
- 25 ▪ hydrogen;
- C₁₋₆-alkyl (especially C₁₋₄-alkyl);
- C₁₋₄-fluoroalkyl;
- C₃₋₆-cycloalkyl;
- C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with

- 5
- hydroxy;
 - C₁₋₄-alkoxy;
 - -L^{X1}-C₃₋₆-cycloalkyl wherein said C₃₋₆-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein L^{X1} independently represents a direct bond or oxygen;
 - C₄₋₆-heterocycloalkyl wherein said C₄₋₆-heterocycloalkyl contains one ring oxygen atom;
 - -NR^{N1}R^{N2} wherein R^{N1} and R^{N2} together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom (i.e. an azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl ring), wherein said ring is mono- or di-substituted with fluoro;
- 10
- -L^{X2}-Ar^{X2} wherein -
 - L^{X2} independently represents a direct bond, C₁₋₃-alkylene, -C₁₋₃-alkylene-O*, or -C₁₋₃-alkylene-O-C₁₋₂-alkylene-*; wherein the asterisks indicate the bond that is attached to the group Ar^{X2}; and
 - Ar^{X2} independently represents aryl (especially phenyl, or naphthyl), or 5- to 10-membered heteroaryl (especially oxadiazolyl, triazolyl, isoxazolyl, pyridinyl, or quinolinyl); wherein said group Ar^{X2} independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - cyano;
 - C₃₋₆-cycloalkyl;
 - C₁₋₃-fluoroalkyl; and
 - Ar^{X3} wherein Ar^{X3} independently represents phenyl, or 5- or 6-membered heteroaryl (especially pyridinyl); wherein said group Ar^{X3} independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₂₋₃-alkyl, C₃₋₅-cycloalkyl, C₁₋₃-fluoroalkyl, and halogen; and
- 20
- 25
- R¹ independently represents hydrogen or -C₁₋₃-alkyl (especially methyl); or
- 30
- ❖ X represents -CR^{X1}R^{X2}, wherein
 - R^{X1} represents hydrogen, and R^{X2} represents hydrogen, or methyl; (i.e. such group X representing -CR^{X1}R^{X2} wherein R^{X1} represents hydrogen is methylene, or ethan-1,1-diyl); or
 - R^{X1} and R^{X2} together with the carbon atom to which they are attached form a ring which is C₃₋₅-cycloalkan-1,1-diyl- (especially cyclopropan-1,1-diyl); and
- 35
- R¹ independently represents

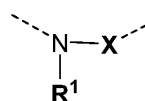
- -C₄₋₆-alkyl (especially 3,3-dimethyl-butyl);
- -C₂₋₆-alkyl, wherein said C₂₋₆-alkyl is mono-substituted with C₁₋₄-alkoxy (especially methoxy, tert-butoxy) (in particular such group is 2-methoxy-ethyl, 3-methoxy-propyl, 3-methoxy-3-methyl-butyl, 2-(tert-butoxy)-ethyl);
- -C₃₋₆-alkyl, wherein said C₃₋₆-alkyl is mono-substituted with phenyl, or benzyloxy;
- -(CH₂)_m-R¹¹ wherein **m** represents the integer 1 or 2; and **R¹¹** independently represents
 - a saturated 5- or 6-membered heterocycloalkyl containing one or two ring oxygen atoms (especially tetrahydrofuranyl, tetrahydropyranyl), wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted with C₁₋₄-alkyl (especially methyl);
 - C₃₋₆-cycloalkyl (especially cyclobutyl, cyclohexyl), wherein said C₃₋₆-cycloalkyl is unsubstituted or mono-substituted with C₁₋₄-alkoxy (especially methoxy);
 - phenyl or 5- or 6-membered heteroaryl (especially pyridinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen [especially such group represents phenyl];
 - a spirocyclic fragment, which is


 - a saturated bicyclic ring, which is

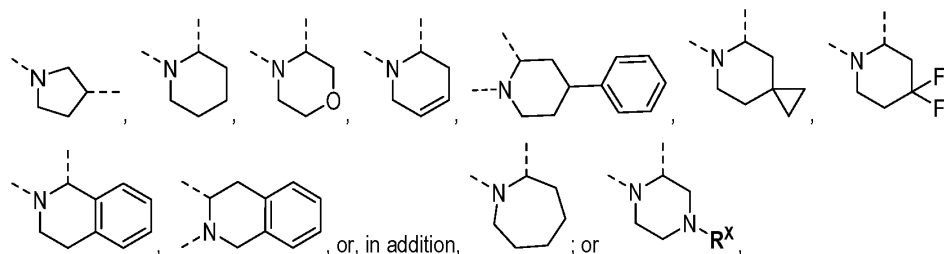

 - a partially aromatic bicyclic ring, which is



❖ or the fragment

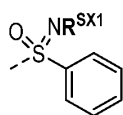


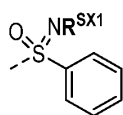
25 represents a heterocyclic ring which is

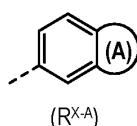


wherein R^x represents

- hydrogen;
- C_{1-4} -alkyl;
- C_{3-4} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with C_{3-4} -cycloalkyl;
- C_{2-4} -alkyl, wherein said C_{2-4} -alkyl is mono-substituted with hydroxy, or C_{1-3} -alkoxy;
- phenyl or 5- or 6-membered heteroaryl (especially pyridinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4} -alkyl, C_{1-3} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano or halogen [especially such group represents phenyl];



- , wherein R^{SX1} represents hydrogen or $-CO-O-C_{1-4}$ -alkyl;
- $-CO-R^{OX1}$, or $-SO_2-R^{OX1}$; wherein R^{OX1} independently represents
 - C_{1-4} -alkyl;
 - C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with C_{1-3} -alkoxy (especially methoxy), tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl (especially quinolinyl), or $-NR^{ONX1}R^{ONX2}$ wherein R^{ONX1} and R^{ONX2} independently represent hydrogen or C_{1-3} -alkyl;
 - tetrahydropyranyl;
 - phenyl or 5- or 6-membered heteroaryl (especially pyridinyl or pyrazinyl), wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4} -alkyl, C_{1-3} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano or halogen; or
 - a group of the structure (R^{X-A}):



- $-CO-O-R^{OX2}$; wherein R^{OX2} represents
 - C_{1-4} -alkyl;
 - 2,2,2-trichloroethyl; or
 - tetrahydropyranyl.

5) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein

❖ **X** represents $-\text{CR}^{\text{X1}}\text{R}^{\text{X2}}$, wherein

➤ R^{X1} and R^{X2} together with the carbon atom to which they are attached form a ring which is:

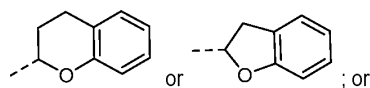
- C_{3-6} -cycloalkan-1,1-diyl- (especially cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, cyclopentane-1,1-diyl);
- C_{5-6} -cycloalkan-1,1-diyl- which is fused to a benzene ring (especially 1,3-dihydro-2H-indene-2,2-diyl);
- C_{3-6} -cycloalkan-1,1-diyl-, wherein said C_{3-6} -cycloalkan-1,1-diyl group is mono-substituted with C_{1-3} -alkoxy, or di-substituted with fluoro (especially 3-methoxy-cyclobutan-1,1-diyl, 3,3-difluoro-cyclobutan-1,1-diyl);

➤ R^{X1} and R^{X2} both independently represent C_{1-4} -alkyl (especially such group **X** is propan-2,2-diyl); or

➤ R^{X1} represents hydrogen, and

R^{X2} represents

- hydrogen;
- C_{1-6} -alkyl (especially C_{1-4} -alkyl);
- C_{1-4} -fluoroalkyl;
- C_{3-6} -cycloalkyl;
- C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with
 - hydroxy;
 - C_{1-4} -alkoxy;
 - $-\text{L}^{\text{X1}}-\text{C}_{3-6}$ -cycloalkyl wherein said C_{3-6} -cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein L^{X1} independently represents a direct bond or oxygen;
 - C_{4-6} -heterocycloalkyl wherein said C_{4-6} -heterocycloalkyl contains one ring oxygen atom;
 - $-\text{NR}^{\text{N1}}\text{R}^{\text{N2}}$ wherein R^{N1} and R^{N2} together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom (i.e. an azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl ring), wherein said ring is mono- or di-substituted with fluoro;
 - a partially aromatic bicyclic ring, which is



▪ $-\text{L}^{\text{X2}}-\text{Ar}^{\text{X2}}$ wherein -

- L^{X2} independently represents a direct bond, C_{1-3} -alkylene, $-\text{C}_{1-3}$ -alkylene- O^* , or $-\text{C}_{1-3}$ -alkylene- $\text{O}-\text{C}_{1-2}$ -alkylene- O^* ; wherein the asterisks indicate the bond that is attached to the group Ar^{X2} ; and Ar^{X2} represents phenyl, wherein said phenyl independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from

- C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - C₃₋₆-cycloalkyl; and
 - C₁₋₃-fluoroalkyl; or
- **L^{x2}** independently represents a direct bond, C₁₋₃-alkylene, -C₁₋₃-alkylene-O-*, or -C₁₋₃-alkylene-O-C₁₋₂-alkylene-*, wherein the asterisks indicate the bond that is attached to the group **Ar^{x2}**; and **Ar^{x2}** independently represents 5- or 6-membered heteroaryl [notably 5-membered heteroaryl containing one to three heteroatoms independently selected from oxygen and nitrogen (especially oxadiazolyl, triazolyl, or isoxazolyl); or 6-membered heteroaryl containing one or two nitrogen atoms (especially pyridinyl or pyrazinyl)]; wherein said heteroaryl independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - C₃₋₆-cycloalkyl;
 - C₁₋₃-fluoroalkyl; and
 - **Ar^{x3}** wherein **Ar^{x3}** independently represents phenyl, or 5- or 6-membered heteroaryl (notably 6-membered heteroaryl containing one or two nitrogen atoms, especially pyridinyl); wherein said group **Ar^{x3}** independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₂₋₃-alkyl, C₃₋₅-cycloalkyl, C₁₋₃-fluoroalkyl, and halogen; and
- **L^{x2}** independently represents a direct bond, C₁₋₃-alkylene, or -C₁₋₃-alkylene-O-*, wherein the asterisk indicates the bond that is attached to the group **Ar^{x2}**; and **Ar^{x2}** independently represents naphthyl or 8- to 10-membered heteroaryl (notably 10-membered heteroaryl containing one nitrogen atom, especially quinoliny); wherein said group **Ar^{x2}** independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - C₃₋₆-cycloalkyl; and
 - C₁₋₃-fluoroalkyl;

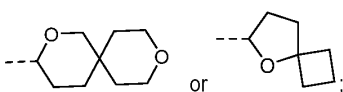
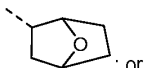
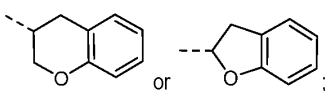
and

R^1 independently represents $-C_{1-3}$ -alkyl (especially methyl); or

❖ X represents $-CR^{X1}R^{X2}$, wherein R^{X1} and R^{X2} both represent hydrogen; and

R^1 independently represents

- 5
- $-C_{4-6}$ -alkyl;
 - $-C_{2-6}$ -alkyl, wherein said C_{2-6} -alkyl is mono-substituted with C_{1-4} -alkoxy (especially methoxy, tert-butoxy);
 - $-C_{3-6}$ -alkyl, wherein said C_{3-6} -alkyl is mono-substituted with phenyl, or benzyloxy;
 - $-(CH_2)_m-R^{11}$ wherein
- 10
- m represents the integer 1 or 2; and
- R^{11} independently represents

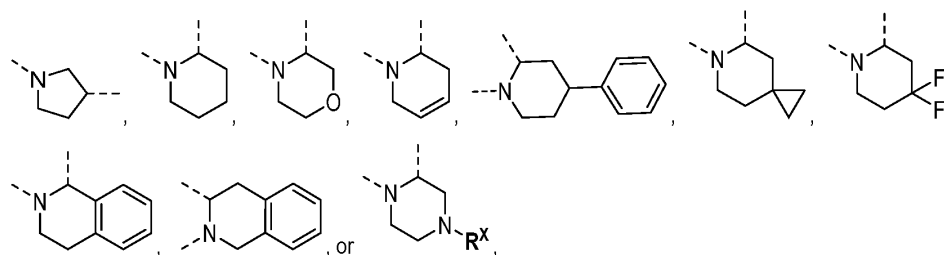
- 15
- a saturated 5- or 6-membered heterocycloalkyl containing one or two ring oxygen atoms, wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted with C_{1-4} -alkyl (especially methyl);
 - C_{3-6} -cycloalkyl (especially cyclobutyl, cyclohexyl), wherein said C_{3-6} -cycloalkyl is unsubstituted or mono-substituted with C_{1-4} -alkoxy (especially methoxy);
 - phenyl;
 - a spirocyclic fragment, which is
- 20
- 
- a saturated bicyclic ring, which is
- 
- or
- a partially aromatic bicyclic ring, which is
- 

❖ or the fragment



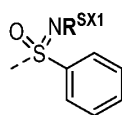
represents a heterocyclic ring which is

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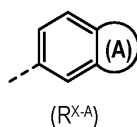


wherein R^X represents

- C_{1-4} -alkyl;
- C_{3-4} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with C_{3-4} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with hydroxy, or C_{1-3} -alkoxy;
- phenyl;
- 6-membered heteroaryl (especially pyridinyl), wherein said 6-membered heteroaryl is unsubstituted or mono-substituted with halogen (especially fluoro);



- , wherein R^{SX1} represents $-\text{CO}-\text{O}-C_{1-4}$ -alkyl;
- $-\text{CO}-R^{OX1}$, or $-\text{SO}_2-R^{OX1}$; wherein R^{OX1} independently represents
 - C_{1-4} -alkyl;
 - C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with C_{1-3} -alkoxy (especially methoxy), tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl (especially quinolinyl), or $-\text{NR}^{ONX1}\text{R}^{ONX2}$ wherein R^{ONX1} and R^{ONX2} independently represent hydrogen or C_{1-3} -alkyl;
 - tetrahydropyranyl;
 - phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C_{1-3} -alkoxy, C_{1-3} -fluoroalkoxy or halogen;
 - 5- or 6-membered heteroaryl (especially pyridinyl, pyrazinyl) wherein said 5- or 6-membered heteroaryl is independently unsubstituted or mono-substituted with C_{1-3} -alkoxy;
 - or
 - a group of the structure (R^{X-A}) :



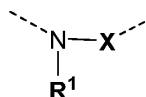
wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and

nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substituents independently are selected from oxo and C₁₋₃-alkyl; or

- $\text{-CO-O-R}^{\text{OX2}}$; wherein R^{OX2} represents
 - C_{1-4} -alkyl;
 - 2,2,2-trichloroethyl; or
 - tetrahydropyranyl.

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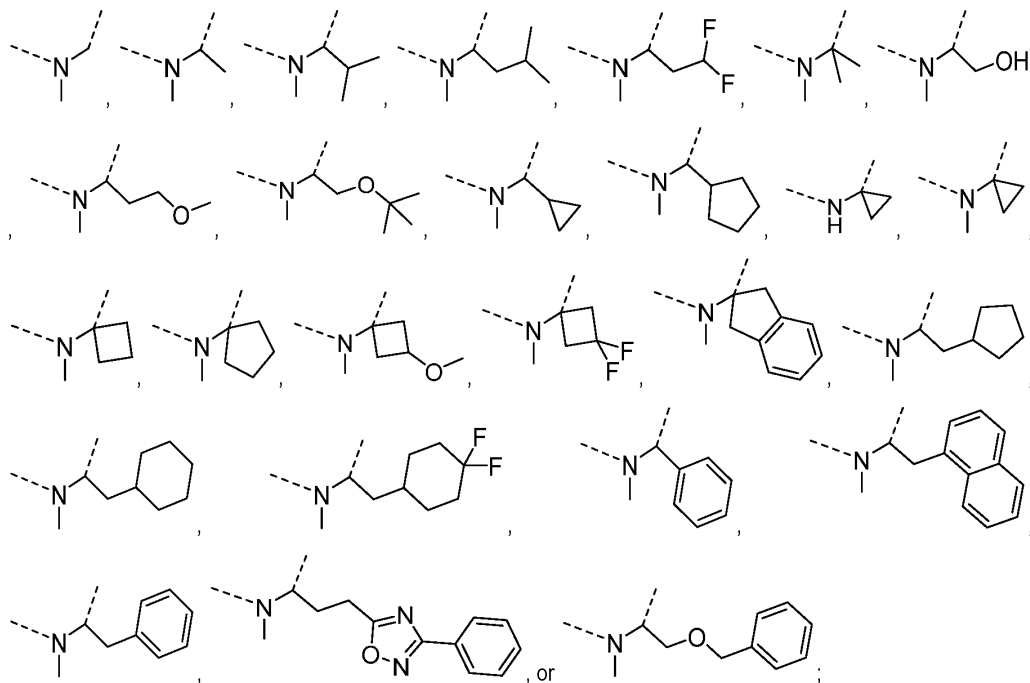
6) Another embodiment relates to compounds according to any one of embodiments 1) to 3), wherein the fragment



represents a group selected from:

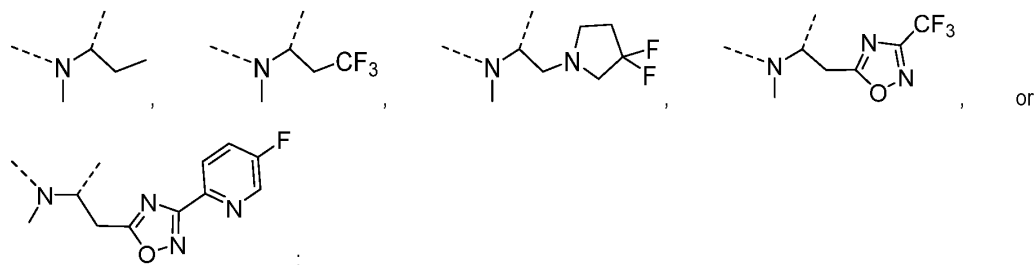
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A)

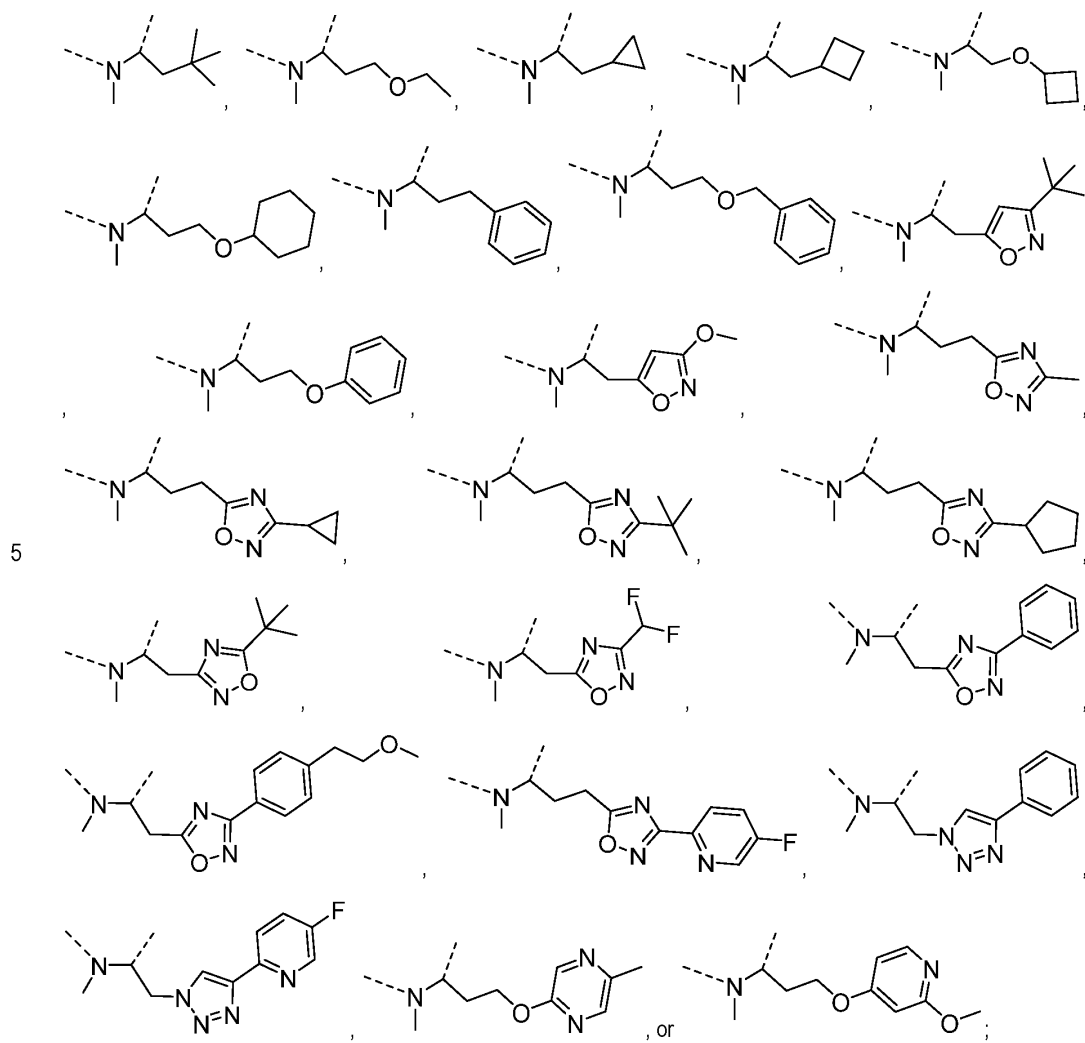


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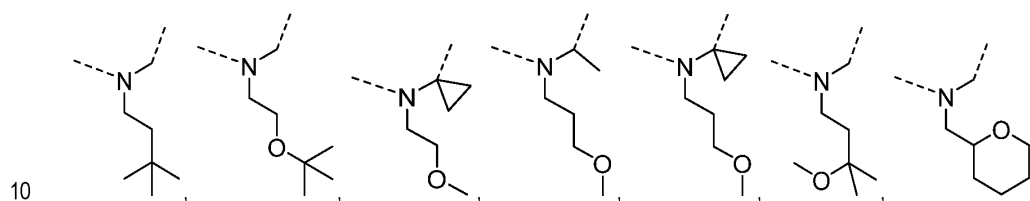
B)

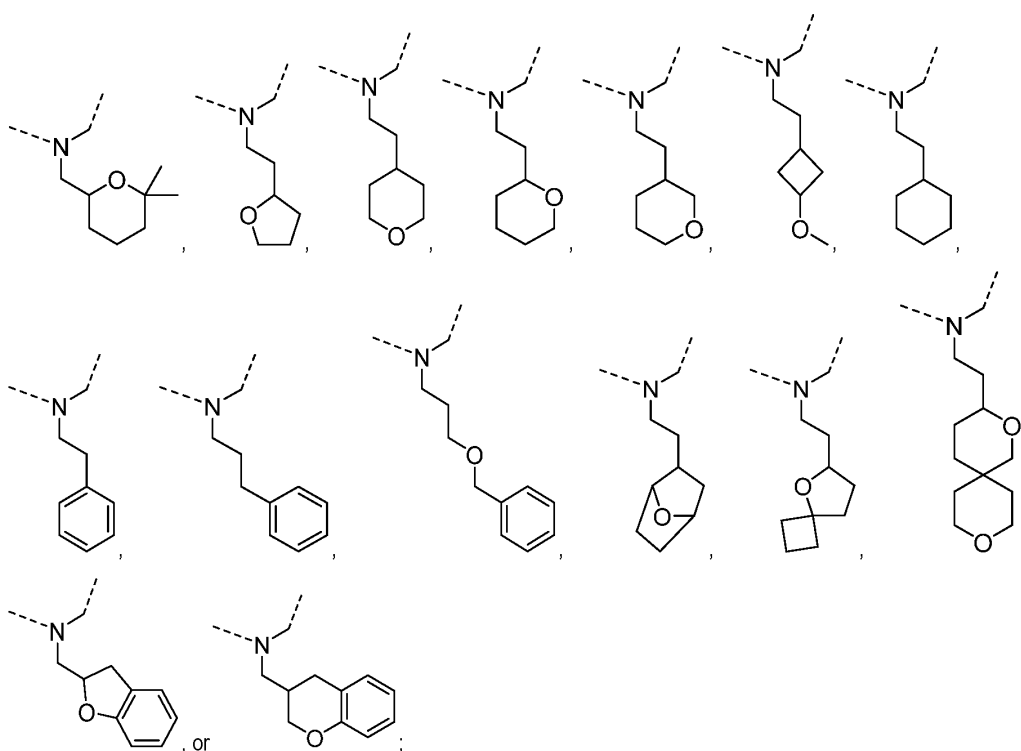


C)

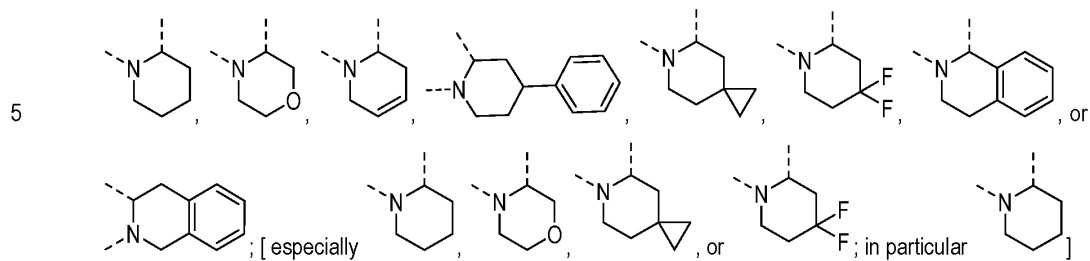


D)

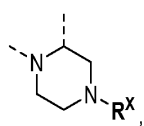




E)



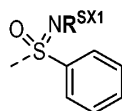
F)



wherein R^x represents

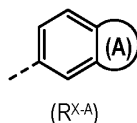
- C₁₋₄-alkyl;
- C₃₋₄-cycloalkyl;
- C₁₋₄-alkyl, wherein said C₁₋₄-alkyl is mono-substituted with C₃₋₄-cycloalkyl;
- C₁₋₄-alkyl, wherein said C₁₋₄-alkyl is mono-substituted with hydroxy, or C₁₋₃-alkoxy;
- phenyl;

- 6-membered heteroaryl (especially pyridinyl), wherein said 6-membered heteroaryl is unsubstituted or mono-substituted with halogen (especially fluoro);



- , wherein R^{SX1} represents $-CO-O-C_{1-4}$ -alkyl;
- $-CO-R^{OX1}$, or $-SO_2-R^{OX1}$; wherein R^{OX1} independently represents

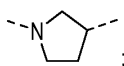
- C_{1-4} -alkyl;
- C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with C_{1-3} -alkoxy (especially methoxy), tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl (especially quinolinyl), or $-NR^{ONX1}R^{ONX2}$ wherein R^{ONX1} and R^{ONX2} independently represent hydrogen or C_{1-3} -alkyl;
- tetrahydropyranyl;
- phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C_{1-3} -alkoxy, C_{1-3} -fluoroalkoxy or halogen;
- 5- or 6-membered heteroaryl (especially pyridinyl, pyrazinyl) wherein said 5- or 6-membered heteroaryl is independently unsubstituted or mono-substituted with C_{1-3} -alkoxy; or
- a group of the structure (R^{X-A}):



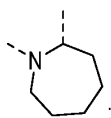
wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substituents independently are selected from oxo and C_{1-3} -alkyl; or

- $-CO-O-R^{OX2}$; wherein R^{OX2} represents
 - C_{1-4} -alkyl;
 - 2,2,2-trichloroethyl; or
 - tetrahydropyranyl;

G)



or H)



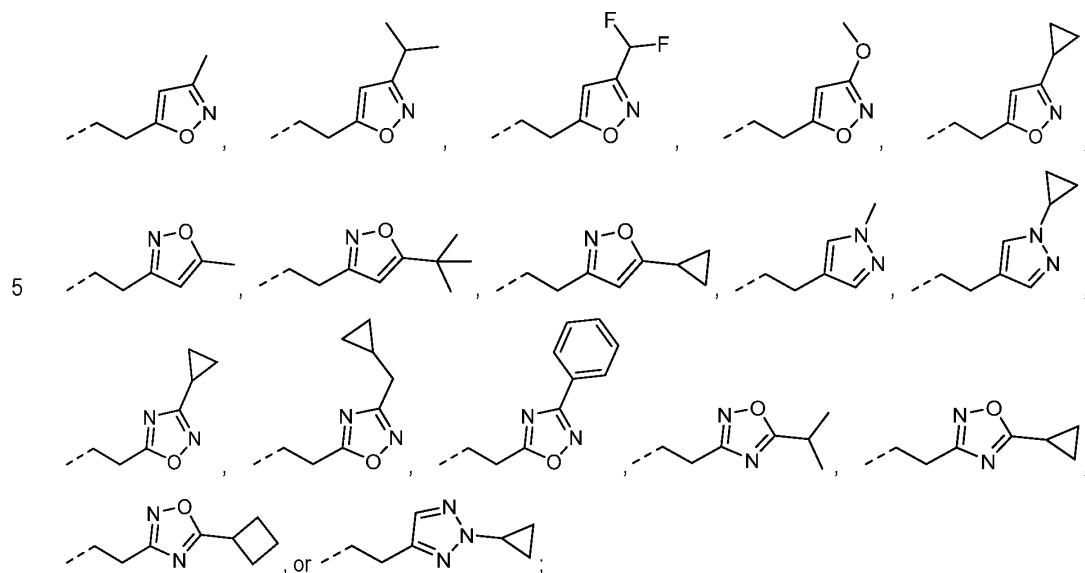
wherein the above groups A), B), C), D), E), F), G) and H) each form a particular sub-embodiment; wherein notably the groups A), B), and C) together form another sub-embodiment, the group D) forms another sub-embodiment, and the groups E), F), G), and H) together form another sub-embodiment. Another particular sub-embodiment is formed by the groups A), D), E), F) and G).

- 5 7) Another embodiment relates to compounds according to any one of embodiments 1) to 6), wherein **R²** represents methyl.
- 8) Another embodiment relates to compounds according to any one of embodiments 1) to 7), wherein **R³** represents isobutyl.
- 9) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein **R⁴** represents
 - 10 a group -CO-NH-**R⁴¹**; wherein **R⁴¹** represents
 - C₂₋₆-alkyl, which is mono-substituted with C₁₋₄-alkoxy (especially methoxy), or C₁₋₄-fluoroalkoxy (especially difluoromethoxy, or trifluoromethoxy);
 - C₁₋₃-alkoxy-C₂₋₃-alkylene-O-CH₂-CH₂-;
 - -CH₂-CH₂-C₅₋₆-heterocycloalkyl, wherein said C₅₋₆-heterocycloalkyl contains one ring oxygen atom, wherein
 - 15 said C₅₋₆-heterocyclyl is unsubstituted, mono- or di-substituted with C₁₋₄-alkyl (especially methyl);
 - -**L¹**-aryl; wherein **L¹** represents -CH₂-CH₂-, -CH₂-CH₂-O-* or -CH₂-CF₂-, -CH₂-(cyclopropan-1,1-diyl)-*, -CH(CH₂-OH)-CH₂-, or -CH₂-CH(OH)-*; wherein asterisks indicate the bond with which **L¹** is attached to the aryl; wherein aryl represents phenyl; wherein said aryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C₁₋₄-alkyl (especially methyl, ethyl, tert-butyl), C₁₋₄-alkoxy (especially methoxy, ethoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen (especially fluoro, chloro, bromo), cyano, hydroxy-C₁₋₃-alkyl, C₂₋₃-alkynyl, morpholin-4-yl, C₁₋₃-alkyl-SO₂-, 5- or 6-membered heteroaryl (especially pyrazolyl, triazolyl, pyrimidinyl, pyrazinyl), or -NR^{N41}R^{N42}, wherein independently **R^{N41}** is hydrogen or C₁₋₄-alkyl, and **R^{N42}** is hydrogen or C₁₋₄-alkyl;
 - -**L²**-**HET¹**; wherein **L²** represents -CH₂-CH₂-, -CH₂-CF₂-, -CH₂-(cyclopropan-1,1-diyl)-*, or -CH₂-CH(OH)-*; wherein asterisks indicate the bond with which **L²** is attached to **HET¹** (especially **L²** represents -CH₂-CH₂-); wherein **HET¹** represents 5- or 6-membered heteroaryl (especially thiophenyl, furanyl, thiazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, or triazolyl; or pyridinyl, pyrimidinyl, or pyrazinyl), wherein said 5- or 6-membered heteroaryl is independently unsubstituted, mono-, or di-substituted, wherein the substituents are independently C₁₋₄-alkyl (especially methyl); C₁₋₄-alkoxy (especially methoxy); C₁₋₃-fluoroalkyl; halogen; C₃₋₆-cycloalkyl (especially cyclopropyl); C₃₋₆-cycloalkyl-methyl; C₁₋₃-alkoxy-C₁₋₃-alkyl; C₂₋₃-alkynyl, benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy), or C₁₋₄-fluoroalkoxy (especially trifluoromethoxy);
 - -CH₂-CH₂-**HET²**, wherein **HET²** represents 9- or 10-membered bicyclic heteroaryl (especially benzoxazolyl, benzisoxazolyl, benzofuranlyl, benzo[d][1,2,3]triazolyl or [1,2,4]triazolo[1,5-a]pyrimidinyl), wherein said **HET²** - 20 is unsubstituted;
 - 25
 - 30
 - 35

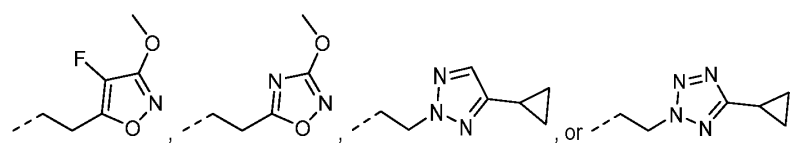
- $-\text{CH}_2-\text{CH}_2-\text{HCy}^1$, wherein HCy^1 represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with C_{1-4} -alkyl (especially methyl); and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, or di-substituted, wherein the substituents are indepently C_{1-4} -alkyl (especially methyl), C_{1-4} -alkoxy (especially methoxy), or halogen (especially chloro, bromo); or
 - $-\text{CH}_2-\text{CH}_2-\text{HCy}^2$, wherein HCy^2 represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring.
- 10) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein R^4 represents a group $-\text{CO}-\text{NH}-\text{R}^{41}$; wherein R^{41} represents
- $-\text{L}^1\text{-aryl}$; wherein L^1 represents $-\text{CH}_2-\text{CH}_2-$, or $-\text{CH}_2-\text{CH}_2-\text{O}-^*$; wherein asterisks indicate the bond with which L^1 is attached to the aryl; wherein aryl represents phenyl; wherein said aryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C_{1-4} -alkyl (especially methyl, ethyl, tert-butyl), C_{1-4} -alkoxy (especially methoxy, ethoxy), C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, halogen (especially fluoro, chloro, bromo), hydroxy- C_{1-3} -alkyl, 5- or 6-membered heteroaryl (especially pyrazolyl, triazolyl, pyrimidinyl, pyrazinyl), or $-\text{NR}^{\text{N}41}\text{R}^{\text{N}42}$, wherein independently $\text{R}^{\text{N}41}$ is hydrogen or C_{1-4} -alkyl, and $\text{R}^{\text{N}42}$ is hydrogen or C_{1-4} -alkyl;
 - $-\text{L}^2\text{-HET}^1$; wherein L^2 represents $-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{CF}_2-$, or $-\text{CH}_2-\text{CH}(\text{OH})-$; wherein asterisks indicate the bond with which L^2 is attached to HET^1 (especially L^2 represents $-\text{CH}_2-\text{CH}_2-$); wherein HET^1 represents 5- or 6-membered heteroaryl (especially thiophenyl, furanyl, thiazolyl, isothiazolyl, pyrazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl), wherein said 5- or 6-membered heteroaryl is independently unsubstituted, mono-, or di-substituted, wherein the substituents are independently C_{1-4} -alkyl (especially methyl, tert-butyl); C_{1-4} -alkoxy (especially methoxy); C_{1-3} -fluoroalkyl; halogen; C_{3-6} -cycloalkyl; benzyl; or phenyl which is unsubstituted, or mono-substituted wherein the substituents independently are C_{1-4} -alkyl (especially methyl), C_{1-4} -alkoxy (especially methoxy), or C_{1-4} -fluoroalkoxy (especially trifluoromethoxy);
 - $-\text{CH}_2-\text{CH}_2-\text{HET}^2$, wherein HET^2 represents 9- or 10-membered bicyclic heteroaryl (especially benzoxazolyl, benzisoxazolyl, benzofuranyl, benzo[d][1,2,3]triazolyl or [1,2,4]triazolo[1,5-a]pyrimidinyl), wherein said HET^2 is unsubstituted;
 - $-\text{CH}_2-\text{CH}_2-\text{HCy}^1$, wherein HCy^1 represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two oxygen atoms; wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, or mono-substituted, wherein the substituents are indepently C_{1-4} -alkyl (especially methyl), C_{1-4} -alkoxy (especially methoxy), or halogen (especially chloro, bromo); or
 - $-\text{CH}_2-\text{CH}_2-\text{HCy}^2$, wherein HCy^2 represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring.

11) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein **R⁴** represents a group -CO-NH-**R⁴¹**; wherein **R⁴¹** represents a group selected from:

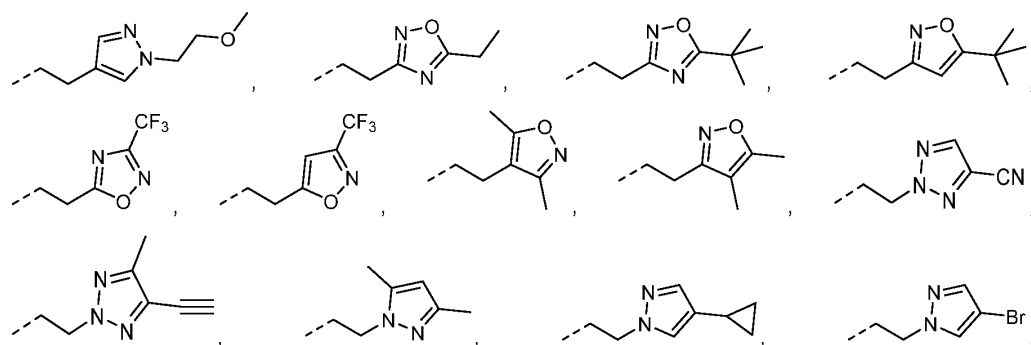
A)

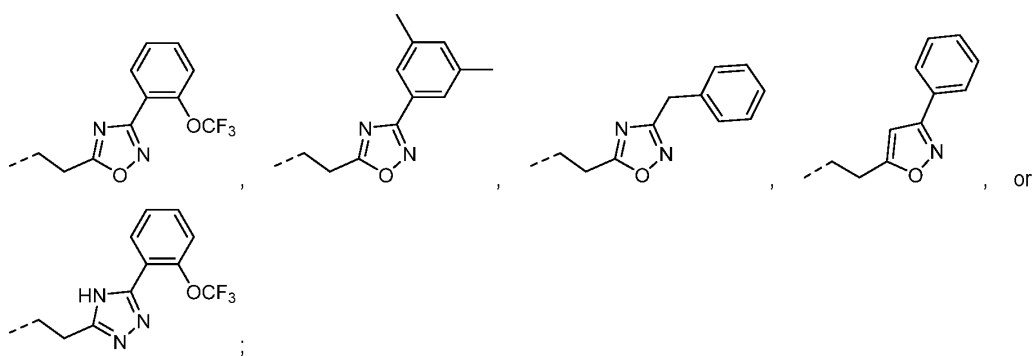


B)

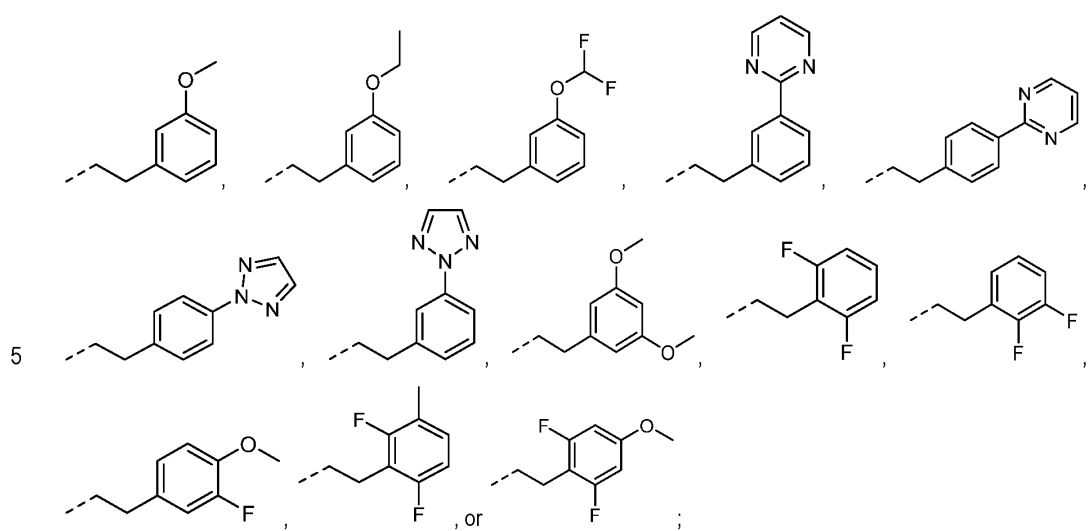


10 C)

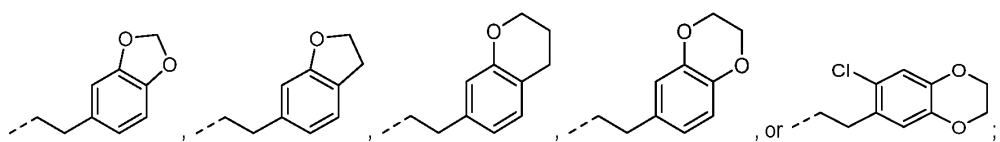




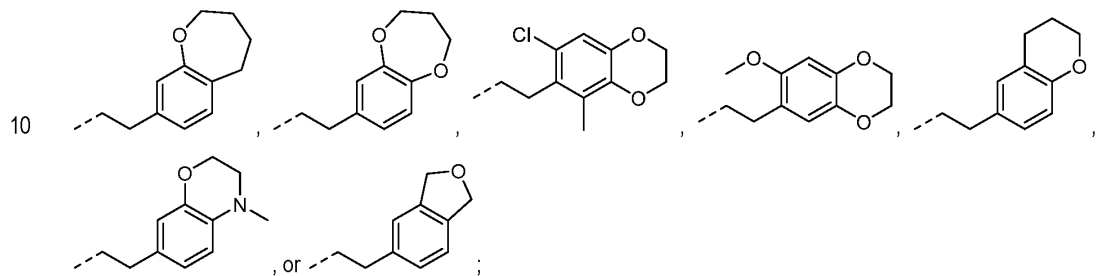
D)



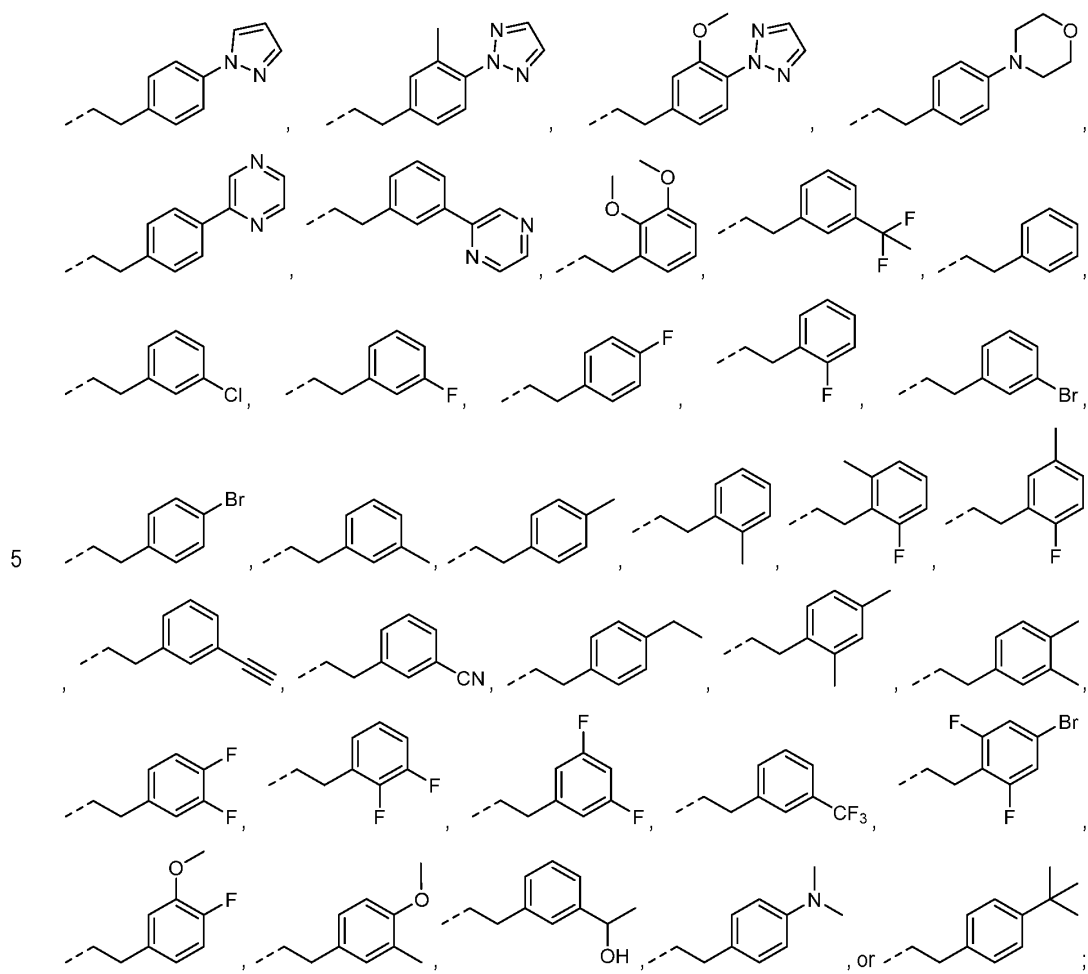
E)



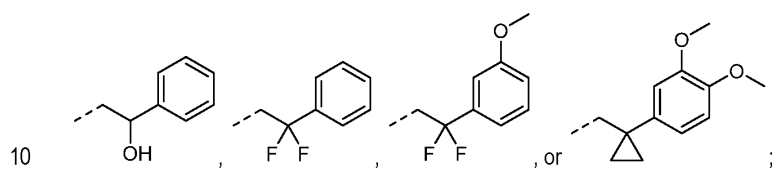
F)



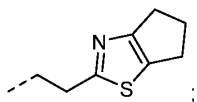
G)



H)

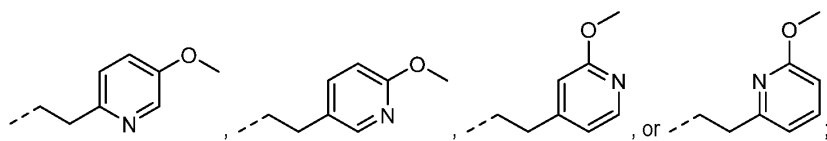


1)

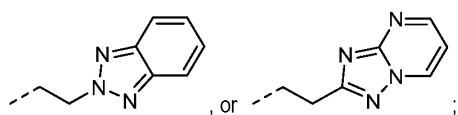


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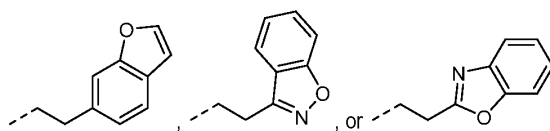
J)



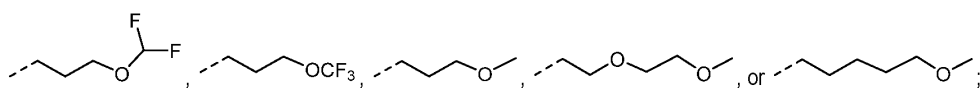
K)



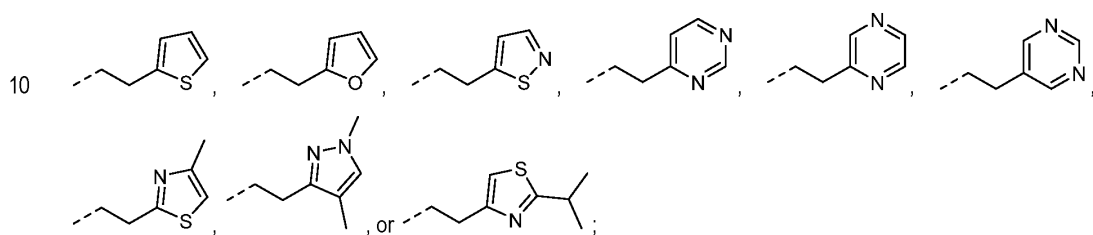
5 L)



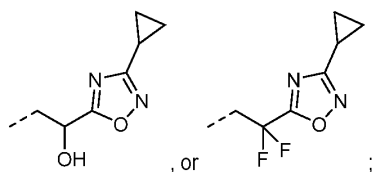
M)



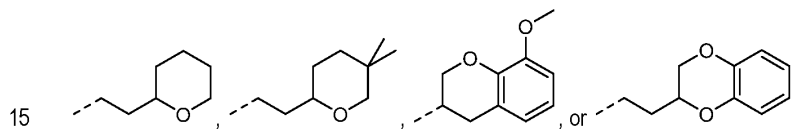
N)



O)



P)



wherein the above groups A), B), C), D), E), F), G), H), I), J), K), L), M), N), O), and P) each form a particular sub-embodiment; wherein notably the groups A) and B) together form a particular sub-embodiment, and the groups D)

and E) together form another particular sub-embodiment. Another particular sub-embodiment is formed by the groups A), D), E), and I), especially A), D), and E). Another particular sub-embodiment is formed by the groups A), B), D), E), I), and K), especially A), B), D) and K).

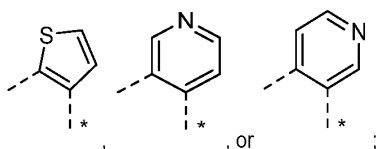
12) Another embodiment relates to compounds according to any one of embodiments 1) to 11), wherein **Ar²** represents phenyl.

13) Another embodiment relates to compounds according to any one of embodiments 1) to 12), wherein **Ar¹** represents

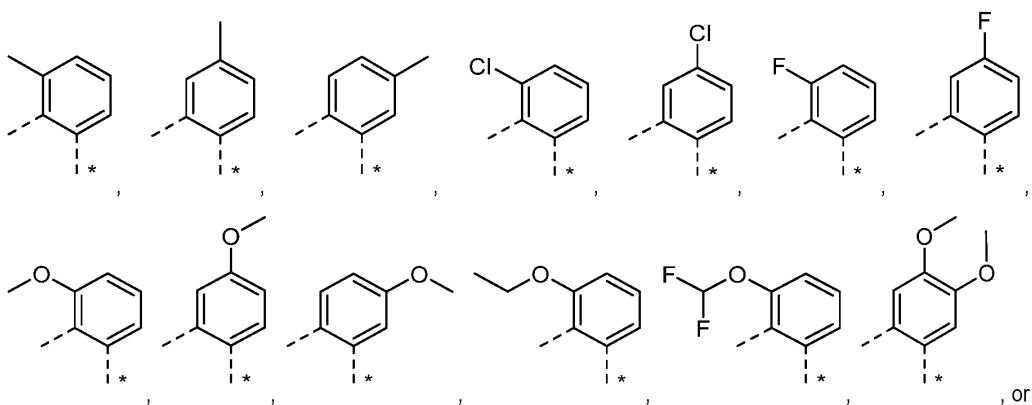
- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy, ethoxy), and halogen (especially fluoro, chloro);
 - phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted; or
 - a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, or mono-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), and halogen (especially fluoro, chloro);
- [wherein it is understood that in the above groups **Ar¹** the -CO- group and the oxygen (i.e. the groups linking **Ar¹** to the rest of the molecule) are attached in ortho arrangement to aromatic ring carbon atoms of **Ar¹**].

14) Another embodiment relates to compounds according to any one of embodiments 1) to 12), wherein **Ar¹** represents a group selected from

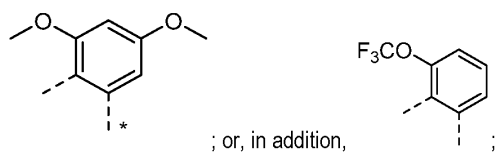
20 A)



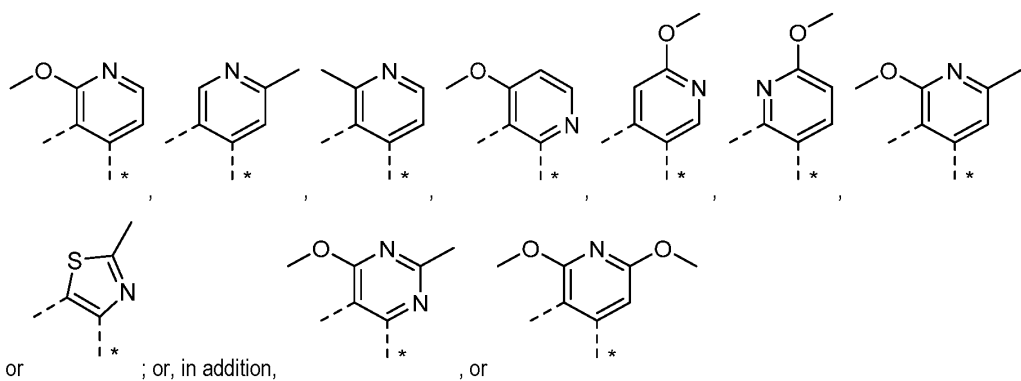
B)



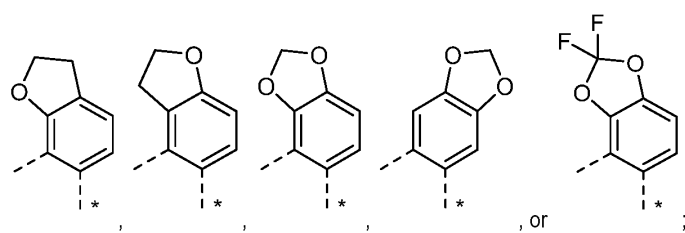
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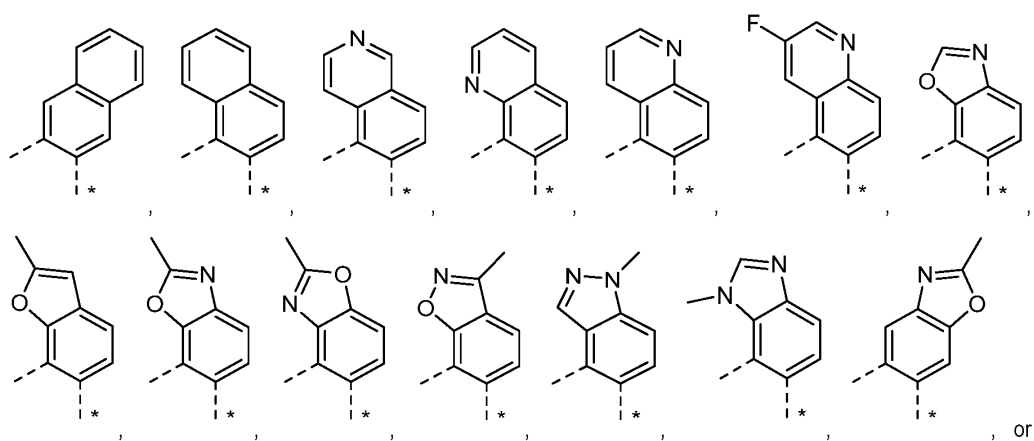
C)



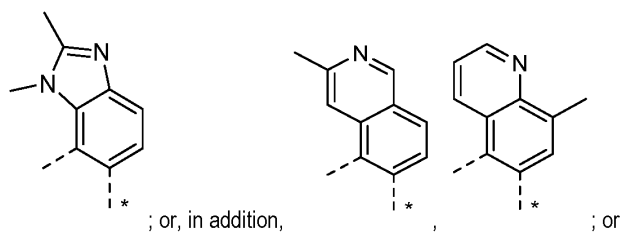
5 D)



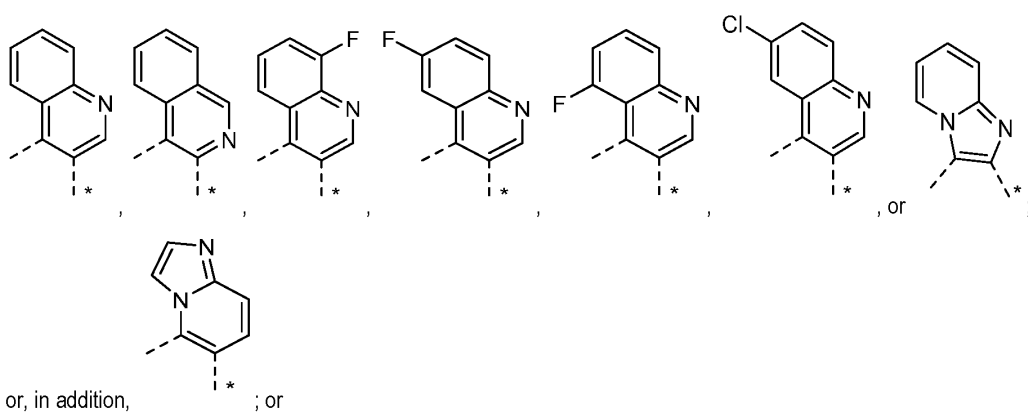
E)



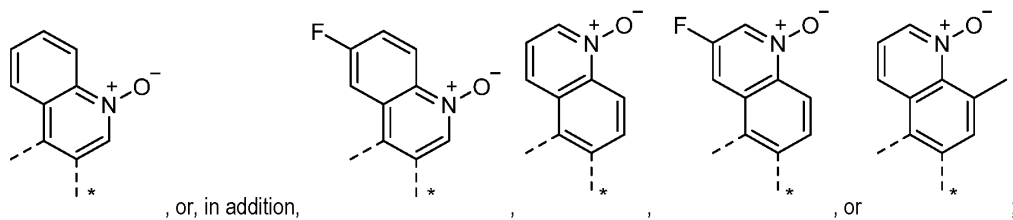
34



F)



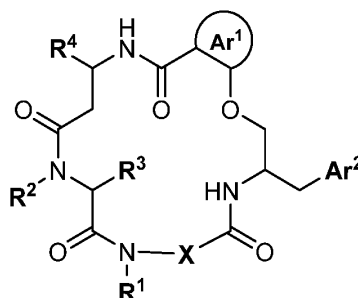
5 G)



wherein in the above groups the asterisks indicate the bond with which said groups are attached to the oxygen (i.e. to the oxygen linking **Ar**¹ to the rest of the molecule);

wherein the above groups A), B), C), D), E), F) and G) each form a particular sub-embodiment.

15) A second aspect of the invention relates to compounds of the Formula (II)



Formula (II)

for use in the treatment of cystic fibrosis;

- 5 wherein **X**, **R¹**, **R²**, **R³**, **R⁴**, **Ar²** independently are as defined for the compounds of Formula (I) in any one of embodiments 1), 2) or 4) to 12); and

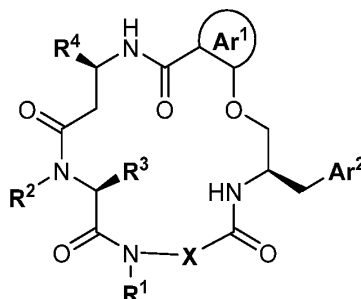
Ar¹ represents

- phenylene wherein said phenylene is unsubstituted;
- 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted (especially pyridin-3,4-diyl, thiophen-2,3-diyl);
- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), C₁₋₄-alkoxy (especially methoxy, ethoxy), C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano, and halogen (especially fluoro, chloro);
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or
- a bicyclic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl (especially methyl), C₁₋₃-fluoroalkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkoxy, cyano, and halogen (especially fluoro, chloro); or
- quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted or mono-substituted with methyl or fluoro;

[wherein it is understood that in the above groups **Ar¹** the -CO- group and the oxygen (i.e. the groups linking **Ar¹** to the rest of the molecule) are attached in ortho arrangement to aromatic ring carbon atoms of **Ar¹**].

16) Another embodiment relates to compounds of the Formula (II) according to embodiment 15), for use in the treatment of cystic fibrosis; wherein **Ar¹** represents unsubstituted phenylene; or represents a group as defined in embodiment 13) or 14).

17) A further embodiment relates to compounds of Formula (II) for use according to embodiment 15) or 16), wherein the compounds are compounds of Formula (II_E):



Formula (II_E).

- 5 The compounds of formula (I) / formula (II) contain at least three stereogenic or asymmetric centers, which are present in (R)- or (S)-configuration as defined in the respective embodiment defining such compound of formula (I) / formula (II). In addition, the compounds of formula (I) / formula (II) may contain one or more further stereogenic or asymmetric centers, such as one or more additional asymmetric carbon atoms. The compounds of formula (I) / formula (II) may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known to a person skilled in the art. In case any stereogenic or asymmetric center in a given chemical name is designated as being in (*RS*)-configuration, this means that such stereogenic or asymmetric center in such compound may be present in (*R*)-configuration, in (*S*)-configuration, or in any mixture of epimers with regard to such center.

Thus, for example the compound (3*S*,7*S*,10*RS*,13*R*)-13-benzyl-10-(tert-butoxymethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide comprises (3*S*,7*S*,10*R*,13*R*)-13-benzyl-10-(tert-butoxymethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide, the compound (3*S*,7*S*,10*S*,13*R*)-13-benzyl-10-(tert-butoxymethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide, and any mixture thereof. Likewise, in a certain chemical structure (such as in Table 3, 4, and 5), a stereogenic or asymmetric center indicated as "abs" represents said stereogenic or asymmetric center in the respective (*R*)- or (*S*)-configuration. A stereogenic or asymmetric center indicated as "&1" represents said stereogenic or asymmetric center in the respective (*RS*)-configuration, i.e. comprising the respective (*R*)- or (*S*)-configuration or any mixture of epimers at such center.

The compounds of formula (I) / formula (II) may further encompass compounds with one or more double bonds which are allowed to be present in *Z*- as well as *E*-configuration and/or compounds with substituents at a ring system which are allowed to be present, relative to each other, in *cis*- as well as *trans*-configuration.

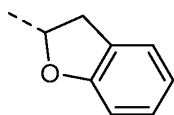
In case a particular compound (or generic structure) is designated as (R)- or (S)-enantiomer, such designation is to be understood as referring to the respective compound (or generic structure) in enriched enantiomeric form, especially in essentially pure enantiomeric form. Likewise, in case a specific asymmetric center in a compound is designated as being in (R)- or (S)-configuration or as being in a certain relative configuration, such designation is to be understood as referring to the compound that is in enriched, especially essentially pure form with regard to the respective configuration of said asymmetric center. In analogy, *cis*- or *trans*-designations are to be understood as referring to the respective stereoisomer of the respective relative configuration in enriched, especially essentially pure form. Likewise, in case a particular compound (or generic structure) is designated as Z- or E-stereoisomer (or in case a specific double bond in a compound is designated as being in Z- or E-configuration), such designation is to be understood as referring to the respective compound (or generic structure) in enriched, especially essentially pure stereoisomeric form (or to the compound that is in enriched, especially essentially pure, form with regard to the respective configuration of the double bond).

The term "enriched", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a ratio of at least 70:30, especially of at least 90:10 (i.e., in a purity of at least 70% by weight, especially of at least 90% by weight), with regard to the respective other stereoisomer / the entirety of the respective other stereoisomers.

The term "essentially pure", when used in the context of stereoisomers, is to be understood in the context of the present invention to mean that the respective stereoisomer is present in a purity of at least 95% by weight, especially of at least 99% by weight, with regard to the respective other stereoisomer / the entirety of the respective other stereoisomers.

The present invention also includes isotopically labelled, especially ^2H (deuterium) labelled compounds of formula (I) / formula (II) according to embodiments 1) to 21), which compounds are identical to the compounds of formula (I) / formula (II) except that one or more atoms have each been replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially ^2H (deuterium) labelled compounds of formula (I) / formula (II) and salts thereof are within the scope of the present invention. In case a certain substituent is specifically indicated as representing hydrogen, it is understood to refer to all isotopes of the atom "H", i.e. the term hydrogen as used for a certain substituent is understood as comprising the isotope ^2H (deuterium); preferably it refers to the isotope ^1H (hydrogen). Substitution of hydrogen with the heavier isotope ^2H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased *in-vivo* half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formula (I) / formula (II) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formula (I) / formula (II) are not isotopically labelled at all. Isotopically labelled compounds of formula (I) / formula (II) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

In this patent application, a bond drawn as a dotted line shows the point of attachment of the radical drawn. For example, the radical drawn below



is the 2,3-dihydrobenzofuran-2-yl group.

- 5 Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any reference to compounds of formula (I) / formula (II) according to embodiments 1) to 21) is to be understood as referring to the compound in free base or salt form, thus, referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

- 10 The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. Such salts include inorganic or organic acid and/or base addition salts depending on the presence of basic and/or acidic groups in the subject compound. For reference see for example "Handbook of Pharmaceutical Salts. Properties, Selection and Use.", P. Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2008; and "Pharmaceutical Salts and Co-crystals", Johan Wouters and Luc Quéré (Eds.),
15 RSC Publishing, 2012.

- Definitions provided herein are intended to apply uniformly to the compounds of formula (I) / formula (II), as defined in any one of embodiments 1) to 17), and, *mutatis mutandis*, throughout the description and the claims unless an otherwise expressly set out definition provides a broader or narrower definition. It is well understood that a definition or preferred definition of a term defines and may replace the respective term independently of (and in combination
20 with) any definition or preferred definition of any or all other terms as defined herein.

Whenever a substituent is denoted as optional, it is understood that such substituent may be absent (i.e. the respective residue is unsubstituted with regard to such optional substituent), in which case all positions having a free valency (to which such optional substituent could have been attached to; such as for example in an aromatic ring the ring carbon atoms and / or the ring nitrogen atoms having a free valency) are substituted with hydrogen where appropriate.

- 25 Likewise, in case the term "optionally" is used in the context of (ring) heteroatom(s), the term means that either the respective optional heteroatom(s), or the like, are absent (i.e. a certain moiety does not contain heteroatom(s) / is a carbocycle / or the like), or the respective optional heteroatom(s), or the like, are present as explicitly defined.

The term "halogen" means fluorine/fluoro, chlorine/chloro, or bromine/bromo; preferably fluorine/fluoro or chlorine/chloro.

- 30 The term "alkyl", used alone or in combination, refers to a saturated straight or branched chain hydrocarbon group containing one to six carbon atoms. The term "C_{x-y}-alkyl" (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example, a C₁₋₆-alkyl group contains from one to six carbon atoms.

Representative examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, 3-methyl-butyl, 2,2-dimethyl-propyl and 3,3-dimethyl-butyl. For avoidance of any doubt, in case a group is referred to as e.g. propyl or butyl, it is meant to be n-propyl, respectively n-butyl. In case **R^{x2}** represents a C₁₋₆-alkyl group, the term especially refers to C₁₋₄-alkyl, in particular to methyl, ethyl, isopropyl, or isobutyl; preferably methyl. In case **R¹** represents -C₁₋₈-alkyl, the term especially means methyl, or 3,3-dimethylbut-1-yl; preferably methyl. In case **R^x** represents C₁₋₄-alkyl, the term especially means methyl, ethyl, isopropyl, or isobutyl. For **R^{ox1}** representing C₁₋₄-alkyl, the term especially means methyl or isobutyl. For **R^{ox2}** representing C₁₋₄-alkyl, the term especially means methyl or ethyl. For **R²** representing C₁₋₄-alkyl the term especially means methyl, or ethyl; preferably methyl. In case **R³** represents -C₁₋₆-alkyl, the term especially means methyl, or isobutyl; preferably isobutyl. A C₁₋₆-alkyl group wherein said C₁₋₆-alkyl is mono-substituted with **R¹¹** especially refers to -(CH₂)_m- groups wherein **m** represents the integer 1 or 2, or to a C₃₋₆-alkyl group, said groups being mono-substituted with **R¹¹** as explicitly defined.

The term "-C_{x-y}-alkylene-", used alone or in combination, refers to bivalently bound alkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of a -C_{1-y}-alkylene group are in 1,1-diyl, in 1,2-diyl, or in 1,3-diyl arrangement.

It is understood that an alkylene group (or a substituted alkyl group) that links two heteroatoms preferably will distance such heteroatoms by at least 2 carbon atoms.

The term "alkoxy", used alone or in combination, refers to an alkyl-O- group wherein the alkyl group is as defined before. The term "C_{x-y}-alkoxy" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example, a C₁₋₄-alkoxy group means a group of the formula C₁₋₄-alkyl-O- in which the term "C₁₋₄-alkyl" has the previously given significance. Representative examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy. Preferred is methoxy.

The term "fluoroalkyl", used alone or in combination, refers to an alkyl group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "C_{x-y}-fluoroalkyl" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example, a C₁₋₃-fluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include especially C₁-fluoroalkyl groups such as trifluoromethyl, and difluoromethyl, as well as 2-fluoroethyl, 2,2-difluoroethyl and 2,2,2-trifluoroethyl. In case **R^{x2}** represents C₁₋₄-fluoroalkyl, the term especially means 2,2-difluoroethyl or 2,2,2-trifluoroethyl.

The term "-C_{x-y}-fluoroalkylene-", used alone or in combination, refers to bivalently bound fluoroalkyl group as defined before containing x to y carbon atoms.

The term "fluoroalkoxy", used alone or in combination, refers to an alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "C_{x-y}-fluoroalkoxy" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example, a C₁₋₃-fluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include

trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy. Preferred are (C₁)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy.

The term "alkynyl", used alone or in combination, refers to a straight or branched hydrocarbon chain containing two to four carbon atoms and one carbon-carbon triple bond. The term "C_{x-y}-alkynyl" (x and y each being an integer), refers to an alkynyl group as defined before containing x to y carbon atoms. For example, a C₂₋₄-alkynyl group contains from two to four carbon atoms. In case **R**³ represents -C₂₋₄-alkynyl, the term especially means prop-1-yn-3-yl. An example of C₂₋₃-alkynyl is ethynyl.

The term "cycloalkyl", used alone or in combination, refers to a saturated monocyclic hydrocarbon ring containing three to six carbon atoms. The term "C_{x-y}-cycloalkyl" (x and y each being an integer), refers to a cycloalkyl group as defined before containing x to y carbon atoms. For example, a C₃₋₆-cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. In case **R**^{x2} represents C₃₋₆-cycloalkyl, the term preferably means cyclopropyl, cyclobutyl, or cyclopentyl. In case **R**¹¹ represents C₃₋₆-cycloalkyl, the term especially means cyclobutyl or cyclohexyl.

The term "-C_{x-y}-cycloalkylene-", used alone or in combination, refers to bivalently bound cycloalkyl group as defined before containing x to y carbon atoms. Preferably, the points of attachment of any bivalently bound cycloalkyl group are in 1,1-diyl arrangement. Examples are cyclopropan-1,1-diyl, cyclobutan-1,1-diyl, and cyclopentan-1,1-diyl; preferred is cyclopropan-1,1-diyl.

Examples of C₃₋₆-cycloalkan-1,1-diyl- are cyclopropan-1,1-diyl, cyclobutan-1,1-diyl and cyclopentane-1,1-diyl. An example of a C₅₋₆-cycloalkan-1,1-diyl- group which is fused to a benzene ring is 1,3-dihydro-2H-indene-2,2-diyl.

The term "heterocycloalkyl", used alone or in combination, and if not explicitly defined in a broader or more narrow way, refers to a saturated monocyclic hydrocarbon ring containing one or two ring heteroatoms independently selected from nitrogen, sulfur, and oxygen. The term "C_{x-y}-heterocycloalkyl" refers to such a heterocycle containing x to y ring atoms. Examples are tetrahydrofuranyl, tetrahydropyranyl, and piperidinyl. Heterocycloalkyl groups are unsubstituted or substituted as explicitly defined. In case **R**¹¹ represents a saturated 5- or 6-membered heterocycloalkyl containing one or two ring heteroatoms, the term especially means tetrahydropyranyl and tetrahydrofuranyl. An example of a C₅₋₆-heterocycloalkyl group containing one ring oxygen atom is especially tetrahydropyranyl.

The term "C₄₋₆-heterocycloalkan-diyl wherein said C₄₋₆-heterocycloalkan-diyl contains one ring oxygen atom" refers to a bivalently bound heterocycloalkyl group containing one ring oxygen atom and the remaining ring carbon atoms. An example of "C₄₋₆-heterocycloalkan-diyl wherein said C₄₋₆-heterocycloalkan-diyl contains one ring oxygen atom" is tetrahydropyran-4,4-diyl. The term "C₄₋₆-heterocycloalkan-diyl wherein said C₄₋₆-heterocycloalkan-diyl contains one ring nitrogen atom", refers to a bivalently bound heterocycloalkyl group containing one ring nitrogen atom and the remaining ring carbon atoms. An example of "C₄₋₆-heterocycloalkan-diyl wherein said C₄₋₆-heterocycloalkan-diyl contains one ring nitrogen atom" is piperidin-4,4-diyl.

The term "aryl", used alone or in combination, means phenyl or naphthyl, especially phenyl. The above-mentioned aryl groups are unsubstituted or substituted as explicitly defined.

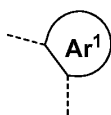
It is understood that a heterocyclic ring, for example "containing one or two heteroatoms independently selected from oxygen and nitrogen" or "containing one oxygen atom", contains exactly the number and type of heteroatoms indicated, the remaining ring atoms being carbon atoms if not explicitly indicated otherwise.

- Examples of the substituent "**HCy¹**" representing a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen" are benzodioxolyl, dihydrobenzofuranyl, dihydrobenzodioxinyl, chromanyl, tetrahydrobenzoxepinyl, dihydrobenzoxazinyl; more particularly benzo[d][1,3]dioxol-5-yl, 1,3-dihydroisobenzofuran-5-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 2,3-dihydrobenzo[b][1,4]dioxin-6-yl, 2,3-dihydrobenzo[b][1,4]dioxin-2-yl, chroman-6-yl, chroman-7-yl, 2,3,4,5-tetrahydrobenzo[b]oxepin-8-yl, 3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl, and 3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl. The above-mentioned **HCy¹** groups are unsubstituted or substituted as explicitly defined.

Preferred example of the substituent "**HCy²**" representing a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring" is 5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl.

- 15 A preferred example of the substituent "**HCy³**" representing a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one oxygen atom" is chroman-3-yl.

Examples of the group **Ar¹** / the fragment:



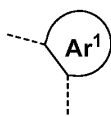
are:

- 20 ■ phenylene or 5- or 6-membered heteroarylene such as thiophene-diyl, thiazole-diyl, or pyridine-diyl;
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, such as benzo[d][1,3]dioxole-diyl, or 2,3-dihydrobenzofuran-diyl;
- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene, such as naphthalene-diyl, benzofuran-diyl, benzo[d]oxazole-diyl, benzo[d]isoxazole-diyl, imidazo[1,2-a]pyridine-diyl, 1H-indazole-diyl, 1H-benzo[d]imidazole-diyl, quinoline-diyl, or isoquinoline-diyl; and
- 25 ■ quinoline-diyl, wherein such quinoline-diyl is present in form of the respective N-oxide, such as quinoline-1-oxide-diyl.

Examples of the group **Ar¹** are especially those, notably as listed above, with the -CO- group and the oxygen (i.e. the groups linking **Ar¹** to the rest of the molecule) attached in ortho arrangement to aromatic ring carbon atoms of **Ar¹**. In

- 30 addition, said groups **Ar¹** are unsubstituted or substituted as explicitly defined.

Particular examples of the fragment:



- phenylene or 5- or 6-membered heteroarylene, such as 1,2-phenylene, thiophene-2,3-diyl, thiazole-4,5-diyl, pyridine-3,4-diyl, or pyridine-2,3-diyl;
- 5 ▪ phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, such as benzo[d][1,3]dioxole-4,5-diyl, benzo[d][1,3]dioxole-5,6-diyl, 2,3-dihydrobenzofuran-6,7-diyl, or 2,3-dihydrobenzofuran-4,5-diyl;
- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene, such as naphthalene-1,2-diyl, naphthalene-2,3-diyl, benzofuran-6,7-diyl, benzo[d]oxazole-4,5-diyl, benzo[d]oxazole-5,6-diyl, benzo[d]oxazole-6,7-diyl, benzo[d]isoxazole-6,7-diyl, imidazo[1,2-a]pyridine-2,3-diyl, 1H-indazole-4,5-diyl, 1H-benzo[d]imidazole-6,7-diyl, quinoline-7,8-diyl, quinoline-3,4-diyl, quinoline-5,6-diyl, isoquinoline-3,4-diyl or isoquinoline-5,6-diyl;
- 10 ▪ quinoline-diyl, wherein such quinoline-diyl is present in form of the respective N-oxide, such as quinoline-1-oxide-3,4-diyl or quinoline-1-oxide-5,6-diyl.
- 15 The above-mentioned groups **Ar¹** are unsubstituted or substituted as explicitly defined.

The term "heteroaryl", used alone or in combination, and if not explicitly defined in a broader or more narrow way, means a 5- to 10-membered monocyclic or bicyclic aromatic ring containing one to a maximum of four heteroatoms, each independently selected from oxygen, nitrogen and sulfur. Representative examples of such heteroaryl groups are 5-membered heteroaryl groups such as furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiophenyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl; 6-membered heteroaryl groups such as pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl; and 8- to 10-membered bicyclic heteroaryl groups such as indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, thienopyridinyl, quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, pyrrolopyridinyl, pyrazolopyridinyl, pyrazolopyrimidinyl, pyrrolopyrazinyl, imidazopyridinyl, imidazopyridazinyl, and imidazothiazolyl. The above-mentioned heteroaryl groups are unsubstituted or substituted as explicitly defined.

In case **R^{ox1}** represents 5- or 6-membered heteroaryl, the term especially means 6-membered heteroaryl containing one or two nitrogen atoms such as pyrazinyl or pyridinyl.

For the substituent **HET¹** representing a "5- or 6-membered heteroaryl", the term especially means the above-mentioned 5- or 6-membered groups such as especially pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl or thiophenyl. Notably, the term refers to 5-membered groups such as especially thiophen-2-yl, thiazol-2-yl, thiazol-4-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl, furan-2-yl, isothiazol-5-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-

oxadiazol-3-yl, 2H-[1,2,3]triazol-2-yl, 2H-[1,2,3]triazol-4-yl, 2H-tetrazol-2-yl; and 6-membered groups such as especially pyridin-2-yl, pyridin-4-yl, pyrazin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl. The above groups are substituted as explicitly defined.

For the substituent **Ar²** representing "5- or 6-membered heteroaryl", the term especially means pyridinyl, in particular pyridine-2-yl.

For the substituent **HET²** representing a "9- or 10-membered bicyclic heteroaryl" the term especially refers to benzoxazolyl, benzisoxazolyl, and benzofuranyl; as well as benzo[d][1,2,3]triazolyl or [1,2,4]triazolo[1,5-a]pyrimidinyl. The above groups are unsubstituted or substituted as explicitly defined. Particular examples are benzofuran-6-yl, benzisoxazol-3-yl, benzoxazol-2-yl, and, in addition, 2H-benzo[d][1,2,3]triazol-2-yl and [1,2,4]triazolo[1,5-a]pyrimidin-2-yl.

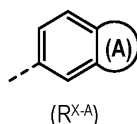
For the substituent **Ar²** representing "9- or 10-membered heteroaryl", the term especially means benzothiophenyl, in particular benzothiophen-3-yl.

For the substituent **HET** representing a "5- to 10-membered heteroaryl", the term especially means 5- or 6-membered heteroaryl groups, or 8- to 10-membered bicyclic heteroaryl groups as defined before; especially pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrazolyl, triazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiophenyl, or benzoxazolyl, benzisoxazolyl, benzofuranyl; or, in addition, benzo[d][1,2,3]triazolyl or [1,2,4]triazolo[1,5-a]pyrimidinyl. The above groups are unsubstituted or substituted as explicitly defined.

For the substituent **Ar^{x2}** representing 5- to 10-membered heteroaryl such heteroaryl is as defined before; especially it represents mono-cyclic 5- or 6-membered heteroaryl [notably 5-membered heteroaryl containing one to three heteroatoms selected from oxygen and nitrogen (especially oxadiazolyl, triazolyl, or isoxazolyl); or 6-membered heteroaryl containing one or two nitrogen atoms (especially pyridinyl)], wherein such mono-cyclic heteroaryl is unsubstituted or substituted as explicitly defined; or it represents bicyclic 8- to 10-membered heteroaryl [notably 10-membered heteroaryl containing one nitrogen atom (especially quinolinyl)], wherein such bicyclic heteroaryl is notably unsubstituted, or substituted as explicitly defined. Particular examples of the substituent **Ar^{x2}** representing 5- to 10-membered heteroaryl are 3-phenyl-[1,2,4]-oxadiazol-5-yl, 3-(5-fluoro-pyridin-2-yl)-[1,2,4]-oxadiazol-5-yl, or 3-trifluoromethyl-[1,2,4]-oxadiazol-5-yl.

For the substituent **Ar^{x3}** representing 5- or 6-membered heteroaryl such heteroaryl notably represents 6-membered heteroaryl containing one or two nitrogen atoms, especially pyridinyl; wherein such 5- or 6-membered heteroaryl heteroaryl is unsubstituted or substituted as explicitly defined. A particular example is 5-fluoro-pyridin-2-yl.

Examples of the fragment:



are the 4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl and 2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl.

The term "cyano" refers to a group -CN.

The term "oxo" refers to a group =O which is preferably attached to a chain or ring carbon atom as for example in a carbonyl group -(CO)-.

In some instances, the compounds of formula (I) / formula (II) may contain tautomeric forms. Such tautomeric forms are encompassed in the scope of the present invention. In case tautomeric forms exist of a certain residue, and only one form of such residue is disclosed or defined, the other tautomeric form(s) are understood to be encompassed in such disclosed residue. For example, 2-oxo-2,3-dihydrobenzo[d]oxazol-yl group is to be understood as also encompassing its tautomeric form (2-hydroxybenzo[d]oxazol-yl).

Whenever the word "between" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a temperature range is described to be between 40 °C and 80 °C, this means that the end points 40 °C and 80 °C are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10°C to Y plus 10°C, and preferably to an interval extending from Y minus 5°C to Y plus 5°C. Besides, the term "room temperature" as used herein refers to a temperature of about 25°C.

18) Another embodiment relates to compounds of Formula (I) according to embodiment 1), wherein said compounds are selected from the compounds of example (as disclosed in the experimental part below):

1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 100; 101; 102; 103; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113; 114; 115; 116; 117; 118; 119; 120; 121; 122; 123; 124; 125; 126; 127; 128; 129; 130; 131; 132; 133; 134; 135; 136; 137; 138; 139; 140; 141; 142; 143; 144; 145; 146; 147; 148; 149; 150; 151; 152; 153; 154; 155; 156; 157; 158; 159; 160; 161; 162; 163; 164; 165; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 176; 177; 178; 179; 180; 181; 182; 183; 184; 185; 186; 187; 188; 189; 190; 191; 192; 193; 194; 195; 196; 197; 198; 199; 200; 201; 202; 203; 204; 205; 206; 207; 208; 209; 210; 211; 212; 213; 214; 215; 216; 217; 218; 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 231; 232; 233; 234; 235; 236; 237; 238; 239; 240; 241; 242; 243; 244; 245; 246; 247; 248; 249; 250; 251; 252; 253; 254; 255; 256; 257; 258; 259; 260; 261; 262; 263; 264; 265; 266; 267; 268; 269; 270; 271; 272; 273; 274; 275; 276; 277; 278; 279; 280; 281; 282; 283; 284; 285; 286; 287; 288; 289; 290; 291; 292; 293; 294; 295; 296; 297; 298; 299; 300; 301; 302; 303; 304; 305; 306; 307; 308; 309; 310; 311; 312; 313; 314; 315; 316; 317; 318; 319; 320; 321; 322; 323; 324; 325; 326; 327; 328; 329; 330; 331; 332; 333; 334; 335; 336; 337; 338; 339; 340; 341; 342; 343; 344; 345; 346; 347; 348; 349; 350; 351; 352; 353; 354; 355; 356; 357; 358; 359; 360; 361; 362; 363; 364; 365; 366; 367; 368; 369; 370; 371; 372; 373;

374; 375; 376; 377; 378; 379; 380; 381; 382; 383; 384; 385; 386; 387; 388; 389; 390; 391; 392; 393; 394; 395; 396;
397; 398; 399; 400; 401; 402; 403; 404; 405; 406; 407; 408; 409; 410; 411; 412; 413; 414; 415; 416; 417; 418; 419;
420; 421; 422; 423; 424; 425; 426; 427; 428; 429; 430; 431; 432; 433; 434; 435; 436; 437; 438; 439; 440; 441; 442;
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5 466; 467; 468; 469; 470; 471; 472; 473; 474; 475; 476; 477; 478; 479; 480; 481; 482; 483; 484; 485; 486; 487; 488;
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558; 559; 560; 561; 562; 563; 564; 565; 566; 567; 568; 569; 570; 571; 572; 573; 574; 575; 576; 577; 578; 579; 580;
10 581; 582; 583; 584; 585; 586; 587; 588; 589; 590; 591; 592; 593; 594; 595; 596; 597; 598; 599; 600; 601; 602; 603;
604; 605; 606; 607; 608; 609; 610; 611; 612; 613; 614; 615; 616; 617; 618; 619; 620; 621; 622; 623; 624; 625; 626;
627; 628; 629; 630; 631; 632; 633; 634; 635; 636; 637; 638; 639; 640; 641; 642; 643; 644; 645; 646; 647; 648; 649;
650; 651; 652; 653; 654; 655; 656; 657; 658; 659; 660; 661; 662; 663; 664; 665; 666; 667; 668; 669; 670; 671; 672;
673; 674; 675; 676; 677; 678; 679; 680; 681; 682; 683; 684; 685; 686; 689; 690; 691; 692; 693; 694; 695; 696; 697;
15 698; 699; 700; 701; 702; 703; 704; 705; 706; 707; 708; 709; 710; 711; 712; 713; 714; 715; 716; 717; 718; 719; 720;
721; 722; 723; 724; 725; 726; 727; 728; 729; 730; 731; 732; 733; 734; 735; 736; 737; 738; 739; 740; 741; 742; 743;
744; 745; 746; 747; 748; 749; 750; 751; 752; 753; 754; 755; 756; 757; 758; 759; 760; 761; 762; 763; and 764.

19) In addition to the compounds listed in embodiment 18), further compounds of Formula (I) according to embodiment 1) are selected from the compounds of example (as disclosed in the experimental part below):

20 765; 766; 767; 768; 769; 770; 771; 772; 773; 774; 775; 776; 777; 778; 779; 780; 781; 782; 783; 784; 785; 786; 787;
788; 789; 790; 791; 792; 793; 794; 795; 796; 797; 798; 799; 800; 801; 802; 803; 804; 805; 806; 807; 808; 809; 810;
811; 812; 813; 814; 815; 816; 817; 818; 819; 820; 821; 822; 823; 824; 825; 826; 827; 828; and 829.

20) In addition to the compounds listed in embodiments 18) and 19), further compounds of Formula (I) according to embodiment 1) are selected from the compounds of example (as disclosed in the experimental part below):

25 830; 831; 832; 833; 834; 835; 836; 837; 838; 839; 840; 841; 842; 843; 844; 845; 846; 847; 848; 849; 850; 851; 852;
853; 854; 855; 856; 857; 858; 859; 860; 861; 862; 863; 864; 865; 866; 867; 868; 869; 870; 871; 872; 873; 874; 875;
876; 877; 878; 879; 880; 881; 882; 883; 884; 885; 886; 887; 888; 889; 890; 891; 892; 893; 894; 895; 896; 897; 898;
899; 900; 901; 902; 903; 904; 905; 906; 907; 908; 909; 910; 911; 912; 913; 914; 915; 916; 917; 918; 919; 920; 921;
922; 923; 924; 925; 926; 927; 928; 929; 930; 931; 932; 933; 934; 935; 936; 937; 938; 939; 940; 941; 942; 943; 944;
30 945; 946; 947; 948; 949; 950; 951; 952; 953; 954; 955; 956; 957; 958; 959; 960; 961; 962; 963; 964; 965; 966; 967;
968; 969; 970; 971; 972; 973; 974; 975; 976; 977; 978; 979; 980; 981; 982; and 983.

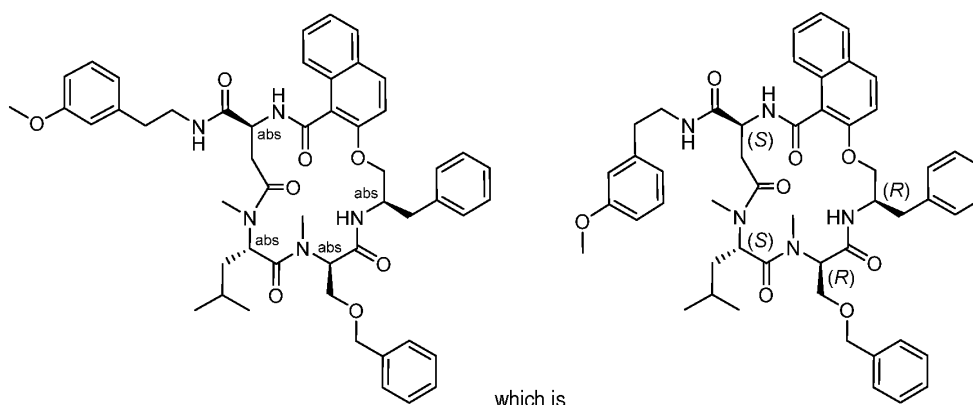
21) Another embodiment relates to compounds of Formula (I) according to embodiment 1), wherein said compounds are selected from the compounds of example (as disclosed in the experimental part below):

72; 127; 131; 132; 140; 171; 256; 275; 276; 281; 282; 315; 316; 355; 372; 374; 379; 380; 381; 383; 389; 391; 393;
35 395; 509; 524; 538; 539; 548; 563; 571; 578; 610; 613; 617; 618; 637; 640; 641; 655; 660; 665; 672; 673; 682; 692;
693; 697; 713; 714; 716; 717; 719; 721; 722; 724; 769; 778; 791; 794; 795; 801; 804; 808; 809; 811; 813; 815; 820;

822; 827; 829; 838; 839; 840; 843; 849; 851; 853; 854; 855; 856; 858; 859; 865; 867; 868; 871; 873; 874; 875; 876; 878; 879; 880; 883; 884; 885; 886; 887; 889; 890; 895; 897; 898; 902; 903; 908; 909; 918; 919; 923; 924; 927; 930; 934; 935; 936; 937; 941; 944; 945; 948; 949; 960; 962; 964; 965; 966; 967; 969; 970; 972; 973; 975; 978; 980; and 981.

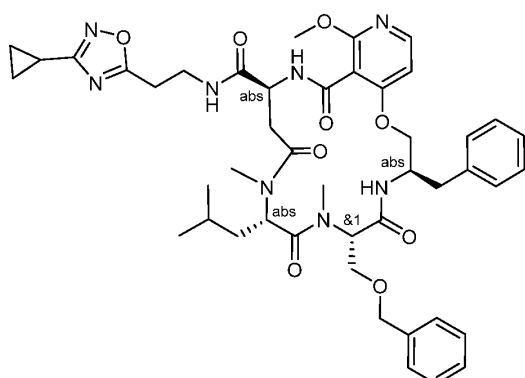
- 5 For avoidance of doubt, the chemical names of said example compounds as listed in embodiments 18), 19) and 21) are disclosed in the experimental part; and the corresponding structures of said example compounds are as shown in Table 3, 4 or 5 below, wherein, in case of doubt the depicted structure shall prevail.

Thus, for example the compound of example 713: (3*S*,7*S*,10*R*,13*R*)-13-benzyl-10-((benzyloxy)methyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-
 10 p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide has the structure depicted in Table 3, wherein said compound is in absolute configuration as drawn:

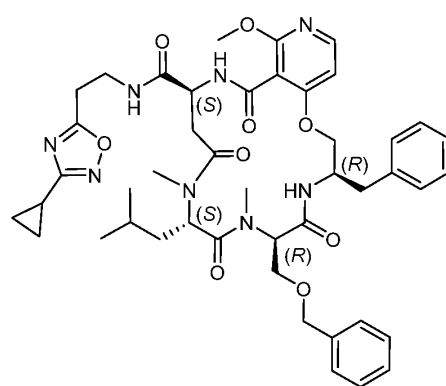
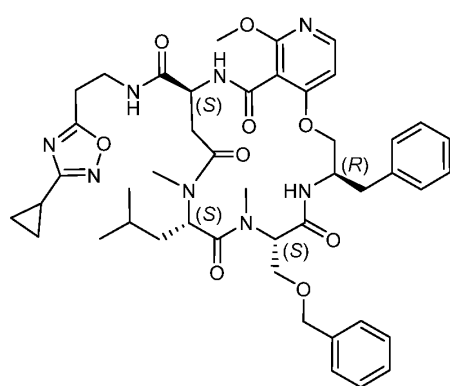


- Likewise, the compound of example 724: (3*R*,6*RS*,9*S*,13*S*)-3-benzyl-6-((benzyloxy)methyl)-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-
 15 tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide has the structure depicted in Table 3, wherein, regarding the chiral centers at carbon atoms 3, 9, and 13, said compound is in absolute configuration as drawn; and with regard to the chiral center at carbon atom 6, the absolute configuration of said chiral center (marked as &1) may be both (*R*) or (*S*):

47

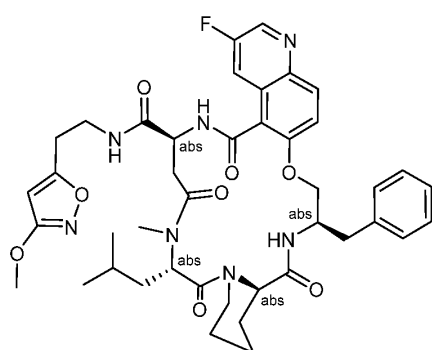


, such compound encompassing the diastereomers:

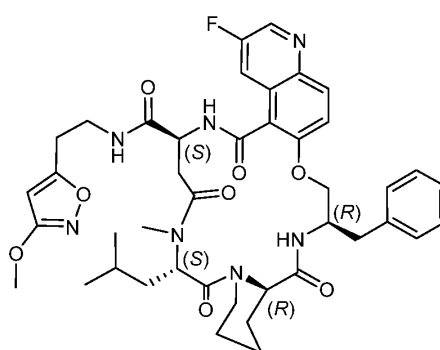


mixture thereof.

Likewise, the compound of example 769: (9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide has the structure depicted in Table 4, wherein said compound is in absolute configuration as drawn:

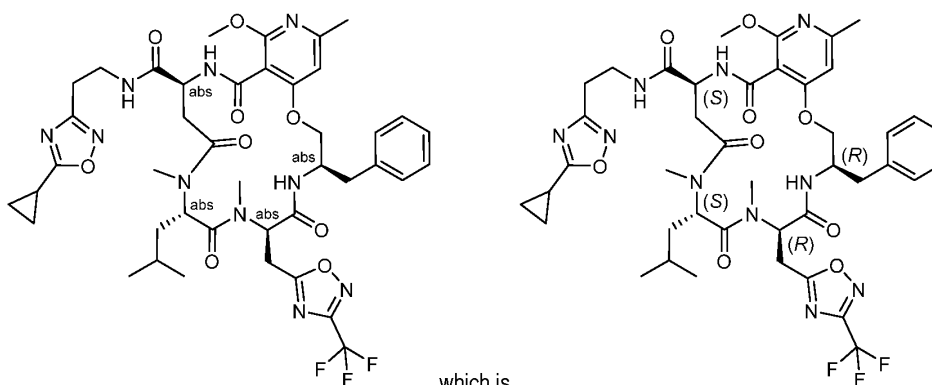


which is



Likewise, the compound of example 820: (3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-

2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide has the structure depicted in Table 4, wherein said compound is in absolute configuration as drawn:



The compounds of formula (I) / formula (II) according to embodiments 1) to 21) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral (such especially oral e.g. in form of a tablet or a capsule) or parenteral administration (including topical application or inhalation).

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula (I) / formula (II) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention / prophylaxis or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formula (I) / formula (II) according to embodiments 1) to 21).

The compounds of formula (I) / formula (II) according to embodiments 1) to 21) are useful for the treatment of CFTR-related diseases and disorders, especially cystic fibrosis.

CFTR-related diseases and disorders may be defined as including especially cystic fibrosis, as well as further CFTR-related diseases and disorders selected from:

- chronic bronchitis; rhinosinusitis; constipation; pancreatitis; pancreatic insufficiency; male infertility caused by congenital bilateral absence of the vas deferens (CBAVD); mild pulmonary disease; allergic bronchopulmonary aspergillosis (ABPA); liver disease; coagulation-fibrinolysis deficiencies, such as protein C deficiency; and diabetes mellitus;
- asthma; COPD; smoke induced COPD; and dry-eye disease; and
- idiopathic pancreatitis; hereditary emphysema; hereditary hemochromatosis; lysosomal storage diseases such as especially I-cell disease pseudo-Hurler; mucopolysaccharidoses; Sandhoff/Tay-Sachs;

osteogenesis imperfecta; Fabry disease; Sjogren's disease; osteoporosis; osteopenia; bone healing and bone growth (including bone repair, bone regeneration, reducing bone resorption and increasing bone deposition); chloride channelopathies, such as myotonia congenita (Thomson and Becker forms); Bartter's syndrome type 3; epilepsy; lysosomal storage disease; Primary Ciliary Dyskinesia (PCD) - a term for inherited disorders of the structure and or function of cilia (including PCD with situs inversus also known as Kartagener syndrome, PCD without situs inversus, and ciliary aplasia); generalized epilepsy with febrile seizures plus (GEFS+); general epilepsy with febrile and afebrile seizures; myotonia; paramyotonia congenital; potassium-aggravated myotonia; hyperkalemic periodic paralysis; long QT syndrome (LQTS); LQTS/Brugada syndrome; autosomal-dominant LQTS with deafness; autosomal-recessive LQTS; LQTS with dysmorphic features; congenital and acquired LQTS; dilated cardiomyopathy; autosomal-dominant LQTS; osteopetrosis; and Bartter syndrome type 3.

The term "treatment of cystic fibrosis" refers to any treatment of cystic fibrosis and includes especially treatment that reduces the severity of cystic fibrosis and/or reduces the symptoms of cystic fibrosis.

The term "cystic fibrosis" refers to any form of cystic fibrosis, especially to a cystic fibrosis that is associated with one or more gene mutation(s). Preferably, such cystic fibrosis is associated with an CFTR trafficking defect (class II mutations) or reduced CFTR stability (class VI mutations) [in particular, an CFTR trafficking defect / class II mutation], wherein it is understood that such CFTR trafficking defect or reduced CFTR stability may be associated with another disease causing mutation of the same or any other class. Such further disease causing CFTR gene mutation comprises class I mutations (no functional CFTR protein), (a further) class II mutation (CFTR trafficking defect), class III mutations (CFTR regulation defect), class IV mutations (CFTR conductance defect), class V mutations (less CFTR protein due to splicing defects), and/or (a further) class VI mutation (less CFTR protein due to reduced CFTR stability). Said one or more gene mutation(s) may for example comprise at least one mutation selected from F508del, A561E, and N1303K, as well as I507del, R560T, R1066C and V520F; in particular F508del. In addition to the above-listed, further CFTR gene mutations comprise for example G85E, R347P, L206W, and M1101K. Said gene mutation(s) may be heterozygous, homozygous or compound heterozygous. Especially said gene mutation is heterozygous comprising one F508del mutation. Further CFTR gene mutations (which are especially class III and/or IV mutations) comprise G551D, R117H, D1152H, A455E, S549N, R347H, S945L, and R117C.

The severity of cystic fibrosis / of a certain gene mutation associated with cystic fibrosis as well as the efficacy of correction thereof may generally be measured by testing the chloride transport effected by the CFTR. In patients, for example average sweat chloride content may be used for such assessment.

The term "symptoms of cystic fibrosis" refers especially to elevated chloride concentration in the sweat; symptoms of cystic fibrosis further comprise chronic bronchitis; rhinosinusitis; constipation; pancreatitis; pancreatic insufficiency; male infertility caused by congenital bilateral absence of the vas deferens (CBAVD); mild pulmonary disease; allergic bronchopulmonary aspergillosis (ABPA); liver disease; coagulation-fibrinolysis deficiencies such as protein C deficiency; and/or diabetes mellitus.

For avoidance of any doubt, if compounds are described as useful for the treatment of certain diseases, such compounds are likewise suitable for use in the preparation of a medicament for the treatment of said diseases. Likewise, such compounds are also suitable in a method for the treatment of such diseases, comprising administering to a subject in need thereof, an effective amount of such compound.

- 5 The term "subject" as used herein refers to a mammal, especially a human.

The present invention further relates to a method of treating cystic fibrosis, comprising the administration of an effective amount of a macrocycle (especially of a 17- or 18-membered macrocycle), or of a pharmaceutically acceptable salt thereof; to a subject in need thereof; wherein the cyclic core of said macrocycle comprises one aromatic moiety (such as an arylene or 5- to 10-membered heteroarylene, wherein said aromatic moiety especially is bound to the rest of the molecule / the ring members of said macrocycle (i) through a carbonyl group and (ii) through an oxygen atom, wherein notably said carbonyl group and said oxygen atom are attached to said aromatic moiety in a 1,2-diyl, or in a 1,3-diyl relationship), at least one beta-amino acid (wherein especially said beta-amino acid is bound through its amino group to the carbonyl group attached to said aromatic moiety), and at least one N-alkylated alpha-amino acid (wherein especially said N-alkylated alpha-amino acid is bound through its N-alkylated amino group to the carbonyl group of said beta-amino acid, and wherein notably such alpha-amino acid is glycine or a natural or non-natural amino acid bearing a hydrocarbon substituent); wherein said macrocycle is a corrector of a class II mutation of human CFTR (wherein especially folding, stability, degradation and/or trafficking of said CFTR, in particular of human F508del-CFTR, is corrected), wherein preferably the activity of said CFTR is corrected with at least the same efficacy as can be achieved with lumacaftor (wherein said activity / efficacy may be tested according to the method disclosed in the experimental part hereinafter).

Besides, any preferences and (sub-)embodiments indicated for the compounds of formula (II) (whether for the compounds themselves, salts thereof, compositions containing the compounds or salts thereof, or uses of the compounds or salts thereof, etc.) apply *mutatis mutandis* to compounds of formula (I).

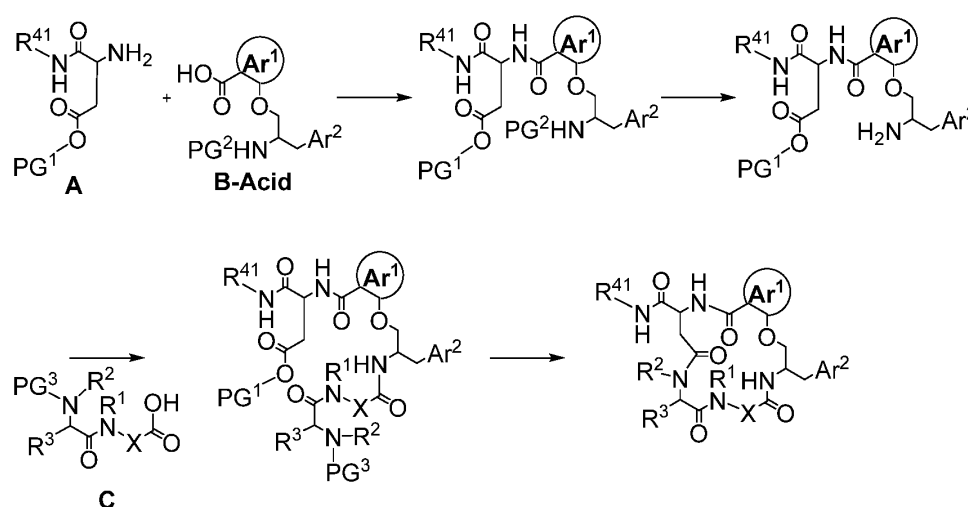
Preparation of compounds of Formula (I) / Formula (II):

- 25 The compounds of formula (I), formula (II), formula (I_E), formula (II_E) can be prepared by well-known literature methods, by the methods given below, by the methods given in the experimental part below or by analogous methods. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures. In some cases, the order of carrying out the following reaction schemes, and/or reaction steps, may be varied to facilitate the reaction or to avoid unwanted reaction products. In the general sequence of reactions outlined below, the generic groups **R¹**, **R²**, **R³**, **R⁴**, **Ar¹** and **Ar²** are as defined for formula (I), formula (II), formula (I_E), formula (II_E). Other abbreviations used herein are explicitly defined, or are as defined in the experimental section. In some instances, the generic groups **R¹**, **R²**, **R³**, **R⁴**, **Ar¹** and **Ar²** might be incompatible with the assembly illustrated in the schemes below and so will require the use of protecting groups (PG). The use of protecting groups is well known in the art (see for example "Protective Groups in Org. Synthesis", 30 T.W. Greene, P.G.M. Wuts, Wiley-Interscience, 1999). For the purposes of this discussion, it will be assumed that

such protecting groups as necessary are in place. In some cases, the final product may be further modified, for example, by manipulation of substituents to give a new final product. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, hydrolysis and transition-metal catalysed cross-coupling reactions which are commonly known to those skilled in the art. The compounds obtained may also be converted into salts, especially pharmaceutically acceptable salts, in a manner known *per se*.

Compounds of formula (I), formula (II), formula (I_E), and formula (II_E) of the present invention can be prepared according to the general sequence of reactions outlined below.

Compounds of formula (I) are prepared following one of the schemes depicted below.



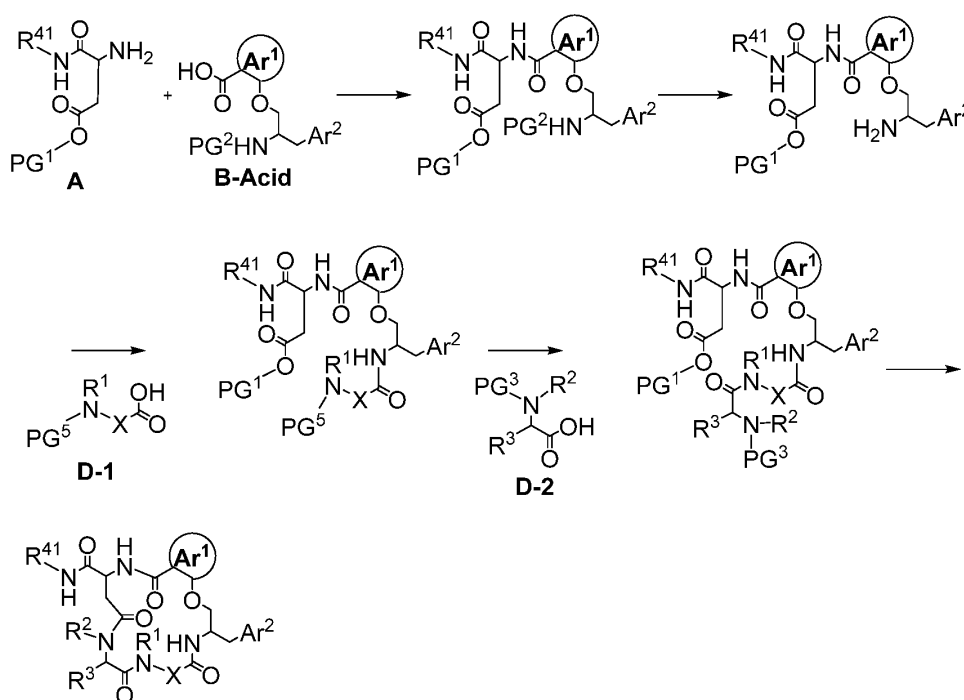
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Reaction Scheme A

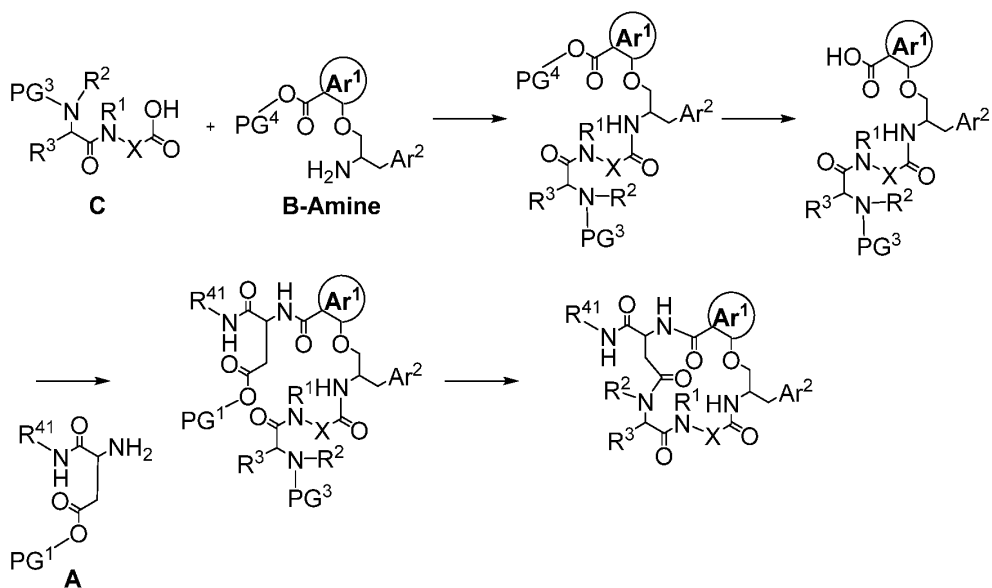
Reaction Scheme A: Syntheses can be performed with racemic or enantiomerically enriched amino acid building blocks. Suitably protected amine building block **A** and acid **B-Acid**, prepared following procedures well described in the literature or in **Reaction Schemes I** and **J** respectively, are treated with a peptide coupling reagent such as HATU, COMU, T3P, PyBop or EDCI/HOBt in a solvent like THF, DMF or NMP in the presence of a base such as TEA or DIPEA at a temperature between -20°C and +75°C, preferably at RT, to generate the corresponding amide intermediate **AB**. Deprotection of the amine function of the intermediate **AB** is achieved according to known methodologies by those skilled in the art, e.g. by treatment with 4M HCl in dioxane or preferably with TFA in the case of a Boc protecting group, or with piperidine or diethylamine in the case of an Fmoc protecting group, or the appropriate treatment in case of other protecting groups such as Cbz or Alloc protecting groups. The deprotected intermediate **AB-Amine** is then reacted with the suitably protected acid **C**, prepared following procedures described in the literature or in the experimental section, according to the peptide coupling conditions already described above for the formation of the **AB** intermediate. The obtained linear intermediate **ABC** is then deprotected before the final peptide coupling macrolactamisation. In some cases, the protecting groups PG¹ and PG³ are sequentially removed, but they are preferably removed simultaneously in one single step. For example, a ^tBu ester and Boc protecting groups are

- removed by treatment with 4M HCl in dioxane or preferably TFA, or alternatively Allyl ester and Alloc protecting groups can be removed by palladium catalyst treatment as extensively reported in the literature. The linear **ABC** deprotected intermediate is then cyclised under standard conditions, i.e. the intermediate can be treated with a coupling reagent such as COMU, T3P, PyBop, EDCI/HOBt, or preferably HATU in diluted conditions such as less than 0.1M soln. of the **ABC** starting material in a solvent like DMF or NMP or a mix. of solvents like DMF/DCM (1:1), in presence of a base such as TEA or DIPEA at a temperature between -20°C and +75°C, preferably at RT to yield the corresponding macrocycle **cABC**. Depending on the nature of the different residues some remaining deprotection steps may be required to yield the final product. Final purification by preparative HPLC, with standard reverse phase or if required, chiral phase columns gives the target compound as a pure stereoisomer.
- 10 **Reaction Scheme B:** In a modified version of **Reaction Scheme A**, the **C** moiety can be introduced stepwise, one amino acid at a time. The **AB** intermediate previously described in **Reaction Scheme A**, and the first amino acid **D-1**, commercially available or prepared following a procedure described in the literature, or in the experimental section below, are treated according to the peptide coupling conditions already described above to form the corresponding peptide bond. Selective deprotection of the amine function of **ABD-1**, such as removing an Fmoc group by treatment
- 15 with piperidine or diethylamine, or removing a Cbz protecting group by hydrogenolysis over a catalyst such as Pd/C or Pd(OH)₂/C in a solvent like EtOAc, THF or dioxane, or preferably removing a Boc protecting group by treatment with 4M HCl in dioxane or with TFA, affords the free amine or its ammonium salt respectively, ready to be coupled with the second amino acid **D-2** in a similar peptide coupling step. The three described coupling/deprotection/coupling steps yield the same linear intermediate **ABC** as the one previously described in **Reaction Scheme A**. The remaining
- 20 steps of the synthesis to furnish the desired macrocycle **cABC** are the same as described above.

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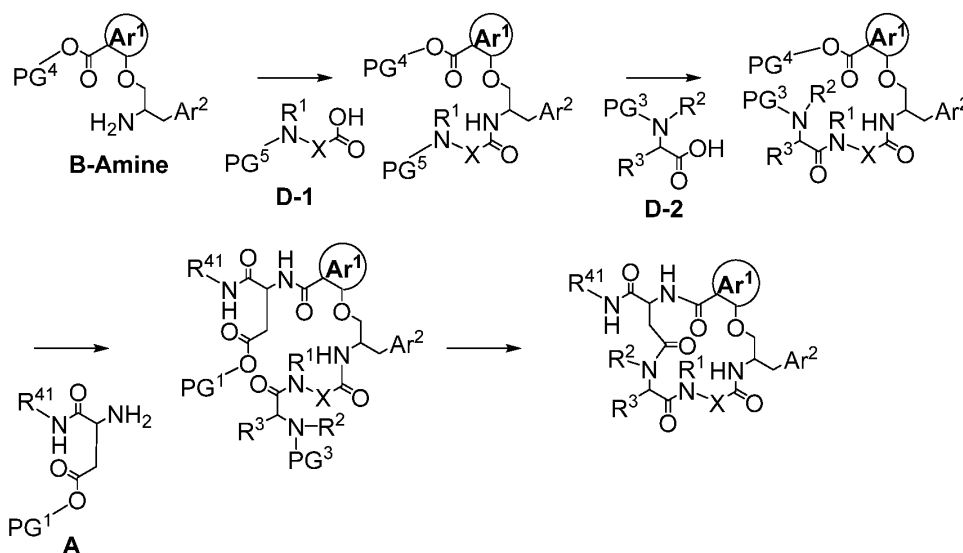


Reaction Scheme B



Reaction Scheme C

Reaction Scheme C: In an alternative approach, the sequence for building the linear intermediate **ABC** can be modified. Suitably protected building block **C** and the amine **B-Amine**, prepared following procedures described in the literature or in **Reaction Schemes K and J** respectively, are treated according to the peptide coupling conditions already described above, with a reagent such as HATU, COMU, T3P, PyBop or EDCI/HOBt in a solvent like THF, DMF or NMP in the presence of a base such as TEA or DIPEA at a temperature between -20°C and +75°C, preferably at RT. Deprotection of the acid function of the intermediate **BC**, i.e. removal of PG4, is achieved according to known methodologies by those skilled in the art, e.g. by treatment with NaOH or LiOH in aqueous methanol at a temperature ranging from 0°C up to 50°C for methyl or ethyl esters or preferably by hydrogenolysis over a catalyst such as Pd/C or Pd(OH)₂/C in a solvent like EtOAc, THF or dioxane for benzyl esters. The deprotected intermediate **BC-Acid** is then reacted with the suitably protected amine building block **A**, prepared following procedures described in the literature or in **Reaction Scheme I** according to the peptide coupling conditions already described previously. The resulting linear **ABC** can then be deprotected and cyclised to yield the final product **cABC** as described in **Reaction Scheme A**.

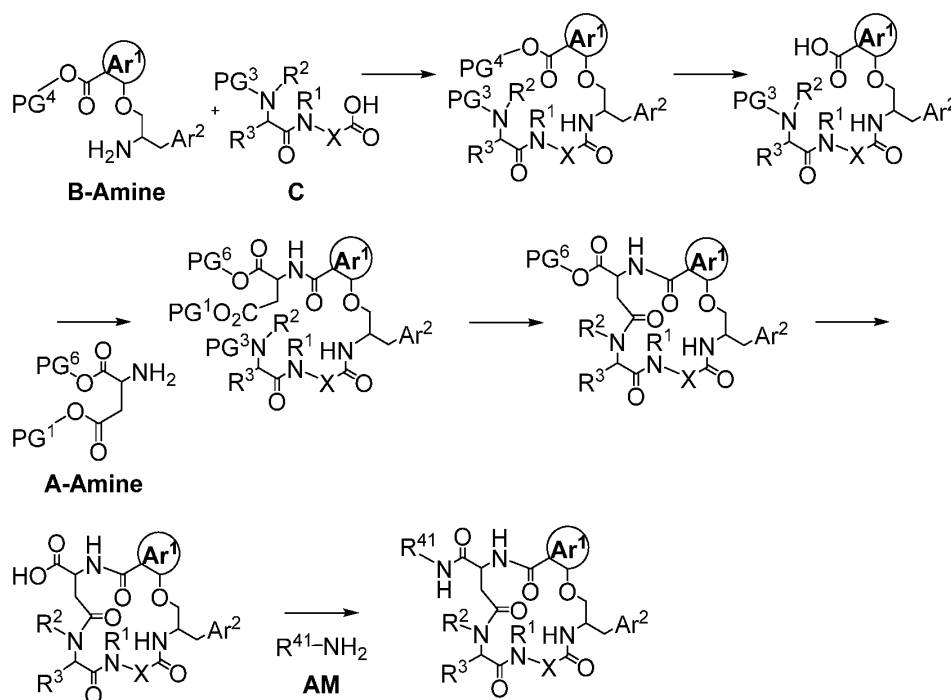


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Reaction Scheme D

Reaction Scheme D: As it is the case when moving from **Reaction Scheme A** to **Reaction Scheme B**, the **C** moiety in **Reaction Scheme C** can be similarly introduced stepwise, one amino acid at a time. Suitably protected acid **D-1** and the amine **B-Amine**, prepared following procedures described in the literature, or in the experimental part, or **Reaction Scheme J**, are treated according to the peptide coupling conditions already described above. Selective deprotection of the amine function of **BD-1**, i.e. removal of PG5, such as removing a Cbz protecting group under acidic conditions or more preferable, removing a Boc protecting group by treatment with 4M HCl in dioxane or preferably with TFA, affords the corresponding ammonium salt without removal of the orthogonal protecting group PG4. The resulting intermediate amine can then be coupled with the second amino acid **D-2** in a similar peptide coupling step.

The three described coupling/deprotection/coupling steps yield the same protected intermediate **BC** as the one previously described in **Reaction Scheme C** at which stage the rest of the synthesis can be performed as described above.

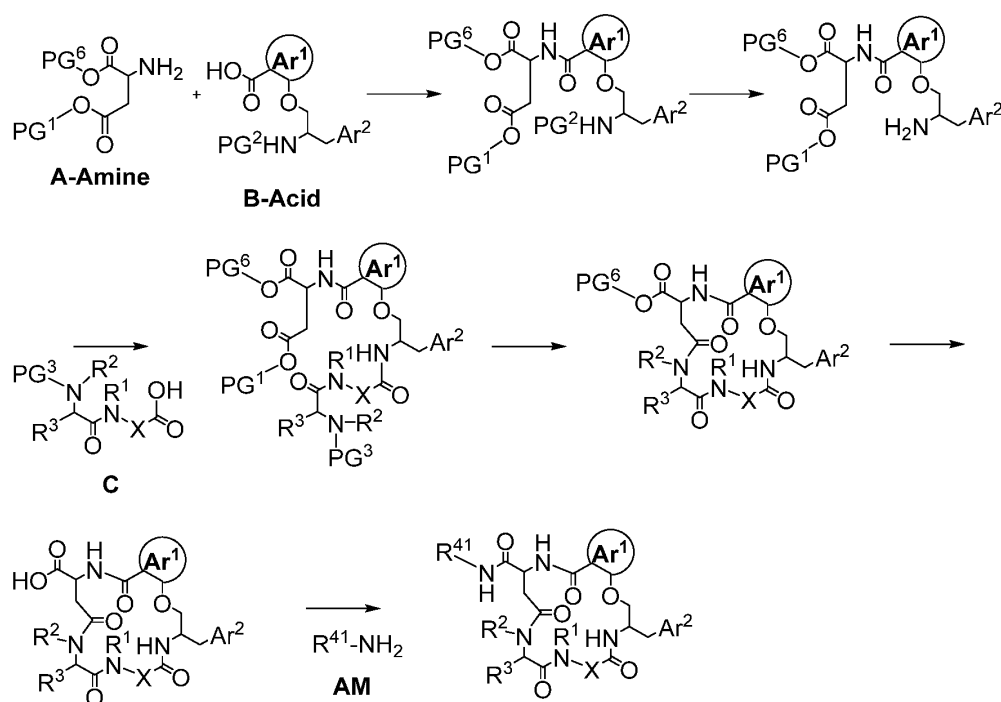


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Reaction Scheme E

Reaction Scheme E: In another variation of **Reaction Scheme C**, the building block **A-Amine** is doubly protected with suitable orthogonal protecting groups on the 2 carboxylic acid functions, such as the α -benzyl ester or α -methyl ester in the presence of a β -butyl ester. Following the sequence described in **Reaction Scheme C** then yields the corresponding linear intermediate **ABC**. Double deprotection of the aspartic acid side chain and the Boc amine using TFA and subsequent cyclisation by a method already described previously yields the cyclised intermediate **cABC**, still protected on **A**. Deprotection of the aspartic acid backbone carboxylic acid, i.e. removal of PG⁶, can be accomplished by treatment with NaOH or LiOH in methanol/water at a temperature ranging from 0°C to 50°C for methyl or ethyl esters or preferably by hydrogenolysis of the benzyl ester over a catalyst such as Pd/C or Pd(OH)₂/C in a solvent like EtOAc, THF or dioxane. The deprotected intermediate **cABC-Acid** is then coupled according to peptide coupling conditions already described above with an amine **AM**, either commercially available or prepared following a procedure described in the literature or in the experimental section to yield the target compound. This strategy is especially efficient for preparation of libraries for the exploration of the **AM** moiety.

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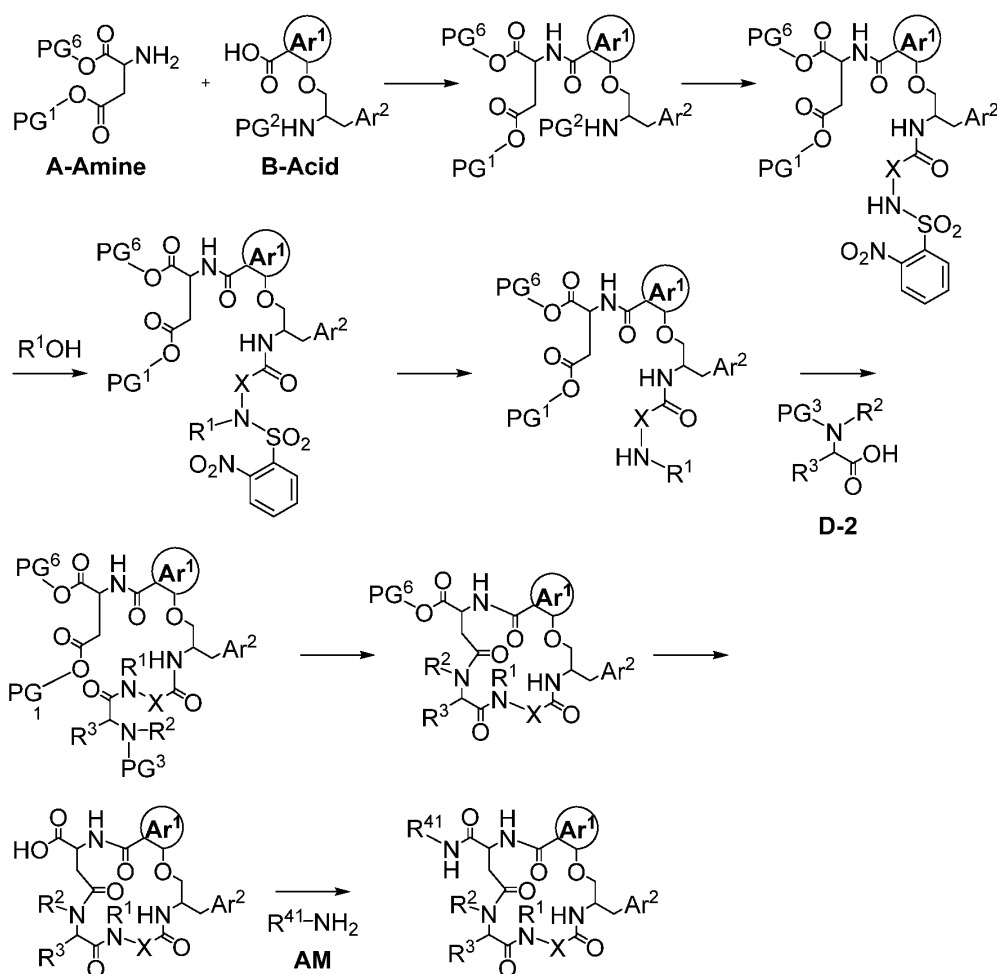
Reaction Scheme F

Reaction Scheme F: The strategy described in **Reaction Scheme E**, introducing the **A** moiety stepwise, can be applied in a different sequence to give the same **cABC-Acid** intermediate, as illustrated in **Reaction Scheme F**. The

5 protected **A-Amine**, doubly protected with suitable orthogonal protecting groups on the 2 carboxylic acid functions, such as the α -benzyl ester or α -methyl ester in the presence of a β -allyl ester can be coupled with the required **B-Acid** and **C** building blocks in the same sequence as described in **Reaction Scheme A** to furnish the corresponding linear intermediate **ABC**. Sequential deprotection of the amine protecting group PG₃, using TFA in the case of a Boc protecting group followed by removal of the aspartic acid side-chain protecting group PG₁, by treatment with 1,3-

10 dimethyl barbituric acid and Pd(PPh₃)₄ in a solvent like DCM in the case of an allyl protecting group, leaves only cyclisation as already described above to give the intermediate **cABC**, still protected on **A** as already described in **Reaction Scheme E**. The remaining steps of the synthesis to furnish the desired macrocycle **cABC** are the same as already described above.

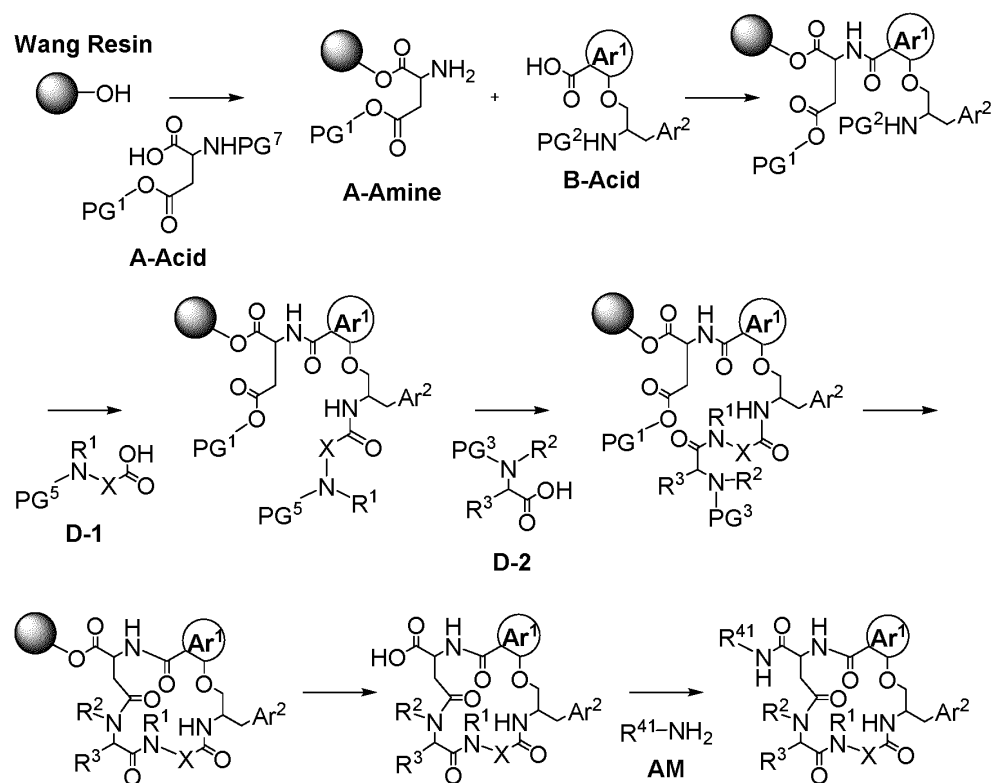
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Reaction Scheme G

Reaction Scheme G: In a variation of **Reaction Scheme F**, and in close similarity to **Reaction Schemes B** and **D**, moiety **C** can be introduced stepwise, one amino acid at a time. Moreover, the amino acid **D-1** can itself be built stepwise, by introducing the desired side-chain R^1 on an already assembled **ABD1** precursor. The amine deprotected **AB** intermediate already described in **Reaction Scheme F** can be coupled with an unsubstituted amino acid precursor of **D-1**, such as the NH-Boc or preferably the NH-nosyl-amino acid according to already described peptide coupling conditions. The NH-Nosyl function can then either be alkylated by treatment with the desired alkyl halide such as the bromide or preferably iodide in the presence of a base, such as K_2CO_3 or preferably, via a Mitsunobu reaction with the desired alcohol, performed according to standard conditions well known to those skilled in the art, e.g. by treatment with DEAD or DIAD with a phosphine ligand like triphenylphosphine at a temperature ranging from -80°C up to 60°C in a solvent such as THF or dioxane. The Nosyl activating/protecting group can then be removed by standard treatment with thiophenol in the presence of a base such as K_2CO_3 in a solvent like DMF to afford the corresponding deprotected intermediate. The amino acid **D-2** can be coupled to this intermediate according to the conditions illustrated in

Reaction Scheme B. The three described coupling/deprotection/coupling steps yield the same deprotected linear intermediate **ABC** as the one previously described in **Reaction Scheme F**. The remaining steps of the synthesis to furnish the desired macrocycle **cABC** are the same as already described above.

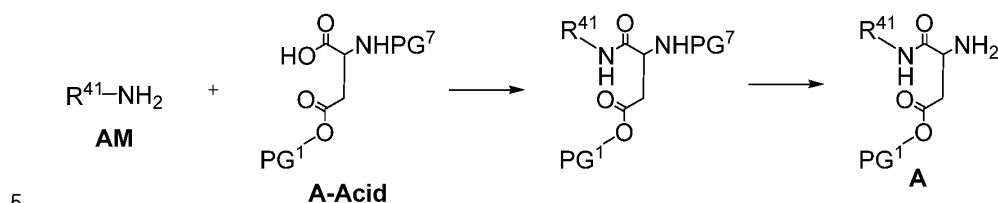


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Reaction Scheme H

Reaction Scheme H: In a further adaptation of **Reaction Scheme F**, the α -carboxylic acid protecting group of the **A-Amine** building block can be solid phase such as a polymer-linked support, enabling the stepwise solid phase peptide synthesis of the cyclised macrocycle precursor according to established methodologies well known to those skilled in the art of polymer supported peptide synthesis. For instance, the amino acid **A-Acid**, suitably orthogonally protected on the amine function by for example an Fmoc protecting group and on the β -carboxylic acid function by for example an allylester, can be introduced on Wang resin by treatment with HOBT and DMAP and a coupling reagent such as DCC or DIC in a solvent mix. such as DCM/DMF allowing suitable swelling of the polymer beads. The subsequent sequence of deprotection of the Fmoc protecting group followed by peptide coupling with standard conditions for polymer peptide synthesis allows the stepwise introduction of the different building blocks, **B-Acid**, **D1** and finally a suitably protected **D2**, like for example alloc-protected **D2** gives the polymer supported linear peptide **ABC**, analogous to the one described in **Reaction Scheme F**. Double deprotection of the allyl ester and the N-alloc protecting groups can be achieved by treatment with a palladium catalyst, potentially in the presence of 1,3 -dimethylbarbituric acid to furnish the still supported linear peptide. Cyclisation under standard peptide coupling conditions can be accomplished

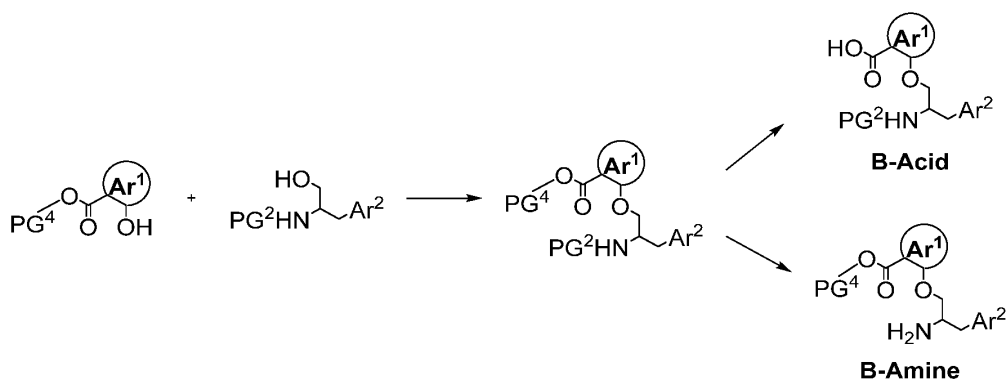
in these circumstances without risk of oligomer formation. The macrocycle **cABC-Acid** already described in **Reaction Scheme F** can then be released from the polymer support by acidic treatment such as with a mix. of TFA/H₂O (95/5). The liberated **cABC-Acid** can then be coupled with the appropriate **AM** amine using coupling conditions as described above to furnish the target compound.



Building blocks **A** are either commercially available, prepared as described in the literature or may be prepared as illustrated in **Reaction Scheme I**. A suitably orthogonally protected **A-Acid**, such as the β -butylester of the N-Fmoc or the β -allylester of the N-Boc aspartic acid, is coupled with the desired **AM** amine according to standard peptide coupling conditions, by treatment with COMU or T3P, HATU, PyBop or another peptide coupling reagent, in a solvent like THF, DMF or NMP in the presence of a base such as TEA or DIPEA at a temperature between -20°C and +75°C, preferably at RT. The resulting intermediate can then be selectively deprotected on the amine functionality without removing the β -ester protecting group PG1, under standard conditions well established in the field of protecting group chemistry. Specific treatment with piperidine or diethylamine to remove the N-Fmoc in the presence of the β -butylester or with TFA or 4M HCl in dioxane to remove the N-Boc in the presence of the β -allylester gives access to the target building block **A** as its free base or its ammonium salt respectively.

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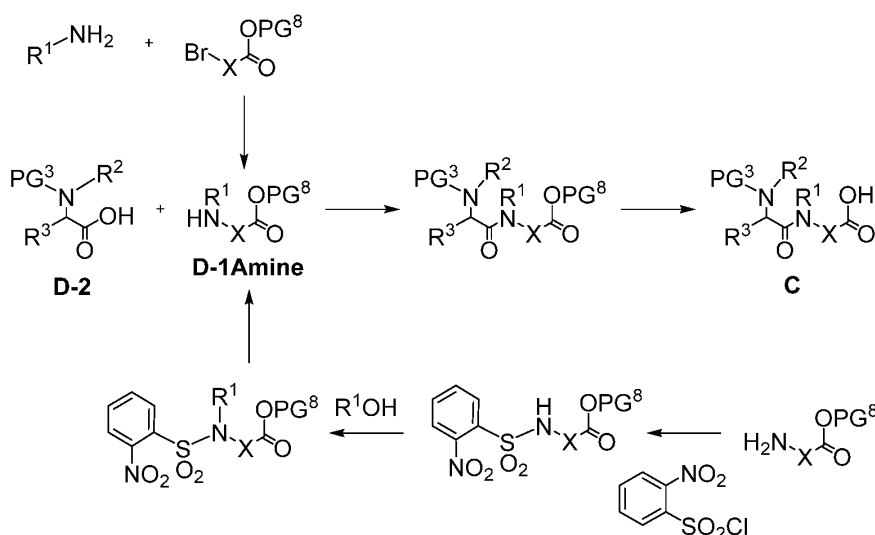
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The building blocks **B**, **B-Acid** or **B-Amine**, are either prepared as described in the literature or may be prepared as illustrated in **Reaction Scheme J**. An appropriate salicylic acid derivative, protected as an ester on the carboxylic acid function, such as a methyl, ethyl, or benzyl ester, are either commercially available or prepared as described in the literature, or may be prepared as described in the experimental section. Similarly, the amino alcohol protected on the

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amine function by the Boc or Cbz groups are either commercially available or readily prepared from the corresponding amino acid, as described in the literature, or may also be prepared as described in the experimental section. The alcohol function of the amino alcohol can be activated upon treatment with methanesulfonyl chloride or toluenesulfonyl chloride or a similar activating agent, in the presence of a base such as DIPEA or TEA and reacted with the phenol function of the salicylic acid ester derivative in a solvent such as THF or DMF to furnish the doubly protected **B** building block. Alternatively, the two building blocks can be reacted together according to Mitsunobu methodology, by treatment with a phosphine ligand like triphenylphosphine and the DEAD or DIAD reagents in a solvent such as THF or dioxane at a temperature ranging from -20°C up to 60°C. The resulting orthogonally protected intermediate can then be selectively deprotected on the acid function or on the amine function to access the corresponding building blocks **B-Acid** or **B-Amine** respectively. For example saponification of a methyl ester with aq. NaOH or LiOH soln. or hydrogenolysis of a benzyl ester over a palladium catalyst such as charcoal supported Pd or Pd(OH)₂ gives access to the corresponding **B-Acid**. Alternatively, Boc deprotection by treatment with TFA or hydrogenolysis of a Cbz protected amine in the case of a methyl ester leads to the corresponding **B-Amine**.



Reaction Scheme K

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Building blocks **C** may be prepared as illustrated in **Reaction Scheme K** from the key intermediate **D-1Amine**. The intermediate **D-1** is either commercially available or prepared as described in the literature or may be prepared as illustrated in this scheme. A suitably PG8 protected bromoacetic acid ester derivative, such as methyl, ethyl or benzyl ester, can be reacted with the appropriate amine R^1NH_2 , in a solvent like MeCN, acetone or DMF in the presence of a base such as K_2CO_3 or DIPEA at a temperature ranging from RT up to 80°C to yield the amine **D-1**. Alternatively, a suitably PG8 protected amino acid ester derivative, such as methyl, ethyl or benzyl ester, can be reacted with nitrobenzenesulfonyl chloride in the presence of a catalytic amount of DMAP, in a solvent such as DCM or THF to yield the corresponding N-Nosyl protected amine. Alkylation of the sulfonamide nitrogen can then be accomplished by Mitsunobu methodology as already described above, i.e. by reaction in the presence of the desired alcohol R^1OH

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- with a phosphine ligand like triphenylphosphine and the DEAD or DIAD reagents, in a solvent such as THF or dioxane at a temperature ranging from 0°C up to 80°C. Subsequent cleavage of the Nosyl group can be achieved by treatment with thiophenol in the presence of a base such as K₂CO₃ in a solvent like DMF or DCM to give the amine building block **D-1**. Coupling with the commercially available **D-2** amino acid, or prepared as described in the literature, according to standard peptide coupling methodology as described above. Deprotection of the ester can then be accomplished by treatment with aq. NaOH or LiOH soln. in the case of a methyl or ethyl ester, or by hydrogenolysis of the benzyl ester over a palladium catalyst such as charcoal supported Pd or Pd(OH)₂ to yield the target **C** building block.
- 10 The following examples are provided to illustrate the invention. These examples are illustrative only and should not be construed as limiting the invention in any way.

Experimental Part

I. Chemistry

- All temperatures are stated in °C. Commercially available starting materials were used as received without further purification. Unless otherwise specified, all reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. Compounds were purified by flash column chromatography on silica gel or by preparative HPLC. Compounds described in the invention are characterised by LC-MS data (retention time t_R is given in min; molecular weight obtained from the mass spectrum is given in g/mol) using the conditions listed below. In cases where compounds of the present invention appear as a mix. of conformational isomers, particularly visible in their LC-MS spectra, the retention time of the most abundant conformer is given.

Analytical LC-MS equipment:

- HPLC pump: Binary gradient pump, Agilent G4220A or equivalent
Autosampler: Gilson LH215 (with Gilson 845z injector) or equivalent
Column compartment: Dionex TCC-3000RS or equivalent
25 Degasser: Dionex SRD-3200 or equivalent
Make-up pump: Dionex HPG-3200SD or equivalent
DAD detector: Agilent G4212A or equivalent
MS detector: Single quadrupole mass analyzer, Thermo Finnigan MSQPlus or equivalent
ELS detector: Sedere SEDEX 90 or equivalent

LC-MS with acidic conditions

Method A: Column: Zorbax SB-aq (3.5 µm, 4.6 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method B: Column: Zorbax RRHD SB-aq (1.8 µm, 2.1 x 50 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 2.0 min (flow: 0.8 mL/min). Detection: UV/Vis + MS.

Method C: Column: Waters XBridge C18 (5 μ m, 4.6 x 30 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method D: Column: Waters BEH C18 (2.1 x 50mm, 2.5 μ m). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 2.0 min (flow: 0.8 mL/min). Detection: UV/Vis + MS.

- 5 **Method E:** Column: Waters XBridge C18 (2.5 μ m, 4.6 x 30 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 1.5 min (flow: 4.5 mL/min). Detection: UV/Vis + MS.

Method F: Column: Waters XSelect CSH C18 (3.5 μ m, 2.1 x 30 mm). Conditions: MeCN + 0.1% formic acid [eluent A]; water + 0.1% formic acid [eluent B]. Gradient: 95% B $\rightarrow$ 2% B over 1.6 min (flow 1 mL/min), Detection: UV/Vis + MS.

- 10 **Method G:** Column: Waters Atlantis T3 (3.0 μ m, 2.1 x 50 mm). Conditions: MeCN + 0.1% formic acid [eluent A]; water + 0.1% formic acid [eluent B]. Gradient: 95% B $\rightarrow$ 2% B over 5 min (flow 0.8 mL/min). Detection: UV/Vis + MS.

Method H: Waters Acquity Binary, Solvent Manager, MS: Waters SQ Detector or Xevo TQD or SYNAPT G2 MS, DAD: Acquity UPLC PDA Detector, ELSD: Acquity UPLC ELSD. Column ACQUITY UPLC CSH C18 1.7 μ m 2.1x50 mm from Waters, thermostated in the Acquity UPLC Column Manager at 60°C. Eluents: A: H₂O + 0.05% formic acid; B: MeCN + 0.045% formic acid. Method: Gradient: 2% B $\rightarrow$ 98% B over 2.0 min. Flow: 1.0 mL/min. Detection: UV 214nm and ELSD, and MS, t_R is given in min.

LC-MS with basic conditions

Method I: Column: Waters BEH C18 (2.5 μ m, 2.1 x 50mm). Conditions: water/NH₃ [c(NH₃) = 13 mmol/l] [eluent A]; MeCN [eluent B]. Gradient: 5% B $\rightarrow$ 95% B over 2 min (flow 0.8 mL/min). Detection: UV/Vis + MS.

- 20 **Method J:** Column: Waters XSelect CSH C18 (3.5 μ m, 2.1 x 30mm). Conditions: 95% MeCN + 5% Water/NH₄HCO₃ [c(NH₄HCO₃) = 10 mmol/l] [eluent A]; Water/NH₄HCO₃ [c(NH₄HCO₃) = 10 mmol/l] [eluent B]. Gradient: 95% B $\rightarrow$ 2% B over 1.6 min (flow 1mL/min), Detection: UV/Vis + MS.

GC-MS

- Agilent 6890N / Column: RXi-5MS 20m, ID 180 μ m, df 0.18 μ m; Velocity 50 cm/s, He carrier gas; 100°C $\rightarrow$ 250°C over 4.5 min; Detection: MS.

Preparative HPLC equipment:

Gilson 333/334 HPLC pump equipped with Gilson LH215, Dionex SRD-3200 degasser,

Dionex ISO-3100A make-up pump, Dionex DAD-3000 DAD detector, Single quadrupole mass analyzer MS detector, Thermo Finnigan MSQ Plus, MRA100-000 flow splitter, Polymer Laboratories PL-ELS1000 ELS detector

- 30 Preparative HPLC with basic conditions

Column: Waters XBridge (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH₄OH (25% aq.) [eluent B]; Gradient see **Prep. HPLC Table 1** (flow: 75 mL/min), the starting percentage of Eluent A (x) is determined depending on the polarity of the compound to purify. Detection: UV/Vis + MS

Prep. HPLC Table 1

t (min)	0	0.01	4.0	6.0	6.2	6.6
Eluent A (%)	x	x	95	95	x	x
Eluent B (%)	100-x	100-x	5	5	100-x	100-x

Preparative HPLC with acidic conditions

Column: Waters Atlantis T3 (10 μ m, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% HCO₂H [eluent B];

- 5 Gradient see **Prep. HPLC Table 2** (flow: 75 mL/min), the starting percentage of Eluent A (x) is determined depending on the polarity of the compound to purify. Detection: UV/Vis + MS

Prep. HPLC Table 2

t (min)	0	0.01	4.0	6.0	6.2	6.6
Eluent A (%)	x	x	95	95	x	x
Eluent B (%)	100-x	100-x	5	5	100-x	100-x

Preparative HPLC for chiral separations

- 10 In most cases, desired diastereoisomers can be isolated or purified by standard preparative scale HPLC according to standard methods well-known to those skilled in the art. In some instances, the use of a chiral chromatography column is advisable to separate complex mixtures of diastereoisomers. Best results are obtained using Chiral Stationary Phase columns, such as Chiralpak IA, IB, or IC columns based on an immobilised amylose or cellulose chiral phase, with an isocratic eluent based on a mix. of MeCN with EtOH or MeOH, in a ratio varying from 9:1 to 1:9. In order to
- 15 compensate for the presence of ionisable functional groups in the compound being purified, modifiers can be added to the solvent mix. such as 0.1% diethylamine for basic derivatives or 0.1% formic acid for acidic ones. Supercritical Fluid Chromatography was used in some cases, using the same Chiral Stationary Phase columns as described above with isocratic eluents composed of 50% to 90% supercritical carbondioxide together with EtOH, MeOH or a 1:1 EtOH:MeCN mix.. Detection: UV/Vis.

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Abbreviations (as used hereinbefore or hereinafter):

- | | |
|-------------------|-----------------------------|
| AcOH | acetic acid |
| Ac ₂ O | acetic anhydride |
| Alloc | allyloxycarbonyl |
| 25 anh. | anhydrous |
| aq. | aqueous |
| atm | atmosphere |
| BnBr | benzyl bromide |
| Boc | <i>tert</i> -butoxycarbonyl |

	Boc ₂ O	di-tert-butyl dicarbonate	
	BOP	(benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium	hexafluorophosphateBuLi
		n-butyllithium	
	CDI	1,1'-carbonyldiimidazole	
5	CD ₃ I	iodomethane-d ₃	
	CHCl ₃	chloroform	
	COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium	
		hexafluorophosphate	
	Cu(OAc) ₂	copper (II) acetate	
10	d	days	
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	
	DCC	N,N'-dicyclohexylcarbodiimide	
	DCE	1,2-dichloroethane	
	DCM	dichloromethane	
15	DEAD	diethyl azodicarboxylate	
	DIAD	diisopropyl azodicarboxylate	
	DIBAL/DIBAL-H	diisobutylaluminium hydride	
	DIC	N,N'-diisopropylcarbodiimide	
	DIPEA	diisopropyl-ethylamine, Hünig's base	
20	DMAP	4-Dimethylaminopyridine	
	DMF	dimethylformamide	
	DMSO	dimethylsulfoxide	
	DPPA	diphenyl phosphorylazide	
	dppf	1,1'-bis(diphenylphosphino)ferrocene	
25	EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide	
	Et	ethyl	
	Et ₂ O	diethylether	
	EtOAc	ethyl acetate	
	EtOH	ethanol	
30	evaporated	evaporated <i>in vacuo</i>	
	Ex.	example	
	FC	flash chromatography on silica gel	
	FDPP	pentafluorophenyl diphenylphosphinate	
	Fmoc	9-Fluorenylmethoxycarbonyl	
35	h	hour(s)	
	HATU	(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid	
		hexafluorophosphate	

	Hept	heptane(s)	
	Hex	hexane(s)HOBT	1-hydroxybenzotriazol
	HPLC	high performance liquid chromatography	
	HV	high vacuum conditions	
5	<i>i</i> Bu	isobutyl	
	<i>i</i> Pr	isopropyl	
	<i>i</i> PrOH	isopropyl alcohol	
	<i>i</i> PrOAc	isopropyl acetate	
	KO ^t Bu	potassium <i>tert</i> -butoxide	
10	LAH	Lithium aluminium hydride	
	LC-MS	liquid chromatography – mass spectrometry	
	Lit.	Literature	
	M	mol/l	
	<i>m</i> CPBA	<i>m</i> -chloroperoxybenzoic acid	
15	Me	methyl	
	MeCN	acetonitrile	
	Mel	iodomethane	
	Meldrum's acid	2,2-Dimethyl-1,3-dioxane-4,6-dione	
	MeOH	methanol	
20	mL	milliliter	
	min	minute(s)	
	mix.	mixture	
	MOM	methoxymethyl	
	MW	microwave	
25	NaBH(OAc) ₃	sodium triacetoxymethylborohydrideNCS	N-chlorosuccinimideNMP
		N-methyl-2-pyrrolidone	
	nosyl	4-Nitrobenzenesulfonyl	
	ⁿ Pr	n-propyl	
	OAc	acetate	
30	org.	organic	
	Pd(^t Bu ₃ P) ₂	bis(tri- <i>tert</i> -butylphosphine)palladium(0)	
	Pd(OAc) ₂	palladium(II) acetate	
	Pd/C	palladium on activated charcoal	
	Pd(OH) ₂ /C	palladium hydroxide on activated charcoal (Pearlman's catalyst)	
35	Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)	
	PdCl ₂ (PPh ₃) ₂	bis(triphenylphosphine)palladium(II) dichloride	
	Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)	

	Pd(dppf)Cl ₂ ·DCM	[1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) complex with dichloromethane
	Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
	Ph	phenyl
5	PhMe	toluene
	PPh ₃	triphenyl phosphine
	prep.	preparative
	PTFE	polytetrafluoroethylene
	PyBOP	(benzotriazol-1-yl-oxy)-tripyrrolidino-phosphonium hexafluorophosphate
10	PyClop	Chlorotripyrrolidinophosphonium hexafluorophosphate
	rac	racemic
	RM	reaction mix.
	Rochelle's salt	sodium potassium tartrate
	RT	room temperature
15	RuPhos	2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
	s	second(s)
	sat.	saturated
	Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
	SM	starting material
20	soln.	solution
	TBAF	tetrabutylammonium fluoride
	TBDMSCl	<i>tert</i> -butyldimethylsilyl chloride
	TBME	<i>tert</i> -butyl methyl ether
	<i>t</i> Bu	<i>tert</i> -butyl = <i>tertiary</i> butyl
25	TEA	triethylamine
	Tf	trifluoromethanesulfonyl
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography
30	TMEDA	N,N,N',N'-tetramethylethylenediamine
	TMS	trimethylsilyl
	tosyl	p-toluene-sulfonyl
	T ₃ P	<i>n</i> -propylphosphonic anhydride
	t _R	retention time
35	triflate	trifluoromethanesulfonate
	<i>p</i> TsOH	<i>p</i> -toluenesulfonic acid
	Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos

2-dicyclohexylphosphin-2',4',6'-triisopropylbiphenyl

A- Preparation of precursors and intermediates**Amines:**

- 5 Commercially available amines are depicted in Table AM-1.

Table AM-1

Amine	Name
AM-1.1	3,4-Methylenedioxyphenethylamine.HCl
AM-1.2	2-(1,3-Dihydro-isobenzofuran-5-yl)-ethylamine
AM-1.3	2-(1,3-Benzoxazol-2-yl)ethanamine.HCl
AM-1.4	3-Methoxyphenethylamine
AM-1.5	4-Methoxyphenethylamine
AM-1.6	Phenethylamine
AM-1.7	3,5-Dimethoxyphenethylamine
AM-1.8	2-(p-tolyl)Ethylamine
AM-1.9	3-Methylphenethylamine
AM-1.10	4-Ethylphenethylamine
AM-1.11	2-(4-tert-Butylphenyl)ethylamine
AM-1.12	4-Bromophenethylamine
AM-1.13	2-Fluorophenethylamine
AM-1.14	2-(3-Chlorophenyl)ethylamine
AM-1.15	3-Bromophenethylamine
AM-1.16	3,4-Dimethylphenethylamine
AM-1.17	2,4-Dimethylphenethylamine
AM-1.18	2-Methylphenethylamine
AM-1.19	2,3-Dimethoxyphenethylamine
AM-1.20	3-Fluorophenethylamine
AM-1.21	4-Fluorophenethylamine
AM-1.22	2-(2,6-Difluorophenyl)ethan-1-amine
AM-1.23	2-(3-Phenyl-[1,2,4]oxadiazol-5-yl)-ethylamine.HCl
AM-1.24	[2-(5-Methyl-1,2,4-oxadiazol-3-yl)ethyl]amine.HCl
AM-1.25	[2-(5-Ethyl-1,2,4-oxadiazol-3-yl)ethyl]amine.HCl
AM-1.26	2-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)ethan-1-amine.HCl
AM-1.27	2-(5-Methyl-1,2-oxazol-4-yl)ethan-1-amine.HCl
AM-1.28	2-(1-Methyl-1H-pyrazol-4-yl)ethanamine

AM-1.29	2-(5- <i>tert</i> -Butyl-1,2,4-oxadiazol-3-yl)ethanamine.HCl
AM-1.30	2-(5- <i>tert</i> -Butyl-1,2-oxazol-3-yl)ethan-1-amine
AM-1.31	2-(5-Methyl-1,2-oxazol-3-yl)ethan-1-amine.HCl
AM-1.32	2-(1,2-Thiazol-5-yl)ethan-1-amine.HCl
AM-1.33	2-(5-Cyclopropyl-1,2-oxazol-3-yl)ethan-1-amine
AM-1.34	2-(3,5-Difluorophenyl)ethan-1-amine
AM-1.35	2-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)ethan-1-amine.HCl
AM-1.36	[2-(5-Cyclobutyl-1,2,4-oxadiazol-3-yl)ethyl]amine.HCl
AM-1.37	2-(1,4-Dimethyl-1 <i>H</i> -pyrazol-3-yl)ethan-1-amine
AM-1.38	2,2-Difluoro-2-phenylethanamine.HCl
AM-1.39	2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-ethylamine.HCl
AM-1.40	2-(3-Methyl-1,2-oxazol-5-yl)ethan-1-amine.HCl
AM-1.41	2-[4-(Difluoromethoxy)phenyl]ethan-1-amine
AM-1.42	2-Pyrazin-2-yl-ethylamine
AM-1.43	2-Pyrimidine-4-yl-ethylamine.HCl
AM-1.44	2-(Pyrimidin-5-yl)ethan-1-amine.2HCl
AM-1.45	3-(Difluoromethoxy)propan-1-amine
AM-1.46	1-(2-Aminoethoxy)-2-methoxyethane
AM-1.47	2-(4-Methyl-1,3-thiazol-2-yl)ethan-1-amine
AM-1.48	2-(5-Methyl-1,3-thiazol-2-yl)ethan-1-amine
AM-1.49	2-{4 <i>H</i> ,5 <i>H</i> ,6 <i>H</i> -Cyclopenta[d][1,3]thiazol-2-yl}ethan-1-amine
AM-1.50	2-(1,2-Benzoxazol-3-yl)ethan-1-amine.HCl
AM-1.51	8-Methoxy-3,4-dihydro-2 <i>H</i> -1-benzopyran-3-amine
AM-1.52	2-(3-Methoxyphenoxy)ethanamine
AM-1.53	2-(4-Methoxyphenoxy)ethanamine
AM-1.54	4-(2-Aminoethyl)benzonitrile.HCl
AM-1.55	2-(3,5-Dimethylisoxazol-4-yl)ethanamine
AM-1.56	2-(2-Isopropyl-1,3-thiazol-4-yl)ethanamine.HCl
AM-1.57	2-(3-(Difluoromethoxy)phenyl)ethan-1-amine
AM-1.58	2-(3-Ethoxyphenyl)ethan-1-amine
AM-1.59	rac-2-(5,5-Dimethyltetrahydro-2 <i>H</i> -pyran-2-yl)ethan-1-amine
AM-1.60	4-(2-Aminoethyl)- <i>N,N</i> -dimethylaniline
AM-1.61	2-(Thiophen-2-yl)ethan-1-amine
AM-1.62	2-(5-Methoxypyridin-2-yl)ethan-1-amine
AM-1.63	2-(Furan-2-yl)ethan-1-amine

AM-1.64	rac-2-(Tetrahydro-2H-pyran-2-yl)ethan-1-amine
AM-1.65	3-Methoxypropan-1-amine
AM-1.66	2-(3,5-Dimethyl-1H-pyrazol-1-yl)ethan-1-amine
AM-1.67	rac-2-(2,3-Dihydrobenzo[b][1,4]dioxin-2-yl)ethan-1-amine.HCl
AM-1.68	5-Methoxypentan-1-amine
AM-1.69	2-(4-(1H-Pyrazol-1-yl)phenyl)ethan-1-amine
AM-1.70	2-(6-Methoxypyridin-2-yl)ethan-1-amine
AM-1.71	4-(2-Aminoethyl)-2-methoxyaniline
AM-1.72	3-Phenylpropan-1-amine
AM-1.73	2-(2,3-Dihydrobenzofuran-5-yl)ethan-1-amine.HCl
AM-1.74	2-(2-Methoxypyridin-4-yl)ethan-1-amine.HCl
AM-1.75	(2,3-Dihydrobenzofuran-2-yl)methanamine
AM-1.76	3-(2-Aminoethyl)benzonitrile
AM-1.77	2-(3-(Trifluoromethyl)phenyl)ethan-1-amine
AM-1.78	2-(3-(Methylsulfonyl)phenyl)ethan-1-amine
AM-1.79	2-(4-Morpholinophenyl)ethan-1-amine
AM-1.80	(1-(3,4-Dimethoxyphenyl)cyclopropyl)methanamine.HCl
AM-1.81	2-(4-Bromo-1H-pyrazol-1-yl)ethanamine.HCl
AM-1.82	2,2-Difluoro-2-(3-methoxyphenyl)ethan-1-amine
AM-1.83	2-(5-Isopropyl-1,2,4-oxadiazol-3-yl)ethan-1-amine.HCl
AM-1.84	2-(3-(Trifluoromethyl)isoxazol-5-yl)ethan-1-amine
AM-1.85	2-(3-(Trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethan-1-amine.HCl
AM-1.86	But-3-yn-1-amine.HCl
AM-1.87	Benzyl 3-aminopropanoate 4-methylbenzenesulfonate
AM-1.88	(S)-2-Amino-1-phenylethan-1-ol
AM-1.89	2-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-2,2-difluoroethan-1-amine
AM-1.90	2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethan-1-ol
AM-1.91	2-(2H-Benzo[d][1,2,3]triazol-2-yl)ethan-1-amine
AM-1.92	3-(Trifluoromethoxy)propan-1-amine
AM-1.93	2-([1,2,4]Triazol[1,5-a]pyrimidin-2-yl)ethan-1-amine
AM-1.94	2-(1-(2-Methoxyethyl)-1H-pyrazol-4-yl)ethan-1-amine
AM-1.95	2-(6-Methoxypyridin-3-yl)ethan-1-amine

Non-commercial amines are synthesised as described below.

2-Chroman-6-yl-ethylamine.HCl (AM-2.1).

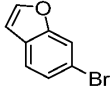
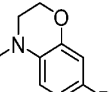
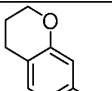
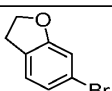
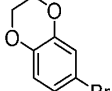
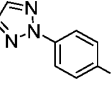
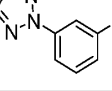
Step 1: Potassium *tert*-butyl *N*-[2-(trifluoroboranuidyl)ethyl]carbamate (693 mg, 2.76 mmol) is added to a RT soln. of 6-bromochroman (600 mg, 2.73 mmol) and Cs₂CO₃ (2.67 g, 8.19 mmol) in PhMe (9.2 mL) and water (3 mL). After

degassing the RM by bubbling argon through the soln., RuPhos 95% (134 mg, 0.273 mmol) and Pd(OAc)₂ (30.7 mg, 0.137 mmol) are added and the resulting mix. is stirred at 95°C for 18 h. The mix. is cooled to RT, then water and EtOAc are added and the RM is filtered over celite. The filtrate is extracted with EtOAc (3x), washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 5% to 25% EtOAc in hept) gives (2-chroman-6-yl-ethyl)-carbamic acid *tert*-butyl ester (543 mg, 72%) as a pale yellow solid. LC-MS B: t_R = 0.97 min; [M+H]⁺ = 222.04.

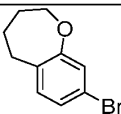
Step 2: 4 M HCl in dioxane (4 mL) is added to a RT soln. of (2-chroman-6-yl-ethyl)-carbamic acid *tert*-butyl ester (540 mg, 1.95 mmol) in dioxane (0.5 mL). The RM is stirred at RT for 4 h, then the mix. is concentrated in vacuo to give **AM-2.1** (412 mg, 99%) as a white solid. LC-MS B: t_R = 0.51 min; [M+H]⁺ = 219.41.

Listed in Table AM-2 below are amines that are prepared from the corresponding starting materials in analogy to the 2-step sequence described for **AM-2.1**.

Table AM-2

Amine	SM	Name	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
AM-2.2		2-Benzofuran-6-yl-ethylamine.HCl	0.5 B	203.35 [+MeCN]
AM-2.3		2-(4-Methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-ethylamine	0.45 B	193.40
AM-2.4		2-Chroman-7-yl-ethylamine.HCl	0.51 B	178.43
AM-2.5		2-(2,3-Dihydro-benzofuran-6-yl)-ethylamine.HCl	0.46 B	164.12
AM-2.6		2-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-ethylamine.HCl	0.46 B	180.26
AM-2.7		2-(4-[1,2,3]Triazol-2-yl-phenyl)-ethylamine.HCl	0.49 B	189.39
AM-2.8		2-(3-[1,2,3]Triazol-2-yl-phenyl)-ethylamine.HCl	0.50 B	189.38

AM-2.9		2-(3-Methyl-4-[1,2,3]triazol-2-yl-phenyl)-ethylamine.HCl	0.76 I	203.32
AM-2.10		2-(1-Cyclopropyl-1H-pyrazol-4-yl)-ethylamine.HCl	0.50 I	152.26
AM-2.11		2-(3-Pyrimidin-2-yl-phenyl)-ethylamine.HCl	0.48 B	200.36
AM-2.12		2-(4-Pyrimidin-2-yl-phenyl)-ethylamine.HCl	0.47 B	200.37
AM-2.13		2-(2-Fluoro-6-methyl-phenyl)-ethylamine.HCl	0.76 I	154.24
AM-2.14		2-(2,6-Difluoro-3-methyl-phenyl)-ethylamine.HCl	0.80 I	172.14
AM-2.15		2-(3-Fluoro-4-methoxy-phenyl)-ethylamine.HCl	0.67 I	170.18
AM-2.16		2-(2,3-Difluoro-phenyl)-ethylamine.HCl	0.70 I	158.21
AM-2.17		2-(4-Fluoro-3-methoxy-phenyl)-ethylamine.HCl	0.73 I	170.17
AM-2.18		2-(2-Fluoro-5-methyl-phenyl)-ethylamine.HCl	0.78 I	154.17
AM-2.19		2-(4-Methoxy-3-methyl-phenyl)-ethylamine.HCl	0.81 I	166.12
AM-2.20		2-(2,4-Difluoro-phenyl)-ethylamine.HCl	0.71 I	158.22

AM-2.21		2-(2,3,4,5-Tetrahydrobenzo[b]oxepin-8-yl)ethan-1-amine.HCl	0.55 B	192.43
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2-(3-(1,1-Difluoroethyl)phenyl)ethan-1-amine hydrochloride (AM-2.22)

Step 1: A mix. of 1-bromo-3-(1,1-difluoroethyl)benzene (200 mg, 0.91 mmol) and potassium (2-((*tert*-butoxycarbonyl)amino)ethyl)trifluoroborate (273 mg, 1.09 mmol) in PhMe (7 mL) and H₂O (2 mL) is degassed with Ar for 10 min before Cs₂CO₃ (884 mg, 2.71 mmol) and Pd(dppf)Cl₂.DCM (74 mg, 0.09 mmol) are added. The RM is degassed with Ar for a further 2 min and then heated to 100°C for 2 h. After cooling to RT the RM is partitioned between sat. aq. NH₄Cl and DCM and extracted. The layers are separated, and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 20% to 100% EtOAc in hept) to give *tert*-butyl (3-(1,1-difluoroethyl)phenethyl)carbamate as a white solid. LC-MS J: t_R = 2.17 min; [M+H]⁺ = 208.1.

Step 2: The title compound is prepared from *tert*-butyl (3-(1,1-difluoroethyl)phenethyl)carbamate in analogy to the procedure described for AM-2.1 step 2. LC-MS J: t_R = 1.77 min; [M+H]⁺ = 186.1.

2-(2-Cyclopropyl-2H-1,2,3-triazol-4-yl)ethan-1-amine hydrochloride (AM-2.23)

Step 1: Cu(OAc)₂ (1.23 g, 6.61 mmol) is added to a mix. of 4,5-dibromo-2H-1,2,3-triazole (1.5 g, 6.61 mmol), cyclopropyl boronic acid (1.17 g, 13.2 mmol), Na₂CO₃ (1.4 g, 13.2 mmol), and 2,2'-bipyridine (1.04 g, 6.61 mmol) in DCE (15 mL) and 2-methylfuran (15 mL) and the RM is heated to 80°C for 48 h. The RM is filtered and the filter cake is rinsed with EtOAc. The filtrate is washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 30% EtOAc in hept) to give 4,5-dibromo-2-cyclopropyl-2H-1,2,3-triazole as a yellow solid. LC-MS D: t_R = 0.92 min; No ionisation.

Step 2: *tert*-Butyl (2-(5-bromo-2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)carbamate is prepared from 4,5-dibromo-2-cyclopropyl-2H-1,2,3-triazole following the procedure described for AM-2.1 step 1. LC-MS B: t_R = 0.91 min; [M+H]⁺ = 331.06.

Step 3: A soln. of *tert*-butyl (2-(5-bromo-2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)carbamate (110 mg, 0.33 mmol) in EtOH (3 mL) is evacuated/purged with N₂ (3x) before 10% Pd/C (23 mg, 5 mol%) is added. The RM is evacuated/purged with H₂ (3x) and stirred under a H₂ atm for 16 h. The RM is filtered through a pad of celite and the filtrate concentrated in vacuo to give *tert*-butyl (2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)carbamate as a white solid. LC-MS I: t_R = 0.83 min; [M+H]⁺ = 253.28.

Step 4: The title compound is prepared from *tert*-butyl (2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)carbamate in analogy to the procedure described for AM-2.1 step 2. LC-MS I: t_R = 0.46 min; [M+H]⁺ = 153.24.

2-(3,4-Dihydro-2H-benzo[b][1,4]dioxepin-7-yl)-ethylamine.HCl (AM-3.1).

Step 1: Di-*tert*-butyl dicarbonate (2.33 g, 10.5 mmol) is added to a RT suspension of dopamine hydrochloride (2.0 g, 10.5 mmol) and NaHCO₃ (886 mg, 10.5 mmol) in THF (50 mL) and the mix. is stirred at RT for 2 h. The product is extracted with EtOAc (3x) and the combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 5% MeOH in DCM) yields *tert*-butyl (3,4-dihydroxyphenethyl)carbamate (2.34 g, 88%) as a white solid. LC-MS I: t_R = 0.64 min; [M-H]⁻ = 252.00.

Step 2: 1,3-Dibromopropane (1.01 mL, 9.75 mmol) is added to a RT suspension of *tert*-butyl (3,4-dihydroxyphenethyl)carbamate (2.24 g, 8.86 mmol) and K₂CO₃ (3.13 g, 22.2 mmol) in DMF (10 mL) and the resulting mix. is stirred at RT overnight. The RM is directly purified by prep. HPLC (basic) to give *tert*-butyl (2-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)ethyl)carbamate (1.25 g, 48%) as a slightly brownish oil. LC-MS I: t_R = 0.98 min; [M+H]⁺ = 294.05.

Step 3: 4 M HCl in dioxane (5.4 mL) is added to a RT soln. of *tert*-butyl (2-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)ethyl)carbamate (1.25 g, 4.28 mmol) in dioxane (20 mL). The RM is stirred at RT for 18 h, then the mix. is concentrated in vacuo to give **AM-3.1** (931 mg, 100%) as a white solid. LC-MS I: t_R = 0.68 min; [M+H]⁺ = 194.13.

2-(3-(Methoxy-d3)phenyl)ethan-1-amine.HCl (AM-3.2)

Step 1: CD₃I (0.25 mL, 4.0 mmol) is added to a RT mix. of *tert*-butyl (3-hydroxyphenethyl)carbamate (638 mg, 2.7 mmol) and K₂CO₃ (557 mg, 4.0 mmol) in DMF (5 mL) and the RM is heated to 50°C for 36 h. The RM is cooled to RT and partitioned between H₂O and EtOAc and extracted. The layers are separated and the aq. phase is re-extracted with EtOAc (2x). The combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give the crude product that is purified by FC (eluting with 0% to 100% EtOAc in hept) to give *tert*-butyl (3-(methoxy-d3)phenethyl)carbamate as a colourless oil. LC-MS J: t_R = 2.09 min; [M+H-Me]⁺ = 240.1.

Step 2: The title compound is prepared from *tert*-butyl (3-(methoxy-d3)phenethyl)carbamate in analogy to the procedure described for AM-2.1 step 2. LC-MS J: t_R = 1.47 min; [M+H]⁺ = 155.1.

2-(2-Fluoro-4-methoxy-phenyl)-ethylamine.HCl (AM-4.1)

Step 1: Molecular sieves 4A (100 mg) are added to a RT soln. of 2-fluoro-4-methoxybenzaldehyde (1.25 g, 7.95 mmol) in nitromethane (16 mL), then butylamine (0.1 mL, 0.938 mmol) and acetic acid (0.01 mL, 1.62 mmol) are added and the mix. is heated to 90°C for 1 h. The RM is concentrated and the residue is partitioned between EtOAc and water. The org. layer is washed with water and brine and concentrated in vacuo. Purification by FC (eluting with 0% to 20% EtOAc in hept) yields 2-fluoro-4-methoxy-1-2-nitro-vinyl-benzene (1.06 g, 68%) as a yellowish solid. LC-MS B: t_R = 0.92 min; No ionisation.

Step 2: Boron trifluoride diethyl etherate (4.19 mL, 32.3 mmol) is added to a 0°C soln. of NaBH₄ (996 mg, 25.8 mmol) in THF (40 mL). The mix. is stirred at 0°C for 10 min, then at RT for 15 min before a soln. of 2-fluoro-4-methoxy-1-2-nitro-vinyl-benzene (1.06 g, 5.38 mmol) in THF (10 mL) is added dropwise and the mix. refluxed at 70°C for 3 h, then allowed to reach RT overnight. The RM is cooled to 0°C before 2 N HCl (35 mL, 69.9 mmol) is added dropwise. After addition, the mix. is stirred at 0°C for 10 min, then at RT for 15 min, before the mix. is heated to 80°C for 1 h. The RM

is cooled to RT and the org. solvent is evaporated, and the remaining aq. layer is cooled to 0°C, before being basified with 10% aq. NaOH. The product is extracted with EtOAc (3x), and the combined org. layers are washed with brine, dried (MgSO₄), filtered, and concentrated. The residue, well dried under HV, is dissolved in DCM (10 mL) and cooled to 0°C before 4 M HCl in dioxane (1.61 mL, 6.45 mmol) is added and the resulting mix. stirred for 1 h. The RM is concentrated and triturated with Et₂O (2x) to yield the title compound **AM-4.1** (957 mg, 87%) as a beige powder. LC-MS B: t_R = 0.49 min; [M+H]⁺ = 170.08.

2-(4-Bromo-2,6-difluoro-phenyl)-ethylamine (AM-4.2)

The title compound is prepared from 4-bromo-2,6-difluorobenzaldehyde in analogy to the synthesis described for **AM-4.1**. LC-MS B: t_R = 0.53 min; [M+H]⁺ = 235.98.

10 2-(2,6-Difluoro-4-methoxy-phenyl)-ethylamine (AM-4.3)

Step 1: Ammonium acetate (179 mg, 2.28 mmol) is added to a RT soln. of 2,6-difluoro-4-methoxybenzaldehyde (1.0 g, 5.69 mmol) in nitromethane (7 mL) and the resulting mix. is refluxed for 40 min. The RM is evaporated and the residue partitioned between water and DCM. The aq. layer is extracted with DCM (2x) and the combined org. layers are washed with brine, dried (MgSO₄), filtered, and concentrated to obtain 1,3-difluoro-5-methoxy-2-(2-nitro-vinyl)-benzene (1.25 g) as an orange oil which is used as such in the next step. LC-MS B: t_R = 0.96 min; [M+H]⁺ = 216.12.

Step 2: The title compound is prepared from 1,3-difluoro-5-methoxy-2-(2-nitro-vinyl)-benzene in analogy to the procedure described for AM-4.1 step 2. LC-MS B: t_R = 0.51 min; [M+H]⁺ = 188.32.

2-(3,4-Difluoro-phenyl)-ethylamine.HCl AM-4.4

Step 1: 1,2-Difluoro-4-(2-nitro-vinyl)-benzene is prepared in analogy to the procedure described for **AM-4.1**, step 1. LC-MS C: t_R = 0.75 min; No ionisation.

Step 2: Concentrated H₂SO₄ (0.710 mL) is added to a 0°C suspension of LiAlH₄ (1.06 g, 26.65 mmol) in THF (35 mL). After stirring for 20 min, a soln. of 1,2-difluoro-4-(2-nitro-vinyl)-benzene (1.10 g, 5.97 mmol) in THF (5 mL) is added dropwise and stirring is continued for 10 min before the cooling bath is removed and the RM is slowly heated to a gentle reflux. After 5 min, the mix. is cooled to 0°C and carefully hydrolysed by dropwise addition of ⁱPrOH (4.4 mL), followed by 2 M aq. NaOH soln. (3.1 mL). The resulting suspension is filtered, and the filter cake rinsed with THF. The filtrate is concentrated and the free amine is dissolved in Et₂O (20 mL) containing ⁱPrOH (0.72 mL) and acidified with 2 M HCl in Et₂O (11.4 mL). The resulting suspension is filtered and the filter cake washed with Et₂O to give the title compound (440 mg, 38%) as a white solid that is further dried under HV. LC-MS C: t_R = 0.40 min; [M+H]⁺ = 199.3.

2-(4,5-dimethylisoxazol-3-yl)ethan-1-amine (AM-5.1)

Step 1: In a Dean Stark Apparatus, pTsOH monohydrate (11.1 mg, 0.06 mmol) is added to a RT soln. of ethyl acetoacetate (1.46 mL, 11.4 mmol) and pyrrolidine (1.92 mL, 22.8 mmol) in PhMe (50 mL) and the resulting mix. is refluxed for 2 h. The volatiles are removed and 3-pyrrolidin-1-yl-but-2-enoic acid ethyl ester (2.03 g, 97%) as an orange oil is used as such in the next step. LC-MS B: t_R = 0.39 min; [M+H]⁺ = 184.45.

Step 2: A soln. of SO₃ Pyridine complex (11.0 g, 69.2 mmol) in DMSO (39.3 mL) is added dropwise to 0°C soln. of 3-(Boc-amino)-1-propanol (4.88 mL, 27.7 mmol) and DIPEA (14.2 mL, 083 mmol) in DCM (83.1 mL). The RM is stirred

at 0°C for 1 h, then at RT for 1 h. The mix. is diluted with HCl and water, then extracted with DCM (3x). The combined org. extracts are washed with water and brine, dried (Na₂SO₄), filtered, and concentrated to give (3-oxo-propyl)-carbamic acid *tert*-butyl ester (4.81 g, 100%) as a colourless oil which is used as such in the next step.

Step 3: A soln. of hydroxylamine hydrochloride (3.90 g, 0.06 mol) in H₂O (25 mL) and a soln. of sodium acetate (9.20 g, 0.11 mol) in H₂O (25 mL) are added to a vigorously stirred soln. of (3-oxo-propyl)-carbamic acid *tert*-butyl ester (4.81 g, 0.028 mol) in EtOH (100 mL). The resulting suspension is stirred at RT for 18 h and then another 3 h at 50°C. The volatiles are removed, and the residue is partitioned between EtOAc and water. The layers are separated and the aq. layer is further extracted with EtOAc. The combined org. extracts are washed with brine, dried (Na₂SO₄), filtered, and concentrated. Purification by FC (eluting with 50% EtOAc in hept) gives (3-hydroxyimino-propyl)-carbamic acid *tert*-butyl ester (4.5 g, 86%) as a colourless oil. LC-MS B: *t_R* = 0.58 min; [M+H]⁺ = 189.43.

Step 4: NCS (2.23 g, 16.4 mmol) is added to a RT soln. of (3-hydroxyimino-propyl)-carbamic acid *tert*-butyl ester (2.80 g, 14.9 mmol) in DCM (80 mL) and the resulting mix. is stirred at RT for 2 h. The mix. is evaporated and directly purified by FC (eluting with 50% EtOAc in hept) to give *tert*-butyl (3-chloro-3-(hydroxyimino)propyl)carbamate (2.02 g, 61%) as an orange oil. LC-MS B: *t_R* = 0.72 min; [M(³⁵Cl)+H]⁺ = 223.37.

Step 5: A soln. of 3-pyrrolidin-1-yl-but-2-enoic acid ethyl ester (1.83 g, 10 mmol) in DCM (15 mL) followed by TEA (2.56 mL, 0.0181 mol) is added to a RT soln. of *tert*-butyl (3-chloro-3-(hydroxyimino)propyl)carbamate (2.02 g, 9.07 mmol) in DCM (15 mL) and the resulting mix. is stirred for 15 min. The RM is concentrated and the residue directly purified by FC (eluting with 50% EtOAc in hept) to yield 3-(2-*tert*-butoxycarbonylamino-ethyl)-5-methyl-isoxazole-4-carboxylic acid ethyl ester (1.60 g) still containing starting material, therefore the product is dissolved in DCM and washed with 2 M aq. HCl. The org. layer is washed with brine, dried (Na₂SO₄), filtered, and concentrated to give 3-(2-*tert*-butoxycarbonylamino-ethyl)-5-methyl-isoxazole-4-carboxylic acid ethyl ester (1.25g, 46%) as slightly yellow oil. LC-MS B: *t_R* = 0.93 min; [M+H]⁺ = 299.30.

Step 6: LAH (76 mg, 2.01 mmol) in Et₂O (15 mL) is added dropwise to a 0°C soln. of 3-(2-*tert*-butoxycarbonylamino-ethyl)-5-methyl-isoxazole-4-carboxylic acid ethyl ester (500 mg, 1.68 mmol) in Et₂O (5 mL). After addition, the resulting mix. is warmed to RT and stirred for 1.5 h. The mix. is cooled to 0°C and very carefully quenched with EtOAc followed by addition of a saturated aq. Rochelle's salt soln. The resulting mix. is warmed to RT and then vigorously stirred for 30 min after which two layers are formed. The layers are separated and the aq. layer is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried (Na₂SO₄), filtered, and evaporated. Purification by FC (eluting with 50% EtOAc in hept) followed by prep. HPLC (basic) gives [2-(4-hydroxymethyl-5-methyl-isoxazol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester (135 mg, 31%) as a white solid. LC-MS I: *t_R* = 0.67 min; [M+H]⁺ = 257.20.

Step 7: 4 M HCl in dioxane (1 mL, 3.99 mmol) is added to a RT soln. of [2-(4-hydroxymethyl-5-methyl-isoxazol-3-yl)-ethyl]-carbamic acid *tert*-butyl ester (100 mg, 0.39 mmol) in dioxane (2 mL) and the resulting mix. is stirred at RT for 6 d. The mix. is concentrated to yield 2-(4-chloromethyl-5-methyl-isoxazol-3-yl)-ethylamine (HCl salt) (77 mg, 93%) as a colourless oil which is used as such in the next step. LC-MS I: *t_R* = 0.56 min; No ionisation.

Step 8: Pd/C (10 mg, 0.01 mmol) is added to a RT soln. (degassed) of 2-(4-chloromethyl-5-methyl-isoxazol-3-yl)-ethylamine (HCl salt) (19 mg, 0.09 mmol) in EtOH (0.5 mL) and EtOAc (0.5 mL). The RM is stirred at RT for 30 min under a H₂ atm. The mix. is filtered, and the filtrate evaporated to yield **AM-5.1** (45 mg, 89%) as a yellow solid which is used as such in the next step. LC-MS I: t_R = 0.51 min; [M+H]⁺ = 141.20.

5 **2-(3-Cyclopropylisoxazol-5-yl)ethan-1-amine.HCl (AM-5.2)**

Step 1: A soln. of DIAD (61.7 mL, 318 mmol) in THF (350 mL) is added dropwise to a 0°C soln. of but-3-yn-1-ol (22.9 mL, 318 mmol), isoindoline-1,3-dione (44.5g, 302 mmol) and PPh₃ (83 g, 318 mmol) in THF (1500 mL) and the RM is stirred for 1 h. The RM is concentrated in vacuo and the residue is dissolved in hot PhMe (370 mL) before MeOH (210 mL) is slowly added. The RM is cooled to RT and MeOH is added until a white solid precipitates. The RM is partially concentrated before the solid is collected by filtration washing with cold PhMe and then air dried to give 2-(but-3-yn-1-yl)isoindoline-1,3-dione. LC-MS F: t_R = 1.81 min; No ionisation.

15 **Step 2:** Na₂CO₃ (22.7 g, 214 mmol) is carefully added to a RT soln. of hydroxylamine.HCl (37.2 g, 535 mmol) in H₂O (125 mL) followed by the slow addition of a soln. of cyclopropanecarbaldehyde (26.7 mL, 357 mmol) in EtOH (100 mL). The RM is stirred for 1 h and then partitioned between H₂O and EtOAc and extracted. The layers are separated and the aq. phase is re-extracted with EtOAc (2x). The combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give the crude product that is recrystallised from n-hept to give E/Z-cyclopropanecarbaldehyde oxime as a white solid. LC-MS F: t_R = 2.13 & 2.30 min; No ionisation.

20 **Step 3:** NCS (34.3 g, 257 mmol) is added portion wise to a 0°C soln. of cyclopropanecarbaldehyde oxime (19.3 g, 226 mmol) and pyridine (0.83 mL, 10.3 mmol) in DMF (100 mL) and the RM is stirred for 3 h. A soln. of 2-(but-3-yn-1-yl)isoindoline-1,3-dione (21.0 g, 103 mmol) in DMF (100 mL) followed by TEA (28.7 mL, 206 mmol) are added and the RM is stirred for 3 h. The RM is partitioned between H₂O and DCM and extracted. The layers are separated and the aq. phase is re-extracted with DCM (2x). The combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give the crude product that is triturated with MeOH to give 2-(2-(3-cyclopropylisoxazol-5-yl)ethyl)isoindoline-1,3-dione as a white solid. LC-MS J: t_R = 1.91 min; [M+H]⁺ = 283.1.

25 **Step 4:** Hydrazine.H₂O (9.44 mL, 194 mmol) is added to a RT suspension of 2-(2-(3-cyclopropylisoxazol-5-yl)ethyl)isoindoline-1,3-dione (28.0 g, 97 mmol) in EtOH (100 mL) and the RM is heated to 80°C for 5 h. The RM is cooled to RT and filtered washing with EtOH. The filtrate is concentrated in vacuo and the residue is suspended in Et₂O and re-filtered washing with Et₂O. The filtrate is partially concentrated before 1M HCl in Et₂O (100 mL) is added and the precipitate is filtered and dried in vacuo to give the title compound as a white solid. LC-MS J: t_R = 1.42 min; [M+H]⁺ = 153.1.

30 **2-(3-(Difluoromethyl)isoxazol-5-yl)ethan-1-amine (AM-5.3)**

Step 1: Imidazole (1.94 g, 28.5 mmol) is added to a RT soln. of but-3-yn-1-ol (1.0 mL, 14.3 mmol) in THF (25 mL) followed by TBDMSCI (2.58 g, 17.1 mmol) and the RM is stirred for 16 h. ⁱPr₂O (25 mL) is added and the precipitate is filtered and washed with additional ⁱPr₂O. The filtrate is washed with sat. aq. NaHCO₃, brine, dried over Na₂SO₄,

filtered and evaporated in vacuo to give (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane as a colourless oil. ¹H NMR (CDCl₃) δ: 3.76 (t, *J* = 7.1 Hz, 2H), 2.43 (td, *J* = 7.1, 2.7 Hz, 2H), 1.98 (t, *J* = 2.7 Hz, 1H), 0.92 (s, 9H), 0.10 (s, 6H).

Step 2: nBuLi (1.6 M in hex, 7.9 mL, 12.6 mmol) is added to a -78°C soln. of (but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (1.85 g, 9.0 mmol) in THF (15 mL) and the RM is warmed to -15°C and stirred for 15 min before
5 being cooled back to -40°C. Ethyl difluoroacetate (1.24 mL, 11.7 mmol) is then added dropwise followed by boron trifluoride etherate (1.55 mL, 12.2 mmol) and the RM is warmed to RT and stirred for 16 h. The reaction is quenched with cold sat. aq. NH₄Cl soln. and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 20% to 50% DCM in hept) to give 6-((*tert*-butyldimethylsilyl)oxy)-1,1-difluorohex-3-yn-2-one as a yellow oil. ¹H NMR (CDCl₃) δ: 5.73 (t, *J* =
10 54.2 Hz, 1H), 3.82 (t, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 6.6 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 6H).

Step 3: Hydroxylamine hydrochloride (0.71 g, 10.2 mmol) followed by CuO (121 mg, 0.85 mmol) are added to a RT soln. of 6-((*tert*-butyldimethylsilyl)oxy)-1,1-difluorohex-3-yn-2-one (2.22 g, 8.5 mmol) in THF (20 mL) and the RM is stirred for 16 h. NaHCO₃ (0.85 g, 10.2 mmol) is added and the RM is stirred for 1 h before the RM is filtered over a short pad of silica gel (eluting with 1:1 Et₂O:THF) to give a mix. of 5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-
15 (difluoromethyl)isoxazole and 2-(3-(difluoromethyl)isoxazol-5-yl)ethan-1-ol.

Step 4: TBAF (1.0 M in THF, 6.0 mL, 6.0 mmol) is added to a RT soln. of 5-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(difluoromethyl)isoxazole and 2-(3-(difluoromethyl)isoxazol-5-yl)ethan-1-ol (2.35 g, 8.5 mmol – estimated) in THF (50 mL) and Et₂O (50 mL) and the RM is stirred for 16 h. The RM is partitioned between sat. aq. NH₄Cl and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts
20 are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 6% MeOH in DCM) to give 2-(3-(difluoromethyl)isoxazol-5-yl)ethan-1-ol as a yellow oil. ¹H NMR (DMSO) δ: 7.23 (t, *J* = 53.2 Hz, 1H), 6.64 (s, 1H), 4.93 (t, *J* = 5.3 Hz, 1H), 3.72 (q, *J* = 6.0 Hz, 2H), 2.96 (t, *J* = 6.3 Hz, 2H).

Step 5: A soln. of DIAD (0.59 mL, 3.0 mmol) in THF (2 mL) is added dropwise to a 0°C soln. of 2-(3-(difluoromethyl)isoxazol-5-yl)ethan-1-ol (412 mg, 2.5 mmol), isoindoline-1,3-dione (409 mg, 2.8 mmol) and PPh₃ (7.95 g, 3.0 mmol) in THF (20 mL) and the RM is stirred for 16 h. The RM is concentrated in vacuo and the residue is purified by FC (eluting with 0% to 30% EtOAc in hept) to give 2-(2-(3-(difluoromethyl)isoxazol-5-yl)ethyl)isoindoline-1,3-dione.
LC-MS J: *t*_R = 1.98 min; [M+H]⁺ = 293.1.

Step 6: Hydrazine.H₂O (380 μL, 0.77 mmol) is added to a RT suspension of 2-(2-(3-(difluoromethyl)isoxazol-5-yl)ethyl)isoindoline-1,3-dione (113 mg, 0.39 mmol) in EtOH (4 mL) and the RM is heated to 80°C for 2 h. The RM is cooled to RT and filtered washing with EtOH. The filtrate is concentrated in vacuo and the residue is suspended in Et₂O and re-filtered washing with Et₂O. The filtrate is concentrated in vacuo to give the title compound as a white solid.
LC-MS I: *t*_R = 0.53 min; [M+H+MeCN]⁺ = 204.32.

2-(2,4,6-Trifluoro-phenyl)-ethylamine.HCl (AM-6.1)

Borane tetrahydrofuran complex 1M soln. In THF (15.5 mL, 15.5 mmol) is added dropwise to 0°C soln. of 2,4,6-trifluorophenylacetonitrile (1.00 g, 5.73 mmol) in THF (10 mL) and the RM is stirred at RT overnight. The RM is cooled to 0 °C before MeOH (5 mL) is added dropwise, then the soln. is stirred at RT for 1 h before being concentrated. The residue is cooled to 0°C, then 1.25 M HCl in MeOH (15.0 mL) is added dropwise and the resulting suspension is stirred a RT for 2 days, then the solvent is removed, and the residue is triturated in Et₂O. The product is isolated by filtration and washed with Et₂O to yield **AM-6.1** (833 mg, 69%) as a white solid. LC-MS B: t_R = 0.45 min; [M+H]⁺ = 176.26.

2-[3-(3-Methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-ethylamine (AM-7.1)

Step 1: NaHCO₃ (1.55 g, 18.4 mmol), followed by hydroxylamine hydrochloride (1.29 g, 18.4 mmol) are added to a RT soln. of 3-methoxybenzonitrile (1.0 g, 7.36 mmol) in MeOH (15 mL) and the resulting white suspension is refluxed (70°C) overnight. The mix. is concentrated and the residue is diluted with EtOAc and washed with brine, dried (MgSO₄), filtered, and concentrated to yield *N*-hydroxy-3-methoxy-benzamidine (1.67 g, 137%) as a yellow oil which is used as such in the next step. LC-MS B : t_R = 0.38 min; [M+H]⁺ = 167.11.

Step 2: TBTU (3.49 g, 10.9 mmol) is added to a 0°C soln. of Boc-beta-ala-OH (1.73 g, 9.06 mmol), *N*-hydroxy-3-methoxy-benzamidine (1.67 g, 9.06 mmol) and DIPEA (4.65 mL, 27.2 mmol) in DCM (45 mL). The ice bath is removed and the mix. is stirred at RT for 18 h. The RM is concentrated and the residue is partitioned between EtOAc (50 mL) and water (50 mL) and the resulting solid is filtered off to yield the intermediate (2-[[[hydroxyimino]-(3-methoxy-phenyl)-methyl]-carbamoyl]-ethyl)-carbamic acid *tert*-butyl ester (1.856 g, 61%). To this white solid is added dioxane (50 mL) and the RM is refluxed (90°C) for 24 h. The mix. is concentrated to yield {2-[3-(3-methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-ethyl}-carbamic acid *tert*-butyl ester (1.90 g, 109%) as a colourless oil which is used as such in the next step. LC-MS B : t_R = 0.95 min; [M+H]⁺ = 320.12.

Step 3: TFA (4.59 mL, 60 mmol) is added to a RT soln. of {2-[3-(3-methoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-ethyl}-carbamic acid *tert*-butyl ester (1.915 g, 6.0 mmol) in DCM (40 mL) and the mix. is stirred at RT for 1 d. The mix. is neutralised with a saturated aq. soln. of NaHCO₃ (50 mL), then DCM (50mL) is added. The two layers are separated and the aq. layer is extracted with DCM (50 mL). The combined org. layers are dried (MgSO₄), filtered, and concentrated to yield **AM-7.1** (1.14 g, 86%) as a yellow oil. LC-MS B : t_R = 0.54 min; [M+H]⁺ = 220.22.

2-[3-(3,5-Dimethyl-phenyl)-[1,2,4]oxadiazol-5-yl]-ethylamine (AM-7.2)

The title compound is prepared from 3,5-dimethylbenzonitrile following the 3-step synthesis described for **AM-7.1**. LC-MS E: t_R = 0.53 min; [M+H]⁺ = 218.22.

2-[3-(2-Trifluoromethoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-ethylamine.HCl (AM-7.3)

Steps 1&2: The title compound is prepared from 3,2-trifluoromethoxy-benzonitrile following the synthesis described for **AM-7.1**, steps 1&2 to yield {2-[3-(2-trifluoromethoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-ethyl}-carbamic acid *tert*-butyl ester. LC-MS E: t_R = 0.88 min; [M+H]⁺ = 318.04.

Step 3: 4 M HCl in dioxane (6 mL) is added to a RT soln. of {2-[3-(2-trifluoromethoxy-phenyl)-[1,2,4]oxadiazol-5-yl]-ethyl}-carbamic acid *tert*-butyl ester (425 mg, 1.14 mmol) in dioxane (3 mL) and the mix. is stirred at RT for 18 h. The RM is concentrated to yield **AM-7.3** (0.41 g, 119 %) as a brownish oil. LC-MS E: t_R = 0.53 min; $[M+H]^+$ = 273.93.

2-[5-(2-Trifluoromethoxy-phenyl)-4H-[1,2,4]triazol-3-yl]-ethylamine (AM-8.1)

- 5 **Step 1:** K_2CO_3 (487 mg, 3.53 mmol) is added to a RT soln. of *tert*-butyl *N*-(2-cyanoethyl)carbamate (1.20 g, 7.05 mmol) and 2-(trifluoromethoxy)benzoic acid hydrazide (1.55 g, 7.05 mmol) in *n*-butanol (50 mL) and the resulting suspension is heated to 120°C for 6.5 h, then stirred at RT overnight, and re-heated to 120°C for another 4.5 h. The mix. is concentrated, and the residue is diluted with DCM and acidified with 1 N HCl. The two layers are separated and the aq. layer is extracted with DCM. The combined org. layers are concentrated and purified by FC (eluting with
10 10% to 30% EtOAc in hept) to yield {2-[5-(2-trifluoromethoxy-phenyl)-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid *tert*-butyl ester (678 mg, 26%) as a colourless oil. LC-MS A: t_R = 0.80 min; $[M+H]^+$ = 373.15.

- Step 2:** 4 M HCl in dioxane (30 mL, 30 mmol) is added dropwise to a 0°C soln. of {2-[5-(2-trifluoromethoxy-phenyl)-4H-[1,2,4]triazol-3-yl]-ethyl}-carbamic acid *tert*-butyl ester (678 mg, 1.82 mmol) in DCM (20 mL). The resulting RM is stirred at RT for 2 h, then the RM is concentrated to yield **AM-8.1** (515 mg, 104%) as a yellow oil, which is used as
15 such in the next step. LC-MS A: t_R = 0.52 min; $[M+H]^+$ = 273.14.

2-(3-Methoxy-4-[1,2,3]triazol-2-yl-phenyl)-ethylamine.HCl (AM-9.1)

- Step 1:** 1H-1,2,3-Triazole (5.0 g, 0.072 mmol) is diluted with water (35 mL) and heated to 50°C before Br_2 (23.1 g, 0.145 mmol) is added dropwise (exothermic). The oil bath is replaced with a water bath to keep the internal temperature below 50°C. After 15 min the resulting orange suspension is quenched with 2 M aq. NaOH (5 mL) and
20 40% sodium bisulfite soln. (2 mL). A 32% aq. NaOH soln. is then added until pH 7 followed by additional 40% sodium bisulfite soln. (10 mL). Due to the exotherm the suspension is cooled to RT before it is filtered. The cake is rinsed with water (3 x 10 mL) and the filtrate is concentrated to yield 4,5-dibromo-2H-[1,2,3]triazole (14.86 g, 90%) as a slightly yellowish solid.

- Step 2:** K_2CO_3 (3.96 g, 28.6 mmol) and 4,5-dibromo-2H-[1,2,3]triazole (6.50 g, 28.6 mmol) are added to a RT soln. of 2-fluoro-5-nitroanisole (5.00 g, 28.6 mmol) in DMF (40 mL) and the mix. is stirred at 45°C for 3 d. The mix. is diluted with H_2O and the formed precipitate is filtered off, washed with water and the collected solid dried under HV to yield 4,5-dibromo-2-(2-methoxy-4-nitro-phenyl)-2H-[1,2,3]triazole (7.51 g, 69%) as a white solid. LC-MS B: t_R = 1.03 min; No ionisation.

- Step 3:** $Pd(OH)_2$ (20%, 1.04 g, 1.96 mmol) is added to a RT soln. (degassed) of 4,5-dibromo-2-(2-methoxy-4-nitro-phenyl)-2H-[1,2,3]triazole (7.4 g, 0.020 mol) in MeOH (70 mL) and the resulting mix. is stirred at RT for 2 h under a H_2 atm. The mix. is filtered over celite which is then copiously washed with MeOH. The filtrate is concentrated and purified by FC (eluting first with EtOAc/hept, then with 100% EtOAc and eventually with 10% MeOH in DCM. The isolated product (130%) is repurified by prep. HPLC (basic) to yield 3-methoxy-4-[1,2,3]triazol-2-yl-phenylamine (2.87 g, 75%)
30 as a brown oil. LC-MS I: t_R = 0.53 min; $[M+H]^+$ = 191.33.

Step 4: *tert*-Butyl nitrite (0.314 mL, 2.65 mmol) is added slowly to a 60°C soln. of CuBr₂ (537 mg, 2.41 mmol) in MeCN (3 mL). A soln. of 3-methoxy-4-[1,2,3]triazol-2-yl-phenylamine (500 mg, 2.41 mmol) in MeCN (3 mL) is added dropwise and after addition the mix. is allowed to reach RT. The mix. is quenched with a soln. of sulfamic acid (47 mg, 0.48 mmol) in water (1 mL) followed by the addition of 2 M aq. HCl (3 mL). MeCN is evaporated before EtOAc is added and the layers are separated. The org. layer is washed with 2 M aq. HCl, water and brine, then dried (Na₂SO₄), filtered, and concentrated. Purification by FC (eluting with 10% to 20% EtOAc in hex) gives 2-(4-bromo-2-methoxyphenyl)-2H-1,2,3-triazole (0.27 g, 46%) as a yellow oil. LC-MS I: t_R = 0.87 min; [M+H]⁺ = 254.13.

Step 5&6: The title compound is prepared from 2-(4-bromo-2-methoxyphenyl)-2H-1,2,3-triazole following the 2- step sequence described for **AM-2.1**. LC-MS I: t_R = 0.61 min; [M+H]⁺ = 260.26.

10 **2-(4-Pyrazin-2-yl-phenyl)-ethylamine (AM-10.1)**

Step 1: K₂CO₃ 2 M in water (2 mL) is added to a RT soln. of 4-(2-nitroethyl)phenylboronic acid (200 mg, 1.03 mmol) and 2-bromopyrazine (168 mg, 1.03 mmol) in dioxane (8 mL). The soln. is degassed for 2 min with argon, then Pd(PPh₃)₄ (35.6 mg, 0.0308 mmol) is added and the mix. heated to 80°C for 18 h. To the mix. is added water and EtOAc. The layers are separated and the aq. layer is re-extracted with EtOAc. The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (EtOAc/ hept 2:3) yields 2-[4-(2-nitro-ethyl)-phenyl]-pyrazine (88 mg, 37%) as a yellow oil. LC-MS B: t_R = 0.84 min; [M+H]⁺ = 230.10.

Step 2: Pd/C (10%, 13.5 mg, 0.019 mmol) is added to a RT soln. of 2-[4-(2-nitro-ethyl)-phenyl]-pyrazine (88 mg, 0.384 mmol) in EtOH/THF and the mix. is stirred at RT for 18 h under a H₂ atm. The mix. is filtered and concentrated. Purification by prep. HPLC (basic) gives **AM-10.1** (65 mg, 85%) as a yellow solid. LC-MS B: t_R = 0.48 min; [M+H]⁺ = 200.20.

2-(3-Pyrazin-2-yl-phenyl)-ethylamine (AM-10.2)

The title compound is prepared from (3-(2-nitroethyl)phenyl)boronic acid following the 2 step procedure described for **AM-10.1**. LC-MS B: t_R = 0.48 min; [M+H]⁺ = 200.19.

2-(7-Methoxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethylamine.HCl (AM-11.1)

Step 1: NBS (8.89 g, 50 mmol) is added portionwise to a RT soln. of 2,3-dihydro-1,4-benzodioxin-6-ol (8.0 g, 50 mmol) in DMF (80 mL) and the mix. is stirred for 2 h, before additional NBS (3.0 g) is added and the mix. is stirred for another 30 min. The mix. is diluted with water and extracted with EtOAc (3x). The combined org. extracts are washed with water (2x), brine, dried over a phase separator and concentrated. Purification by FC (eluting with 0% to 30% EtOAc in hept) yields 7-bromo-2,3-dihydro-benzo[1,4]dioxin-6-ol (5.98 g, 90%) as a red oil. LC-MS B: t_R = 0.74 min; No ionisation.

Step 2: Mel (3.26 mL, 51.8 mmol) is added to a RT soln. of 7-bromo-2,3-dihydro-benzo[1,4]dioxin-6-ol (5.981 g, 25.9 mmol) and Cs₂CO₃ (10.12 g, 31.1 mmol) in DMF (60 mL) and the mix. is stirred for 1.5 h. The mix. is diluted with water and extracted with Et₂O (3x). The combined org. layers are washed with water, brine, dried over a phase separator, and concentrated. Purification by FC (eluting with 0% to 30% EtOAc in hept) yields 6-bromo-7-methoxy-2,3-dihydro-benzo[1,4]dioxine (5.85 g, 92%) as a white powder. LC-MS B: t_R = 0.90 min; [M+H]⁺ = 244.13.

Step 3&4: The title compound is prepared from 6-bromo-7-methoxy-2,3-dihydro-benzo[1,4]dioxine following the 2-step procedure described for **AM-2.1**. LC-MS B: t_R = 0.52 min; $[M+H]^+$ = 210.24.

2-(7-Chloro-5-methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethylamine.HCl (AM-12.1)

Step 1: 1,2-Dibromoethane (8.85 mL, 101 mmol) is added to a RT soln. of 3-methylcatechol (5.0 g, 40.3 mmol) and
5 K_2CO_3 (22.27 g, 161 mmol) in DMF (70 mL) and the resulting mix. is stirred for 18 h. The mix. is diluted with water and the extracted with Et_2O (3x). The combined org. layers are washed with water and brine, dried over a phase separator, and concentrated. Purification by FC (eluting with 0% to 25% EtOAc in hept), yields 5-methyl-2,3-dihydro-benzo[1,4]dioxine (3.05 g, 50%) as a colourless oil. LC-MS B: t_R = 0.83 min; No ionisation.

Step 2: NBS (3.39 g, 19.1 mmol) is added portionwise to 0°C soln. of 5-methyl-2,3-dihydro-benzo[1,4]dioxine (2.864
10 g, 19.1 mmol) in THF (60 mL) and the RM is stirred at RT for 18 h. To the mix. is added NBS (286 mg) and stirring is continued for another 30 min. The mix. is diluted with water and extracted with EtOAc (3x). The combined org. extracts are washed with water (2x), brine, dried over a phase separator, and concentrated. Purification by FC (eluting with 0% to 30% EtOAc in hept), yields 6-bromo-5-methyl-2,3-dihydro-benzo[1,4]dioxine (4.40 g, 100%) as a light orange oil. LC-MS B: t_R = 0.96 min; No ionisation.

Step 3: [2-(5-Methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-carbamic acid *tert*-butyl ester is prepared from 6-bromo-5-methyl-2,3-dihydro-benzo[1,4]dioxine following the reaction described for **AM-2.1**, step 1. LC-MS B: t_R = 0.95 min; No ionisation.

Step 4: NCS (307 mg, 2.25 mmol) is added portionwise to a RT soln. of [2-(5-methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-carbamic acid *tert*-butyl ester (600 mg, 2.05 mmol) in DMF (10 mL) and the mix. is heated to 50°C for 18 h.
20 The mixture is diluted with water and extracted with EtOAc (3x). The combined org. extracts are washed with water, brine, dried over a phase separator, and concentrated. Purification by FC (eluting with 0% to 20% EtOAc in hept) yields [2-(7-chloro-5-methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-carbamic acid *tert*-butyl ester (581 mg, 87%) as a slightly orange oil.

Step 5: The title compound is prepared from [2-(7-chloro-5-methyl-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethyl]-carbamic acid *tert*-butyl ester following the reaction described for **AM-2.1**, step 2. LC-MS B: t_R = 0.58 min; $[M+H]^+$ = 228.11.

2-(7-Chloro-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethylamine.HCl (AM-12.2)

The title compound is prepared from 6-bromo-2,3-dihydrobenzo[b][1,4]dioxine following the 3-step sequence of reactions described for **AM-12.1**, step 3 to 5. LC-MS B: t_R = 0.54 min; $[M+H]^+$ = 214.22.

2-(3-Methoxyisoxazol-5-yl)ethan-1-amine hydrochloride (AM-13.1)

Step 1: DPPA (1.32 mL, 6.1 mmol) is added dropwise to a RT soln. of 3-(3-methoxyisoxazol-5-yl)propanoic acid (1.0
30 g, 5.55 mmol) and TEA (0.93 mL, 6.66 mmol) in PhMe (25 mL) and the RM is heated to 100°C for 1.5 h. 2-Methylpropan-2-ol (1.06 mL, 11.1 mmol) is added and the RM is heated to reflux for 16 h. The RM is cooled to RT and partitioned between sat. aq. $NaHCO_3$ and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (2x) and the combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in

vacuo. The crude product is purified by FC (eluting with 0% to 100% EtOAc in hept) to give *tert*-butyl (2-(3-methoxyisoxazol-5-yl)ethyl)carbamate as a colourless oil. LC-MS F: t_R = 1.80 min; $[M+H]^+$ = 243.1.

Step 2: The title compound is prepared from *tert*-butyl (2-(3-methoxyisoxazol-5-yl)ethyl)carbamate in analogy to the procedure described for AM-2.1 step 2. LC-MS B: t_R = 0.28 min; $[M+H]^+$ = 143.09.

5 **2-(3-(Methoxy-d3)isoxazol-5-yl)ethan-1-amine hydrochloride (AM-13.2)**

Step 1: H₂SO₄ (136 μ L, 2.55 mmol) is added to a RT soln. of pent-4-ynoic acid (5.0 g, 51 mmol) in EtOH (50 mL) and the RM is heated to 70°C for 2 h. The RM is partitioned between water and EtOAc and the layers are separated. The org. phase is washed with H₂O (2x) before a soln. of KHCO₃ (10.21 g, 102 mmol) in H₂O (25 mL) is added followed by the dropwise addition of a soln. of hydroxycarbonimidic dibromide (10.34 g, 51 mmol) in EtOAc (200 mL). The RM
10 is stirred at RT for 48 h and then washed with H₂O, brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 1% to 15% EtOAc in hept) to give ethyl 3-(3-bromoisoxazol-5-yl)propanoate as a white solid. LC-MS F: t_R = 1.87 min; $[M+H]^+$ = 247.0.

Step 2: Na (1.15 g, 50 mmol) is added portionwise to methanol-d₃ (11.53 mL, 285 mmol) in an ice bath and when all solids are dissolved, ethyl 3-(3-bromoisoxazol-5-yl)propanoate (1.0 g, 4.0 mmol) is added and the resulting soln. is
15 irradiated in a MW oven at 110°C for 75 min. The RM is diluted with H₂O and then poured into 2M HCl (35 mL) and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 5% to 10% MeOH in DCM) to give 3-(3-(methoxy-d₃)isoxazol-5-yl)propanoic acid as a white solid. LC-MS F: t_R = 1.07 min; $[M+H]^+$ = 175.0.

Steps 3-4: The title compound is prepared from 3-(3-(methoxy-d₃)isoxazol-5-yl)propanoic acid in analogy to the
20 procedure described for AM-13.1. LC-MS F: t_R = 0.13 min; $[M+H]^+$ = 146.0.

2-(4-(3-Methoxypropyl)-1H-pyrazol-1-yl)ethan-1-amine dihydrochloride (AM-14.1)

Step 1: A mix. of carbamic acid, *N*-[2-(4-bromo-1H-pyrazol-1-yl)ethyl]-, 1,1-dimethylethyl ester (300 mg, 1.03 mmol) and trans-3-methoxy-1-propenylboronic acid pinacol ester (0.71 mL, 1.07 mmol) in dioxane (3 mL) and H₂O (3 mL) is degassed with Ar for 10 min before Cs₂CO₃ (1.18 g, 3.62 mmol) and Pd(dppf)Cl₂.DCM (25.3 mg, 0.03 mmol) are
25 added. The RM is degassed with Ar for a further 2 min and then irradiated in a MW oven at 90°C for 20 min (cooling function on). After cooling to RT the RM is partitioned between water and DCM and extracted. The layers are separated, and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with brine, dried (Mg₂SO₄), filtered and evaporated in vacuo. The crude product is purified by prep. HPLC (acidic, 5% to 95%) to give *tert*-butyl (2-(4-(3-methoxyprop-1-en-1-yl)-1H-pyrazol-1-yl)ethyl)carbamate (187 mg, 64%) as a colourless oil. LC-MS
30 B: t_R = 0.78 min; $[M+H]^+$ = 282.29.

Step 2: Pd/C (10%, 34 mg, 0.032 mmol) is added to a RT soln. of *tert*-butyl (2-(4-(3-methoxyprop-1-en-1-yl)-1H-pyrazol-1-yl)ethyl)carbamate (180 mg, 0.64 mmol) in MeOH and the mix. is stirred at RT for 1 h under a H₂ atm. The mix. is filtered and concentrated to yield *tert*-butyl (2-(4-(3-methoxypropyl)-1H-pyrazol-1-yl)ethyl)carbamate (180 mg, 99%) as a colourless oil. LC-MS B: t_R = 0.78 min; $[M+H]^+$ = 284.28.

Step 3: 4 M HCl in dioxane (4.4 mL, 6.18 mmol) is added to a RT soln. of *tert*-butyl (2-(4-(3-methoxypropyl)-1H-pyrazol-1-yl)ethyl)carbamate (175 mg, 0.62 mmol) in dioxane (5 mL) and the resulting mix. is stirred for 30 min. The RM is concentrated in vacuo to yield the title compound **AM-14.1** (157 mg, 99%) as a colourless oil. LC-MS B: t_R = 0.42 min; $[M+H]^+$ = 184.40.

5 **2-(4-Cyclopropyl-1H-pyrazol-1-yl)ethan-1-amine dihydrochloride (AM-15.1)**

Step 1: A mix. of carbamic acid, N-[2-(4-bromo-1H-pyrazol-1-yl)ethyl]-, 1,1-dimethylethyl ester (500 mg, 1.72 mmol) and cyclopropylboronic acid (459 mg, 5.34 mmol) in THF (10 mL) is degassed with Ar for 10 min before Cs_2CO_3 (1.97 g, 6.03 mmol) and $Pd(dppf)Cl_2 \cdot DCM$ (42.2 mg, 0.052 mmol) are added. The RM is degassed with Ar for a further 2 min and then irradiated in a MW oven at 70°C for 30 min (cooling function on). After cooling to RT the RM is partitioned
10 between water and DCM and extracted. The layers are separated, and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with brine, dried (Mg_2SO_4), filtered, and evaporated in vacuo. The crude product is purified by FC (eluting with 15% to 50% EtOAc in hept, R_f = 0.48 in EtOAc/ hept 1:1) to give *tert*-butyl (2-(4-cyclopropyl-1H-pyrazol-1-yl)ethyl)carbamate (187 mg, 64%) as a colourless oil. LC-MS B: t_R = 0.78 min; $[M+H]^+$ = 282.29.

15 **Step 2:** 5 M HCl in *i*-PrOH (2.3 mL, 11.5 mmol) is added to *tert*-butyl (2-(4-cyclopropyl-1H-pyrazol-1-yl)ethyl)carbamate (580 mg, 2.31 mmol) at RT and the RM is stirred for 30 min. The RM is concentrated in vacuo to yield the title compound **AM-15.1** (157 mg, 99%) as a colourless oil. LC-MS B: t_R = 0.42 min; $[M+H]^+$ = 184.40.

2-(4-Methoxy-1H-pyrazol-1-yl)ethan-1-amine dihydrochloride (AM-16.1)

Step 1: *tert*-Butyl N-(2-bromoethyl)carbamate (1.61 g, 7.06 mmol) is added to a RT suspension of 4-methoxy-1H-pyrazole hydrochloride (1.00 g, 7.06 mmol) and Cs_2CO_3 (6.97 g, 21.2 mmol) in MeCN (16.3 mL) and the RM is heated
20 to 80°C for 18 h. The RM is allowed to reach RT, then it is filtered and the filter cake rinsed with DCM. Purification by FC (eluting with 20% to 60% EtOAc in hept with R_f = 0.18 (hept/EtOAc 1:1) yields *tert*-butyl (2-(4-methoxy-1H-pyrazol-1-yl)ethyl)carbamate (1.473 g, 87%) as a white solid.

Step 2: 4 M HCl in dioxane (13.8 mL, 55.3 mmol) is added to a 0°C suspension of *tert*-butyl (2-(4-methoxy-1H-pyrazol-1-yl)ethyl)carbamate (1.47 g, 5.53 mmol) in DCM (9.5 mL) and the RM is allowed to reach RT overnight. The RM is concentrated and co-evaporated with DCM under HV to obtain the title compound **AM-16.1** (1.36 g, 94%) as an off-white solid. LC-MS B: t_R = 0.36 min; No ionisation.

2-(5-Cyclopropyl-2H-tetrazol-2-yl)ethan-1-amine hydrochloride (AM-16.2)

The title compound is prepared from 5-cyclopropyl-2H-1,2,3,4-tetrazole following the sequence of reactions described
30 for **AM-16.1**, using K_2CO_3 instead of Cs_2CO_3 . LC-MS I: t_R = 0.44 min; $[M+H]^+$ = 154.25.

2-(3-Ethynylphenyl)ethan-1-amine.TFA (AM-17.1)

Step 1: *tert*-Butyl (3-bromophenethyl)carbamate is prepared from 2-(3-bromophenyl)ethan-1-amine in analogy to the procedure described for AM-3.1 step 1. LC-MS B: t_R = 1.00 min; $[M+H-Me]^+$ = 285.12.

Step 2: A degassed mix. of *tert*-butyl (3-bromophenethyl)carbamate (10.51 g, 35 mmol), trimethylsilylacetylene (14.8 mL, 105 mmol), XPhos Pd G2 (1.38 g, 1.75 mmol) and TEA (14.6 mL, 105 mmol) in DMF (120 mL) is stirred at 60°C
35

for 18 h. The RM is partitioned between water and Et₂O and the layers are separated. The aq. phase is re-extracted with Et₂O (2x) and the combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 60% EtOAc in hept) to give *tert*-butyl (3-((trimethylsilyl)ethynyl)phenethyl)carbamate as a brown oil. LC-MS B: *t*_R = 1.13 min; [M+H-Bu]⁺ = 262.27.

- 5 **Step 3:** TFA (15 mL, 196 mmol) is added to a RT soln. of *tert*-butyl (3-((trimethylsilyl)ethynyl)phenethyl)carbamate (10.36 g, 32.6 mmol) in DCM (100 mL) and the RM is stirred for 1 h before being concentrated in vacuo. The residue is co-evaporated with DCM (2x) to give the title compound as a yellow solid. LC-MS B: *t*_R = 0.49 min; [M+H]⁺ = 146.19.

2-(3-Methoxy-1,2,4-oxadiazol-5-yl)ethan-1-amine hydrochloride (AM-18.1)

- Step 1:** HATU (11.82 g, 31.1 mmol) is added to a RT solution of boc-beta-Ala-OH (5.0 g, 25.9 mmol), o-methylisourea bisulfate (4.5 g, 25.9 mmol, and DIPEA (18.1 mL, 104 mmol) in DMF (150 mL) and the RM is stirred at RT for 1.5 h. 10 Water and EtOAc are added to the RM, then the two layers are separated and the inorg. layer is extracted with EtOAc (2x). The combined org. layers are washed with brine, dried (Na₂SO₄), filtered, and concentrated to give the crude product that is purified by FC (eluting with 20% to 100% EtOAc in hept) to give *tert*-butyl (3-((imino(methoxy)methyl)amino)-3-oxopropyl)carbamate as a white solid. LC-MS I: *t*_R = 0.64 min; [M+H]⁺ = 246.36.

- 15 **Step 2:** 1,8-Diazabicyclo[5.4.0]undec-7-ene (8.96 mL, 59.3 mmol) is added to a RT soln. of *tert*-butyl (3-((imino(methoxy)methyl)amino)-3-oxopropyl)carbamate (6.19 g, 24.7 mmol) and NBS (10.56 g, 59.3 mmol) in EtOAc (120 mL) and the RM is stirred for 5 h. Additional 1,8-diazabicyclo[5.4.0]undec-7-ene (1.85 mL, 12.4 mmol) and NBS (2.2 g, 12.4 mmol) are added and stirring is continued for 16 h. The suspension is filtered and the filtrate is washed with water, sat. aq. NaHCO₃ soln. and brine before being evaporated to dryness. The crude product is purified by FC 20 (eluting with 20% to 100% EtOAc in hept) to give *tert*-butyl (2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)carbamate as a colourless oil. LC-MS I: *t*_R = 0.75 min; [M+H]⁺ = 244.33.

- Step 3:** 4 M HCl in dioxane (0.62 mL, 2.47 mmol) is added to a RT solution of *tert*-butyl (2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)carbamate (150 mg, 0.62 mmol) in DCM (2 mL) and the RM is stirred for 4 days at RT, then at 50°C for 6 h. The mixture is evaporated to yield the title compound **A-18.1** (79 mg, 71%) as a white solid. LC-MS I: *t*_R = 0.35 min; 25 [M+H]⁺ = 144.21.

2-(4-Cyclopropyl-2H-1,2,3-triazol-2-yl)ethan-1-amine hydrochloride (AM-19.1)

- Step 1:** Pd(OAc)₂ (17.1 mg, 0.076 mmol) is added to a RT solution of *tert*-butyl *N*-[2-(4-bromo-2H-1,2,3-triazol-2-yl)ethyl]carbamate (291 mg, 1 mmol), cyclopropylboronic acid (112 mg, 1.3 mmol), potassium phosphate tribasic (758 mg, 3.5 mmol), and tricyclohexylphosphine (45.1 mg, 0.156 mmol) in toluene (22 mL) and water (0.22 mL). The mixture 30 is heated to 100°C for 18 h. The RM is allowed to cool down to RT, then the mixture is filtered, and the filtrate concentrated. Purification by FC (eluting with 5% to 40% EtOAc in hept with *R*_F = 0.27 in hept/EtOAc 7:3) yields *tert*-butyl (2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)carbamate (194 mg, 77%) as a yellow oil. LC-MS B: *t*_R = 0.82 min; [M+H]⁺ = 253.34.

- Step 2:** 4 M HCl in dioxane (4.9 mL, 19.6 mmol) is added to a RT solution of *tert*-butyl (2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)carbamate (550 mg, 1.96 mmol) in DCM (3.4 mL). The RM is stirred at RT for 30 min, then the RM 35

is concentrated to give title compound **AM-19.1** (432 mg, 98%) as a white solid which is used as such in the next step.
LC-MS B: t_R = 0.37 min; $[M+H]^+$ = 153.11.

2-(2-Aminoethyl)-2H-1,2,3-triazole-4-carbonitrile trifluoroacetate (AM-19.2)

Step 1: Vinylboronic anhydride pyridine complex (355 mg, 1.47 mmol) and 2 M aq. K_2CO_3 (2.5 mL) are added to a RT soln. of *tert*-butyl *N*-(2-(4-bromo-2H-1,2,3-triazol-2-yl)ethyl)carbamate (429 mg, 1.47 mmol) in 1,2-dimethoxyethane (7 mL) and the RM is purged with Ar for 10 min before $Pd(PPh_3)_4$ (34.8 mg, 0.03 mmol) is added. The mixture is heated to 80°C for 18 h. The RM is cooled to RT, filtered, and the filtrate is partitioned between water and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (2x) and the combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by prep. HPLC (acidic) to give *tert*-butyl (2-(4-vinyl-2H-1,2,3-triazol-2-yl)ethyl)carbamate as a brown oil. LC-MS B: t_R = 0.81 min; $[M+H]^+$ = 239.14.

Step 2: $KMnO_4$ (401 mg, 1.0 mmol) is added to a RT soln. of *tert*-butyl (2-(4-vinyl-2H-1,2,3-triazol-2-yl)ethyl)carbamate (118 mg, 0.50 mmol) in a 1:1 mix. of water:acetone (6 mL) and the RM is stirred for 18 h. The RM is filtered and evaporated in vacuo and the crude product is purified by prep. HPLC (acidic) to give 2-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2H-1,2,3-triazole-4-carboxylic acid as a white solid. LC-MS B: t_R = 0.61 min; $[M+H]^+$ = 257.11.

Step 3: HATU (294 mg, 0.77 mmol) is added to a RT soln. of 2-(2-((*tert*-butoxycarbonyl)amino)ethyl)-2H-1,2,3-triazole-4-carboxylic acid (66 mg, 0.26 mmol) in DMF (1 mL) and the RM is stirred for 1 h before 25% aq. NH_3 (0.99 mL, 6.4 mmol) is added and stirring is continued for 1 h. The RM is directly purified by prep. HPLC (basic) to give *tert*-butyl (2-(4-carbamoyl-2H-1,2,3-triazol-2-yl)ethyl)carbamate as a white solid. LC-MS B: t_R = 0.58 min; $[M+H]^+$ = 256.13.

Step 4: Burgess reagent (97 mg, 0.38 mmol) is added to a RT soln. of *tert*-butyl (2-(4-carbamoyl-2H-1,2,3-triazol-2-yl)ethyl)carbamate (49 mg, 0.19 mmol) in DCM (2 mL) and the RM is stirred for 18 h. The RM is poured into water, diluted with DCM and extracted. The layers are separated and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by prep. HPLC (acidic) to give *tert*-butyl (2-(4-cyano-2H-1,2,3-triazol-2-yl)ethyl)carbamate as a colourless oil. LC-MS B: t_R = 0.80 min; $[M+H]^+$ = 238.14.

Step 5: The title compound is prepared from *tert*-butyl (2-(4-cyano-2H-1,2,3-triazol-2-yl)ethyl)carbamate in analogy to the procedure described for AM-17.1 step 3. LC-MS B: t_R = 0.22 min; $[M+H]^+$ = 138.16.

2-(4-Ethynyl-5-methyl-2H-1,2,3-triazol-2-yl)ethan-1-amine (AM-19.3)

Step 1: NaH 60% dispersion in mineral oil (1.48 g, 37 mmol) is added portionwise to a 0°C soln. of 4,5-dibromo-2H-1,2,3-triazole (4.0 g, 17.6 mmol) in DMF (120 mL) and the RM is warmed to RT and stirred for 30 min before being cooled back to 0°C. *N*-(2-bromoethyl)phthalimide (9.9 g, 37 mmol) is added portionwise and the RM is warmed to RT and stirred for 42 h. The RM is quenched into ice water and the precipitate is collected by filtration. The filter cake is

washed with Et₂O to give 2-(2-(4,5-dibromo-2H-1,2,3-triazol-2-yl)ethyl)isoindoline-1,3-dione as a white solid. LC-MS I: t_R = 0.98 min; No ionisation.

Step 2: ZnMe₂ (2 M in PhMe, 0.50 mL, 1.0 mmol) is added dropwise to a RT soln. of 2-(2-(4,5-dibromo-2H-1,2,3-triazol-2-yl)ethyl)isoindoline-1,3-dione (500 mg, 1.25 mmol), and Pd(dppf)Cl₂.DCM (10 mg, 0.013 mmol) in dioxane (2 mL) and the RM is heated to 70°C and stirred for 3 h. The RM is concentrated in vacuo and the residue is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by prep. HPLC (basic) to give 2-(2-(4-bromo-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)isoindoline-1,3-dione as a white solid. LC-MS I: t_R = 0.92 min; No ionisation.

Step 3: A degassed mix. of 2-(2-(4-bromo-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)isoindoline-1,3-dione (85 mg, 0.25 mmol), (tert-butyldimethylsilyl)acetylene (73 mg, 0.51 mmol), XPhos Pd G2 (20 mg, 0.03 mmol) and KOAc (75 mg, 0.76 mmol) in DMF (2 mL) is stirred at 70°C for 30 min. The RM is filtered through a Whatman filter and directly purified by prep. HPLC (basic) to give 2-(2-(4-((tert-butyldimethylsilyl)ethynyl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)isoindoline-1,3-dione as a white solid. LC-MS I: t_R = 1.32 min; [M+H]⁺ = 395.29.

Step 4: Hydrazine monohydrate (0.18 mL, 2.43 mmol) is added to a RT solution of 2-(2-(4-((tert-butyldimethylsilyl)ethynyl)-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)isoindoline-1,3-dione (32 mg, 0.08 mmol) in EtOH (1 mL) and the RM is heated to reflux for 2.5 h. The RM is cooled to RT and MeCN is added. The resulting suspension is filtered and the filter cake is discarded. The filtrate is concentrated in vacuo to give 2-(4-((tert-butyldimethylsilyl)ethynyl)-5-methyl-2H-1,2,3-triazol-2-yl)ethan-1-amine as a yellow oil. LC-MS I: t_R = 1.14 min; [M+H+MeCN]⁺ = 306.14.

Step 5: 1 M aq. NaOH (0.25 mL, 0.25 mmol) is added to a RT soln. of 2-(4-((tert-butyldimethylsilyl)ethynyl)-5-methyl-2H-1,2,3-triazol-2-yl)ethan-1-amine (26 mg, 0.1 mmol) in EtOH (0.75 mL) and the RM is heated to 60°C for 3 h. The RM is concentrated before water and DCM are added. The layers are separated and the aq. phase is extracted with DCM (1x). The combined org. layers are dried over a phase separator and concentrated in vacuo to give the title compound as a yellow oil. LC-MS I: t_R = 0.51 min; [M+H]⁺ = 151.22.

2-(4-Fluoro-3-methoxyisoxazol-5-yl)ethan-1-amine hydrochloride (AM-20.1)

Step 1: In a microwave tube, phthalic anhydride (354 mg, 2.36 mmol) is added to a RT suspension of **AM-13.1** (402 mg, 2.25 mmol) and DIPEA (0.47 mL, 2.7 mmol) in dioxane (12 mL). The tube is sealed and heated to 100°C for 48 h. Water is added to the RM, the mixture is acidified with 1 M HCl and the product extracted with EtOAc, dried (MgSO₄), filtered, and concentrated to yield 2-(2-(3-methoxyisoxazol-5-yl)ethyl)isoindoline-1,3-dione (718 mg) as a white solid which was used as such in the next step. LC-MS B: t_R = 0.85 min; [M+H]⁺ = 273.09.

Step 2: Selectfluor (1.07 g, 2.87 mmol) is added to a 40°C solution of 2-(2-(3-methoxyisoxazol-5-yl)ethyl)isoindoline-1,3-dione (710 mg, 2.61 mmol) in tetramethylene sulfone (21.7 mL, 226 mmol) and the RM is heated to 120°C for 18 h. The resulting dark brown solution is allowed to cool down to around 50°C, then the RM is poured into pre-stirred H₂O (30 mL), followed by EtOAc (10 mL). The two layers are separated and the inorg. layer is extracted with EtOAc

(5 mL). The comb. org. layers are washed with brine, dried (Na₂SO₄), filtered, and concentrated. Purification by prep HPLC (acidic) yields 2-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)isoindoline-1,3-dione (89 mg, 12%) as a colorless oil. LC-MS B: t_R = 0.90 min; [M+H]⁺ = 291.02.

Step 3: Hydrazine monohydrate (0.222 mL, 2.93 mmol) is added to a RT solution of 2-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)isoindoline-1,3-dione (85 mg, 0.293 mmol) in EtOH (3 mL) and the RM is heated to 80°C for 1 h. The RM is cooled down to RT and a white precipitate is formed. Ether is added and the solid (sideproduct) is triturated before filtered off. The filtrate is concentrated to yield title compound **AM-20.1** (40 mg, 85%) as a colorless oil which was used as such in the next step. LC-MS B: t_R = 0.33 min; [M+H]⁺ = 161.08.

General method 1 for the synthesis of building blocks A

10 **tert-Butyl (S)-3-amino-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (A-1.1)**

Step 1: HATU (4.53 g, 11.9 mmol) is added to a RT soln. of Fmoc-L-aspartic acid beta-*tert*-butyl ester (5.0 g, 11.9 mmol), 3-methoxyphenethylamine (AM-1.4, 2.0 g, 13.1 mmol) and DIPEA (4.08 mL, 23.8 mmol) in DMF (40 mL) and the RM is stirred for 1 h. The RM is partitioned between water and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (2x) and the combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and
15 evaporated in vacuo. The crude product is purified by FC (eluting with 20% to 80% EtOAc in hept) to give *tert*-butyl (S)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate as a white solid. LC-MS B: t_R = 1.12 min; [M+H]⁺ = 545.11.

Step 2: Piperidine (4.95 mL, 49.5 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (5.45 g, 9.9 mmol) in DCM (60 mL) and
20 the RM is stirred for 2 h. The RM is concentrated in vacuo and the residue directly purified by FC (eluting with 100:2:0.5 DCM:MeOH:NH₃) to give the title compound as a colourless oil. LC-MS B: t_R = 0.67 min; [M+H]⁺ = 323.34.

Listed in Table A-1 below are building blocks A that are prepared in analogy to the 2-step sequence described above for A-1.1.

Table A-1

No.	Starting Material	Product	t _R [min]	MS-data
			LC-MS Method	m/z [M+H] ⁺
A-1.2	2-(Chroman-7-yl)ethan-1-amine hydrochloride (AM-2.4)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(chroman-7-yl)ethyl)amino)-4-oxobutanoate	0.86 I	349.21
A-1.3	2-(2,3-Dihydrobenzofuran-6-yl)ethan-1-amine hydrochloride (AM-2.5)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(2,3-dihydrobenzofuran-6-yl)ethyl)amino)-4-oxobutanoate	0.81 I	335.24
A-1.4	2-(4-Bromophenyl)ethan-1-amine (AM-1.12)	<i>tert</i> -Butyl (S)-3-amino-4-((4-bromophenethyl)amino)-4-oxobutanoate	0.90 I	371.13

A-1.5	2-(2,3,4,5-Tetrahydrobenzo[b]oxepin-8-yl)ethan-1-amine hydrochloride (AM-2.21)	<i>tert</i> -Butyl (S)-3-amino-4-oxo-4-((2-(2,3,4,5-tetrahydrobenzo[b]oxepin-8-yl)ethyl)amino)butanoate	0.93 I	363.21
A-1.6	2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)ethan-1-amine hydrochloride (AM-2.6)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)amino)-4-oxobutanoate	0.66 B	351.47
A-1.7	2-(4-(2H-1,2,3-Triazol-2-yl)phenyl)ethan-1-amine hydrochloride (AM2.7)	<i>tert</i> -Butyl (S)-4-((4-(2H-1,2,3-triazol-2-yl)phenethyl)amino)-3-amino-4-oxobutanoate	0.69 B	360.45
A-1.8	2-(3-Methylisoxazol-5-yl)ethan-1-amine hydrochloride (AM-1.40)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate	0.64 I	298.26
A-1.9	2-(3-Bromophenyl)ethan-1-amine	<i>tert</i> -Butyl (S)-3-amino-4-((3-bromophenethyl)amino)-4-oxobutanoate	0.73 B	371.36
A-1.10	2-(3-(Difluoromethoxy)phenyl)ethan-1-amine (AM-1.57)	<i>tert</i> -Butyl (S)-3-amino-4-((3-(difluoromethoxy)phenethyl)amino)-4-oxobutanoate	0.73 B	359.45
A-1.11	2-(5,6-Dihydro-4H-cyclopenta[d]thiazol-2-yl)ethan-1-amine (AM-1.49)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)amino)-4-oxobutanoate	0.64 B	340.15
A-1.12	2-(3-Ethoxyphenyl)ethan-1-amine (AM-1.58)	<i>tert</i> -Butyl (S)-3-amino-4-((3-ethoxyphenethyl)amino)-4-oxobutanoate	0.90 I	337.25
A-1.13	(<i>RS</i>)-2-(5,5-Dimethyltetrahydro-2H-pyran-2-yl)ethan-1-amine (AM-1.59)	<i>tert</i> -Butyl (S)-3-amino-4-((2-((<i>RS</i>)-5,5-dimethyltetrahydro-2H-pyran-2-yl)ethyl)amino)-4-oxobutanoate	0.88 I	329.27
A-1.14	2-(Benzo[d][1,3]dioxol-5-yl)ethan-1-amine hydrochloride	<i>tert</i> -Butyl (S)-3-amino-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-4-oxobutanoate	0.67 B	337.20
A-1.15	2-(3,5-Dimethoxyphenyl)ethan-1-amine (AM-1.7)	<i>tert</i> -Butyl (S)-3-amino-4-((3,5-dimethoxyphenethyl)amino)-4-oxobutanoate	0.69 B	353.20
A-1.16	2-(Benzo[d]oxazol-2-yl)ethan-1-amine hydrochloride (AM-1.3)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(benzo[d]oxazol-2-yl)ethyl)amino)-4-oxobutanoate	0.65 B	334.35

A-1.17	2-(3-(2H-1,2,3-Triazol-2-yl)phenyl)ethan-1-amine hydrochloride (AM-2.8)	<i>tert</i> -Butyl (S)-4-((3-(2H-1,2,3-triazol-2-yl)phenethyl)amino)-3-amino-4-oxobutanoate	0.69 B	360.51
A-1.18	2-(5-Cyclopropylisoxazol-3-yl)ethan-1-amine (AM-1.33)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(5-cyclopropylisoxazol-3-yl)ethyl)amino)-4-oxobutanoate	0.76 I	324.27
A-1.19	2-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)ethan-1-amine hydrochloride (AM-1.26)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)amino)-4-oxobutanoate	0.70 I	325.31
A-1.20	2-(2,6-Difluorophenyl)ethan-1-amine (AM-1.22)	<i>tert</i> -Butyl (S)-3-amino-4-((2,6-difluorophenethyl)amino)-4-oxobutanoate	0.87 I	329.26
A-1.21	2-(4-(Pyrimidin-2-yl)phenyl)ethan-1-amine hydrochloride (AM-2.12)	<i>tert</i> -Butyl (S)-3-amino-4-oxo-4-((4-(pyrimidin-2-yl)phenethyl)amino)butanoate	0.66 B	371.22
A-1.22	2-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)ethan-1-amine hydrochloride (AM-1.35)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate	0.72 I	325.29
A-1.23	2-(3-(Methoxy-d3)phenyl)ethan-1-amine (AM-3.2)	<i>tert</i> -Butyl (S)-3-amino-4-((3-(methoxy-d3)phenethyl)amino)-4-oxobutanoate	0.82 I	326.33
A-1.24	2-(3-Cyclopropylisoxazol-5-yl)ethan-1-amine hydrochloride (AM-5.2)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-cyclopropylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate	0.73 I	324.31
A-1.25	4-Ethylphenethylamine (AM-1.10)	<i>tert</i> -Butyl (S)-3-amino-4-((4-ethylphenethyl)amino)-4-oxobutanoate	0.98 I	321.38
A-1.26	2-(3-(1,1-Difluoroethyl)phenyl)ethan-1-amine (AM-2.22)	<i>tert</i> -Butyl (S)-3-amino-4-((3-(1,1-difluoroethyl)phenethyl)amino)-4-oxobutanoate	2.0 J	357.1
A-1.27	2-(3-(Pyrimidin-2-yl)phenyl)ethan-1-amine dihydrochloride (AM-2.11)	<i>tert</i> -butylButyl (S)-3-amino-4-oxo-4-((3-(pyrimidin-2-yl)phenethyl)amino)butanoate	0.66 B	371.23
A-1.28	2-(3-Methoxyisoxazol-5-yl)ethan-1-amine hydrochloride (AM-13.1)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-methoxyisoxazol-5-yl)ethyl)amino)-4-oxobutanoate	0.68 I	314.36

A-1.29	2-(3-(Methoxy-d3)isoxazol-5-yl)ethan-1-amine hydrochloride (AM-13.2)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-(methoxy-d3)isoxazol-5-yl)ethyl)amino)-4-oxobutanoate	0.67 I	317.39
A-1.30	2-(2-Cyclopropyl-2H-1,2,3-triazol-4-yl)ethan-1-amine hydrochloride (AM-2.23)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)amino)-4-oxobutanoate	0.69 I	324.36
A-1.31	2-(3-(Trifluoromethyl)isoxazol-5-yl)ethan-1-amine (AM-1.84)	<i>tert</i> -Butyl (S)-3-amino-4-oxo-4-((2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)amino)butanoate	0.85 I	352.23
A-1.32	2-(3-(Difluoromethyl)isoxazol-5-yl)ethan-1-amine (AM-5.3)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-(difluoromethyl)isoxazol-5-yl)ethyl)amino)-4-oxobutanoate	0.75 I	334.32
A-1.33	But-3-yn-1-amine hydrochloride (AM-1.86)	<i>tert</i> -Butyl (S)-3-amino-4-(but-3-yn-1-ylamino)-4-oxobutanoate	1.63 J	185.1 (- ^t Bu)
A-1.34	Benzyl 3-aminopropanoate 4-methylbenzenesulfonate (AM-1.87)	<i>tert</i> -Butyl (S)-3-amino-4-((3-(benzyloxy)-3-oxopropyl)amino)-4-oxobutanoate	1.84 J	351.2
A-1.35	(S)-2-Amino-1-phenylethan-1-ol (AM-1.88)	<i>tert</i> -Butyl (S)-3-amino-4-(((S)-2-hydroxy-2-phenylethyl)amino)-4-oxobutanoate	0.70 I	309.31
A-1.36	2-(3-Methoxy-1,2,4-oxadiazol-5-yl)ethan-1-amine hydrochloride (AM-18.1)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate	0.62 I	315.44
A-1.37	2-(5-Cyclopropyl-2H-tetrazol-2-yl)ethan-1-amine hydrochloride (AM-16.2)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)amino)-4-oxobutanoate	0.96 I	325.47
A-1.38	2-(4-Cyclopropyl-2H-1,2,3-triazol-2-yl)ethan-1-amine hydrochloride (AM-19.1)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)amino)-4-oxobutanoate	0.59 B	324.03
A-1.39	2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethan-1-ol (AM-1.90)	<i>tert</i> -Butyl (S)-3-amino-4-(((R)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-hydroxyethyl)amino)-4-oxobutanoate (chiral separation before F-moc deprotection)	0.53 A	341.28
A-1.40	2-Amino-1-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethan-1-ol (AM-1.90)	<i>tert</i> -Butyl (S)-3-amino-4-(((S)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-hydroxyethyl)amino)-4-oxobutanoate	0.53 A	341.23

		(chiral separation before F-moc deprotection)		
A-1.41	2-(2 <i>H</i> -Benzo[d][1,2,3]triazol-2-yl)ethan-1-amine (AM-1.91)	<i>tert</i> -Butyl (S)-4-((2-(2 <i>H</i> -benzo[d][1,2,3]triazol-2-yl)ethyl)amino)-3-amino-4-oxobutanoate	0.61 A	334.26
A-1.42	3-(Trifluoromethoxy)propan-1-amine (AM-1.92)	<i>tert</i> -Butyl (S)-3-amino-4-oxo-4-((3-(trifluoromethoxy)propyl)amino)butanoate	0.63 A	315.24
A-1.43	3-(Difluoromethoxy)propan-1-amine (AM-1.45)	<i>tert</i> -Butyl (S)-3-amino-4-((3-(difluoromethoxy)propyl)amino)-4-oxobutanoate	0.59 A	297.28
A-1.44	2-([1,2,4]Triazolo[1,5- <i>a</i>]pyrimidin-2-yl)ethan-1-amine (AM-1.93)	<i>tert</i> -Butyl (S)-4-((2-([1,2,4]triazolo[1,5- <i>a</i>]pyrimidin-2-yl)ethyl)amino)-3-amino-4-oxobutanoate	0.46 A	335.33
A-1.45	2-(1-(2-Methoxyethyl)-1 <i>H</i> -pyrazol-4-yl)ethan-1-amine (AM-1.94)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(1-(2-methoxyethyl)-1 <i>H</i> -pyrazol-4-yl)ethyl)amino)-4-oxobutanoate	0.53 A	341.31
A-1.46	2-(4-Fluoro-3-methoxyisoxazol-5-yl)ethan-1-amine hydrochloride (AM-20.1)	<i>tert</i> -Butyl (S)-3-amino-4-((2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)amino)-4-oxobutanoate	0.71 I	332.50

General method 2 for the synthesis of building blocks A

4-Allyl 1-benzyl L-aspartate hydrochloride (A-2.1)

- Step 1:** Benzyl bromide (2.15 mL, 17.7 mmol) is added to a RT mix. of Boc-L-aspartic acid-beta-allyl ester (5.0 g, 17.7 mmol) and KHCO₃ (1.8 g, 17.7 mmol) in DMF (30 mL) and the RM is stirred for 16 h. The RM is concentrated in vacuo and the residue is partitioned between H₂O and EtOAc and extracted. The layers are separated and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 4-allyl 1-benzyl (*tert*-butoxycarbonyl)-L-aspartate as a yellow oil. LC-MS B: t_R = 1.01 min; [M+H]⁺ = 364.45.
- Step 2:** 4M HCl in dioxane (17.7 mL, 71 mmol) is added to a soln. of 4-allyl 1-benzyl (*tert*-butoxycarbonyl)-L-aspartate (6.43 g, 17.7 mmol) in dioxane (40 mL) and the RM is stirred for 5 h at RT. The volatiles are removed in vacuo and the residue is triturated with Et₂O to give the title compound as a white solid. LC-MS B: t_R = 0.61 min; [M+H]⁺ = 264.34.

Allyl (S)-3-amino-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride (A-2.2)

Step 1: Allyl (S)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate is prepared from (S)-4-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid in analogy to the procedure described for A-1.1 step 1. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 421.16.

- 5 **Step 2:** The title compound is prepared from (S)-4-(allyloxy)-2-((*tert*-butoxycarbonyl)amino)-4-oxobutanoic acid in analogy to the procedure described for A-2.1 step 2. LC-MS B: t_R = 0.61 min; $[M+H]^+$ = 321.20..

Listed in Table A-2 below are building blocks A that are prepared in analogy to the 2-step sequence described above for A-2.2.

Table A-2

No.	Starting Material	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
A-2.3	(S)-4-(Allyloxy)-2-((<i>tert</i> -butoxycarbonyl)amino)-4-oxobutanoic acid	Allyl (S)-3-amino-4-((3-methoxyphenethyl)amino)-4-oxobutanoate hydrochloride	0.74 I	307.21
A-2.4	(S)-4-(Allyloxy)-2-((<i>tert</i> -butoxycarbonyl)amino)-4-oxobutanoic acid	Allyl (S)-3-amino-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride	0.57 I	282.21

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General method 1 for the synthesis of building blocks B**Benzyl (R)-2-(2-amino-3-phenylpropoxy)-4,6-dimethoxybenzoate hydrochloride (B-1.1)**

- Step 1:** $KHCO_3$ (1.6 g, 15.8 mmol) and benzyl bromide (2.1 mL, 17.3 mmol) are added to a soln. of 2-hydroxy-4,6-dimethoxybenzoic acid (3 g, 14.4 mmol) in DMF (40 mL) and the RM is stirred for 16 h. The RM is filtered and the filtrate concentrated in vacuo. The residue is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 5% to 40% EtOAc in hept) to give benzyl 2-hydroxy-4,6-dimethoxybenzoate as a white solid. LC-MS B: t_R = 1.04 min; $[M+H]^+$ = 289.23.

- Step 2:** DIAD (3.0 mL, 15 mmol) is added to a 0°C mix. of 2-hydroxy-4,6-dimethoxybenzoate (3.16 g, 10.7 mmol), *tert*-butyl (R)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (4.12 g, 16.1 mmol), and PPh_3 (4.27 g, 16.1 mmol) in THF (40 mL) and the RM is stirred for 16 h at RT. The mix. is concentrated and the residue directly purified by FC (eluting with 20% to 100% EtOAc in hept) to give benzyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-4,6-dimethoxybenzoate as a colourless oil. LC-MS B: t_R = 1.16 min; $[M+H]^+$ = 522.26.

- Step 3:** 4M HCl in dioxane (21 mL, 86.3 mmol) is added to a soln. of benzyl (R)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-4,6-dimethoxybenzoate (4.64 g, 8.63 mmol) in dioxane (40 mL) and the RM is stirred for 5 h at RT.

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The volatiles are removed in vacuo and the residue is triturated with Et₂O (3x) to give the title compound as a white solid. LC-MS B: t_R = 0.84 min; [M+H]⁺ = 422.36.

Listed in Table B-1 below are building blocks B that are prepared in analogy to the 3-step sequence described above for B-1.1. In cases where the HCl salt is highly hygroscopic, the amine is subjected to a basic workup to liberate its

5 free base.

Table B-1

No.	Starting Material	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
B-1.2	2-Hydroxy-6-methylbenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-6-methylbenzoate	2.28 J	376.2
B-1.3	2-Hydroxy-5-methylbenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-5-methylbenzoate	1.83 F	376.2
B-1.4	2-Hydroxy-4-methylbenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-4-methylbenzoate	1.83 F	376.2
B-1.5	2-Hydroxy-6-methoxybenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-6-methoxybenzoate hydrochloride	1.06 I	392.14
B-1.6	2-Hydroxy-5-methoxybenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-5-methoxybenzoate	2.26 J	392.2
B-1.7	2-Hydroxy-4-methoxybenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-4-methoxybenzoate	2.88 F	392.2
B-1.8	5-Chloro-2-hydroxybenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-5-chlorobenzoate	1.80 F	396.1
B-1.9	5-Fluoro-2-hydroxybenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-5-fluorobenzoate	2.29 J	380.2
B-1.10	4-Hydroxy-6-methylnicotinic acid	Benzyl (R)-4-(2-amino-3-phenylpropoxy)-6-methylnicotinate dihydrochloride	2.08 J	377.1
B-1.11	2-Hydroxy-4,5-dimethoxybenzoic acid	Benzyl (R)-2-(2-amino-3-phenylpropoxy)-4,5-dimethoxybenzoate	1.75 F	422.2
B-1.12	3-Hydroxy-2-naphthoic acid	Benzyl (R)-3-(2-amino-3-phenylpropoxy)-2-naphthoate hydrochloride	1.83 F	412.2

B-1.13	2-Hydroxy-1-naphthoic acid	Benzyl (<i>R</i>)-2-(2-amino-3-phenylpropoxy)-1-naphthoate hydrochloride	0.88 B	412.37
B-1.14	3-Hydroxyquinoline-4-carboxylic acid	Benzyl (<i>R</i>)-3-(2-amino-3-phenylpropoxy)quinoline-4-carboxylate dihydrochloride	0.83 B	413.34
B-1.16	6-Hydroxy-2H-1,3-benzodioxole-5-carboxylic acid	Benzyl (<i>R</i>)-6-(2-amino-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylate hydrochloride	0.84 B	406.13
B-1.19	6-Fluoro-3-hydroxyquinoline-4-carboxylic acid	Benzyl (<i>R</i>)-3-(2-amino-3-phenylpropoxy)-6-fluoroquinoline-4-carboxylate dihydrochloride	1.12 I	431.24
B-1.20	8-Fluoro-3-hydroxyquinoline-4-carboxylic acid	Benzyl (<i>R</i>)-3-(2-amino-3-phenylpropoxy)-8-fluoroquinoline-4-carboxylate dihydrochloride	0.83 B	431.19
B-1.21	2-Fluoro-6-hydroxybenzoic acid	Benzyl (<i>R</i>)-2-(2-amino-3-phenylpropoxy)-6-fluorobenzoate hydrochloride	0.83 B	380.15
B-1.22	2-Hydroxy-4-methoxybenzoic acid	Benzyl (<i>R</i>)-2-(2-amino-3-phenylpropoxy)-4-methoxybenzoate hydrochloride	0.87 B	392.27
B-1.23	3-Hydroxyquinoline-4-carboxylic acid	Benzyl (<i>S</i>)-3-(2-amino-3-phenylpropoxy)quinoline-4-carboxylate dihydrochloride	1.07 I	413.24
B-1.26	6-Chloro-3-hydroxyquinoline-4-carboxylic acid	Benzyl (<i>R</i>)-3-(2-amino-3-phenylpropoxy)-6-chloroquinoline-4-carboxylate dihydrochloride	0.94 D	447.09

Benzyl (*R*)-2-(2-amino-3-phenylpropoxy)-6-ethoxybenzoate hydrochloride (B-1.17)

Step 1: Benzyl bromide (0.92 mL, 7.6 mmol) is added to a RT mix. of 2,6-dihydroxybenzoic acid (1.0 g, 6.3 mmol) and NaHCO₃ (582 mg, 6.9 mmol) in DMF (16 mL) and the RM is heated to 60°C for 6 h. The RM is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 10% EtOAc in hept) to give benzyl 2,6-dihydroxybenzoate as a colourless oil. LC-MS B: t_R = 0.98 min; [M+H]⁺ = 245.35.

Step 2: Ethyl iodide (0.086 mL, 1.1 mmol) is added to a RT mix. of benzyl 2,6-dihydroxybenzoate (376 mg, 1.1 mmol) and Cs_2CO_3 (351 mg, 1.1 mmol) in DMF (15 mL) and the RM is stirred for 16 h. The RM is partitioned between water and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (2x) and the combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 10% EtOAc in hept) to give benzyl 2-ethoxy-6-hydroxybenzoate as a yellow solid. LC-MS B: t_R = 1.01 min; $[\text{M}+\text{H}]^+ = 273.29$.

Steps 3-4: The title compound is prepared from benzyl 2-ethoxy-6-hydroxybenzoate following steps 2&3 described for B-1.1. LC-MS B: t_R = 0.85 min; $[\text{M}+\text{H}]^+ = 406.40$.

Benzyl (*R*)-4-(2-amino-3-phenylpropoxy)-2-methoxynicotinate (B-1.18)

Step 1: CDI (615 mg, 3.8 mmol) is added to a soln. of 4-hydroxy-2-methoxynicotinic acid (452 mg, 2.7 mmol) in DMF (5 mL) and the RM is heated to 60°C for 2 h. After cooling to 0°C, additional DMF (5 mL), benzyl alcohol (0.5 mL, 4.8 mmol), and NaH (118 mg, 2.95 mmol) are added and the RM is warmed to RT and stirred for 16 h. The RM is partitioned between 1N HCl and DCM and the layers are separated. The aq. phase is re-extracted with DCM (1x) and the combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 35% EtOAc in hept) to give benzyl 4-hydroxy-2-methoxynicotinate as a white solid. LC-MS F: t_R = 2.07 min; $[\text{M}+\text{H}]^+ = 260.0$.

Step 2: Benzyl (*R*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxynicotinate is prepared from benzyl 4-hydroxy-2-methoxynicotinate and *tert*-butyl (*R*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 step 2. LC-MS J: t_R = 2.34 min; $[\text{M}+\text{H}]^+ = 493.2$.

Step 3: TFA (3.65 mL, 4.77 mmol) is added to a 0°C soln. of benzyl (*R*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxynicotinate (235 mg, 0.48 mmol) in DCM (6 mL) and the RM is warmed to RT and stirred for 3 h. The RM is concentrated in vacuo and the residue partitioned between DCM and sat. aq. NaHCO_3 and the layers are separated. The aq. phase is re-extracted with DCM (1x) and the combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to give the title compound as a yellow oil. LC-MS I: t_R = 1.01 min; $[\text{M}+\text{H}]^+ = 393.15$.

(*R*)-2-(2-((*tert*-Butoxycarbonyl)amino)-3-(pyridin-2-yl)propoxy)-1-naphthoic acid (B-1.24)

Step 1: Benzyl 2-hydroxy-1-naphthoate is prepared from 2-hydroxy-1-naphthoic acid in analogy to the procedure described for B-1.1 step 1. LC-MS B: t_R = 1.08 min; $[\text{M}+\text{H}]^+ = 279.51$.

Step 2: (*R*)-2-((*tert*-Butoxycarbonyl)amino)-3-(pyridin-2-yl)propanoic acid (500 mg, 1.8 mmol) is added to a 0°C suspension of LAH (85 mg, 2.2 mmol) in Et_2O (13 mL) and the RM is warmed to RT and stirred for 1 h. The RM is cooled to 0°C and quenched with EtOAc before a sat. aq. Rochelle's salt soln. is added and vigorous stirring is maintained for 30 min after which the layers are separated. The aq. phase is re-extracted with EtOAc (3x) and the combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to give *tert*-butyl (*R*)-(1-hydroxy-3-(pyridin-2-yl)propan-2-yl)carbamate as a yellow oil. LC-MS I: t_R = 0.63 min; $[\text{M}+\text{H}]^+ = 253.22$.

Step 3: Benzyl (*R*)-2-2-((*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propoxy)-1-naphthoate is prepared from the products of steps 1&2 above in analogy to the procedure described for B-1.1 step 2. LC-MS I: t_R = 1.23 min; $[M+H]^+$ = 514.18.

Step 4: A soln. of benzyl (*R*)-2-2-((*tert*-butoxycarbonyl)amino)-3-(pyridin-2-yl)propoxy)-1-naphthoate (108 mg, 0.17 mmol) in MeOH (3 mL) is evacuated/purged with N_2 (3x) before 10% Pd/C (18 mg, 10 mol%) is added. The RM is evacuated/purged with H_2 (3x) and stirred under a H_2 atm for 2 h. The RM is filtered through a pad of celite and the filtrate concentrated in vacuo to give the title compound as a white solid. LC-MS I: t_R = 0.48 min; $[M+H]^+$ = 423.23.

(*R*)-3-(3-(Benzo[b]thiophen-3-yl)-2-((*tert*-butoxycarbonyl)amino)propoxy)quinoline-4-carboxylic acid (B-1.25)

Step 1: A soln. of TMS-diazomethane (2 M in Et_2O , 0.6 mL, 1.2 mmol) is added to a 0°C soln. of (*R*)-3-(benzo[b]thiophen-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoic acid (128 mg, 0.4 mmol) in MeOH (2 mL) and the RM is warmed to RT and stirred for 2 h. The RM is subsequently purified by prep. HPLC (basic) to furnish methyl (*R*)-3-(benzo[b]thiophen-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate as a white solid. LC-MS I: t_R = 1.08 min; $[M+H]^+$ = 336.25.

Step 2: $NaBH_4$ (30 mg, 0.78 mmol) is added to a 0°C mix. of methyl (*R*)-3-(benzo[b]thiophen-3-yl)-2-((*tert*-butoxycarbonyl)amino)propanoate (130 mg, 0.39 mmol) in EtOH (1 mL) and H_2O (1 mL) and the RM is warmed to RT and stirred for 16 h. The RM is subsequently purified by prep. HPLC (basic) to furnish *tert*-butyl (*R*)-3-(benzo[b]thiophen-3-yl)-3-hydroxypropan-2-yl)carbamate as a colourless oil. LC-MS I: t_R = 0.97 min; $[M+H]^+$ = 308.16.

Step 3: Benzyl 3-hydroxyquinoline-4-carboxylate is prepared from 3-hydroxyquinoline-4-carboxylic acid in analogy to the procedure described for B-1.1 step 1. LC-MS B: t_R = 0.95 min; $[M+H]^+$ = 280.19.

Step 4: Benzyl (*R*)-3-(3-(benzo[b]thiophen-3-yl)-2-((*tert*-butoxycarbonyl)amino)propoxy)quinoline-4-carboxylate is prepared from the products of steps 2&3 above in analogy to the procedure described for B-1.1 step 2. LC-MS I: t_R = 0.85 min; $[M+H]^+$ = 569.24.

Step 5: $LiOH \cdot H_2O$ (20 mg, 0.48 mmol) is added to a mix. of benzyl (*R*)-3-(3-(benzo[b]thiophen-3-yl)-2-((*tert*-butoxycarbonyl)amino)propoxy)quinoline-4-carboxylate (136 mg, 0.24 mmol) in 2:1 THF: H_2O (3 mL) and the RM is heated to 50°C for 16 h. The RM is concentrated in vacuo and the residue is partitioned between 1M aq. HCl and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to give the title compound as a yellow solid. LC-MS B: t_R = 0.96 min; $[M+H]^+$ = 479.23.

Benzyl (*R*)-3-(2-amino-3-phenylpropoxy)-5-fluoroquinoline-4-carboxylate dihydrochloride (B-1.27)

Step 1: 4-Fluoroindoline-2,3-dione (4.8 g, 27.6 mmol) is added to a RT soln. of KOH (18.6 g, 331 mmol) in water (80 mL) followed by bromopyruvic acid (6.47 g, 38 mmol) and the RM is stirred for 16 h. Additional KOH (4.6 g, 83 mmol) and bromopyruvic acid (2.88 g, 17.3 mmol) are added and stirring is continued for another 16 h. The RM is poured into 1M aq. HCl and the resulting precipitate is collected by filtration and washed with water and EtOAc and then dried in a vacuum oven at 40°C to give 5-fluoro-3-hydroxyquinoline-4-carboxylic acid as a brown solid. LC-MS B: t_R = 0.39 min; $[M+H]^+$ = 208.09.

Steps 2-4: The title compound is prepared from 5-fluoro-3-hydroxyquinoline-4-carboxylic acid following the sequence of reactions as described for B-1.1. LC-MS B: $t_R = 0.83$ min; $[M+H]^+ = 431.14$.

General method 2 for the synthesis of building blocks B

5 Methyl (*R*)-2-(2-amino-3-phenylpropoxy)-6-fluorobenzoate hydrochloride (B-2.1)

Step 1: Methyl (*R*)-2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-6-fluorobenzoate is prepared from methyl 2-fluoro-6-hydroxybenzoate and *tert*-butyl (*R*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 step 2. LC-MS J: $t_R = 2.28$ min; $[M-Boc+H]^+ = 304.1$.

Step 2: The title compound is prepared in analogy to the procedure described for B-1.1 step 3. LC-MS J: $t_R = 1.95$ min; $[M+H]^+ = 304.1$.

Listed in Table B-2 below are building blocks B that are prepared in analogy to the 2-step sequence described above for B-2.1. In cases where the HCl salt is highly hygroscopic, the amine is subjected to a basic workup to liberate its free base.

Table B-2

No.	Starting Material	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
B-2.2	Ethyl 2-chloro-6-hydroxybenzoate	Ethyl (<i>R</i>)-2-(2-amino-3-phenylpropoxy)-6-chlorobenzoate hydrochloride	2.05 J	334.1
B-2.3	Ethyl 4-hydroxy-2-methylthiazole-5-carboxylate	Ethyl (<i>R</i>)-4-(2-amino-3-phenylpropoxy)-2-methylthiazole-5-carboxylate hydrochloride	2.00 J	321.1
B-2.4	Methyl 3-hydroxythiophene-2-carboxylate	Methyl (<i>R</i>)-3-(2-amino-3-phenylpropoxy)thiophene-2-carboxylate hydrochloride	1.94 J	292.0
B-2.13	Methyl 2-hydroxy-5-methoxybenzoate	Methyl (<i>R</i>)-2-(2-amino-3-phenylpropoxy)-5-methoxybenzoate hydrochloride	0.73 B	316.31
B-2.14	Ethyl 2-hydroxybenzoate	Ethyl (<i>R</i>)-2-(2-amino-3-phenylpropoxy)benzoate hydrochloride	0.99 I	300.29

Methyl (*R*)-6-(2-amino-3-phenylpropoxy)-2-methylbenzo[d]oxazole-7-carboxylate hydrochloride (B-2.5)

Step 1: Nitric acid (0.36 mL, 6.0 mmol) is carefully added to a 0°C soln. of methyl 2,6-dihydroxybenzoate (1.0 g, 6.0 mmol) in acetic acid (10 mL) and the RM is warmed to RT and stirred for 1 h. The RM is poured into cold water and the precipitate collected by filtration and washed with additional cold water before being dried in vacuo to give methyl 2,6-dihydroxy-3-nitrobenzoate as a pink solid. LC-MS B: t_R = 0.75 min; No ionisation. ^1H NMR (DMSO) δ : 11.73 (s, 1 H), 10.94 (s, 1 H), 8.05 (d, J = 9.4 Hz, 1 H), 6.60 (d, J = 9.4 Hz, 1 H), 3.81 (s, 3 H).

Step 2: 4M HCl in dioxane (1.45 mL, 5.8 mmol) is added to a suspension of methyl 2,6-dihydroxy-3-nitrobenzoate (500 mg, 2.3 mmol) in triethyl ortho acetate (13.5 mL, 72 mmol) and the RM is evacuated/purged with N_2 (3x) before 10% Pd/C (173 mg, 7 mol%) is added. The RM is evacuated/purged with H_2 (3x) and stirred under a H_2 atm for 16 h. The RM is filtered through a pad of celite and the filtrate concentrated in vacuo to give methyl 6-hydroxy-2-methylbenzo[d]oxazole-7-carboxylate as a yellow solid. LC-MS B: t_R = 0.78 min; $[\text{M}+\text{H}]^+$ = 208.32. ^1H NMR (DMSO) δ : 10.69 (s, 1 H), 7.76 (d, J = 8.7 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 1 H), 3.97 (s, 3 H), 2.60 (s, 3 H).

Steps 3-4: The title compound is prepared from methyl 6-hydroxy-2-methylbenzo[d]oxazole-7-carboxylate following the sequence of reactions described for B-2.1. LC-MS B: t_R = 0.69 min; $[\text{M}+\text{H}]^+$ = 341.35. Note: Title compound is unstable and should not be stored for prolonged periods.

Methyl (*R*)-6-(2-amino-3-phenylpropoxy)benzo[d]oxazole-7-carboxylate hydrochloride (B-2.6)

The title compound is prepared following the sequence of reactions described for B-2.5, substituting triethyl ortho acetate for trimethyl ortho formate in step 2. LC-MS B: t_R = 0.66 min; $[\text{M}+\text{H}]^+$ = 327.27. Note: Title compound is unstable and should not be stored for prolonged periods.

Methyl (*R*)-6-(2-amino-3-phenylpropoxy)-1-methyl-1H-benzo[d]imidazole-7-carboxylate dihydrochloride (B-2.7)

Step 1: Methylamine (2 M in MeOH, 7.9 mL, 15.8 mmol) is added to a RT soln. of methyl 2,6-difluoro-3-nitrobenzoate (5.0 g, 22.6 mmol) in MeOH (40 mL) and the RM is stirred for 1 h. The RM is concentrated in vacuo and the residue suspended in a mix. of PrOH and water before being filtered. The filter cake is washed with water and dried before being purified by FC (eluting with 0% to 20% EtOAc in hept) to give methyl 6-fluoro-2-(methylamino)-3-nitrobenzoate as a yellow solid. LC-MS B: t_R = 0.87 min; $[\text{M}+\text{H}]^+$ = 229.38.

Step 2: NaH 60% Dispersion in mineral oil (549 mg, 13.7 mmol) is added portionwise to a 0°C soln. of Boc-D-phenylalaninol (2.93 g, 11.4 mmol) in THF (60 mL) and after stirring for 10 min a soln. of methyl 6-fluoro-2-(methylamino)-3-nitrobenzoate (2.4 g, 10.4 mmol) in THF (10 mL) is added. The RM is warmed to RT and stirred for 1 h before being cooled back to 0°C and quenched with water. The THF is evaporated in vacuo and the remaining aqueous phase is diluted with additional water and extracted with EtOAc (3x). The combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 30% EtOAc in hept) to give methyl (*R*)-6-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-(methylamino)-3-nitrobenzoate as a yellow solid. LC-MS B: t_R = 1.09 min; $[\text{M}+\text{H}]^+$ = 460.26.

Steps 3-4: The title compound is prepared from methyl (*R*)-6-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-(methylamino)-3-nitrobenzoate following the hydrogenation/cyclisation followed by Boc-cleavage sequence of reactions described for B-2.6. LC-MS B: t_R = 0.54 min; $[M+H]^+$ = 340.41.

Methyl (*R*)-6-(2-amino-3-phenylpropoxy)-2-methylbenzo[d]oxazole-5-carboxylate hydrochloride (B-2.8)

- 5 The title compound is prepared from methyl 2,4-dihydroxybenzoate following the sequence of reactions described for B-2.5. LC-MS B: t_R = 0.70 min; $[M+H]^+$ = 341.39.

Methyl (*R*)-6-(2-amino-3-phenylpropoxy)-1,2-dimethyl-1H-benzo[d]imidazole-7-carboxylate hydrochloride (B-2.9)

- 10 The title compound is prepared from methyl 2,6-difluoro-3-nitrobenzoate following the sequence of reactions described for B-2.7, using triethyl ortho acetate instead of trimethyl ortho formate. LC-MS B: t_R = 0.50 min; $[M+H]^+$ = 354.45.

Ethyl (*R*)-2-(2-amino-3-phenylpropoxy)imidazo[1,2-*a*]pyridine-3-carboxylate dihydrochloride (B-2.10)

- Step 1:** 2-Aminopyridine (7.08 g, 75 mmol) is suspended in diethyl bromomalonate (38.5 mL, 226 mmol) and heated to 100 °C for 1.5 h. The RM is partitioned between water and EtOAc and the layers are separated. The org. phase is discarded and the aq. phase is freeze dried to give the crude product that is purified by prep. HPLC (basic) to give
15 ethyl 2-hydroxyimidazo[1,2-*a*]pyridine-3-carboxylate as a cream solid. LC-MS J: t_R = 0.41 min; $[M+H]^+$ = 207.1.

Steps 2-3: The title compound is prepared from ethyl 2-hydroxyimidazo[1,2-*a*]pyridine-3-carboxylate in analogy to the procedure described for B-2.1. LC-MS I: t_R = 0.91 min; $[M+H]^+$ = 340.28.

Methyl (*R*)-5-(2-amino-3-phenylpropoxy)-2,3-dihydrobenzofuran-4-carboxylate hydrochloride (B-2.11)

- Steps 1-2:** A suspension of methyl 2,5-dihydroxybenzoate (1.02 g, 6.1 mmol) and $MgSO_4$ (2.1 g, 17.5 mmol) in Et_2O
20 (10 mL) is purged with argon for 10 min before Ag_2O (3.46 g, 14.9 mmol) is added and the RM is stirred for 16 h. The RM is filtered over a pad of celite and the filtrate is concentrated in vacuo to give the crude product methyl 3,6-dioxocyclohexa-1,4-diene-1-carboxylate that is re-dissolved in PhMe (50 mL) before *n*-butyl vinyl ether (1.7 mL, 13.1 mmol) is added and the RM is heated to 45°C for 19 h. The RM is poured into water and the phases are separated. The aq. phase is extracted with EtOAc (3x) and the combined org. phases are washed with brine, dried over Na_2SO_4 ,
25 filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 1% to 50% EtOAc in hept) to give methyl 2-butoxy-5-hydroxy-2,3-dihydrobenzofuran-4-carboxylate as a white solid. LC-MS J: t_R = 2.23 min; $[M+H]^+$ = 267.1.

- Step 3:** TFA (0.9 mL, 11.75 mmol) is added to a soln. of methyl 2-butoxy-5-hydroxy-2,3-dihydrobenzofuran-4-carboxylate (761 mg, 2.86 mmol) in PhMe (25 mL) and the RM is heated to reflux for 4.5 h. The RM is poured into
30 water and the phases are separated. The aq. phase is extracted with EtOAc (3x) and the combined org. phases are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 50% EtOAc in hept) to give methyl 5-hydroxybenzofuran-4-carboxylate as a white solid. LC-MS J: t_R = 2.00 min; No ionisation. ^1H NMR (DMSO) δ : 10.83 (bs, 1 H), 8.12 (d, J = 2.2 Hz, 1 H), 7.82 (d, J = 8.9 Hz, 1 H), 7.19 (d, J = 2.1 Hz, 1 H), 6.95 (d, J = 8.9 Hz, 1 H), 4.00 (s, 3 H).

Step 4: A soln. of methyl 5-hydroxybenzofuran-4-carboxylate (395 mg, 2.06 mmol) and AcOH (1.3 mL, 22.5 mmol) in EtOAc (20 mL) is evacuated/purged with N₂ (3x) before 10% Pd/C (109 mg, 5 mol%) is added. The RM is evacuated/purged with H₂ (3x) and stirred under a H₂ atm for 21 h. The RM is filtered through a pad of celite and the filtrate concentrated in vacuo to give methyl 6-hydroxy-2-methylbenzo[d]oxazole-7-carboxylate as a white solid. LC-MS F: t_R = 1.88 min; [M+H]⁺ = 195.0.

Steps 5-6: The title compound is prepared from methyl 5-hydroxy-2,3-dihydrobenzofuran-4-carboxylate in analogy to the procedure described for B-2.1. LC-MS J: t_R = 1.97 min; [M+H]⁺ = 328.1.

Methyl (R)-3-(2-amino-3-phenylpropoxy)-6-methoxypicolinate hydrochloride (B-2.12)

Step 1: Cs₂CO₃ (2.4 g, 7.4 mmol) and BnBr (1.31 mL, 11.1 mmol) are added to a RT soln. of methyl 3-hydroxypicolinate (0.94 g, 6.1 mmol) in DMF (20 mL) and the RM is heated to 70°C for 2 h. The RM is concentrated in vacuo and the residue is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 30% to 45% EtOAc in hept) to give methyl 3-(benzyloxy)picolinate as a brown oil. LC-MS J: t_R = 1.86 min; [M+H]⁺ = 244.0.

Step 2: mCPBA (1.51 g, 6.1 mmol) is added to a 0°C soln. of methyl 3-(benzyloxy)picolinate (1.19 g, 4.9 mmol) in DCM (10 mL) and the RM is warmed to RT and stirred for 16 h. The RM is partitioned between sat. aq. NaHSO₃ and DCM and extracted. The layers are separated, and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with sat. aq. NaHCO₃, dried over Na₂SO₄, filtered and evaporated in vacuo to give 3-(benzyloxy)-2-(methoxycarbonyl)pyridine 1-oxide as a brown solid. LC-MS J: t_R = 1.72 min; [M+H]⁺ = 260.0.

Step 3: Ac₂O (7.0 mL, 74.2 mmol) is added to 3-(benzyloxy)-2-(methoxycarbonyl)pyridine 1-oxide (1.27 g, 4.9 mmol) and the RM is heated to 100°C for 1 h. Additional Ac₂O (7 mL, 74.2 mmol) is added and heating continued for 2 h. EtOH (10 mL) is added and the RM is heated to reflux for 1 h before being cooled to RT overnight. The RM is concentrated in vacuo and the residue azeotroped with PhMe (1x) before 2M NaOH in MeOH (10 mL) is added and the RM is heated to 80°C for 3 h. The MeOH is evaporated in vacuo and the remaining aq. is acidified with 1M HCl before being extracted with DCM (4x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 3-(benzyloxy)-6-hydroxypicolinic acid as a brown solid. LC-MS G: t_R = 2.74 min; [M+H]⁺ = 246.0.

Step 4: Ag₂CO₃ (4.5 g, 16.3 mmol) and MeI (0.56 mL, 9.0 mmol) are added to a suspension of 3-(benzyloxy)-6-hydroxypicolinic acid (1.0 g, 4.1 mmol) in acetone (60 mL) and the RM is heated to reflux for 2 h. The RM is cooled to RT and acidified with 1 M HCl before being concentrated in vacuo. The residue is partitioned between water and DCM and extracted. The layers are filtered and separated, and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 10% to 70% EtOAc in hept) to give methyl 3-(benzyloxy)-6-methoxypicolinate as a colourless oil. LC-MS J: t_R = 1.98 min; [M+H]⁺ = 274.2.

Step 5: A soln. of methyl 3-(benzyloxy)-6-methoxypicolinate (847 mg, 2.94 mmol) in EtOH (20 mL) is evacuated/purged with N₂ (3x) before 10% Pd/C (157 mg, 5 mol%) is added. The RM is evacuated/purged with H₂ (3x) and stirred under a H₂ atm for 2 h. The RM is filtered through a pad of celite and the filtrate concentrated in vacuo to give methyl 3-hydroxy-6-methoxypicolinate as a white solid. LC-MS J: t_R = 1.48 min; No ionisation.

- 5 **Steps 6-7:** The title compound is prepared from methyl 3-hydroxy-6-methoxypicolinate in analogy to the procedure described for B-2.1. LC-MS J: t_R = 1.85 min; [M+H]⁺ = 317.2.

Methyl (R)-5-(2-amino-3-phenylpropoxy)-2-methylbenzo[d]oxazole-4-carboxylate hydrochloride (B-2.15)

The title compound is prepared from methyl 2,5-dihydroxybenzoate following the sequence of reactions described for B-2.5. LC-MS D: t_R = 0.63 min; [M+H]⁺ = 341.37.

- 10 **Methyl (R)-3-(2-amino-3-phenylpropoxy)isoquinoline-4-carboxylate dihydrochloride (B-2.16)**

Step 1: NBS (1.30 g, 7.3 mmol) is added portionwise to a 0°C soln. of isoquinolin-3-amine (1.0 g, 6.9 mmol) in DCM (20 mL) and EtOH (10 mL) and the RM is stirred for 30 min before being warmed to RT overnight. The RM is concentrated in vacuo and the residue is triturated with DCM and filtered. The filtrate is concentrated in vacuo and the residue purified by FC (eluting with 25% to 40% EtOAc in hept) to give 4-bromoisoquinolin-3-amine as a brown solid.

- 15 Subsequent trituration with Pr₂O further enhances its purity. LC-MS J: t_R = 1.84 min; [M+H]⁺ = 223.0.

Step 2: A soln. of 4-bromoisoquinolin-3-amine (796 mg, 3.6 mmol) and DIPEA (1.87 mL, 10.7 mmol) in DMF (10 mL) and MeOH (5 mL) is evacuated/purged with CO (3x) before Pd(dppf)Cl₂ (261 mg, 0.36 mmol) is added. The RM is evacuated/purged with CO (3x) and stirred under a CO atm at 75°C for 20 h. The RM is cooled to RT and concentrated in vacuo and the residue is partitioned between water and EtOAc and extracted. The layers are separated, and the

20 aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give methyl 3-aminoisoquinoline-4-carboxylate as a yellow solid. LC-MS J: t_R = 1.78 min; [M+H]⁺ = 203.1.

Step 3: A soln. of NaNO₂ (135 mg, 2.0 mmol) in H₂O (0.6 mL) is added to a 0°C suspension of methyl 3-aminoisoquinoline-4-carboxylate (330 mg, 1.63 mmol) in 2.5M aq. H₂SO₄ (4 mL, 10 mmol) and the RM is stirred for

25 1.5 h. The RM is neutralised by the addition of 2M aq. NaOH and extracted with EtOAc (4x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give methyl 3-hydroxyisoquinoline-4-carboxylate as a yellow solid. LC-MS F: t_R = 1.52 min; [M+H]⁺ = 204.0.

Steps 4-5: The title compound is prepared from methyl 3-hydroxyisoquinoline-4-carboxylate following the sequence of reactions described for B-2.1. LC-MS J: t_R = 1.97 min; [M+H]⁺ = 337.2.

- 30 **Methyl (R)-6-(2-amino-3-phenylpropoxy)imidazo[1,2-a]pyridine-5-carboxylate dihydrochloride (B-2.17)**

Step 1: Br₂ (0.81 mL, 15.7 mmol) is added dropwise to a 0°C soln. of methyl-3-hydroxypicolinate (2.41 g, 15.7 mmol) in water (110 mL) and the RM is warmed to RT and stirred overnight. The RM is quenched with 40% aq. sodium bisulfite soln. and extracted with DCM (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give methyl 6-bromo-3-hydroxypicolinate as a white solid. LC-MS G: t_R = 3.19 min;

35 [M+H]⁺ = 231.9.

Step 2: Methyl (R)-6-bromo-3-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)picolinate is prepared from methyl 6-bromo-3-hydroxypicolinate and *tert*-butyl (R)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 step 2. LC-MS F: t_R = 2.16 min; $[M+H-Bu]^+$ = 409.0.

Step 3: Pd₂(dba)₃ (483 mg, 0.53 mmol) and XPhos (201 mg, 0.42 mmol) are added to a RT mix. of methyl (R)-6-bromo-3-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)picolinate (5.0 g, 10.5 mmol), benzyl carbamate (1.67 g, 11.1 mmol) and Cs₂CO₃ (5.15 g, 15.8 mmol) in dioxane (130 mL) and the RM is heated to 95°C and stirred for 48 h. The RM is cooled to RT, filtered and the filtrate is concentrated in vacuo before being purified by FC (eluting with 0% to 40% EtOAc in hept) to give methyl (R)-6-(((benzyloxy)carbonyl)amino)-3-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)picolinate as an orange solid. LC-MS F: t_R = 2.24 min; $[M+H]^+$ = 536.2.

Step 4: A soln. of methyl (R)-6-(((benzyloxy)carbonyl)amino)-3-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)picolinate (1.43 g, 2.19 mmol) in EtOH (20 mL) is purged with N₂/vacuum (3x) before 10% Pd/C (70 mg, 0.07 mmol) is added. After inertising another three times a H₂ balloon is connected and the RM is stirred at 55°C for 1 h. The mix. is filtered over a celite plug rinsing with EtOH. The filtrate is concentrated to give methyl (R)-6-amino-3-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)picolinate as a yellow oil. LC-MS J: t_R = 2.00 min; $[M+H]^+$ = 402.2.

Step 5: 50% aq. 2-Chloroacetaldehyde (0.475 mL, 3.74 mmol) is added to a mix. of methyl (R)-6-amino-3-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)picolinate (0.50 g, 1.25 mmol) and NaHCO₃ (209 mg, 2.49 mmol) in EtOH (15 mL) and the RM is heated to 70°C and stirred for 5 h. The RM is concentrated in vacuo and the residue is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 50% to 100% EtOAc in hept) to give methyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)imidazo[1,2-a]pyridine-5-carboxylate as a white solid. LC-MS I: t_R = 1.01 min; $[M+H]^+$ = 426.52.

Step 6: The title compound is prepared in analogy to the procedure described for B-1.1 step 3. LC-MS J: t_R = 1.83 min; $[M+H]^+$ = 326.2.

25

General method 3 for the synthesis of building blocks B

Ethyl (R)-4-(2-amino-3-phenylpropoxy)nicotinate dihydrochloride (B-3.1)

Step 1: H₂SO₄ (1.86 mL, 34.9 mmol) is added dropwise to a 0°C soln. of 4-hydroxynicotinic acid (5.0 g, 34.9 mmol) in EtOH (50 mL) and the RM is heated to reflux for 3 d. After concentration in vacuo, sat. aq. NaHCO₃ is carefully added to the residue and the solid filtered off and dried to give ethyl 4-hydroxynicotinate as an off-white solid. LC-MS D: t_R = 0.37 min; $[M+H]^+$ = 168.05.

Step 2: Ethyl (R)-4-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)nicotinate is prepared from ethyl 4-hydroxynicotinate and *tert*-butyl (R)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 step 2. LC-MS J: t_R = 2.17 min; $[M+H]^+$ = 401.2.

Step 3: The title compound is prepared in analogy to the procedure described for B-1.1 step 3. LC-MS B: t_R = 0.52 min; $[M+H]^+$ = 301.28.

Listed in Table B-3 below are building blocks B that are prepared in analogy to the 3-step sequence described above for **B-3.1**. In cases where the HCl salt is highly hygroscopic, the amine is subjected to a basic workup to liberate its free base.

Table B-3

No.	Starting Material	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
B-3.2	3-Hydroxyisonicotinic acid	Ethyl (<i>R</i>)-3-(2-amino-3-phenylpropoxy)isonicotinate dihydrochloride	1.88 J	301.1

General method 4 for the synthesis of building blocks B

Benzyl (*R*)-2-(2-amino-3-phenylpropoxy)-6-(trifluoromethoxy)benzoate hydrochloride (B-4.1)

Step 1: A soln. of 3-(trifluoromethoxy)phenol (5.0 g, 28.1 mmol) in THF (40 mL) is added dropwise to a RT suspension of NaH (1.35 g, 33.7 mmol) in THF (50 mL) and the resulting mix. is stirred for 15 min before methoxymethyl bromide (2.98 mL, 36.5 mmol) is added dropwise. After stirring for 1 h the RM is quenched by the addition of sat. aq. Na_2CO_3 , diluted with some water, and extracted with Pr_2O . The org. phase is washed with $NaHCO_3$, brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to give 1-(methoxymethoxy)-3-(trifluoromethoxy)benzene as a colourless oil. LC-MS J: t_R = 2.13 min; No ionisation.

Step 2: A soln. of 1-(methoxymethoxy)-3-(trifluoromethoxy)benzene (3.0 g, 13.5 mmol) in THF (7 mL) is added dropwise to a $-78^\circ C$ soln. of $sBuLi$ (1.4 M in cyclohexane, 12.54 mL, 17.55 mmol) in a mix. of THF (10 mL) and cyclohexane (15 mL) and the RM is stirred for 1.5 h. The RM is quenched onto freshly ground dry ice and then warmed to RT. After stirring for 15 min, a few drops of MeOH are added before the RM is concentrated in vacuo. The intermediate lithium carboxylate is dissolved in DMF (20 mL) before $KHCO_3$ (0.41 g, 4.1 mmol) and benzyl bromide (1.93 mL, 16.2 mmol) are added and the RM is stirred for 18 h. The RM is filtered and the filtrate concentrated in vacuo. The residue is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 15% EtOAc in hept) to give benzyl 2-(methoxymethoxy)-6-(trifluoromethoxy)benzoate as a colourless oil. LC-MS J: t_R = 2.24 min; $[M+H]^+$ = 357.1.

Step 3: TFA (2 mL, 26.1 mmol) is added to a soln. of benzyl 2-(methoxymethoxy)-6-(trifluoromethoxy)benzoate (1.39 g, 3.9 mmol) in DCM (20 mL) and the resulting mix. is stirred for 1 h. The RM is concentrated in vacuo and the residue is co-evaporated with DCM (2x) to give benzyl 2-hydroxy-6-(trifluoromethoxy)benzoate as a white solid. LC-MS J: t_R = 2.22 min; $[M-H]^-$ = 311.0.

Step 4: Benzyl (*R*)-2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-6-(trifluoromethoxy)benzoate is prepared from benzyl 2-hydroxy-6-(trifluoromethoxy)benzoate and *tert*-butyl (*R*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 Step 2. LC-MS J: t_R = 2.50 min; $[M-Boc+H]^+$ = 446.1.

Step 5: The title compound is prepared in analogy to the procedure described for B-1.1 Step 3. LC-MS J: t_R = 2.30 min; $[M+H]^+$ = 446.1.

Listed in Table B-4 below are building blocks B that are prepared in analogy to the 5-step sequence described above for **B-4.1**. In cases where the HCl salt is highly hygroscopic, the amine is subjected to a basic workup to liberate its free base.

Table B-4

No.	Starting Material	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
B-4.2	Benzo[d][1,3]dioxol-5-ol	Benzyl (<i>R</i>)-5-(2-amino-3-phenylpropoxy)benzo[d][1,3]dioxole-4-carboxylate hydrochloride	2.09 J	406.1
B-4.3	Benzo[d][1,3]dioxol-2,2-d2-5-ol	Benzyl (<i>R</i>)-5-(2-amino-3-phenylpropoxy)benzo[d][1,3]dioxole-4-carboxylate-2,2-d2 hydrochloride	2.16 J	408.2
B-4.4	2,2-Difluorobenzo[d][1,3]dioxol-5-ol	Benzyl (<i>R</i>)-5-(2-amino-3-phenylpropoxy)-2,2-difluorobenzo[d][1,3]dioxole-4-carboxylate hydrochloride	2.31 J	442.1

Ethyl (*R*)-4-(2-amino-3-phenylpropoxy)-2-methylnicotinate dihydrochloride (B-4.5)

Step 1: NaH (370 mg, 9.26 mmol) is added to a 0°C soln. of 2-chloro-4-hydroxypyridine (1.0 g, 7.72 mmol) in DMF (20 mL) and the RM is warmed to RT and stirred for 15 min before being cooled back to 0°C. Chloromethyl methyl ether (1.17 mL, 15.4 mmol) is added and the RM is warmed to RT and stirred for 1 h. The RM is quenched by the addition of sat. aq. Na_2CO_3 , diluted with some water, and extracted with Et_2O . The org. phase is washed with $NaHCO_3$, brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to give the crude product that is purified by FC (eluting with 20% to 100% EtOAc in hept) to give 2-chloro-4-(methoxymethoxy)pyridine as a colourless oil. LC-MS I: t_R = 0.72 min; $[M+H]^+$ = 174.09.

Step 2: nBuLi (2.5 M in hex, 1.18 mL, 2.94 mmol) is added to a -78°C soln. of 2-chloro-4-(methoxymethoxy)pyridine (413 mg, 2.36 mmol) in THF (7 mL) and after stirring for 30 min the RM is added via cannula to a -78°C soln. of ethyl chloroformate (0.23 mL, 2.36 mmol) in THF (4 mL) and stirred for 1 h at -78°C. The RM is warmed to RT and stirred for 2 h before being quenched with $NaHCO_3$ and extracted with EtOAc (3x). The combined org. extracts are washed

with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 10% to 70% EtOAc in hept) to give ethyl 2-chloro-4-(methoxymethoxy)nicotinate as a yellow oil. LC-MS B: t_R = 0.82 min; [M+H]⁺ = 246.29.

Step 3: ZnMe₂ (2 M in PhMe, 0.46 mL, 0.93 mmol) is added dropwise to a RT soln. of ethyl 2-chloro-4-(methoxymethoxy)nicotinate (120 mg, 0.46 mmol), and Pd(dppf)Cl₂.DCM (3.8 mg, 0.005 mmol) in dioxane (2 mL) and the RM is heated to 90°C and stirred for 1 h. The RM is concentrated in vacuo and the residue is partitioned between water and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by prep. HPLC (basic) to give ethyl 4-(methoxymethoxy)-2-methylnicotinate as a colourless oil. LC-MS I: t_R = 0.71 min; [M+H]⁺ = 226.18.

Step 4: 4M HCl in dioxane (0.55 mL) is added to a RT soln. of ethyl 4-(methoxymethoxy)-2-methylnicotinate (50 mg, 0.22 mmol) in dioxane (1 mL) and the RM is stirred for 16 h. The volatiles are removed in vacuo and the residue is suspended in Et₂O and concentrated to give ethyl 4-hydroxy-2-methylnicotinate hydrochloride as a white solid. LC-MS I: t_R = 0.30 min; [M+H]⁺ = 182.23.

Step 5: Ethyl (*R*)-4-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methylnicotinate is prepared from ethyl 4-hydroxy-2-methylnicotinate hydrochloride and *tert*-butyl (*R*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 Step 2. LC-MS B: t_R = 0.82 min; [M+H]⁺ = 415.41.

Step 6: The title compound is prepared in analogy to the procedure described for B-1.1 Step 3. LC-MS B: t_R = 0.52 min; [M+H]⁺ = 315.32.

20 **Benzyl (*R*)-6-(2-amino-3-phenylpropoxy)-2,3-dihydrobenzofuran-7-carboxylate hydrochloride (B-4.6)**

Step 1: Benzyl bromide (8.9 mL, 74.6 mmol) and K₂CO₃ (14.7 g, 107 mmol) are added to a RT soln. of 6-hydroxybenzofuran-3(2H)-one (8.0 g, 53.3 mmol) in DMF (80 mL) and the RM is stirred for 2 h. The RM is poured into cold water and the precipitate is collected by filtration and dried at 40°C in a vacuum oven for 48 h. 6-(benzyloxy)benzofuran-3(2H)-one is isolated as an orange solid. LC-MS J: t_R = 2.03 min; [M+H]⁺ = 241.0.

Step 2: 6-(benzyloxy)Benzofuran-3(2H)-one (11.25 g, 46.8 mmol) is added portionwise to a 0°C soln. of AlCl₃ (6.87 g, 51.5 mmol) and LiAlH₄ (19.5 mL, 46.8 mmol, 2.4M in THF) in THF (200 mL) and the RM is warmed to RT and stirred for 2 h. The RM is cooled to 0°C and quenched with 0.5M aq. NaOH (400 mL) and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 6-(benzyloxy)benzofuran as an orange oil. GC-MS MC: t_R = 4.74 min; [M]⁺ = 224.1. Note: Contains 6-(benzyloxy)-2,3-dihydrobenzofuran as a minor side product.

Step 3: 2,3-Dihydrobenzofuran-6-ol is prepared from 6-(benzyloxy)benzofuran following the procedure described for B-2.11 step 4. GC-MS MC: t_R = 3.38 min; [M]⁺ = 136.1.

Steps 4-8: The title compound is prepared from 2,3-dihydrobenzofuran-6-ol in analogy to the procedure described for B-4.1. LC-MS J: t_R = 2.30 min; [M+H]⁺ = 446.1.

Benzyl (R)-6-(2-amino-3-phenylpropoxy)quinoline-5-carboxylate dihydrochloride (B-4.7)

Step 1: A soln. of Br₂ (0.37 mL, 7.2 mmol) in AcOH (5 mL) is added to a RT soln. of quinolin-6-ol (1.0 g, 6.9 mmol) and NaOAc (0.62 g, 7.6 mmol) in AcOH (15 mL) and the RM is stirred for 30 min. The RM is quenched with sat. aq. NaHSO₃ and neutralised with 2M aq. NaOH and Na₂CO₃ before being extracted with EtOAc (2x). The combined org. extracts are washed with brine and concentrated in vacuo. The residue is taken up in PhMe and concentrated in vacuo (2x) to give 5-bromoquinolin-6-ol as a brown solid. LC-MS J: t_R = 1.16 min; [M+H]⁺ = 221.9.

Step 2: 5-Bromo-6-(methoxymethoxy)quinoline is prepared from 5-bromoquinolin-6-ol in analogy to the procedure described for B-4.1 step 1. LC-MS J: t_R = 2.30 min; [M+H]⁺ = 446.1.

Step 3: nBuLi (1.6 M in hex, 5.7 mL, 9.1 mmol) is added dropwise to a -78°C soln. of 5-bromo-6-(methoxymethoxy)quinoline (2.45 g, 9.1 mmol) in THF (50 mL) and the RM is stirred for 30 min. The RM is quenched with freshly ground dry ice (12 g, 273 mmol) and then warmed to RT and stirred for 30 min. The RM is concentrated in vacuo and the intermediate lithium carboxylate is dissolved in DMF (30 mL) before benzyl bromide (1.3 mL, 11 mmol) is added and the RM is heated to 60°C for 10 min. The RM is cooled to RT and partitioned between sat. aq. NaHCO₃ and EtOAc and extracted. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 30% to 100% EtOAc in hept) to give benzyl 6-(methoxymethoxy)quinoline-5-carboxylate as a yellow oil. LC-MS J: t_R = 2.02 min; [M+H]⁺ = 324.1.

Steps 4-6: The title compound is prepared from benzyl 6-(methoxymethoxy)quinoline-5-carboxylate in analogy to the procedure described for B-4.1 steps 3-5. LC-MS B: t_R = 0.77 min; [M+H]⁺ = 413.16.

Benzyl (R)-7-(2-amino-3-phenylpropoxy)quinoline-8-carboxylate dihydrochloride (B-4.8)

Step 1: DCM (40 mL) is added to a soln. of quinolin-7-ol (10 g, 68.9 mmol) in AcOH (20 mL) and the resulting suspension is cooled to 0°C before a soln. of Br₂ (3.87 mL, 75 mmol) in AcOH (20 mL) is added slowly and the RM is stirred for 2 h. The suspension is diluted with EtOAc and filtered and the filter residue is washed with EtOAc and Et₂O and dried in vacuo at 40°C to give 8-bromoquinolin-7-ol hydrobromide as a brown solid. LC-MS J: t_R = 0.27 min; [M+H]⁺ = 225.9.

Steps 2-6: The title compound is prepared from 8-bromoquinolin-7-ol hydrobromide in analogy to the procedure described for B-4.7 steps 2-6. LC-MS J: t_R = 2.07 min; [M+H]⁺ = 413.1.

Benzyl (R)-6-(2-amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxylate dihydrochloride (B-4.9)

The title compound is prepared from 3-fluoroquinolin-6-ol in analogy to the procedure described for B-4.7. LC-MS J: t_R = 2.16 min; [M+H]⁺ = 431.2.

Benzyl (R)-2-(2-amino-3-phenylpropoxy)-4-methoxynicotinate hydrochloride (B-4.10)

Step 1: Benzyl 2-fluoro-4-methoxynicotinate is prepared from 2-fluoro-4-methoxypyridine in analogy to the procedure described for B-4.7 step-3. LC-MS F: t_R = 1.96 min; [M+H]⁺ = 262.0.

Step 2: A soln. of KO^tBu (258 mg, 2.3 mmol) in THF (3.5 mL) is added to a 0°C soln. of benzyl 2-fluoro-4-methoxynicotinate (600 mg, 2.3 mmol) and *tert*-butyl (*R*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (577 mg, 2.3 mmol) in THF (20 mL) and the RM is warmed to RT and stirred for 30 min. The RM is concentrated in vacuo and residue is purified by FC (eluting with 10% to 45% EtOAc in hept) to give benzyl (*R*)-2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-4-methoxynicotinate as a colourless oil. LC-MS F: t_R = 2.30 min; $[M+H]^+$ = 493.1.

Step 3: The title compound is prepared from benzyl (*R*)-2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-4-methoxynicotinate in analogy to the procedure described for B-1.1 step 3. LC-MS F: t_R = 1.76 min; $[M+H]^+$ = 393.1.

Benzyl (*R*)-5-(2-amino-3-phenylpropoxy)-2-methoxyisonicotinate trifluoroacetate (B-4.11)

Step 1: 2-Methoxy-5-(methoxymethoxy)pyridine is prepared from 6-methoxypyridin-3-ol in analogy to the procedure described for B-4.1 step 1. LC-MS J: t_R = 1.67 min; $[M+H]^+$ = 170.1.

Steps 2-5: The title compound is prepared from 2-methoxy-5-(methoxymethoxy)pyridine in analogy to the procedure described for B-4.7 steps 3-6 substituting HCl for TFA in the Boc cleavage step. LC-MS J: t_R = 2.16 min; $[M+H]^+$ = 393.1.

Ethyl (*R*)-4-(2-amino-3-phenylpropoxy)-2-methoxy-6-methylnicotinate (B-4.12)

Step 1: 4-(Benzyloxy)-6-methylpyridin-2-ol is prepared from 6-methylpyridine-2,4-diol following the procedure described for B-4.6 step 1. LC-MS I: t_R = 0.71 min; $[2M+H]^+$ = 431.31.

Step 2: Mel (0.438 mL, 6.97 mmol) is added to a RT mix. of 4-(benzyloxy)-6-methylpyridin-2-ol (500 mg, 2.32 mmol) and Ag₂CO₃ (1.29 g, 4.65 mmol) in DCM (20 mL) and the RM is irradiated in a MW oven at 100°C for 1 h. The RM is filtered and the solids washed with DCM before the filtrate is concentrated in vacuo and the residue is purified by FC (eluting with 20% to 100% EtOAc in hept) to give 4-(benzyloxy)-2-methoxy-6-methylpyridine as a colourless oil. LC-MS I: t_R = 1.07 min; $[M+H]^+$ = 230.25.

Step 3: nBuLi (2.5 M in hex, 3.63 mL, 9.1 mmol) is added dropwise to a -78°C soln. of 4-(benzyloxy)-2-methoxy-6-methylpyridine (1.66 g, 7.3 mmol) in THF (25 mL) and the RM is stirred for 30 min before ethyl chloroformate (0.70 mL, 7.3 mmol) is added dropwise. The RM is warmed to RT and quenched by addition of sat. aq. NaHCO₃ and extracted with EtOAc. The layers are separated and the aq. phase is re-extracted with EtOAc (2x) and the combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 20% EtOAc in hept) to give ethyl 4-(benzyloxy)-2-methoxy-6-methylnicotinate as a colourless oil. LC-MS I: t_R = 1.11 min; $[M+H]^+$ = 302.29.

Steps 4-6: The title compound is prepared from ethyl 4-(benzyloxy)-2-methoxy-6-methylnicotinate in analogy to the procedure described for B-2.12 steps 5-7. Note: Boc-cleavage is performed using TFA instead of HCl and the title compound is isolated as its free base after a basic workup. LC-MS I: t_R = 0.97 min; $[M+H]^+$ = 345.32.

Ethyl (*R*)-4-(2-amino-3-phenylpropoxy)-2-(methoxy-d3)-6-methylnicotinate (B-4.13)

The title compound is prepared in analogy to the procedure described for B-4.12, substituting Mel by CD₃I in step 2. LC-MS I: t_R = 0.97 min; $[M+H]^+$ = 348.35.

Benzyl (R)-6-(2-amino-3-phenylpropoxy)-8-methylquinoline-5-carboxylate (B-4.14)

Step 1: Meldrum's acid (6.04 g, 41.1 mmol) and triethyl orthoformate (6.06 mL, 35.7 mmol) are added to a RT soln. of 4-methoxy-2-methylaniline (5.0 g, 35.7 mmol) in EtOH (50 mL) and the RM is heated to 80°C for 2h. The RM is cooled to RT and the precipitate is collected by filtration washing with EtOH and dried under HV to give 5-(((4-methoxy-2-methylphenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione as a white solid. LC-MS B: t_R = 0.90 min; $[M+H]^+$ = 292.13.

Step 2: 5-(((4-Methoxy-2-methylphenyl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.19 g, 28.1 mmol) is dissolved in Dowtherm A (50 mL) and heated to 250°C for 5 min. The RM is cooled to RT and diluted with Et₂O and the precipitate is collected by filtration and washed with Et₂O before being dried under HV to give 6-methoxy-8-methylquinolin-4-ol as a brown solid. LC-MS B: t_R = 0.58 min; $[M+H]^+$ = 190.21.

Step 3: Phosphorous tribromide (2.16 mL, 22.7 mmol) is added to a RT soln. of 6-methoxy-8-methylquinolin-4-ol (3.91 g, 20.7 mmol) in DMF (75 mL) and the RM is heated to 45°C for 1h. The RM is cooled to RT, diluted with water and the pH is adjusted to 8 by the addition of sat. aq. NaHCO₃ soln. The precipitate is collected by filtration and dissolved in EtOAc, washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 10% EtOAc in hept) to give 4-bromo-6-methoxy-8-methylquinoline as a white solid. LC-MS B: t_R = 0.82 min; $[M+H]^+$ = 254.03.

Step 4: nBuLi (1.6 M in hex, 35.7 mL, 57.1 mmol) is added dropwise to a -78°C soln. of 4-bromo-6-methoxy-8-methylquinoline (7.2 g, 28.5 mmol) in THF and the RM is stirred for 30 min. The reaction is quenched with sat. aq. NH₄Cl soln. and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 20% EtOAc in hept) to give 6-methoxy-8-methylquinoline as a yellow oil. LC-MS B: t_R = 0.49 min; $[M+H]^+$ = 174.26.

Step 5: 5-Bromo-6-methoxy-8-methylquinoline is prepared from 6-methoxy-8-methylquinoline in analogy to the procedure described for B-4.7 step 1. LC-MS B: t_R = 0.74 min; $[M+H]^+$ = 252.09.

Step 6: BBr₃ (1 M in DCM, 42.5 mL, 42.5 mmol) is added dropwise to a 0°C soln. of 5-Bromo-6-methoxy-8-methylquinoline (3.57 g, 14.2 mmol) in DCM (70 mL). The cooling bath is removed and the RM is stirred at RT for 2 h. The RM is carefully quenched into cold MeOH and concentrated in vacuo. The residue is co-evaporated with PhMe, EtOAc and DCM to give 5-bromo-8-methylquinolin-6-ol as a yellow solid. LC-MS B: t_R = 0.55 min; $[M+H]^+$ = 238.01.

Step 7: tert-Butyl (R)-1-((5-bromo-8-methylquinolin-6-yl)oxy)-3-phenylpropan-2-yl)carbamate is prepared from 5-bromo-8-methylquinolin-6-ol and tert-butyl (R)-1-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 Step 2. LC-MS B: t_R = 1.10 min; $[M+H]^+$ = 472.94.

Step 8: nBuLi (1.6 M in hex, 0.54 mL, 0.86 mmol) is added dropwise to a -78°C soln. of tert-butyl (R)-1-((5-bromo-8-methylquinolin-6-yl)oxy)-3-phenylpropan-2-yl)carbamate (185 mg, 0.39 mmol) in THF (2 mL) and the RM is stirred for 30 min before benzyl chloroformate (0.058 mL, 0.41 mmol) is added dropwise. The RM is warmed to RT and quenched by addition of sat. aq. NaHCO₃ and extracted with EtOAc. The layers are separated and the aq. phase is re-extracted with EtOAc (2x) and the combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in

vacuo. The crude product is purified by prep. HPLC (acidic) to give benzyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-8-methylquinoline-5-carboxylate as a white solid. LC-MS B: t_R = 1.11 min; $[M+H]^+$ = 527.33.

Step 9: TFA (4.0 mL, 52.2 mmol) is added to a RT soln. of benzyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-8-methylquinoline-5-carboxylate (550 mg, 1.04 mmol) in DCM (5 mL) and the RM is stirred for 1 h.

- 5 The RM is concentrated in vacuo and the residue is co-evaporated with DCM (2x) before being purified by prep. HPLC (Basic) to give the title compound as a yellow oil. LC-MS B: t_R = 0.78 min; $[M+H]^+$ = 427.23.

Benzyl (R)-4-(2-amino-3-phenylpropoxy)-2-methoxy-6-methylnicotinate (B-4.15)

Step 1: NaOH 16% aq. soln. (100 mL, 472 mmol) is added to a RT soln. of ethyl (R)-4-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxy-6-methylnicotinate (**B-4.12, step 5**) (42 g, 94.5 mmol) in MeOH (300 mL) and heated to 90°C for 4 h. The RM is cooled to RT and concentrated in vacuo. The remaining aq. phase is extracted with *i*PrOAc (3x) and the org. phases are discarded. The aq. phase is cooled to 0°C and acidified with 1M aq. HCl soln. and the precipitate is filtered and washed with water. The solids are dissolved in DCM and remaining water is separated before the org. phase is dried over Na₂SO₄, filtered and evaporated in vacuo to give (R)-4-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxy-6-methylnicotinic acid as a yellow oil. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 417.20.

- 15 **Step 2:** K₂CO₃ (1.33 g, 9.6 mmol) and BnBr (0.51 mL, 4.3 mmol) are added to a RT soln. of (R)-4-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxy-6-methylnicotinic acid (2.0 g, 4.8 mmol) in DMF (8 mL) and the RM is heated to 40°C and stirred for 4 h. The RM is poured into water and extracted with TBME (2x). The combined org. extracts are washed with water, dried over Na₂SO₄, filtered and evaporated in vacuo to give benzyl (R)-4-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxy-6-methylnicotinate as a colourless oil. LC-MS B: t_R = 1.17 min; $[M+H]^+$ = 507.24.

Step 3: The title compound is prepared from benzyl (R)-4-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxy-6-methylnicotinate in analogy to the procedure described for B-1.1 step 3. Note: Boc-cleavage is performed using TFA instead of HCl and the title compound is isolated as its free base after a basic workup. LC-MS B: t_R = 0.79 min; $[M+H]^+$ = 407.22.

- 25 **Benzyl (R)-4-(2-amino-3-phenylpropoxy)-6-methoxy-2-methylpyrimidine-5-carboxylate trifluoroacetate (B-4.16)**

Step 1: nBuLi (1.6 M in hex, 34.5 mL, 55.2 mmol) is added dropwise to a -78°C soln. of DIPEA (7.74 mL 55.2 mmol) in THF (35 mL) and the RM is stirred for 5 min. A soln. of 4,6-dichloro-2-methylpyrimidine (5.0 g, 30.7 mmol) in THF (40 mL) is added dropwise to the freshly prepared LDA and stirring is continued at -78°C for 1 h. The RM is quenched with freshly ground dry ice (20 g, 454 mmol) and stirred for 5 min before being warmed to RT over 20 min and stirred for a further 15 min. The RM is concentrated in vacuo to give lithium 4,6-dichloro-2-methylpyrimidine-5-carboxylate as a brown solid which is used further without purification. LC-MS J: t_R = 0.16 min; $[M-H]^-$ = 204.9.

- 30 **Step 2:** KHCO₃ (6.15 g, 61.4 mmol) and BnBr (10.95 mL, 92 mmol) are added to a RT soln. of lithium 4,6-dichloro-2-methylpyrimidine-5-carboxylate (6.54 g, 30.7 mmol) in DMF (50 mL) and the RM is stirred for 18 h. The RM is quenched by the addition of H₂O and brine and extracted with EtOAc (3x). The combined org. extracts are washed

with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 5% EtOAc in hept) to give benzyl 4,6-dichloro-2-methylpyrimidine-5-carboxylate as a colourless oil. LC-MS J: t_R = 2.13 min; [M+H]⁺ = 296.9.

Step 3: NaOMe (30% soln. in MeOH, 1.0 mL, 5.41 mmol) is added dropwise to a 0°C soln. of benzyl 4,6-dichloro-2-methylpyrimidine-5-carboxylate (2.68 g, 5.41 mmol) in THF (15 mL) and the RM is stirred for 1 h. The RM is quenched with 1M aq. HCl and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 7% EtOAc in hept) to give benzyl 4-chloro-6-methoxy-2-methylpyrimidine-5-carboxylate as a colourless oil. LC-MS J: t_R = 2.15 min; [M+H]⁺ = 293.1.

Step 4: NaH (60% dispersion in mineral oil, 128 mg, 3.21 mmol) is added to a 0°C soln. of allyl alcohol (0.21 mL, 3.1 mmol) in THF (10 mL) and the resulting suspension is stirred for 10 min before being slowly added to a -10°C soln. of benzyl 4-chloro-6-methoxy-2-methylpyrimidine-5-carboxylate in THF (15 mL) and the RM is stirred for 1 h. The RM is quenched with 1M aq. HCl and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 10% EtOAc in hept) to give benzyl 4-(allyloxy)-6-methoxy-2-methylpyrimidine-5-carboxylate as a colourless oil. LC-MS J: t_R = 2.24 min; [M+H]⁺ = 315.1.

Step 5: Pd(PPh₃)₄ (43.7 mg, 0.038 mmol) is added to a RT soln. (degassed) of benzyl 4-(allyloxy)-6-methoxy-2-methylpyrimidine-5-carboxylate (170 mg, 0.54 mmol) and 1,3-dimethylbarbituric acid (127 mg, 0.81 mmol) in MeCN (10 mL) and the RM is heated to 50°C for 2.5 h. The RM is filtered and concentrated to give benzyl 4-hydroxy-6-methoxy-2-methylpyrimidine-5-carboxylate as a grey solid. LC-MS J: t_R = 1.63 min; [M+H]⁺ = 275.1.

Steps 6&7: The title compound is prepared from benzyl 4-hydroxy-6-methoxy-2-methylpyrimidine-5-carboxylate in analogy to the procedure described for B-1.1 steps 2&3 substituting HCl for TFA in the Boc cleavage step. LC-MS J: t_R = 2.17 min; [M+H]⁺ = 408.2.

Ethyl (R)-4-(2-amino-3-phenylpropoxy)-2,6-dimethoxynicotinate (B-4.17)

Step 1: A soln. of benzyl alcohol (0.82 mL, 7.85 mmol) and KO^tBu (867 mg, 7.5 mmol) in DMF (4 mL) is added to a -78°C soln. of 2,4,6-trifluoropyridine (1.0 g, 7.14 mmol) in DMF (4 mL) and the RM is stirred for 10 min. The RM is quenched with water and warmed to 0°C before being filtered. The filter residue is re-crystallised from hept to give 4-(benzyloxy)-2,6-difluoropyridine as a white solid. LC-MS B: t_R = 0.99 min; [M+H]⁺ = 222.27.

Step 2: A suspension of 4-(benzyloxy)-2,6-difluoropyridine (1.71 g, 7.56 mmol) in NaOMe (25 wt. % in MeOH, 6.9 mL, 30.2 mmol) is heated to 60°C for 18 h. The RM is concentrated in vacuo and the residue is partitioned between water and TBME and the layers are separated. The aq. phase is re-extracted with TBME (2x) and the combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 4-(benzyloxy)-2,6-dimethoxypyridine as a colourless oil. LC-MS B: t_R = 1.02 min; [M+H]⁺ = 246.29.

Steps 3-6: The title compound is prepared from 4-(benzyloxy)-2,6-dimethoxypyridine in analogy to the procedure described for B-4.12 steps 3-6. Note: Boc-cleavage is performed using TFA instead of HCl and the title compound is isolated as its free base after a basic workup. LC-MS B: t_R = 0.73 min; $[M+H]^+$ = 361.23.

Benzyl (S)-6-(2-amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxylate dihydrochloride (B-4.18)

- 5 The title compound is prepared from 3-fluoroquinolin-6-ol in analogy to the procedure described for B-4.7 and using *tert*-butyl (S)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in the Mitsunobu step. LC-MS I: t_R = 1.07 min; $[M+H]^+$ = 431.08.

General method 5 for the synthesis of building blocks B

10 **Benzyl (R)-2-(2-amino-3-phenylpropoxy)-6-(methoxy-d3)benzoate hydrochloride (B-5.1)**

- Step 1:** DMAP (120 mg, 0.99 mmol) is added to a 0°C soln. of 2,6-dihydroxybenzoic acid (3.0 g, 19.7 mmol) in 1,2-dimethoxyethane (15 mL) followed by the dropwise addition of acetone (1.9 mL, 25.8 mmol) and thionyl chloride (1.85 mL, 25.2 mmol) and the RM is stirred for 30 min before being warmed to RT and stirred for 16 h. The RM is quenched by the addition of sat. aq. NaHCO_3 and extracted with Et_2O (4x). The combined org. extracts are washed with brine,
15 dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 50% EtOAc in hept) to give 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one as a white solid. LC-MS F: t_R = 1.93 min; $[M+H]^+$ = 195.1.

- Step 2:** CD_3I (0.8 mL, 12.9 mmol) is added to a soln. of 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (1.76 g, 8.6 mmol) and K_2CO_3 (1.79 g, 12.9 mmol) in DMF (25 mL) and the RM is heated to 50°C for 1 h. The RM is partitioned
20 between water and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (1x) and the combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 10% to 100% EtOAc in hept) to give 5-(methoxy-d3)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one as an off-white solid. LC-MS J: t_R = 1.82 min; $[M+H]^+$ = 212.1.

- Step 3:** NaH (0.65 g, 16.3 mmol) is added to a soln. of benzyl alcohol (1.7 mL, 16.3 mmol) in DMF (45 mL) and the
25 RM is stirred for 30 min before a soln. of 5-(methoxy-d3)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (1.72 g, 8.1 mmol) in DMF (5 mL) is added and stirring continued for 1 h. The RM is partitioned between 1N HCl and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (1x) and the combined org. layers are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 50% EtOAc in hept) to give benzyl 2-hydroxy-6-(methoxy-d3)benzoate as a colourless oil. LC-MS J: t_R = 2.13 min;
30 $[M+H]^+$ = 262.1.

Step 4: Benzyl (R)-2-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-6-(methoxy-d3)benzoate is prepared from benzyl 2-hydroxy-6-(methoxy-d3)benzoate and *tert*-butyl (R)-(1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 Step 2. LC-MS J: t_R = 2.39 min; $[M-\text{Boc}+H]^+$ = 395.2.

Step 5: The title compound is prepared in analogy to the procedure described for B-1.1 Step 3. LC-MS J: t_R = 2.15 min; $[M+H]^+$ = 395.1.

Benzyl (R)-2-(2-amino-3-phenylpropoxy)-6-(difluoromethoxy)benzoate hydrochloride (B-5.2)

Step 1: A soln. of KOH (4.57 g, 81 mmol) in water (12 mL) is added to a 0°C soln. of 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (B-5.1 Step 1, 1.58 g, 8.1 mmol) in MeCN (12 mL) and the biphasic RM is stirred for 5 min before bromodifluoromethyl diethylphosphonate (2.0 mL, 11.4 mmol) is added dropwise. After stirring for 1.5 h EtOAc (25 mL) is added and the phases are separated. The aq. phase is re-extracted with EtOAc (1x) and the combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 5-(difluoromethoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one as a brown oil. LC-MS J: t_R = 2.0 min; $[M+H]^+$ = 245.1.

Steps 2-4: The title compound is prepared from 5-(difluoromethoxy)-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one following the sequence of reactions described for B-5.1. LC-MS J: t_R = 2.20 min; $[M+H]^+$ = 428.1.

Methyl (R)-6-(2-amino-3-phenylpropoxy)-2-methylbenzofuran-7-carboxylate hydrochloride (B-5.3)

Step 1: K₂CO₃ (2.38 g, 17.2 mmol) and 3-bromopropyne (80% soln. in PhMe, 1.67 mL, 15.5 mmol) are added to a RT soln. of 5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (B-5.1 Step 1, 3.0 g, 15.4 mmol) in acetone (60 mL) and the RM is heated to 55°C for 21 h. The mix. is concentrated, and the residue partitioned between water and EtOAc. The layers are separated and the aq. layer re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The crude product is purified by FC (eluting with 5% to 35% EtOAc in hept) to give 2,2-dimethyl-5-(prop-2-yn-1-yloxy)-4H-benzo[d][1,3]dioxin-4-one as a white solid. LC-MS J: t_R = 1.83 min; $[M+H]^+$ = 233.1.

Step 2: NaOMe (30% soln. in MeOH, 1.9 mL, 10.1 mmol) is added to a 0°C soln. of 2,2-dimethyl-5-(prop-2-yn-1-yloxy)-4H-benzo[d][1,3]dioxin-4-one (1.53 g, 6.6 mmol) in DMF (15 mL) and the RM is warmed to RT and stirred for 1 h. The RM is quenched with 1M aq. HCl and extracted with EtOAc (3x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered, and evaporated in vacuo to give methyl 2-hydroxy-6-(prop-2-yn-1-yloxy)benzoate as a beige solid. LC-MS J: t_R = 1.79 min; $[M+H]^+$ = 207.0.

Step 3: A mix. of methyl 2-hydroxy-6-(prop-2-yn-1-yloxy)benzoate (1.33 g, 6.5 mmol), CsF (1.5 g, 9.9 mmol), and diethylaniline (18 mL) is purged with N₂ before being irradiated in a MW oven at 200°C for 55 min. The RM is diluted with EtOAc and washed with 1M aq. HCl. The aq. phase is extracted with EtOAc (2x) and the combined org. extracts are washed with 1M HCl, brine, dried over Na₂SO₄, filtered, and evaporated in vacuo. The crude product is purified by FC (eluting with 1% to 15% EtOAc in hept) to give methyl 6-hydroxy-2-methylbenzofuran-7-carboxylate as a white solid. LC-MS F: t_R = 1.98 min; $[M+H]^+$ = 207.0.

Steps 4-5: The title compound is prepared from methyl 6-hydroxy-2-methylbenzofuran-7-carboxylate in analogy to the procedure described for B-1.1 steps 2-3. LC-MS J: t_R = 1.98 min; $[M+H]^+$ = 340.1.

General method 6 for the synthesis of building blocks B

Methyl (R)-6-(2-amino-3-phenylpropoxy)-3-methylbenzo[d]isoxazole-7-carboxylate hydrochloride (B-6.1)

Step 1: Hexamethylenetetramine (8.1 g, 57.1 mmol) is added to a soln. of 3-methyl-1,2-benzisoxazol-6-ol (2.0 g, 13.4 mmol) in AcOH (40 mL) and the RM is heated to 100°C for 2 h. 2M aq. HCl (40 mL) is added and stirring is continued at 100°C for 30 min. The RM is cooled with an ice bath and the resulting solids are collected by filtration. The filtrate is concentrated in vacuo and re-cooled to 0°C before the solids are again collected by filtration. Both crops are combined and dried in vacuo to give 6-hydroxy-3-methylbenzo[d]isoxazole-7-carbaldehyde as a beige powder. LC-MS B: t_R = 0.72 min; No ionisation. ^1H NMR (DMSO) δ : 11.67 (s, 1 H), 10.43 (s, 1 H), 7.94 (d, J = 8.7 Hz, 1 H), 7.03 (d, J = 8.7 Hz, 1 H).

Step 2: 2-Methyl-2-butene (7.33 mL, 69.2 mmol) is added in one portion to a RT soln. of 6-hydroxy-3-methylbenzo[d]isoxazole-7-carbaldehyde (1.09 g, 6.1 mmol) in THF (40 mL) and *tert*-butanol (12 mL) followed by a soln. of NaClO₂ (2.06 g, 18.2 mmol) and NaH₂PO₄·2H₂O (4.3 g, 27.3 mmol) in H₂O (12 mL) and the RM is stirred at RT for 30 min. The solids are collected by filtration, washed with cold 1M aq. HCl and dried in vacuo to give 6-hydroxy-3-methylbenzo[d]isoxazole-7-carboxylic acid as a white solid. LC-MS B: t_R = 0.63 min; $[\text{M}+\text{H}]^+$ = 194.31.

Steps 3-5: The title compound is prepared from 6-hydroxy-3-methylbenzo[d]isoxazole-7-carboxylic acid following the sequence of reactions described for B-3.1. LC-MS B: t_R = 0.70 min; $[\text{M}+\text{H}]^+$ = 341.38.

Methyl (R)-5-(2-amino-3-phenylpropoxy)-1-methyl-1H-indazole-4-carboxylate hydrochloride (B-6.2)

The title compound is prepared from 1-methyl-1H-indazol-5-ol following the sequence of reactions described for B-6.1. LC-MS B: t_R = 0.70 min; $[\text{M}+\text{H}]^+$ = 340.36.

General method 7 for the synthesis of building blocks B**Methyl (R)-6-(2-amino-3-phenylpropoxy)isoquinoline-5-carboxylate dihydrochloride (B-7.1)**

Step 1: Br₂ (0.78 mL, 15.2 mmol) is added dropwise to a suspension of isoquinolin-6-ol (2.0 g, 13.8 mmol) in CHCl₃ (30 mL) in a water bath and the RM is stirred for 2 h. EtOAc is added and the solids are collected by filtration and washed with EtOAc and then hept. The filter residue is neutralised by suspending in sat. aq. NaHCO₃ and re-filtered before washing with H₂O and then hept. The filter residue is suspended in MeCN and evaporated in vacuo to give 5-bromoisoquinolin-6-ol as a brown solid. LC-MS J: t_R = 0.33 min; $[\text{M}+\text{H}]^+$ = 224.0.

Step 2: *tert*-Butyl (R)-((5-bromoisoquinolin-6-yl)oxy)-3-phenylpropan-2-yl)carbamate is prepared from 5-bromoisoquinolin-6-ol and *tert*-butyl (R)-((1-hydroxy-3-phenylpropan-2-yl)carbamate in analogy to the procedure described for B-1.1 Step 2. LC-MS J: t_R = 2.28 min; $[\text{M}+\text{H}]^+$ = 457.1.

Step 3: A soln. of DIPEA (0.76 mL, 4.4 mmol) in MeOH (3 mL) is purged with Ar before Pd(OAc)₂ (74 mg, 0.33 mmol) and Xantphos (190 mg, 0.33 mmol) are added and the catalyst mix. is heated to 70°C for 20 min. In a separate flask a soln. of *tert*-butyl (R)-((5-bromoisoquinolin-6-yl)oxy)-3-phenylpropan-2-yl)carbamate (1.0 g, 2.19 mmol) in MeOH (40 mL) is first purged with Ar before being purged with CO and then heated to 70°C under a CO atm before the hot catalyst soln. is added via syringe and the RM is stirred for 20 h. The RM is cooled to RT and concentrated in vacuo and the residue is partitioned between sat. aq. NaHCO₃ and DCM and extracted. The layers are separated and the

aq. phase is re-extracted with DCM (1x) and the combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 25% to 80% EtOAc in hept) to give methyl (*R*)-6-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)isoquinoline-5-carboxylate as a black solid. LC-MS J: t_R = 2.11 min; [M+H]⁺ = 437.2.

- 5 **Step 4:** The title compound is prepared from methyl (*R*)-6-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)isoquinoline-5-carboxylate in analogy to the procedure described for B-1.1 Step 3. LC-MS J: t_R = 1.83 min; [M+H]⁺ = 337.2.

Benzyl (*R*)-6-(2-amino-3-phenylpropoxy)-3-methylisoquinoline-5-carboxylate dihydrochloride (B-7.2)

- 10 **Step 1:** Trifluoromethanesulfonic anhydride (26.2 mL, 158 mmol) is added dropwise to a -10°C soln. of 2-hydroxy-4-methoxybenzaldehyde (16 g, 105 mmol) and pyridine (42.5 mL, 526 mmol) in DCM (70 mL) and the RM is stirred for 30 min. The RM is quenched with ice water and acidified with 1M aq. HCl before being extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 2-formyl-5-methoxyphenyl trifluoromethanesulfonate as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 10.13 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H).

- 15 **Step 2:** A RT soln. of 2-formyl-5-methoxyphenyl trifluoromethanesulfonate (19.6 g, 66.4 mmol) and TEA (93 mL, 664 mmol) in DMF (400 mL) is purged with Ar for 30 min. Prop-1-yne (1 M in DMF, 133 mL, 133 mmol), CuI (1.27 g, 6.64 mmol) and Pd(PPh₃)₄ (5.0 g, 4.33 mmol) are added successively and the RM is stirred closed for 2 h. The RM is filtered through a pad of celite and the filtrate partially concentrated in vacuo before being diluted with EtOAc and washed successively with 1M KHSO₄ soln. and brine and concentrated in vacuo. The crude product is purified by FC (eluting with 0% to 30% EtOAc in hept) to give 4-methoxy-2-(prop-1-yn-1-yl)benzaldehyde as a yellow solid. LC-MS J: t_R = 1.80 min; [M+H]⁺ = 175.1.

- 20 **Step 3:** A RT soln. of 4-methoxy-2-(prop-1-yn-1-yl)benzaldehyde (10.3 g, 58.8 mmol) in MeOH (350 mL) is purged with Ar for 5 min in an autoclave. NH₃ 7M in MeOH (150 mL, 1050 mmol) is added and the RM is heated to 65°C at 2 bar for 4 h. The RM is concentrated in vacuo and the residue is co-evaporated with DCM (2x) to give 6-methoxy-3-methylisoquinoline as a brown solid. LC-MS J: t_R = 1.81 min; [M+H]⁺ = 174.1.

Step 4: BBr₃ (1 M in DCM, 55.4 mL, 55.4 mmol) is added dropwise to a -78°C soln. of 6-methoxy-3-methylisoquinoline (5.0 g, 27.7 mmol) in DCM (100 mL). The cooling bath is removed and the RM is stirred at RT for 30 h. The RM is carefully quenched into cold MeOH and concentrated in vacuo. The residue is co-evaporated with PhMe, EtOAc and DCM to give 3-methylisoquinolin-6-ol as a brown solid. LC-MS J: t_R = 1.10 min; [M+H]⁺ = 160.1.

- 30 **Steps 5-6:** *tert*-Butyl (*R*)-(1-((5-bromo-3-methylisoquinolin-6-yl)oxy)-3-phenylpropan-2-yl)carbamate is prepared from 3-methylisoquinolin-6-ol following steps 1&2 described for B-7.1. LC-MS J: t_R = 2.20 min; [M+H]⁺ = 471.1.

- Step 7:** A RT soln. of *tert*-butyl (*R*)-(1-((5-bromo-3-methylisoquinolin-6-yl)oxy)-3-phenylpropan-2-yl)carbamate (2.5 g, 5.30 mmol), benzyl alcohol (2.76 mL, 26.5 mmol) and DIPEA (2.78 mL, 15.9 mmol) in PhMe (20 mL) is purged with Ar for 10 min. The RM is then purged with CO and heated to 88°C under a CO atm before a soln. of Pd(^tBu₃P)₂ (271 mg, 0.53 mmol) in PhMe (5.5 mL) is added via syringe pump (3 mL/h). The temperature is increased to 95°C and the RM is stirred under a CO atm for 24 h. The RM is cooled to RT and concentrated in vacuo and the residue is partitioned

between sat. aq. NaHCO₃ and EtOAc and extracted. The layers are separated and the aq. phase is re-extracted with EtOAc (1x) and the combined org. layers are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 5% to 65% EtOAc in hept) to give benzyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-3-methylisoquinoline-5-carboxylate as a colourless oil. LC-MS J: t_R = 2.19 min; [M+H]⁺ = 527.2.

Step 8: The title compound is prepared from benzyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-3-methylisoquinoline-5-carboxylate in analogy to the procedure described for B-1.1 Step 3. LC-MS J: t_R = 1.95 min; [M+H]⁺ = 427.2.

10 Synthesis of building blocks B-Acids

(R)-6-(2-((tert-Butoxycarbonyl)amino)-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylic acid (B-Acid-1)

Step 1: Benzyl 6-hydroxybenzo[d][1,3]dioxole-5-carboxylate is prepared from 6-hydroxybenzo[d][1,3]dioxole-5-carboxylic acid in analogy to the procedure described for B-1.1 step 1. LC-MS I: t_R = 1.12 min; [M+H]⁺ = 272.94.

Step 2: Benzyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylate is prepared from benzyl 6-hydroxybenzo[d][1,3]dioxole-5-carboxylate in analogy to the procedure described for B-1.1 step 2. LC-MS I: t_R = 1.27 min; [M+H]⁺ = 506.02.

Step 3: The title compound is prepared from benzyl (R)-6-(2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylate in analogy to the procedure described for B-1.24 step 4. LC-MS I: t_R = 0.53 min; [M+H]⁺ = 416.01.

20 (R)-2-(2-((tert-Butoxycarbonyl)amino)-3-phenylpropoxy)-4,5-dimethoxybenzoic acid (B-Acid-2)

The title compound is prepared from 2-hydroxy-4,5-dimethoxybenzoic acid following the 3-step sequence as described for B-Acid-1. LC-MS B: t_R = 0.98 min; [M+H]⁺ = 432.18.

(R)-2-(2-((tert-Butoxycarbonyl)amino)-3-phenylpropoxy)-6-methoxybenzoic acid (B-Acid-3)

The title compound is prepared from 2-hydroxy-6-methoxybenzoic acid following the 3-step sequence as described for B-Acid-1. LC-MS I: t_R = 0.52 min; [M+H]⁺ = 401.88.

(R)-6-(2-(((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylic acid (B-Acid-4)

Step 1: Benzyl (R)-6-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylate is prepared from benzyl 6-hydroxybenzo[d][1,3]dioxole-5-carboxylate in analogy to the procedure described for B-1.1 step 2 substituting *tert*-butyl (R)-(1-hydroxy-3-phenylpropan-2-yl)carbamate by benzyl (R)-(1-hydroxy-3-phenylpropan-2-yl)carbamate. LC-MS I: t_R = 1.27 min; [M+H]⁺ = 540.20.

Step 2: A soln. of benzyl (R)-6-(2-(((benzyloxy)carbonyl)amino)-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylate (2.4 g, 4.45 mmol) in THF (40 mL) is evacuated/purged with N₂ (3x) before 10% Pd/C (473 mg, 10 mol%) is added. The RM is evacuated/purged with H₂ (3x) and stirred under a H₂ atm for 2 h. The RM is filtered through a pad of celite

and the filtrate concentrated in vacuo to give (R)-6-(2-amino-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylic acid as a white solid. LC-MS B: t_R = 0.65 min; $[M+H]^+$ = 316.13.

Step 3: N-(9-Fluorenylmethoxycarbonyloxy)succinimide (1.45 g, 4.28 mmol) is added to a RT soln. of (R)-6-(2-amino-3-phenylpropoxy)benzo[d][1,3]dioxole-5-carboxylic acid (1.35 g, 4.28 mmol) and Na_2CO_3 (926 mg, 8.56 mmol) in a mix. of dioxane (40 mL) and water (8 mL) and the RM is stirred for 16 h. The RM is concentrated in vacuo and the residue partitioned between 1M HCl and EtOAc and extracted. The layers are filtered and separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo. The crude product is purified by FC (eluting with 0% to 5% MeOH in DCM) to give the title compound as a white solid. LC-MS B: t_R = 1.09 min; $[M+H]^+$ = 538.24.

(R)-2-((tert-Butoxycarbonyl)amino)-3-phenylpropoxy)-1-naphthoic acid (B-Acid-5)

The title compound is prepared from 2-hydroxy-1-naphthoic acid following the 3-step sequence as described for B-Acid-1. LC-MS B: t_R = 1.02 min; $[M+H]^+$ = 422.33.

(R)-3-((tert-Butoxycarbonyl)amino)-3-phenylpropoxy)quinoline-4-carboxylic acid (B-Acid-6)

The title compound is prepared from 3-hydroxyquinoline-4-carboxylic acid following the 3-step sequence as described for B-Acid-1. LC-MS B: t_R = 0.88 min; $[M+H]^+$ = 423.35.

(R)-4-((tert-Butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxynicotinic acid (B-Acid-7)

The title compound is prepared from 4-hydroxy-2-methoxynicotinic acid following the 3-step sequence as described for B-Acid-1. LC-MS B: t_R = 0.90 min; $[M+H]^+$ = 403.20.

(R)-6-(((Allyloxy)carbonyl)amino)-3-phenylpropoxy)-3-fluoroquinoline-5-carboxylic acid (B-Acid-8)

Step 1 : Under N_2 , benzyl (R)-6-(2-amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxylate dihydrochloride (**B-4.9**) (0.46 g, 0.92 mmol) is dissolved in MeOH (10 mL); the vessel is purged with N_2 /vacuum (3x) before 10% Pd/C (50 mg) is added. After inertising another three times a H_2 balloon is connected and the RM is stirred for 1 h under H_2 atmosphere. The heterogeneous reaction mixture is filtered over a glass fiber filter (washing with methanol/THF). The filtrate is then concentrated to dryness under reduced pressure to yield 0.43 g of (R)-6-(2-amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxylic acid as a crude yellow oil which is used as such in the next step. LC-MS B: t_R = 0.62 min; $[M+H]^+$ = 341.21.

Step 2: (R)-6-(2-Amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxylic acid (436 mg, 1.28 mmol) is taken up in THF (10 mL) and water (10 mL). To the resulting light suspension is added $NaHCO_3$ (430 mg, 5.12 mmol) followed by allyl chloroformate (0.155 mL, 1.41 mmol). The reaction mixture is stirred for 1 h at RT. The reaction mixture is diluted/partitioned between water and EtOAc and acidified carefully with some HCl (2N) down to pH~3. The layers are separated and the inorg. layer is extracted further with EtOAc (2x). The combined organic extracts are washed with acidified water and brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to yield the title compound as a yellow oil (0.39 g). No purification at this stage. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 425.23.

(R)-4-(2-(((Allyloxy)carbonyl)amino)-3-phenylpropoxy)-2-methoxy-6-methylnicotinic acid (B-Acid-9)

The title compound is prepared as a colorless oil from benzyl (R)-4-(2-Amino-3-phenylpropoxy)-2-methoxy-6-methylnicotinate (**B-4.15**) following the 2-step sequence described for B-Acid-8. LC-MS B: t_R = 0.89 min; $[M+H]^+$ = 401.07.

5 General method 1 for the synthesis of building blocks C***N*-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methylglycine (C-1.1)**

Step 1: K_2CO_3 (7.15 g, 51.7 mmol) is added to a RT soln. of Boc-*N*-methylglycine (7.12 g, 36.9 mmol) in acetone (100 mL) followed by the dropwise addition of benzyl bromide (4.93 mL, 40.6 mmol). The resulting mix. is heated to 45°C and stirred for 16 h. The mix. is cooled to RT before being filtered and the filtrate is concentrated to give benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglycinate that is used without purification. LC-MS B: t_R = 0.99 min; $[M+H]^+$ = 280.36.

Step 2: 4 M HCl in dioxane (34.3 mL, 0.137 mol) is added to a RT soln. of benzyl *N*-(*tert*-butoxycarbonyl)-*N*-methylglycinate (11.0 g, 34.2 mmol) in dioxane (10 mL) and the resulting mix. is stirred for 2 h. The suspension is filtered and washed with Et_2O (2x) to give benzyl methylglycinate HCl as a white solid. LC-MS B: t_R = 0.48 min; $[M+H]^+$ = 180.49.

Step 3: A soln. of benzyl methylglycinate HCl (7.96 g, 36.9 mmol) and DIPEA (9.48 mL, 55.4 mmol) in DMF (30 mL) is added to a prestirred RT soln. of Boc-*N*-methyl-L-leucine (9.07 g, 36.9 mmol), HATU (14.03 g, 36.9 mmol) and DIPEA (9.48 mL, 55.4 mmol) in DMF (70 mL) and the resulting mix. is stirred for 2 h. The mix. is concentrated, and the residue partitioned between water and EtOAc. The layers are separated and the aq. layer re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried ($MgSO_4$), filtered, and evaporated to give the crude product that is triturated with Et_2O to give benzyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methylglycinate as a colourless oil. LC-MS B: t_R = 1.11 min; $[M+H]^+$ = 407.47.

Step 4: A soln. of benzyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methylglycinate (14.2 g, 34.2 mmol) in EtOH (200 mL) is purged with N_2 /vacuum (3x) before 10% Pd/C (1.82 g, 1.7 mmol) is added. After inertising another three times a H_2 balloon is connected and the RM is stirred for 2.5 h. The mix. is concentrated and filtered over a celite plug rinsing with EtOH. The filtrate is concentrated to give the title compound as a colourless oil. LC-MS B: t_R = 0.84 min; $[M+H]^+$ = 317.31.

(S)-1-(2-(((*tert*-Butoxycarbonyl) (methyl)amino)-*N*,4-dimethylpentanamido)cyclopropane-1-carboxylic acid (C-1.2)

Step 1: KtOBu (49.6 g, 0.43 mol) is added to a RT soln. of THF (600 mL). A soln. of 1-(Boc-amino)cyclopropanecarboxylic acid (40.0 g, 0.195 mol) in THF (400 mL) is added to the above suspension, then dimethylsulfate (19.6 mL, 0.205 mol) is added carefully (exothermic) and the RM stirred at RT for 2 h, before dimehtylsulfate (1 mL, 0.01 mol) is added and stirring continued for another 1 h at RT. The reaction is quenched with H_2O (400 mL) and acidified with 32% aq. HCl (80 mL). The layers are separated and the aq. layer is extracted with DCM (500 mL). The combined org. layers are concentrated to a reduced volume, then the org. layer is washed with H_2O (300 mL) before being concentrated. Hept is added to the oily residue and the obtained suspension is left at RT

overnight. Next morning, the mix. is filtered and the obtained solid is rinsed with hept (30 mL) and dried to yield 1-(*tert*-butoxycarbonyl-methyl-amino)-cyclopropanecarboxylic acid (21.5 g, 51%) as a white solid. LC-MS B: t_R = 0.71 min; $[M+H]^+$ = 216.39.

Step 2-5: The title compound is prepared from 1-(*tert*-butoxycarbonyl-methyl-amino)-cyclopropanecarboxylic acid following the sequence of reactions described for **C-1.1**, steps 1-4. LC-MS B: t_R = 0.87 min; $[M+H]^+$ = 343.26.

1-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-1,2,3,6-tetrahydropyridine-2-carboxylic acid (C-1.3)

Step 1: H₂SO₄ (92 μ L, 1.72 mmol) is added to a 0°C soln. of (*S*)-*N*-Boc-1,2,3,6-tetrahydro-2-pyridinecarboxylic acid (400 mg, 1.72 mmol) in MeOH (5 mL) and the resulting mix. is heated to reflux for 4 h. The RM is slowly poured into a 0°C soln. of sat. NaHCO₃ and extracted with EtOAc (3x). The combined org. extracts are dried (MgSO₄), filtered, and concentrated to give methyl (*S*)-1,2,3,6-tetrahydropyridine-2-carboxylate as an orange oil. LC-MS I: t_R = 0.46 min; $[M+H]^+$ = 142.16.

Steps 2&3: The title compound is prepared from Boc-*N*-methyl-L-leucine and (*S*)-1,2,3,6-tetrahydropyridine-2-carboxylate following the sequence of reactions described for **C-2.1**. LC-MS B: t_R = 0.92 min; $[M+H]^+$ = 355.34. Epimerisation of the tetrahydropyridine 2-position was observed and this building block is used further as a mix. of diastereoisomers.

***N*-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methyl-D-alanine (C-1.4)**

Step 1: MeI (1.0 mL, 16.06 mmol) is added to a 0°C soln. of (*tert*-butoxycarbonyl)-D-alanine (2.01 g, 10.62 mmol) in THF (10 mL), then NaH (1.08 g, 27.1 mmol) is added. After 30 min at 0°C, the RM is warmed to RT and stirring is continued for 3 h. The mix. is quenched with water and acidified with 0.5 M KHSO₄ (pH 2). The layers are separated and the aq. layer is extracted with EtOAc (3x 20 mL). The combined org. layers are washed with brine, dried (Na₂SO₄), filtered, and evaporated to yield *N*-(*tert*-butoxycarbonyl)-*N*-methyl-D-alanine as a brown oil which is used as such in the next step.

Steps 2-5: The title compound is prepared from *N*-(*tert*-butoxycarbonyl)-*N*-methyl-D-alanine following the 4-step sequence of reactions described for **C-1.1**, steps 1-4. LC-MS F: t_R = 1.98 min; $[M+H]^+$ = 331.20. ¹H NMR (400 MHz, DMSO) δ 5.03 – 4.46 (m, 2H), 2.95 – 2.83 (m, 2H), 2.75 – 2.54 (m, 4H), 1.58 – 1.44 (m, 2H), 1.41 (s, 10H), 1.31 – 1.23 (m, 3H), 1.23 – 1.17 (m, 1H), 0.94 – 0.84 (m, 6H).

General method 2 for the synthesis of building blocks C

(*R*)-4-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl) morpholine-3-carboxylic acid (C-2.1)

Step 1: HATU (4.64 g, 12.2 mmol) is added portionwise to a RT soln. of Boc-*N*-methyl-L-leucine (3.0 g, 12.2 mmol), (*R*)-methyl morpholine-3-carboxylate (1.85 g, 12.2 mmol), and DIPEA (6.3 mL, 36.6 mmol) in DMF (30 mL) and the resulting mix. is stirred for 1 h. Water is added and the mix. is extracted with EtOAc (3x). The combined org. extracts are successively washed with sat. aq. NaHCO₃, water, and brine, dried (Na₂SO₄), filtered, and concentrated.

Purification by FC (eluting with 0% to 100% EtOAc in hept) gives methyl (*R*)-4-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)morpholine-3-carboxylate as a colourless oil. LC-MS B: t_R = 0.97 min; $[M+H]^+$ = 373.50.

- Step 2:** 2 M aq. NaOH (11.7 mL, 22.6 mmol) is added to a RT soln. of methyl (*R*)-4-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)morpholine-3-carboxylate (4.37 g, 11.7 mmol) in MeOH (55 mL) and the mix. is stirred at RT for 4.5 h. The volatiles are removed in vacuo and the aq. residue is neutralised with 2 M aq. HCl before being extracted with DCM (3x). The combined org. layers are dried (Na_2SO_4), filtered, and evaporated in vacuo to give the title compound as a white solid. LC-MS B: t_R = 0.86 min; $[M+H]^+$ = 359.49.

Listed in Table C-2 below are building blocks C that are prepared from the corresponding starting materials in analogy to the 2-step sequence described above for **C-2.1**.

10 **Table C-2**

No.	SM A	SM B	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
C-2.2	Boc- <i>N</i> -Methyl-L-leucine	(<i>R</i>)-Piperidine-2-carboxylic acid methyl ester HCl	(<i>R</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)piperidine-2-carboxylic acid	0.93 B	357.51
C-2.3	Boc- <i>N</i> -Methyl-L-leucine	(<i>S</i>)-Methyl pyrrolidine-3-carboxylate HCl	(<i>S</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)pyrrolidine-3-carboxylic acid	0.82 B	343.51
C-2.4	Boc- <i>N</i> -Methyl-L-leucine	Methyl 3-methoxy-1-(methylamino)cyclobutane-1-carboxylate HCl as a mix. of stereoisomers Aurum Pharmatech TR33962	(<i>S</i>)-1-(2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3-methoxycyclobutane-1-carboxylic acid	0.89 B	387.24
C-2.5	D2-1.1	(<i>R</i>)-Piperidine-2-carboxylic acid methyl ester HCl	(<i>R</i>)-1-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)amino)-3-cyclopentylpropanoyl)piperidine-2-carboxylic acid	0.98 B	383.42

C-2.6	D2-1.1	(R)-Methyl morpholine-3-carboxylate	(R)-4-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-3-cyclopentylpropanoyl)morpholine-3-carboxylic acid	0.92 B	385.25
C-2.7	Boc-N-Methyl-L-leucine	Methyl 1-aminocyclopropanecarboxylate	(S)-1-(2-((tert-Butoxycarbonyl)(methyl)amino)-4-methylpentanamido)cyclopropane-1-carboxylic acid	0.83 B	329.39
C-2.8	Boc-N-Methyl-L-leucine	(S)-Piperidine-2-carboxylic acid methyl ester HCl	(S)-1-[(S)-2-(N-(tert-Butoxycarbonyl)-N-methylamino)-4-methylpentanoyl]-L-leucyl)piperidine-2-carboxylic acid	0.54 I	357.33
C-2.9	Boc-N-Methyl-L-leucine	Methyl 4,4-difluoropiperidine-2-carboxylate hydrochloride	1-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-4,4-difluoropiperidine-2-carboxylic acid	0.56 I	393.28
C-2.10	Boc-N-Methyl-L-leucine	1,2,3,4-Tetrahydro-1-isoquinoline carboxylic acid ethyl ester HCl, CAS 106181-28-6, AstaTech Lot C2130-078	2-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid	0.57 I	405.25
C-2.11	Boc-N-Methyl-L-leucine	1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic acidmethyl ester (HCl salt)	2-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid	0.56 I	405.31
C-2.12	Boc-N-Methyl-L-leucine	Methyl 2-(methylamino)-2-phenyl- acetate (HCl salt)	2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-2-phenylacetic acid	0.98 B	393.30

C-2.15	Boc- <i>N</i> -Methyl-L-leucine	Methyl 4,4,4-trifluoro-2-(methylamino)butanoate (HCl-salt)	(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-4,4,4-trifluorobutanoic acid	0.56 I	399.27
C-2.16	Boc- <i>N</i> -Methyl-L-leucine	Methyl 3-cyclobutoxy-2-(methylamino)propanoate hydrochloride	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>O</i> -cyclobutyl- <i>N</i> -methylserine	0.99 A	401.22
C-2.17	Boc- <i>N</i> -Methyl-L-leucine	Methyl azepane-2-carboxylate hydrochloride	1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)azepane-2-carboxylic acid	0.95 A	371.30

6-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-6-azaspiro[2.5]octane-5-carboxylic acid (C-2.13)

- Step 1:** (Trimethylsilyl)diazomethane soln. (2.0 M in hex, 0.75 mL, 1.49 mmol) is added to a 0°C soln. of commercially available 6-azaspiro[2.5]octane-5-carboxylic acid hydrochloride in MeOH (2 mL). The RM is warmed to RT and stirred for 30 min. The mix. is concentrated to yield rac-6-aza-spiro[2.5]octane-5-carboxylic acid methyl ester which is used as such in the next step. LC-MS I: t_R = 0.66 min; $[M+H]^+$ = 170.18.

Steps 2&3: The title compound is prepared from rac-6-aza-spiro[2.5]octane-5-carboxylic acid methyl ester following the 2-step procedure described for **C-2.1**. LC-MS I: t_R = 1.27 min; $[M+H]^+$ = 397.34.

O-Benzyl-*N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methylserine (C-2.14)

- Step 1:** Thionyl chloride is added to a 0°C solution of O-benzyl-*N*-methyl-DL-serine (3.10 g, 14.8 mmol) in DCM (20 mL) and the RM is stirred at 60°C for 16 h. The mix. is poured into ice water and extracted with DCM (3x). The combined organic layers are washed with brine, dried (MgSO₄), filtered, and concentrated in vacuo. Purification by FC (eluting with 0% to 20% EtOAc in hept) yields methyl O-benzyl-*N*-methylserinate as a colourless oil. LC-MS B: t_R = 0.53 min; $[M+H]^+$ = 224.04.
- Steps 2&3:** The title compound is prepared from methyl O-benzyl-*N*-methylserinate following the 2-step procedure described for **C-2.1**. LC-MS B: t_R = 1.01 min; $[M+H]^+$ = 437.30.

General method 3 for the synthesis of building blocks C

(*R*)-1-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-4-methylpiperazine-2-carboxylic acid (C-3.1)

- Step 1:** Sodium acetate (3.36 g, 41 mmol), followed by TFA (0.63 mL, 8.2 mmol) and formaldehyde 37% aq. (2.92 mL, 39 mmol) are added to a RT soln. of 1-*tert*-butyl 2-methyl (2*R*)-piperazine-1,2-dicarboxylate (2.0 g, 8.2 mmol) in MeOH (40 mL) and the resulting mix. is stirred for 30 min. The mix. is cooled to 0°C before NaBH₃CN (1.74 g, 26.3

mmol) is added portionwise. The mix. is warmed to RT and stirred for 5 h before being concentrated. The residue is partitioned between EtOAc and 1 M aq. NaOH and extracted. The layers are separated, and the aq. layer re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried (Na₂SO₄), filtered, and evaporated to give 1-(*tert*-butyl) 2-methyl (*R*)-4-methylpiperazine-1,2-dicarboxylate as a colourless oil. LC-MS I: t_R = 0.81 min; [M+H]⁺ = 259.22.

Step 2: Methyl (*R*)-4-methylpiperazine-2-carboxylate dihydrochloride is prepared from 1-(*tert*-butyl) 2-methyl (*R*)-4-methylpiperazine-1,2-dicarboxylate in analogy to the procedure described for **C-1.1**, step 2. LC-MS I: t_R = 0.34 min; [M+H]⁺ = 159.16.

Steps 3&4: The title compound is prepared from Boc-*N*-methyl-L-leucine and methyl (*R*)-4-methylpiperazine-2-carboxylate dihydrochloride following the 2-step sequence of reactions described for **C-2.1**. LC-MS B: t_R = 0.67 min; [M+H]⁺ = 372.51.

Listed in Table C-3 below are building blocks C that are prepared from the corresponding starting materials in analogy to the 4-step sequence described above for **C-3.1**.

Table C-3

No.	SM	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-3.2	Acetaldehyde	(<i>R</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)-4-ethylpiperazine-2-carboxylic acid	0.56 I	386.00
C-3.3	Acetone	(<i>R</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)-4-isopropylpiperazine-2-carboxylic acid	0.71 B	400.51
C-3.4	Isobutyraldehyde	(<i>R</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)-4-isobutylpiperazine-2-carboxylic acid	0.75 B	414.45
C-3.5	Cyclobutanol	(<i>R</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)-4-cyclobutylpiperazine-2-carboxylic acid	0.73 B	412.48
C-3.6	Cyclopropanone	(<i>R</i>)-1-(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)-4-(cyclopropylmethyl)piperazine-2-carboxylic acid	0.56 I	412.30

(*R*)-1-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-4-cyclopropylpiperazine-2-carboxylic acid (HCl-salt) (C-3.7)

Step 1: (1-Ethoxycyclopropoxy)trimethylsilane (2.6 mL, 12.80 mmol), NaBH₃CN (0.66 g, 9.98 mmol), and AcOH (0.5 mL, 8.74 mmol) are added to a RT soln. of methyl (*R*)-1-Boc-piperazine-2-carboxylate (1.54 g, 6.30 mmol) in MeOH (30 mL) and THF (30 mL) and the resulting mix. is heated to 60°C for 16 h. Water (5 mL) is added to the cooled mix. followed by 1 M aq. NaOH (10 mL) and after stirring for 15 min the volatiles are removed under reduced pressure.

The residue is extracted with DCM (2x) and the combined org. extracts are washed with brine, dried (Na₂SO₄), filtered, and evaporated to give 1-(*tert*-butyl) 2-methyl (*R*)-4-cyclopropylpiperazine-1,2-dicarboxylate as a colourless oil. LC-MS B: *t_R* = 0.58 min; [M+H]⁺ = 285.31.

- Steps 2-4:** The title compound is prepared from 1-(*tert*-butyl) 2-methyl (*R*)-4-cyclopropylpiperazine-1,2-dicarboxylate following 3-step sequence as described for **C-3.1**, steps 2 to 4. LC-MS B: *t_R* = 0.73 min; [M+H]⁺ = 398.43.

General method 4 for the synthesis of building blocks C

N-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-(chroman-3-ylmethyl)glycine (**C-4.1**)

- Step 1:** HATU (219 mg, 0.58 mmol) is added to a RT soln. of Boc-*N*-methyl-L-leucine (135 mg, 0.55 mmol), **IM-1.3** (155 mg, 0.5 mmol), and DIPEA (0.34 mL, 2 mmol) in DMF (2 mL) and the resulting mix. is stirred for 1 h. The RM is directly purified by prep. HPLC (basic) to yield benzyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-((chroman-3-yl)methyl)glycinate (218 mg, 81%). LC-MS I: *t_R* = 1.35 min; [M+H]⁺ = 539.23.

- Step 2:** LiOH (52.9 mg, 1.26 mmol) is added to a RT soln. of benzyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-((chroman-3-yl)methyl)glycinate (218 mg, 0.4 mmol) in THF/H₂O (2:1) (2 mL) and the mix. is stirred at RT overnight. The volatiles are removed in vacuo and the aq. residue is acidified with 2 M aq. HCl before being extracted with EtOAc (3x). The combined org. layers are dried (MgSO₄), filtered, and evaporated to give the title compound **C-4.1** (200 mg, 71%) as a white solid. LC-MS I: *t_R* = 0.62 min; [M+H]⁺ = 449.25.

Listed in Table C-4 below are building blocks C that are prepared from the corresponding starting materials in analogy to the 2-step sequence described above for **C-4.1**.

Table C-4

No.	SM A	SM B	Product	<i>t_R</i> [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-4.2	Boc- <i>N</i> -Methyl-L-leucine	IM-1.1	<i>N</i> -(2-(<i>tert</i> -Butoxy)ethyl)- <i>N</i> -(<i>N</i> -(<i>tert</i> -butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)glycine	0.99 B	403.46
C-4.3	Boc- <i>N</i> -Methyl-L-leucine	IM-1.2	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -((3-methyltetrahydrofuran-3-yl)methyl)glycine	0.93 D	402.26
C-4.4	Boc- <i>N</i> -Methyl-L-leucine	IM-1.4	<i>N</i> -(2-(7-Oxabicyclo[2.2.1]heptan-2-yl)ethyl)- <i>N</i> -(<i>N</i> -(<i>tert</i> -butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)glycine	0.95 D	427.39

C-4.5	Boc- <i>N</i> -Methyl-L-leucine	IM-1.5	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-(5,5-dimethyltetrahydrofuran-2-yl)ethyl)glycine	1.12 D	441.36
C-4.6	Boc- <i>N</i> -Methyl-L-leucine	IM-1.6	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-(tetrahydrofuran-2-yl)ethyl)glycine	0.97 D	401.25
C-4.7	Boc- <i>N</i> -Methyl-L-leucine	IM-1.7	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-(tetrahydro-2 <i>H</i> -pyran-3-yl)ethyl)glycine	0.97 D	415.42
C-4.8	Boc- <i>N</i> -Methyl-L-leucine	IM-1.8	<i>N</i> -(2-(2,9-Dioxaspiro[5.5]undecan-3-yl)ethyl)- <i>N</i> -(<i>N</i> -(<i>tert</i> -butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)glycine	1.00 D	485.31
C-4.9	Boc- <i>N</i> -Methyl-L-leucine	IM-1.9	<i>N</i> -(2-(1,4-Dioxan-2-yl)ethyl)- <i>N</i> -(<i>N</i> -(<i>tert</i> -butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)glycine	0.88 D	403.4
C-4.10	Boc- <i>N</i> -Methyl-L-leucine	IM-1.10	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-(tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	1.05 D	415.43
C-4.11	Boc- <i>N</i> -Methyl-L-leucine	IM-1.11	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-(3-methoxycyclobutyl)ethyl)glycine	0.54-0.58 I	415.25
C-4.12	D2-1.3	IM-1.12	<i>N</i> -(2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)pent-4-ynoyl)- <i>N</i> -(2-cyclohexylethyl)glycine	0.58 I	395.22

General method 5 for the synthesis of building blocks C

(*S*)-2-(2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-2,3-dihydro-1*H*-indene-2-carboxylic acid (C-5.1)

- 5 **Step 1:** HATU (1.24 g, 3.25 mmol) is added to a RT soln. of Boc-*N*-methyl-L-leucine (800 mg, 3.25 mmol), methyl 2-amino-indan-2-carboxylate HCl (764 mg, 3.25 mmol), and DIPEA (2.23 mL, 13 mmol) in DMF (8 mL). The RM is stirred at RT for 1 h, then diluted with water (20 mL) and DCM (50 mL). The layers are separated and the aq. layer is extracted with DCM (2x 50 mL). The combined org. layers are washed with brine (20 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 20% to 55% EtOAc in hept, R_f = 0.34 in EtOAc/hept 3:7) yields methyl
- 10 (*S*)-2-(2-((*tert*-butoxycarbonyl)amino)-4-methylpentanamido)-2,3-dihydro-1*H*-indene-2-carboxylate (1.07 g, 79%) as a colourless oil. LC-MS B: t_R = 1.07 min; [M+H]⁺ = 419.17.

Step 2: NaH (36.6 mg, 0.956 mmol) is added to a 0°C soln. of methyl (S)-2-{2-((*tert*-butoxycarbonyl)amino)-4-methylpentanamido)-2,3-dihydro-1*H*-indene-2-carboxylate (200 mg, 0.478 mmol) in DMF (6 mL). After 10 min stirring, MeI (60 µL, 0.96 mmol) is added and the ice bath removed. The mix. is stirred at RT for 1 h, then the RM is partitioned between 2 N HCl (6 mL) and DCM (75 mL), and the layers are separated. The aq. layer is re-extracted with DCM (2x 75 mL) and the combined org. layers are washed with brine (30 mL), dried (Na₂SO₄), filtered, and evaporated. The crude product is purified by FC (eluting with 35% to 80% EtOAc in hept) to give methyl (S)-2-{2-((*tert*-butoxycarbonyl)amino)-*N*,4-dimethylpentanamido)-2,3-dihydro-1*H*-indene-2-carboxylate as a colourless oil. LC-MS B: t_R = 1.11 min; [M+H]⁺ = 433.07.

Step 3: 4 M NaOH soln. (21 mL, 83.2 mmol) is added to a RT soln. of methyl (S)-2-{2-((*tert*-butoxycarbonyl)amino)-*N*,4-dimethylpentanamido)-2,3-dihydro-1*H*-indene-2-carboxylate (90 mg, 2.08 mmol) in MeOH (30 mL), and the RM is stirred at 50°C for 4 h. The RM is cooled to RT, then the mix. is diluted with DCM (100 mL) and acidified with a 2 M HCl soln. (10 mL). The layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated to yield the title compound **C-5.1** (796 mg, 91 %) as a white foam which is used as such in the next step. LC-MS B: t_R = 1.01 min; [M+H]⁺ = 419.09.

Listed in Table C-5 below are building blocks C that are prepared from the corresponding starting materials in analogy to the 3-step sequence described above for **C-5.1**.

Table C-5

No.	SM A	SM B	Product	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-5.2	Boc- <i>N</i> -Methyl-L-leucine	Methyl alpha-aminoisobutyrate HCl	(S)-2-{2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-2-methylpropanoic acid	0.88 B	345.26
C-5.3	Boc- <i>N</i> -Methyl-L-leucine	Methyl 2-amino-2-cyclopropylacetate (HCl salt)	2-((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-2-cyclopropylacetic acid	0.91 B	357.32
C-5.4	Boc- <i>N</i> -Methyl-L-leucine	Methyl 1-amino-3,3-difluorocyclobutane-1-carboxylate (HCl salt)	(S)-1-{2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3,3-difluorocyclobutane-1-carboxylic acid	0.95 B	393.30

General method 6 for the synthesis of building blocks C**(*R*)-1-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-4-(3-hydroxypropyl)piperazine-2-carboxylic acid HCl salt (C-6.1)**

Step 1: K₂CO₃ (1.66 g, 12 mmol) is added to a RT soln. of 1-(*tert*-butyl) 2-methyl (*R*)-piperazine-1,2-dicarboxylate (1.0 g, 4.01 mmol) and benzyl 3-bromopropyl ether (0.95 mL, 5.22 mmol) in MeCN (10 mL) and the resulting mix. is stirred at 60°C for 17 h. Water (20 mL) and DCM (75 mL) are added to the RM, then the two layers are separated and the aq. layer is extracted with DCM (2x 50 mL). The combined org. extracts are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 5% to 25% EtOAc in hept) yields (*R*)-4-(3-benzyloxy-propyl)-piperazine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (1.58 g, 100%) as a colourless oil. LC-MS B: t_R = 0.75 min; [M+H]⁺ = 393.43.

Step 2: 4 M HCl in dioxane (5 mL, 20 mmol) is added to a RT soln. of (*R*)-4-(3-benzyloxy-propyl)-piperazine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (1.57 g, 4 mmol) in dioxane (7 mL) and the resulting mix. is stirred at 50°C for 2 h. The RM is cooled to RT, then diluted with DCM (100 mL) and sat. aq. K₂CO₃ (20 mL) is added. The layers are separated and the aq. layer is extracted with DCM (2 x 75 mL). The combined org. layers are washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated to give (*R*)-4-(3-benzyloxy-propyl)-piperazine-2-carboxylic acid methyl ester (1.06 g, 91%) as colourless oil which is used as such in the next step. LC-MS B: t_R = 0.53 min; [M+H]⁺ = 293.32.

Step 3: HATU (1.36 g, 3.58 mmol) is added to a RT soln. of Boc-*N*-methyl-L-leucine (880 mg, 3.58 mmol), (*R*)-4-(3-benzyloxy-propyl)-piperazine-2-carboxylic acid methyl ester (1.05 g, 3.58 mmol), and DIPEA (1.84 mL, 10.7 mmol) in DMF (11 mL). The resulting mix. is stirred at RT for 1 h, the RM is diluted with DCM (100 mL) and water (10 mL). The layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 15% to 42% EtOAc in hept) yields methyl (*R*)-4-(3-(benzyloxy)propyl)-1-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)piperazine-2-carboxylate (1.67 g, 90%) as a colourless oil. LC-MS B: t_R = 0.90 min; [M+H]⁺ = 520.39.

Step 4: 2 M NaOH soln. (32 mL, 63.9 mmol) is added to a RT soln. of methyl (*R*)-4-(3-(benzyloxy)propyl)-1-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)piperazine-2-carboxylate (1.66 g, 3.19 mmol) in MeOH (60 mL) and the RM is stirred at 50°C for 1 h. The RM is cooled to RT and the RM is diluted with DCM (100 mL) and acidified with a 25% aq. HCl soln. (10 mL). The layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated to yield (*R*)-4-(3-benzyloxy-propyl)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperazine-2-carboxylic acid (1.47 g, 85 %) as a white solid which is used as such in the next step. LC-MS B: t_R = 0.84 min; [M+H]⁺ = 506.36.

Step 5: A soln. of (*R*)-4-(3-benzyloxy-propyl)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperazine-2-carboxylic acid (1.74 g, 3.21 mmol) in EtOH (20 mL) is inertised with N₂/vacuum (3x) before 10% Pd/C (171 mg, 0.16 mmol) is added. After inertising another three times a H₂ balloon is connected and the RM is stirred at

RT for 18 h. The mix. is concentrated and filtered over a celite plug rinsing with EtOH. The filtrate is concentrated to give the title compound **C-6.1** (1.14 g, 79%) as a white solid. LC-MS B: t_R = 0.67 min; $[M+H]^+$ = 416.34.

(R)-1-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-4-(2-hydroxyethyl)piperazine-2-carboxylic acid HCl-salt (C-6.2)

- 5 The title compound is prepared following the 5-step sequence described for **C-6.1**, using in step 1 benzyl 2-bromoethyl ether instead of benzyl 3-bromopropyl ether. LC-MS B: t_R = 0.67 min; $[M+H]^+$ = 402.07.

(R)-1-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-4-(2-methoxyethyl)piperazine-2-carboxylic acid HCl salt (C-6.3)

- Step 1:** 1-Bromo-2-methoxyethane (4.31 mL, 44.9 mmol) is added to a RT soln. of 1-(tert-butyl) 2-methyl (R)-piperazine-1,2-dicarboxylate (4.00 g, 16 mmol) and DIPEA (8.41 mL, 48.1 mmol) in MeCN (87 mL). The resulting mix. is stirred at 80°C for 18 h. The mix. is concentrated, and the residue partitioned between water (10 mL) and DCM (50 mL). The layers are separated, and the aq. layer re-extracted with DCM (2x 75 mL). The combined org. extracts are washed with brine (50 mL), dried ($MgSO_4$), filtered, and evaporated to give (R)-4-(2-methoxy-ethyl)-piperazine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester as an orange oil. LC-MS B: t_R = 0.54 min; $[M+H]^+$ = 303.36.

- 15 **Steps 2 to 4:** The title compound is prepared from (R)-4-(2-methoxy-ethyl)-piperazine-1,2-dicarboxylic acid 1-tert-butyl ester 2-methyl ester following the sequence of reactions described for **C-6.1**, steps 2 to 4. LC-MS B: t_R = 0.71 min; $[M+H]^+$ = 416.36.

(S)-1-(2-((tert-Butoxycarbonyl)(methyl)amino)-N-(3-methoxypropyl)-4-methylpentanamido)cyclopropane-1-carboxylic acid (C-6.4)

- 20 **Step 1:** 1-(3-Methoxy-propylamino)-cyclopropanecarboxylic acid methyl ester is prepared from methyl 1-aminocyclopropanecarboxylate and 1-bromo-3-methoxypropane following the reaction described for **C-6.3**, step 1. LC-MS B: t_R = 0.39 min; $[M+H]^+$ = 188.43.

Steps 2&3: The title compound is prepared from 1-(3-methoxy-propylamino)-cyclopropanecarboxylic acid methyl ester following the sequence of reactions described for **C-6.1**, steps 3&4. LC-MS B: t_R = 0.91 min; $[M+H]^+$ = 401.30.

- 25 **General method 7 for the synthesis of building blocks C**

(R)-1-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-4-((2,2,2-trichloroethoxy)carbonyl)piperazine-2-carboxylic acid (C-7.1)

- Step 1:** 2,2,2-Trichloroethyl chloroformate (1.2 mL, 8.54 mmol) is added to a RT soln. of 1-(tert-butyl) 2-methyl (R)-piperazine-1,2-dicarboxylate (2.0 g, 8.02 mmol) and DIPEA (2.88 mL, 16.5 mmol) in DCM (40 mL). The resulting mix. is stirred at RT for 45 min. The RM is diluted with DCM (100 mL) and water (20 mL). The layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by FC (eluting with 20% to 60% EtOAc in hept, R_f = 0.3 in EtOAc/hept 1:1) yields 1-(tert-butyl) 2-methyl 4-(2,2,2-trichloroethyl) (R)-piperazine-1,2,4-tricarboxylate (2.90 g, 74%) as a white solid. LC-MS B: t_R = 1.13 min; $[M+H]^+$ = 545.75.

Steps 2 to 4: The title compound is prepared from 1-(*tert*-butyl) 2-methyl 4-(2,2,2-trichloroethyl) (R)-piperazine-1,2,4-tricarboxylate following the sequence of reactions described for **C-6.1**, steps 2 to 4. LC-MS B: t_R = 1.03 min; $[M+H]^+$ = 531.98.

5 General method 8 for the synthesis of building blocks C

(R)-1-(N-(*tert*-Butoxycarbonyl)-N-methyl-L-leucyl)-4-phenylpiperazine-2-carboxylic acid (C-8.1)

Step 1: Cu(OAc)₂ (749 mg, 6.2 mmol) is added to a RT soln. of 1-(*tert*-butyl) 2-methyl (R)-piperazine-1,2-dicarboxylate (1.00 g, 4.01 mmol) and phenylboronic acid (749 mg, 4.01 mmol) in DCM (20 mL) and the resulting mix. is stirred at RT overnight. The RM is diluted with DCM and washed with cold water (20 mL), and brine (20 mL). The org. layer is dried (MgSO₄), filtered, and evaporated. Purification by prep. HPLC (basic) yields (R)-4-phenyl-piperazine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (337 mg, 26%) as a colourless oil. LC-MS B: t_R = 1.02 min; $[M+H]^+$ = 321.13.

Step 2: TFA (0.8 mL, 10.6 mmol) is added to a soln. of (R)-4-phenyl-piperazine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (337 mg, 1.06 mmol) in DCM (40 mL) and the resulting mix. is stirred for 24 h. The RM is diluted with DCM (10 mL) and neutralised with a sat. aq. soln. of NaHCO₃ (30 mL). The layers are separated, and the aq. layer re-extracted with DCM (20 mL). The combined org. extracts are dried (Na₂SO₄), filtered, and concentrated to give (R)-4-phenyl-piperazine-2-carboxylic acid methyl ester (232 mg, 100%) as a yellowish oil. LC-MS B: t_R = 0.52 min; $[M+H]^+$ = 221.32.

Steps 3&4: The title compound is prepared from Boc-N-methyl-L-leucine and (R)-4-phenyl-piperazine-2-carboxylic acid methyl ester following the sequence of reactions described for **C-2.1**. LC-MS B: t_R = 1.03 min; $[M+H]^+$ = 433.9.

(RS)-1-(N-(*tert*-Butoxycarbonyl)-N-methyl-L-leucyl)-4-(5-fluoropyridin-2-yl)piperazine-2-carboxylic acid (C-8.2)

Step 1: A mixture of 1-*tert*-butyl 2-methyl (2R)-piperazine-1,2-dicarboxylate (2500 mg, 10 mmol), 2-bromo-5-fluoropyridine (2161 mg, 12 mmol), tris(dibenzylideneacetone)dipalladium(0) (473 mg, 0.501 mmol) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (426 mg, 1 mmol) in toluene (30 mL) is degassed and inertised with Argon. The RM is then heated up to 100°C for 4h30 to reach complete conversion as monitored by LC-MS. The solution is cooled back to RT and is filtered over a glass fiber filter. Water is added to the resulting filtrate and the org. layer is collected; the inorg. phase is then further extracted with EtOAc (2x). The combined organic phase is successively washed with sat. aq. NH₄Cl, sat. aq. NaHCO₃ and brine, dried over MgSO₄ then concentrated under reduced pressure. The crude is purified by FC (0% to 30% EtOAc in Hept) to yield 1-(*tert*-butyl) 2-methyl (R)-4-(5-fluoropyridin-2-yl)piperazine-1,2-dicarboxylate as a yellow oil (2.21 g). LC-MS B: t_R = 0.92 min; $[M+H]^+$ = 340.16.

Step 2-4: The title compound is prepared from boc-N-methyl-L-leucine and 1-(*tert*-butyl) 2-methyl (R)-4-(5-fluoropyridin-2-yl)piperazine-1,2-dicarboxylate following the sequence of reactions 2 to 4 described for **C-8.1**. Extensive epimerization is observed at the piperazine chiral center at the end of the 4 step sequence. LC-MS B: t_R = 0.96 min; $[M+H]^+$ = 453.37.

General method 9 for the synthesis of building blocks C**(*R*)-1-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-4-(pyridin-3-ylsulfonyl)piperazine-2-carboxylic acid (C-9.1)**

Step 1: Pyridine-3-sulfonyl chloride (2.33 g, 12.8 mmol) is added to a RT soln. of 1-(*tert*-butyl) 2-methyl (*R*)-piperazine-1,2-dicarboxylate (2.00 g, 8.02 mmol) and TEA (3.37 mL, 24.1 mmol) in DCM (80 mL) and the resulting mix. is stirred at RT for 1 h. The RM is diluted with DCM (75 mL) and water (10 mL). The layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 80% to 85% EtOAc in hept, R_f = 0.42 in EtOAc/ hept 7:3) yields (*R*)-4-(pyridine-3-sulfonyl)-piperazine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (3.06 g, 99%) as a white foam. LC-MS B: t_R = 0.89 min; [M+H]⁺ = 386.16.

Step 2: 4 M HCl in dioxane (9.73 mL, 38.9 mmol) is added to a RT soln. of (*R*)-4-(pyridine-3-sulfonyl)-piperazine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (3.0 g, 7.78 mmol) in dioxane (10 mL). The resulting mix. is stirred at 50°C for 2 h. The suspension is filtered and the solids are rinsed with TBME (20 mL) to give methyl (*R*)-4-(pyridin-3-ylsulfonyl)piperazine-2-carboxylate dihydrochloride (3.12 g, 112%) as a white solid. LC-MS B: t_R = 0.44 min; [M+H]⁺ = 286.15.

Steps 3&4: The title compound is prepared from Boc-*N*-methyl-L-leucine and (methyl (*R*)-4-(pyridin-3-ylsulfonyl)piperazine-2-carboxylate dihydrochloride following the sequence of reactions described for **C-2.1**. LC-MS B: t_R = 0.93 min; [M+H]⁺ = 499.27.

(*R*)-1-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-4-((5-methoxypyridin-3-yl)sulfonyl)piperazine-2-carboxylic acid (C-9.2)

The title compound is prepared following the 4-step sequence described for **C-9.1** using in step 1, 5-methoxy-pyridine-3-sulfonyl chloride instead of pyridine-3-sulfonyl chloride. LC-MS B: t_R = 0.96 min; [M+H]⁺ = 529.10.

General method 10 for the synthesis of building blocks C

Listed in Table C-10 below are building blocks C that are prepared from the corresponding starting materials in analogy to the sequence described above for **C-1.1**, steps 3&4.

Table C-10

No.	SM A	SM B	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-10.1	D2-1.1	IM-2.2	<i>N</i> -((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopentylpropanoyl)- <i>N</i> -(((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.55-0.62 I	427.25

C-10.2	D2-1.1	IM-2.1	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopentylpropanoyl)- <i>N</i> -(((S)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.59-0.61 I	427.24
C-10.3	D2-1.2	IM-2.2	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclohexylpropanoyl)- <i>N</i> -(((R)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.58-0.66 I	441.28
C-10.4	D2-1.2	IM-2.1	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclohexylpropanoyl)- <i>N</i> -(((S)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.59-0.64 I	441.27
C-10.5	D2-2.1	IM-2.1	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclobutylpropanoyl)- <i>N</i> -(((S)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.55-0.59 I	413.22
C-10.6	D2-2.1	IM-2.2	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclobutylpropanoyl)- <i>N</i> -(((R)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.53-0.60 I	413.20
C-10.7	D2-1.4	IM-2.2	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoyl)- <i>N</i> -(((R)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.48-0.53 I	399.21
C-10.8	D2-1.4	IM-2.3	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoyl)- <i>N</i> -(2-((S)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.51-0.56 I	413.3
C-10.9	D2-1.4	IM-2.4	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoyl)- <i>N</i> -(2-((R)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.52-0.58 I	413.23
C-10.10	D2-2.1	IM-2.3	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclobutylpropanoyl)- <i>N</i> -(2-((S)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.55-0.60 I	427.34
C-10.11	D2-2.1	IM-2.4	<i>N</i> -((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclobutylpropanoyl)- <i>N</i> -(2-((R)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.55-0.60 I	427.33
C-10.12	Boc- <i>N</i> -Methyl-L-leucine	IM-2.3	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-((S)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.53-0.61 I	415.25
C-10.13	Boc- <i>N</i> -Methyl-L-leucine	IM-2.4	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-((R)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.53-0.61 I	415.25

C-10.14	D2-1.1	IM-1.10	<i>N</i> -((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopentylpropanoyl)- <i>N</i> -(2-(tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	1.01 B	441.39
C-10.15	D2-1.2	IM-1.10	<i>N</i> -((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclohexylpropanoyl)- <i>N</i> -(2-(tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.61-0.65 I	455.31
C-10.16	D2-1.1	IM-1.12	(<i>S</i>)- <i>N</i> -(2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopentylpropanoyl)- <i>N</i> -(2-cyclohexylethyl)glycine	0.70 I	439.29
C-10.17	D2-1.2	IM-1.12	(<i>S</i>)- <i>N</i> -(2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclohexylpropanoyl)- <i>N</i> -(2-cyclohexylethyl)glycine	0.73 I	453.34
C-10.18	D2-2.1	IM-1.12	(<i>S</i>)- <i>N</i> -(2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclobutylpropanoyl)- <i>N</i> -(2-cyclohexylethyl)glycine	0.67 I	425.28
C-10.19	Boc- <i>N</i> -Methyl-L-leucine	IM-1.12	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-cyclohexylethyl)glycine	0.72 I	413.26
C-10.20	Boc- <i>N</i> -Methyl-L-leucine	IM-2.2	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.51-0.59 I	401.89
C-10.21	Boc- <i>N</i> -Methyl-L-leucine	IM-2.1	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.54 I	401.87
C-10.22	Boc- <i>N</i> -Methyl-L-leucine	IM-1.10	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-(tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	1.05 B	415.43
C-10.23	Boc- <i>N</i> -methyl-glycine	IM-1.12	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methylglycyl)- <i>N</i> -(2-cyclohexylethyl)glycine	2.09 F	No ionisation
C-10.24	Boc- <i>N</i> -methyl-L-alanine	IM-1.12	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-alanyl)- <i>N</i> -(2-cyclohexylethyl)glycine	2.20 F	371.20
C-10.25	Boc- <i>N</i> -methyl-L-leucine	IM-1.15	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(3-phenylpropyl)glycine	1.78-1.84 J	421.20
C-10.26	D2-1.4	IM-1.12	(<i>S</i>)- <i>N</i> -(2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoyl)- <i>N</i> -(2-cyclohexylethyl)glycine	0.63 I	411.28

General method 11 for the synthesis of building blocks C**(S)-1-(2-((*tert*-Butoxycarbonyl)(methyl)amino)-3-cyclopentyl-*N*-methylpropanamido)cyclopropane-1-carboxylic acid (C-11.1)**

Step 1: Benzyl chloroformate (4.6 mL, 30.6 mmol) is added to a RT soln. of methyl 1-aminocyclopropanecarboxylate (3.25 g, 27.7 mmol) and NaHCO₃ (9.64 g, 115 mmol) in DCM (30 mL) and H₂O (30 mL). The resulting mix. is stirred at RT. After 2 h, the two layers are separated, and the aq. layer extracted with DCM (2x 30 mL). The combined org. extracts are concentrated to obtain 1-benzoyloxycarbonylamino-cyclopropanecarboxylic acid methyl ester (7.28 g, 106%) as a yellow solid. LC-MS B: t_R = 0.79 min; [M+H]⁺ = 250.37.

Step 2: NaH (1.85 g, 46.3 mmol) is added to a 0°C soln. of DMF (45 mL), followed by a soln. of 1-benzoyloxycarbonylamino-cyclopropanecarboxylic acid methyl ester (7.28 g, 29.2 mmol) in DMF (30 mL). After 45 min, MeI (5.5 mL, 87.5 mmol) is added and the mix. is warmed to RT overnight. The RM is partitioned between H₂O (50 mL) and EtOAc (150 mL) and the layers are separated. The aq. layer is re-extracted with EtOAc (2x 75 mL) and the combined org. layers are washed with brine (40 mL), dried (MgSO₄), filtered, and evaporated to obtain 1-(benzyloxycarbonyl-methyl-amino)-cyclopropanecarboxylic acid methyl ester (7.70 g, 100%) as an orange liquid which is used as such in the next step. LC-MS B: t_R = 0.88 min; [M+H]⁺ = 264.33.

Step 3: A soln. of 1-(benzyloxycarbonyl-methyl-amino)-cyclopropanecarboxylic acid methyl ester (4.00 g, 11.4 mmol) in MeOH (18 mL) is inertised with N₂/vacuum (3x) before 10% Pd/C (606 mg, 0.57 mmol) is added. After inertising another three times a H₂ balloon is connected and the RM is stirred for 18 h. The mix. is concentrated and filtered over a celite plug rinsing with EtOH. The filtrate is concentrated (careful, product is volatile) to give 1-methylamino-cyclopropanecarboxylic acid methyl ester (653 mg, 44%). LC-MS B: t_R = 0.26 min; [M+H]⁺ = 130.24.

Steps 4&5: The title compound is prepared from **D2-1.1** and 1-methylamino-cyclopropanecarboxylic acid methyl ester, following the 2 -step sequence described for **C-2.1**. LC-MS B: t_R = 0.92 min; [M+H]⁺ = 369.29.

General method 12 for the synthesis of building blocks C***N*-(*N*-(*tert*-Butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-(3-methoxypropyl)-D-alanine (C-12.1)**

Step 1: NaH₃BCN (398 mg, 6.02 mmol) is added to a RT soln. of D-alanine methyl ester HCl (600 mg, 4.3 mmol), 3-methoxy-propionaldehyde (429 mg, 4.73 mmol), molecular sieves 3A (450 mg), and AcOH (0.295 mL, 5.16 mmol) in MeOH (19 mL). The resulting mix. is stirred at RT for 35 min. The mix. is concentrated and to the residue is added DCM. The org. layer is washed with sat. NaHCO₃ and the aq. layer is re-extracted with DCM. The combined org. extracts are washed with brine, dried (MgSO₄), filtered, and concentrated to yield (*R*)-2-(3-methoxy-propylamino)-propionic acid methyl ester (615 mg, 82%) as a colourless oil. LC-MS B: t_R = 0.33; [M+H]⁺ = 176.50.

Steps 2&3: The title compound is prepared from (*R*)-2-(3-methoxy-propylamino)-propionic acid methyl ester following the 2-step sequence described for **C-2.1**. LC-MS B: t_R = 0.91 min; [M+H]⁺ = 389.42.

General method 13 for the synthesis of building blocks C**(S)-1-((*tert*-Butoxycarbonyl)(methyl)amino)-N-(2-methoxyethyl)-4-methylpentanamido)cyclopropane-1-carboxylic acid (C-13.1)**

Step 1: Benzyl bromide (4.41 mL, 36.4 mmol) is added to a suspension of 1-*tert*-butoxycarbonylamino-cyclopropanecarboxylic acid (7.00 g, 33.0 mmol) and K₂CO₃ (6.92 g, 49.6 mmol) in MeCN (320 mL). The resulting mix. is heated to 60°C for 15 h. The RM is concentrated and to the residue is added EtOAc and water. The org. layer is separated and washed with brine, dried (MgSO₄), filtered, and concentrated to yield 1-*tert*-butoxycarbonylamino-cyclopropanecarboxylic acid benzyl ester (9.97 g, 104%) as a white solid. LC-MS B: t_R = 0.95 min; [M+H]⁺ = 292.31.

Step 2: 4 M HCl in dioxane (84.0 mL, 336 mmol) is added to a RT suspension of 1-*tert*-butoxycarbonylamino-cyclopropanecarboxylic acid benzyl ester (9.97 g, 33.0 mmol) in DCM (20 mL) and the resulting mix. stirred at RT for 1.5 h. The RM is concentrated and co-evaporated with DCM at HV to obtain 1-amino-cyclopropanecarboxylic acid benzyl ester HCl (7.93 g, 105%) as a white solid. LC-MS B: t_R = 0.50 min; [M+H]⁺ = 192.34.

Step 3: 2-Nitrobenzenesulfonyl chloride (8.30 g, 36.4 mmol) is added portionwise to a 0°C suspension of 1-amino-cyclopropanecarboxylic acid benzyl ester HCl (7.93 g, 33.0 mmol) and TEA (13.9 mL, 99.1 mmol) in DCM (70 mL). The ice bath is removed after 30 min and the mix. is stirred at RT for 1.5 h. The RM is partitioned between sat. NaHCO₃ and DCM and the layers are separated. The aq. layer is re-extracted with DCM and the combined org. layers are washed with brine (40 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (EtOAc/hept 3:7 to 1:1, R_f = 0.21 in EtOAc/hept 3:7) yields 1-(2-nitro-benzenesulfonylamino)-cyclopropanecarboxylic acid benzyl ester (12.05 g, 97%) as an orange oil. LC-MS B: t_R = 0.96 min; [M+H]⁺ = 377.29.

Step 4: DIAD (2.1 mL, 10.2 mmol) is added dropwise to a 0°C soln. of 1-(2-nitro-benzenesulfonylamino)-cyclopropanecarboxylic acid benzyl ester (2.00 g, 5.31 mmol), 2-methoxy-ethanol (0.635 mL, 7.97 mmol), and PPh₃ (2.83 g, 10.2 mmol) in THF (55 mL). The resulting mix. is stirred at 0°C for 5 min then at RT for 3 h. The mix. is concentrated and purified by FC (EtOAc/hept, 3:7 to 1:1, R_f = 0.39 in EtOAc/hept 1:1) to yield benzyl 1-((N-(2-methoxyethyl)-2-nitrophenyl)sulfonamido)cyclopropane-1-carboxylate (3.55 g, 154%) as a yellow oil. LC-MS B: t_R = 1.03 min; [M+H]⁺ = 435.20.

Step 5: Thiophenol (0.844 mL, 7.97 mmol) is added dropwise to a RT soln. of benzyl 1-((N-(2-methoxyethyl)-2-nitrophenyl)sulfonamido)cyclopropane-1-carboxylate (3.55 g, 5.31 mmol) and K₂CO₃ (1.18 g, 8.5 mmol) in DMF (28 mL). The resulting mix. is stirred at RT for 2 h. The mix. is partitioned between EtOAc and water. The org. layer is separated, dried (MgSO₄), filtered, and concentrated until only DMF is present. Purification by prep. HPLC (basic) yields 1-(2-methoxy-ethylamino)-cyclopropanecarboxylic acid benzyl ester (848 mg, 64%) as a colourless oil. LC-MS B: t_R = 0.58 min; [M+H]⁺ = 250.33.

Steps 6&7: The title compound is prepared from 1-(2-methoxy-ethylamino)-cyclopropanecarboxylic acid benzyl ester following the sequence of reactions described for **C-1.1**, steps 3&4. LC-MS B: t_R = 0.91 min; [M+H]⁺ = 389.42.

General method 14 for the synthesis of building blocks C**(*R*)-1-(*N*-(*tert*-Butoxycarbonyl)-*N*-ethyl-L-leucyl)piperidine-2-carboxylic acid (C-14.1)**

Step 1: Acetaldehyde (2.33 mL, 41.2 mmol) is added to a RT soln. of Fmoc-Leu-OH (3.00 g, 8.23 mmol), and *p*TsOH.H₂O (145 mg, 0.82 mmol) in PhMe (150 mL) and the resulting mix. is refluxed with a Dean Stark apparatus for 19 h. Acetaldehyde (2.33 mL, 41.2 mmol) is added again after 4 h and 6 h. The mix. is cooled to RT before being partitioned between EtOAc and sat. aq. NaHCO₃. The phases are separated and the aq. phase is re-extracted with EtOAc (2x). The combined org. layers are dried (Na₂SO₄), filtered, and concentrated. Purification by FC (eluting with 5% to 20% EtOAc in hept) yields (9*H*-fluoren-9-yl)methyl (4*S*)-4-isobutyl-(2*R*,*S*)-2-methyl-5-oxooxazolidine-3-carboxylate as a yellow oil. LC-MS B: *t*_R = 1.13 min; [M+H]⁺ = 380.15.

Step 2: TFA (31.3 mL, 0.40 mol) followed by triethylsilane (3.89 mL, 23.9 mmol) are added to a RT soln. of (9*H*-fluoren-9-yl)methyl (4*S*)-4-isobutyl-(2*R*,*S*)-2-methyl-5-oxooxazolidine-3-carboxylate (3.0 g, 8.0 mmol) in DCM (30 mL) and the resulting mix. is stirred for 19 h. The mix. is concentrated and co-evaporated with DCM (2x). Purification by FC (eluting with 50% EtOAc in hept & 1% AcOH) yields *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-ethyl-L-leucine as a yellow oil. LC-MS B: *t*_R = 1.05 min; [M+H]⁺ = 382.16.

Step 3: Methyl (*R*)-1-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-ethyl-L-leucyl)piperidine-2-carboxylate is prepared from *N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-ethyl-L-leucine and (*R*)-piperidine-2-carboxylic acid methyl ester HCl-salt following the procedure described for **C-2.1**, step 1. LC-MS I: *t*_R = 1.36 min; [M+H]⁺ = 507.33.

Step 4: A RT soln. of methyl (*R*)-1-(*N*-(((9*H*-fluoren-9-yl)methoxy)carbonyl)-*N*-ethyl-L-leucyl)piperidine-2-carboxylate (1.98 g, 3.91 mmol) and 2 M aq. NaOH (3.9 mL, 7.82 mmol) in MeOH (7.8 mL) is stirred for 18 h. The MeOH is evaporated in vacuo and the residue diluted with water and extracted with EtOAc (3x). The combined org. extracts are discarded and the aq. phase is evaporated to dryness to give (*R*)-1-(ethyl-L-leucyl)piperidine-2-carboxylic acid as a white solid. LC-MS B: *t*_R = 0.55 min; [M+H]⁺ = 271.30.

Step 5: A soln. of Boc anhydride (898 mg, 4.12 mmol) in DMF (3.5 mL) is added to a RT soln. of (*R*)-1-(ethyl-L-leucyl)piperidine-2-carboxylic acid (1.06 g, 3.92 mmol) in DMF (3.5 mL) and 1 M aq. NaOH (3.9 mL, 3.92 mmol). After 19 h TEA (1.09 mL, 7.84 mmol) is added and after another 5 h additional Boc anhydride (170 mg, 0.78 mmol) is added and stirring is continued for 1 h. The RM is acidified with 2 M aq. HCl and extracted with TBME (2x). The combined org. extracts are washed with water, dried (Na₂SO₄), filtered, and concentrated. Purification by prep. HPLC (acidic) gives the title compound **C-14.1** as a colourless oil. LC-MS B: *t*_R = 0.98 min; [M+H]⁺ = 371.21.

General method 16 for the synthesis of building blocks C***N*-(*N*-((Allyloxy)carbonyl)-*N*-methyl-L-leucyl)-*N*-(2-cyclohexylethyl)glycine (C-16.1)**

Steps 1&2: The title compound is prepared from **D2-3.1** and **IM-1.12** following the procedure described for **C-4.1**, steps 1&2. LC-MS I: *t*_R = 0.64 min; [M+H]⁺ = 397.29.

Listed in Table C-16 below are building blocks C that are prepared from **D2-3.1** and the corresponding starting material in analogy to the sequence described above for **C-16.1**.

Table C-16

No.	SM	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-16.2	IM-2.5	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(((<i>S</i>)-chroman-3-yl)methyl)glycine	0.56 I	433.14
C-16.3	IM-2.6	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(((<i>R</i>)-chroman-3-yl)methyl)glycine	0.56 I	433.17
C-16.4	IM-2.2	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.50 I	385.18
C-16.5	IM-2.1	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.49 I	385.17
C-16.6	IM-2.3	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-((<i>S</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.52-0.54 I	399.21
C-16.7	IM-2.4	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -(2-((<i>R</i>)-tetrahydro-2 <i>H</i> -pyran-2-yl)ethyl)glycine	0.52-0.54 I	399.21
C-16.8	IM-1.16	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -((2,3-dihydrobenzofuran-2-yl)methyl)glycine	0.95 B	419.37
C-16.9	IM-1.14	<i>N</i> -(<i>N</i> -((Allyloxy)carbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -((6,6-dimethyltetrahydro-2 <i>H</i> -pyran-2-yl)methyl)glycine	0.98 B	413.43

5 General method 17 for the synthesis of building blocks C

N-(*N*-((Allyloxy)carbonyl)-*N*-methyl-L-leucyl)-*N*-methyl-D-phenylalanine (C-17.1)

Step 1: PyClop (352 mg, 0.82 mmol) is added to a RT soln. of **IM-3.1** (200 mg, 0.682 mmol), **D2-3.1** (156 mg, 0.682 mmol), and DIPEA (0.36 mmol, 2.05 mmol) in DCM (3 mL) and the RM is heated to 40°C overnight. Water (5 mL) is added to the RM and the product is extracted with DCM (2x). The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC yields methyl *N*-(*N*-((allyloxy)carbonyl)-*N*-methyl-L-leucyl)-*N*-methyl-D-phenylalaninate. LC-MS B: t_R = 1.06 min; [M+H]⁺ = 405.19.

Step 2: LiOH·H₂O (40.1 mg, 0.96 mmol) is added to a RT soln. of methyl *N*-(*N*-((allyloxy)carbonyl)-*N*-methyl-L-leucyl)-*N*-methyl-D-phenylalaninate (193 mg, 0.478 mmol) in a solvent mix of THF/MeOH/H₂O 2/1/1 (2.5mL) and the RM is heated to 100°C for 15 h. THF and MeOH are evaporated and the residue is acidified with 1 M HCl to pH 1, then extracted with EtOAc (3x). The combined org. layers are dried (MgSO₄), filtered, and evaporated to yield **C-17.1**, which is used as such in the next step. LC-MS I: t_R = 0.53-0.56 min; [M+H]⁺ = 391.23.

Listed in Table C-17 below are building blocks C that are prepared from **D2-3.1** and the corresponding starting material in analogy to the sequence described above for **C-17.1**.

Table C-17

No.	SM	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-17.2	IM-3.2	(<i>R</i>)-2-((<i>S</i>)-2-(((Allyloxy)carbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3-cyclohexylpropanoic acid	1.03 B	397.25
C-17.3	IM-3.3	(<i>R</i>)-2-((<i>S</i>)-2-(((Allyloxy)carbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-2-cyclopentylacetic acid	0.96 B	369.13
C-17.4	Methyl 1-(methylamino)cyclopentane-1-carboxylate	(<i>S</i>)-1-(2-(((Allyloxy)carbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)cyclopentane-1-carboxylic acid	0.89 B	355.23
C-17.5	IM-4.1	(<i>S</i>)-1-(2-(((Allyloxy)carbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3,3-difluorocyclobutane-1-carboxylic acid	1.00 B	391.17

5 General method 18 for the synthesis of building blocks C

2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(4,4-difluorocyclohexyl)propanoic acid (C-18.1)

Step 1: NaH 60% dispersion in mineral oil (374 mg, 9.76 mmol) is added to a 0°C suspension of 2-((*tert*-butoxycarbonylamino)-3-(4,4-difluorocyclohexyl)propanoic acid (1.0 g, 3.25 mmol) in THF (20 mL). The RM is stirred at 0°C for 10 min, then at RT for another 10 min. The RM is cooled back to 0°C and MeI (0.614 mL, 9.76 mmol) is added dropwise and the RM is warmed to RT overnight. Water and EtOAc are added, then the two layers are separated. The aq. layer is washed with EtOAc (2x) and the combined org. layers are dried (Na₂SO₄), filtered, and concentrated. Purification by FC (eluting with 0% to 30% EtOAc in hept) yields methyl-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(4,4-difluorocyclohexyl)propanoate (434 mg, 40%) as a colourless oil. LC-MS B: t_R = 1.04 min; [M+H]⁺ = 336.26.

Step 2: TFA (0.99 mL, 12.9 mmol) is added to a RT soln. of methyl-2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(4,4-difluorocyclohexyl)propanoate (300 mg, 0.61 mmol) in DCM (10 mL) and the RM is stirred at RT for 2 h. The volatiles are removed in vacuo, and the residue co-evaporated with DCM (3x) to give methyl-3-(4,4-difluorocyclohexyl)-2-

(methylamino)propanoate 2,2,2-trifluoroacetate which is used as such in the next step. LC-MS B: t_R = 0.56 min; $[M+H]^+$ = 236.31.

- Steps 3&4:** The title compound is prepared from methyl-3-(4,4-difluorocyclohexyl)-2-(methylamino)propanoate 2,2,2-trifluoroacetate and Boc-*N*-methyl-L-leucine, following the sequence of reactions described for **C-2.1**, steps 1&2. LC-MS B: t_R = 1.03 min; $[M+H]^+$ = 449.27.

Listed in Table C-18 below are building blocks C that are prepared from Boc-*N*-methyl-L-leucine and the corresponding SM in analogy to the 4-step sequence described above for **C-18.1**. Alternatively, in step 2, Boc deprotection can be performed in the presence of 4 M HCl in dioxane instead of TFA.

Table C-18

No.	SM Step 1	SM Step 3	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
C-18.2	Boc-O-benzyl-D-homoserine	Boc- <i>N</i> -methyl-L-leucine	O-Benzyl- <i>N</i> -(<i>N</i> -(<i>tert</i> -butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -methyl-D-homoserine	1.02 B	451.22
C-18.3	Boc-D-Val-OH	Boc- <i>N</i> -methyl-L-leucine	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -methyl-D-valine	0.96 B	359.33
C-18.4	Boc-D-Leu-OH	Boc- <i>N</i> -methyl-L-leucine	<i>N</i> -(<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-L-leucyl)- <i>N</i> -methyl-D-leucine	1.00 B	373.33
C-18.5	(<i>R</i>)- <i>N</i> -Boc-2-aminobutyric acid ⁺	Boc- <i>N</i> -Methyl-L-leucine	(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)butanoic acid	0.92 B	345.31
C-18.6	(<i>R</i>)-Boc-2-amino-4,4-difluoro-butylric acid ⁺	Boc- <i>N</i> -Methyl-L-leucine	(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-4,4-difluorobutanoic acid	0.93 B	381.26
C-18.7	(<i>R</i>)- <i>N</i> -Boc-2-amino-3-cyclopropylpropanoic acid	Boc- <i>N</i> -Methyl-L-leucine	(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3-cyclopropylpropanoic acid	0.98 B	371.53
C-18.8	(<i>R</i>)- <i>N</i> -Boc-2-amino-3-cyclobutylpropanoic acid	Boc- <i>N</i> -Methyl-L-leucine	(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3-cyclobutylpropanoic acid	1.00 B	385.20

C-18.9	<i>rac</i> -N-Boc-O-ethyl-homoserine	Boc-N-Methyl-L-leucine	(RS)-N-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-O-ethyl-N-methylhomoserine	0.92 B	389.37
C-18.10	(R)-N-Boc-2-amino-4,4-dimethylpentanoic acid*	Boc-N-Methyl-L-leucine	(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-4,4-dimethylpentanoic acid	1.03 B	387.26

* SM used in step 1 is synthesized from commercially available unprotected amino acids using standard boc protection conditions.

General method 19 for the synthesis of building blocks C

1-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-4-phenylpiperidine-2-carboxylic acid (C-19.1)

- 5 **Step 1:** K₂CO₃ (860 mg, 6.22 mmol) is added to a RT soln. of 4-phenylpiperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (1.0 g, 3.11 mmol) and MeI (0.775 mL, 12.4 mmol) in DMF (8 mL) and the RM is stirred at RT for 20 min. Water (10 mL) and DCM (100 mL) are added to the RM, then the layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated to yield 1-(*tert*-butyl) 2-methyl 4-phenylpiperidine-1,2-dicarboxylate (1.14 g, 105%) as a yellow oil which is used as such in the next step. LC-MS B: t_R = 1.03 min; [M+H]⁺ = 320.29.

Step 2: 5 M HCl in *i*PrOH (3.44 mL, 17.2 mmol) is added to a RT soln. of 1-(*tert*-butyl) 2-methyl 4-phenylpiperidine-1,2-dicarboxylate (1.10 g, 3.44 mmol) in *i*PrOH (5 mL) and the RM is stirred at RT for 2 h, then at 50°C for 30 min. The mix. is concentrated to yield methyl-4-phenylpiperidine-2-carboxylate HCl salt (878 mg, 100%) as a yellow powder which is used as such in the next step. LC-MS B: t_R = 0.56 min; [M+H]⁺ = 220.35.

- 15 **Steps 3&4:** The title compound is prepared from methyl-4-phenylpiperidine-2-carboxylate HCl salt and Boc-N-methyl-L-leucine, following the sequence of reactions described for **C-2.1**, steps 1&2. LC-MS B: t_R = 1.03 min; [M+H]⁺ = 449.27.

General method 20 for the synthesis of building blocks C

- 20 **(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoic acid (C-20.1)**

Step 1: HATU (1.52 g, 4 mmol) is added to a RT soln. of Boc-D-Glu-Ome (1.00 g, 3.64 mmol), *N*-hydroxyacetamidine (296 mg, 4 mmol), and DIPEA (1.87 mL, 10.9 mmol) in DCM (10 mL) and the RM is stirred at RT for 30 min. The mix. is concentrated to yield the desired intermediate. LC-MS B: t_R = 0.82 min; [M+H]⁺ = 380.29. The crude intermediate is dissolved in dioxane (10 mL) and stirred at 80°C overnight. Water (10 mL) and DCM (100 mL) are added to the RM, then the layers are separated and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 10% to 20%

EtOAc in hept with $R_f = 0.12$ in EtOAc/hept 1:9) yields methyl (R)-2-((*tert*-butoxycarbonyl)amino)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoate (952 mg, 72%) as a colourless oil. LC-MS B: $t_R = 1.04$ min; $[M+H]^+ = 362.25$.

Step 2: Methyl (R)-2-amino-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoate HCl salt is prepared from methyl (R)-2-((*tert*-butoxycarbonyl)amino)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoate following the procedure described for **C-19.1**, step

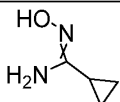
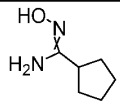
5 2.

Steps 3: Methyl (R)-2-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-4-methylpentanamido)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoate is prepared from methyl (R)-2-amino-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoate HCl salt and Boc-*N*-methyl-L-leucine following the reaction described for **C-2.1**, step 1. LC-MS B: $t_R = 1.10$ min; $[M+H]^+ = 489.22$.

10 **Step 4:** NaH (216 mg, 5.65 mmol) is added to a 0°C soln. of methyl (R)-2-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-4-methylpentanamido)-4-(3-phenyl-1,2,4-oxadiazol-5-yl)butanoate (920 mg, 1.88 mmol) in DMF (9 mL). After 5 min stirring, MeI (0.469 mL, 7.53 mmol) is added to the 0°C soln., then the ice bath is removed, and the RM stirred at RT for 4 h. Reaction control by LC/MS shows that during the methylation also saponification occurred (t_R different than SM). Water (15 mL) and TBME (20 mL) are added to the RM, then the layers are separated and the aq. layer is washed with TBME (1x 20 mL). The aq. layer is treated with 2 M HCl (10 mL) and extracted with DCM (2x 20 mL).
15 The combined DCM layers are washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to yield title compound **C-20.1** (688 mg, 75%) as a yellow oil, which was used as such in the next step. LC-MS B: $t_R = 1.03$ min; $[M+H]^+ = 489.24$.

Listed in Table C-20 are building blocks C, prepared according to the 4-step sequence described above for **C-20.1**. In
20 cases where saponification does not happen during methylation conditions, an extra step is added to saponify the ester to the carboxylic acid (4 N NaOH in MeOH in analogy to step 3 of **C-5.1**).

Table C-20

No.	SM hydroxyacet- imidamide*	Conditions for Step 4	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
C- 20.2		-20°C 3 min	(R)-2-((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)butanoic acid	0.97 A	453.21
C- 20.3		-20°C 20 min	(R)-2-((S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-4-(3-cyclopentyl-1,2,4-oxadiazol-5-yl)butanoic acid	1.04 A	481.19

C- 20.4		0°C to RT 10 min at RT	(R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-4-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)butanoic acid	1.03 A	469.22
C- 20.5		0°C 20 min	(R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-4-(3-methyl-1,2,4-oxadiazol-5-yl)butanoic acid	0.89 A	427.25

*If not commercially available, hydroxyacetimidamide are synthesized via standard conditions from their corresponding nitrile.

General method 21 for the synthesis of building blocks C

5 **N-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-N,O-dimethylhomoserine (C-21.1)**

Step 1: Mel (0.67 mL, 10.6 mmol) is added to a RT soln. of Boc-D-homoserine (2.0 g, 8.85 mmol) and K₂CO₃ (1.85g, 13.3 mmol) in DMF (30 mL) and the RM is stirred at RT for 16 h. The mix. is poured into ice water and extracted with EtOAc (3x). The combined org. layers are washed with water and brine, dried (MgSO₄), filtered, and concentrated to yield *tert*-butyl (R)-(2-oxotetrahydrofuran-3-yl)carbamate (2.07 g, 116%) as a light yellow solid. LC-MS B: t_R = 0.60 min; No ionisation.

Step 2: TFA (3.29 mL, 43 mmol) is added to a RT soln. of *tert*-butyl (R)-(2-oxotetrahydrofuran-3-yl)carbamate (2.0 g, 8.6 mmol) in DCM (20 mL) and the RM is stirred at RT for 6 h. The volatiles are removed in vacuo, co-evaporated with DCM (3x) to give the crude (R)-3-aminodihydrofuran-2(3H)-one 2,2,2-trifluoroacetate (3.0 g, 160%) which is used as such in the next step. By LC-MS no product formation could be detected, only the disappearance of SM is followed.

15 **Step 3:** HATU (5.83 g, 15.3 mmol) is added to a RT soln. of (R)-3-aminodihydrofuran-2(3H)-one 2,2,2-trifluoroacetate (3.00 g), Boc-N-methyl-L-leucine (3.70 g, 14.6 mmol) and DIPEA (7.16 mL, 41.8 mmol) in DMF (20 mL) and the RM is stirred for 1 h. The mix. is partitioned between water and EtOAc and the layers are separated, and the aq. layer is re-extracted with EtOAc (2x). The combined org. extracts are washed with water and brine, dried (Na₂SO₄), filtered, and evaporated. Purification by FC (eluting with 50% EtOAc in hept) yields *tert*-butyl methyl((S)-4-methyl-1-oxo-1-
20 (((R)-2-oxotetrahydrofuran-3-yl)amino)pentan-2-yl)carbamate (2.21 g, 75%) as a colourless oil. LC-MS B: t_R = 0.87 min; [M+H]⁺ = 329.28 .

Step 4: An aq. 8 M NaOH soln. (1.7 mL, 13.5 mmol) is added to a RT soln. of *tert*-butyl methyl((S)-4-methyl-1-oxo-1-
(((R)-2-oxotetrahydrofuran-3-yl)amino)pentan-2-yl)carbamate (2.21 g, 6.73 mmol) in dioxane (20 mL) and the RM is stirred at 50°C for 1 h. The RM is concentrated to dryness, then the crude is taken up in DCM and acidified with a 2
25 N aq. HCl soln. (pH 3). The layers are separated and the aq. layer is extracted with DCM (3x). The combined org. layers are washed with brine, dried (MgSO₄), filtered, and concentrated to yield *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-

leucylhomoserine (2.40 g, 100%) as a colourless oil, which is used as such in the next step. Epimerization occurred during lactone opening. LC-MS B: t_R = 0.75 min; $[M+H]^+$ = 347.30.

- Step 5:** NaH 60% dispersion in mineral oil (796 mg, 20.8 mmol) is added portionwise to a RT soln. of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucylhomoserine (2.40 mg, 6.93 mmol) in DMF (50 mL), then MeI (1.74 mL, 27.7 mmol) is added and stirring at RT continued for 1 h. The mix. is partitioned between water and EtOAc. The layers are separated and the aq. layer re-extracted with EtOAc (2x). The combined org. extracts are washed with water and brine, dried (Na_2SO_4), filtered, and evaporated. Purification by FC (eluting with 100% EtOAc) yields methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*,*O*-dimethylhomoserinate (692 mg, 26%) as a yellowish oil. LC-MS B: t_R = 0.99 min; $[M+H]^+$ = 389.26.
- Step 6:** An aq. 8 M NaOH soln. (1.7 mL, 3.56 mmol) is added to a RT soln. of methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*,*O*-dimethylhomoserinate (692 mg, 1.78 mmol, 1 eq) in dioxane (20 mL) and the RM is stirred at 50°C for 1 h. The RM is concentrated to dryness, then the crude is taken up in DCM and acidified with a 2 N aq. HCl soln. (pH 3). The layers are separated, and the aq. layer is extracted with DCM (3x). The combined org. layers are washed with brine, dried ($MgSO_4$), filtered, and concentrated to yield the title compound **C-21.1** (750 mg, 112%) as a colourless oil which is used as such in the next step. LC-MS B: t_R = 0.88 min; $[M+H]^+$ = 375.32.

General method 22 for the synthesis of building blocks C

(*R*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)propanoic acid (C-22.1)

- Step 1:** Benzyl bromide (4.71 mL, 38.8 mmol) is added to a RT solution of Boc-D-Asp-OMe (10.00 g, 38.8 mmol) and DIPEA (26.6 mL, 155 mmol) in DMF (71 mL) and the RM is heated to 50°C for 2 h. The solution is allowed to reach RT, then water and Et_2O are added and the layers separated. The inorg. layer is extracted with Et_2O (1x). The combined org. layers are washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by FC (eluting with 0% to 30% EtOAc in hept with R_f = 0.24 in EtOAc/hept 1:4) yields 4-benzyl 1-methyl (*tert*-butoxycarbonyl)-D-aspartate (12.7 g, 97%) as a colorless oil. LC-MS B: t_R = 0.97 min; $[M+H]^+$ = 337.96.
- Step 2:** 4 M HCl in dioxane (57.9 mL, 240 mmol) is added to a RT solution of 4-benzyl 1-methyl (*tert*-butoxycarbonyl)-D-aspartate (8.19 g, 24 mmol) in dioxane (42.3 mL) and the resulting RM is heated to 50°C for 30 min. The mixture is allowed to reach RT, then concentrated to yield 4-benzyl 1-methyl D-aspartate HCl-salt (6.90 g, 92%) of a yellowish solid which is used as such in the next step. LC-MS B: t_R = 0.53 min; $[M+H]^+$ = 238.30.
- Step 3:** HATU (10.38 g, 26.5 mmol) is added to a RT solution of 4-benzyl 1-methyl D-aspartate HCl-salt (6.84 g, 22.1 mmol), boc-*N*-methyl-L-leucine (5.58 g, 22.1 mmol), and DIPEA (19.9 mL, 110 mmol) in MeCN (83 mL). The resulting mixture is stirred at RT for 10 min. Water (135 mL) and DCM (315 mL) is added to the RM, then the layers are separated and the inorg. layer is extracted with DCM. The combined org. layers are washed with brine (50 mL), dried over a phase separator and concentrated. Purification by FC (eluting with 0% to 40% EtOAc) yields 4-benzyl 1-methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl-D-aspartate (9.70 g, 94%) as a yellowish oil. LC-MS B: t_R = 1.10 min; $[M+H]^+$ = 465.03.

Step 4: NaH (1.02 g, 26.5 mmol) is added to a -20°C solution of 4-benzyl 1-methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl-D-aspartate (4.53 g, 8.83 mmol) and MeI (2.22 mL, 35.3 mmol) in DMF (73 mL). The resulting solution is stirred at -20°C for 15 min, then quenched with 1 M aq. HCl soln. (224 mL) and diluted with isopropyl acetate. The layers are separated and the inorg. layer is extracted with isopropyl acetate (1x). The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 10% to 40% EtOAc in hept with R_f = 0.31 in EtOAc/hept 1:1) yields 4-benzyl 1-methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methyl-D-aspartate (3.9 g, 92%) as a yellowish oil. LC-MS B: t_R = 1.11 min; [M+H]⁺ = 479.16.

Step 5: Pd/C (10%, 387 mg, 0.364 mmol) is added to a RT soln. of 4-benzyl 1-methyl *N*-(*N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-leucyl)-*N*-methyl-D-aspartate (3.89 g, 7.28 mmol) in MeOH (34 mL) and the RM is stirred at RT for 1 h under a H₂ atm. The RM is filtered and concentrated to yield (*R*)-3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-4-methoxy-4-oxobutanoic acid (3.2 g, 114%) as a colorless oil, which is used as such in the next step. LC-MS B: t_R = 0.89 min; [M+H]⁺ = 389.33.

Step 6: PyBOP (1.73 g, 3.25 mmol) is added to a RT soln. of (*R*)-3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-4-methoxy-4-oxobutanoic acid (1.00 g, 2.5 mmol), 5-fluoro-*N*'-hydroxypicolinimide (631 mg, 3.75 mmol), and DIPEA (1.28 mL, 7.49 mmol) in DCM (2.8 mL). The resulting RM is stirred at RT for 10 min. The solvent is removed in vacuo and the residue re-dissolved in dioxane (2.8 mL). The resulting mix. is heated to 100°C for 3.5 h, then to 90°C overnight. Next morning, the heating was increased to 100°C for another 8 h. The RM is allowed to reach RT before concentrated in vacuo, then water and DCM is added. The layers are separated and the inorg. layer is extracted with DCM (1x). The combined org. layers are dried over a phase separator and concentrated. Purification by FC (eluting with 10% to 50% EtOAc in hept with R_f = 0.36 in EtOAc/hept 1:1) yields methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)propanoate (931 g, 73%) as a yellowish solid. LC-MS B: t_R = 1.04 min; [M+H]⁺ = 508.18.

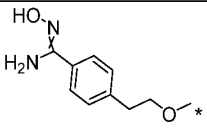
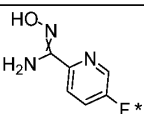
Step 7: 4 M NaOH soln. (3.70 mL, 14.8 mmol) is added to a RT soln. of methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)propanoate (1.50 g, 2.96 mmol) in MeOH (15 mL), and the RM is stirred at RT for 15 min. The RM is diluted with DCM (50 mL) and acidified with 2 M HCl soln. (20 mL). The layers are separated and the inorg. layer is extracted with DCM. The combined org. layers are washed with brine (30 mL), dried (MgSO₄), filtered, and concentrated to yield the title compound **C-22.1** (1.40 g, 96 %) as an off-white foam which is used as such in the next step. LC-MS B: t_R = 0.95 min; [M+H]⁺ = 494.18.

(*R*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)propanoic acid (C-22.2)

The title compound is prepared following the 7-step sequence described for **C-22.1**, using in step 6, commercially available 2,2,2-trifluoro-*N*'-hydroxyacetimidamide instead of 5-fluoro-*N*'-hydroxypicolinimide. LC-MS B: t_R = 1.02 min; [M+H]⁺ = 467.11.

Listed in Table C-22 below are building blocks C, prepared according to the 7-step sequence described above for **C-22.1**. In step 6, (*R*)-3-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-4-methoxy-4-oxobutanoic acid and their corresponding hydroxyacetimidamide are used. For **C-22.5**, synthesis is performed in analogy to **C-22.1**, using in step 1 boc-D-Glu-OMe instead of boc-D-Asp-OMe and in step 6 the corresponding hydroxyacetimidamide as outlined in Table C-22.

Table C-22

No.	SM hydroxyacetimidamide*	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
C-22.3		(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3-(3-(difluoromethyl)-1,2,4-oxadiazol-5-yl)propanoic acid	0.95 A	449.10
C-22.4		(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-3-(3-(4-(2-methoxyethyl)phenyl)-1,2,4-oxadiazol-5-yl)propanoic acid	1.06 A	533.17
C-22.5		(<i>R</i>)-2-((<i>S</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)- <i>N</i> ,4-dimethylpentanamido)-4-(3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)butanoic acid	0.97 A	508.21

*If not commercially available, hydroxyacetimidamide are synthesized via standard conditions from their corresponding nitrile.

General method C-23 for the synthesis of building blocks C

10 2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3,3-difluoropyrrolidin-1-yl)propanoic acid (C-23.1)

Step 1: NaH (1.02 g, 25.4 mmol) is added in four portions over 2 h, to a 0 °C solution of benzyl (*tert*-butoxycarbonyl)-L-serinate (1.50 g, 5.08 mmol) and MeI (1.59 mL, 25.4 mmol) in THF (30 mL). The ice bath is removed and the RM stirred at RT for 2 h. The mixture is cooled to 0 °C, then water is added carefully (strong gas evolution). Mixture is washed with Et₂O and organic layer is discarded. The water layer is acidified with 10% citric acid solution, then extracted with EtOAc (2x). The combined org. layers are washed with brine, dried (Na₂SO₄), filtered, and concentrated to yield 2-((*tert*-butoxycarbonyl)(methyl)amino)acrylic acid (1.178 g). Acetone (30 mL) is added to this crude material, followed by K₂CO₃ (1.81 g, 13.08 mmol), and benzyl bromide (1.04 mL, 8.72 mmol). The mixture is stirred at 50 °C for 50 min, then the suspension is diluted with water, partially concentrated to remove the acetone, then extracted with EtOAc (3x). The combined org. layers are washed with brine, dried (Na₂SO₄), filtered, and concentrated. Purification

by FC (eluting with 5 % to 100% EtOAc in hept) yields benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acrylate (760 mg, 59%) as a yellow oil. LC-MS J: t_R = 2.13 min; $[M+H]^+$ = no ionization.

Step 2: K_2CO_3 (378 mg, 3.78 mmol) is added to a solution of 3,3-difluoropyrrolidine HCl (493 mg, 3.43 mmol) in 2-propanol (0.69 mL) and water (61.8 μ l, 3.43 mmol), then benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acrylate (200 mg, 0.686 mmol) is added the resulting RM is heated to 60°C for 18 h. The solution is concentrated, then sat. $NaHCO_3$ soln. and EtOAc are added. The org. layer is collected and the inorg. layer is extracted with EtOAc (2x). The combined org. layers are washed with brine, dried (Na_2SO_4), filtered, and concentrated. Purification by prep. HPLC (basic) yields benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(3,3-difluoropyrrolidin-1-yl)propanoate (321 mg, 117%) as a yellowish oil. LC-MS J: t_R = 2.11 min; $[M+H]^+$ = 399.20

Step 3: TFA (2.0 mL, 26.0 mmol) is added to a RT soln. of benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino)-3-(3,3-difluoropyrrolidin-1-yl)propanoate (0.140 g, 0.320 mmol) in DCM (2.0 mL) and the RM is stirred at RT for 2 h. The volatiles are removed in vacuo, and the residue co-evaporated with DCM (2x) to give benzyl 3-(3,3-difluoropyrrolidin-1-yl)-2-(methylamino)propanoate TFA-salt as an oil which is used as such in the next step.

Steps 4 and 5: The title compound is prepared from Boc-*N*-methyl-L-leucine and benzyl 3-(3,3-difluoropyrrolidin-1-yl)-2-(methylamino)propanoate TFA-salt following the sequence of reactions described for **C-1.1**, step 3 and 4. LC-MS F: t_R = 1.93 min; $[M+H]^+$ = 436.20.

2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(pyrrolidin-1-yl)propanoic acid (C-23.2)

The title compound is prepared following the 5-step sequence described for **C-23.1**, using in step 2 following conditions. Pyrrolidine (0.213 mL, 2.57 mmol) is added to a RT solution of benzyl 2-((*tert*-butoxycarbonyl)(methyl)amino)acrylate (500 mg, 1.716 mmol) in EtOH (10 mL) and the RM is heated to 50°C for 1.5 h. The RM is concentrated and directly purified by prep HPLC to yield desired intermediate (53 mg, 76%) as a clear oil. Following step 3 to 5 (as described for C-23.1) yields desired title compound **C-23.2**. LC-MS J: t_R = 1.69 min; $[M+H]^+$ = 400.30

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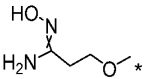
General method 24 for the synthesis of building blocks C

(*R*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-phenyl-1,2,4-oxadiazol-5-yl)propanoic acid (C-24.1)

The title compound is prepared following the 4-step sequence described for **C-20.1**, using Boc-D-Asp-OMe instead of Boc-D-Glu-OMe in step 1. In most cases, a saponification step (4 N NaOH in MeOH) is added. LC-MS A: t_R = 1.04 min; $[M+H]^+$ = 475.23

30

Table C-24

No.	SM hydroxyacetimidamide*	Product	t_R [min]	MS-data
			LC-MS Method	m/z [M+H] ⁺
C- 24.2		(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3-(3-(2-methoxyethyl)-1,2,4-oxadiazol-5-yl)propanoic acid	1.00 A	471.42
C- 24.3		(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3-(3-methyl-1,2,4-oxadiazol-5-yl)propanoic acid	0.88 A	413.25

*If not commercially available, hydroxyacetimidamide are synthesized via standard conditions from their corresponding nitrile.

5 General method 25 for the synthesis of building blocks C

(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3-(3-methoxyisoxazol-5-yl)propanoic acid (C-25.1)

- Step 1:** Ethyl chloroformate (3.54 mL, 36.4 mmol) is added dropwise to a 0°C solution of 3-methoxy-1,2-oxazole-5-carboxylic acid (4.98 g, 33.1 mmol) and TEA (5.29 mL, 38.0 mmol) in THF (132 mL). The RM is stirred at 0°C for 1.5 h, then a solution of NaBH₄ (3.79 g, 99.2 mmol) in water (53 mL) is added dropwise at 0°C and the resulting RM stirred at 0°C for 10 min. The RM is allowed to warm up to RT, then DCM is added, and the two layers are separated. The inorg. layer is extracted with DCM (2x), and the combined org. layers are washed with brine, dried (over phase separator), and concentrated. Purification by FC (eluting with 10% to 50% EtOAc in hept., with R_f = 0.38 in hept./EtOAc 1:1) gives (3-methoxyisoxazol-5-yl)methanol (1.39 g, 33%) as a colorless oil. LC-MS A: t_R = 0.39 min; [M+H]⁺ = 130.10.
- Step 2:** PBr₃ (1.03 mL, 10.8 mmol) is added dropwise to a 0°C solution of (3-methoxyisoxazol-5-yl)methanol (1.39 g, 10.8 mmol) in Et₂O (115 mL). The ice bath is removed and the resulting RM is stirred at RT for 48 h. The RM is diluted with EtOAc and sat. aq. Na₂CO₃ soln. The layers are separated and the inorg. layer is extracted with EtOAc (1x). The combined org. layers are dried (MgSO₄), filtered, and concentrated to yield 5-(bromomethyl)-3-methoxyisoxazole (1.65 g, 80%) as a slightly yellow oil which is used as such in the next step. LC-MS A: t_R = 0.71 min; [M+H]⁺ = no ionization.
- Step 3:** n-BuLi (1.6 M in hexanes, 6.03 mL, 9.53 mmol) was added dropwise to a -75°C solution of (S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (1.5 mL, 8.1 mmol) in THF (74 mL). The resulting solution is stirred for 30 min, then a solution of 5-(bromomethyl)-3-methoxyisoxazole (1.64 g, 8.1 mmol) in THF (60 mL) is added and the RM is stirred at -75°C for 1.5 h. 1 M aq. NH₄Cl soln (86 mL) and Et₂O is added to the RM, the two layers are separated and the inorg. layer is dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 0% to 20% of EtOAc in hept., R_f = 0.32 in hept./EtOAc 4:1) yields 5-(((2R,5S)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-3-methoxyisoxazole (1.30 g, 55%) as a slightly yellow oil. LC-MS A: t_R = 0.91 min; [M+H]⁺ = 296.24.

Step 4: 1 M aq. HCl soln (8.1 mL, 8.21 mmol) is added to a RT solution of 5-(((2*R*,5*S*)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)methyl)-3-methoxyisoxazole (1.31 g, 4.1 mmol) in MeCN (41.4 mL). The RM is stirred at RT for 30 min, then the solvent is removed, and the residue treated with 1 M aq. NH₃ soln. until pH= 9. DCM is added to the RM and the two layers are separated. The inorg. layer is extracted with DCM (1x) and the combined org. layers are dried (over phase separator) and concentrated. Purification by FC (eluting with 0 to 2% MeOH in DCM (containing 0.5% NH₄OH), with *R_f* = 0.20 in DCM/MeOH/NH₄OH 100:2:0.5) yields methyl (*R*)-2-amino-3-(3-methoxyisoxazol-5-yl)propanoate (756 mg, 92%) as a yellow oil. LC-MS A: *t_R* = 0.35 min; [M+H]⁺ = 201.34.

Step 5: HATU (1.648 g, 4.20 mmol) is added to a RT solution of methyl (*R*)-2-amino-3-(3-methoxyisoxazol-5-yl)propanoate (750 mg, 3.50 mmol), boc-*N*-methyl-L-leucine (886 mg, 3.5 mmol), and DIPEA (1.8 mL, 10.5 mmol) in MeCN (12.8 mL). The RM is stirred at RT for 10 min, then water and DCM are added, and the layers are separated. The inorg. layers are extracted with DCM (1x) and the combined org. layers are dried (over phase separator) and concentrated. Purification by FC (eluting with 10% to 40% EtOAc in hept., with *R_f*=0.23 in hept./EtOAc 7:3) yields methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-4-methylpentanamido)-3-(3-methoxyisoxazol-5-yl)propanoate (1.40 g, 94%) as a colorless oil. LC-MS A: *t_R* = 0.99 min; [M+H]⁺ = 428.19.

Step 6: NaH (376 mg, 9.82 mmol) is added to a -20°C solution of methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-4-methylpentanamido)-3-(3-methoxyisoxazol-5-yl)propanoate (1.40 g, 3.27 mmol) and MeI (0.82 mL, 13.1 mmol) in DMF (28 mL). The RM is stirred at -20°C for 11 min, then the RM is quenched with 1 M aq. HCl soln (84 mL) followed by the addition of Et₂O. The layers are separated and the inorg. layer is extracted with Et₂O (1x). The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 5% to 40% of EtOAc in hept., with *R_f* = 0.26 in hept/EtOAc 7:3) yields methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-methoxyisoxazol-5-yl)propanoate (1.30 g, 90%) as a yellowish oil. LC-MS A: *t_R* = 1.03 min; [M+H]⁺ = 442.20.

Step 7: 4 M aq. NaOH soln (28.8 mL, 114 mmol) is added to a RT solution of methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-methoxyisoxazol-5-yl)propanoate (1.303 g, 2.86 mmol) in MeOH (41.2 mL). The RM is heated to 50°C and stirred at this temperature for 10 min, then the RM is allowed to reach RT. 2 M aq. HCl soln (165 mL) and DCM (105 mL) are added, the layers separated, and the inorg. layer extracted with DCM (1x). The combined org. layers are dried (over phase separator) and concentrated to yield the title compound (1.20 g, 99%) as a colorless oil. LC-MS A: *t_R* = 0.92 min; [M+H]⁺ = 428.17.

(*R*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(3-(*tert*-butyl)isoxazol-5-yl)propanoic acid (C-25.2)

The title compound is prepared following the 7-step sequence described for **C-25.1**, using in step 1 3-*tert*-butyl-1,2-oxazole-5-carboxylic acid instead of 3-methoxy-1,2-oxazole-5-carboxylic acid. LC-MS A: *t_R* = 1.14 min; [M+H]⁺ = 468.46.

(R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3-(5-(tert-butyl)-1,2,4-oxadiazol-3-yl)propanoic acid (C-25.3)

The title compound is prepared following step 3 to step 7, described for **C-25.1**, using in step 3, 5-(tert-butyl)-3-(chloromethyl)-1,2,4-oxadiazole instead of 5-(bromomethyl)-3-methoxyisoxazole. LC-MS A: t_R = 1.00 min; $[M+H]^+$ = 455.09.

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(R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoic acid (26.1)

Step 1: Copper(II) acetate (66.5 mg, 0.348 mmol) is added to a RT solution of 3-azido-N-Boc-D-alanine methyl ester (850 mg, 3.48 mmol), phenylacetylene (0.39 mL, 3.48 mmol), and (+)-sodium L-ascorbate (141 mg, 0.696 mmol) in a 1:1 mixture of tBuOH/H₂O (11.9 mL), then the RM is stirred at RT for 20 min. The RM is diluted with DCM and brine, the layers are separated and the org. layer is dried (with phase separator) and concentrated to yield methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (1.07 g, 89%) a slightly yellowish solid. LC-MS A: t_R = 0.89 min; $[M+H]^+$ = 347.19.

Step 2: 4 M HCl in dioxane (7.6 mL, 30.7 mmol) is added to a RT solution of methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (1.06 g, 3.07 mmol) in dioxane (5.4 mL). The RM is heated to 50°C for 30 min. The RM is allowed to reach RT, then the RM is concentrated to yield methyl (R)-2-amino-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate dihydrochloride (980 mg, 100%) of a yellowish solid. LC-MS A: t_R = 0.49 min; $[M+H]^+$ = 247.28.

Step 3: HATU (1.437 g, 3.67 mmol) is added to a RT solution of methyl (R)-2-amino-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate dihydrochloride (975 mg, 3.05 mmol), boc-N-methyl-L-leucine (773 mg, 3.05 mmol) and DIPEA (2.61 mL, 15.3 mmol) in MeCN (10.9 mL). The RM is stirred at RT for 10 min, then water and DCM are added. The layers are separated, the inorg. layer extracted with DCM (1x), and the combined org. layers are dried (over phase separator) and concentrated. Purification by FC (eluting with 20% to 60% EtOAc in hept. with R_f = 0.28 in EtOAc/hept 1:1) yields methyl (R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methylpentanamido)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (1.90 g, 130%) as an orange oil. LC-MS A: t_R = 1.04 min; $[M+H]^+$ = 474.17.

Step 4: NaH (381 mg, 9.95 mmol) is added to a -20°C solution of methyl (R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-4-methylpentanamido)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (1.772 g, 3.32 mmol) and MeI (0.834 mL, 13.3 mmol) in DMF (28.2 mL). The RM is stirred at -20°C for 17 min, then quenched with 1 M aq. HCl soln (84.6 mL) and Et₂O. The layers are separated and the inorg. layers are extracted with Et₂O (1x). The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 0% to 60% EtOAc in hept. with R_f = 0.52 in hept/EtOAc 4:6) yields methyl (R)-2-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3-(4-phenyl-1H-1,2,3-triazol-1-yl)propanoate (612 mg, 39%) as a yellow oil. LC-MS A: t_R = 1.07 min; $[M+H]^+$ = 488.19.

Step 5: 4 M aq. NaOH soln (10.3 mL, 40.7 mmol) is added to a RT solution of methyl (*R*)-2-((*S*)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propanoate (607 mg, 1.02 mmol) in MeOH (14.4 mL). The RM is heated to 50°C for 12 min, then allowed to reach RT before 2 M aq. HCl soln (59 mL) and DCM (35 mL) are added. The layers are separated, and the inorg. layer is extracted with DCM (1x).

5 The combined org. layers are dried (over phase separator) and concentrated. Purification by prep HPLC (acidic conditions) yields title compound (337 mg, 70%) as a white foam. LC-MS A: t_R = 0.97 min; $[M+H]^+$ = 474.18.

(*R*)-2-((*S*)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)-3-(4-(5-fluoropyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)propanoic acid (C-26.2)

The title compound is prepared following the 5-step sequence described for **C-26.1**, using in step 1 2-ethynyl-5-fluoropyridine instead of phenylacetylene. LC-MS A: t_R = 0.94 min; $[M+H]^+$ = 493.36.

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General method 27 for the synthesis of building blocks C

N-(N-(*tert*-Butoxycarbonyl)-N-methyl-L-leucyl)-O-cyclohexyl-N-methyl-D-homoserine (C-27.1)

Step 1: To a suspension of sodium hydride (suspension in oil, 60%) (1017 mg, 26.5 mmol) in DMF (10 mL) is added dropwise a solution of Boc-D-homoserine (3000 mg, 13.3 mmol) in DMF (10 mL) at 0°C and the solution is stirred for 20 min. To this solution is added tetrabutylammonium iodide (49.5 mg, 0.133 mmol) and the resulting mixture is stirred for 30 min, and 3-Bromocyclohexene (2 mL, 15.6 mmol) is added. After stirring for 2 h at RT, sodium iodide (2010 mg, 13.3 mmol) is added and the RM is stirred at rt overnight. Water and EtOAc are added and the 2 phases are separated. The inorg. layer is extracted further with EtOAc (2X). The combined org. layers are dried over Na₂SO₄, filtered and concentrated to yield N-(*tert*-butoxycarbonyl)-O-(cyclohex-2-en-1-yl)-D-homoserine (3.06g) as a brown oil which is used as such in the next step. LC-MS B. t_R = 0.86 min; $[M+H]^+$ = 300.33.

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Step 2: Under argon, N-(*tert*-butoxycarbonyl)-O-(cyclohex-2-en-1-yl)-D-homoserine (3060 mg, 10.2 mmol) is solubilized in a mixture of DCM (10 mL) and MeOH (10 mL). This solution is cooled down to 0°C and trimethylsilyldiazomethane (ca. 10% in Hexane, ca. 0.6mol/L) (21 mL, 12.3 mmol) is added slowly. The solution is stirred for 1h at RT. Solvents are removed to dryness. The crude material is absorbed over Isolute and purified via FC, using a gradient of Heptane/ EtOAc from 100:0 to 60:40 to give 0.9 g of the methyl N-(*tert*-butoxycarbonyl)-O-(cyclohex-2-en-1-yl)-D-homoserinate as a light yellow oil. LC-MS B: t_R = 0.98 min; $[M+H]^+$ = 314.34.

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Step 3: Under N₂, methyl N-(*tert*-butoxycarbonyl)-O-(cyclohex-2-en-1-yl)-D-homoserinate (900 mg, 2.87 mmol) is dissolved in MeOH (20 mL); the vessel is purged with N₂/vacuum (3x) before 10% Pd/C (90 mg) is added. After inertising another three times a H₂ balloon is connected and the RM is stirred for 1 h under H₂ atmosphere. The heterogeneous reaction mixture is filtered over a glass fiber filter (washing with methanol/THF). The filtrate is then concentrated to dryness under reduced pressure to yield 0.82 g of methyl N-(*tert*-butoxycarbonyl)-O-cyclohexyl-D-homoserinate as a colorless oil which is used as such in the next step. LC-MS B: t_R = 1.01 min; $[M+H]^+$ = 316.37.

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Step 4: Sodium hydride (60 % dispersion in mineral oil) (149 mg, 3.9 mmol) is added portionwise to a RT solution of methyl N-(*tert*-butoxycarbonyl)-O-cyclohexyl-D-homoserinate (820 mg, 2.6 mmol) and iodomethane (0.245 mL, 3.9

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mmol) in DMF (8 mL) under argon and the resulting mixture is stirred for 1h. The RM is partitioned between water and EtOAc. The layers are separated and the inorg. layer is extracted further with EtOAc (2x). The combined org. extracts are washed with water and brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give 0.84 g of methyl N-(tert-butoxycarbonyl)-O-cyclohexyl-N-methyl-D-homoserinate as a yellowish oil. No purification at this stage. LC-MS B: t_R = 1.06 min; [M+H]⁺ = 330.37.

Step 5 to 7: The title compound is prepared as a colorless oil from Boc-N-methyl-L-leucine and methyl N-(tert-butoxycarbonyl)-O-cyclohexyl-N-methyl-D-homoserinate following the sequence of reactions described for **C-18.1**, step 2 to 4. LC-MS B: t_R = 1.06 min; [M+H]⁺ = 443.44.

N-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-O-phenyl-D-homoserine (C-27.2)

Step 1: To a solution of (R)-4-bromo-2-[[[(tert-butoxy)carbonyl]amino]butanoic acid tert-butyl ester (300 mg, 0.843 mmol) in DMF (2 mL) at RT is added phenol (0.0786 mL, 0.885 mmol) and K₂CO₃ (349 mg, 2.53 mmol). The RM is stirred at 60°C RT for 1 hr. Water and EtOAc are added and the 2 phases are separated. The inorg. layer is extracted further with EtOAc (2X). The combined org. layers are dried over Na₂SO₄, filtered and concentrated. Crude is absorbed over isolate and the product is purified by FC (Heptane/EtOAc, from 100/0 to 50/50) to give tert-butyl N-(tert-butoxycarbonyl)-O-phenyl-D-homoserinate as a light-yellow oil (267 mg). LC-MS B: t_R = 1.08 min; [M+H]⁺ = 352.32.

Step 2: Sodium hydride (60 % dispersion in mineral oil) (43.7 mg, 1.14 mmol) is added portionwise to a RT solution of tert-butyl N-(tert-butoxycarbonyl)-O-phenyl-D-homoserinate (267 mg, 0.76 mmol) and iodomethane (0.0717 mL, 1.14 mmol) in DMF (5 mL) under argon and the resulting mixture is stirred for 1h. The RM is partitioned between water and EtOAc. The layers are separated, and the aq. phase is re-extracted with EtOAc (2x). The combined org. extracts are washed with water and brine, dried over Na₂SO₄, filtered and evaporated in vacuo to give tert-butyl N-(tert-butoxycarbonyl)-N-methyl-O-phenyl-D-homoserinate (226 mg) as a pale orange oil. No purification at this step. LC-MS B: t_R = 1.13 min; [M+H]⁺ = 366.31.

Step 3: TFA (0.474 mL, 6.18 mmol) is added to a RT solution of tert-butyl N-(tert-butoxycarbonyl)-N-methyl-O-phenyl-D-homoserinate (226 mg, 0.618 mmol) in DCM (5 mL) and the resulting mixture is stirred at RT for 6h. The volatiles are removed extensively in vacuo; the resulting residue is dissolved back in DCM to repeat the co-evaporation process 2 further times to give the crude product (266 mg) as the (1:1) 2,2,2-trifluoroacetate salt of (R)-1-carboxy-N-methyl-3-phenoxypropan-1-aminium, as a brown oil which is used as such in the next step. LC-MS B: t_R = 0.44 min; [2M+H]⁺ = 419.36.

Step 4: Thionyl chloride (0.375 mL, 5.08 mmol) is added at rt to a solution of (R)-1-carboxy-N-methyl-3-phenoxypropan-1-aminium 2,2,2-trifluoroacetate (266 mg, 1.27 mmol) in MeOH (5 mL). The RM is stirred at 60°C for 16 h. The mixture is poured into ice water and extracted with DCM (3x). The combined org. layers are washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude methyl N-methyl-O-phenyl-D-homoserinate (101 mg) as a colorless oil. No purification at this stage. LC-MS B: t_R = 0.54 min; [M+H]⁺ = 224.31.

Step 5&6: The title compound is prepared as a colorless oil from Boc-N-methyl-L-leucine and methyl N-methyl-O-phenyl-D-homoserinate following the sequence of reactions described for **C-2.1**, step 1 and 2. LC-MS B: t_R = 1.03 min; $[M+H]^+$ = 437.31.

5 General method 28 for the synthesis of building blocks C

(RS)-N-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-O-(5-methylpyrazin-2-yl)homoserine (**C-28.1**)

Step 1-3: The sequence of the 3 first reactions described for **C-18.2** gives the key intermediate methyl O-benzyl-N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-D-homoserinate as a colorless oil after purification by FC (0 to 100% of EtOAc in Heptane). LC-MS B: t_R = 1.12 min; $[M+H]^+$ = 465.38.

- 10 **Step 4:** Under N_2 , methyl O-benzyl-N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-D-homoserinate (5500 mg, 11.8 mmol) is dissolved in MeOH (100 mL); the vessel is purged with N_2 /vacuum (3x) before $Pd(OH)_2/C$ (20 wt. %) (830 mg) is added. After inertising another three times a H_2 balloon is connected and the RM is stirred for 16 h under H_2 atmosphere. The heterogeneous RM is filtered over a glass fiber filter (washing with methanol/THF). The filtrate is then concentrated to dryness under reduced pressure to yield 4.36 g of methyl N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-D-homoserinate as a colorless oil which is used as such in the next step. LC-MS B: t_R = 0.87 min; $[M+H]^+$ = 375.07.

- 20 **Step 5:** DIAD (0.194 mL, 0.966 mmol) is added dropwise to an ice-chilled suspension of 2-hydroxy-5-methylpyrazine (80 mg, 0.69 mmol), methyl N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-D-homoserinate (271 mg, 0.725 mmol), NEt_3 (0.0962 mL, 0.69 mmol) and polymer supported triphenylphosphine (1.32 mmol/g) (787 mg, 1.04 mmol) in THF (30 mL). The resulting RM is stirred at RT for 1h. The polymer is filtered off. Water is added to the filtrate and the resulting inorg. layer is extracted with EtO₂ (3x). The combined org. extracts are washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by FC (50% to 100% EtOAc in Heptane) yields a mixture of epimers methyl (RS)-N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-O-(5-methylpyrazin-2-yl)homoserinate (376 mg) as a white solid. LC-MS B: t_R = 1.07 & 1.08 min; $[M+H]^+$ = 467.47.

- 25 **Step 6:** To the mixture of epimers methyl (RS)-N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-O-(5-methylpyrazin-2-yl)homoserinate (376 mg, 0.806 mmol) in dioxane (10 mL) is added NaOH 1M (1.6 mL, 1.61 mmol). The RM is stirred at 50°C for 1 h; it is then left returning to RT and is treated with 0.5 ml of saturated NH_4Cl solution. The resulting mixture is concentrated to dryness. The crude residue is partitioned between DCM and Water and the DCM layer is collected. The inorg. layer is acidified with a few drops of 2N aq. HCl solution (down to pH ~ 3) and is extracted with DCM (3x). The combined org. layers are washed with acidified brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield the title compound (RS)-N-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-N-methyl-O-(5-methylpyrazin-2-yl)homoserine (**C-28.1**) as a colorless oil (334 mg) which is used as such in the next steps. LC-MS B: t_R = 0.94 & 0.95 min; $[M+H]^+$ = 453.47.

(RS)-N-(N-(tert-Butoxycarbonyl)-N-methyl-L-leucyl)-O-(2-methoxypyridin-4-yl)-N-methylhomoserine (C-28.2)

The title compound is prepared following the 6-step sequence described for **C-28.1**, using in step 5 commercially available 2-methoxy-4-pyridinol instead of 2-hydroxy-5-methylpyrazine, yielding **C-28.2** as a colorless oil of a mixture of indistinguishable epimers. LC-MS B: t_R = 0.76 min; $[M+H]^+$ = 468.47.

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General method 29 for the synthesis of building blocks C**(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-3,3-dimethylbutanoic acid (C-29.1)**

Step 1: To a pale-yellow solution of 3-methyl-D-valine methyl ester (1080 mg, 7.14 mmol) in dioxane (20 mL) is added NaOH 1 M (14.3 mL, 14.3 mmol). The resulting mixture is then treated with Boc_2O (1.84 mL, 7.85 mmol) and stirred at room temperature for 24h. The mixture is concentrated under reduced pressure and the residue is partitioned between sat. aq. NH_4Cl solution and DCM. The inorg. layer is extracted further with DCM (2x) and the combined org. extracts are dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue is redissolved in MeCN and washed with Heptane then coevaporated with Et_2O to afford the methyl (R)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoate as a colorless oil (1.08 g). No further purification at this stage. LC-MS B: t_R = 0.92 min; $[M+H]^+$ = 246.22 & $[2M+H]^+$ = 491.27.

Step 2: Sodium hydride (60 % dispersion in mineral oil) (253 mg, 6.6 mmol) is added portionwise, at RT, under argon, to a solution of methyl (R)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoate (1080 mg, 4.4 mmol) and iodomethane (0.415 mL, 6.6 mmol) in DMF (17 mL). The resulting mixture is stirred at RT for 1h. The RM is quenched by careful addition of sat. aq. NH_4Cl and the aq. layer is extracted with EtOAc (3x). The combined org. extracts are washed with a sat. aq. thiosulfate solution then with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure to give methyl (R)-2-((tert-butoxycarbonyl)(methyl)amino)-3,3-dimethylbutanoate (1.58 g) as a yellowish liquid which is used as such in the next step. LC-MS B: t_R = 1.01 min; $[M+H]^+$ = 260.23.

Step 3-5: The title compound is prepared as an off-white solid from Boc-N-methyl-L-leucine and methyl (R)-2-((tert-butoxycarbonyl)(methyl)amino)-3,3-dimethylbutanoate following the sequence of reactions described for **C-18.1**, step 2 to 4; Purification by FC (0% to 100% EtOAc in Heptane, monitoring with ELSD). LC-MS B: t_R = 1.02 min; $[M+H]^+$ = 373.32.

(R)-2-((S)-2-((tert-Butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)-4-phenylbutanoic acid (C-29.2)

The title compound is prepared following the 5-step sequence described for **C-29.1**, starting in Step 1 from commercially available ethyl (R)-2-amino-4-phenylbutanoate hydrochloride instead of 3-methyl-D-valine methyl ester, yielding **C-29.2** as a yellow oil. LC-MS B: t_R = 1.03 min; $[M+H]^+$ = 421.38.

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Building Blocks D**O-Benzyl-N-(tert-Butoxycarbonyl)-N-methylserine (D1-1.1)**

Step 1: Paraformaldehyde (579 mg, 4.5 mmol) is added to a RT soln. of Boc-D-Ser-(Bzl)-OH (271 mg, 0.9 mmol) and pTsOH (15.8 mg, 0.09 mmol) in PhMe (9 mL) and the RM is refluxed in a Dean Stark apparatus overnight. The mix. is washed with aq. NaHCO₃, the org. layer is separated, dried (MgSO₄) and concentrated under reduced pressure. Purification by FC (eluting from 0% to 70% EtOAc in hept) yields *tert*-butyl (R)-4-((benzyloxy)methyl)-5-oxooxazolidine-3-carboxylate (178 mg, 65%) as a white solid. LC-MS B: t_R = 0.98 min; [M+H]⁺ = 308.09.

Step 2: TFA (2.0 mL, 26.1 mmol) is added to a RT soln. of *tert*-butyl (R)-4-((benzyloxy)methyl)-5-oxooxazolidine-3-carboxylate (179 mg, 0.581 mmol) and triethylsilane (0.5 mL, 3.1 mmol) in CHCl₃ (3 mL) and the RM is stirred at RT for 3 h. The mix. is concentrated, and the residue is re-dissolved in TBME and extracted with aq. NaHCO₃. The aq. layer is acidified with 1 N HCl to pH 3 and extracted with TBME. The org. layer is concentrated to yield O-benzyl-N-methyl-DL-serine as a white solid which is used as such in the next step. LC-MS B: t_R = 0.43 min; [M+H]⁺ = 210.34.

Step 3: Di-*tert*-butyl dicarbonate (128 mg, 0.581 mmol) is added to a RT soln. of O-benzyl-N-methyl-D-serine (122 mg, 0.581 mmol) and TEA (0.404 mL, 2.9 mmol) in THF (6 mL) and the RM is stirred at RT overnight. The mix. is concentrated and to the residue is added TBME and water. The layers are separated and the aq. layer is acidified (pH 5) with 10% citric acid. The aq. layer is extracted with TBME (3x) and the combined org. layers are dried (MgSO₄), filtered, and concentrated to yield the title compound **D1-1.1** (136 mg, 76%) as a viscous yellow oil. LC-MS B: t_R = 0.88 min; [M+H]⁺ = 310.17. Whether racemization occurs during this synthetic step or in an earlier step was not determined. The racemic mix. is used as such in the next step.

Listed in Table D1-1 below are building blocks D1 that are prepared from the corresponding starting materials in analogy to the sequence described above for **D1-1.1**.

Table D1-1

No.	SM	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
D1-1.2	Boc-D-Ser-(tBu)-OH	<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>O</i> -(<i>tert</i> -butyl)- <i>N</i> -methylserine Racemisation occurred	0.85 B	276.22

N-(((9H-Fluoren-9-yl)oxy)carbonyl)-N-(3,3-dimethylbutyl)glycine (D1-2.1)

Step 1: In a Dean-Stark apparatus, pTsOH (65.3 mg, 0.336 mmol) is added to a RT suspension of Fmoc-Gly-OH (1.0 g, 3.36 mmol) and 3,3-dimethylbutyraldehyde (0.489 mL, 3.7 mmol) in PhMe (60 mL) and the resulting turbid mix. is refluxed at 110°C for 4 h. After cooling to RT the RM is diluted with EtOAc and the product is washed with sat. aq. NaHCO₃ (2x). The org. layer is dried (MgSO₄), filtered, and concentrated to give (9H-fluoren-9-yl)methyl 2-neopentyl-

5-oxooxazolidine-3-carboxylate as a light yellow solid (0.99 g, 78%) which is used as such in the next step. LC-MS B: $t_R = 1.13$ min; $[M+H]^+ = 380.19$.

Step 2: TFA (4.94 mL, 64.6 mmol) is added to a RT soln. of (9H-fluoren-9-yl)methyl 2-neopentyl-5-oxooxazolidine-3-carboxylate (980 mg, 2.58 mmol) and triethylsilane (1.25 mL, 7.75 mmol) in DCM (13 mL) and the resulting mix. is stirred at RT overnight. The RM is diluted with DCM and washed with water (2x). The org. layer is dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 0% to 50% EtOAc in hept and 0.5% AcOH) yields the title compound **D1-2.1** (866 mg, 88%) as a colourless solid. LC-MS B: $t_R = 1.05$ min; $[M+H]^+ = 382.18$.

Listed in Table D1-2 below are building blocks D (Fmoc-protected) that are prepared from the corresponding starting material in analogy to the sequence described above for **D1-2.1**. In Step 2, in some cases the triethylsilane is omitted.

10 **Table D1-2**

No.	SM	Product	t_R [min] LC-MS Method	MS-data m/z [M+H] ⁺
D1-2.2	2-Cyclohexylacetaldehyde	<i>N</i> -(((9H-Fluoren-9-yl)methoxy)carbonyl)- <i>N</i> -(2-cyclohexylethyl)glycine	1.10 B	408.23
D1-2.3	Paraformaldehyde	(<i>S</i>)-2-(((9H-Fluoren-9-yl)methoxy)carbonyl)(methylamino)-3-cyclobutylpropanoic acid	1.04 B	380.40

***N*-(((9H-Fluoren-9-yl)methoxy)carbonyl)-*N*-phenethylglycine (D1-2.4)**

Step 1: TEA (1.67 mL, 12 mmol) is added to a RT soln. of phenylacetaldehyde (0.78 mL, 6 mmol) and glycine *tert*-butyl ester HCl-salt (1.0 g, 6 mmol) in MeOH (40 mL). After 1 h at RT, NaBH(OAc)₃ (2.68 g, 12 mmol) is added and the RM is stirred at RT overnight. The RM is filtered, concentrated and partitioned between EtOAc and aq. NaHCO₃. The org. layer is separated and the aq. layer is extracted with EtOAc. The combined org. layers are washed with brine, dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 50% EtOAc in hept) yields *tert*-butyl phenethylglycinate (0.193 g, 14%) as a colourless oil. LC-MS D $t_R = 0.63$ min; $[M+H]^+ = 236.45$.

Step 2: *N*-(9-Fluorenylmethoxycarbonyloxy)succinimide (417 mg, 1.23 mmol) is added to a RT suspension of *tert*-butyl phenethylglycinate (193 mg, 0.82 mmol) and sodium carbonate (261 mg, 2.46 mmol) in dioxane (5 mL) and water (3 mL) and the RM is stirred at RT overnight. The dioxane is evaporated and the residue is partitioned between EtOAc and water. The org. layer is dried (MgSO₄), filtered, and concentrated to give *tert*-butyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*N*-phenethylglycinate (0.484 g, 129%) which is used as such in the next step. LC-MS D $t_R = 1.34$ min; $[M+H]^+ = 458.29$.

Step 3: TFA (0.4 mL, 5.05 mmol) is added to a 0°C soln. of *tert*-butyl *N*-(((9H-fluoren-9-yl)methoxy)carbonyl)-*N*-phenethylglycinate (484 mg, 0.505 mmol) in DCM (2 mL) and the resulting RM is stirred at RT overnight. The mix. is

concentrated and the crude product is purified by FC (eluting with DCM / MeOH 19:1) to give the title compound **D1-2.4** (0.266 g, 131%) as a colourless oil. LC-MS D t_R = 1.09 min; $[M+H]^+$ = 402.17.

Listed in Table D1-2 below are building blocks D (Fmoc-protected) that are prepared from the corresponding starting material in analogy to the sequence described above for **D1-2.4**.

5 **Table D1-2**

No.	SM	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
D1-2.5	3-(benzyloxy)propional	<i>N</i> -((((9 <i>H</i> -Fluoren-9-yl)methoxy)carbonyl)- <i>N</i> -(3-(benzyloxy)propyl)glycine	1.11 B	446.30
D1-2.6	2-(oxan-4-yl)acetaldehyde	<i>N</i> -((((9 <i>H</i> -Fluoren-9-yl)methoxy)carbonyl)- <i>N</i> -(2-(tetrahydro-2 <i>H</i> -pyran-4-yl)ethyl)glycine	0.95 D	410.43

1-((*tert*-Butoxycarbonyl)(methyl)amino)cyclobutane-1-carboxylic acid is commercially available and abbreviated with **D1-3.0**.

2-((*tert*-Butoxycarbonyl)(methyl)amino)-3-cyclopentylpropanoic acid (D1-4.1)

- 10 NaH (187 mg, 4.88 mmol) is added to a 0°C soln. of 2-(((*tert*-butoxy)carbonyl)amino)-3-cyclopentylpropanoic acid (432 mg, 1.63 mmol) in THF (8 mL), then MeI (0.51 mL, 8.13 mmol) is added and the RM is allowed to reach RT while stirring for 10 h. The RM is quenched with H₂O and extracted with EtOAc to yield the title compound **D1-4.1** (318 mg, 72%) which is used as such in the next step. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 272.30.

Listed in Table D1-4 below are building blocks **D1** that are prepared from the corresponding starting materials in analogy to the method described above for **D1-4.1**.

- 15

Table D1-4

No.	SM	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
D1-4.2	(<i>R</i>)-2-((<i>tert</i> -Butoxycarbonyl)amino)-3-(naphthalen-1-yl)propanoic acid	(<i>R</i>)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-(naphthalen-1-yl)propanoic acid	0.51 I	330.23
D1-4.3	(<i>tert</i> -Butoxycarbonyl)-D-valine	<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-D-valine	0.39 I	232.30
D1-4.4	(<i>tert</i> -Butoxycarbonyl)-D-leucine	<i>N</i> -(<i>tert</i> -Butoxycarbonyl)- <i>N</i> -methyl-D-leucine	0.45 I	246.31

D1-4.5	(R)-2-((<i>tert</i> -Butoxycarbonyl)amino)-3-cyclohexylpropanoic acid	(R)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclohexylpropanoic acid	0.57 	286.34
D1-4.6	2-((<i>tert</i> -Butoxycarbonyl)amino)-4,4-difluorobutanoic acid	2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-4,4-difluorobutanoic acid	0.37 	No mass

(S)-2-((*tert*-Butoxycarbonyl-methyl-amino)-3-cyclopentyl-propionic acid (D2-1.1)

- NaH (914 mg, 22.9 mmol) is added to a 0°C soln. of (S)-2-((*tert*-butoxycarbonyl)amino)-3-cyclopentylpropanoic acid (2.0 g, 7.62 mmol) in THF (32 mL). After 5 min, MeI (1.9 mL, 30.5 mmol) is added, the ice bath removed and the mix.
- 5 stirred at RT overnight. The reaction is diluted with DCM (100 mL) and quenched with 2 M aq. HCl (27 mL --> pH=1). The layers are separated and the aq. layer is extracted with DCM (2x 100 mL). The combined org. layers are washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated to yield the title compound (2.28 g, 110%) as an orange oil. LC-MS B: t_R = 0.94 min; [M+H]⁺ = 272.30.

- Listed in Table D2-1 below are building blocks **D2** that are prepared from the corresponding starting materials in analogy to the method described above for **D2-1.1**.
- 10

Table D2-1

No.	SM	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
D2-1.2	Boc-beta-Cyclohexyl-L-alanine monohydrate	(S)-2-((<i>tert</i> -Butoxycarbonyl-methyl-amino)-3-cyclohexyl-propionic acid	0.98 B	286.31
D2-1.3	(2S)-2-[[(<i>tert</i> -Butoxy)carbonyl]amino]-3-cyclopentylpropanoic acid	(S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)pent-4-ynoic acid	0.94 B	272.33.
D2-1.4	(S)-2-(Boc-Amino)-3-cyclopropylpropanoic acid	(S)-2-((<i>tert</i> -Butoxycarbonyl)(methyl)amino)-3-cyclopropylpropanoic acid	0.81 B	244.34

(S)-2-((*tert*-Butoxycarbonyl)(methyl)amino)-3-cyclobutylpropanoic acid (D2-2.1)

- Step 1:** Citric acid is added to a RT soln. of Boc-Ala(beta-cyclobutyl)-OH diisopropylamine (1.0 g, 2.84 mmol) in H₂O to lower the pH to 4, then the free carboxylic acid is extracted with DCM (3x) to yield Boc-Ala(beta-cyclobutyl)-OH (692 mg, 2.84 mmol) which is used as such in the next step.
- 15

Step 2: NaH (60 % dispersion in mineral oil, 341 mg, 8.53 mmol) is added to a 0°C soln. of Boc-Ala(beta-cyclobutyl)-OH (692 mg, 2.84 mmol) in THF (10 mL) followed by the dropwise addition of MeI (1.43 mL, 22.8 mmol). The resulting

mix. is stirred at RT for 18 h. The RM is quenched with water and extracted with TBME (3x). The aq. layer is acidified with citric acid to pH 4 and extracted with EtOAc (3x). The combined EtOAc layers are dried (MgSO₄), filtered, and concentrated to yield **D2-2.1** (801 mg, 109%) which is used as such in the next step. LC-MS B: t_R = 0.89 min; [M+H]⁺ = 258.08.

5 ***N*-((Allyloxy)carbonyl)-*N*-methyl-L-leucine (D2-3.1)**

Step 1: 4 M HCl in dioxane (11 mL, 44 mmol) is added to a RT soln. of Boc-*N*-Me-Leu-OH (2.78 g, 11 mmol) in DCM (20 mL). The mix. is stirred at RT for 2 h. The RM is concentrated to yield (S)-4-methyl-2-methylamino-pentanoic acid (2.14 g) which is used as such in the next step.

Step 2: Allyl chloroformate (1.27 mL, 11.6 mmol) is added to (S)-4-methyl-2-methylamino-pentanoic acid (1.59 g, 11 mmol) and Na₂CO₃ (4.08 g, 38.5 mmol) in dioxane/H₂O 3/5 (48 mL). The mix. is stirred at RT overnight, then the RM is diluted with EtOAc and acidified to pH 2 using 2 M aq. HCl. The layers are separated and the aq. layer is extracted with EtOAc (2x). The combined org. layers are dried (Na₂SO₄), filtered, and concentrated to yield **D2-3.1** (2.5 g, 99%) which is used as such in the next step. LC-MS B: t_R = 0.80 min; [M+H]⁺ = 230.43.

Intermediates

15 **Benzyl (2-(*tert*-butoxy)ethyl)glycinate (IM-1.1)**

A soln. of benzyl bromoacetate (0.165 mL, 1 mmol) in MeCN (2 mL) is added dropwise to a RT soln. of 2-(*tert*-butoxy)ethan-1-amine (493 mg, 4 mmol) in MeCN (3 mL) and the RM is stirred at RT for 50 min. The precipitate is filtered off and the filtrate is directly purified by prep. HPLC (basic) to yield **IM-1.1** (214 mg, 81%) as a colourless oil. LC-MS I: t_R = 0.93 min; [M+H]⁺ = 266.25.

20 Listed in Table IM-1 below are Intermediates that are prepared from the corresponding starting materials in analogy to the method described above for **IM-1.1**.

Table IM-1

No.	SM	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
IM-1.2	C-(3-Methyl-tetrahydro-furan-3-yl)-methylamine	Benzyl (<i>R</i>)-((3-methyltetrahydrofuran-3-yl)methyl)glycinate	0.82 I	264.21
IM-1.3	1-(3,4-Dihydro-2 <i>H</i> -chromen-3-yl)methanamine	rac-Benzyl (<i>R</i>)-(chroman-3-ylmethyl)glycinate	1.03 I	312.23
IM-1.4	2-{7-Oxabicyclo[2.2.1]heptan-2-yl}ethan-1-amine	Benzyl (2-(7-oxabicyclo[2.2.1]heptan-2-yl)ethyl)glycinate	0.82 I	289.97
IM-1.5	2-{5-Oxaspiro[3.4]octan-6-yl}ethan-1-amine	Benzyl (2-(5-oxaspiro[3.4]octan-6-yl)ethyl)glycinate	0.99 I	304.21

IM-1.6	2-(Oxolan-2-yl)ethan-1-amine	Benzyl (2-(tetrahydrofuran-2-yl)ethyl)glycinate	0.81 I	264.23
IM-1.7	2-(Oxan-3-yl)ethan-1-amine	Benzyl (2-(tetrahydro-2H-pyran-3-yl)ethyl)glycinate	0.85 I	278.24
IM-1.8	2-{2,9-Dioxaspiro[5.5]undecan-3-yl}ethan-1-amine	Benzyl (2-(2,9-dioxaspiro[5.5]undecan-3-yl)ethyl)glycinate	0.87 I	348.22
IM-1.9	1,4-Dioxane-2-methanamine.HCl	Benzyl ((1,4-dioxan-2-yl)methyl)glycinate	0.71 I	266.16
IM-1.10	2-(Tetrahydropyran-2-yl)ethylamine.HCl	Benzyl (2-(tetrahydro-2H-pyran-2-yl)ethyl)glycinate	0.90 I	278.21
IM-1.11	2-(3-Methoxycyclobutyl)ethan-1-amine	Benzyl (2-(3-methoxycyclobutyl)ethyl)glycinate	0.88 I	278.20
IM-1.12	2-Cyclohexylethylamine	Benzyl (2-cyclohexylethyl)glycinate	1.19 I	276.26
IM-1.13	(Tetrahydro-2H-pyran-3-yl)methanamine	Benzyl ((tetrahydro-2H-pyran-3-yl)methyl)glycinate	0.81 I	264.33
IM-1.14	(6,6-Dimethyltetrahydro-2H-pyran-2-yl)methanamine	[(6,6-Dimethyl-tetrahydro-pyran-2-yl)methyl]-amino]-acetic acid benzyl ester	1.02 I	292.32
IM-1.15	AM-1.72	Benzylbenzyl (3-phenylpropyl)glycinate	2.18 J	284.2
IM-1.16	AM-1.75	Benzylbenzyl ((2,3-dihydrobenzofuran-2-yl)methyl)glycinate	0.99 I	298.29

Benzyl (S)-((tetrahydro-2H-pyran-2-yl)methyl)glycinate (IM-2.1)

Step 1: NaH (60% dispersion in mineral oil, 2.41 g, 60.1 mmol) is added to a 0°C soln. of tetrahydropyran-2-methanol (6.0 g, 50.1 mmol) in THF (300 mL). The RM is warmed to RT and after stirring for 30 min benzyl bromide (7.29 mL, 60.1 mmol) is added and the mix. is stirred at RT overnight. Sat aq. NH₄Cl is added and the mix. is extracted with EtOAc (2x). The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (hept/EtOAc 1:0 to 9:1) yields rac-2-((benzyloxy)methyl)tetrahydro-2H-pyran (10.3 g, 100%) as a colourless oil.

Step 2: Chiral separation yields (R)-2-((benzyloxy)methyl)tetrahydro-2H-pyran and (S)-2-((benzyloxy)methyl)tetrahydro-2H-pyran which were used as such in the next step. The configuration is assigned by optical rotation.

Step 3: 10% Pd/C (2.54 g, 2.39 mmol) is added to a RT soln. of (S)-2-((benzyloxy)methyl)tetrahydro-2H-pyran (4.92 g, 23.9 mmol) in MeOH (100 mL) and the RM is stirred at RT for 3 h under a H₂ atm. The RM is filtered, and the filtrate is concentrated under reduced pressure. Purification by Kugelrohrdestillation yields (S)-(tetrahydro-2H-pyran-2-yl)methanol (2.54 g, 92%) as a colourless oil.

- 5 **Step 4:** 2-Nitrobenzenesulfonyl chloride (7.54 g, 33 mmol) is added portionwise to a 0°C soln. of H-Gly-OBzl HCl (6.11 g, 30 mmol) and TEA (8.77 mL, 63 mmol) in DCM (45 mL). The mix. is warmed to RT and stirred for 1 h. The RM is concentrated, then EtOAc and water are added to the residue. The layers are separated and the aq. layer is extracted with EtOAc. The combined org. layers are dried (MgSO₄), filtered, and concentrated. Purification by FC (hept/EtOAc 0:1 to 1:1) yields benzyl ((2-nitrophenyl)sulfonyl)glycinate (10.56 g, 100%) as a white solid. LC-MS B: t_R = 0.93 min; [M+H]⁺ = 351.26.
- 10

- Step 5:** DIAD (1 mL, 5 mmol) is added to a RT soln. of benzyl ((2-nitrophenyl)sulfonyl)glycinate (1.75 g, 5 mmol), (S)-2-((benzyloxy)methyl)tetrahydro-2H-pyran (639 mg, 5.5 mmol), and PPh₃ (1.66 g, 6 mmol) in THF (50 mL) and the RM is stirred for 1 h. The RM is concentrated and directly purified by prep. HPLC (basic) to yield (S)-N-(2-(N-(2-(benzyloxy)-2-oxoethyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)sulfamoyl)phenyl)-N-oxohydroxylammonium (2.1 g, 94%) as a pale brownish oil. LC-MS I: t_R = 1.11 min; [M+H]⁺ = 449.12.
- 15

- Step 6:** Thiophenol (0.681 mL, 6.56 mmol) is added to a RT suspension of (S)-N-(2-(N-(2-(benzyloxy)-2-oxoethyl)-N-((tetrahydro-2H-pyran-2-yl)methyl)sulfamoyl)phenyl)-N-oxohydroxylammonium (2.10 g, 4.69 mmol) and K₂CO₃ (992 mg, 7.03 mmol) in DMF (25 mL). The RM is stirred at RT for 1 h, then the solids are filtered off and the filtrate is concentrated and purified by prep. HPLC (basic) to yield **IM-2.1** (976 mg, 79%) as a colourless oil. LC-MS I: t_R = 0.88 min; [M+H]⁺ = 264.22.
- 20

Listed in Table IM-2 below are Intermediates that are prepared in analogy to the sequence described for **IM-2.1**.

Table IM-2

No.	SM	Product	t _R [min]	MS-data
			LC-MS Method	m/z [M+H] ⁺
IM-2.2	(R)-(Tetrahydro-2H-pyran-2-yl)methanol (see IM-2.1 , steps 1 to 3)	Benzyl (R)-((tetrahydro-2H-pyran-2-yl)methyl)glycinate	0.88 I	264.21
IM-2.3	(S)-2-(Tetrahydro-2H-pyran-2-yl)ethan-1-ol (synthesised in analogy to IM-2.1 , steps 1 to 3)	Benzyl (S)-2-(tetrahydro-2H-pyran-2-yl)ethylglycinate	0.90 I	278.24
IM-2.4	(R)-2-(Tetrahydro-2H-pyran-2-yl)ethan-1-ol (synthesised in analogy to IM-2.1 , steps 1 to 3)	Benzyl (R)-2-(tetrahydro-2H-pyran-2-yl)ethylglycinate	0.90 I	278.25

IM-2.5	(S)-Chroman-3-ylmethanol	Benzyl (S)-(chroman-3-ylmethyl)glycinate	1.05 I	312.23
IM-2.6	(R)-Chroman-3-ylmethanol	Benzyl (R)-(chroman-3-ylmethyl)glycinate	1.05 I	312.25

Methyl methyl-D-phenylalaninate (IM-3.1).

Step 1: NaH (60% dispersion in mineral oil, 265 mg, 6.92 mmol) is added to a 0°C soln. of Boc-D-Phe-OH (458 mg, 1.73 mmol) in DMF (8 mL), then MeI (0.05 mL, 0.8 mmol) is added and the RM is warmed to RT overnight. The solvent is evaporated and the crude product is purified by FC to yield methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-D-phenylalaninate.

Step 2: 4 M HCl in dioxane (0.24 mL, 0.682 mmol) is added to a 0°C soln. of methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-D-phenylalaninate (200 mg, 0.682 mmol) in DCM (3 mL) and the mix. is stirred at RT for 2 h. The RM is concentrated in vacuo to yield the title compound as a white solid. LC-MS B: $t_R = 0.46$ min; $[M+H]^+ = 194.21$.

Listed in Table IM-3 below are intermediates that are prepared from the corresponding starting materials in analogy to the sequence described above for **IM-3.1**.

Table IM-3

No.	SM	Product	t_R [min] LC-MS Method	MS-data m/z $[M+H]^+$
IM-3.2	Boc-beta-Cyclohexyl-D-alanine monohydrate	Methyl (R)-3-cyclohexyl-2-(methylamino)propanoate	0.58 B	200.39
IM-3.3	Boc-D-Cyclopentyl-glycine	Methyl (R)-2-cyclopentyl-2-(methylamino)acetate (HCl-salt)	0.45 B	172.00

3,3-Difluoro-1-methylamino-cyclobutanecarboxylic acid methyl ester (IM-4.1)

Step 1: 2.0 M (trimethylsilyl)diazomethane in Et₂O (0.27 mL, 0.54 mmol) is added to a 0°C soln. of 1-[(*tert*-butoxy)carbonyl](methylamino)-3,3-difluorocyclobutane-1-carboxylic acid (100 mg, 0.36 mmol) in MeOH (1 mL). The RM is warmed to RT and stirring is continued for 6 h. The RM is concentrated and purified by FC (hept/EtOAc 4:1) to yield methyl 1-[(*tert*-butoxycarbonyl)(methylamino)-3,3-difluorocyclobutane-1-carboxylate (52 mg, 52%) as a clear oil. LC-MS I: $t_R = 0.98$ min; $[M+H]^+ = 280.25$.

Step 2: The title compound **IM-4.1** is prepared from methyl 1-[(*tert*-butoxycarbonyl)(methylamino)-3,3-difluorocyclobutane-1-carboxylate following the procedure described in **IM-3.1**, step 2. LC-MS I: $t_R = 0.57$ min; $[M+H]^+ = 180.31$.

2((2-Nitrobenzen)sulfonamido)acetic acid (IM-5.1)

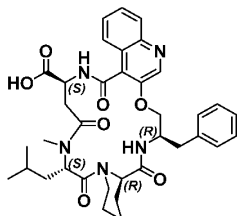
2-Nitrobenzenesulfonyl chloride (5.71 g, 25 mmol) is added portionwise to a 60°C soln. of glycine (1.89 g, 25 mmol) and 32 % aq. NaOH (5 mL, 50 mmol) in H₂O (20 mL). After the addition is complete the RM is stirred for 30 min at 60°C before being cooled to 0°C. The mix. is acidified with conc. HCl to pH 1, and the formed precipitate is isolated by filtration to yield **IM-5.1** (4.34 g, 67%) as a white solid. LC-MS B: t_R = 0.6 min; [M+H]⁺ = 261.25.

Commercially available Sulfonylchlorides**Table SCI**

Sulfonyl-chloride	Name
SCI-1	Benzenesulfonyl chloride
SCI-2	Pyridine-3-sulfonyl chloride
SCI-3	Pyridine-2-sulfonyl chloride
SCI-4	Pyridine-4-sulfonyl chloride
SCI-5	3-Methoxybenzenesulfonyl chloride
SCI-6	3-(Trifluoromethoxy)benzenesulfonyl chloride
SCI-7	2-Fluoro-5-methoxybenzenesulfonyl chloride
SCI-8	5-Methoxypyridine-3-sulfonyl chloride
SCI-9	4-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-sulfonyl chloride
SCI-10	2-Oxo-2,3-dihydrobenzo[d]oxazole-6-sulfonyl chloride
SCI-11	Phenylmethanesulfonyl chloride
SCI-12	Quinolin-7-ylmethanesulfonyl chloride
SCI-13	Methanesulfonyl chloride
SCI-14	2-Methoxyethane-1-sulfonyl chloride
SCI-15	3-Methoxypropane-1-sulfonyl chloride
SCI-16	2-(Dimethylamino)ethane-1-sulfonyl chloride
SCI-17	Tetrahydro-2H-pyran-4-sulfonyl chloride
SCI-18	(Tetrahydro-2H-pyran-4-yl)methanesulfonyl chloride
SCI-19	2-Morpholinoethane-1-sulfonyl chloride
SCI-20	3-Morpholinopropane-1-sulfonyl chloride

Synthesis of Macrocycles bearing a carboxylic acid group

(9*S*,13*S*,19*aR*,22*R*)-22-Benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19*a*,20,21,22,23-hexadecahydro-16*H*-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-*c*]quinoline-9-carboxylic acid (MC-COOH-1)



5

Step 1: HATU (4.12 g, 10.3 mmol) is added to a RT soln. of **B-1.14** (5.0 g, 10.3 mmol), **C-2.2** (3.67 g, 10.3 mmol), and DIPEA (5.29 mL, 30.9 mmol) in DMF (100 mL). The resulting mix. is stirred at RT for 10 min, then the mix. is partitioned between water and EtOAc. The layers are separated and the aq. layer is re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried (MgSO₄), filtered, and evaporated to obtain 3-[(*R*)-2-[(*R*)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperidine-2-carbonyl]-amino]-3-phenyl-propoxy]-quinoline-4-carboxylic acid benzyl ester (8.78 g, 114%) as a white solid which is used as such in the next step. LC-MS I: *t_R* = 1.43 min; [M+H]⁺ = 751.46.

10

Step 2: A RT soln. of 3-[(*R*)-2-[(*R*)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperidine-2-carbonyl]-amino]-3-phenyl-propoxy]-quinoline-4-carboxylic acid benzyl ester (8.79 g, 11.3 mmol) in EtOH (100 mL) is evacuated/purged with N₂ (3x) before Pd/C (604 mg, 0.567 mmol) is added. The RM is evacuated/purged with H₂ (3x) and stirred under a H₂ atm for 18 h. The RM is filtered and the filter cake rinsed with EtOH. The filtrate is concentrated to yield 3-[(*R*)-2-[(*R*)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperidine-2-carbonyl]-amino]-3-phenyl-propoxy]-quinoline-4-carboxylic acid (7.81 g, 104%) as an off-white solid which is used as such in the next step. LC-MS I: *t_R* = 0.68 min; [M+H]⁺ = 661.20.

15

Step 3: Benzyl bromide (3.46 mL, 28.6 mmol) is added to a RT soln. of Fmoc-L-aspartic acid beta-*tert*-butyl ester (10.0 g, 23.8 mmol) and KHCO₃ (2.65 g, 26.2 mmol) in DMF (60 mL) and the resulting mix. is stirred at RT for 18 h. The mix. is concentrated and to the residue is added EtOAc and water. The layers are separated, and the aq. layer is re-extracted with EtOAc (2x). The combined org. layers are washed with water and brine, dried (MgSO₄), filtered, and concentrated to obtain (*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-succinic acid 1-benzyl ester 4-*tert*-butyl ester (12.21 g, 102%) as a white powder which is used as such in the next step. LC-MS B: *t_R* = 1.19 min; [M+H]⁺ = 502.28.

20

Step 4: Piperidine (11.8 mL, 118 mmol) is added to a RT soln. of (*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-succinic acid 1-benzyl ester 4-*tert*-butyl ester (12.21 g, 23.6 mmol) in DCM (150 mL). The resulting mix. is stirred at RT for 2 h. The mix. is concentrated in vacuo at 40°C to yield a white solid, which is triturated with hept. The solid is filtered off and purified by FC (eluting with 10% to 100% EtOAc in hept) to give (*S*)-2-amino-succinic acid 1-benzyl ester 4-*tert*-butyl ester (5.44 g, 82%) as a yellowish oil. LC-MS B: *t_R* = 0.68 min; [M+H]⁺ = 280.36.

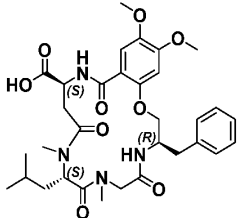
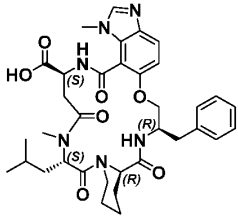
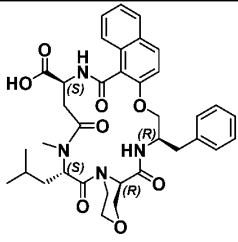
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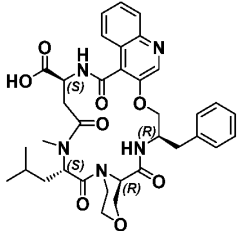
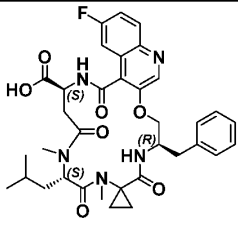
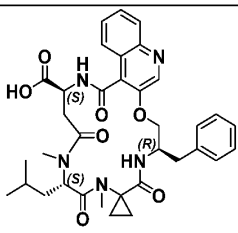
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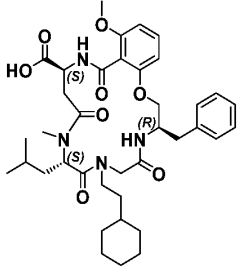
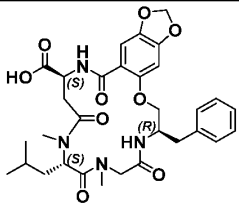
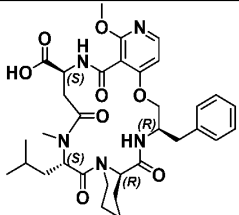
- Steps 5:** HATU (3.61 g, 9.03 mmol) is added to a RT soln. of 3-[(*R*)-2-[(*R*)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperidine-2-carbonyl]-amino]-3-phenyl-propoxy]-quinoline-4-carboxylic acid (6.63 g, 9.03 mmol), (*S*)-2-amino-succinic acid 1-benzyl ester 4-*tert*-butyl ester (2.55 g, 9.03 mmol), and DIPEA (4.64 mL, 27.1 mmol) in DMF (100 mL). The resulting mix. is stirred at RT for 1 h, then the mix. is partitioned between water and EtOAc. The layers are separated and the aq. re-extracted with EtOAc (2x). The combined org. extracts are washed with brine, dried (MgSO₄), filtered, and evaporated to yield (*S*)-2-[(3-[(*R*)-2-[(*R*)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperidine-2-carbonyl]-amino)-3-phenyl-propoxy]-quinoline-4-carbonyl]-amino)-succinic acid 1-benzyl ester 4-*tert*-butyl ester (7.54 g) as a pink solid which is used as such in the next step. LC-MS I: *t_R* = 1.44 min; [M+H]⁺ = 922.70.
- Step 6:** TFA (69.1 mL, 897 mmol) is added to a RT soln. of (*S*)-2-[(3-[(*R*)-2-[(*R*)-1-[(*S*)-2-(*tert*-butoxycarbonyl-methyl-amino)-4-methyl-pentanoyl]-piperidine-2-carbonyl]-amino)-3-phenyl-propoxy]-quinoline-4-carbonyl]-amino)-succinic acid 1-benzyl ester 4-*tert*-butyl ester (7.54 g, 5.64 mmol) in DCM (150 mL). The resulting mix. is stirred for 3 h, then concentrated and co-evaporated with DCM (2x). The residue is taken up in DMF (100 mL), and to the soln. is added DIPEA (7.72 mL, 45.1 mmol) and HATU (2.57 g, 6.77 mmol). The mix. is stirred at RT for 1 h, then the mix. is partitioned between water and EtOAc. The layers are separated and the aq. re-extracted with EtOAc (2x). The combined org. extracts are washed with water (2x) and brine (2x), dried (MgSO₄), filtered, and evaporated. Purification by FC (eluting with 100% EtOAc) yields benzyl (9*S*,13*S*,19*aR*,22*R*)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19*a*,20,21,22,23-hexadecahydro-16*H*-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-*c*]quinoline-9-carboxylate (2.45 g, 58%) as a pink solid. LC-MS I: *t_R* = 1.20 min; [M+H]⁺ = 748.48.
- Step 7:** A suspension of benzyl (9*S*,13*S*,19*aR*,22*R*)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19*a*,20,21,22,23-hexadecahydro-16*H*-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-*c*]quinoline-9-carboxylate (2.45 g, 2.95 mmol) in EtOH (25 mL) is evacuated/purged with H₂ (3x) before Pd/C (157 mg, 0.147 mmol) is added. The RM is evacuated/purged with H₂ (3x) and stirred under a H₂ atm for 24 h. The mix. is filtered and the filter cake is rinsed with EtOH. The filtrate is concentrated and purified by FC (eluting with 4% MeOH in DCM) to give the title compound (1.57 g, 81%) as an off-white solid. LC-MS I: *t_R* = 0.54 min; [M+H]⁺ = 658.42.

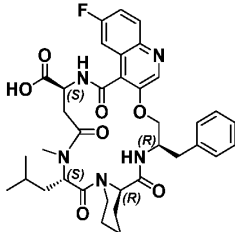
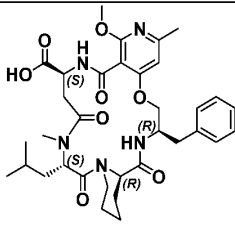
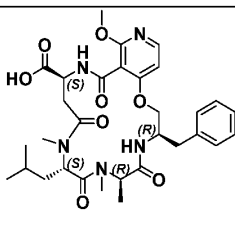
Listed in Table MC-COOH-A below are carboxylic acids that are prepared from the corresponding starting materials in analogy to the 7-step sequence described above for **MC-COOH-1**.

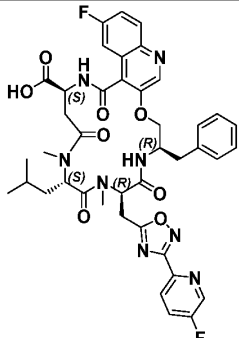
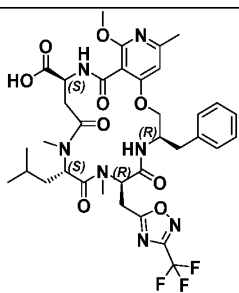
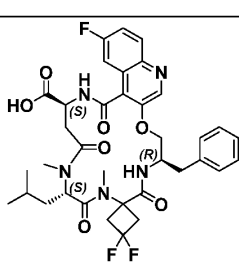
Table MC-COOH-A

No.	Structure	BB-B	BB-C	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
MC-COOH-2		B-1.11	C-1.1	(3R,9S,13S)-3-Benzyl-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacyclodecane-13-carboxylic acid	0.84 B	627.16
MC-COOH-3		B-2.7	C-2.2	(8S,12S,18aR,21R)-21-Benzyl-12-isobutyl-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxylic acid	0.51 I	661.46
MC-COOH-4		B-1.13	C-2.1	(4aR,7R,18S,22S)-7-Benzyl-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxylic acid	0.92 B	659.25

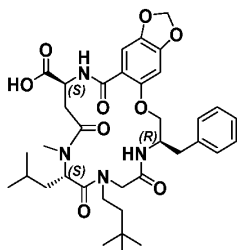
				cycloheptadecine-18-carboxylic acid		
MC-COOH-5		B-1.14	C-2.1	(9S,13S,19aR,22R)-22-Benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxylic acid	0.84 B	660.32
MC-COOH-6		B-1.19	C-1.2	(3'S,7'S,13'R)-13'-Benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxylic acid	0.92 B	662.19
MC-COOH-7		B-1.14	C-1.2	(3'S,7'S,13'R)-13'-Benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxylic acid	0.52 I	644.27

MC-COOH-15		B-1.5	C-10.19	(3R,9S,13S)-3-Benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid	0.66 I	693.46
MC-COOH-16		B-1.16	C-1.1	(4R,10S,14S)-4-Benzyl-107R,13S,17S)-7-benzyl-13-isobutyl-8,11,14-dimethyl-6,9,12,16,15,19-tetraoxo-2,20,22-trioxa-56,7,8,9,10,11,15-tetraaza-tricyclo[12,13,14,15.7.0.019,23]tetracos-1(,16,17),,18,23-triene-14-19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxylic acid	0.45 I	610.87
MC-COOH-24		B-1.18	C-2.2	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxylic acid	0.54 I	638.27

MC-COOH-25		B-1.19	C-2.2	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxylic acid	0.55 I	676.40
MC-COOH-26		B-4.15	C-2.2	(7S,11S,17aR,20R)-20-Benzyl-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxylic acid	0.52 I	652.17
MC-COOH-27		B-1.18	C-1.4	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-6,7,10-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid	1.66 J	612.20

MC-COOH-28		B-1.19	C-22.1	(3 <i>S</i> ,7 <i>S</i> ,10 <i>R</i> ,13 <i>R</i>)-13-Benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16- <i>c</i>]quinoline-3-carboxylic acid	0.97	813.14
MC-COOH-29		B-4.15	C-22.2	(3 <i>R</i> ,6 <i>R</i> ,9 <i>S</i> ,13 <i>S</i>)-3-Benzyl-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4- <i>p</i>][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid	0.97	762.31
MC-COOH-30		B-1.19	C-5.4	(3' <i>S</i> ,7' <i>S</i> ,13' <i>R</i>)-13'-benzyl-3,3,20'-trifluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16- <i>c</i>]quinoline]-3'-carboxylic acid	0.97 B	712.07

(7R,13S,17S)-7-Benzyl-11-(3,3-dimethylbutyl)-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxylic acid (MC-COOH-8)

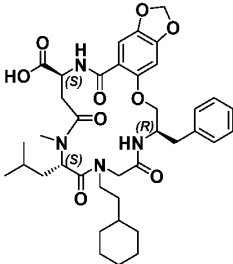
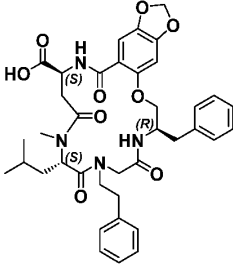
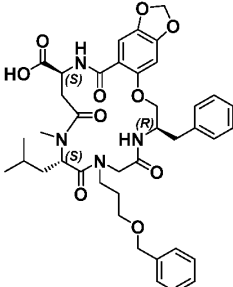


- 5 The synthesis is performed according to a general method for the solid-phase synthesis. The Wang resin (153 mg, 0.135 mmol) is swollen in DMF (5 mL) for 1 h. The solvent is drained off and the resin is treated with a soln. of **Fmoc-Asp(OAll)-OH** (272 mg, 0.675 mmol), TBTU (214 mg, 0.648 mmol), DIPEA (0.236 mL, 1.35 mmol) in DMF (3 mL) for 3 h. The Fmoc deprotection is performed by treating the resin (2 x 5 min) with a soln. of piperidine 20% in DMF (3 mL). After filtration, the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The resin is treated with a soln. of
- 10 **B-Acid-4** (394 mg, 0.675 mmol), TBTU (214 mg, 0.648 mmol), HOBT (103 mg, 0.675 mmol) and DIPEA (0.236 mL, 1.35 mmol) in DMF (3 mL) for 3 h. After filtration the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The Fmoc deprotection is performed by treating the resin (2 x 5 min) with a soln. of piperidine 20% in DMF (3 mL). After filtration the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The resin is then treated with a soln. **D1-2.1** (257 mg, 0.675 mmol), TBTU (214 mg, 0.648 mmol), HOBT (103 mg, 0.675 mmol), and DIPEA (0.236 mL, 1.35 mmol)
- 15 in DMF (3 mL) for 3 h. After filtration the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The Fmoc deprotection is performed by treating the resin (2 x 5 min) with a soln. of piperidine 20% in DMF (3 mL). After filtration, the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The resin is then treated with a soln. of **Fmoc-NMeLeu-OH** (253 mg, 0.675 mmol), TBTU (214 mg, 0.648 mmol), HOBT (103 mg, 0.675 mmol), and DIPEA (0.236 mL, 1.35 mmol) in DMF (3 mL) for 3 h. After filtration, the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The Fmoc deprotection is performed by treating the resin (2 x 5 min) with a soln. of piperidine/ DBU/ DMF (1/1/48) (2 x 3 mL x 5 min). After filtration, the resin is washed with DMF (3 x 4 mL) and DCM (3 x 4 mL). The resin is then treated with a soln. of Pd(PPh₃)₄ (78 mg, 0.0675 mmol) and 1,3-dimethylbarbituric (106 mg, 0.675 mmol) in THF for 10 h. After filtration, the resin is washed successively with a soln. of 0.5% DIPEA in DMF (4 x 3 mL) and a soln. of 0.5% sodium diethyldithiocarbamate in DMF (4 x 3 mL) and finally with DMF (4 x 3 mL). The cyclisation of the linear peptide is
- 20 performed by treating the resin with a soln. of pentafluorophenyl diphenylphosphinate (104 mg, 0.27 mmol) in DMF/DCM (2 mL) for 5 h. Finally, the macrocycle is cleaved from the resin using a soln. of TFA in DCM (1/1, 3 mL) for 2 h. After purification of the crude mix. by prep. HPLC (acidic), the title compound **MC-COOH-8** (22 mg, 26%) is obtained as a white solid. LC-MS D t_R = 1.03 min; [M+H]⁺ = 681.31.

Listed in Table MC-COOH-B below are carboxylic acids that are prepared from the corresponding starting materials

- 30 in analogy to the solid phase synthesis described above for **MC-COOH-8**.

Table MC-COOH-B

No.	Structure	SM BB-B	SM BB-D1	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
MC-COOH-9		B-Acid -4	D1-2.2	(7R,13S,17S)-7-Benzyl-11-(2-cyclohexylethyl)-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxylic acid	1.11 D	707.31
MC-COOH-10		B-Acid -4	D1-2.4	(7R,13S,17S)-7-Benzyl-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-11-phenethyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxylic acid	0.98 D	701.21
MC-COOH-11		B-Acid -4	D1-2.5	(7R,13S,17S)-7-Benzyl-11-(3-(benzyloxy)propyl)-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxylic acid	1.00 D	745.31

butoxycarbonyl)amino)-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate HCl (11.71 g, 100%). LC-MS I: t_R = 1.24 min; $[M+H]^+$ = 677.42.

Step 2: 4 M HCl in dioxane (34.5 mL, 138 mmol) is added to 4-allyl 1-benzyl (2-((R)-2-amino-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate HCl (11.712 g, 17.3 mmol) in DCM (135 mL). The mix. is stirred at RT for 4 h and
5 evaporated to yield 4-allyl 1-benzyl (2-((R)-2-amino-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate HCl (11.71 g, 100%) as a white solid which is used as such in the next step. LC-MS I: t_R = 1.07 min; $[M+H]^+$ = 577.36.

Step 3: IM-5.1 (639 mg, 2.44 mmol), 4-allyl 1-benzyl (2-((R)-2-amino-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate HCl (1.695 g, 2.44 mmol), HATU (956 mg, 2.44 mmol) and DIPEA (2.44 mL, 14.3 mmol) are dissolved in DMF (12 mL). The mix. is stirred at RT for 2 h. The solvent is evaporated and the crude mix. is purified by FC (eluting
10 with 0-5% MeOH in DCM) to give 4-allyl 1-benzyl (4,5-dimethoxy-2-((R)-2-((2-nitrophenyl)sulfonamido)acetamido)-3-phenylpropoxy)benzoyl)-L-aspartate (964 mg, 48%) as a colourless oil. LC-MS B: t_R = 1.1 min; $[M+H]^+$ = 819.32.

Step 4: DIAD (227 mg, 0.968 mmol) is added to a RT soln. (degassed) of 4-allyl 1-benzyl (4,5-dimethoxy-2-((R)-2-((2-nitrophenyl)sulfonamido)acetamido)-3-phenylpropoxy)benzoyl)-L-aspartate (864 mg, 0.88 mmol), 2-cyclohexylethanol (0.136 mL, 0.968 mmol), and PPh_3 (267 mg, 0.968 mmol) in DCM (5 mL). The RM is stirred at RT
15 for 1 h, then the solvent is evaporated and the crude product purified by FC (eluting with 0% to 10% EtOAc in hept) to give 4-allyl 1-benzyl (2-((R)-2-((N-(2-cyclohexylethyl)-2-nitrophenyl)sulfonamido)acetamido)-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate (810 mg, 89%) as a white solid. LC-MS B: t_R = 1.24 min; $[M+H]^+$ = 929.38.

Step 5: K_2CO_3 (169 mg, 1.2 mmol) is added to a RT soln. of 4-allyl 1-benzyl (2-((R)-2-((N-(2-cyclohexylethyl)-2-nitrophenyl)sulfonamido)acetamido)-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate (811 mg, 0.8 mmol) and
20 thiophenol (0.116 mL, 1.12 mmol) in DMF (4 mL). The RM is stirred at RT for 1 h, then the solvent is evaporated and the crude product purified by prep. HPLC (basic) to give 4-allyl 1-benzyl (2-((R)-2-((2-cyclohexylethyl)amino)acetamido)-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate (665 mg, 112%) as a colourless oil. LC-MS B: t_R = 0.99 min; $[M+H]^+$ = 744.41.

Step 6: HATU (42.2 mg, 0.108 mmol) is added to a RT soln. of 4-allyl 1-benzyl (2-((R)-2-((2-cyclohexylethyl)amino)acetamido)-3-phenylpropoxy)-4,5-dimethoxybenzoyl)-L-aspartate (133 mg, 0.098 mmol), **D2-1.4** (28.6 mg, 0.117 mmol), and DIPEA (0.0934 mL, 0.545 mmol) in DMF (2 mL). The RM is stirred at RT for 1 h, then
25 the solvent is evaporated and the crude product purified by prep. HPLC (basic) to give 4-allyl 1-benzyl (2-(((6S,12R)-12-benzyl-8-(2-cyclohexylethyl)-6-(cyclopropylmethyl)-2,2,5-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-yl)oxy)-4,5-dimethoxybenzoyl)-L-aspartate (104 mg, 97.1%) as a white solid. LC-MS B: t_R = 1.29 min; $[M+H]^+$ =
30 969.66.

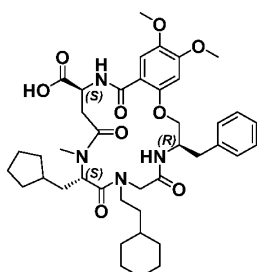
Step 7: 4 M HCl in dioxane (2.0 mL, 2.0 mmol) is added to 4-allyl 1-benzyl (2-(((6S,12R)-12-benzyl-8-(2-cyclohexylethyl)-6-(cyclopropylmethyl)-2,2,5-trimethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-yl)oxy)-4,5-dimethoxybenzoyl)-L-aspartate (104 mg, 0.104 mmol) in DCM (3 mL). The RM is stirred at RT for 4 h, then the solvent
35 is evaporated and the crude residue is dissolved in degassed DCM (3 mL) and treated with $Pd(PPh_3)_4$ (12.3 mg, 0.0104 mmol) and 1,3-dimethylbarbituric acid (32.9 mg, 0.208 mmol). The RM is stirred for 1 h at RT, then filtered

through a Whatman filter and the solvent evaporated to give (S)-4-(benzyloxy)-3-(2-((R)-2-(2-((S)-N-(2-cyclohexylethyl)-3-cyclopropyl-2-(methylamino)propanamido)acetamido)-3-phenylpropoxy)-4,5-dimethoxybenzamido)-4-oxobutanoic acid (104 mg, 120%) as a colourless oil which is used as such in the next step. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 829.36.

- 5 **Step 8:** FDPP (38 mg, 0.14 mmol) is added to a RT soln. of (S)-4-(benzyloxy)-3-(2-((R)-2-(2-((S)-N-(2-cyclohexylethyl)-3-cyclopropyl-2-(methylamino)propanamido)acetamido)-3-phenylpropoxy)-4,5-dimethoxybenzamido)-4-oxobutanoic acid (40 mg, 0.05 mmol) in DCM. The RM is heated to 50°C for 12 h, then the solvent is evaporated and the crude product purified by prep. HPLC (basic) to give benzyl (3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-(cyclopropylmethyl)-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-
10 2,3,4,5,6,7,8,9,10,11,12,13,14,15 tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylate (11 mg, 13%) as a white solid. LC-MS B: t_R = 1.18 min; $[M+H]^+$ = 811.43.

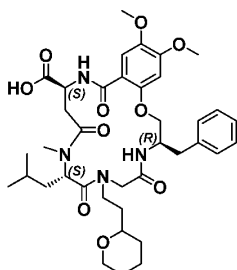
- Step 9:** Pd/C (10%, 1.84 mg, 0.0017 mmol) is added to a RT soln. (degassed) of benzyl (3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-(cyclopropylmethyl)-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-
2,3,4,5,6,7,8,9,10,11,12,13,14,15 tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylate
15 (14 mg, 0.017 mmol) in MeOH (2 mL). The RM is stirred at RT under a H₂ atm for 1 h, then the mix. is filtered through a Whatman filter and the filtrate is concentrated to yield the title compound **MC-COOH-13** (14 mg, 113%) as a colourless oil which is used as such in the next step. LC-MS B: t_R = 1.01 min; $[M+H]^+$ = 721.35.

- (3R,9S,13S)-3-Benzyl-7-(2-cyclohexylethyl)-9-(cyclopentylmethyl)-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-
20 13-carboxylic acid (**MC-COOH-14**)



The title compound is prepared in analogy to the procedure described for **MC-COOH-13**, replacing in step 6, **D2-1.4** with **D2-1.1**. LC-MS B: t_R = 1.19 min; $[M+H]^+$ = 896.38.

(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-7-(2-((RS)-tetrahydro-2H-pyran-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid (MC-COOH-18)

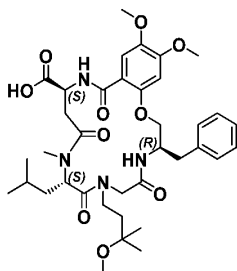


- 5 **Steps 1-6:** The intermediate is prepared in analogy to the procedure described for **MC-COOH-13**, following steps 1-6, where in step 4, 2-(tetrahydro-2H-pyran-2-yl)ethanol instead of 2-cyclohexylethanol, and in step 5, **D2-3.1** instead of **D2-1.4** are used.

Step 7: Pd(PPh₃)₄ (29.8 mg, 0.025 mmol) is added to a RT soln. (degassed) of the intermediate from step 6 (242 mg, 0.252 mmol) and 1,3-dimethylbarbituric acid (79.6 mg, 0.505 mmol) in DCM (2 mL) and the RM is stirred at RT for 1.5 h. The RM is filtered and concentrated and used as such in the next step. LC-MS I: t_R = 0.68 min; [M+H]⁺ = 833.60.

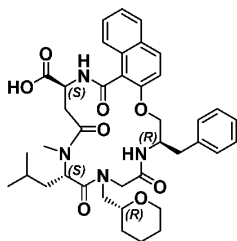
- 10 **Steps 8&9:** The title compound **MC-COOH-18** is prepared following the procedure described for **MC-COOH-13**, steps 8&9. LC-MS I: t_R = 0.53/0.54 min; [M+H]⁺ = 725.50.

(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-7-(3-methoxy-3-methylbutyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid (MC-COOH-19)



The title compound is prepared in analogy to the 9-step synthesis described for **MC-COOH-18**. In step 4, 3-methoxy-3-methyl-1-butanol instead of 2-(tetrahydro-2H-pyran-2-yl)ethanol is used. LC-MS B: t_R = 0.90 min; [M+H]⁺ = 713.36.

(3S,7S,13R)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylic acid (MC-COOH-20)



- 5 **Steps 1&2:** 4-Allyl 1-benzyl (2-((R)-2-amino-3-phenylpropoxy)-1-naphthoyl)-L-aspartate hydrochloride is prepared following the synthesis of **MC-COOH-13**, steps 1&2, using **A-2.1** and **B-Acid-5**. LC-MS B: $t_R = 0.9$ min; $[M+H]^+ = 567.28$.

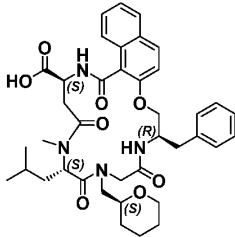
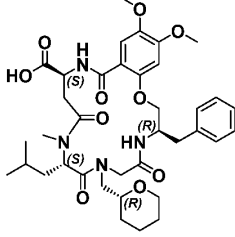
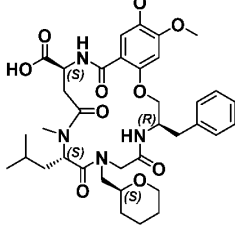
- Step 3:** HATU (87.5 mg, 0.23 mmol) is added to a RT soln. of 4-allyl 1-benzyl (2-((R)-2-amino-3-phenylpropoxy)-1-naphthoyl)-L-aspartate hydrochloride (127 mg, 0.20 mmol), **C-16.4** (84.6 mg, 0.22 mmol) and DIPEA (0.14 mL, 0.8 mmol) in DMF (3 mL) and the RM is stirred at RT for 2 h. The solvent is evaporated and the crude product is purified by prep. HPLC (basic) to yield 4-allyl 1-benzyl (2-(((2R,8S)-2-benzyl-8-isobutyl-9-methyl-4,7,10-trioxo-6-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-1-naphthoyl)-L-aspartate (142 mg, 76%). LC-MS I: $t_R = 1.34$ min; $[M+H]^+ = 933.56$.
- 10

- Step 4:** $Pd(PPh_3)_4$ (29.8 mg, 0.025 mmol) is added to a RT soln. (degassed) of 4-allyl 1-benzyl (2-(((2R,8S)-2-benzyl-8-isobutyl-9-methyl-4,7,10-trioxo-6-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-1-naphthoyl)-L-aspartate (145 mg, 0.152 mmol) and 1,3-dimethylbarbituric acid (47.8 mg, 0.30 mmol) in DCM (3 mL) and the RM is stirred at RT for 1 h. The RM is filtered and concentrated and used as such in the next step. LC-MS I: $t_R = 0.68$ min; $[M+H]^+ = 809.52$.
- 15

- Steps 5&6:** The title compound **MC-COOH-20** is prepared following steps 8&9 described for **MC-COOH-13**. LC-MS D: $t_R = 0.98$ min; $[M+H]^+ = 701.10$.
- 20

Listed in Table MC-COOH-C below are carboxylic acids that are prepared from the corresponding starting materials in analogy to the synthesis described above for **MC-COOH-20**.

Table MC-COOH-C

No.	Structure	SM BB-B	SM BB-C	Product	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
MC-COOH-21		B-Acid -5	C-16.5	(3S,7S,13R)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylic acid	1.00 D	709.01
MC-COOH-22		B-Acid -2	C-16.4	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-7-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid	0.92 B	711.34
MC-COOH-23		B-Acid -2	C-16.5	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxylic acid	0.94 B	711.34

Synthesis of Compounds of Formula (I)**General Method: GM-1**

- A stock soln. of the corresponding **MC-COOH** (0.05 mmol) and DIPEA (0.15 mmol) in DMF (0.5 mL) is added to each tube containing the corresponding amine **AM**. After stirring for 2 min another stock soln. of HATU (0.05 mmol) in DMF (0.5 mL) is added to each tube and the resulting mixtures are shaken at RT for 1 h. The mixtures are directly purified

by prep. HPLC (basic) and the fractions are dried in a Genevac HT12 vacuum centrifuge at 40°C to obtain the expected products. In some cases, chiral chromatography is used to obtain the desired product as a pure stereoisomer.

General Method: GM-2

Example 222: (4aR,7R,18S,22S)-7-Benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

Step 1: HATU (201 mg, 0.53 mmol) is added to a RT soln. of **B-1.13** (239 mg, 0.53 mmol), **C-2.1** (203 mg, 0.53 mmol) and DIPEA (0.27 mL, 1.58 mmol) in DMF (5 mL) and the RM is stirred for 30 min. The RM is then directly purified by prep. HPLC (basic) to give benzyl 2-((R)-2-((R)-4-(N-(*tert*-butoxycarbonyl)-N-methyl-L-leucyl)morpholine-3-carboxamido)-3-phenylpropoxy)-1-naphthoate as a white solid. LC-MS I: t_R = 1.40 min; $[M+H]^+$ = 752.46.

Step 2: A soln. of benzyl 2-((R)-2-((R)-4-(N-(*tert*-butoxycarbonyl)-N-methyl-L-leucyl)morpholine-3-carboxamido)-3-phenylpropoxy)-1-naphthoate (308 mg, 0.41 mmol) in EtOH (3 mL) is evacuated/purged with N_2 (3x) before 10% Pd/C (22 mg, 5 mol%) is added. The RM is evacuated/purged with H_2 (3x) and stirred under a H_2 atm for 2 h. The RM is filtered through a pad of celite and the filtrate concentrated in vacuo to give 2-((R)-2-((R)-4-(N-(*tert*-butoxycarbonyl)-N-methyl-L-leucyl)morpholine-3-carboxamido)-3-phenylpropoxy)-1-naphthoic acid as a white solid. LC-MS I: t_R = 0.65 min; $[M+H]^+$ = 662.38.

Step 3: HATU (96 mg, 0.24 mmol) is added to a RT soln. of 2-((R)-2-((R)-4-(N-(*tert*-butoxycarbonyl)-N-methyl-L-leucyl)morpholine-3-carboxamido)-3-phenylpropoxy)-1-naphthoic acid (160 mg, 0.24 mmol), **A-1.1** (78 mg, 0.24 mmol) and DIPEA (82 μ L, 0.48 mmol) in DMF (3 mL) and the RM is stirred for 1h. The RM is then directly purified by prep. HPLC (basic) to give *tert*-butyl (S)-3-(2-((R)-2-((R)-4-(N-(*tert*-butoxycarbonyl)-N-methyl-L-leucyl)morpholine-3-carboxamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate as a white solid. LC-MS I: t_R = 1.36 min; $[M+H]^+$ = 966.74.

Step 4: TFA (2.1 mL, 28 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(2-((R)-2-((R)-4-(N-(*tert*-butoxycarbonyl)-N-methyl-L-leucyl)morpholine-3-carboxamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (174 mg, 0.18 mmol) in DCM (5 mL) and the RM is stirred for 2 h. The RM is concentrated in vacuo and the residue is re-dissolved in DCM and again concentrated in vacuo (2x). The residue is dissolved in DMF (4 mL) before DIPEA (0.24 mL, 1.4 mmol) and HATU (80 mg, 0.21 mmol) are added and the RM is stirred for 1 h. The RM is then directly purified by prep. HPLC (basic) to give the title compound as a white solid. LC-MS I: t_R = 1.09 min; $[M+H]^+$ = 792.45.

Note: In cases where the product of step 1 above is a methyl or ethyl ester instead of the described benzyl ester (e.g. Example 228 below), a basic hydrolysis using 10 eq. 2M aq. NaOH soln. in MeOH at RT or heated up to 80°C is performed. The subsequent reaction sequence then remains the same as described for Example 222. In some cases, chiral chromatography is used to obtain the desired product as a pure stereoisomer.

General Method: GM-3

Example 689: (3'S,7'S,13'R)-13'-Benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

5 **Step 1:** HATU (169 mg, 0.435 mmol) is added to a RT soln. of **B-1.19** (200 mg, 0.396 mmol), **D1-3.0** (95 mg, 0.415 mmol), and DIPEA (0.34 mL, 1.98 mmol) in DMF (4 mL) and the RM is stirred for 16 h. The RM is purified directly by prep. HPLC (basic) to yield 3-((R)-2-([1-(*tert*-butoxycarbonyl-methyl-amino)-cyclobutanecarbonyl]-amino)-3-phenyl-propoxy)-6-fluoro-quinoline-4-carboxylic acid benzyl ester (220 mg, 87%) which is used as such in the next step.

10 **Step 2:** 4.0 M HCl in dioxane (0.385 mL, 1.54 mmol) is added to a RT soln. of 3-((R)-2-([1-(*tert*-butoxycarbonyl-methyl-amino)-cyclobutanecarbonyl]-amino)-3-phenyl-propoxy)-6-fluoro-quinoline-4-carboxylic acid benzyl ester (220 mg, 0.385 mmol) in DCM (2 mL) and the RM is stirred at RT for 2 h. The solvent is evaporated and crude benzyl (R)-6-fluoro-3-(2-(1-(methylamino)cyclobutane-1-carboxamido)-3-phenylpropoxy)quinoline-4-carboxylate (195 mg) is used as such in the next step.

15 **Step 3:** HATU (164 mg, 0.423 mmol) is added to a RT soln. of benzyl (R)-6-fluoro-3-(2-(1-(methylamino)cyclobutane-1-carboxamido)-3-phenylpropoxy)quinoline-4-carboxylate (195 mg, 0.385 mmol), Boc-*N*-methyl-L-leucine (99.4 mg, 0.404 mmol), and DIPEA (0.33 mL, 1.93 mmol) in DMF (4 mL) and the RM is stirred at RT for 16 h. The RM is purified directly by prep. HPLC (basic) to yield benzyl 3-((R)-2-(1-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxylate (207 mg, 70%). LC-MS I: t_R = 1.45-1.48 min; $[M+H]^+$ = 769.48.

20 **Step 4:** LiOH.H₂O (35.1 mg, 0.84 mmol) is added to a RT soln. of benzyl 3-((R)-2-(1-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxylate (207 mg, 0.270 mmol) in THF/H₂O 2/1 (3 mL) and the RM is stirred at 60°C for 3 d. The THF is evaporated and the residue is acidified with 1 M HCl to pH 1 and extracted with EtOAc (3x). The combined org. layers are dried (MgSO₄), filtered, and evaporated to yield crude 3-((R)-2-(1-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxylic acid (182 mg) which is used as such in the next step. LC-MS I: t_R = 0.70 min; $[M+H]^+$ = 679.45.

30 **Step 5:** HATU (28.6 mg, 0.0737 mmol) is added to a RT soln. of 3-((R)-2-(1-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxylic acid (45.5 mg, 0.067 mmol), **A-1.24** (22 mg, 0.07 mmol), and DIPEA (0.0573 mL, 0.335 mmol) in DMF (2 mL) and the RM is stirred at RT for 16 h. The RM is purified directly by prep. HPLC (basic) to yield *tert*-butyl (S)-3-(3-((R)-2-(1-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-cyclopropylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate (44 mg, 67%). LC-MS B: t_R = 1.24 min; $[M+H]^+$ = 984.40.

Step 6: TFA (2 mL, 26 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(3-((R)-2-(1-((S)-2-((*tert*-butoxycarbonyl)(methyl)amino)-*N*,4-dimethylpentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-cyclopropylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate (44 mg, 0.045 mmol) in DMF (2 mL) and the resulting mix. is stirred at RT for 2 h. The mix. is concentrated and co-evaporated with DCM (2x) to yield (S)-4-((2-(3-cyclopropylisoxazol-5-yl)ethyl)amino)-3-(3-((R)-2-(1-((S)-*N*,4-dimethyl-2-(methylamino)pentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxamido)-4-oxobutanoic acid trifluoroacetate (53 mg) which is used as such in the next step. LC-MS I: t_R = 0.58 min; $[M+H]^+$ = 828.28.

Step 7: HATU (108 mg, 0.283 mmol) is added to a RT soln. of (S)-4-((2-(3-cyclopropylisoxazol-5-yl)ethyl)amino)-3-(3-((R)-2-(1-((S)-*N*,4-dimethyl-2-(methylamino)pentanamido)cyclobutane-1-carboxamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxamido)-4-oxobutanoic acid trifluoroacetate (53 mg) and DIPEA (0.162 mL, 0.945 mmol) in DMF (0.5 mL)/DCM (4.5 mL), and the RM is stirred at RT for 16 h. The RM is concentrated and purified by prep. HPLC (basic) to yield the title compound (30 mg) as a solid. LC-MS I: t_R = 1.07 min; $[M+H]^+$ = 810.29.

General Method: GM-4

Example 700: (3S,7S,13R)-*N*-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(((S)-chroman-3-yl)methyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

Steps 1&2: Allyl (S)-3-(2-((R)-2-amino-3-phenylpropoxy)-1-naphthamido)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride is prepared following the synthesis described for **GM-5**, steps 1&2, using **A-2.2** and **B-Acid-5**. LC-MS B: t_R = 0.88 min; $[M+H]^+$ = 624.23.

Step 3: HATU (41.8 mg, 0.11 mmol) is added to a RT soln. of allyl (S)-3-(2-((R)-2-amino-3-phenylpropoxy)-1-naphthamido)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride (66 mg, 0.1 mmol), **C-16.2** (47.6 mg, 0.11 mmol), and DIPEA (0.051 mL, 0.3 mmol) in DMF (1 mL) and the RM is stirred at RT for 30 min. Purification by prep. HPLC (acidic) yields allyl (S)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2-(((2R,8S)-2-benzyl-6-(((S)-chroman-3-yl)methyl)-8-isobutyl-9-methyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-1-naphthamido)-4-oxobutanoate (87 mg, 84%) as a white solid. LC-MS I: t_R = 1.33 min; $[M+H]^+$ = 1038.74.

Step 4: Pd(Ph₃)₄ (9.63 mg, 0.0082 mmol) is added to a RT soln. of allyl (S)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2-(((2R,8S)-2-benzyl-6-(((S)-chroman-3-yl)methyl)-8-isobutyl-9-methyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-1-naphthamido)-4-oxobutanoate (87.7 mg, 0.082 mmol) and 1,3-dimethylbarbituric acid (25.8 mg, 0.163 mmol) in DCM (1 mL) and the RM is stirred at RT for 2 h. The RM is concentrated to yield (S)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2-((R)-2-(2-((S)-*N*-(((S)-chroman-3-yl)methyl)-4-methyl-2-(methylamino)pentanamido)acetamido)-3-phenylpropoxy)-1-naphthamido)-4-oxobutanoic acid which is used as such in the next step. LC-MS I: t_R = 0.69 min; $[M+H]^+$ = 914.75.

Step 5: HATU (31.1 mg, 0.082 mmol) is added to a RT soln. of (S)-4-((2-(benzo[d][1,3]dioxol-5-yl)ethyl)amino)-3-(2-((R)-2-(2-((S)-*N*-(((S)-chroman-3-yl)methyl)-4-methyl-2-(methylamino)pentanamido)acetamido)-3-phenylpropoxy)-1-

naphthamido)-4-oxobutanoic acid (74.7 mg, 0.082 mmol) and DIPEA (70 μ L, 0.41 mmol) in DMF (1 mL) and the RM is stirred at RT for 30 min. Purification by prep. HPLC (basic) yields the title compound (49.6 mg, 97%) as a white solid. LC-MS I: t_R = 1.19 min; $[M+H]^+$ = 896.69.

Example 976: (3S,7S,10R,13R)-13-Benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-10-(2-ethoxyethyl)-

5 **20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide**

Step 1: HATU (424 mg, 1.11 mmol) is added to a RT solution of **B-Acid-8** (394 mg, 0.928 mmol), **A-1.22** (361 mg, 1.11 mmol) and DIPEA (0.477 mL, 2.78 mmol) in DMF (5 mL) under argon and the resulting mixture is stirred for 1h. The RM is partitioned between water and EtOAc. The layers are separated and the inorg. layer is extracted further with EtOAc (2x). The combined org. extracts are washed with water and brine, dried over Na_2SO_4 , filtered and evaporated under reduced pressure to give the crude product; It is purified by FC, eluting with 0% to 100% EtOAc in Heptane to give tert-butyl (S)-3-(6-((R)-2-(((allyloxy)carbonyl)amino)-3-phenylpropoxy)-3-fluoroquinoline-5-carboxamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate as a beige solid (334 mg). LC-MS B: t_R = 1.09 min; $[M+H]^+$ = 731.48.

15 **Step 2:** Under an argon atmosphere, tert-butyl (S)-3-(6-((R)-2-(((allyloxy)carbonyl)amino)-3-phenylpropoxy)-3-fluoroquinoline-5-carboxamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (334 mg, 0.457 mmol) is dissolved in MeOH (10 mL) and 1,3-dimethylbarbituric acid (144 mg, 0.914 mmol) then $Pd(PPh_3)_4$ (27.2 mg, 0.0229 mmol) are added to the solution. The RM is stirred at RT for 1hr to reach full conversion. The RM is evaporated under reduced pressure and the resulting crude is purified by FC eluting from 0% to 20% MeOH in DCM to yield tert-butyl (S)-3-(6-((R)-2-amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate as a brown oil (142 mg). LC-MS B: t_R = 0.81 min; $[M+H]^+$ = 647.46.

Step 3: HATU (100 mg, 0.264 mmol) is added to a RT solution of **C-18.9** (85.5 mg, 0.22 mmol), tert-butyl (S)-3-(6-((R)-2-amino-3-phenylpropoxy)-3-fluoroquinoline-5-carboxamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (142 mg, 0.22 mmol) and DIPEA (0.113 mL, 0.66 mmol) in DMF (2 mL) under argon and the RM is stirred for 1h. The mixture is partitioned between water and EtOAc. The layers are separated and the inorg. layer is extracted further with EtOAc (2x). The combined org. extracts are washed with water and brine, dried over Na_2SO_4 , filtered and evaporated under reduced pressure to give the crude product. Purification by FC, eluting with 50% EtOAc in Heptane gives tert-butyl (S)-3-(6-(((6S,9RS,12R)-12-benzyl-9-(2-ethoxyethyl)-6-isobutyl-2,2,5,8-tetramethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-yl)oxy)-3-fluoroquinoline-5-carboxamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate as a white powder (114 mg). LC-MS B: t_R = 1.25 min; $[M+H]^+$ = 1017.93.

Step 4: The title compound is prepared as a white powder from tert-butyl (S)-3-(6-(((6S,9RS,12R)-12-benzyl-9-(2-ethoxyethyl)-6-isobutyl-2,2,5,8-tetramethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-yl)oxy)-3-fluoroquinoline-5-carboxamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate following the conditions described for **GM-2, Step 4**. LC-MS I: t_R = 1.06 min; $[M+H]^+$ = 843.73.

General Method: GM-5

Example 713: (3S,7S,10R,13R)-13-Benzyl-10-((benzyloxy)methyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

5 **Step 1:** HATU (1.15 g, 2.95 mmol) is added to a RT soln. of **A-2.3** (1.0 g, 2.95 mmol) **B-Acid-5** (1.26 g, 2.95 mmol) and DIPEA (2.1 mL, 11.9 mmol) in DCM (10 mL) and the RM is stirred at RT overnight. Sat. aq. NaHCO₃ is added and the mix. is extracted with DCM. The org. layer is concentrated and the crude product purified by FC (eluting with 0% to 50% EtOAc in hept) to yield allyl (S)-3-(2-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (1.65 g, 79%). LC-MS B: t_R = 1.16 min; [M+H]⁺ = 710.37.

Step 2: 4 M HCl in dioxane (2.33 mL, 9.31 mmol) is added to allyl (S)-3-(2-((R)-2-((tert-butoxycarbonyl)amino)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (1.65 g, 2.33 mmol) in DCM (10 mL) and the RM is stirred at RT for 2 h. The mix. is concentrated to yield allyl (S)-3-(2-((R)-2-amino-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (1.7 g, 120%) which is used as such in the next step.

15 LC-MS B: t_R = 1.08 min; [M+H]⁺ = 610.43.

Step 3: HATU (42.7 mg, 0.11 mmol) is added to a RT soln. of allyl (S)-3-(2-((R)-2-amino-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (64.6 mg, 0.1 mmol), **D1-1.1** (34 mg, 0.11 mmol) and DIPEA (0.051 mL, 0.3 mmol) in DMF (1 mL) and the RM is stirred at RT for 30 min. Purification by prep. HPLC (acidic) yields allyl (S)-3-(2-((R)-2-((R)-3-(benzyloxy)-2-((tert-butoxycarbonyl)(methyl)amino)propanamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (47 mg, 52%) as the major epimer. LC-MS B: t_R = 1.22 min; [M+H]⁺ = 901.13. The minor epimer allyl (S)-3-(2-((R)-2-((S)-3-(benzyloxy)-2-((tert-butoxycarbonyl)(methyl)amino)propanamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (21 mg, 24%) is also isolated. LC-MS B: t_R = 1.24 min; [M+H]⁺ = 901.14.

Step 4: 4 M HCl in dioxane (0.1 mL, 0.4 mmol) is added to a RT soln. of allyl (S)-3-(2-((R)-2-((R)-3-(benzyloxy)-2-((tert-butoxycarbonyl)(methyl)amino)propanamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (47 mg, 0.051 mmol) in DCM (1 mL) and the RM is stirred at RT for 1 h. The RM is concentrated to yield allyl (S)-3-(2-((R)-2-((R)-3-(benzyloxy)-2-(methylamino)propanamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate hydrochloride (42.8 mg, 100%) as a white solid which is used as such in the next step. LC-MS B: t_R = 0.97 min; [M+H]⁺ = 801.05.

30 **Step 5:** HATU (21.8 mg, 0.056 mmol) is added to a RT soln. of allyl (S)-3-(2-((R)-2-((R)-3-(benzyloxy)-2-(methylamino)propanamido)-3-phenylpropoxy)-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate hydrochloride (42.8 mg, 0.0511 mmol), **D2-3.1** (12.9 mg, 0.056 mmol) and DIPEA (0.026 mL, 0.153 mmol) in DMF (0.5 mL) and the RM is stirred at RT for 1 h. Purification by prep. HPLC (acidic) yields allyl (S)-3-(2-(((2R,5R,8S)-2-benzyl-5-((benzyloxy)methyl)-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-1-

naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (41.5 mg, 80%) as a white solid. LC-MS B: t_R = 1.26 min; $[M+H]^+$ = 1012.27.

Step 6: $Pd(Ph_3)_4$ (4.83 mg, 0.004 mmol) is added to a RT soln. of allyl (S)-3-(2-(((2R,5R,8S)-2-benzyl-5-((benzyloxy)methyl)-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy))-1-

- 5 naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoate (41.5 mg, 0.04 mmol) and 1,3-dimethylbarbituric acid (12.9 mg, 0.08 mmol) in DCM (1 mL) and the RM is stirred at RT for 1 h. The RM is concentrated to yield (S)-3-(2-(((R)-2-(((R)-3-(benzyloxy)-2-((S)-N,4-dimethyl-2-(methylamino)pentanamido)propanamido)-3-phenylpropoxy))-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoic acid which is used as such in the next step. LC-MS B: t_R = 0.94 min; $[M+H]^+$ = 888.15.

- 10 **Step 7:** HATU (15.9 mg, 0.041 mmol) is added to a RT soln. of (S)-3-(2-(((R)-2-(((R)-3-(benzyloxy)-2-((S)-N,4-dimethyl-2-(methylamino)pentanamido)propanamido)-3-phenylpropoxy))-1-naphthamido)-4-((3-methoxyphenethyl)amino)-4-oxobutanoic acid (36.4 mg, 0.041 mmol) and DIPEA (35.1 μ L, 0.205 mmol) in DMF (1 mL) and the RM is stirred at RT for 20 min. Purification by prep. HPLC (acidic) yields the title compound (29.3 mg, 82%) as pale yellow solid. LC-MS B: t_R = 1.18 min; $[M+H]^+$ = 870.1.

- 15 **General Method: GM-6**

Example 722: (3S,7S,10R,13R)-10,13-Dibenzyl-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide

- Step 1:** HATU (192 mg, 0.49 mmol) is added to a RT soln. of **B-1.19** (227 mg, 0.45 mmol), **C-17.1** (178 mg, 0.45 mmol), and DIPEA (0.39 mL, 0.3 mmol) in DMF (4 mL) and the RM is stirred at RT for 16 h. Purification by prep. HPLC (basic) yields benzyl 3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxylate (269 mg, 70%). LC-MS I: t_R = 1.42 min; $[M+H]^+$ = 803.46.

- Step 2:** $LiOH \cdot H_2O$ (35.1 mg, 0.84 mmol) is added to a RT soln. of benzyl 3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxylate (269 mg) in THF/ H_2O 2/1 (3 mL) and the RM is stirred at 60°C for 3 d. The THF is evaporated and the residue is acidified with 1 M HCl to pH 1 and extracted with EtOAc (3x). The org. layers are combined, dried ($MgSO_4$), filtered, and evaporated to yield 3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxylic acid (250 mg, 105%) which is used as such in the next step. LC-MS I: t_R = 0.71/0.72 min; $[M+H]^+$ = 713.42. A double peak visible by LC-MS indicates that epimerisation of one chiral centre occurred.

Step 3: HATU (96 mg, 0.25 mmol) is added to a RT soln. of 3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxylic acid (114 mg, 0.23 mmol), **A-1.8** (78.1 mg, 0.24 mmol), and DIPEA (0.19 mL, 1.13 mmol) in DMF (4 mL) and the RM is stirred at RT for 16 h. Purification by prep. HPLC (acidic) yields *tert*-butyl (S)-3-(3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-

trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate (187 mg, 56%). LC-MS B: t_R = 1.21 min; $[M+H]^+$ = 992.37.

Step 4: TFA (2 mL, 26 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoate (187 mg, 0.189 mmol) in DCM (3 mL) and the resulting mix. is stirred at RT for 2 h. The mix. is concentrated and co-evaporated with DCM (2x) to yield (S)-3-(3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoic acid (180 mg) which is used as such in the next step. LC-MS I: t_R = 0.66/0.68 min; $[M+H]^+$ = 936.3. A double peak visible by LC-MS indicates that epimerisation of one chiral centre occurred.

Step 5: Pd(Ph₃)₄ (22.3 mg, 0.019 mmol) is added to a RT soln. of (S)-3-(3-(((2R,5R,8S)-2,5-dibenzyl-8-isobutyl-6,9-dimethyl-4,7,10-trioxo-11-oxa-3,6,9-triazatetradec-13-en-1-yl)oxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoic acid (177 mg, 0.19 mmol) and 1,3-dimethylbarbituric acid (59.6 mg, 0.38 mmol) in DCM (1 mL) and the RM is stirred at RT for 1 h. The RM is concentrated to yield (S)-3-(3-(((R)-2-(((S)-N,4-dimethyl-2-(methylamino)pentanamido)-3-phenylpropanamido)-3-phenylpropoxy)-6-fluoroquinoline-4-carboxamido)-4-((2-(3-methylisoxazol-5-yl)ethyl)amino)-4-oxobutanoic acid (165 mg) which is used as such in the next step. LC-MS I: t_R = 0.64 min; $[M+H]^+$ = 852.59.

Step 6: The title compound is synthesised following the synthesis described for **GM-5**, step 7. LC-MS I: t_R = 1.11 min; $[M+H]^+$ = 834.77.

20 General Method: GM-7

Example 724: (3R,6RS,9S,13S)-3-Benzyl-6-((benzyloxy)methyl)-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

Step 1: HATU (1.49 g, 3.86 mmol) is added to a RT suspension of **A-1.22** (1.25 g, 3.86 mmol), **B-Acid-7** (1.55 g, 3.86 mmol), and DIPEA (2.0 mL, 11.6 mmol) in DCM (30 mL), then DMF (5 mL) is added to obtain a clear soln. The RM is stirred at RT overnight. The RM is concentrated and purified by FC (eluting with 0% to 100% EtOAc in hept) to yield *tert*-butyl (S)-3-(4-((R)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (2.79 g, 100%). LC-MS I: t_R = 1.12 min; $[M+H]^+$ = 709.20.

Step 2: 4 M HCl in dioxane (2.0 mL, 8.0 mmol) is added to *tert*-butyl (S)-3-(4-((R)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (2.79 g, 3.94 mmol) in DCM (30 mL) and MeOH (5 mL). The RM is stirred at RT for 48 h. The mix. is concentrated to yield *tert*-butyl (S)-3-(4-((R)-2-amino-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride (2.55 g, 100%) as a yellow solid, which is used as such in the next step. LC-MS I: t_R = 0.90 min; $[M+H]^+$ = 609.35.

Step 3: HATU (128 mg, 0.33 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(4-((R)-2-amino-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride (304 mg, 0.33 mmol), **D1-1.1** (96 mg, 0.30 mmol), and DIPEA (0.15 mL, 0.9 mmol) in DMF (3 mL) and the RM is stirred at RT for 15 min. Purification by prep. HPLC (basic) yields *tert*-butyl (S)-3-(4-((R)-2-(3-(benzyloxy)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (108 mg, 40%) as a white solid. LC-MS I: $t_R = 1.23$ min; $[M+H]^+ = 900.76$.

Step 4: 4 M HCl in dioxane (0.06 mL, 0.24 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(4-((R)-2-(3-(benzyloxy)-2-((*tert*-butoxycarbonyl)(methyl)amino)propanamido)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (108 mg, 0.12 mmol) in MeOH (1 mL) and the RM is stirred at RT for 48 h. The RM is concentrated to yield *tert*-butyl (S)-3-(4-((R)-2-((RS)-3-(benzyloxy)-2-(methylamino)propanamido)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride (101 mg, 100%) as a white solid which is used as such in the next step. LC-MS I: $t_R = 1.05$ min; $[M+H]^+ = 800.64$.

Step 5: HATU (56.4 mg, 0.14 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(4-((R)-2-(3-(benzyloxy)-2-(methylamino)propanamido)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate hydrochloride (100 mg, 0.12 mmol), Boc-*N*-methyl-L-leucine (36.4 mg, 0.14 mmol) and DIPEA (0.08 mL, 0.48 mmol) in DMF (1.2 mL) and the RM is stirred at RT for 15 min. Purification by prep. HPLC (basic) yields *tert*-butyl (S)-3-(4-(((6S,9RS,12R)-12-benzyl-9-((benzyloxy)methyl)-6-isobutyl-2,2,5,8-tetramethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-yl)oxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (60 mg, 49%) as a white solid. LC-MS I: $t_R = 1.38$ min; $[M+H]^+ = 1027.94$.

Step 6: TFA (0.6 mL, 7.83 mmol) is added to a RT soln. of *tert*-butyl (S)-3-(4-(((6S,9RS,12R)-12-benzyl-9-((benzyloxy)methyl)-6-isobutyl-2,2,5,8-tetramethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-yl)oxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoate (60.3 mg, 0.06 mmol) in DCM (1 mL) and the resulting mix. is stirred at RT for 1 h. The mix. is concentrated and co-evaporated with DCM (2x) to yield (S)-3-(4-((R)-2-(3-(benzyloxy)-2-((S)-*N*,4-dimethyl-2-(methylamino)pentanamido)propanamido)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoic acid (55 mg, 100%) which is used as such in the next step. LC-MS I: $t_R = 0.64$ min; $[M+H]^+ = 871.79$.

Step 7: HATU (23 mg, 0.046 mmol) is added to a RT soln. of (S)-3-(4-((R)-2-(3-(benzyloxy)-2-((S)-*N*,4-dimethyl-2-(methylamino)pentanamido)propanamido)-3-phenylpropoxy)-2-methoxynicotinamido)-4-((2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)amino)-4-oxobutanoic acid (51.1 mg, 0.06 mmol) and DIPEA (50 μ L, 0.29 mmol) in DMF (1 mL) and the RM is stirred at RT for 30 min. Purification by prep. HPLC (basic) yields the title compound (29.3 mg, 82%) as pale yellow solid. LC-MS 036: $t_R = 1.08$ min; $[M+H]^+ = 853.34$.

General Method: GM-8

Example 725: (4aR,7R,18S,22S)-7-Benzyl-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

- 5 **Step 1:** HATU (1.86 g, 4.89 mmol) is added to a RT soln. of **C-7.1** (2.48 g, 4.65 mmol), **B-1.13** (2.37 g, 4.65 mmol), and DIPEA (2.4 mL, 14 mmol) in MeCN (14.5 mL) and the RM is stirred at RT for 30 min. Water (10 mL) and DCM (100 mL) are added to the RM and the layers are separated. The aq. layer is extracted with DCM (2x 75 mL) and the combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 15-45% EtOAc/hept, $R_f = 0.45$ in EtOAc/hept 3:7) yields 2,2,2-trichloroethyl (R)-3-(((R)-1-((1-
10 ((benzyloxy)carbonyl)naphthalen-2-yl)oxy)-3-phenylpropan-2-yl)carbamoyl)-4-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)piperazine-1-carboxylate (2.25 g, 52 %) as a white foam. LC-MS B: $t_R = 1.33$ min; $[M+H]^+ = 927.11$.

- Step 2:** Pd/C (129 mg, 0.121 mmol) is added to a RT soln. (degassed) of 2,2,2-trichloroethyl (R)-3-(((R)-1-((1-
((benzyloxy)carbonyl)naphthalen-2-yl)oxy)-3-phenylpropan-2-yl)carbamoyl)-4-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)piperazine-1-carboxylate (2.24 g, 2.42 mmol) in MeOH (20 mL). The RM is stirred at RT for 18 h under a H₂
15 atm. The mix. is filtered and the filtrate concentrated to yield 2-((R)-2-((R)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-4-((2,2,2-trichloroethoxy)carbonyl)piperazine-2-carboxamido)-3-phenylpropoxy)-1-naphthoic acid (2.01 g, 100%) as a white foam which is used as such in the next step. LC-MS B: $t_R = 1.21$ min; $[M+H]^+ = 836.91$.

- Step 3:** HATU (355 mg, 0.933 mmol) is added to a RT soln. of 2-((R)-2-((R)-1-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)-4-((2,2,2-trichloroethoxy)carbonyl)piperazine-2-carboxamido)-3-phenylpropoxy)-1-naphthoic acid (600 mg, 0.718 mmol), **A-1.8** (256 mg, 0.86 mmol), and DIPEA (0.369 mL, 2.15 mmol) in MeCN (6 mL) and the RM is stirred at RT for 1 h. Water (8 mL) and DCM (80 mL) are added to the RM, then the layers are separated. The aq. layer is extracted with DCM (2x 75 mL) and the combined org. layers are washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 20% to 60% EtOAc in hept, with $R_f = 0.26$ in EtOAc/hept 1:1) yields 2,2,2-trichloroethyl (R)-3-(((R)-1-((1-(((S)-4-(tert-butoxy)-1-((2-(3-methylisoxazol-5-yl)ethyl)amino)-1,4-dioxobutan-2-yl)carbamoyl)naphthalen-2-yl)oxy)-3-phenylpropan-2-yl)carbamoyl)-4-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)piperazine-1-carboxylate (512 mg, 64%) as a white foam. LC-MS B: $t_R = 1.30$ min; $[M+H]^+ = 1116.18$.
25

- Step 4:** TFA (1.73 mL, 22.4 mmol) is added to a RT soln. of 2,2,2-trichloroethyl (R)-3-(((R)-1-((1-(((S)-4-(tert-butoxy)-1-((2-(3-methylisoxazol-5-yl)ethyl)amino)-1,4-dioxobutan-2-yl)carbamoyl)naphthalen-2-yl)oxy)-3-phenylpropan-2-yl)carbamoyl)-4-(N-(tert-butoxycarbonyl)-N-methyl-L-leucyl)piperazine-1-carboxylate (500 mg, 0.448 mmol) in DCM (5 mL) and the RM is stirred at RT for 3 h. The mix. is concentrated and co-evaporated with DCM before being dried under HV. LC-MS B $t_R = 0.89$ min; $[M+H]^+ = 960.02$. The dried residue is taken up in MeCN (5 mL), then DIPEA (0.384 mL, 2.24 mmol) and HATU (256 mg, 0.672 mmol) are added and the RM is stirred at RT for 30 min. Water (10 mL) and DCM (100 mL) are added to the RM and the layers are separated. The aq. layer is extracted with DCM (2x 75 mL) and the combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated.
30 Purification by FC (eluting with 35% to 100% EtOAc in hept, $R_f = 0.28$ in EtOAc/hept 7:3) yields 2,2,2-trichloroethyl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-18-((2-(3-methylisoxazol-5-yl)ethyl)carbamoyl)-5,16,20,23-

tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate (293 mg, 69%) as a white foam. LC-MS B: t_R = 1.13 min; $[M+H]^+$ = 940.04.

Step 5: Zinc powder (176 mg, 2.69 mmol) is added to a RT soln. of 2,2,2-trichloroethyl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-18-((2-(3-methylisoxazol-5-yl)ethyl)carbamoyl)-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate (260 mg, 0.269 mmol) and AcOH (0.339 mL, 5.92 mmol) in DCM (5 mL) and the RM is stirred at RT for 1 h. To the RM is added sat. NaHCO_3 (10 mL) and DCM (50 mL), and the layers are separated. The aq. layer is extracted with DCM (2x 25 mL) and the combined org. layers are washed with brine (10 mL), dried (MgSO_4), filtered, and concentrated to yield the title compound (215 mg, 104%) as a white foam. LC-MS B: t_R = 0.80 min; $[M+H]^+$ = 765.67.

General Method: GM-9

Example 761: (8'R,14'S,18'S)-8'-Benzyl-14'-isobutyl-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-N-(2-(3-phenylisoxazol-5-yl)ethyl)-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide

Step 1: Methyl 6-((R)-2-(1-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)cyclopropane-1-carboxamido)-3-phenylpropoxy)-2-methylbenzo[d]oxazole-7-carboxylate is prepared from **B-2.5** (302 mg, 0.65 mmol) and **C-1.2** (221 mg, 0.65 mmol) in analogy to the procedure described for Example 222, step 1. LC-MS J: t_R = 2.30 min; $[M+H]^+$ = 665.3.

Step 2: A RT soln. of methyl 6-((R)-2-(1-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)cyclopropane-1-carboxamido)-3-phenylpropoxy)-2-methylbenzo[d]oxazole-7-carboxylate (315 mg, 0.47 mmol) and 2M aq. NaOH (4.74 mL, 9.48 mmol) in MeOH (10 mL) is stirred for 16 h. The RM is concentrated in vacuo and the residue is partitioned between water and EtOAc and the layers are separated. The aq. phase is re-extracted with EtOAc (2x) and the combined org. extracts are washed with brine, dried over Na_2SO_4 , filtered and evaporated in vacuo to give 6-((R)-2-(1-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)cyclopropane-1-carboxamido)-3-phenylpropoxy)-2-methylbenzo[d]oxazole-7-carboxylic acid as a white solid. LC-MS J: t_R = 1.82 min; $[M+H]^+$ = 651.2.

Steps 3&4: (8'R,14'S,18'S)-8'-benzyl-N-(but-3-yn-1-yl)-14'-isobutyl-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide is prepared from 6-((R)-2-(1-((S)-2-((tert-butoxycarbonyl)(methyl)amino)-N,4-dimethylpentanamido)cyclopropane-1-carboxamido)-3-phenylpropoxy)-2-methylbenzo[d]oxazole-7-carboxylic acid and **A-1.33** in analogy to the sequence of reactions as described for Example 222, steps 3-4. LC-MS J: t_R = 1.97 min; $[M+H]^+$ = 699.2.

Step 5: NCS (64 mg, 0.48 mmol) is added to a RT soln. of (E)-benzaldehyde oxime (48 mg, 0.40 mmol) in DMF (0.5 mL) and the RM is stirred for 16 h. The RM is partitioned between water and Et_2O and the layers are separated. The

aq. phase is re-extracted with Et₂O (2x) and the combined org. extracts are washed with brine and dried over a stream of air to give (Z)-N-hydroxybenzimidoyl chloride. **Note:** Compound is unstable and is used directly in the next step.

Step 6: A RT mix. of (8'R,14'S,18'S)-8'-benzyl-N-(but-3-yn-1-yl)-14'-isobutyl-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-

- 5 oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide (45 mg, 0.06 mmol), (Z)-N-hydroxybenzimidoyl chloride (30 mg, 0.19 mmol), CuI (0.2 mg, 1.29 μ mol), and K₂CO₃ (36 mg, 0.26 mmol) in THF (1 mL) is stirred for 48 h. The RM is concentrated in vacuo and re-dissolved in DMF before being directly purified by prep. HPLC (basic) to give the title compound as a white solid. LC-MS H: t_R = 1.19 min; [M+H]⁺ = 818.8.

Example 762: (8'R,14'S,18'S)-8'-Benzyl-14'-isobutyl-N-(2-(3-isopropylisoxazol-5-yl)ethyl)-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide

- The title compound is prepared from (8'R,14'S,18'S)-8'-benzyl-N-(but-3-yn-1-yl)-14'-isobutyl-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide (Ex. 761, steps 1-4) and (Z)-N-hydroxyisobutyrimidoyl chloride (prepared from (E)-isobutyraldehyde oxime, see Ex. 761, step 5) in analogy to the procedure described for Ex. 761, step 6. LC-MS H: t_R = 1.14 min; [M+H]⁺ = 784.6.

Example 763: (3'S,7'S,13'R)-13'-Benzyl-N-(2-(3-benzyl-1,2,4-oxadiazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

- 20 **Steps 1-4:** Benzyl 3-((3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamido)propanoate is prepared from **B-1.14**, **C-1.2**, and **A-1.34** in analogy to the sequence of reactions described for Ex. 222, steps 1-4. LC-MS J: t_R = 2.07 min; [M+H]⁺ = 805.4.

- 25 **Step 5:** 3-((3'S,7'S,13'R)-13'-Benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamido)propanoic acid is prepared from benzyl 3-((3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamido)propanoate following the
- 30 hydrogenation procedure described for Ex. 222, step 2. LC-MS J: t_R = 1.63 min; [M+H]⁺ = 715.3.

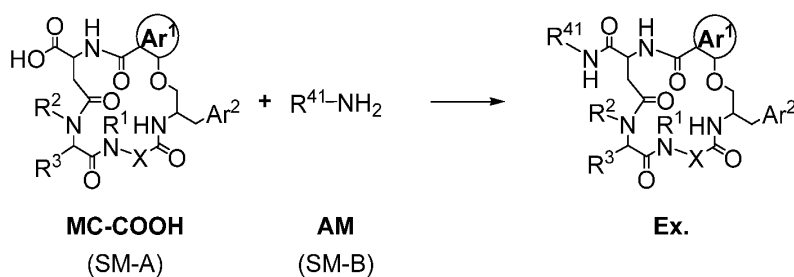
Step 6: Hydroxylamine.HCl (1.19 g, 17.1 mmol) is added to a RT soln. of benzyl cyanide (1.0 mL, 8.5 mmol) in MeOH (20 mL) followed by a soln. of NaOH (0.68 g, 17.1 mmol) in water (5 mL) and the RM is stirred for 16 h. The RM is concentrated in vacuo and the residue is co-evaporated with PhMe (2x) to give N'-hydroxy-2-phenylacetimidamide as a colourless oil. **Note:** Used directly as such in the next step.

Step 7: HATU (38 mg, 0.10 mmol) is added to a RT soln. of 3-((3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamido)propanoic acid (50 mg, 0.07 mmol) and DIPEA (35 μ L, 0.20 mmol) in NMP (1 mL) and the RM is stirred for 10 min before a soln. of N'-hydroxy-2-phenylacetimidamide (33 mg, 0.22 mmol) in NMP (200 μ L) is added and stirring is continued for 30 min. The RM is then heated to 80°C for 16 h. The RM is directly purified by prep. HPLC (basic) to give the title compound as a white solid. LC-MS H: t_R = 1.22 min; $[M+H]^+$ = 829.8.

Example 764: (3'S,7'S,13'R)-13'-Benzyl-N-(2-(3-(cyclopropylmethyl)-1,2,4-oxadiazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

Step 1: Hydroxylamine 50% aq. soln. (0.19 mL, 1.48 mmol) is added to a RT soln. of 2-cyclopropylacetonitrile (100 mg, 1.23 mmol) in EtOH (1.5 mL) and the RM is heated to reflux for 24 h. The RM is concentrated in vacuo and the residue is co-evaporated with PhMe (2x) to give 2-cyclopropyl-N'-hydroxyacetimidamide as a colourless oil. **Note:** Used directly as such in the next step.

Steps 2-7: The title compound is prepared from 3-((3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamido)propanoic acid (Ex. 763, steps 1-5) and 2-cyclopropyl-N'-hydroxyacetimidamide in analogy to the procedure described for Ex. 763, step 7. LC-MS H: t_R = 1.17 min; $[M+H]^+$ = 793.7.



GM-1

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Listed in Table MC-1 below are compounds of general formula (I) that are prepared from their corresponding building blocks **MC-COOH** (SM-A) and **amine** (SM-B) as described above in General Method 1 (**GM-1**). In the following tables * denotes an example compound isolated during the synthesis, most often separated by prep. HPLC purification of the final synthetic step as a minor epimer due to epimerisation of a chiral centre. In certain cases, an enantiomerically or diastereomerically pure building block(s) undergoes epimerisation during the synthesis and the example compound is isolated as a mixture of epimers.

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Table MC-1 (GM-1)

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
1	MC-COOH-8	AM-1.1	1.14 (I)	828.23
2	MC-COOH-9	AM-1.1	1.23 (D)	854.37
3	MC-COOH-2	AM-2.1	1.00 (I)	786.23
4	MC-COOH-2	AM-2.2	0.99 (I)	770.2
5	MC-COOH-10	AM-1.1	1.12 (D)	848.27
6	MC-COOH-11	AM-1.1	1.14 (D)	892.29
7	MC-COOH-12	AM-1.1	1.00 (B)	770.46
8	MC-COOH-2	AM-2.3	0.98 (D)	801.37
9	MC-COOH-13	AM-1.1	1.13 (B)	868.35
10	MC-COOH-14	AM-1.1	1.19 (B)	896.38
11	MC-COOH-15	AM-2.1	1.27 (I)	852.27
12	MC-COOH-15	AM-3.1	1.24 (I)	868.28
13	MC-COOH-15	AM-1.2	1.20 / 1.22 (I)	838.25
14	MC-COOH-15	AM-2.2	1.26 (I)	836.24
15	MC-COOH-15	AM-2.5	1.24 (I)	838.25
16	MC-COOH-15	AM-1.3	1.21 / 1.22 (I)	837.22
17	MC-COOH-3	AM-1.4	1.06 (I)	794.64
18	MC-COOH-15	AM-1.42	1.11 (I)	798.49
19	MC-COOH-15	AM-1.43	1.09 (I)	798.5
20	MC-COOH-15	AM-1.44	1.09 (I)	798.47
21	MC-COOH-15	AM-1.45	1.19 (I)	800.56
22	MC-COOH-15	AM-1.46	1.14 (I)	794.56
23	MC-COOH-3	AM-1.47	0.97 (I)	785.28
24	MC-COOH-3	AM-1.48	0.97 (I)	785.28
25	MC-COOH-3	AM-1.5	1.04 (I)	794.32
26	MC-COOH-3	AM-1.57	1.07 (I)	830.22
27	MC-COOH-3	AM-1.6	1.06 (I)	764.32
28	MC-COOH-3	AM-2.8	1.04 (I)	831.34
29	MC-COOH-3	AM-1.49	1.05 (I)	811.63
30	MC-COOH-3	AM-1.50	1.05 (I)	805.67
31	MC-COOH-3	AM-2.7	1.06 (I)	831.68
32	MC-COOH-4	AM-1.51	1.09 (I)	820.61
33	MC-COOH-4	AM-1.52	1.08 (I)	808.38

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
34	MC-COOH-4	AM-1.53	1.07 (I)	808.38
35	MC-COOH-4	AM-11.1	1.06 (I)	850.42
36	MC-COOH-4	AM-12.1	1.16 (I)	868.42
37	MC-COOH-4	AM-12.2	1.11 (I)	854.38
38	MC-COOH-4	AM-1.50	1.06 (B)	803.39
39	MC-COOH-4	AM-2.6	1.04 (I)	820.39
40	MC-COOH-4	AM-1.54	1.03 (I)	787.41
41	MC-COOH-4	AM-2.8	1.07 (I)	829.31
42	MC-COOH-4	AM-2.5	1.06 (I)	804.39
43	MC-COOH-4	AM-1.55	0.99 (I)	781.29
44	MC-COOH-4	AM-1.25	1.00 (B)	782.26
45	MC-COOH-4	AM-1.26	1.02 (B)	794.43
46	MC-COOH-5	AM-1.56	1.01 (I)	812.24
47	MC-COOH-5	AM-1.10	1.1 (I)	791.27
48	MC-COOH-5	AM-1.11	1.18 (I)	819.32
49	MC-COOH-5	AM-1.12	1.08 (I)	841.18
50	MC-COOH-5	AM-1.13	1.01 (I)	781.16
51	MC-COOH-5	AM-1.14	1.06 (I)	797.12
52	MC-COOH-5	AM-1.15	1.07 (I)	841.14
53	MC-COOH-5	AM-2.6	0.96 (I)	821.25
54	MC-COOH-5	AM-2.5	0.98 (I)	805.26
55	MC-COOH-5	AM-2.7	0.99 (I)	830.17
56	MC-COOH-5	AM-2.8	0.98 (I)	830.16
57	MC-COOH-5	AM-1.7	0.99 (I)	823.32
58	MC-COOH-5	AM-1.6	1.01 (I)	763.28
59	MC-COOH-5	AM-4.1	1.01 (I)	811.26
60	MC-COOH-5	AM-1.8	1.05 (I)	777.28
61	MC-COOH-5	AM-1.16	1.09 (I)	791.3
62	MC-COOH-5	AM-1.9	1.05 (I)	777.28
63	MC-COOH-5	AM-1.17	1.1 (I)	791.3
64	MC-COOH-5	AM-1.18	1.05 (I)	777.28
65	MC-COOH-5	AM-1.19	1.00 (I)	823.29
66	MC-COOH-5	AM-1.20	1.01 (I)	781.17
67	MC-COOH-5	AM-1.21	1.02 (I)	781.16

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
68	MC-COOH-5	AM-1.22	1.03 (I)	799.25
69	MC-COOH-5	AM-1.23	1.01 (I)	831.25
70	MC-COOH-4	AM-5.1	1.03 (I)	781.51
71	MC-COOH-1	AM-1.7	1.08 (I)	821.36
72	MC-COOH-1	AM-1.22	1.12 (I)	797.15
73	MC-COOH-1	AM-6.1	1.15 (I)	815.31
74	MC-COOH-1	AM-4.3	1.14 (I)	827.3
75	MC-COOH-1	AM-4.4	1.13 (I)	797.18
76	MC-COOH-1	AM-1.23	1.1 (I)	829.23
77	MC-COOH-1	AM-1.6	1.11 (I)	761.3
78	MC-COOH-1	AM-1.24	0.95 (I)	767.29
79	MC-COOH-1	AM-1.25	1.00 (I)	781.22
80	MC-COOH-1	AM-1.26	1.02 (I)	793.34
81	MC-COOH-1	AM-1.19	1.09 (I)	821.41
82	MC-COOH-1	AM-1.27	0.99 (I)	766.04
83	MC-COOH-1	AM-1.28	0.92 (I)	765.21
84	MC-COOH-1	AM-1.5	1.09 (I)	791.31
85	MC-COOH-1	AM-1.29	1.1 (I)	809.37
86	MC-COOH-1	AM-7.2	1.14 (B)	857.37
87	MC-COOH-1	AM-7.3	1.14 (B)	913.34
88	MC-COOH-1	AM-8.1	1.02 (B)	912.5
89	MC-COOH-1	AM-1.30	1.17 (I)	808.81
90*	MC-COOH-1	AM-1.30	1.12 (I)	808.75
91	MC-COOH-1	AM-2.17	1.09 (I)	809.26
92	MC-COOH-1	AM-2.18	1.15 (I)	793.22
93	MC-COOH-1	AM-9.1	1.03 (I)	858.29
94	MC-COOH-1	AM-2.20	1.13 (I)	797.06
95	MC-COOH-1	AM-2.19	1.14 (I)	805.28
96	MC-COOH-1	AM-1.9	1.15 (I)	775.22
97	MC-COOH-1	AM-2.16	1.12 (I)	797.15
98	MC-COOH-1	AM-1.31	0.99 (I)	765.98
99	MC-COOH-1	AM-4.2	1.22 (I)	875.17
100	MC-COOH-1	AM-2.15	1.08 (I)	809.23
101	MC-COOH-16	AM-3.1	0.99 (I)	785.90

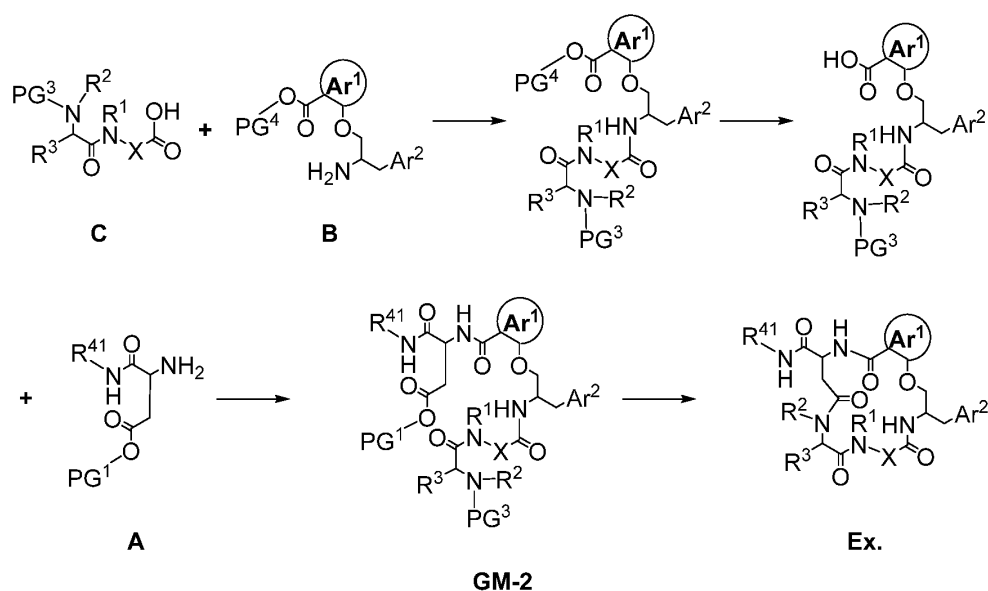
Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
102	MC-COOH-1	AM-2.14	1.17 (I)	811.24
103	MC-COOH-1	AM-1.32	0.98 (I)	768.14
104	MC-COOH-1	AM-2.13	1.16 (I)	793.25
105	MC-COOH-1	AM-1.33	1.04 (I)	792.25
106	MC-COOH-5	AM-1.33	0.97 (I)	794.61
107	MC-COOH-5	AM-1.30	1.06 (I)	810.62
108	MC-COOH-7	AM-1.6	1.08 (I)	747.6
109	MC-COOH-7	AM-1.7	1.05 (I)	807.65
110	MC-COOH-7	AM-1.22	1.09 (I)	783.58
111	MC-COOH-7	AM-1.5	1.05 (I)	777.59
112	MC-COOH-7	AM-1.9	1.12 (I)	761.6
113	MC-COOH-7	AM-4.4	1.10 (I)	783.56
114	MC-COOH-7	AM-1.25	0.96 (I)	767.59
115	MC-COOH-7	AM-1.26	0.98 (I)	779.59
116	MC-COOH-7	AM-1.29	1.07 (I)	795.63
117	MC-COOH-7	AM-1.31	0.96 (I)	752.55
118	MC-COOH-7	AM-1.33	1.01 (I)	778.63
119	MC-COOH-7	AM-1.30	1.10 (I)	794.66
120	MC-COOH-7	AM-1.34	1.10 (I)	783.58
121	MC-COOH-7	AM-1.35	0.99 (I)	779.62
122	MC-COOH-1	AM-2.12	1.05 (I)	839.3
123	MC-COOH-1	AM-2.11	1.03 (I)	839.29
124	MC-COOH-1	AM-2.10	0.97 (I)	791.27
125	MC-COOH-1	AM-2.9	1.10 (I)	842.32
126	MC-COOH-1	AM-1.34	1.16 (I)	797.48
127	MC-COOH-1	AM-1.35	1.06 (I)	793.51
128	MC-COOH-1	AM-1.36	1.10 (I)	807.56
129	MC-COOH-1	AM-1.37	1.00 (I)	779.55
130	MC-COOH-5	AM-7.1	1.01 (I)	861.95
131	MC-COOH-6	AM-1.4	1.09 (I)	795.52
132	MC-COOH-6	AM-1.22	1.11 (I)	801.5
133	MC-COOH-6	AM-10.1	1.03 (I)	843.54
134	MC-COOH-6	AM-10.2	1.02 (I)	843.54
135	MC-COOH-6	AM-2.7	1.09 (I)	832.56

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
136	MC-COOH-6	AM-2.8	1.08 (I)	832.54
137	MC-COOH-6	AM-2.12	1.05 (I)	843.55
138	MC-COOH-6	AM-2.11	1.03 (I)	843.56
139	MC-COOH-6	AM-2.10	0.96 (I)	795.57
140	MC-COOH-6	AM-1.35	1.02 (I)	797.37
141	MC-COOH-6	AM-1.31	0.98 (I)	770.52
142	MC-COOH-6	AM-1.33	1.03 (I)	796.55
143	MC-COOH-6	AM-1.28	0.91 (I)	769.53
144	MC-COOH-6	AM-1.26	1.00 (I)	797.41
145	MC-COOH-7	AM-1.38	1.10 (I)	783.54
146	MC-COOH-6	AM-1.39	0.95 (I)	771.46
147	MC-COOH-6	AM-1.40	1.00 (B)	770.08
148	MC-COOH-2	AM-2.4	1.00 (I)	786.58
149	MC-COOH-15	AM-2.6	1.22 (I)	854.25
150	MC-COOH-15	AM-1.57	1.27 (I)	862.14
151	MC-COOH-16	AM-1.19	0.99 (I)	774.16
152	MC-COOH-2	AM-1.73	0.96 (I)	772.18
153	MC-COOH-16	AM-1.5	1.15 (H)	744.7
154	MC-COOH-17	AM-1.1	1.03 (B)	856.32
155	MC-COOH-18	AM-1.1	1.25 (H)	872.7
156	MC-COOH-19	AM-1.1	1.21 (H)	860.9
157	MC-COOH-15	AM-1.59	1.33 (I)	832.92
158	MC-COOH-15	AM-1.74	1.19 (I)	827.34
159	MC-COOH-22	AM-1.1	1.05 (B)	858.41
160	MC-COOH-23	AM-1.1	1.07 (B)	858.42
161	MC-COOH-2	AM-2.21	1.23 (H)	800.8
162	MC-COOH-20	AM-1.1	1.32 (H)	848.8
163	MC-COOH-21	AM-1.1	1.33 (H)	848.8
164	MC-COOH-20	AM-1.4	1.33 (H)	834.8
165	MC-COOH-21	AM-1.4	1.36 (H)	834.8
166	MC-COOH-6	AM-1.80	1.26 (H)	851.7
167	MC-COOH-6	AM-1.78	1.12 (H)	843.7
168	MC-COOH-6	AM-1.76	1.21 (H)	790.7
169	MC-COOH-6	AM-1.77	1.34 (H)	833.7

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
170	MC-COOH-6	AM-1.79	1.20 (H)	850.7
171	MC-COOH-25	AM-1.83	1.27 (H)	813.7
172	MC-COOH-6	AM-15.1	1.16 (H)	795.6
173	MC-COOH-6	AM-1.81	1.17 (H)	833.5
174	MC-COOH-6	AM-14.1	1.13 (H)	827.7
175	MC-COOH-7	AM-1.82	1.26 (H)	813.7
176	MC-COOH-24	AM-2.10	1.08 (H)	771.8
177	MC-COOH-24	AM-1.84	1.24 (H)	800.6
178	MC-COOH-24	AM-1.85	1.22 (H)	801.6
179	MC-COOH-24	AM-15.1	1.14 (H)	771.7
180	MC-COOH-24	AM-1.4	1.20 (H)	771.7
181	MC-COOH-24	AM-2.12	1.17 (H)	819.7
182	MC-COOH-24	AM-1.23	1.23 (H)	809.7
183	MC-COOH-24	AM-1.6	1.22 (H)	741.7
184	MC-COOH-24	AM-1.12	1.30 (H)	819.6
185	MC-COOH-24	AM-1.5	1.20 (H)	771.7
186	MC-COOH-24	AM-1.9	1.26 (H)	755.7
187	MC-COOH-24	AM-2.23	1.11 (H)	772.6
188	MC-COOH-6	AM-16.1	1.07 (H)	785.6
189	MC-COOH-24	AM-17.1	1.23 (H)	765.6
190	MC-COOH-24	AM-1.49	1.19 (H)	788.7
191	MC-COOH-24	AM-5.3	1.16 (H)	782.7
192	MC-COOH-2	AM-1.8	1.20 (H)	744.7
193	MC-COOH-2	AM-1.5	1.13 (H)	760.7
194	MC-COOH-2	AM-1.58	1.19 (H)	774.7
195	MC-COOH-2	AM-1.4	1.14 (H)	760.7
196	MC-COOH-2	AM-1.13	1.16 (H)	748.6
197	MC-COOH-2	AM-1.60	0.94 (H)	773.8
198	MC-COOH-15	AM-1.1	1.42 (H)	840.7
199	MC-COOH-15	AM-1.4	1.44 (H)	826.8
200	MC-COOH-15	AM-3.2	1.45 (H)	829.7
201	MC-COOH-15	AM-1.58	1.48 (H)	840.7
202	MC-COOH-15	AM-1.8	1.50 (H)	810.7
203	MC-COOH-15	AM-1.60	1.24 (H)	839.7

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
204	MC-COOH-15	AM-1.13	1.46 (H)	814.7
205	MC-COOH-15	AM-1.7	1.44 (H)	856.8
206	MC-COOH-15	AM-1.61	1.44 (H)	802.7
207	MC-COOH-15	AM-1.62	1.18 (H)	827.7
208	MC-COOH-15	AM-1.63	1.40 (H)	786.6
209	MC-COOH-15	AM-1.66	1.35 (H)	814.8
210	MC-COOH-15	AM-1.65	1.33 (H)	764.6
211	MC-COOH-15	AM-1.6	1.45 (H)	796.7
212	MC-COOH-15	AM-1.64	1.42 (H)	804.7
213	MC-COOH-15	AM-1.67	1.46 (H)	854.8
214	MC-COOH-15	AM-1.40	1.34 (H)	801.8
215	MC-COOH-15	AM-1.10	1.53 (H)	824.8
216	MC-COOH-15	AM-1.68	1.38 (H)	792.8
217	MC-COOH-15	AM-1.69	1.43 (H)	862.8
218	MC-COOH-15	AM-1.71	1.24 (H)	841.8
219	MC-COOH-15	AM-1.5	1.44 (H)	826.8
220	MC-COOH-15	AM-1.70	1.42 (H)	827.7
221	MC-COOH-5	AM-1.84	1.18 (H)	822.6
765	MC-COOH-27	AM-20.1	1.07 (H)	754.4
766	MC-COOH-26	AM-20.1	1.19 (H)	794.5
767	MC-COOH-24	AM-20.1	1.14 (H)	780.4
830	MC-COOH-6	AM-1.94	0.99 (H)	813.4
831	MC-COOH-24	AM-1.89	1.17 (H)	809.4
832	MC-COOH-24	AM-1.91	1.08 (H)	782.4
833	MC-COOH-24	AM-16.2	1.05 (H)	773.4
834	MC-COOH-26	AM-19.3	1.11 (H)	784.4
835	MC-COOH-26	AM-16.2	1.09 (H)	787.4
836	MC-COOH-26	AM-19.2	1.08 (H)	771.4
837	MC-COOH-28	AM-19.1	1.15 (H)	947.4
838	MC-COOH-30	AM-16.2	1.15 (H)	847.4
839	MC-COOH-30	AM-13.1	1.13 (H)	836.4
840	MC-COOH-28	AM-1.91	1.16 (H)	957.4
841	MC-COOH-30	AM-1.35	1.17 (H)	847.4
842	MC-COOH-28	AM-1.88	1.11 (H)	932.4

Ex.	SM-A MC-COOH	SM-B AM	t _R [min] LC-MS Method	MS-data m/z [M+H] ⁺
843	MC-COOH-28	AM-1.95	1.14 (H)	947.4
844	MC-COOH-28	AM-1.93	0.98 (H)	958.4
845	MC-COOH-28	AM-1.65	1.09 (H)	884.4
846	MC-COOH-28	AM-1.92	1.21 (H)	938.4
847	MC-COOH-28	AM-1.62	0.96 (H)	947.4
848	MC-COOH-29	AM-1.88	1.18 (H)	881.4
849	MC-COOH-29	AM-1.35	1.20 (H)	897.4
850	MC-COOH-24	AM-1.45	1.06 (H)	745.4



Listed in Table MC-2 below are compounds of general formula (I) that are prepared from the corresponding building blocks A, B, and C in analogy to the corresponding General Method 2 (**GM-2**) (See Ex. 222).

5 **Table MC-2 (GM-2)**

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
223	A-1.14	B-1.16	C-1.1	1.13	758.6
224	A-1.1	B-1.16	C-1.1	1.15	744.7
225	A-1.12	B-1.16	C-1.1	1.21	758.7
226	A-1.6	B-1.16	C-1.1	1.11	772.5
227	A-1.25	B-1.16	C-1.1	1.27	742.6
228	A-1.14	B-2.13	C-1.1	1.14	744.5
229	A-1.14	B-1.3	C-1.1	1.17	728.6

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
230	A-1.1	B-1.3	C-1.1	1.20	714.7
231	A-1.1	B-2.13	C-1.1	1.17	730.7
232	A-1.1	B-1.22	C-1.1	1.16	730.7
233	A-1.1	B-1.4	C-1.1	1.19	714.7
234	A-1.14	B-1.9	C-1.1	1.16	732.5
235	A-1.14	B-1.2	C-1.1	1.15	728.5
236	A-1.14	B-1.12	C-1.1	1.22	764.7
237	A-1.1	B-1.8	C-1.1	1.22	732.7 [M-H] ⁻
238	A-1.1	B-1.12	C-1.1	1.25	750.6
239	A-1.25	B-1.5	C-1.1	1.24	728.6
240	A-1.1	B-2.4	C-1.1	1.13	706.6
241	A-1.1	B-2.3	C-1.1	1.13	721.6
242	A-1.14	B-5.1	C-10.19	1.42	843.8
243	A-1.1	B-5.1	C-10.19	1.45	829.7
244	A-1.23	B-5.1	C-10.19	1.44	832.9
245	A-1.2	B-2.13	C-1.1	1.21	756.7
246	A-1.14	B-1.2	C-10.19	1.46	824.7
247	A-1.1	B-1.2	C-10.19	1.49	810.7
248	A-1.14	B-2.13	C-10.19	1.44	840.8
249	A-1.1	B-2.13	C-10.19	1.47	826.8
250	A-1.14	B-1.12	C-10.19	1.51	860.7
251	A-1.1	B-1.12	C-10.19	1.53	846.7
252	A-1.25	B-3.1	C-1.1	1.04	699.5
253	A-1.14	B-1.8	C-10.19	1.49	844.6
254	A-1.1	B-1.8	C-10.19	1.51	828.8 [M-H] ⁻
255	A-1.14	B-1.1	C-10.19	1.42	870.7
256	A-1.1	B-1.1	C-10.19	1.44	856.9
257	A-1.14	B-1.5	C-10.23	1.24	784.6
258	A-1.1	B-1.5	C-10.23	1.26	770.7
259	A-1.4	B-1.5	C-2.1	1.22	820.5
260	A-1.5	B-1.5	C-2.1	1.22	812.7
261	A-1.2	B-3.1	C-10.19	1.31	823.7
262	A-1.3	B-3.1	C-10.19	1.26	809.7
263	A-1.14	B-1.5	C-10.24	1.28	798.8
264	A-1.1	B-1.5	C-10.24	1.29	784.8
265	A-1.14	B-3.2	C-10.19	1.36	811.7
266	A-1.1	B-3.2	C-10.19	1.39	797.7
267	A-1.14	B-1.13	C-10.19	1.49	860.7
268	A-1.1	B-1.13	C-10.19	1.51	846.7
269	A-1.14	B-1.13	C-1.1	1.20	764.7
270	A-1.14	B-1.10	C-10.19	1.16	825.8
271	A-1.1	B-1.10	C-10.19	1.18	811.7
272	A-1.14	B-1.1	C-10.24	1.27	828.7
273	A-1.1	B-1.1	C-10.24	1.30	814.6

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
274	A-1.14	B-1.5	C-10.26	1.38	838.7
275	A-1.2	B-1.1	C-10.19	1.47	882.9
276	A-1.3	B-1.1	C-10.19	1.44	868.8
277	A-1.1	B-2.1	C-1.1	1.14	718.6
278	A-1.14	B-2.1	C-1.1	1.11	732.6
279	A-1.14	B-2.2	C-1.1	1.15	746.7 [M-H] ⁻
280	A-1.1	B-1.17	C-2.2	1.30	784.6
281	A-1.14	B-1.18	C-10.19	1.37	841.7
282	A-1.1	B-1.18	C-10.19	1.39	827.8
283	A-1.6	B-1.17	C-2.2	1.27	812.8
284	A-1.14	B-1.13	C-10.2	1.37	874.8
285	A-1.14	B-1.13	C-10.4	1.42	888.8
286	A-1.14	B-1.13	C-10.1	1.39	874.8
287	A-1.14	B-1.13	C-10.3	1.44	888.8
288	A-1.14	B-1.13	C-10.14	1.38	888.8
289	A-1.14	B-1.13	C-10.15	1.43	902.8
290	A-1.14	B-1.13	C-10.16	1.54	886.8
291	A-1.14	B-1.13	C-10.17	1.58	900.9
292	A-1.14	B-1.13	C-10.18	1.50	872.7
293	A-1.1	B-1.13	C-10.2	1.40	860.7
294	A-1.1	B-1.13	C-10.4	1.45	874.7
295	A-1.1	B-1.13	C-10.1	1.42	860.7
296	A-1.1	B-1.13	C-10.3	1.47	874.7
297	A-1.1	B-1.13	C-4.10	1.35	848.7
298	A-1.1	B-1.13	C-10.14	1.41	874.8
299	A-1.1	B-1.13	C-10.15	1.46	888.9
300	A-1.1	B-1.13	C-10.16	1.57	872.8
301	A-1.1	B-1.13	C-10.17	1.60	886.9
302	A-1.1	B-1.13	C-10.18	1.53	858.7
303	A-1.1	B-1.13	C-10.19	1.51	846.8
304	A-1.14	B-1.5	C-4.10	1.24	842.7
305	A-1.14	B-1.5	C-10.20	1.26	828.7
306	A-1.14	B-1.5	C-10.21	1.24	828.6
307	A-1.14	B-1.5	C-10.1	1.32	854.8
308	A-1.14	B-1.5	C-10.2	1.30	854.8
309	A-1.14	B-1.5	C-10.4	1.35	868.7
310	A-1.1	B-1.5	C-4.10	1.27	828.7
311	A-1.1	B-1.5	C-10.20	1.28	814.7
312	A-1.1	B-1.5	C-10.21	1.26	814.7
313	A-1.1	B-1.5	C-10.1	1.35	840.7
314	A-1.1	B-1.5	C-10.4	1.38	854.7
315	A-1.1	B-1.14	C-10.19	1.43	847.8
316	A-1.23	B-1.14	C-10.19	1.43	850.8
317	A-1.1	B-4.1	C-1.1	1.23	784.6

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
318	A-1.14	B-1.14	C-1.1	1.10	765.5
319	A-1.1	B-1.14	C-1.1	1.12	751.6
320	A-1.23	B-1.14	C-1.1	1.12	754.6
321	A-1.14	B-4.2	C-1.1	1.09	758.6
322	A-1.14	B-4.3	C-1.1	1.09	760.5
323	A-1.1	B-4.2	C-1.1	1.12	744.6
324	A-1.1	B-4.3	C-1.1	1.11	746.6
325	A-1.15	B-1.13	C-2.1	1.25	822.7
326	A-1.14	B-1.13	C-2.1	1.23	806.7
327	A-1.16	B-1.13	C-2.1	1.21	803.7
328	A-1.15	B-2.7	C-2.2	1.04	824.8
329	A-1.14	B-2.7	C-2.2	1.01	808.6
330	A-1.14	B-1.13	C-4.4	1.26	874.7
331	A-1.14	B-1.13	C-4.5	1.38	888.8
332	A-1.14	B-1.13	C-4.6	1.27	848.8
333	A-1.14	B-1.13	C-4.7	1.27	862.7
334	A-1.14	B-1.13	C-4.8	1.29	932.8
335	A-1.14	B-1.13	C-4.2	1.35	850.7
336	A-1.14	B-1.13	C-4.11	1.29	862.7
337	A-1.14	B-1.13	C-10.5	1.33	860.6
338	A-1.14	B-1.13	C-10.6	1.35	860.7
339	A-1.14	B-1.13	C-4.12	1.38	842.8
340	A-1.14	B-1.13	C-10.7	1.29	846.8
341	A-1.14	B-1.13	C-10.26	1.45	858.8
342	A-1.1	B-2.6	C-2.8	1.19	781.6
343	A-1.1	B-2.6	C-2.2	1.22	781.7
344	A-1.8	B-1.14	C-10.19	1.32	822.7
345	A-1.14	B-4.2	C-10.19	1.41	854.7
346	A-1.1	B-4.2	C-10.19	1.43	840.7
347	A-1.23	B-4.2	C-10.19	1.43	843.7
348	A-1.1	B-2.7	C-3.7	0.96	835.8
349	A-1.14	B-1.20	C-1.1	1.12	783.5
350	A-1.1	B-1.20	C-1.1	1.14	769.6
351	A-1.1	B-2.15	C-2.2	1.22	795.6
352	A-1.1	B-2.5	C-3.3	0.78	838.8
353	A-1.1	B-2.7	C-3.3	0.68	837.7
354	A-1.1	B-1.13	C-6.3	0.97	849.7
355	A-1.1	B-1.13	C-3.5	0.97	845.7
356	A-1.1	B-1.13	C-3.7	1.246	831.8
357*	A-1.1	B-1.13	C-3.7	1.17	831.7
358	A-1.14	B-1.13	C-10.8	1.29	860.8
359	A-1.14	B-1.13	C-10.9	1.28	860.7
360	A-1.14	B-1.13	C-10.10	1.34	874.8
361	A-1.14	B-1.13	C-10.11	1.34	874.8

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
362	A-1.14	B-1.13	C-10.12	1.33	862.8
363	A-1.14	B-1.13	C-10.13	1.33	862.8
364	A-1.1	B-2.7	C-3.4	0.82	851.7
365	A-1.1	B-1.14	C-2.2	1.27	791.8
366	A-1.1	B-1.14	C-2.8	1.24	791.7
367	A-1.8	B-1.14	C-2.2	1.15	766.6
368	A-1.15	B-2.15	C-2.2	1.22	825.7
369	A-1.1	B-1.13	C-7.1	1.44	965.7
370	A-1.11	B-1.13	C-2.1	1.23	809.6
371	A-1.10	B-1.13	C-2.1	1.29	828.7
372	A-1.1	B-1.14	C-3.4	0.97	848.7
373*	A-1.1	B-1.14	C-3.4	0.95	848.7
374	A-1.1	B-1.14	C-3.3	0.84	834.6
375	A-1.8	B-1.14	C-3.3	0.74	809.7
376	A-1.1	B-1.13	C-1.3	1.34	788.6
377	A-1.15	B-2.9	C-2.2	0.94	838.8
378	A-1.9	B-1.13	C-2.1	1.16 Method I	842.52
379	A-1.14	B-2.5	C-10.19	1.38	865.8
380	A-1.1	B-2.5	C-10.19	1.41	851.7
381	A-1.23	B-2.5	C-10.19	1.41	854.7
382	A-1.14	B-1.20	C-10.19	1.42	879.8
383	A-1.1	B-1.20	C-10.19	1.44	865.7
384	A-1.23	B-1.20	C-10.19	1.44	868.8
385	A-1.1	B-1.13	C-1.2	1.30	776.6
386	A-1.1	B-1.13	C-2.7	1.31	762.6
387	A-1.7	B-1.13	C-2.1	1.26	829.8
388*	A-1.1	B-1.14	C-3.7	1.14	832.7
389	A-1.1	B-1.14	C-3.7	1.13	832.7
390*	A-1.1	B-1.14	C-3.5	0.93	846.8
391	A-1.1	B-1.14	C-3.5	0.89	846.7
392*	A-1.14	B-1.14	C-3.7	1.13	846.8
393	A-1.14	B-1.14	C-3.7	1.13	846.8
394*	A-1.14	B-1.14	C-3.5	0.91	860.8
395	A-1.14	B-1.14	C-3.5	0.88	860.8
396	A-1.1	B-1.13	C-6.4	1.34	834.8
397	A-1.12	B-1.13	C-2.1	1.31	806.8
398	A-1.10	B-1.14	C-3.7	1.20	868.8
399*	A-1.10	B-1.14	C-3.7	1.18	868.7
400	A-1.12	B-1.14	C-3.7	1.22	846.8
401*	A-1.12	B-1.14	C-3.7	1.20	846.8
402	A-1.8	B-1.14	C-3.7	1.01	805.8 [M-H] ⁻
403*	A-1.8	B-1.14	C-3.7	1.03	807.7
404	A-1.11	B-1.14	C-3.7	1.14	849.8
405*	A-1.11	B-1.14	C-3.7	1.16	849.8

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
406	A-1.1	B-2.8	C-2.2	1.27	795.8
407	A-1.1	B-2.8	C-2.1	1.13	797.6
408	A-1.14	B-4.4	C-1.1	1.20	794.6
409	A-1.1	B-4.4	C-1.1	1.22	780.6
410	A-1.8	B-2.5	C-10.19	1.230	826.8
411	A-1.8	B-1.20	C-10.19	1.34	840.8
412	A-1.1	B-1.14	C-2.1	1.16	793.6
413*	A-1.1	B-1.14	C-2.1	1.16	793.6
414	A-1.10	B-1.14	C-6.3	0.94	886.7
415	A-1.11	B-1.14	C-6.3	0.87	867.7
416	A-1.1	B-1.13	C-6.2	0.90	835.6
417	A-1.1	B-2.5	C-3.7	1.09	836.6
418	A-1.12	B-2.5	C-3.7	1.15	850.7
419	A-1.10	B-2.5	C-3.7	1.14	872.7
420	A-1.11	B-2.5	C-3.7	1.07	853.6
421	A-1.6	B-2.5	C-3.7	1.07	864.8
422	A-1.26	B-2.5	C-10.19	1.46	885.8
423	A-1.1	B-6.2	C-2.2	1.25	794.6
424	A-1.1	B-6.2	C-2.1	1.13	796.7
425	A-1.1	B-2.5	C-3.6	0.81	850.7
426	A-1.10	B-2.5	C-3.6	0.86	886.7
427	A-1.12	B-2.5	C-3.6	0.85	864.7
428	A-1.7	B-2.5	C-3.6	0.82	887.8
429	A-1.8	B-6.2	C-2.2	1.13	769.6
430	A-1.14	B-2.10	C-1.1	1.11	754.7
431	A-1.1	B-1.13	C-12.1	1.35	822.7
432	A-1.8	B-1.14	C-11.1	1.16	778.7
433	A-1.1	B-1.14	C-1.2	1.21	777.6
434	A-1.8	B-1.14	C-1.2	1.08	752.7
435	A-1.8	B-2.5	C-2.6	1.06	798.7
436	A-1.8	B-2.5	C-2.5	1.19	796.6
437*	A-1.8	B-2.5	C-2.5	1.16	796.8
438	A-1.1	B-1.18	C-1.2	1.13	757.6
439	A-1.1	B-1.20	C-1.2	1.23	795.7
440	A-1.8	B-1.20	C-1.2	1.09	770.6
441	A-1.1	B-4.7	C-1.1	1.01	751.7
442	A-1.1	B-2.10	C-1.2	1.19	766.6
443	A-1.8	B-1.20	C-2.2	1.17	784.7
444	A-1.8	B-4.5	C-2.2	0.83	730.6
445	A-1.8	B-1.14	C-10.20	1.13	810.6
446	A-1.8	B-1.14	C-10.12	1.13	824.7
447	A-1.1	B-4.6	C-1.2	1.18	768.6
448	A-1.8	B-2.10	C-1.2	1.06	741.6
449	A-1.1	B-2.10	C-1.1	1.12	740.5

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
450	A-1.1	B-2.11	C-1.1	1.17	742.6
451	A-1.1	B-1.13	C-6.1	0.89	849.7
452	A-1.8	B-1.13	C-6.1	0.78	824.7
453	A-1.17	B-1.14	C-1.2	1.21	814.8
454	A-1.7	B-1.14	C-1.2	1.21	814.6
455	A-1.8	B-4.6	C-2.2	1.13	757.6
456	A-1.1	B-4.6	C-2.2	1.25	782.6
457	A-1.1	B-1.13	C-13.1	1.33	820.7
458	A-1.8	B-1.14	C-7.1	1.25	941.6
459	A-1.1	B-1.14	C-3.1	0.82	806.8
460	A-1.1	B-4.7	C-1.2	1.09	777.7
461	A-1.17	B-1.14	C-2.2	1.27	828.7
462	A-1.17	B-1.14	C-2.8	1.24	828.7
463	A-1.7	B-1.14	C-2.2	1.28	828.8
464	A-1.7	B-1.14	C-2.8	1.24	828.6
465	A-1.1	B-7.1	C-1.1	0.82	751.6
466	A-1.17	B-1.18	C-2.2	1.21	808.7
467	A-1.17	B-1.18	C-2.8	1.17	808.6
468	A-1.7	B-1.18	C-2.2	1.21	808.7
469	A-1.1	B-2.10	C-2.2	1.25	780.6
470	A-1.8	B-2.10	C-2.2	1.12	755.6
471	A-1.1	B-4.8	C-1.2	0.89	777.7
472	A-1.7	B-4.7	C-2.2	1.16	828.8
473	A-1.7	B-4.7	C-2.8	1.13	828.6
474	A-1.8	B-4.7	C-2.2	1.02	766.7
475	A-1.8	B-1.13	C-9.1	1.15	907.7
476	A-1.24	B-1.14	C-1.2	1.14	778.7
477	A-1.8	B-1.18	C-2.2	1.09	746.7
478	A-1.20	B-1.18	C-2.2	1.24	777.7
479	A-1.8	B-1.13	C-9.2	1.19	937.7
480	A-1.8	B-1.19	C-2.2	1.19	784.7
481	A-1.7	B-1.19	C-2.2	1.32	846.7
482	A-1.20	B-2.5	C-2.2	1.26	801.6
483	A-1.19	B-1.18	C-2.2	1.12	773.6
484	A-1.20	B-2.10	C-2.2	1.28	786.7
485	A-1.20	B-2.7	C-2.2	1.06	800.6
486	A-1.19	B-4.7	C-2.2	1.07	793.8
487	A-1.8	B-1.23	C-2.2	1.12	766.7
488	A-1.1	B-2.12	C-1.2	1.15	757.6
489	A-1.19	B-1.19	C-2.1	1.12	813.7
490	A-1.20	B-6.2	C-2.2	1.28	800.6
491	A-1.20	B-4.6	C-2.2	1.28	788.6
492	A-1.7	B-1.13	C-2.4	1.32	857.8
493	A-1.7	B-1.14	C-2.4	1.23	858.7

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
494	A-1.1	B-7.1	C-1.2	0.91	777.7
495	A-1.8	B-1.14	C-5.1	1.24	828.6
496	A-1.21	B-1.14	C-1.2	1.18	825.8
497	A-1.18	B-1.20	C-2.8	1.20	810.6
498	A-1.19	B-1.20	C-2.2	1.20	811.6
499	A-1.24	B-1.20	C-2.2	1.22	810.6
500	A-1.24	B-1.20	C-2.8	1.18	810.6
501	A-1.22	B-1.20	C-2.2	1.22	811.7
502	A-1.27	B-1.14	C-1.2	1.15	825.7
503	A-1.1	B-1.14	C-5.2	1.21	779.7
504	A-1.18	B-4.7	C-2.2	1.11	792.8
505	A-1.22	B-4.7	C-2.2	1.07	793.6
506	A-1.8	B-1.14	C-14.1	1.20	780.8
507	A-1.1	B-4.9	C-1.1	1.14	769.5
508	A-1.8	B-1.13	C-5.3	1.22	765.7
509	A-1.1	B-1.14	C-8.1	1.36	868.7
510	A-1.8	B-1.14	C-8.1	1.26	843.8
511	A-1.22	B-1.18	C-2.2	1.14	773.7
512	A-1.18	B-1.18	C-2.2	1.16	772.7
513	A-1.1	B-4.10	C-1.1	1.07	731.6
514	A-1.24	B-4.7	C-2.2	1.09	792.7
515	A-1.22	B-4.11	C-2.2	1.21	773.7
516	A-1.19	B-4.11	C-2.2	1.19	773.7
517	A-1.24	B-2.12	C-2.2	1.16	772.7
518	A-1.18	B-2.12	C-2.2	1.18	772.6
519	A-1.24	B-1.19	C-1.2	1.18	796.6
520	A-1.19	B-1.19	C-2.8	1.18	811.7
521	A-1.22	B-1.19	C-2.8	1.20	811.7
522	A-1.7	B-1.20	C-2.2	1.29	846.7
523	A-1.24	B-1.18	C-2.2	1.15	772.7
524	A-1.24	B-1.19	C-8.1	1.34	887.7
525	A-1.22	B-1.19	C-8.1	1.33	888.7
526	A-1.18	B-4.11	C-2.2	1.22	772.7
527	A-1.8	B-1.26	C-2.2	1.23	800.6
528	A-1.1	B-1.26	C-2.2	1.36	823.9 [M-H] ⁻
529	A-1.22	B-2.12	C-2.2	1.16	773.7
530	A-1.1	B-2.16	C-1.1	1.20	751.6
531	A-1.1	B-5.3	C-1.1	1.19	754.7
532	A-1.24	B-5.3	C-1.1	1.11	755.6
533	A-1.28	B-4.12	C-2.2	1.01 Method I	776.7
534	A-1.8	B-1.27	C-2.2	1.14	784.6
535	A-1.1	B-1.27	C-2.2	1.07 Method B	809.26
536	A-1.1	B-2.5	C-8.1	1.32	872.7
537	A-1.1	B-1.19	C-2.3	1.15	795.6

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
538	A-1.1	B-1.18	C-8.1	1.30	848.8
539	A-1.19	B-1.19	C-18.1	1.34	903.8
540	A-1.19	B-1.19	C-18.1	1.30	903.8
541	A-1.19	B-4.9	C-2.2	1.21	811.6
542	A-1.8	B-1.18	C-8.1	1.20	823.7
543	A-1.24	B-4.7	C-1.2	1.01	778.6
544	A-1.19	B-4.7	C-1.2	0.99	779.7
545	A-1.24	B-4.9	C-1.2	1.16	796.6
546	A-1.19	B-4.9	C-1.2	1.14	797.6
547	A-1.8	B-1.14	C-18.3	1.19	768.6
548	A-1.8	B-1.14	C-18.4	1.25	782.6
549*	A-1.1	B-1.18	C-8.1	1.30	848.8
550*	A-1.8	B-1.18	C-8.1	1.19	823.8
551	A-1.1	B-5.3	C-1.2	1.25	780.8
552	A-1.24	B-5.3	C-1.2	1.19	781.7
553	A-1.19	B-5.3	C-1.2	1.17	782.7
554	A-1.22	B-5.3	C-1.2	1.17	782.6
555	A-1.1	B-2.16	C-1.2	1.28	777.6
556	A-1.24	B-2.16	C-1.2	1.21	778.7
557	A-1.19	B-1.18	C-18.1	1.20	865.8
558	A-1.19	B-1.18	C-18.1	1.24	865.7
559	A-1.31	B-1.14	C-2.2	1.29	820.6
560	A-1.31	B-1.19	C-2.2	1.33	838.6
561	A-1.19	B-5.3	C-1.1	1.09	756.6
562	A-1.22	B-5.3	C-1.1	1.10	756.6
563	A-1.19	B-1.27	C-2.2	1.17	811.6
564	A-1.8	B-1.14	C-2.14	1.26	846.6
565	A-1.18	B-4.12	C-2.2	1.21	786.6
566	A-1.8	B-1.14	C-21.1	1.09	784.6
567	A-1.19	B-4.12	C-2.2	1.17	787.6
568	A-1.31	B-4.12	C-2.2	1.28	814.7
569	A-1.1	B-1.18	C-2.10	1.24	819.6
570	A-1.8	B-1.18	C-3.4	0.80	803.7
571	A-1.19	B-1.18	C-20.1	1.26	905.8
572*	A-1.1	B-1.14	C-1.4	1.19	765.7
573	A-1.8	B-1.14	C-1.4	1.09	740.7
574	A-1.24	B-1.14	C-1.4	1.15	766.7
575	A-1.1	B-5.3	C-1.4	1.25	768.7
576	A-1.8	B-5.3	C-1.4	1.12	743.7
577*	A-1.19	B-1.18	C-20.1	1.22	905.7
578	A-1.8	B-1.14	C-18.2	1.27	860.7
579*	A-1.8	B-1.14	C-18.2	1.23	860.7
580	A-1.28	B-4.12	C-2.13	1.24	802.6
581	A-1.28	B-4.13	C-2.2	1.15	779.6

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
582	A-1.28	B-1.18	C-10.19	1.30	818.7
583	A-1.14	B-1.4	C-1.1	1.16	728.6
584	A-1.1	B-2.13	C-2.3	1.16	756.7
585	A-1.14	B-1.11	C-10.19	1.41	870.7
586	A-1.1	B-1.11	C-10.19	1.44	856.7
587	A-1.1	B-2.13	C-2.2	1.30	770.6
588	A-1.1	B-2.13	C-2.1	1.17	772.6
589	A-1.14	B-3.1	C-10.19	1.24	811.6
590	A-1.1	B-3.1	C-10.19	1.26	797.7
591	A-1.1	B-1.5	C-2.2	1.25	770.6
592	A-1.3	B-3.1	C-2.8	1.04	753.7
593	A-1.3	B-3.1	C-2.2	1.05	753.7
594	A-1.6	B-3.1	C-2.2	1.03	769.7
595	A-1.1	B-1.13	C-1.1	1.22	750.6
596	A-1.2	B-1.11	C-10.19	1.48	882.8
597	A-1.3	B-1.11	C-10.19	1.43	868.8
598	A-1.1	B-2.5	C-1.1	1.08	755.5
599	A-1.2	B-1.13	C-10.19	1.54	872.9
600	A-1.3	B-1.13	C-10.19	1.51	856.8 [M-H] ⁻
601	A-1.1	B-1.1	C-2.8	1.24	800.8
602	A-1.1	B-1.1	C-2.2	1.26	800.7
603	A-1.1	B-1.13	C-2.2	1.37	790.8
604	A-1.1	B-1.13	C-2.8	1.34	790.8
605	A-1.1	B-1.5	C-3.2	0.79	799.8
606	A-1.8	B-1.13	C-2.8	1.22	765.7
607	A-1.8	B-1.13	C-2.2	1.24	765.6
608	A-1.8	B-1.13	C-2.1	1.13	767.6
609	A-1.8	B-1.1	C-2.2	1.14	775.6
610	A-1.14	B-1.14	C-10.19	1.41	861.7
611	A-1.1	B-1.5	C-3.3	0.81	813.8
612	A-1.1	B-1.5	C-3.4	0.95	827.7
613	A-1.15	B-1.13	C-3.4	1.05	877.8
614	A-1.1	B-2.5	C-2.2	1.23	795.6
615	A-1.1	B-2.5	C-2.8	1.20	795.8
616	A-1.14	B-5.2	C-1.1	1.15	780.5
617	A-1.8	B-1.13	C-3.4	0.94	822.7
618	A-1.15	B-1.13	C-3.3	0.92	863.8
619	A-1.1	B-2.5	C-3.4	0.95	852.8
620	A-1.8	B-2.5	C-3.4	0.84	827.8
621*	A-1.8	B-2.5	C-3.4	0.83	827.8
622	A-1.8	B-1.14	C-3.4	0.86	823.7
623	A-1.8	B-1.13	C-3.3	0.82	808.7
624	A-1.1	B-6.1	C-2.1	1.12	797.6
625	A-1.10	B-2.5	C-2.1	1.15	833.7

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
626	A-1.14	B-1.13	C-10.25	1.39	868.8
627	A-1.6	B-1.20	C-2.1	1.15	839.7
628	A-1.1	B-2.5	C-1.2	1.17	781.7
629	A-1.8	B-6.1	C-2.2	1.14	770.7
630	A-1.8	B-6.1	C-2.5	1.21	796.6
631*	A-1.8	B-6.1	C-2.5	1.18	796.6
632	A-1.8	B-2.5	C-2.2	1.10	770.6
633	A-1.8	B-1.13	C-2.4	1.19	795.7
634	A-1.20	B-6.1	C-2.2	1.28	801.7
635	A-1.20	B-6.1	C-2.8	1.25	801.7
636	A-1.20	B-1.19	C-2.2	1.34	815.7
637	A-1.19	B-1.19	C-2.2	1.23	811.7
638	A-1.18	B-1.20	C-2.2	1.23	810.6
639	A-1.18	B-1.19	C-2.2	1.26	810.7
640	A-1.24	B-1.19	C-2.2	1.25	810.7
641	A-1.22	B-1.19	C-2.2	1.24	811.8
642	A-1.24	B-1.14	C-2.2	1.20	792.6
643	A-1.18	B-1.19	C-2.1	1.15	812.6
644	A-1.24	B-1.19	C-2.1	1.13	812.6
645	A-1.22	B-1.19	C-2.1	1.13	813.7
646	A-1.22	B-1.14	C-14.1	1.25	807.7
647	A-1.1	B-4.11	C-1.1	1.14	731.5
648	A-1.24	B-4.11	C-1.2	1.14	758.7
649	A-1.19	B-4.11	C-1.2	1.12	759.7
650	A-1.1	B-4.11	C-1.2	1.21	757.6
651	A-1.7	B-1.21	C-2.2	1.28	795.7
652	A-1.24	B-4.11	C-2.2	1.21	772.7
653	A-1.7	B-4.3	C-2.2	1.26	823.7
654	A-1.8	B-1.13	C-1.2	1.18	751.7
655	A-1.24	B-4.9	C-2.2	1.23	810.6
656	A-1.22	B-4.12	C-2.2	1.19	787.6
657	A-1.22	B-4.13	C-2.2	1.19	790.7
658	A-1.24	B-4.12	C-2.2	1.19	786.6
659	A-1.24	B-4.13	C-2.2	1.19	789.7
660	A-1.24	B-1.27	C-2.2	1.19	810.8
661	A-1.24	B-1.18	C-18.1	1.22	864.8
662	A-1.24	B-1.18	C-18.1	1.26	864.7
663	A-1.24	B-1.18	C-2.9	1.12	808.6
664	A-1.18	B-4.13	C-2.2	1.21	789.7
665	A-1.30	B-1.19	C-2.2	1.22	810.8
666	A-1.19	B-4.13	C-2.2	1.17	790.7
667	A-1.31	B-4.12	C-2.8	1.25	814.7
668	A-1.24	B-1.18	C-2.13	1.23	798.7
669	A-1.24	B-1.18	C-2.13	1.18	798.8

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
670 Epimer 1	A-1.24	B-1.18	C-19.1	1.23	848.8
671 Epimer 2	A-1.24	B-1.18	C-19.1	1.26	848.8
672 Epimer 3	A-1.24	B-1.18	C-19.1	1.28	848.7
673 Epimer 4	A-1.24	B-1.18	C-19.1	1.30	848.7
674 Epimer 1	A-1.24	B-1.14	C-19.1	1.27	868.7
675 Epimer 2	A-1.24	B-1.14	C-19.1	1.31	868.7
676 Epimer 3	A-1.24	B-1.14	C-19.1	1.33	868.7
677 Epimer 4	A-1.24	B-1.14	C-19.1	1.35	868.7
678	A-1.8	B-1.18	C-2.11	1.15	794.6
679	A-1.8	B-1.18	C-2.10	1.14	794.6
680	A-1.1	B-1.14	C-1.4	1.21	765.7
681	A-1.19	B-1.18	C-2.12	1.19	809.6
682	A-1.18	B-1.18	C-18.1	1.27	864.7
683	A-1.8	B-4.12	C-2.13	1.22	786.6
684	A-1.28	B-4.12	C-2.13	1.20	802.7
685	A-1.30	B-4.13	C-2.2	1.16	789.6
686	A-1.28	B-1.14	C-1.2	1.09	768.6
687	A-1.14	B-2.14	C-1.1	1.13	714.7
688	A-1.6	B-2.14	C-1.1	1.12	728.7
768	A-1.1	B-1.18	C-1.4	1.12	745.5
769	A-1.28	B-4.9	C-2.2	1.18	800.5
770	A-1.28	B-4.9	C-2.8	1.14	800.4
771	A-1.28	B-1.18	C-1.4	1.02	736.4
772	A-1.28	B-4.15	C-1.4	1.07	750.5
773	A-1.8	B-4.15	C-18.2	1.11	748.5
774	A-1.1	B-4.15	C-18.2	1.23	773.5
775	A-1.8	B-4.15	C-18.6	1.13	784.5
776	A-1.28	B-1.18	C-2.15	1.14	804.4
777	A-1.24	B-4.9	C-2.8	1.18	810.5
778	A-1.38	B-4.9	C-2.2	1.22	810.5
779	A-1.38	B-4.9	C-2.8	1.18	810.5
780	A-1.22	B-4.9	C-2.2	1.22	811.5
781	A-1.18	B-4.9	C-2.2	1.23	810.5
782	A-1.19	B-1.18	C-22.1	1.11	910.5
783	A-1.28	B-1.18	C-22.1	1.09	899.5
784	A-1.28	B-4.15	C-18.2	1.12	764.5

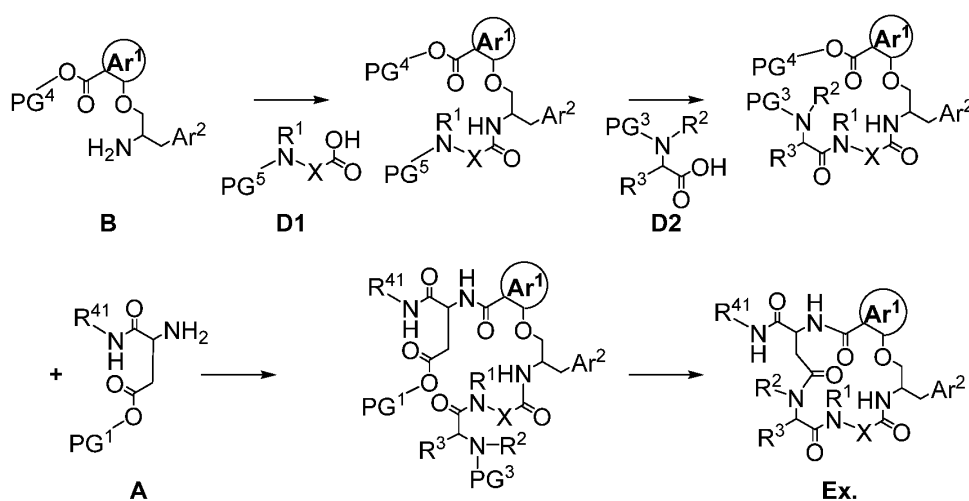
Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
785	A-1.28	B-4.15	C-18.6	1.14	800.5
786	A-1.28	B-4.9	C-1.4	1.11	774.4
787	A-1.38	B-4.9	C-1.4	1.15	784.5
788	A-1.1	B-2.17	C-1.4	0.88	754.5
789	A-1.28	B-2.17	C-1.4	0.80	745.5
790	A-1.24	B-2.17	C-1.4	0.83	755.5
791	A-1.28	B-4.15	C-2.15	1.19	818.4
792*	A-1.28	B-4.15	C-2.15	1.17	818.4
793	A-1.19	B-4.9	C-2.8	1.16	811.5
794	A-1.19	B-4.9	C-22.1	1.19	948.5
795	A-1.28	B-4.9	C-22.1	1.17	937.5
796	A-1.28	B-7.2	C-2.2	0.86	796.5
797	A-1.24	B-4.9	C-1.4	1.16	784.5
798	A-1.18	B-4.9	C-1.4	1.17	784.5
799	A-1.19	B-4.9	C-1.4	1.13	785.5
800	A-1.22	B-4.9	C-1.4	1.15	785.4
801	A-1.19	B-4.9	C-18.6	1.20	835.5
802*	A-1.19	B-4.9	C-18.6	1.17	835.5
803	A-1.19	B-4.9	C-18.2	1.18	799.4
804	A-1.37	B-4.9	C-22.1	1.18	948.5
805	A-1.30	B-4.9	C-2.2	1.19	810.3
806	A-1.37	B-4.15	C-2.15	1.21	829.5
807	A-1.8	B-4.9	C-22.1	1.16	921.5
808	A-1.22	B-4.9	C-22.1	1.20	948.5
809	A-1.28	B-1.19	C-22.2	1.28	910.4
810*	A-1.28	B-1.19	C-22.2	1.25	910.4
811	A-1.19	B-1.19	C-22.2	1.31	921.5
812*	A-1.19	B-1.19	C-22.2	1.28	921.5
813	A-1.19	B-1.19	C-22.1	1.20	948.5
814*	A-1.19	B-1.19	C-22.1	1.18	948.5
815	A-1.28	B-1.19	C-22.1	1.18	937.5
816*	A-1.28	B-1.19	C-22.1	1.16	937.5
817	A-1.37	B-4.9	C-1.2	1.12	797.5
818	A-1.28	B-4.9	C-1.2	1.11	786.5
819	A-1.28	B-4.9	C-18.6	1.17	824.4
820	A-1.19	B-4.15	C-22.2	1.26	897.5
821	A-1.36	B-4.9	C-2.2	1.15	801.5
822	A-1.28	B-4.14	C-2.2	1.11	796.5
823	A-1.37	B-7.2	C-2.2	0.87	807.5
824	A-1.8	B-7.2	C-1.4	0.80	754.5
825	A-1.28	B-7.2	C-1.4	0.81	770.5
826	A-1.22	B-7.2	C-1.4	0.83	781.5
827	A-1.28	B-1.19	C-23.1	1.13	879.5
828	A-1.35	B-4.15	C-18.4	1.26	787.5

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
829	A-1.37	B-4.9	C-2.2	1.19	811.5
851	A-1.19	B-1.19	C-20.5	1.09	881.4
852	A-1.8	B-1.23	C-8.2	1.11	862.4
853	A-1.1	B-1.23	C-8.2	1.21	887.4
854	A-1.28	B-1.18	C-18.1	1.14	854.4
855	A-1.8	B-1.18	C-27.2	1.13	826.4
856	A-1.28	B-1.18	C-27.2	1.14	842.4
857	A-1.19	B-1.18	C-2.16	1.13	817.4
858	A-1.8	B-1.18	C-27.1	1.19	832.5
859	A-1.19	B-1.18	C-24.1	1.17	891.4
860	A-1.1	B-4.16	C-1.4	1.12	760.4
861	A-1.19	B-1.18	C-25.1	1.02	844.4
862	A-1.24	B-4.16	C-1.4	1.07	761.4
863	A-1.19	B-1.18	C-2.17	1.08	787.4
864	A-1.19	B-1.18	C-20.2	1.07	869.4
865	A-1.1	B-4.15	C-29.1	1.30	801.5
866	A-1.8	B-4.15	C-29.1	1.20	776.4
867	A-1.19	B-1.18	C-22.4	1.17	949.5
868	A-1.28	B-1.18	C-22.4	1.15	938.4
869	A-1.8	B-4.17	C-2.2	1.08	776.4
870	A-1.24	B-4.17	C-2.2	1.13	802.4
871	A-1.38	B-1.18	C-22.4	1.19	948.5
872	A-1.36	B-1.14	C-1.2	1.00	769.4
873	A-1.1	B-4.15	C-18.10	1.31	815.5
874	A-1.8	B-4.15	C-29.2	1.20	824.4
875	A-1.1	B-4.15	C-29.2	1.29	849.5
876	A-1.8	B-4.15	C-18.10	1.22	790.4
877	A-1.28	B-4.15	C-18.9	1.07	808.4
878	A-1.28	B-4.15	C-18.10	1.23	806.4
879	A-1.19	B-4.9	C-25.1	1.10	882.4
880	A-1.28	B-4.9	C-25.1	1.08	871.4
881	A-1.19	B-1.18	C-20.4	1.16	885.5
882	A-1.19	B-1.18	C-26.1	1.06	890.4
883	A-1.19	B-1.18	C-20.3	1.18	897.5
884	A-1.28	B-1.18	C-20.3	1.16	886.4
885	A-1.19	B-1.19	C-26.2	1.11	947.4
886	A-1.19	B-1.19	C-25.2	1.23	908.4
887	A-1.19	B-1.19	C-22.5	1.14	962.4
888	A-1.37	B-4.14	C-2.2	1.07	807.4
889	A-1.19	B-7.2	C-22.2	0.92	917.4
890	A-1.37	B-7.2	C-22.2	0.92	917.4
891	A-1.40	B-4.9	C-22.1	1.06	964.39
892	A-1.39	B-4.9	C-22.1	1.07	964.4
893	A-1.37	B-4.9	C-18.6	1.12	835.4

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
894	A-1.8	B-4.9	C-18.9	1.09	816.4
895	A-1.28	B-4.9	C-18.9	1.10	832.4
896	A-1.37	B-4.9	C-18.9	1.12	843.4
897	A-1.28	B-4.15	C-22.2	1.17	886.4
898	A-1.28	B-7.2	C-22.2	0.91	906.4
899	A-1.28	B-4.18	C-2.2	1.08	800.4
900	A-1.19	B-7.2	C-1.2	0.78	793.4
901	A-1.28	B-7.2	C-1.2	0.76	782.4
902	A-1.37	B-4.15	C-22.2	1.18	897.4
903	A-1.41	B-4.15	C-22.2	1.21	906.4
904	A-1.41	B-7.2	C-1.2	0.80	802.4
905	A-1.19	B-7.2	C-22.1	0.84	944.4
906	A-1.28	B-7.2	C-22.1	0.83	933.4
907	A-1.37	B-7.2	C-22.1	0.84	944.4
908	A-1.44	B-4.9	C-22.2	1.08	931.4
909	A-1.28	B-4.14	C-22.2	1.16	906.4
910	A-1.24	B-4.15	C-18.9	1.10	818.4
911	A-1.36	B-4.9	C-1.2	1.02	787.4
912	A-1.28	B-4.7	C-2.2	0.97	782.4
913	A-1.28	B-7.2	C-18.9	0.83	828.4
914	A-1.36	B-7.2	C-18.9	0.80	829.4
915	A-1.37	B-7.2	C-18.9	0.83	839.5
916	A-1.36	B-4.9	C-22.1	1.08	938.4
917	A-1.36	B-7.2	C-22.1	0.82	934.4
918	A-1.36	B-7.2	C-22.2	0.89	907.4
919	A-1.36	B-4.15	C-22.2	1.15	887.4
920	A-1.36	B-4.14	C-2.2	1.02	797.4
921	A-1.37	B-7.2	C-22.3	0.86	899.4
922	A-1.36	B-4.9	C-5.4	1.10	837.4
923	A-1.37	B-4.14	C-22.2	1.17	917.4
924	A-1.37	B-4.9	C-22.2	1.21	921.4
925	A-1.42	B-4.9	C-22.2	1.28	911.3
926	A-1.28	B-4.9	C-2.4	1.06	830.4
927	A-1.36	B-4.14	C-22.2	1.14	907.4
928*	A-1.37	B-4.14	C-2.2	1.06	807.4
929	A-1.36	B-4.9	C-18.9	1.08	833.4
930	A-1.36	B-1.19	C-2.2	1.09	801.4
931	A-1.28	B-7.2	C-18.6	0.82	820.4
932	A-1.36	B-7.2	C-18.6	0.80	821.4
933	A-1.37	B-7.2	C-18.6	0.84	831.4
934	A-1.36	B-4.9	C-22.2	1.18	911.3
935	A-1.19	B-4.14	C-22.2	1.18	917.4
936	A-1.22	B-4.14	C-22.2	1.19	917.4
937	A-1.41	B-4.9	C-22.2	1.24	930.4

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
938	A-1.36	B-7.2	C-2.15	0.84	839.4
939*	A-1.36	B-7.2	C-2.15	0.82	839.4
940*	A-1.36	B-4.9	C-2.15	1.11	843.3
941	A-1.36	B-4.9	C-2.15	1.13	843.3
942	A-1.36	B-4.15	C-2.15	1.10	819.4
943	A-1.39	B-4.15	C-22.2	1.16	913.4
944	A-1.43	B-4.9	C-22.2	1.23	893.3
945	A-1.46	B-4.15	C-22.2	1.21	904.4
946	A-1.8	B-4.9	C-18.6	1.10	808.4
947	A-1.36	B-4.9	C-18.6	1.08	825.4
948	A-1.28	B-1.18	C-22.2	1.13	872.4
949	A-1.36	B-1.18	C-22.2	1.11	873.4
950	A-1.19	B-7.2	C-2.15	0.87	849.4
951	A-1.22	B-7.2	C-2.15	0.88	849.4
952	A-1.22	B-7.2	C-5.4	0.85	843.4
953	A-1.28	B-7.2	C-5.4	0.83	832.4
954	A-1.36	B-7.2	C-5.4	0.81	833.4
955	A-1.37	B-7.2	C-5.4	0.84	843.4
956	A-1.24	B-7.2	C-2.15	0.89	848.4
957	A-1.28	B-7.2	C-2.15	0.86	838.4
958	A-1.18	B-7.2	C-2.15	0.90	848.4
959	A-1.37	B-7.2	C-2.15	0.87	849.4
960	A-1.46	B-7.2	C-2.15	0.90	856.4
961	A-1.45	B-4.15	C-22.2	1.12	913.4
962	A-1.45	B-4.9	C-22.2	1.14	937.4
963	A-1.46	B-4.9	C-1.2	1.10	804.4
964	A-1.22	B-4.9	C-22.2	1.23	921.4
965	A-1.8	B-4.9	C-22.2	1.19	894.4
966	A-1.39	B-4.9	C-22.2	1.17	937.4
967	A-1.46	B-4.9	C-18.6	1.15	842.3
968	A-1.46	B-4.15	C-18.6	1.12	818.4
969	A-1.46	B-4.9	C-5.4	1.17	854.3
970	A-1.46	B-7.2	C-18.6	0.86	838.4
971	A-1.36	B-4.9	C-25.3	1.18	899.4
972	A-1.28	B-4.9	C-25.3	1.20	898.4
973	A-1.46	B-4.9	C-2.2	1.16	818.4
974	A-1.28	B-2.5	C-2.15	1.09	828.4
975	A-1.36	B-4.14	C-2.15	1.08	839.4

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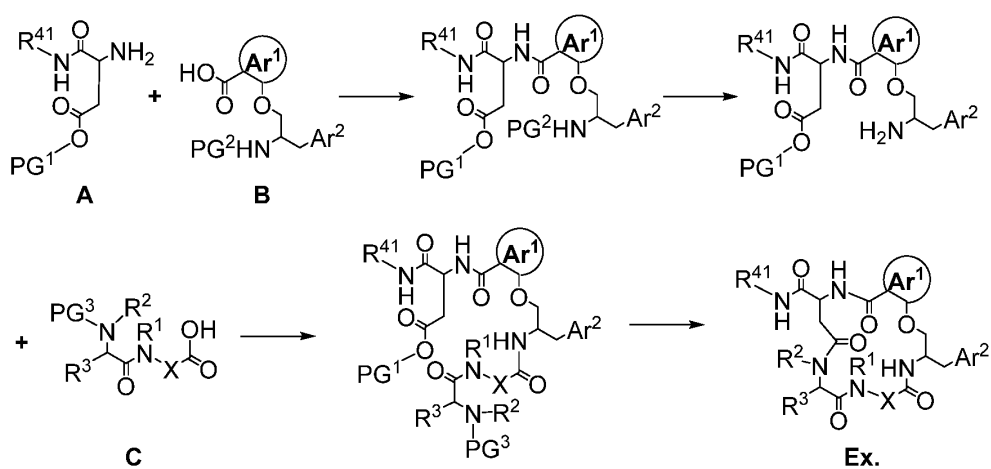


Listed in Table MC-3 below are compounds of general formula (I) that are prepared from the corresponding building blocks A, B, D1, and D2 in analogy to the corresponding General Method 3 (**GM-3**) (see Ex. 689).

Table MC-3 (GM-3)

Ex.	A	B	D1	D2	t_R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
690	A-1.8	B-1.19	D1-3.0	Boc-N-methyl-L-leucine	1.18	784.6
691	A-1.19	B-1.19	D1-3.0	Boc-N-methyl-L-leucine	1.22	811.7
692	A-1.22	B-1.19	D1-3.0	Boc-N-methyl-L-leucine	1.23	811.6
693	A-1.19	B-1.19	D1-4.1	Boc-N-methyl-L-leucine	1.41	853.8
694	A-1.19	B-1.19	D1-4.1	Boc-N-methyl-L-leucine	1.36	853.8
695*	A-1.8	B-1.14	D1-4.2	Boc-N-methyl-L-leucine	1.28	866.8
696	A-1.22	B-1.19	D1-4.5	Boc-N-methyl-L-leucine	1.45	867.8
697	A-1.24	B-1.19	D1-4.5	Boc-N-methyl-L-leucine	1.45	866.8
698	A-1.8	B-1.14	D1-4.2	Boc-N-methyl-L-leucine	1.32	866.7
699	A-1.8	B-1.14	D1-4.6	Boc-N-methyl-L-leucine	1.15	790.7

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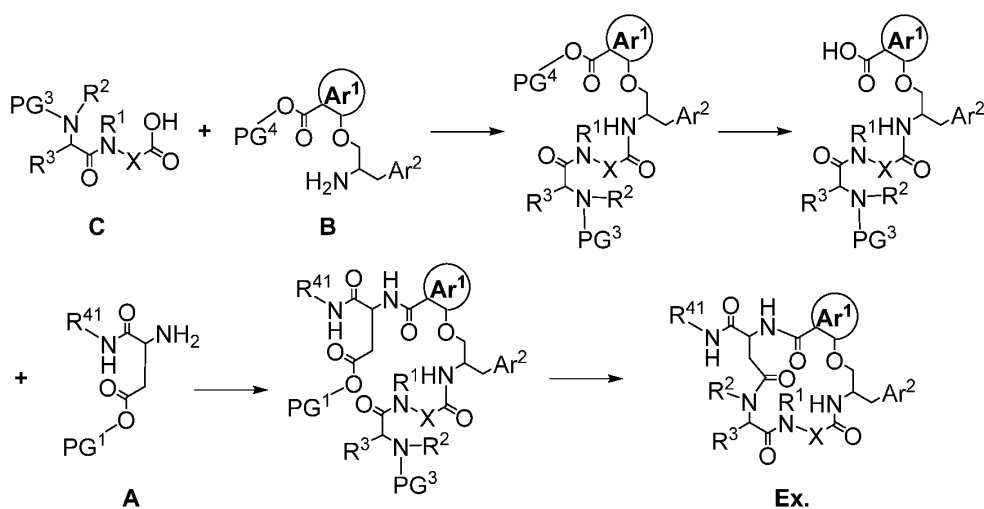
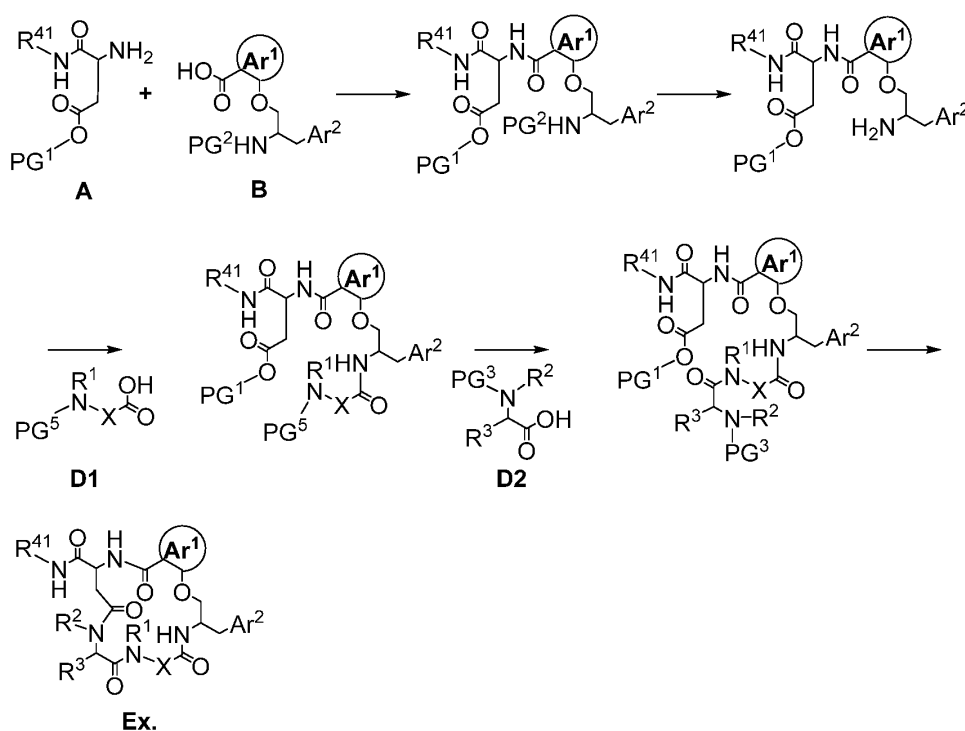
**GM-4**

Listed in Table MC-4 below are compounds of general formula (I) that are prepared from the corresponding building blocks A, B, and C in analogy to the corresponding General Method 4 (**GM-4**) (see Ex. 700 or Ex. 976 depending on the Protecting Group strategy).

5 **Table MC-4 (GM-4)**

Ex.	A	B	C	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
701	A-2.3	B-1.24	C-16.1	1.26	847.8
702	A-2.4	B-Acid-6	C-16.8	1.19	844.8
703	A-2.4	B-1.25	C-16.6	1.22	880.7
704	A-2.4	B-Acid-6	C-16.2	1.21	858.6
705	A-2.4	B-Acid-6	C-16.3	1.21	858.8
706	A-2.4	B-Acid-6	C-16.9	1.23	838.6
707	A-2.4	B-Acid-6	C-16.9	1.26	838.8
708	A-2.4	B-Acid-6	C-17.4	1.17	780.8
709	A-2.4	B-Acid-6	C-17.2	1.38	822.7
710	A-2.4	B-Acid-6	C-17.3	1.27	794.6
711	A-2.4	B-Acid-6	C-17.5	1.16	802.6
712	A-2.2	B-Acid-5	C-16.3	1.38	896.8
976	A-1.22	B-Acid-8	C-18.9	1.14	843.4
977	A-1.28	B-Acid-9	C-28.1	1.07	872.4
978	A-1.28	B-Acid-9	C-28.2	1.00	887.4
979	A-1.28	B-Acid-9	C-18.7	1.12	790.4
980	A-1.28	B-Acid-9	C-18.8	1.20	804.4

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Listed in Table MC-5 below are compounds of general formula (I) that are prepared from the corresponding building blocks in analogy to the corresponding General Methods, **GM-5** (see Ex. 713), **GM-6** (see Ex. 722), **GM-7** (see Ex. 724), **GM-8** (see Ex. 725) or **GM-9** (see Ex. 761).

Table MC-5 (GM-5 to GM-9)

Ex.	GM	A	B	C	D1	D2	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
714	GM-5	A-2.4	B-Acid-5		D1-1.1	D2-3.1	1.34	845.8
715	GM-5	A-2.3	B-Acid-5		D1-1.1	D2-3.1	1.43	870.8
716	GM-5	A-2.4	B-Acid-5		D1-1.1	D2-3.1	1.32	845.7
717	GM-5	A-2.3	B-Acid-5		D1-1.2	D2-3.1	1.44	836.8
718	Isolated as sideproduct from Ex. 717						1.20	780.7
719	GM-5	A-2.4	B-Acid-5		D1-1.2	D2-3.1	1.33	811.7
720	Isolated as sideproduct from Ex. 719						1.06	755.6
721	GM-6	A-1.8	B-1.19	C-17.3			1.31	812.6
723*	GM-6	A-1.8	B-1.19	C-17.1			1.27	834.7
726	GM-8	A-1.1	B-1.13	C-7.1			0.87	791.8
727	GM-8	A-1.8	B-1.14	C-7.1			0.70	767.6
728	Isolated as sideproduct from Ex. 422						1.32	865.7
762	GM-9		B-2.5	C-1.2			1.14	784.6
763	GM-9		B-1.14	C-1.2			1.22	829.8
764	GM-9		B-1.14	C-1.2			1.17	793.7

Post Modifications (PM)

PM-1: Sulfonamide formation

5 **Example 729: (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(phenylsulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide**

Benzenesulfonyl chloride (0.04 mL, 0.15mmol) is added to a RT soln. of **Ex. 726** (40 mg, 0.0506 mmol) and TEA (0.0213 mL, 0.152 mmol) in DCM (0.5 mL) and the mix. is stirred at RT overnight. The mix. is concentrated and the residue is taken up in MeCN/DMF and directly purified by prep. HPLC (basic) to yield the title compound (18 mg, 38%)
10 as a white solid. LC-MS B: t_R = 1.14 min; [M+H]⁺ = 931.45.

PM-2: Amide coupling

Example 750: (4aR,7R,18S,22S)-3-Acetyl-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
15 (H)ATU (22.2 mg, 0.0582 mmol) is added to a RT soln. of **Ex. 726** (40 mg, 0.0506 mmol), DIPEA (20 µL, 0.126 mmol), and acetic acid (1.15 eq) in DMF (0.5 mL). The RM is stirred at RT for 1 h. The RM is directly purified by prep. HPLC (basic) to yield the title compound (28 mg, 66%) as a white solid. LC-MS B: t_R = 1.03 min; [M+H]⁺ = 833.41.

PM-3A: Carbamate formation

Example 754: Methyl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate

- 5 Methyl chloroformate (ca 6 μ L mL, 0.0759 mmol) is added to a RT soln. of **Ex. 726** (30 mg, 0.0379 mmol) and TEA (16 μ L, 0.114 mmol) in DCM (0.5 mL), and the RM is stirred at RT for 1.5 h. The RM is diluted with DMF and directly purified by prep. HPLC (basic) to yield the title compound (22 mg, 69%) as a white solid. LC-MS B: t_R = 1.08 min; $[M+H]^+$ = 849.44.

PM-3B: Carbamate formation

- 10 **Example 756: Tetrahydro-2H-pyran-4-yl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate**
Tetrahydro-2H-pyran-4-ol (6 μ L, 0.0607 mmol) is added to a RT suspension of *N,N'*-disuccinimidyl carbonate (24.5 mg, 0.091 mmol) and TEA (26 μ L, 0.182 mmol) in MeCN (0.4 mL). The RM is stirred at RT overnight, then to the RM
15 is added a soln. of **Ex. 726** (40 mg, 0.0506 mmol) in MeCN (0.4 mL) and the RM is stirred at RT for 3 h. The mix. is diluted with MeCN and directly purified by prep. HPLC (basic) to yield the title compound (28 mg, 61%) as a white solid. LC-MS B: t_R = 1.10 min; $[M+H]^+$ = 919.53.

PM-4: Boc-protected Sulfonimidamide

- Example 757: tert-Butyl (((4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-yl)(oxo)(phenyl)-l6-sulfaneylidene)carbamate**
20 **Step 1:** NaOCl 10% (250 mL, 413 mmol) is added dropwise at a 0°C soln. of *t*-butanol (31 mL, 327 mmol) and AcOH (20 mL, 350 mmol) (slightly exothermic). The resulting emulsion is stirred at 0°C for 10 min then transferred to a separating funnel. The aq. layer is discarded and the remaining yellow liquid is washed with water (2x), then dried
25 (CaCl₂), filtered to yield *tert*-butyl hypochlorite (8.5 g, 21%) as a yellow non-viscous oil.
Step 2: Lithium bis(trimethylsilyl)amide soln. (1.0 M in THF, 1.35 mL, 1.35 mmol) is added dropwise to a 0°C soln. of benzenesulfonamide (100 mg, 0.673 mmol) in THF (1.5 mL). The brown turbid mix. is stirred at 0°C for 1 h, then a soln. of di-*tert*-butyl dicarbonate (0.156 mL, 0.673 mmol) in THF (0.5 mL) is added dropwise. The ice bath is removed, and the soln. stirred at RT for 15 min. To the RM is added water (10 mL) and DCM (100 mL). The layers are separated
30 and the aq. layer is extracted with DCM (2x 75 mL). The combined org. layers are washed with brine (50 mL), dried (MgSO₄), filtered, and concentrated. Purification by FC (eluting with 15% to 55% EtOAc in hept, R_f = 0.24 in EtOAc/hept 3:7) yields *tert*-butyl (phenylsulfenyl)carbamate (140 mg, 86%) as a colourless oil. LC-MS B: t_R = 0.78 min; $[M+H]^+$ = 241.97.

Step 3: Freshly prepared *tert*-butyl hypochlorite (41.2 mg, 0.379 mmol) is added to a 0°C soln. of *tert*-butyl (phenylsulfinyl)carbamate (54.9 mg, 0.228 mmol) in DCM (3 mL). The resulting mix. is stirred at 0°C for 30 min, then a RT soln. of **Ex. 726** (150 mg, 0.19 mmol) and DIPEA (0.0974 mL, 0.569 mmol) in DCM (5 mL) is added dropwise at 0°C. The ice bath is removed and the RM is stirred at RT for 30 min. To the reaction is added water (10 mL) and DCM (50 mL) and the layers are separated. The aq. layer is extracted with DCM (2x 35 mL) and the combined org. layers are washed with brine (10 mL), dried (MgSO₄), filtered, and concentrated. Purification by prep. HPLC (basic) yields **Ex. 757** (70 mg, 36%) as a white solid. LC-MS B: *t_R* = 1.19 min; [M+H]⁺ = 1030.28.

PM-5: Sulfonimidamide

Example 758: (4aR,7R,18S,22S)-7-Benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(phenylsulfonimidoyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

Iodotrimethylsilane (9 µL, 0.058 mmol) is added to a RT soln. of **Ex. 757** (30 mg, 0.029 mmol) in MeCN (0.5 mL) and the RM is stirred at RT for 5 min. The RM is directly purified by prep. HPLC (basic) to yield the title compound (44 mg, 81%) as a white solid. LC-MS B: *t_R* = 1.08/1.09 min; [M+H]⁺ = 930.64.

PM-6: Nitrile formation

Example 759: (4aR,7R,18S,22S)-7-Benzyl-N-(3-cyanophenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

A mix. of **Ex. 378** (20 mg, 0.02 mmol) and CuCN (9 mg, 0.1 mmol) in pyridine (0.5 mL) is heated at 140°C for 72 h. The RM is directly purified by prep. HPLC (basic) to give the title compound as a white solid. LC-MS B: *t_R* = 1.05 min; [M+H]⁺ = 787.28.

PM-7: N-Oxide formation

Example 760: (9S,13S,19aR,22R)-22-Benzyl-13-isobutyl-9-((3-methoxyphenethyl)carbamoyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline 2-oxide

mCPBA (11 mg, 0.05 mmol) is added to a 0°C soln. of **Ex. 365** (30 mg, 0.04 mmol) in DCM (0.5 mL) and the RM is warmed to RT and stirred for 4 h. The RM is diluted with DCM and quenched with a sat. aq. Na₂S₂O₃ soln. The layers are separated and the aq. phase is re-extracted with DCM (2x). The combined org. extracts are washed with brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The crude product is purified by prep. HPLC (acidic) to give the title compound as a white solid. LC-MS B: *t_R* = 1.03 min; [M+H]⁺ = 807.36.

Listed in Table MC-6 below are compounds of formula (I) that are prepared using one of the above described post modification methods (PM) using the corresponding starting materials. Conditions may vary slightly.

Table MC-6:

Ex.	PM	SM-A (Ex.)	SM-B	t _R [min] LC-MS Method H	MS-data m/z [M+H] ⁺
730	PM-1	Ex. 726	SCI-20	0.90	982.8
731	PM-1	Ex. 726	SCI-13	1.24	869.7
732	PM-1	Ex. 726	SCI-6	1.45	1015.7
733	PM-1	Ex. 726	SCI-14	1.27	913.7
734	PM-1	Ex. 726	SCI-17	1.28	939.8
735	PM-1	Ex. 726	SCI-16	0.89	926.8
736	PM-1	Ex. 726	SCI-11	1.37	945.8
737	PM-1	Ex. 726	SCI-10	1.24	988.8
738	PM-1	Ex. 726	SCI-12	1.36	994.8 [M-H] ⁻
739	PM-1	Ex. 726	SCI-5	1.37	961.8
740	PM-1	Ex. 726	SCI-7	1.37	979.8
741	PM-1	Ex. 726	SCI-9	1.37	1002.8
742	PM-1	Ex. 726	SCI-2	1.27	930.8 [M-H] ⁻
743	PM-1	Ex. 726	SCI-15	1.30	927.8
744	PM-1	Ex. 726	SCI-8	1.31	962.7
745	PM-1	Ex. 726	SCI-19	0.98	968.8
746	PM-1	Ex. 726	SCI-18	1.28	953.8
747	PM-1	Ex. 726	SCI-3	1.28	932.7
748	PM-1	Ex. 727	SCI-9	1.19	978.8
749	PM-1	Ex. 727	SCI-6	1.28	991.7
751	PM-2	Ex. 726	isovaleric acid	1.32	875.8
752	PM-2	Ex. 726	3-methoxypropanoic acid	1.21	877.8
753	PM-2	Ex. 726	pyrazinecarboxylic acid	1.20	897.8
755	PM-3A	Ex. 726	ethyl chloroformate	1.30	863.8
981	PM-7	Ex. 809		1.15	926.3
982	PM-7	Ex. 909		1.11	922.4
983	PM-7	Ex. 934		1.10	927.3

Listed in the Table of Examples below are example compounds of formula (I) prepared according to the above described methods. The configuration at stereocentres that are not mentioned in the compound name are unknown however only one epimer is present.

Table of Examples

Ex.	Compound of Formula (I)
1	(7R,13S,17RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-11-(3,3-dimethylbutyl)-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide

2	(7R,13S,17S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-11-(2-cyclohexylethyl)-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
3	(3R,9S,13S)-3-benzyl-N-(2-(chroman-6-yl)ethyl)-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
4	(3R,9S,13S)-N-(2-(benzofuran-6-yl)ethyl)-3-benzyl-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
5	(7R,13S,17RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-11-phenethyl-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
6	(7R,13S,17RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-11-(3-(benzyloxy)propyl)-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
7	(7R,13S,17S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-13-(cyclobutylmethyl)-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
8	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-N-(2-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)ethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
9	(3R,9S,13RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-(cyclopropylmethyl)-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
10	(3R,9S,13RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-(cyclopentylmethyl)-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
11	(3R,9S,13RS)-3-benzyl-N-(2-(chroman-6-yl)ethyl)-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
12	(3R,9S,13RS)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
13	(3R,9S,13RS)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(1,3-dihydroisobenzofuran-5-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

14	(3R,9S,13RS)-N-(2-(benzofuran-6-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
15	(3R,9S,13RS)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
16	(3R,9S,13RS)-N-(2-(benzo[d]oxazol-2-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
17	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
18	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-N-(2-(pyrazin-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
19	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-N-(2-(pyrimidin-4-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
20	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-N-(2-(pyrimidin-5-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
21	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(3-(difluoromethoxy)propyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
22	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(2-(2-methoxyethoxy)ethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
23	(8RS,12S,18aR,21R)-21-benzyl-12-isobutyl-5,11-dimethyl-N-(2-(4-methylthiazol-2-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
24	(8RS,12S,18aR,21R)-21-benzyl-12-isobutyl-5,11-dimethyl-N-(2-(5-methylthiazol-2-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
25	(8RS,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(4-methoxyphenethyl)-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide

26	(8RS, 12S, 18aR, 21R)-21-benzyl-N-(3-(difluoromethoxy)phenethyl)-12-isobutyl-5, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-5H, 15H-imidazo[4', 5':5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
27	(8RS, 12S, 18aR, 21R)-21-benzyl-12-isobutyl-5, 11-dimethyl-6, 10, 13, 19-tetraoxo-N-phenethyl-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-5H, 15H-imidazo[4', 5':5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
28	(8RS, 12S, 18aR, 21R)-N-(3-(2H-1, 2, 3-triazol-2-yl)phenethyl)-21-benzyl-12-isobutyl-5, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-5H, 15H-imidazo[4', 5':5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
29	(8S, 12S, 18aR, 21R)-21-benzyl-N-(2-(5, 6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-12-isobutyl-5, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-5H, 15H-imidazo[4', 5':5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
30	(8S, 12S, 18aR, 21R)-N-(2-(benzo[d]isoxazol-3-yl)ethyl)-21-benzyl-12-isobutyl-5, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-5H, 15H-imidazo[4', 5':5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
31	(8S, 12S, 18aR, 21R)-N-(4-(2H-1, 2, 3-triazol-2-yl)phenethyl)-21-benzyl-12-isobutyl-5, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-5H, 15H-imidazo[4', 5':5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
32	(4aR, 7R, 18S, 22S)-7-benzyl-22-isobutyl-N-(8-methoxychroman-3-yl)-21-methyl-5, 16, 20, 23-tetraoxo-1, 2, 4, 4a, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, 22, 23-hexadecahydronaphtho[1, 2-p][1, 4]oxazino[3, 4-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-18-carboxamide
33	(4aR, 7R, 18S, 22S)-7-benzyl-22-isobutyl-N-(2-(3-methoxyphenoxy)ethyl)-21-methyl-5, 16, 20, 23-tetraoxo-1, 2, 4, 4a, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, 22, 23-hexadecahydronaphtho[1, 2-p][1, 4]oxazino[3, 4-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-18-carboxamide
34	(4aR, 7R, 18S, 22S)-7-benzyl-22-isobutyl-N-(2-(4-methoxyphenoxy)ethyl)-21-methyl-5, 16, 20, 23-tetraoxo-1, 2, 4, 4a, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, 22, 23-hexadecahydronaphtho[1, 2-p][1, 4]oxazino[3, 4-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-18-carboxamide
35	(4aR, 7R, 18S, 22S)-7-benzyl-22-isobutyl-N-(2-(7-methoxy-2, 3-dihydrobenzo[b][1, 4]dioxin-6-yl)ethyl)-21-methyl-5, 16, 20, 23-tetraoxo-1, 2, 4, 4a, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, 22, 23-hexadecahydronaphtho[1, 2-p][1, 4]oxazino[3, 4-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-18-carboxamide
36	(4aR, 7R, 18S, 22S)-7-benzyl-N-(2-(7-chloro-5-methyl-2, 3-dihydrobenzo[b][1, 4]dioxin-6-yl)ethyl)-22-isobutyl-21-methyl-5, 16, 20, 23-tetraoxo-1, 2, 4, 4a, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, 22, 23-hexadecahydronaphtho[1, 2-p][1, 4]oxazino[3, 4-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-18-carboxamide

37	(4aR,7R,18S,22S)-7-benzyl-N-(2-(7-chloro-2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
38	(4aR,7R,18S,22S)-N-(2-(benzo[d]isoxazol-3-yl)ethyl)-7-benzyl-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
39	(4aR,7R,18S,22S)-7-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
40	(4aR,7R,18S,22S)-7-benzyl-N-(4-cyanophenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
41	(4aR,7R,18S,22S)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-7-benzyl-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
42	(4aR,7R,18S,22S)-7-benzyl-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
43	(4aR,7R,18S,22S)-7-benzyl-N-(2-(3,5-dimethylisoxazol-4-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
44	(4aR,7R,18S,22S)-7-benzyl-N-(2-(5-ethyl-1,2,4-oxadiazol-3-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
45	(4aR,7R,18S,22S)-7-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
46	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(2-(2-isopropylthiazol-4-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
47	(9S,13S,19aR,22R)-22-benzyl-N-(4-ethylphenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
48	(9S,13S,19aR,22R)-22-benzyl-N-(4-(tert-butyl)phenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

49	(9S, 13S, 19aR, 22R)-22-benzyl-N-(4-bromophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
50	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-fluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
51	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3-chlorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
52	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3-bromophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
53	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
54	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
55	(9S, 13S, 19aR, 22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
56	(9S, 13S, 19aR, 22R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
57	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3,5-dimethoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
58	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-N-phenethyl-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
59	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-fluoro-4-methoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
60	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(4-methylphenethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide

61	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3,4-dimethylphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
62	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(3-methylphenethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
63	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,4-dimethylphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
64	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-methylphenethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
65	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,3-dimethoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
66	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3-fluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
67	(9S, 13S, 19aR, 22R)-22-benzyl-N-(4-fluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
68	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,6-difluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
69	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-N-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
70	(4aR, 7R, 18S, 22S)-7-benzyl-N-(2-(4,5-dimethylisoxazol-3-yl)ethyl)-22-isobutyl-21-methyl-5, 16, 20, 23-tetraoxo-1, 2, 4, 4a, 5, 6, 7, 8, 16, 17, 18, 19, 20, 21, 22, 23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-18-carboxamide
71	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3,5-dimethoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
72	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,6-difluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide

73	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-N-(2,4,6-trifluorophenethyl)-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
74	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,6-difluoro-4-methoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
75	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3,4-difluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
76	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-N-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
77	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-N-phenethyl-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
78	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(5-methyl-1,2,4-oxadiazol-3-yl)ethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
79	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-ethyl-1,2,4-oxadiazol-3-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
80	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
81	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,3-dimethoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
82	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(5-methylisoxazol-4-yl)ethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
83	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
84	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-N-(4-methoxyphenethyl)-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide

85	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-(tert-butyl)-1,2,4-oxadiazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
86	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-(3,5-dimethylphenyl)-1,2,4-oxadiazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
87	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(2-(3-(2-(trifluoromethoxy)phenyl)-1,2,4-oxadiazol-5-yl)ethyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
88	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(2-(5-(2-(trifluoromethoxy)phenyl)-4H-1,2,4-triazol-3-yl)ethyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
89	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-(tert-butyl)isoxazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
90	(9S,13S,19aS,22R)-22-benzyl-N-(2-(5-(tert-butyl)isoxazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
91	(9S,13S,19aR,22R)-22-benzyl-N-(4-fluoro-3-methoxyphenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
92	(9S,13S,19aR,22R)-22-benzyl-N-(2-fluoro-5-methylphenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
93	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(3-methoxy-4-(2H-1,2,3-triazol-2-yl)phenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
94	(9S,13S,19aR,22R)-22-benzyl-N-(2,4-difluorophenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
95	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(4-methoxy-3-methylphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

96	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(3-methylphenethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
97	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,3-difluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
98	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(5-methylisoxazol-3-yl)ethyl)-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
99	(9S, 13S, 19aR, 22R)-22-benzyl-N-(4-bromo-2,6-difluorophenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
100	(9S, 13S, 19aR, 22R)-22-benzyl-N-(3-fluoro-4-methoxyphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
101	(7R, 13S, 17S)-7-benzyl-N-(2-(3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)ethyl)-13-isobutyl-11, 14-dimethyl-9, 12, 15, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19-tetradecahydro-[1,3]dioxolo[4', 5':4, 5]benzo[1,2-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-17-carboxamide
102	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,6-difluoro-3-methylphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
103	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-N-(2-(isothiazol-5-yl)ethyl)-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
104	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-fluoro-6-methylphenethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
105	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
106	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
107	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-(tert-butyl)isoxazol-3-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1,4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide

108	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-phenethyl-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
109	(3'S,7'S,13'R)-13'-benzyl-N-(3,5-dimethoxyphenethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
110	(3'S,7'S,13'R)-13'-benzyl-N-(2,6-difluorophenethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
111	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(4-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
112	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-N-(3-methylphenethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
113	(3'S,7'S,13'R)-13'-benzyl-N-(3,4-difluorophenethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
114	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-ethyl-1,2,4-oxadiazol-3-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
115	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
116	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-(tert-butyl)-1,2,4-oxadiazol-3-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
117	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-N-(2-(5-methylisoxazol-3-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
118	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
119	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-(tert-butyl)isoxazol-3-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

120	(3'S,7'S,13'R)-13'-benzyl-N-(3,5-difluorophenethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
121	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
122	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(4-(pyrimidin-2-yl)phenethyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
123	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(3-(pyrimidin-2-yl)phenethyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
124	(9S,13S,19aR,22R)-22-benzyl-N-(2-(1-cyclopropyl-1H-pyrazol-4-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
125	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-N-(3-methyl-4-(2H-1,2,3-triazol-2-yl)phenethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
126	(9S,13S,19aR,22R)-22-benzyl-N-(3,5-difluorophenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
127	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
128	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
129	(9S,13S,19aR,22R)-22-benzyl-N-(2-(1,4-dimethyl-1H-pyrazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
130	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(2-(3-(3-methoxyphenyl)-1,2,4-oxadiazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
131	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

132	(3'S,7'S,13'R)-13'-benzyl-N-(2,6-difluorophenethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
133	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(4-(pyrazin-2-yl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
134	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(3-(pyrazin-2-yl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
135	(3'S,7'S,13'R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
136	(3'S,7'S,13'R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
137	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(4-(pyrimidin-2-yl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
138	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(3-(pyrimidin-2-yl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
139	(3'S,7'S,13'R)-13'-benzyl-N-(2-(1-cyclopropyl-1H-pyrazol-4-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
140	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
141	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(5-methylisoxazol-3-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
142	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
143	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

144	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
145	(3'S,7'S,13'R)-13'-benzyl-N-(2,2-difluoro-2-phenylethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
146	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
147	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
148	(3R,9S,13S)-3-benzyl-N-(2-(chroman-7-yl)ethyl)-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
149	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
150	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(3-(difluoromethoxy)phenethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
151	(7R,13S,17RS)-7-benzyl-N-(2,3-dimethoxyphenethyl)-13-isobutyl-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
152	(3R,9S,13RS)-3-benzyl-N-(2-(2,3-dihydrobenzofuran-5-yl)ethyl)-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
153	(7R,13S,17S)-7-benzyl-13-isobutyl-N-(4-methoxyphenethyl)-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
154	(7R,13S,17S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-13-isobutyl-14-methyl-9,12,15,19-tetraoxo-11-(2-(tetrahydro-2H-pyran-4-yl)ethyl)-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
155	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-7-(2-((RS)-tetrahydro-2H-pyran-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

156	(3R,9S,13RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-17,18-dimethoxy-7-(3-methoxy-3-methylbutyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
157	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-((RS)-2-(5,5-dimethyltetrahydro-2H-pyran-2-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
158	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(2-(2-methoxypyridin-4-yl)ethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
159	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-7-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
160	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
161	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-N-(2-(2,3,4,5-tetrahydrobenzo[b]oxepin-8-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
162	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
163	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
164	(3RS,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
165	(3RS,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
166	(3'S,7'S,13'R)-13'-benzyl-N-((1-(3,4-dimethoxyphenyl)cyclopropyl)methyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10']-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3'-carboxamide
167	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(3-(methylsulfonyl)phenethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10']-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3'-carboxamide

168	(3'S,7'S,13'R)-13'-benzyl-N-(3-cyanophenethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
169	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(3-(trifluoromethyl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
170	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(4-morpholinophenethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
171	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(5-isopropyl-1,2,4-oxadiazol-3-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
172	(3'S,7'S,13'R)-13'-benzyl-N-(2-(4-cyclopropyl-1H-pyrazol-1-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
173	(3'S,7'S,13'R)-13'-benzyl-N-(2-(4-bromo-1H-pyrazol-1-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
174	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-N-(2-(4-(3-methoxypropyl)-1H-pyrazol-1-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
175	(3'S,7'S,13'R)-13'-benzyl-N-(2,2-difluoro-2-(3-methoxyphenyl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
176	(7S,11S,17aR,20R)-20-benzyl-N-(2-(1-cyclopropyl-1H-pyrazol-4-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
177	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-N-(2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
178	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-N-(2-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)ethyl)-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
179	(7S,11S,17aR,20R)-20-benzyl-N-(2-(4-cyclopropyl-1H-pyrazol-1-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide

180	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
181	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-N-(4-(pyrimidin-2-yl)phenethyl)-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
182	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-N-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
183	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-N-phenethyl-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
184	(7S,11S,17aR,20R)-20-benzyl-N-(4-bromophenethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
185	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-N-(4-methoxyphenethyl)-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
186	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-N-(3-methylphenethyl)-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
187	(7S,11S,17aR,20R)-20-benzyl-N-(2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
188	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-N-(2-(4-methoxy-1H-pyrazol-1-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
189	(7S,11S,17aR,20R)-20-benzyl-N-(3-ethynylphenethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
190	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
191	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-(difluoromethyl)isoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide

192	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-N-(4-methylphenethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
193	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-N-(4-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
194	(3R,9S,13S)-3-benzyl-N-(3-ethoxyphenethyl)-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
195	(3R,9S,13S)-3-benzyl-9-isobutyl-17,18-dimethoxy-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
196	(3R,9S,13S)-3-benzyl-N-(2-fluorophenethyl)-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
197	(3R,9S,13S)-3-benzyl-N-(4-(dimethylamino)phenethyl)-9-isobutyl-17,18-dimethoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
198	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
199	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
200	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(3-(methoxy-d3)phenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
201	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(3-ethoxyphenethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
202	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-N-(4-methylphenethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
203	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(4-(dimethylamino)phenethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

204	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-fluorophenethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
205	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(3,5-dimethoxyphenethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
206	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-N-(2-(thiophen-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
207	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(2-(5-methoxypyridin-2-yl)ethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
208	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(furan-2-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
209	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(3,5-dimethyl-1H-pyrazol-1-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
210	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(3-methoxypropyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
211	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-N-phenethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
212	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-N-(2-((RS)-tetrahydro-2H-pyran-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
213	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-((RS)-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)ethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
214	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
215	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(4-ethylphenethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

216	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(5-methoxypentyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
217	(3R,9S,13S)-N-(4-(1H-pyrazol-1-yl)phenethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
218	(3R,9S,13S)-N-(4-amino-3-methoxyphenethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
219	(3R,9S,13RS)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(4-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
220	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(2-(6-methoxypyridin-2-yl)ethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
221	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
222	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
223	(7R,13S,17S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-13-isobutyl-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
224	(7R,13S,17S)-7-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
225	(7R,13S,17S)-7-benzyl-N-(3-ethoxyphenethyl)-13-isobutyl-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
226	(7R,13S,17S)-7-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-13-isobutyl-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
227	(7R,13S,17S)-7-benzyl-N-(4-ethylphenethyl)-13-isobutyl-11,14-dimethyl-9,12,15,19-tetraoxo-6,7,8,9,10,11,12,13,14,15,16,17,18,19-tetradecahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide

228	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-17-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
229	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-7,10,17-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
230	(3R,9S,13S)-3-benzyl-9-isobutyl-N-(3-methoxyphenethyl)-7,10,17-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
231	(3R,9S,13S)-3-benzyl-9-isobutyl-17-methoxy-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
232	(3R,9S,13S)-3-benzyl-9-isobutyl-18-methoxy-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
233	(3R,9S,13S)-3-benzyl-9-isobutyl-N-(3-methoxyphenethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
234	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-17-fluoro-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
235	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-7,10,16-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
236	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydronaphtho[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
237	(3R,9S,13S)-3-benzyl-17-chloro-9-isobutyl-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
238	(3R,9S,13S)-3-benzyl-9-isobutyl-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydronaphtho[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
239	(3R,9S,13S)-3-benzyl-N-(4-ethylphenethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

240	(6R,12S,16S)-6-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-10,13-dimethyl-8,11,14,18-tetraoxo-5,6,7,8,9,10,11,12,13,14,15,16,17,18-tetradecahydrothieno[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-16-carboxamide
241	(6R,12S,16S)-6-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-2,10,13-trimethyl-8,11,14,18-tetraoxo-5,6,7,8,9,10,11,12,13,14,15,16,17,18-tetradecahydrothiazolo[5,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-16-carboxamide
242	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-(methoxy-d3)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
243	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-(methoxy-d3)-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
244	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-(methoxy-d3)-N-(3-(methoxy-d3)phenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
245	(3R,9S,13S)-3-benzyl-N-(2-(chroman-7-yl)ethyl)-9-isobutyl-17-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
246	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-10,16-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
247	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-N-(3-methoxyphenethyl)-10,16-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
248	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-17-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
249	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-17-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
250	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydronaphtho[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
251	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydronaphtho[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

252	(3R,9S,13S)-3-benzyl-N-(4-ethylphenethyl)-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
253	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-17-chloro-7-(2-cyclohexylethyl)-9-isobutyl-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
254	(3R,9S,13S)-3-benzyl-17-chloro-7-(2-cyclohexylethyl)-9-isobutyl-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
255	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
256	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16,18-dimethoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
257	(3R,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
258	(3R,13S)-3-benzyl-7-(2-cyclohexylethyl)-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
259	(7S,11S,20R,22aR)-20-benzyl-N-(4-bromophenethyl)-7-isobutyl-14-methoxy-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydrobenzo[p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
260	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-14-methoxy-8-methyl-6,9,13,22-tetraoxo-N-(2-(2,3,4,5-tetrahydrobenzo[b]oxepin-8-yl)ethyl)-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydrobenzo[p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
261	(3R,9S,13S)-3-benzyl-N-(2-(chroman-7-yl)ethyl)-7-(2-cyclohexylethyl)-9-isobutyl-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
262	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-9-isobutyl-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
263	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-16-methoxy-9,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

264	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-16-methoxy-N-(3-methoxyphenethyl)-9,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
265	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[4,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
266	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[4,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
267	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
268	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
269	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
270	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-10,18-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
271	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-N-(3-methoxyphenethyl)-10,18-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
272	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-16,18-dimethoxy-9,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
273	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-16,18-dimethoxy-N-(3-methoxyphenethyl)-9,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
274	(3R,9S,13RS)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-(cyclopropylmethyl)-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
275	(3R,9S,13S)-3-benzyl-N-(2-(chroman-7-yl)ethyl)-7-(2-cyclohexylethyl)-9-isobutyl-16,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

276	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-9-isobutyl-16,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
277	(3R,9S,13S)-3-benzyl-16-fluoro-9-isobutyl-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
278	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-16-fluoro-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
279	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-16-chloro-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
280	(7S,11S,20R,22aR)-20-benzyl-14-ethoxy-7-isobutyl-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
281	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
282	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
283	(7S,11S,20R,22aR)-20-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-14-ethoxy-7-isobutyl-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
284	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclopentylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
285	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclohexylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
286	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclopentylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
287	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclohexylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

288	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclopentylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((SR)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
289	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclohexylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((SR)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
290	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-7-(cyclopentylmethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
291	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-7-(cyclohexylmethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
292	(3RS,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclobutylmethyl)-9-(2-cyclohexylethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
293	(3RS,7S,13R)-13-benzyl-7-(cyclopentylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
294	(3RS,7S,13R)-13-benzyl-7-(cyclohexylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
295	(3RS,7S,13R)-13-benzyl-7-(cyclopentylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
296	(3RS,7S,13R)-13-benzyl-7-(cyclohexylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
297	(3RS,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((SR)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
298	(3RS,7S,13R)-13-benzyl-7-(cyclopentylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((SR)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
299	(3RS,7S,13R)-13-benzyl-7-(cyclohexylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((SR)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

300	(3RS,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-(cyclopentylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
301	(3RS,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-(cyclohexylmethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
302	(3RS,7S,13R)-13-benzyl-7-(cyclobutylmethyl)-9-(2-cyclohexylethyl)-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
303	(3RS,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
304	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-7-(2-((RS)-tetrahydro-2H-pyran-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
305	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-7-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
306	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-16-methoxy-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
307	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-(cyclopentylmethyl)-16-methoxy-10-methyl-5,8,11,15-tetraoxo-7-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
308	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-(cyclopentylmethyl)-16-methoxy-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
309	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-(cyclohexylmethyl)-16-methoxy-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
310	(3R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-7-(2-((RS)-tetrahydro-2H-pyran-2-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
311	(3R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-7-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

312	(3R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
313	(3R,9S,13S)-3-benzyl-9-(cyclopentylmethyl)-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-7-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
314	(3R,9S,13S)-3-benzyl-9-(cyclohexylmethyl)-16-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-7-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
315	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
316	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-N-(3-(methoxy-d3)phenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
317	(3R,9S,13S)-3-benzyl-9-isobutyl-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-16-(trifluoromethoxy)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
318	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
319	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
320	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-(methoxy-d3)phenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
321	(8R,14S,18S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-8-benzyl-14-isobutyl-12,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
322	(8R,14S,18S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-8-benzyl-14-isobutyl-12,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-2,2-d2-18-carboxamide
323	(8R,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-12,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

324	(8R,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-12,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-2,2-d2-18-carboxamide
325	(4aR,7R,18S,22S)-7-benzyl-N-(3,5-dimethoxyphenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
326	(4aR,7R,18S,22S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-7-benzyl-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
327	(4aR,7R,18S,22S)-N-(2-(benzo[d]oxazol-2-yl)ethyl)-7-benzyl-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
328	(8S,12S,18aR,21R)-21-benzyl-N-(3,5-dimethoxyphenethyl)-12-isobutyl-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
329	(8S,12S,18aR,21R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-21-benzyl-12-isobutyl-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
330	(3S,7S,13R)-9-(2-(7-oxabicyclo[2.2.1]heptan-2-yl)ethyl)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
331	(3S,7S,13R)-9-(2-(5-oxaspiro[3.4]octan-6-yl)ethyl)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
332	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(2-(tetrahydrofuran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
333	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(2-(tetrahydro-2H-pyran-3-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
334	(3S,7S,13R)-9-(2-(2,9-dioxaspiro[5.5]undecan-3-yl)ethyl)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
335	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-(tert-butoxy)ethyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

336	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-9-(2-(3-methoxycyclobutyl)ethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
337	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclobutylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((S)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
338	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclobutylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
339	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-6-methyl-1,5,8,11-tetraoxo-7-(prop-2-yn-1-yl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
340	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclopropylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
341	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-7-(cyclopropylmethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
342	(8S,12S,18aS,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-11-methyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
343	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-11-methyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
344	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
345	(8R,14S,18S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-15-methyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
346	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-N-(3-methoxyphenethyl)-15-methyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
347	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-N-(3-(methoxy-d3)phenethyl)-15-methyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

348	(8S,12S,18aR,21R)-21-benzyl-17-cyclopropyl-12-isobutyl-N-(3-methoxyphenethyl)-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
349	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-18-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
350	(3S,7S,13R)-13-benzyl-18-fluoro-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
351	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[5',4':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
352	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-17-isopropyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
353	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-17-isopropyl-N-(3-methoxyphenethyl)-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
354	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-3-(2-methoxyethyl)-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
355	(4aR,7R,18S,22S)-7-benzyl-3-cyclobutyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
356	(4aR,7R,18S,22S)-7-benzyl-3-cyclopropyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
357	(4aS,7R,18S,22S)-7-benzyl-3-cyclopropyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
358	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclopropylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((S)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
359	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclopropylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((R)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

360	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclobutylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((S)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
361	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-(cyclobutylmethyl)-6-methyl-1,5,8,11-tetraoxo-9-(2-((R)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
362	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(2-((S)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
363	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(2-((R)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
364	(8S,12S,18aR,21R)-21-benzyl-12,17-diisobutyl-N-(3-methoxyphenethyl)-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
365	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
366	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
367	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
368	(8S,12S,18aR,21R)-21-benzyl-N-(3,5-dimethoxyphenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[5',4':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
369	2,2,2-trichloroethyl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate
370	(4aR,7R,18S,22S)-7-benzyl-N-(2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
371	(4aR,7R,18S,22S)-7-benzyl-N-(3-(difluoromethoxy)phenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

372	(9S,13S,19aR,22R)-22-benzyl-13,18-diisobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
373	(9S,13S,19aS,22R)-22-benzyl-13,18-diisobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
374	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-18-isopropyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
375	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-18-isopropyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
376	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-4,4a,5,6,7,8,16,17,18,19,20,21,22,23-tetradecahydro-1H-naphtho[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
377	(8S,12S,18aR,21R)-21-benzyl-N-(3,5-dimethoxyphenethyl)-12-isobutyl-4,5,11-trimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
378	(4aR,7R,18S,22S)-7-benzyl-N-(3-bromophenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
379	(8R,14S,18S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-2,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
380	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-N-(3-methoxyphenethyl)-2,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
381	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-N-(3-(methoxy-d3)phenethyl)-2,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
382	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-18-fluoro-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide

383	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-18-fluoro-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
384	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-18-fluoro-7-isobutyl-N-(3-(methoxy-d3)phenethyl)-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
385	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-naphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-3'-carboxamide
386	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-6'-methyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-naphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-3'-carboxamide
387	(4aR,7R,18S,22S)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-7-benzyl-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
388	(9S,13S,19aS,22R)-22-benzyl-18-cyclopropyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
389	(9S,13S,19aR,22R)-22-benzyl-18-cyclopropyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
390	(9S,13S,19aS,22R)-22-benzyl-18-cyclobutyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
391	(9S,13S,19aR,22R)-22-benzyl-18-cyclobutyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
392	(9S,13S,19aS,22R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-22-benzyl-18-cyclopropyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
393	(9S,13S,19aR,22R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-22-benzyl-18-cyclopropyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
394	(9S,13S,19aS,22R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-22-benzyl-18-cyclobutyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

395	(9S, 13S, 19aR, 22R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-22-benzyl-18-cyclobutyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
396	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-9'-(3-methoxypropyl)-6'-methyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-naphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-3'-carboxamide
397	(4aR,7R,18S,22S)-7-benzyl-N-(3-ethoxyphenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
398	(9S, 13S, 19aR, 22R)-22-benzyl-18-cyclopropyl-N-(3-(difluoromethoxy)phenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
399	(9S, 13S, 19aS, 22R)-22-benzyl-18-cyclopropyl-N-(3-(difluoromethoxy)phenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
400	(9S, 13S, 19aR, 22R)-22-benzyl-18-cyclopropyl-N-(3-ethoxyphenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
401	(9S, 13S, 19aS, 22R)-22-benzyl-18-cyclopropyl-N-(3-ethoxyphenethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
402	(9S, 13S, 19aR, 22R)-22-benzyl-18-cyclopropyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
403	(9S, 13S, 19aS, 22R)-22-benzyl-18-cyclopropyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
404	(9S, 13S, 19aR, 22R)-22-benzyl-18-cyclopropyl-N-(2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
405	(9S, 13S, 19aS, 22R)-22-benzyl-18-cyclopropyl-N-(2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
406	(7S, 11S, 21R, 23aR)-21-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-8,16-dimethyl-6,9,13,23-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,20,21,22,23,23a-hexadecahydro-2H-oxazolo[5',4':4,5]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide

407	(7S,11S,21R,23aR)-21-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-8,16-dimethyl-6,9,13,23-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,20,21,22,23,23a-hexadecahydro-[1,4]oxazino[3,4-f]oxazolo[5',4':4,5]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
408	(8R,14S,18S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-8-benzyl-2,2-difluoro-14-isobutyl-12,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
409	(8R,14S,18S)-8-benzyl-2,2-difluoro-14-isobutyl-N-(3-methoxyphenethyl)-12,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydro-[1,3]dioxolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
410	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-14-isobutyl-2,15-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
411	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-18-fluoro-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
412	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
413	(9S,13S,19aS,22R)-22-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
414	(9S,13S,19aR,22R)-22-benzyl-N-(3-(difluoromethoxy)phenethyl)-13-isobutyl-18-(2-methoxyethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
415	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-13-isobutyl-18-(2-methoxyethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
416	(4aR,7R,18S,22S)-7-benzyl-3-(2-hydroxyethyl)-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
417	(8S,12S,18aR,21R)-21-benzyl-17-cyclopropyl-12-isobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide

418	(8S,12S,18aR,21R)-21-benzyl-17-cyclopropyl-N-(3-ethoxyphenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
419	(8S,12S,18aR,21R)-21-benzyl-17-cyclopropyl-N-(3-(difluoromethoxy)phenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
420	(8S,12S,18aR,21R)-21-benzyl-17-cyclopropyl-N-(2-(5,6-dihydro-4H-cyclopenta[d]thiazol-2-yl)ethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
421	(8S,12S,18aR,21R)-21-benzyl-17-cyclopropyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
422	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-N-(3-(1,1-difluoroethyl)phenethyl)-14-isobutyl-2,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
423	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-3,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-3H,15H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-e]indazole-8-carboxamide
424	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-3,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,15,16,18,18a,19,20,21,22-hexadecahydro-3H-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-e]indazole-8-carboxamide
425	(8S,12S,18aR,21R)-21-benzyl-17-(cyclopropylmethyl)-12-isobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
426	(8S,12S,18aR,21R)-21-benzyl-17-(cyclopropylmethyl)-N-(3-(difluoromethoxy)phenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
427	(8S,12S,18aR,21R)-21-benzyl-17-(cyclopropylmethyl)-N-(3-ethoxyphenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
428	(8S,12S,18aR,21R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-21-benzyl-17-(cyclopropylmethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-

	hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
429	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-3,11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-3H,15H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-e]indazole-8-carboxamide
430	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
431	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-9-(3-methoxypropyl)-6,10-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
432	(3'S,7'S,13'R)-13'-benzyl-7'-(cyclopentylmethyl)-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
433	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
434	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
435	(8S,12S,18aR,21R)-21-benzyl-12-(cyclopentylmethyl)-4,11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,15,16,18,18a,19,20,21,22-hexadecahydro-[1,4]oxazino[3,4-f]oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
436	(8S,12S,18aR,21R)-21-benzyl-12-(cyclopentylmethyl)-4,11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
437	(8S,12S,18aS,21R)-21-benzyl-12-(cyclopentylmethyl)-4,11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
438	(3'R,9'S,13'S)-3'-benzyl-9'-isobutyl-16'-methoxy-N-(3-methoxyphenethyl)-7',10'-dimethyl-5',8',11',15'-tetraoxo-2',3',4',5',8',9',10',11',12',13',14',15'-dodecahydro-7'H-spiro[cyclopropane-1,6'-pyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-13'-carboxamide
439	(3'S,7'S,13'R)-13'-benzyl-18'-fluoro-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

440	(3'S,7'S,13'R)-13'-benzyl-18'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
441	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
442	(3'R,9'S,13'S)-3'-benzyl-9'-isobutyl-N-(3-methoxyphenethyl)-7',10'-dimethyl-5',8',11',15'-tetraoxo-2',3',4',5',8',9',10',11',12',13',14',15'-dodecahydro-7'H-spiro[cyclopropane-1,6'-pyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-13'-carboxamide
443	(9S,13S,19aR,22R)-22-benzyl-3-fluoro-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
444	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4,10-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
445	(3S,7S,13R)-13-benzyl-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-9-(((R)-tetrahydro-2H-pyran-2-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
446	(3S,7S,13R)-13-benzyl-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-9-(2-(((S)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
447	(8R,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-12,15-dimethyl-10,13,16,20-tetraoxo-2,3,7,8,9,10,13,14,15,16,17,18,19,20-tetradecahydro-12H-spiro[benzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11,1'-cyclopropane]-18-carboxamide
448	(3'R,9'S,13'S)-3'-benzyl-9'-isobutyl-7',10'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5',8',11',15'-tetraoxo-2',3',4',5',8',9',10',11',12',13',14',15'-dodecahydro-7'H-spiro[cyclopropane-1,6'-pyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-13'-carboxamide
449	(3R,9S,13S)-3-benzyl-9-isobutyl-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-pyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
450	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14,19,20-hexadecahydrobenzofuro[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
451	(4aR,7R,18S,22S)-7-benzyl-3-(3-hydroxypropyl)-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

452	(4aR,7R,18S,22S)-7-benzyl-3-(3-hydroxypropyl)-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
453	(3'S,7'S,13'R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
454	(3'S,7'S,13'R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
455	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-11-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-3,4,6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-octadecahydro-15H-benzofuro[7,6-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
456	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-11-methyl-6,10,13,19-tetraoxo-3,4,6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-octadecahydro-15H-benzofuro[7,6-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
457	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-9'-(2-methoxyethyl)-N-(3-methoxyphenethyl)-6'-methyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-naphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-3'-carboxamide
458	2,2,2-trichloroethyl (9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-9-((2-(3-methylisoxazol-5-yl)ethyl)carbamoyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-18H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-18-carboxylate
459	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-12,18-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
460	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
461	(9S,13S,19aR,22R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
462	(9S,13S,19aR,22R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

463	(9S,13S,19aR,22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
464	(9S,13S,19aS,22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
465	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
466	(7S,11S,17aR,20R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
467	(7S,11S,17aS,20R)-N-(3-(2H-1,2,3-triazol-2-yl)phenethyl)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
468	(7S,11S,17aR,20R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
469	(7S,11S,22R,24aR)-22-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-8-methyl-6,9,13,24-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,21,22,23,24,24a-hexadecahydro-2H-pyrido[2,1-f]pyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
470	(7S,11S,22R,24aR)-22-benzyl-7-isobutyl-8-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,9,13,24-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,21,22,23,24,24a-hexadecahydro-2H-pyrido[2,1-f]pyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
471	(9'R,15'S,19'S)-9'-benzyl-15'-isobutyl-N-(3-methoxyphenethyl)-13',16'-dimethyl-11',14',17',21'-tetraoxo-8',9',10',11',14',15',16',17',18',19',20',21'-dodecahydro-13'H-spiro[cyclopropane-1,12'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-h]quinoline]-19'-carboxamide
472	(9S,13S,19aR,22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
473	(9S,13S,19aS,22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
474	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide

475	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-3-(pyridin-3-ylsulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
476	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
477	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
478	(7S,11S,17aR,20R)-20-benzyl-N-(2,6-difluorophenethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
479	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-3-((5-methoxypyridin-3-yl)sulfonyl)-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
480	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
481	(9S,13S,19aR,22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
482	(8S,12S,18aR,21R)-21-benzyl-N-(2,6-difluorophenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
483	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
484	(7S,11S,22R,24aR)-22-benzyl-N-(2,6-difluorophenethyl)-7-isobutyl-8-methyl-6,9,13,24-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,21,22,23,24,24a-hexadecahydro-2H-pyrido[2,1-f]pyrido[2',1':2,3]imidazo[4,5-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
485	(8S,12S,18aR,21R)-21-benzyl-N-(2,6-difluorophenethyl)-12-isobutyl-5,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-5H,15H-imidazo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide

486	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
487	(9S,13S,19aR,22S)-22-benzyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
488	(3'R,9'S,13'S)-3'-benzyl-9'-isobutyl-17'-methoxy-N-(3-methoxyphenethyl)-7',10'-dimethyl-5',8',11',15'-tetraoxo-2',3',4',5',8',9',10',11',12',13',14',15'-dodecahydro-7'H-spiro[cyclopropane-1,6'-pyrido[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-13'-carboxamide
489	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,16,17,19,19a,20,21,22,23-hexadecahydro-[1,4]oxazino[3',4':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
490	(8S,12S,18aR,21R)-21-benzyl-N-(2,6-difluorophenethyl)-12-isobutyl-3,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-3H,15H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-e]indazole-8-carboxamide
491	(8S,12S,18aR,21R)-21-benzyl-N-(2,6-difluorophenethyl)-12-isobutyl-11-methyl-6,10,13,19-tetraoxo-3,4,6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-octadecahydro-15H-benzofuro[7,6-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
492	(1r,3S,3'S,7'S,13'R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-13'-benzyl-7'-isobutyl-3-methoxy-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-naphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-3'-carboxamide
493	(1r,3S,3'S,7'S,13'R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-13'-benzyl-7'-isobutyl-3-methoxy-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
494	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
495	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-1,2',3,3',4',5',6',7',8',9',11',12',13',14'-tetradecahydro-1'H-spiro[indene-2,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
496	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(4-(pyrimidin-2-yl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
497	(9S,13S,19aS,22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

498	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
499	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
500	(9S, 13S, 19aS, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
501	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
502	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-N-(3-(pyrimidin-2-yl)phenethyl)-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
503	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9,10,10-tetramethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
504	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
505	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
506	(9S, 13S, 19aR, 22R)-22-benzyl-12-ethyl-13-isobutyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
507	(3S,7S,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
508	(3S,7S,10R,13R)-13-benzyl-10-cyclopropyl-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
509	(9S, 13S, 19aR, 22R)-22-benzyl-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

510	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
511	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
512	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
513	(3R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
514	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
515	(7S,11S,17aRS,20R)-20-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:4',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
516	(7S,11S,17aRS,20R)-20-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:4',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
517	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:2',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
518	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:2',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
519	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
520	(9S,13S,19aS,22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
521	(9S,13S,19aS,22R)-22-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide

522	(9S,13S,19aR,22R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-22-benzyl-3-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
523	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
524	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
525	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
526	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:4',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
527	(9S,13S,19aR,22R)-22-benzyl-5-chloro-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
528	(9S,13S,19aR,22R)-22-benzyl-5-chloro-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
529	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:2',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
530	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]isoquinoline-3-carboxamide
531	(8R,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrobenzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
532	(8R,14S,18S)-8-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-14-isobutyl-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrobenzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
533	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide

534	(9S, 13S, 19aR, 22R)-22-benzyl-6-fluoro-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
535	(9S, 13S, 19aR, 22R)-22-benzyl-6-fluoro-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
536	(8S, 12S, 18aR, 21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-17-phenyl-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
537	(7S, 4R, 9S, 13S)-4-benzyl-16-fluoro-9-isobutyl-N-(3-methoxyphenethyl)-10-methyl-6,8,11,15-tetraoxo-2-oxa-5,10,14-triaza-1(3,4)-quinolina-7(3,1)-pyrrolidinacyclopentadecaphane-13-carboxamide
538	(7S, 11S, 20R, 22aR)-20-benzyl-7-isobutyl-14-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-2-phenyl-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-pyrazino[2,1-f]pyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
539	(3S, 7S, 10R, 13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-10-((4,4-difluorocyclohexyl)methyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
540	(3S, 7S, 10S, 13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-10-((4,4-difluorocyclohexyl)methyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
541	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
542	(7S, 11S, 20R, 22aR)-20-benzyl-7-isobutyl-14-methoxy-8-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,9,13,22-tetraoxo-2-phenyl-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-pyrazino[2,1-f]pyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
543	(3'S, 7'S, 13'R)-13'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
544	(3'S, 7'S, 13'R)-13'-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide

545	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
546	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
547	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-10-isopropyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
548	(3S,7S,10R,13R)-13-benzyl-7,10-diisobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
549	(7S,11S,20R,22aS)-20-benzyl-7-isobutyl-14-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-2-phenyl-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-pyrazino[2,1-f]pyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
550	(7S,11S,20R,22aS)-20-benzyl-7-isobutyl-14-methoxy-8-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,9,13,22-tetraoxo-2-phenyl-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-pyrazino[2,1-f]pyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
551	(8R,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,13,14,15,16,17,18,19,20-dodecahydro-12H-spiro[benzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11,1'-cyclopropane]-18-carboxamide
552	(8R,14S,18S)-8-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-14-isobutyl-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,13,14,15,16,17,18,19,20-dodecahydro-12H-spiro[benzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11,1'-cyclopropane]-18-carboxamide
553	(8R,14S,18S)-8-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-14-isobutyl-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,13,14,15,16,17,18,19,20-dodecahydro-12H-spiro[benzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11,1'-cyclopropane]-18-carboxamide
554	(8R,14S,18S)-8-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-14-isobutyl-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,13,14,15,16,17,18,19,20-dodecahydro-12H-spiro[benzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11,1'-cyclopropane]-18-carboxamide
555	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(3-methoxyphenethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]isoquinoline]-3'-carboxamide
556	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]isoquinoline]-3'-carboxamide

557	(3R,6S,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-6-((4,4-difluorocyclohexyl)methyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
558	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-6-((4,4-difluorocyclohexyl)methyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
559	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
560	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-N-(2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
561	(8R,14S,18S)-8-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-14-isobutyl-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrobenzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
562	(8R,14S,18S)-8-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-14-isobutyl-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrobenzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
563	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-6-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
564	(3S,7S,10R,13R)-13-benzyl-10-((benzyloxy)methyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
565	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
566	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-10-(2-methoxyethyl)-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
567	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide

568	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-N-(2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
569	(7S,11S,19bRS,22R)-22-benzyl-11-isobutyl-4-methoxy-N-(3-methoxyphenethyl)-10-methyl-5,9,12,20-tetraoxo-5,6,7,8,9,10,11,12,15,19b,20,21,22,23-tetradecahydro-14H-pyrido[3',4':16,17][1]oxa[4,7,10,14]tetraazacycloheptadecino[6,7-a]isoquinoline-7-carboxamide
570	(7S,11S,20R,22aR)-20-benzyl-2,7-diisobutyl-14-methoxy-8-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-pyrazino[2,1-f]pyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
571	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-6-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
572	(3S,7S,10S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
573	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-6,9,10-trimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
574	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
575	(8R,11RS,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-2,11,12,15-tetramethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrobenzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
576	(8R,11RS,14S,18S)-8-benzyl-14-isobutyl-2,11,12,15-tetramethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrobenzofuro[7,6-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
577	(3R,6S,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-6-(2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
578	(3S,7S,10R,13R)-13-benzyl-10-(2-(benzyloxy)ethyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide

579	(3S,7S,10S,13R)-13-benzyl-10-(2-(benzyloxy)ethyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
580	(7'S,11'S,17a'R,20'R)-20'-benzyl-11'-isobutyl-4'-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-2',10'-dimethyl-5',9',12',18'-tetraoxo-5',6',7',8',9',10',11',12',14',15',17',17a',18',19',20',21'-hexadecahydrospiro[cyclopropane-1,16'-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-7'-carboxamide
581	(7S,11S,17aR,20R)-20-benzyl-11-isobutyl-4-(methoxy-d3)-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
582	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
583	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
584	(13S,4R,10S,14S)-4-benzyl-14-isobutyl-74-methoxy-N-(3-methoxyphenethyl)-13-methyl-2,8,12,15-tetraoxo-6-oxa-3,9,13-triaza-1(3,1)-pyrrolidina-7(1,2)-benzenacyclopentadecaphane-10-carboxamide
585	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
586	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-17,18-dimethoxy-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
587	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-15-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
588	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-15-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydrobenzo[p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
589	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
590	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-9-isobutyl-N-(3-methoxyphenethyl)-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

591	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-14-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
592	(7S,11S,17aS,20R)-20-benzyl-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-11-isobutyl-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
593	(7S,11S,17aR,20R)-20-benzyl-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-11-isobutyl-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
594	(7S,11S,17aR,20R)-20-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-11-isobutyl-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
595	(3S,7S,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
596	(3R,9S,13S)-3-benzyl-N-(2-(chroman-7-yl)ethyl)-7-(2-cyclohexylethyl)-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
597	(3R,9S,13S)-3-benzyl-7-(2-cyclohexylethyl)-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-9-isobutyl-17,18-dimethoxy-10-methyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
598	(8R,14S,18S)-8-benzyl-14-isobutyl-N-(3-methoxyphenethyl)-2,12,15-trimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
599	(3S,7S,13R)-13-benzyl-N-(2-(chroman-7-yl)ethyl)-9-(2-cyclohexylethyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
600	(3S,7S,13R)-13-benzyl-9-(2-cyclohexylethyl)-N-(2-(2,3-dihydrobenzofuran-6-yl)ethyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
601	(7S,11S,20R,22aS)-20-benzyl-7-isobutyl-14,16-dimethoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
602	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-14,16-dimethoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide

603	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
604	(4aS,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
605	(7S,11S,20R,22aR)-20-benzyl-2-ethyl-7-isobutyl-14-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
606	(4aS,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
607	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
608	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
609	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-14,16-dimethoxy-8-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
610	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(2-cyclohexylethyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
611	(7S,11S,20R,22aR)-20-benzyl-7-isobutyl-2-isopropyl-14-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
612	(7S,11S,20R,22aR)-20-benzyl-2,7-diisobutyl-14-methoxy-N-(3-methoxyphenethyl)-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
613	(4aR,7R,18S,22S)-7-benzyl-N-(3,5-dimethoxyphenethyl)-3,22-diisobutyl-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
614	(8S,12S,18aR,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide

615	(8S,12S,18aS,21R)-21-benzyl-12-isobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
616	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-16-(difluoromethoxy)-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
617	(4aR,7R,18S,22S)-7-benzyl-3,22-diisobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
618	(4aR,7R,18S,22S)-7-benzyl-N-(3,5-dimethoxyphenethyl)-22-isobutyl-3-isopropyl-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
619	(8S,12S,18aR,21R)-21-benzyl-12,17-diisobutyl-N-(3-methoxyphenethyl)-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
620	(8S,12S,18aR,21R)-21-benzyl-12,17-diisobutyl-4,11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
621	(8S,12S,18aS,21R)-21-benzyl-12,17-diisobutyl-4,11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-oxazolo[4',5':5,6]benzo[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
622	(9S,13S,19aR,22R)-22-benzyl-13,18-diisobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
623	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-3-isopropyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
624	(4aRS,7R,17S,21S)-7-benzyl-21-isobutyl-N-(3-methoxyphenethyl)-12,20-dimethyl-5,15,19,22-tetraoxo-1,2,4,4a,5,6,7,8,15,16,17,18,19,20,21,22-hexadecahydroisoxazolo[4',5':5,6]benzo[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-17-carboxamide
625	(8S,12S,18aR,21R)-21-benzyl-N-(3-(difluoromethoxy)phenethyl)-12-isobutyl-4,11-dimethyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,15,16,18,18a,19,20,21,22-hexadecahydro-[1,4]oxazino[3,4-f]oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-8-carboxamide
626	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-9-(3-phenylpropyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

627	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4': 6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
628	(8'R, 14'S, 18'S)-8'-benzyl-14'-isobutyl-N-(3-methoxyphenethyl)-2', 12', 15'-trimethyl-10', 13', 16', 20'-tetraoxo-7', 8', 9', 10', 13', 14', 15', 16', 17', 18', 19', 20'-dodecahydro-12'H-spiro[cyclopropane-1, 11'-oxazolo[4', 5': 5, 6]benzo[1, 2-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine]-18'-carboxamide
629	(8S, 12S, 18aR, 21R)-21-benzyl-12-isobutyl-3, 11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-15H-isoxazolo[4', 5': 5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
630	(8S, 12S, 18aR, 21R)-21-benzyl-12-(cyclopentylmethyl)-3, 11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-15H-isoxazolo[4', 5': 5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
631	(8S, 12S, 18aR, 21R)-21-benzyl-12-(cyclopentylmethyl)-3, 11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-15H-isoxazolo[4', 5': 5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
632	(8S, 12S, 18aR, 21R)-21-benzyl-12-isobutyl-4, 11-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-15H-oxazolo[4', 5': 5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
633	(1r, 3S, 3'S, 7'S, 13'R)-13'-benzyl-7'-isobutyl-3-methoxy-6', 9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1', 5', 8', 11'-tetraoxo-2', 3', 4', 5', 6', 7', 8', 9', 11', 12', 13', 14'-dodecahydro-1'H-spiro[cyclobutane-1, 10'-naphtho[1, 2-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine]-3'-carboxamide
634	(8S, 12S, 18aR, 21R)-21-benzyl-N-(2,6-difluorophenethyl)-12-isobutyl-3, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-15H-isoxazolo[4', 5': 5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
635	(8S, 12S, 18aR, 21R)-21-benzyl-N-(2,6-difluorophenethyl)-12-isobutyl-3, 11-dimethyl-6, 10, 13, 19-tetraoxo-6, 7, 8, 9, 10, 11, 12, 13, 16, 17, 18, 18a, 19, 20, 21, 22-hexadecahydro-15H-isoxazolo[4', 5': 5, 6]benzo[1, 2-p]pyrido[2, 1-f][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-8-carboxamide
636	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2,6-difluorophenethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1': 6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
637	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropyl-1, 2, 4-oxadiazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1': 6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
638	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-3-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1': 6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide

639	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
640	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
641	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropyl-1, 2, 4-oxadiazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
642	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
643	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
644	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
645	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropyl-1, 2, 4-oxadiazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 19, 19a, 20, 21, 22, 23-hexadecahydro-[1, 4]oxazino[3', 4':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
646	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropyl-1, 2, 4-oxadiazol-5-yl)ethyl)-12-ethyl-13-isobutyl-7, 11, 14, 20-tetraoxo-7, 8, 9, 10, 11, 12, 13, 14, 17, 18, 19, 19a, 20, 21, 22, 23-hexadecahydro-16H-pyrido[2', 1':6, 7][1]oxa[4, 7, 10, 14]tetraazacycloheptadecino[17, 16-c]quinoline-9-carboxamide
647	(3R, 9S, 13S)-3-benzyl-9-isobutyl-17-methoxy-N-(3-methoxyphenethyl)-7, 10-dimethyl-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[4, 3-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide
648	(3'R, 9'S, 13'S)-3'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-9'-isobutyl-17'-methoxy-7', 10'-dimethyl-5', 8', 11', 15'-tetraoxo-2', 3', 4', 5', 8', 9', 10', 11', 12', 13', 14', 15'-dodecahydro-7'H-spiro[cyclopropane-1, 6'-pyrido[4, 3-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine]-13'-carboxamide
649	(3'R, 9'S, 13'S)-3'-benzyl-N-(2-(5-cyclopropyl-1, 2, 4-oxadiazol-3-yl)ethyl)-9'-isobutyl-17'-methoxy-7', 10'-dimethyl-5', 8', 11', 15'-tetraoxo-2', 3', 4', 5', 8', 9', 10', 11', 12', 13', 14', 15'-dodecahydro-7'H-spiro[cyclopropane-1, 6'-pyrido[4, 3-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine]-13'-carboxamide
650	(3'R, 9'S, 13'S)-3'-benzyl-9'-isobutyl-17'-methoxy-N-(3-methoxyphenethyl)-7', 10'-dimethyl-5', 8', 11', 15'-tetraoxo-2', 3', 4', 5', 8', 9', 10', 11', 12', 13', 14', 15'-dodecahydro-7'H-spiro[cyclopropane-1, 6'-pyrido[4, 3-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine]-13'-carboxamide

651	(7S, 11S, 20R, 22aR)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-20-benzyl-14-fluoro-7-isobutyl-8-methyl-6,9,13,22-tetraoxo-1,3,4,6,7,8,9,10,11,12,13,19,20,21,22,22a-hexadecahydro-2H-benzo[p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-11-carboxamide
652	(7S, 11S, 17aRS, 20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-3-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:4',3'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
653	(8S, 12S, 18aR, 21R)-N-(4-(2H-1,2,3-triazol-2-yl)phenethyl)-21-benzyl-12-isobutyl-11-methyl-6,10,13,19-tetraoxo-6,7,8,9,10,11,12,13,16,17,18,18a,19,20,21,22-hexadecahydro-15H-[1,3]dioxolo[4',5':5,6]benzo[1,2-p]pyrido[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-4,4-d2-8-carboxamide
654	(3'S, 7'S, 13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-naphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-3'-carboxamide
655	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
656	(7S, 11S, 17aR, 20R)-20-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
657	(7S, 11S, 17aR, 20R)-20-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-11-isobutyl-4-(methoxy-d3)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
658	(7S, 11S, 17aR, 20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
659	(7S, 11S, 17aR, 20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-(methoxy-d3)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
660	(9S, 13S, 19aR, 22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-6-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
661	(3R, 6S, 9S, 13S)-3-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-6-((4,4-difluorocyclohexyl)methyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

662	(3R,6R,9S,13S)-3-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-6-((4,4-difluorocyclohexyl)methyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
663	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-16,16-difluoro-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
664	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-11-isobutyl-4-(methoxy-d3)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
665	(9S,13S,19aR,22R)-22-benzyl-N-(2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
666	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-11-isobutyl-4-(methoxy-d3)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
667	(7S,11S,17aS,20R)-20-benzyl-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-N-(2-(3-(trifluoromethyl)isoxazol-5-yl)ethyl)-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
668	(7'S,11'S,17a'R,20'R)-20'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11'-isobutyl-4'-methoxy-10'-methyl-5',9',12',18'-tetraoxo-5',6',7',8',9',10',11',12',14',15',17',17a',18',19',20',21'-hexadecahydrospiro[cyclopropane-1,16'-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-7'-carboxamide
669	(7'S,11'S,17a'S,20'R)-20'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11'-isobutyl-4'-methoxy-10'-methyl-5',9',12',18'-tetraoxo-5',6',7',8',9',10',11',12',14',15',17',17a',18',19',20',21'-hexadecahydrospiro[cyclopropane-1,16'-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-7'-carboxamide
670	(7S,11S,17aS,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-16-phenyl-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
671	(7S,11S,17aS,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-16-phenyl-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
672	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-16-phenyl-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide

673	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-16-phenyl-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
674	(9S,13S,19aS,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
675	(9S,13S,19aS,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
676	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
677	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-18-phenyl-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
678	(7S,11S,19aR,22R)-22-benzyl-11-isobutyl-4-methoxy-10-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,9,12,20-tetraoxo-5,6,7,8,9,10,11,12,19,19a,20,21,22,23-tetradecahydro-14H-pyrido[3',4':16,17][1]oxa[4,7,10,14]tetraazacycloheptadecino[7,6-b]isoquinoline-7-carboxamide
679	(7S,11S,19bR,22R)-22-benzyl-11-isobutyl-4-methoxy-10-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,9,12,20-tetraoxo-5,6,7,8,9,10,11,12,15,19b,20,21,22,23-tetradecahydro-14H-pyrido[3',4':16,17][1]oxa[4,7,10,14]tetraazacycloheptadecino[6,7-a]isoquinoline-7-carboxamide
680	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
681	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-6-phenyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
682	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-6-((4,4-difluorocyclohexyl)methyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
683	(7'S,11'S,17a'R,20'R)-20'-benzyl-11'-isobutyl-4'-methoxy-2',10'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5',9',12',18'-tetraoxo-5',6',7',8',9',10',11',12',14',15',17',17a',18',19',20',21'-hexadecahydrospiro[cyclopropane-1,16'-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-7'-carboxamide
684	(7'S,11'S,17a'S,20'R)-20'-benzyl-11'-isobutyl-4'-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-2',10'-dimethyl-5',9',12',18'-tetraoxo-5',6',7',8',9',10',11',12',14',15',17',17a',18',19',20',21'-

	hexadecahydrospiro[cyclopropane-1,16'-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-7'-carboxamide
685	(7S,11S,17aR,20R)-20-benzyl-N-(2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)-11-isobutyl-4-(methoxy-d3)-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
686	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
687	(3R,9S,13S)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-3-benzyl-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
688	(3R,9S,13S)-3-benzyl-N-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethyl)-9-isobutyl-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydrobenzo[p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
689	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
690	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
691	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
692	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
693	(3S,7S,10R,13R)-13-benzyl-10-(cyclopentylmethyl)-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
694	(3S,7S,10S,13R)-13-benzyl-10-(cyclopentylmethyl)-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
695	(3S,7S,10S,13R)-13-benzyl-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-10-(naphthalen-1-ylmethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide

696	(3S,7S,10R,13R)-13-benzyl-10-(cyclohexylmethyl)-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
697	(3S,7S,10R,13R)-13-benzyl-10-(cyclohexylmethyl)-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
698	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-10-(naphthalen-1-ylmethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
699	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
700	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(((S)-chroman-3-yl)methyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
701	(3S,7S,13R)-9-(2-cyclohexylethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6-methyl-1,5,8,11-tetraoxo-13-(pyridin-2-ylmethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
702	(3S,7S,13R)-13-benzyl-9-((2,3-dihydrobenzofuran-2-yl)methyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
703	(3S,7S,13R)-13-(benzo[b]thiophen-3-ylmethyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-9-(2-((S)-tetrahydro-2H-pyran-2-yl)ethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
704	(3S,7S,13R)-13-benzyl-9-(((S)-chroman-3-yl)methyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
705	(3S,7S,13R)-13-benzyl-9-(((R)-chroman-3-yl)methyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
706	(3S,7S,13R)-13-benzyl-9-(((R)-6,6-dimethyltetrahydro-2H-pyran-2-yl)methyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
707	(3S,7S,13R)-13-benzyl-9-(((S)-6,6-dimethyltetrahydro-2H-pyran-2-yl)methyl)-7-isobutyl-6-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide

708	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopentane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
709	(3S,7S,10R,13R)-13-benzyl-10-(cyclohexylmethyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
710	(3S,7S,10R,13R)-13-benzyl-10-cyclopentyl-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
711	(3'S,7'S,13'R)-13'-benzyl-3,3-difluoro-7'-isobutyl-6',9'-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
712	(3S,7S,13R)-N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-13-benzyl-9-(((R)-chroman-3-yl)methyl)-7-isobutyl-6-methyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
713	(3S,7S,10R,13R)-13-benzyl-10-((benzyloxy)methyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
714	(3S,7S,10R,13R)-13-benzyl-10-((benzyloxy)methyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
715	(3S,7S,10S,13R)-13-benzyl-10-((benzyloxy)methyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
716	(3S,7S,10S,13R)-13-benzyl-10-((benzyloxy)methyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
717	(3S,7S,10RS,13R)-13-benzyl-10-(tert-butoxymethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
718	(3S,7S,10RS,13R)-13-benzyl-10-(hydroxymethyl)-7-isobutyl-N-(3-methoxyphenethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
719	(3S,7S,10RS,13R)-13-benzyl-10-(tert-butoxymethyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide

720	(3S,7S,10RS,13R)-13-benzyl-10-(hydroxymethyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydronaphtho[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
721	(3S,7S,10R,13R)-13-benzyl-10-cyclopentyl-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
722	(3S,7S,10R,13R)-10,13-dibenzyl-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
723	(3S,7S,10S,13R)-10,13-dibenzyl-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
724	(3R,6RS,9S,13S)-3-benzyl-6-((benzyloxy)methyl)-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
725	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-21-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
726	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
727	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
728	(8R,14S,18S)-8-benzyl-12-(2-cyclohexylethyl)-N-(3-((RS)-1-hydroxyethyl)phenethyl)-14-isobutyl-2,15-dimethyl-10,13,16,20-tetraoxo-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
729	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(phenylsulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
730	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-3-((3-morpholinopropyl)sulfonyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

731	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-3-(methylsulfonyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
732	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-((3-(trifluoromethoxy)phenyl)sulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
733	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-3-((2-methoxyethyl)sulfonyl)-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
734	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-((tetrahydro-2H-pyran-4-yl)sulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
735	(4aR,7R,18S,22S)-7-benzyl-3-((2-(dimethylamino)ethyl)sulfonyl)-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
736	(4aR,7R,18S,22S)-7-benzyl-3-(benzylsulfonyl)-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
737	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-((2-oxo-2,3-dihydrobenzo[d]oxazol-5-yl)sulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
738	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-((quinolin-8-ylmethyl)sulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
739	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-3-((3-methoxyphenyl)sulfonyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
740	(4aR,7R,18S,22S)-7-benzyl-3-((2-fluoro-5-methoxyphenyl)sulfonyl)-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
741	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-3-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)sulfonyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

742	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(pyridin-3-ylsulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
743	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-3-((3-methoxypropyl)sulfonyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
744	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-3-((5-methoxypyridin-3-yl)sulfonyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
745	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-3-((2-morpholinoethyl)sulfonyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
746	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(((tetrahydro-2H-pyran-4-yl)methyl)sulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
747	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(pyridin-2-ylsulfonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
748	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-18-((4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-7-yl)sulfonyl)-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
749	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-18-((3-(trifluoromethoxy)phenyl)sulfonyl)-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
750	(4aR,7R,18S,22S)-3-acetyl-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
751	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-3-(3-methylbutanoyl)-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
752	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-3-(3-methoxypropanoyl)-21-methyl-5,16,20,23-tetraoxo-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide

753	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(pyrazine-2-carbonyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
754	methyl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate
755	ethyl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate
756	tetrahydro-2H-pyran-4-yl (4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxylate
757	tert-butyl (((4aR,7R,18S,22S)-7-benzyl-22-isobutyl-18-((3-methoxyphenethyl)carbamoyl)-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-3H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-yl)(oxo)(phenyl)-16-sulfaneylidene)carbamate
758	(4aR,7R,18S,22S)-7-benzyl-22-isobutyl-N-(3-methoxyphenethyl)-21-methyl-5,16,20,23-tetraoxo-3-(phenylsulfonimidoyl)-2,3,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydro-1H-naphtho[1,2-p]pyrazino[2,1-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
759	(4aR,7R,18S,22S)-7-benzyl-N-(3-cyanophenethyl)-22-isobutyl-21-methyl-5,16,20,23-tetraoxo-1,2,4,4a,5,6,7,8,16,17,18,19,20,21,22,23-hexadecahydronaphtho[1,2-p][1,4]oxazino[3,4-f][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
760	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-9-((3-methoxyphenethyl)carbamoyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline 2-oxide
761	(8'R,14'S,18'S)-8'-benzyl-14'-isobutyl-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-N-(2-(3-phenylisoxazol-5-yl)ethyl)-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide
762	(8'R,14'S,18'S)-8'-benzyl-14'-isobutyl-N-(2-(3-isopropylisoxazol-5-yl)ethyl)-2',12',15'-trimethyl-10',13',16',20'-tetraoxo-7',8',9',10',13',14',15',16',17',18',19',20'-dodecahydro-12'H-spiro[cyclopropane-1,11'-oxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine]-18'-carboxamide
763	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-benzyl-1,2,4-oxadiazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide

764	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-(cyclopropylmethyl)-1,2,4-oxadiazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
765	(3R,6R,9S,13S)-3-benzyl-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-9-isobutyl-16-methoxy-6,7,10-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
766	(7S,11S,17aR,20R)-20-benzyl-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
767	(7S,11S,17aR,20R)-20-benzyl-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
768	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-6,7,10-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
769	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
770	(9S,13S,19aS,22R)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
771	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,7,10-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
772	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,7,10,18-tetramethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
773	(3R,6R,9S,13S)-3-benzyl-6-ethyl-9-isobutyl-16-methoxy-7,10,18-trimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
774	(3R,6R,9S,13S)-3-benzyl-6-ethyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
775	(3R,6R,9S,13S)-3-benzyl-6-(2,2-difluoroethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

776	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
777	(9S,13S,19aS,22R)-22-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
778	(9S,13S,19aR,22R)-22-benzyl-N-(2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
779	(9S,13S,19aS,22R)-22-benzyl-N-(2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
780	(9S,13S,19aR,22R)-22-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
781	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
782	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-6-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
783	(3R,6R,9S,13S)-3-benzyl-6-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
784	(3R,6R,9S,13S)-3-benzyl-6-ethyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
785	(3R,6R,9S,13S)-3-benzyl-6-(2,2-difluoroethyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
786	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide

787	(3S,7S,10R,13R)-13-benzyl-N-(2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)-20-fluoro-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
788	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(3-methoxyphenethyl)-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydroimidazo[1',2':1,6]pyrido[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
789	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydroimidazo[1',2':1,6]pyrido[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
790	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydroimidazo[1',2':1,6]pyrido[2,3-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-3-carboxamide
791	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
792	(3R,6S,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
793	(9S,13S,19aS,22R)-22-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
794	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
795	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
796	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-5,12-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-9-carboxamide
797	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-20-fluoro-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide

798	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
799	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
800	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-20-fluoro-7-isobutyl-6,9,10-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
801	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-10-(2,2-difluoroethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
802	(3S,7S,10S,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-10-(2,2-difluoroethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
803	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-10-ethyl-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
804	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
805	(9S,13S,19aR,22R)-22-benzyl-N-(2-(2-cyclopropyl-2H-1,2,3-triazol-4-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
806	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
807	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
808	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide

809	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
810	(3S,7S,10S,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
811	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
812	(3S,7S,10S,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
813	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
814	(3S,7S,10S,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
815	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
816	(3S,7S,10S,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
817	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-20'-fluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
818	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide

819	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
820	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
821	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
822	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-2,12-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
823	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-13-isobutyl-5,12-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-9-carboxamide
824	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-6,9,10,20-tetramethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
825	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,10,20-tetramethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
826	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-7-isobutyl-6,9,10,20-tetramethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
827	(3S,7S,10R,13R)-13-benzyl-10-((3,3-difluoropyrrolidin-1-yl)methyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
828	(3R,6R,9S,13S)-3-benzyl-N-((S)-2-hydroxy-2-phenylethyl)-6,9-diisobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
829	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-5-fluoro-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide

830	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-N-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10']-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3'-carboxamide
831	(7S,11S,17aR,20R)-20-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2,2-difluoroethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
832	(7S,11S,17aR,20R)-N-(2-(2H-benzo[d][1,2,3]triazol-2-yl)ethyl)-20-benzyl-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
833	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
834	(7S,11S,17aR,20R)-20-benzyl-N-(2-(4-ethynyl-5-methyl-2H-1,2,3-triazol-2-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
835	(7S,11S,17aR,20R)-20-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
836	(7S,11S,17aR,20R)-20-benzyl-N-(2-(4-cyano-2H-1,2,3-triazol-2-yl)ethyl)-11-isobutyl-4-methoxy-2,10-dimethyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
837	(3S,7S,10R,13R)-13-benzyl-N-(2-(4-cyclopropyl-2H-1,2,3-triazol-2-yl)ethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
838	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-3,3,20'-trifluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10']-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3'-carboxamide
839	(3'S,7'S,13'R)-13'-benzyl-3,3,20'-trifluoro-7'-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10']-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3'-carboxamide
840	(3S,7S,10R,13R)-N-(2-(2H-benzo[d][1,2,3]triazol-2-yl)ethyl)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide

841	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-3,3,20'-trifluoro-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
842	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-N-((S)-2-hydroxy-2-phenylethyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
843	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(6-methoxypyridin-3-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
844	(3S,7S,10R,13R)-N-(2-([1,2,4]triazolo[1,5-a]pyrimidin-2-yl)ethyl)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
845	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(3-methoxypropyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
846	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-N-(3-(trifluoromethoxy)propyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
847	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(5-methoxypyridin-2-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
848	(3R,6R,9S,13S)-3-benzyl-N-((S)-2-hydroxy-2-phenylethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
849	(3R,6R,9S,13S)-3-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
850	(7S,11S,17aR,20R)-20-benzyl-N-(3-(difluoromethoxy)propyl)-11-isobutyl-4-methoxy-10-methyl-5,9,12,18-tetraoxo-5,6,7,8,9,10,11,12,15,16,17,17a,18,19,20,21-hexadecahydro-14H-dipyrido[2,1-f:3',4'-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide

851	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-10-(2-(3-methyl-1,2,4-oxadiazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
852	(9S,13S,19aR,22R)-22-benzyl-18-(5-fluoropyridin-2-yl)-13-isobutyl-12-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
853	(9S,13S,19aR,22R)-22-benzyl-18-(5-fluoropyridin-2-yl)-13-isobutyl-N-(3-methoxyphenethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrazino[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
854	(3R,6R,9S,13S)-3-benzyl-6-((4,4-difluorocyclohexyl)methyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
855	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-7,10-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,8,11,15-tetraoxo-6-(2-phenoxyethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
856	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-6-(2-phenoxyethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
857	(3R,6R,9S,13S)-3-benzyl-6-(cyclobutoxymethyl)-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
858	(3R,6R,9S,13S)-3-benzyl-6-(2-(cyclohexyloxy)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
859	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-6-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
860	(7S,11S,14R,17R)-17-benzyl-11-isobutyl-4-methoxy-N-(3-methoxyphenethyl)-2,10,13,14-tetramethyl-5,9,12,15-tetraoxo-5,6,7,8,9,10,11,12,13,14,15,16,17,18-tetradecahydropyrimido[5,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-7-carboxamide
861	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-6-((3-methoxyisoxazol-5-yl)methyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

862	(7S, 11S, 14R, 17R)-17-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-4-methoxy-2, 10, 13, 14-tetramethyl-5, 9, 12, 15-tetraoxo-5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18-tetradecahydropyrimido[5, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-7-carboxamide
863	(7S, 11S, 18aR, 21R)-21-benzyl-N-(2-(5-cyclopropyl-1, 2, 4-oxadiazol-3-yl)ethyl)-11-isobutyl-4-methoxy-10-methyl-5, 9, 12, 19-tetraoxo-5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 18a, 19, 20, 21, 22-octadecahydroazepino[2, 1-f]pyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-7-carboxamide
864	(3R, 6R, 9S, 13S)-3-benzyl-N-(2-(5-cyclopropyl-1, 2, 4-oxadiazol-3-yl)ethyl)-6-(2-(3-cyclopropyl-1, 2, 4-oxadiazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7, 10-dimethyl-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide
865	(3R, 6R, 9S, 13S)-3-benzyl-6-(tert-butyl)-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-7, 10, 18-trimethyl-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide
866	(3R, 6R, 9S, 13S)-3-benzyl-6-(tert-butyl)-9-isobutyl-16-methoxy-7, 10, 18-trimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide
867	(3R, 6R, 9S, 13S)-3-benzyl-N-(2-(5-cyclopropyl-1, 2, 4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-6-((3-(4-(2-methoxyethyl)phenyl)-1, 2, 4-oxadiazol-5-yl)methyl)-7, 10-dimethyl-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide
868	(3R, 6R, 9S, 13S)-3-benzyl-9-isobutyl-16-methoxy-6-((3-(4-(2-methoxyethyl)phenyl)-1, 2, 4-oxadiazol-5-yl)methyl)-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7, 10-dimethyl-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide
869	(7S, 11S, 17aR, 20R)-20-benzyl-11-isobutyl-2, 4-dimethoxy-10-methyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5, 9, 12, 18-tetraoxo-5, 6, 7, 8, 9, 10, 11, 12, 15, 16, 17, 17a, 18, 19, 20, 21-hexadecahydro-14H-dipyrido[2, 1-f:3', 4'-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-7-carboxamide
870	(7S, 11S, 17aR, 20R)-20-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-11-isobutyl-2, 4-dimethoxy-10-methyl-5, 9, 12, 18-tetraoxo-5, 6, 7, 8, 9, 10, 11, 12, 15, 16, 17, 17a, 18, 19, 20, 21-hexadecahydro-14H-dipyrido[2, 1-f:3', 4'-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-7-carboxamide
871	(3R, 6R, 9S, 13S)-3-benzyl-N-(2-(4-cyclopropyl-2H-1, 2, 3-triazol-2-yl)ethyl)-9-isobutyl-16-methoxy-6-((3-(4-(2-methoxyethyl)phenyl)-1, 2, 4-oxadiazol-5-yl)methyl)-7, 10-dimethyl-5, 8, 11, 15-tetraoxo-2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15-tetradecahydropyrido[3, 4-p][1]oxa[4, 7, 10, 14]tetraazacycloheptadecine-13-carboxamide

872	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline]-3'-carboxamide
873	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-7,10,18-trimethyl-6-neopentyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
874	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-7,10,18-trimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-5,8,11,15-tetraoxo-6-phenethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
875	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(3-methoxyphenethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-phenethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
876	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-7,10,18-trimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-6-neopentyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
877	(3R,6R,9S,13S)-3-benzyl-6-(2-ethoxyethyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
878	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-6-neopentyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
879	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-10-((3-methoxyisoxazol-5-yl)methyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
880	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-10-((3-methoxyisoxazol-5-yl)methyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
881	(3R,6R,9S,13S)-3-benzyl-6-(2-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)ethyl)-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
882	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-6-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

883	(3R,6R,9S,13S)-3-benzyl-6-(2-(3-cyclopentyl-1,2,4-oxadiazol-5-yl)ethyl)-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-9-isobutyl-16-methoxy-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
884	(3R,6R,9S,13S)-3-benzyl-6-(2-(3-cyclopentyl-1,2,4-oxadiazol-5-yl)ethyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
885	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-10-((4-(5-fluoropyridin-2-yl)-1H-1,2,3-triazol-1-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
886	(3S,7S,10R,13R)-13-benzyl-10-((3-(tert-butyl)isoxazol-5-yl)methyl)-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
887	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-20-fluoro-10-(2-(3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)ethyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-3-carboxamide
888	(9S,13S,19aR,22R)-22-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-13-isobutyl-2,12-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
889	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
890	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
891	(3S,7S,10R,13R)-13-benzyl-N-((S)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-hydroxyethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
892	(3S,7S,10R,13R)-13-benzyl-N-((R)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-hydroxyethyl)-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide

893	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-10-(2,2-difluoroethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
894	(3S,7S,10R,13R)-13-benzyl-10-(2-ethoxyethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
895	(3S,7S,10R,13R)-13-benzyl-10-(2-ethoxyethyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
896	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-10-(2-ethoxyethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
897	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
898	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
899	(9S,13S,19aR,22S)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
900	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-7'-isobutyl-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
901	(3'S,7'S,13'R)-13'-benzyl-7'-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
902	(3R,6R,9S,13S)-3-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
903	(3R,6R,9S,13S)-N-(2-(2H-benzo[d][1,2,3]triazol-2-yl)ethyl)-3-benzyl-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

904	(3'S,7'S,13'R)-N-(2-(2H-benzo[d][1,2,3]triazol-2-yl)ethyl)-13'-benzyl-7'-isobutyl-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
905	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
906	(3S,7S,10R,13R)-13-benzyl-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
907	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
908	(3S,7S,10R,13R)-N-(2-([1,2,4]triazolo[1,5-a]pyrimidin-2-yl)ethyl)-13-benzyl-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
909	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
910	(3R,6R,9S,13S)-3-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-6-(2-ethoxyethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
911	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
912	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
913	(3S,7S,10R,13R)-13-benzyl-10-(2-ethoxyethyl)-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
914	(3S,7S,10R,13R)-13-benzyl-10-(2-ethoxyethyl)-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide

915	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-10-(2-ethoxyethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
916	(3S,7S,10R,13R)-13-benzyl-20-fluoro-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
917	(3S,7S,10R,13R)-13-benzyl-10-((3-(5-fluoropyridin-2-yl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
918	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
919	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
920	(9S,13S,19aR,22R)-22-benzyl-13-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-2,12-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
921	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-10-((3-(difluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
922	(3'S,7'S,13'R)-13'-benzyl-3,3,20'-trifluoro-7'-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
923	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-7-isobutyl-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
924	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
925	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-N-(3-(trifluoromethoxy)propyl)-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-

	1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
926	(1r,3S,3'S,7'S,13'R)-13'-benzyl-20'-fluoro-7'-isobutyl-3-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
927	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
928	(9S,13S,19aS,22R)-22-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-13-isobutyl-2,12-dimethyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
929	(3S,7S,10R,13R)-13-benzyl-10-(2-ethoxyethyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
930	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-13-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline-9-carboxamide
931	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
932	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
933	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-10-(2,2-difluoroethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
934	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
935	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-7-isobutyl-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
936	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-7-isobutyl-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide

937	(3S,7S,10R,13R)-N-(2-(2H-benzo[d][1,2,3]triazol-2-yl)ethyl)-13-benzyl-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
938	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
939	(3S,7S,10S,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
940	(3S,7S,10S,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
941	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
942	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-(2,2,2-trifluoroethyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
943	(3R,6R,9S,13S)-3-benzyl-N-((R)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-hydroxyethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
944	(3S,7S,10R,13R)-13-benzyl-N-(3-(difluoromethoxy)propyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
945	(3R,6R,9S,13S)-3-benzyl-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
946	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
947	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide

948	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
949	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-7,10-dimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
950	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
951	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
952	(3'S,7'S,13'R)-13'-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-3,3-difluoro-7'-isobutyl-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
953	(3'S,7'S,13'R)-13'-benzyl-3,3-difluoro-7'-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
954	(3'S,7'S,13'R)-13'-benzyl-3,3-difluoro-7'-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
955	(3'S,7'S,13'R)-13'-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-3,3-difluoro-7'-isobutyl-6',9',20'-trimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline]-3'-carboxamide
956	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropylisoxazol-5-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
957	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
958	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropylisoxazol-3-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide

959	(3S,7S,10R,13R)-13-benzyl-N-(2-(5-cyclopropyl-2H-tetrazol-2-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
960	(3S,7S,10R,13R)-13-benzyl-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
961	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-6-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
962	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-N-(2-(1-(2-methoxyethyl)-1H-pyrazol-4-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
963	(3'S,7'S,13'R)-13'-benzyl-20'-fluoro-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclopropane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
964	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
965	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-6,9-dimethyl-N-(2-(3-methylisoxazol-5-yl)ethyl)-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
966	(3S,7S,10R,13R)-13-benzyl-N-((R)-2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-hydroxyethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
967	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-20-fluoro-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
968	(3R,6R,9S,13S)-3-benzyl-6-(2,2-difluoroethyl)-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-9-isobutyl-16-methoxy-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

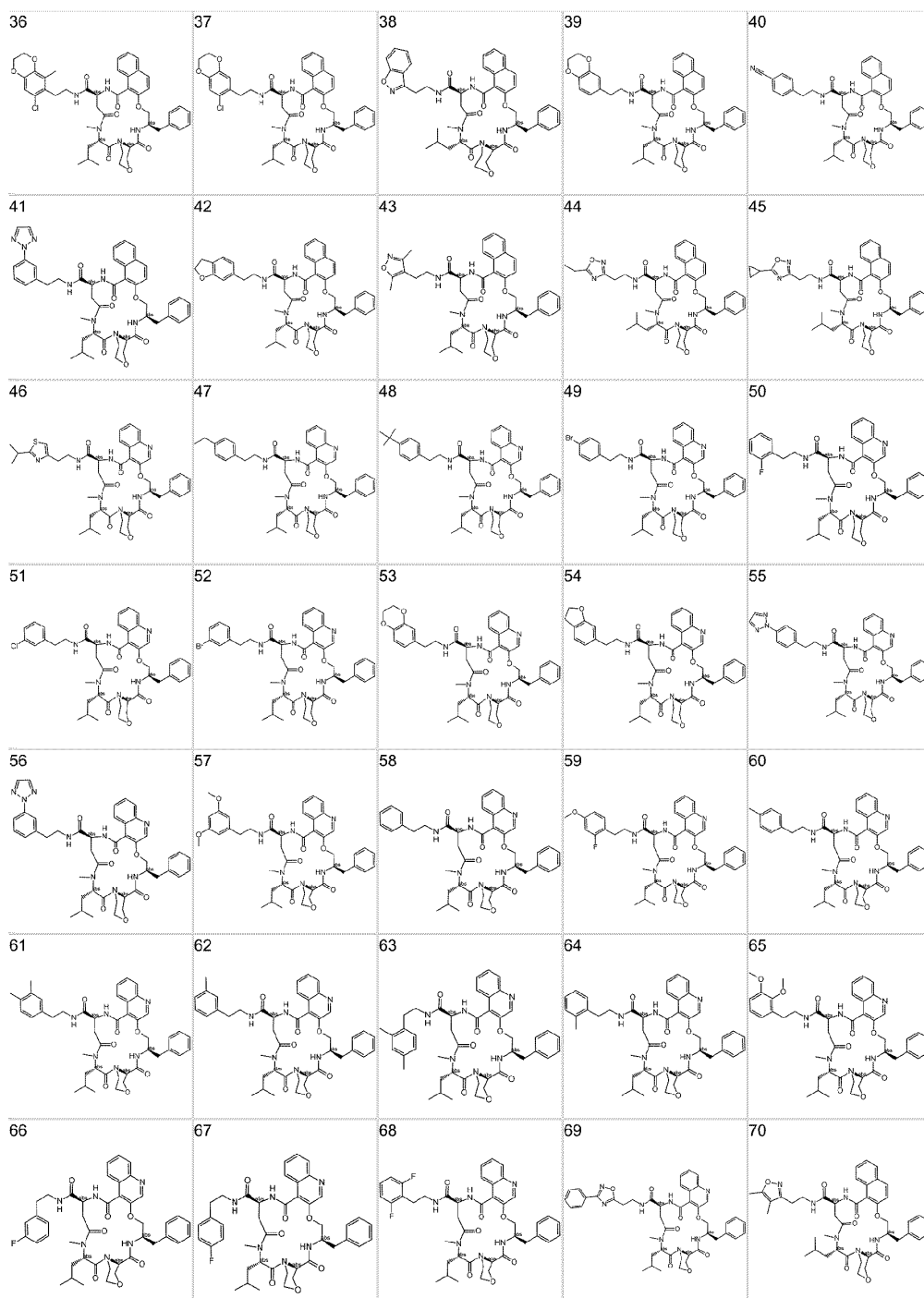
969	(3'S,7'S,13'R)-13'-benzyl-3,3,20'-trifluoro-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-7'-isobutyl-6',9'-dimethyl-1',5',8',11'-tetraoxo-2',3',4',5',6',7',8',9',11',12',13',14'-dodecahydro-1'H-spiro[cyclobutane-1,10'-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline]-3'-carboxamide
970	(3S,7S,10R,13R)-13-benzyl-10-(2,2-difluoroethyl)-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-7-isobutyl-6,9,20-trimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]isoquinoline-3-carboxamide
971	(3S,7S,10R,13R)-13-benzyl-10-((5-(tert-butyl)-1,2,4-oxadiazol-3-yl)methyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
972	(3S,7S,10R,13R)-13-benzyl-10-((5-(tert-butyl)-1,2,4-oxadiazol-3-yl)methyl)-20-fluoro-7-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
973	(9S,13S,19aR,22R)-22-benzyl-5-fluoro-N-(2-(4-fluoro-3-methoxyisoxazol-5-yl)ethyl)-13-isobutyl-12-methyl-7,11,14,20-tetraoxo-7,8,9,10,11,12,13,14,17,18,19,19a,20,21,22,23-hexadecahydro-16H-pyrido[2',1':6,7][1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-9-carboxamide
974	(8R,11RS,14S,18S)-8-benzyl-14-isobutyl-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-2,12,15-trimethyl-10,13,16,20-tetraoxo-11-(2,2,2-trifluoroethyl)-7,8,9,10,11,12,13,14,15,16,17,18,19,20-tetradecahydrooxazolo[4',5':5,6]benzo[1,2-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-18-carboxamide
975	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-N-(2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-(2,2,2-trifluoroethyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
976	(3S,7S,10R,13R)-13-benzyl-N-(2-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)ethyl)-10-(2-ethoxyethyl)-20-fluoro-7-isobutyl-6,9-dimethyl-1,5,8,11-tetraoxo-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline-3-carboxamide
977	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-6-(2-((5-methylpyrazin-2-yl)oxy)ethyl)-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
978	(3R,6R,9S,13S)-3-benzyl-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-6-(2-((2-methoxypyridin-4-yl)oxy)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
979	(3R,6R,9S,13S)-3-benzyl-6-(cyclopropylmethyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide

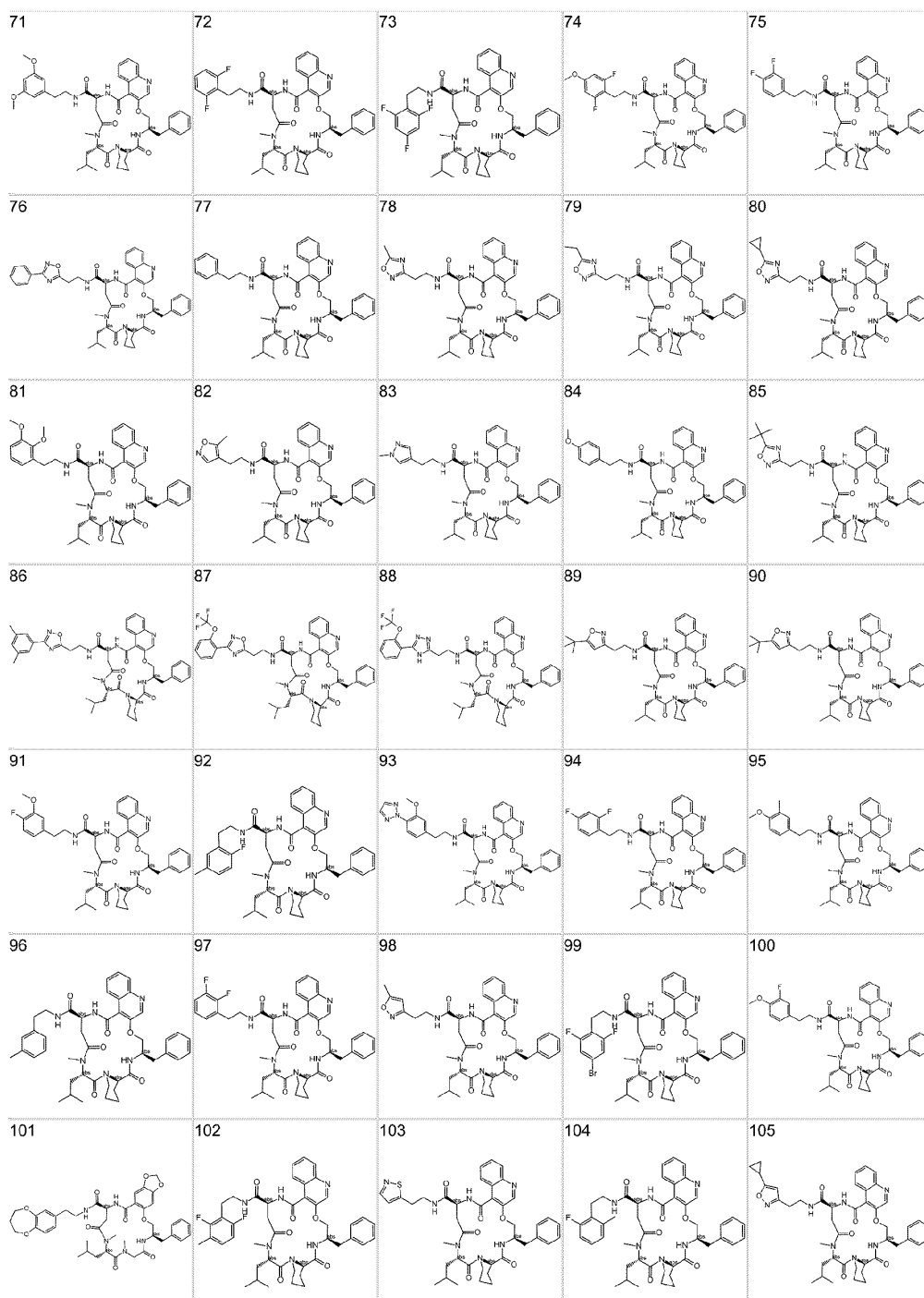
980	(3R,6R,9S,13S)-3-benzyl-6-(cyclobutylmethyl)-9-isobutyl-16-methoxy-N-(2-(3-methoxyisoxazol-5-yl)ethyl)-7,10,18-trimethyl-5,8,11,15-tetraoxo-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydropyrido[3,4-p][1]oxa[4,7,10,14]tetraazacycloheptadecine-13-carboxamide
981	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-3-((2-(3-methoxyisoxazol-5-yl)ethyl)carbamoyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[17,16-c]quinoline 17-oxide
982	(3S,7S,10R,13R)-13-benzyl-7-isobutyl-3-((2-(3-methoxyisoxazol-5-yl)ethyl)carbamoyl)-6,9,17-trimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline 18-oxide
983	(3S,7S,10R,13R)-13-benzyl-20-fluoro-7-isobutyl-3-((2-(3-methoxy-1,2,4-oxadiazol-5-yl)ethyl)carbamoyl)-6,9-dimethyl-1,5,8,11-tetraoxo-10-((3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)methyl)-1,2,3,4,5,6,7,8,9,10,11,12,13,14-tetradecahydro-[1]oxa[4,7,10,14]tetraazacycloheptadecino[16,17-f]quinoline 18-oxide

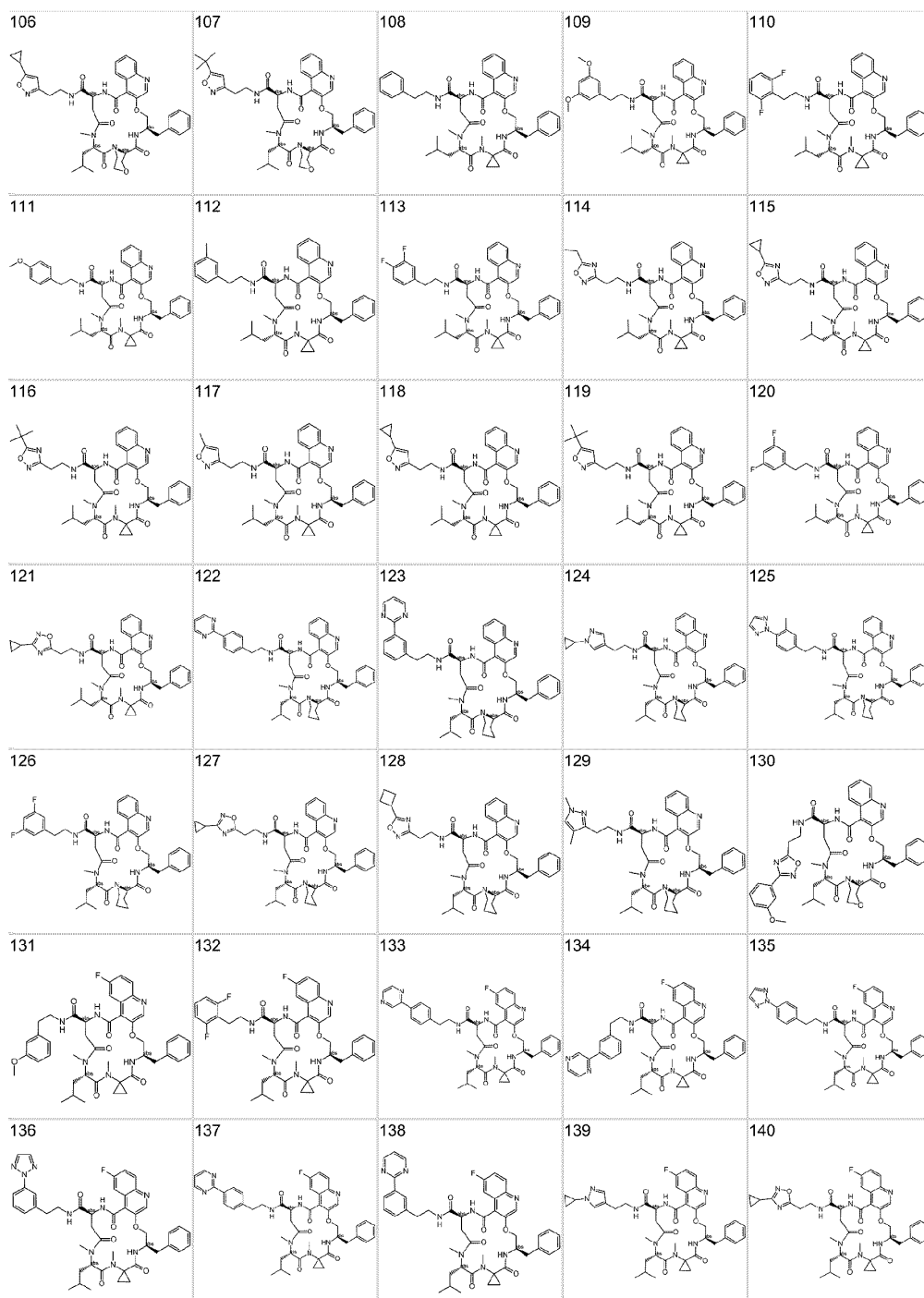
Table 3: Structures of compounds of Example 1 to 764

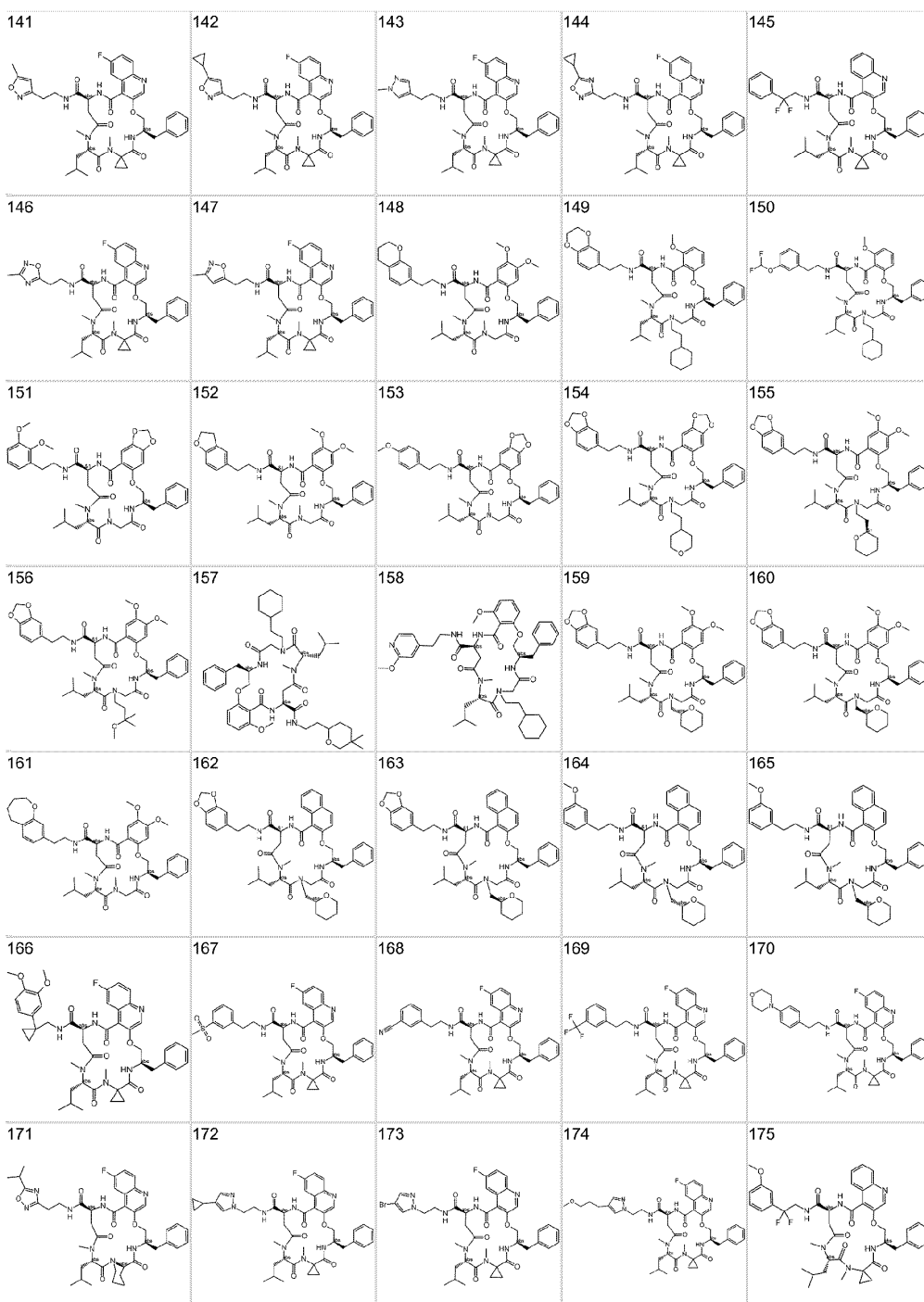
1	2	3	4	5
6	7	8	9	10
11	12	13	14	15
16	17	18	19	20
21	22	23	24	25
26	27	28	29	30
31	32	33	34	35

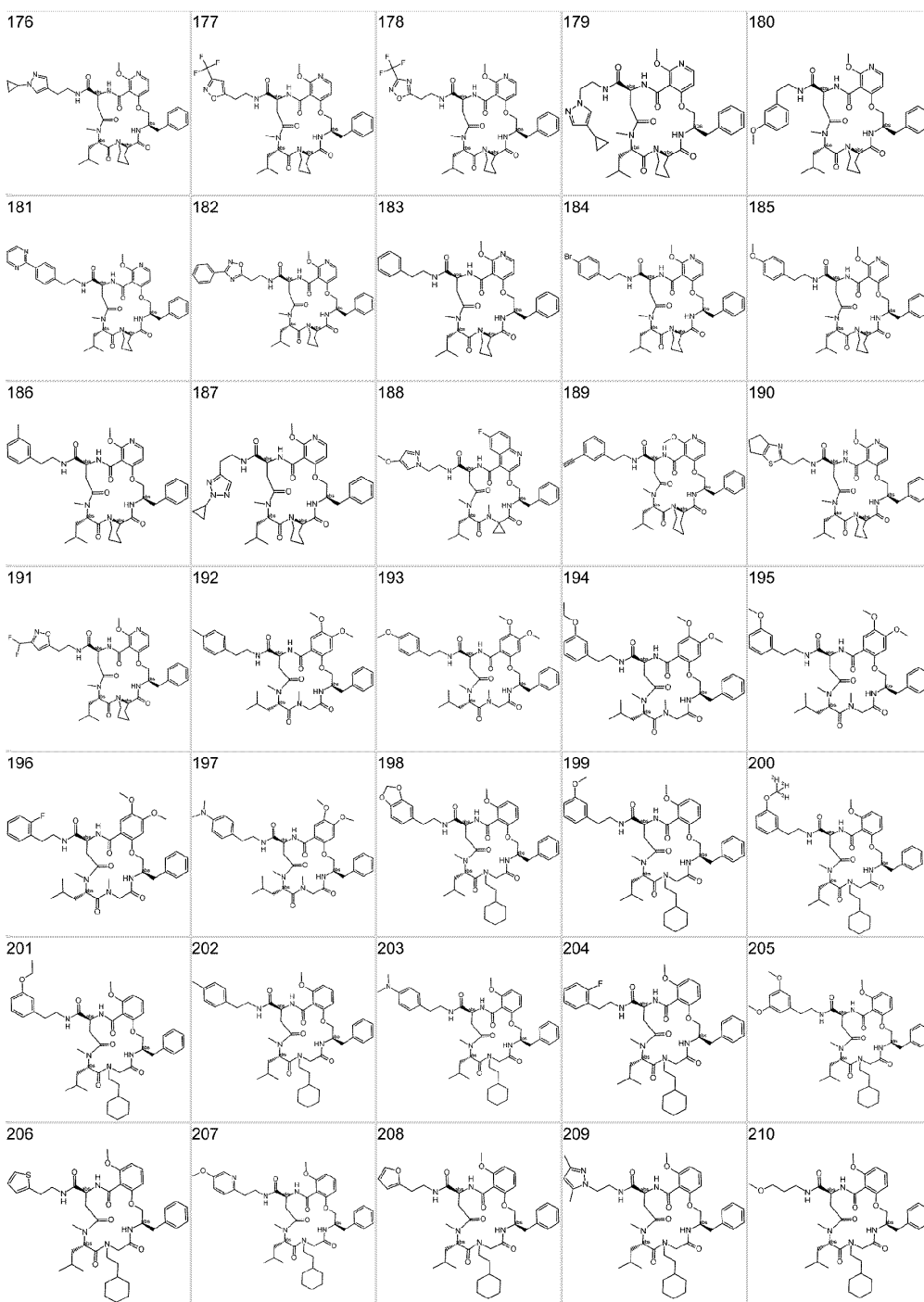
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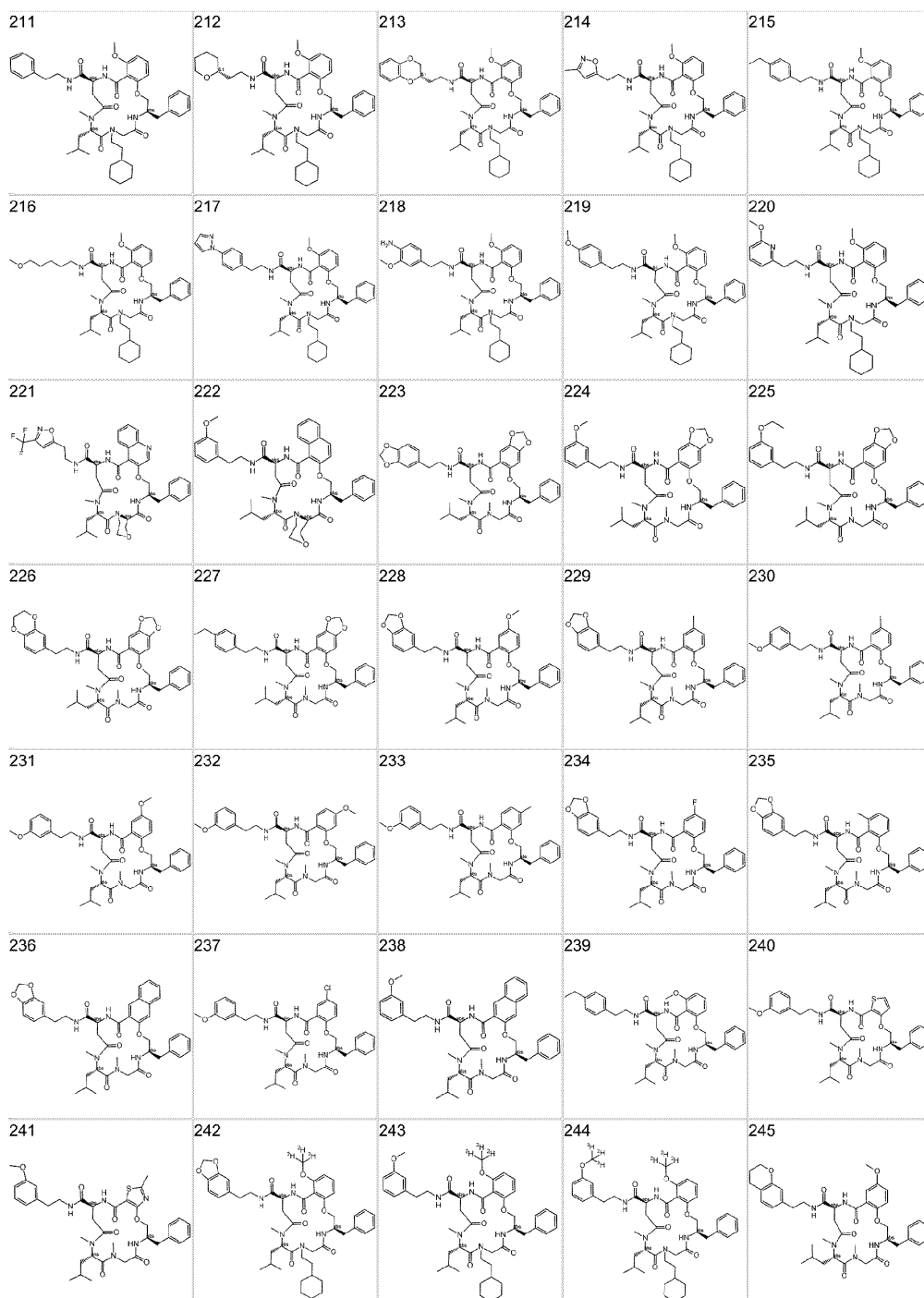


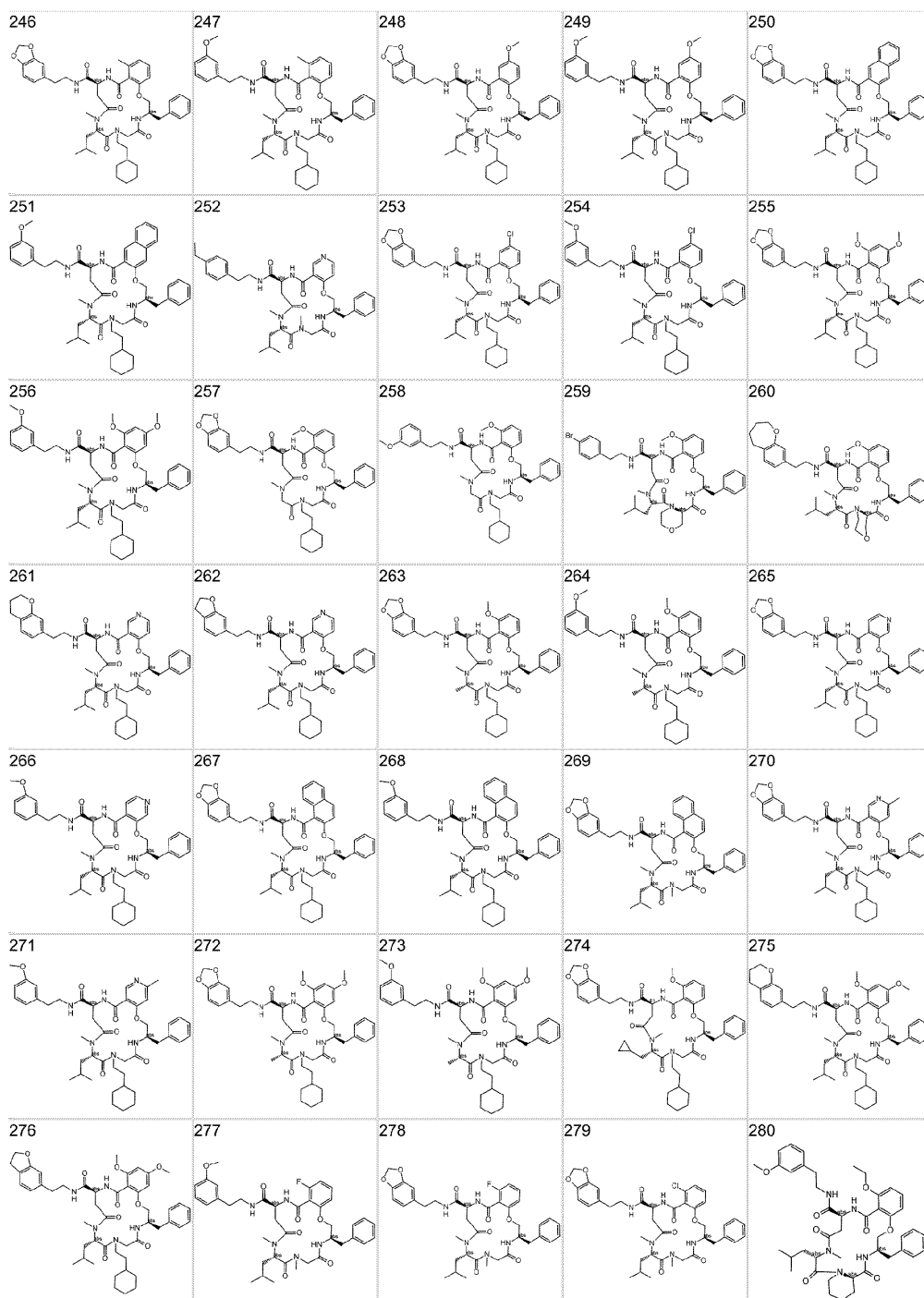


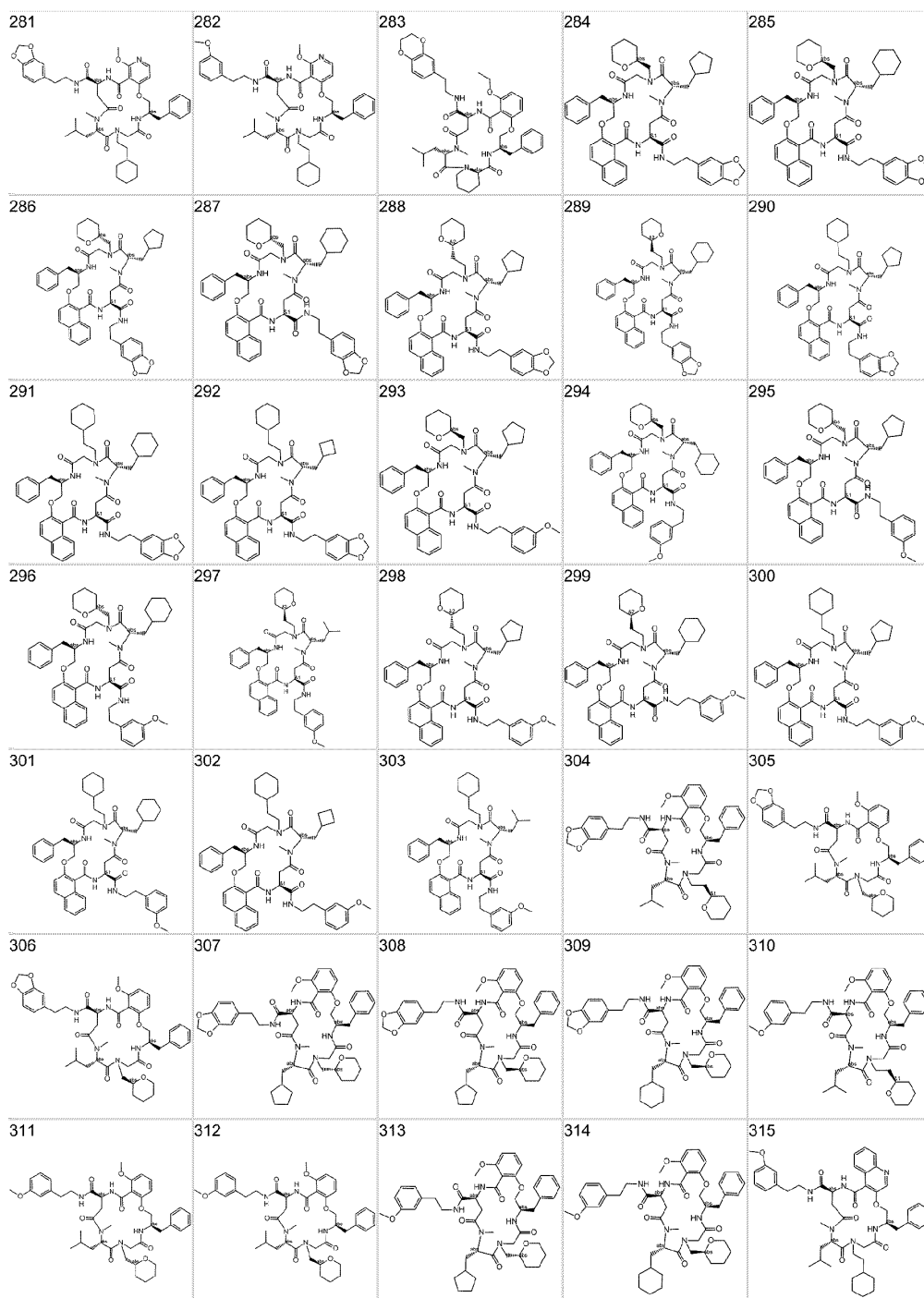




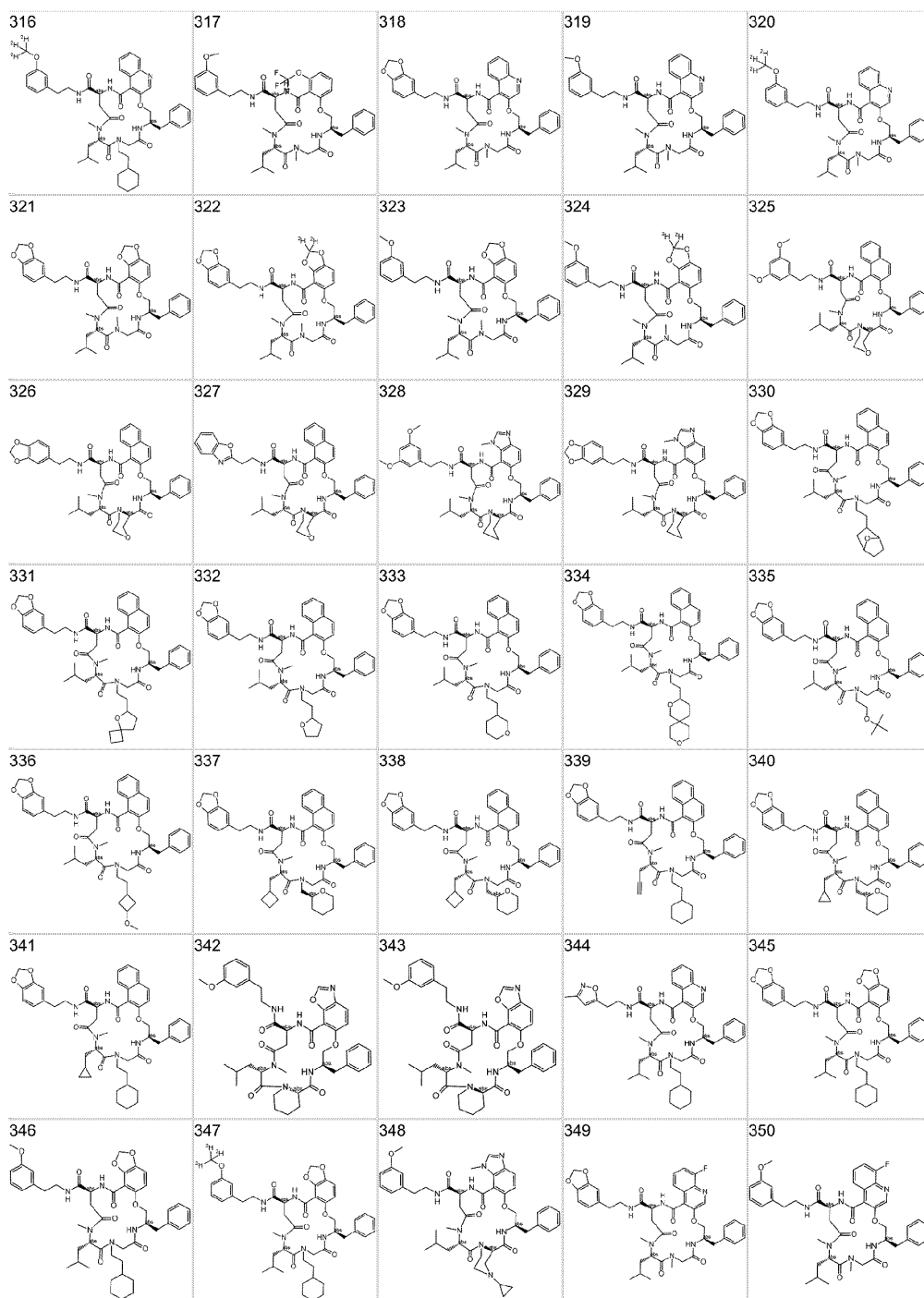
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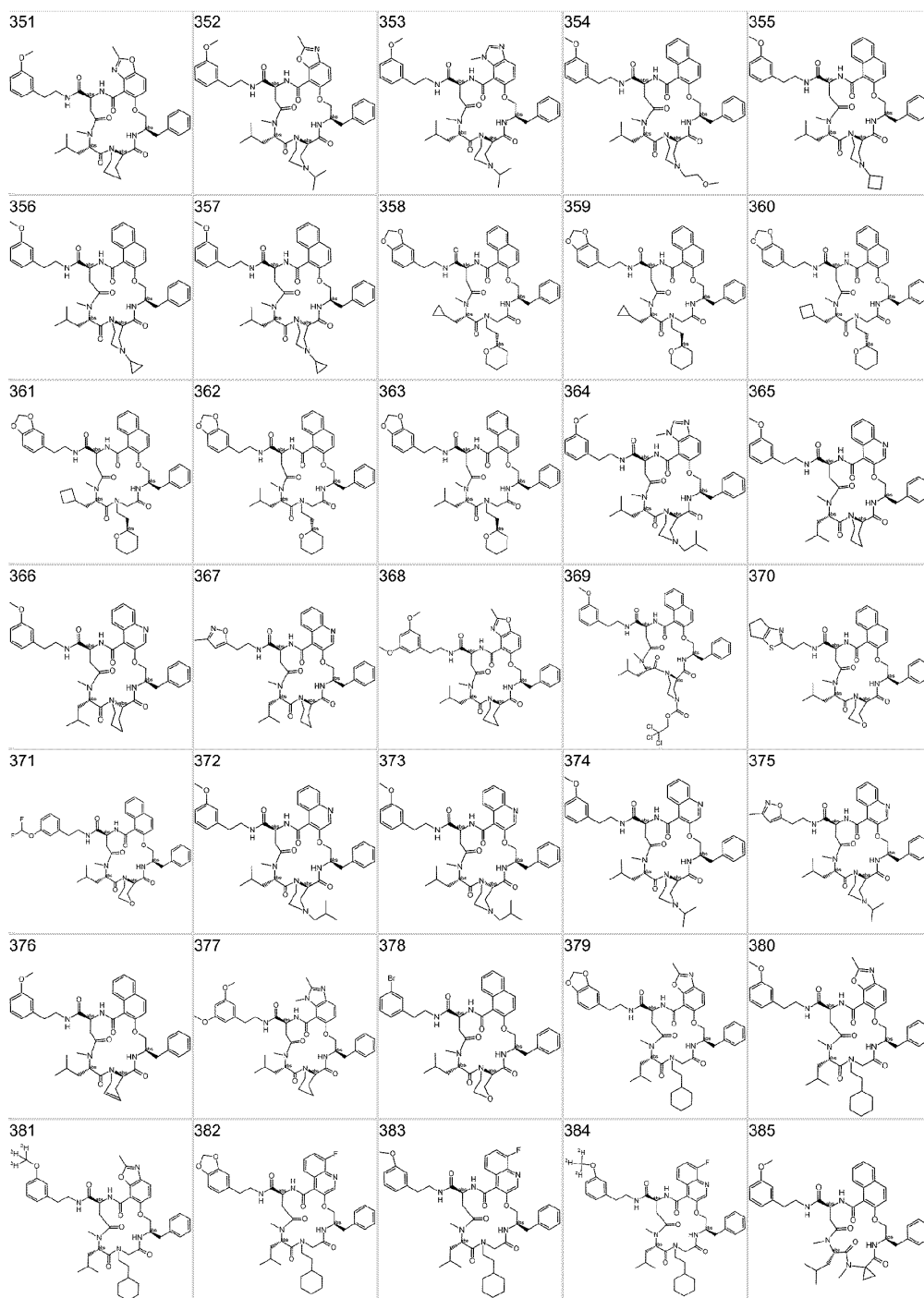




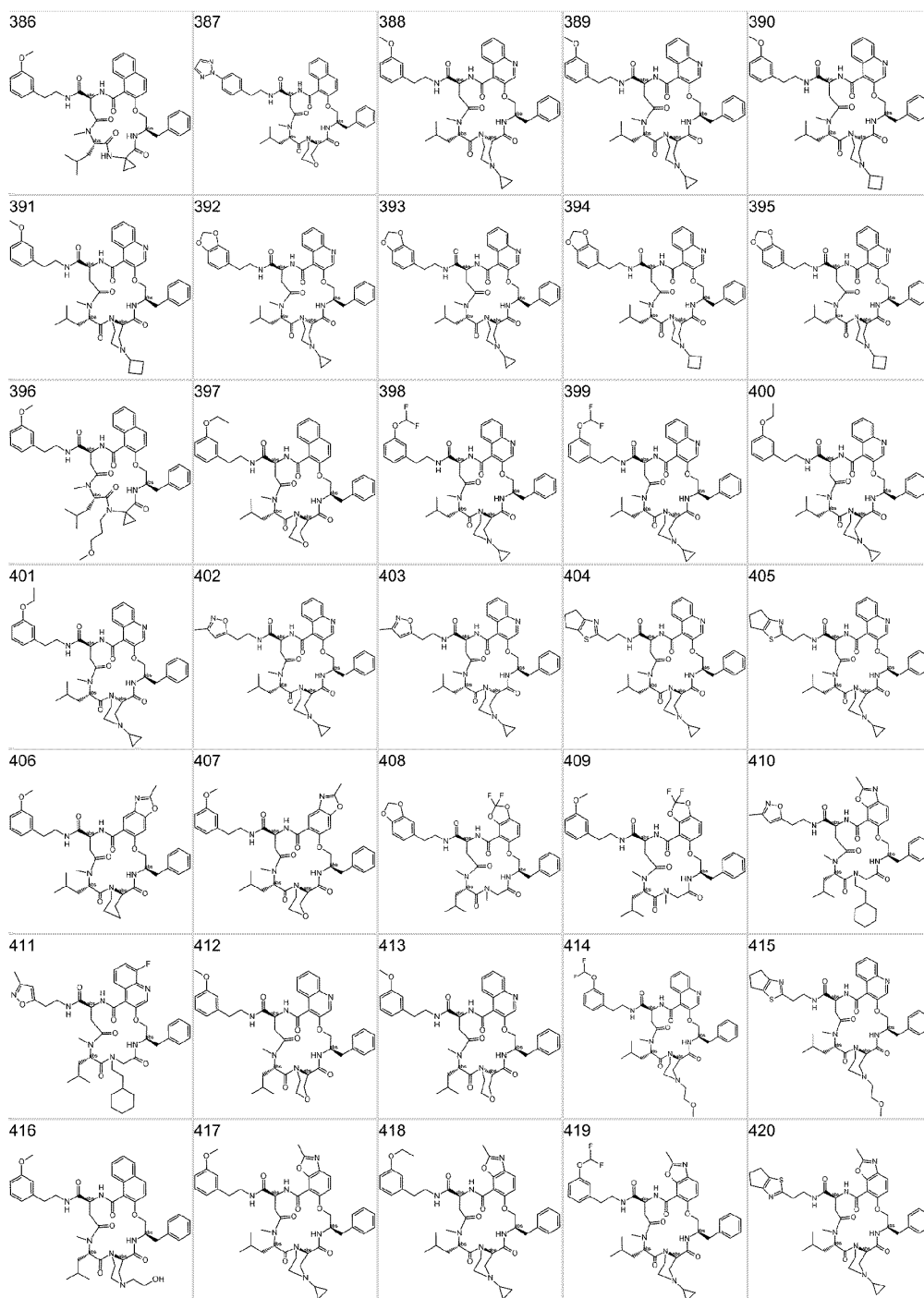


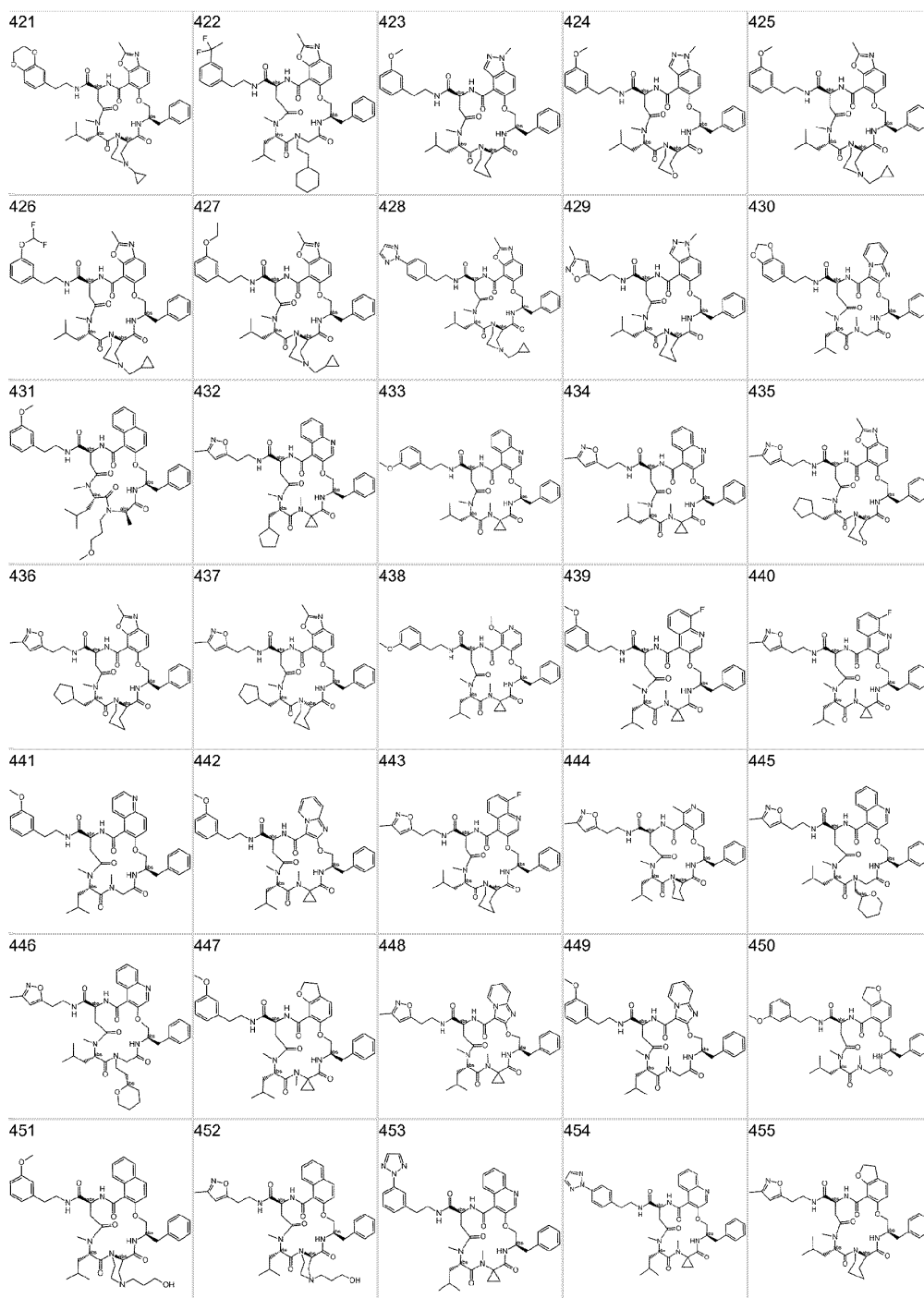
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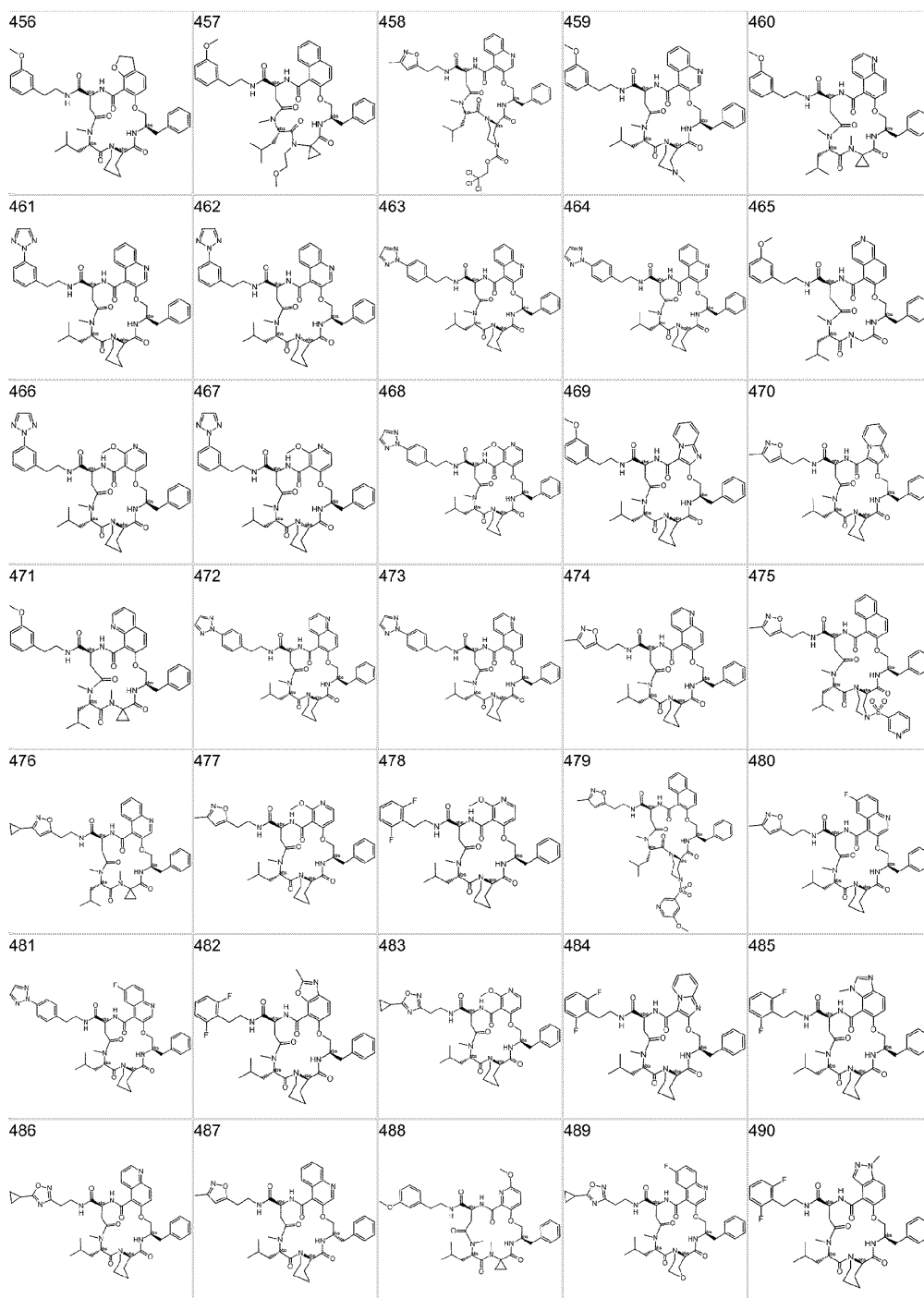


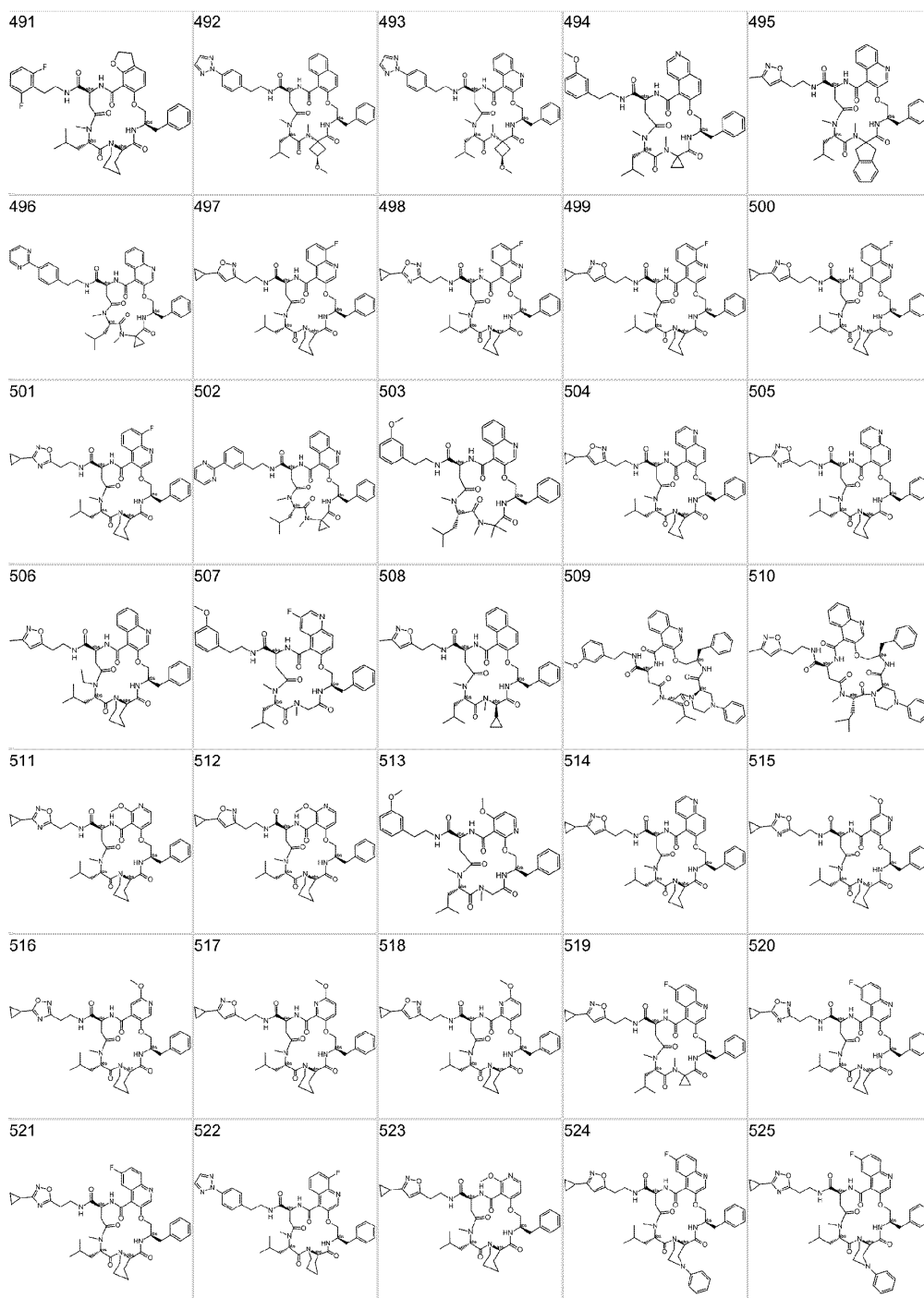


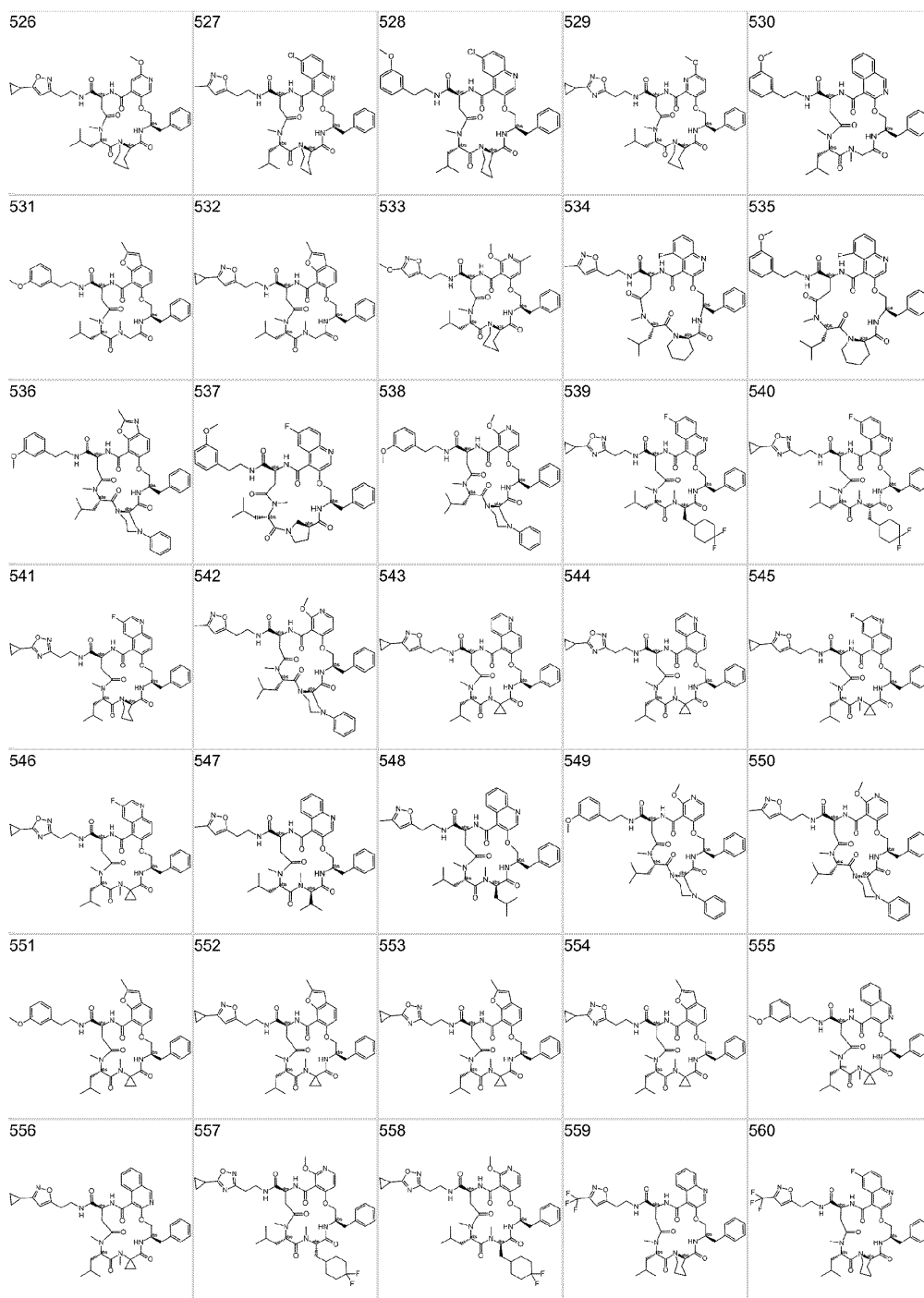
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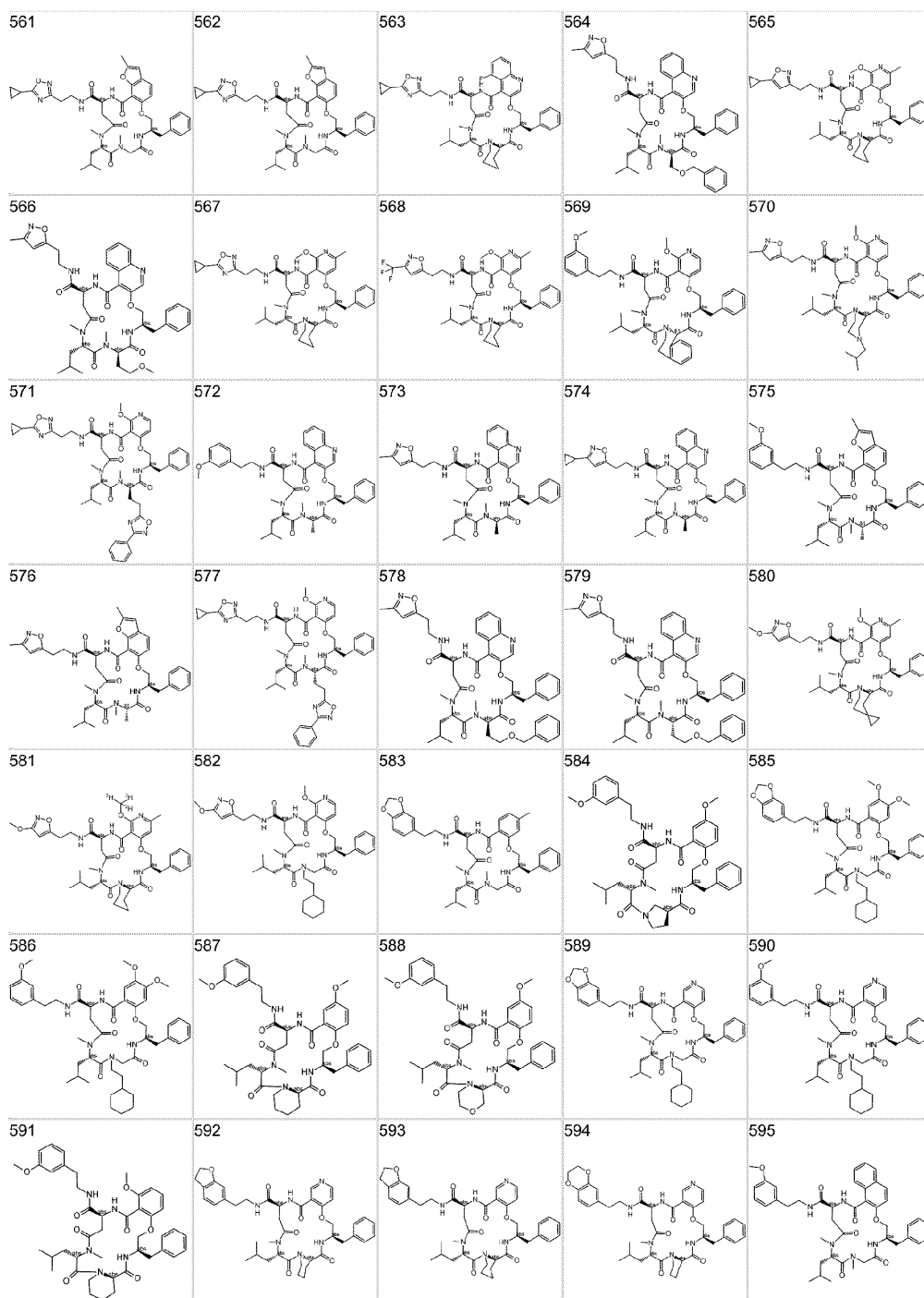


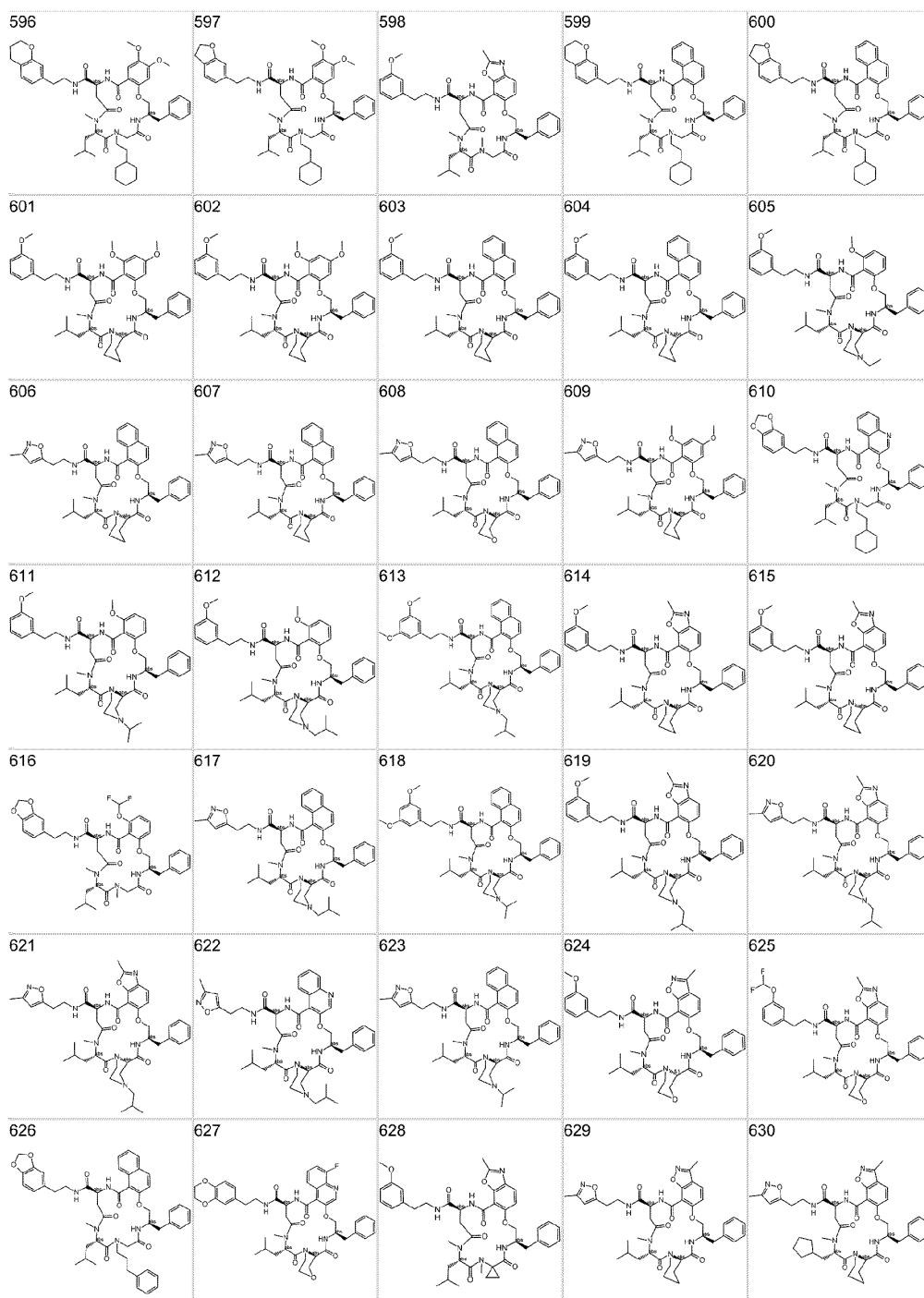


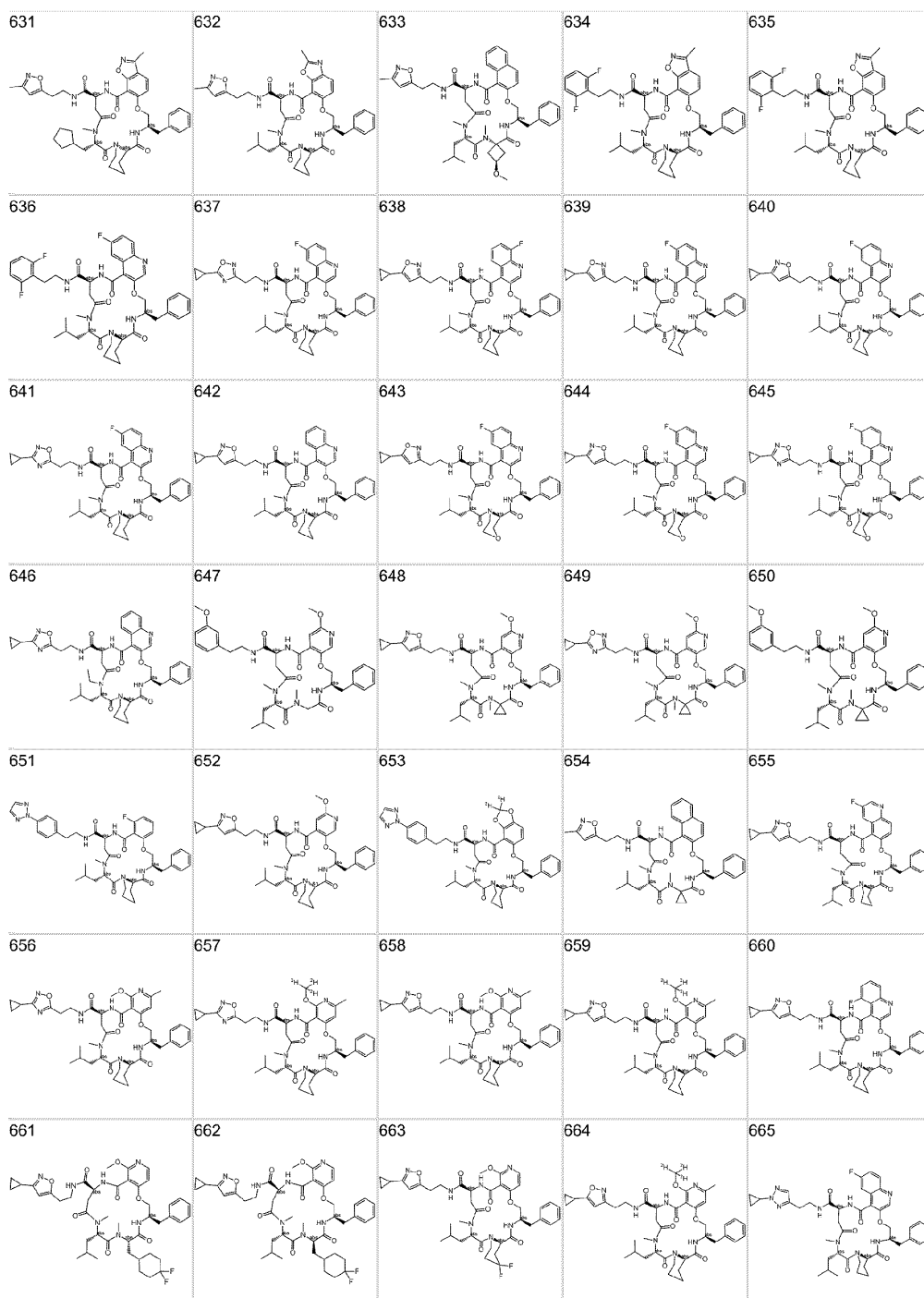


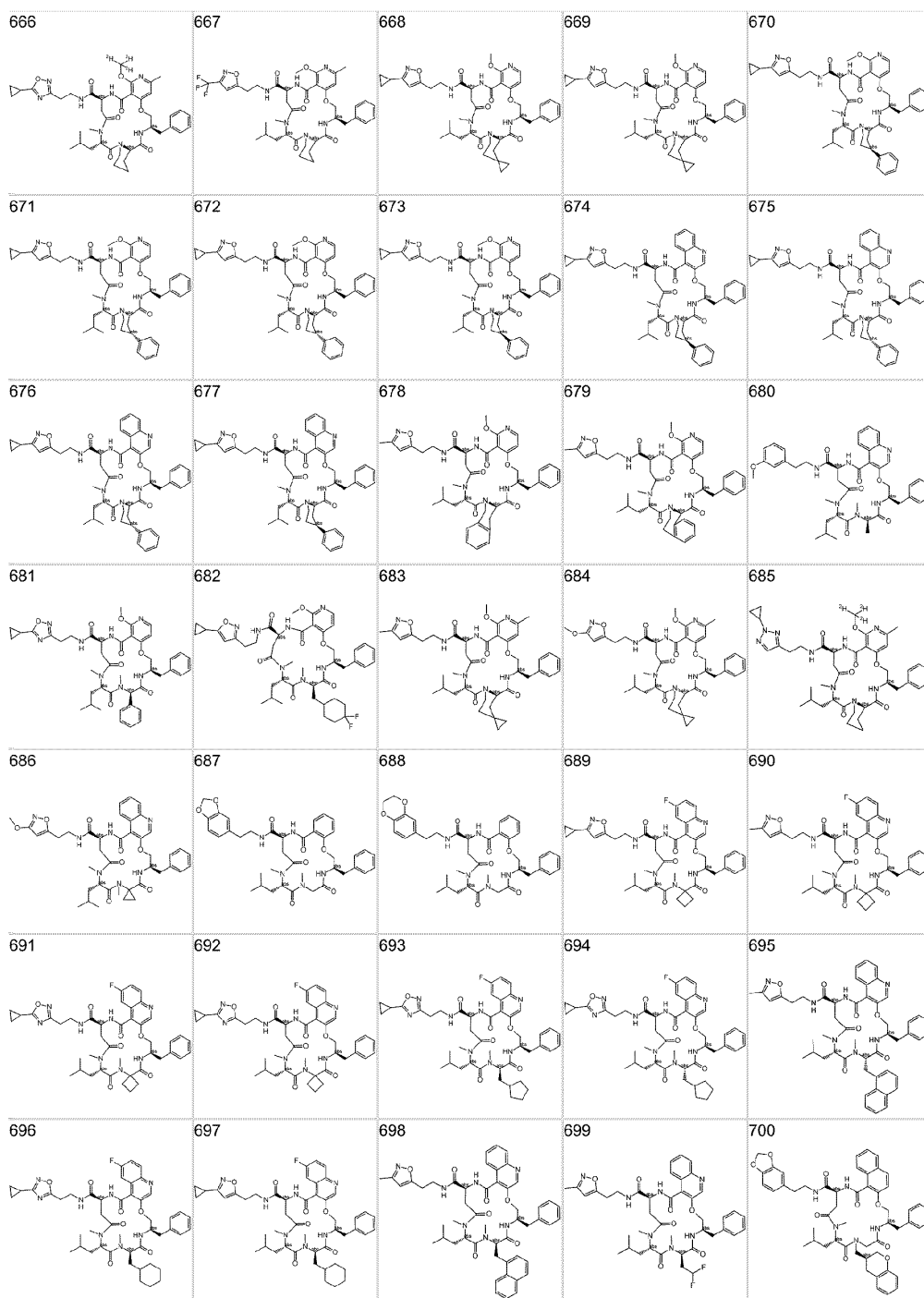


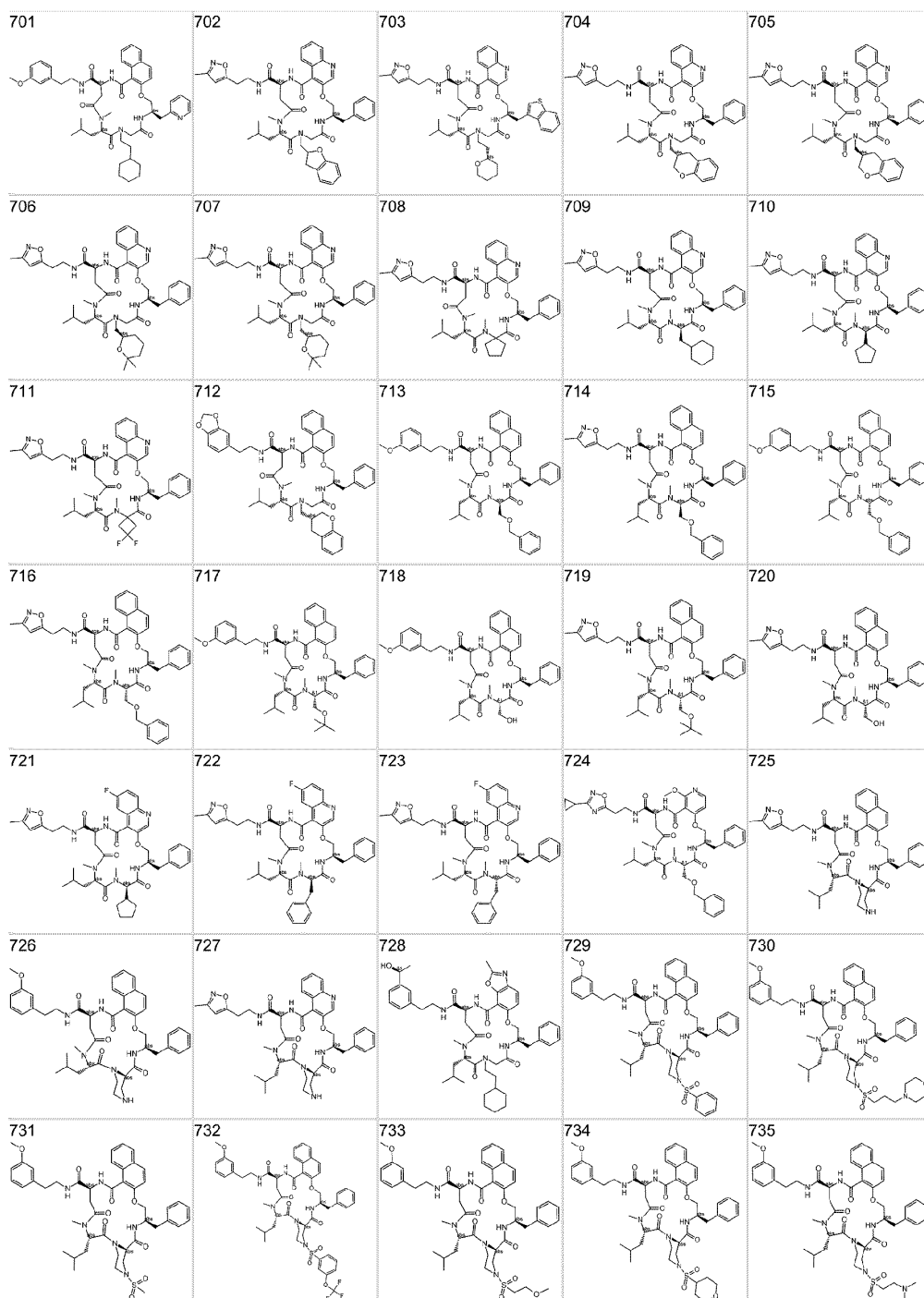












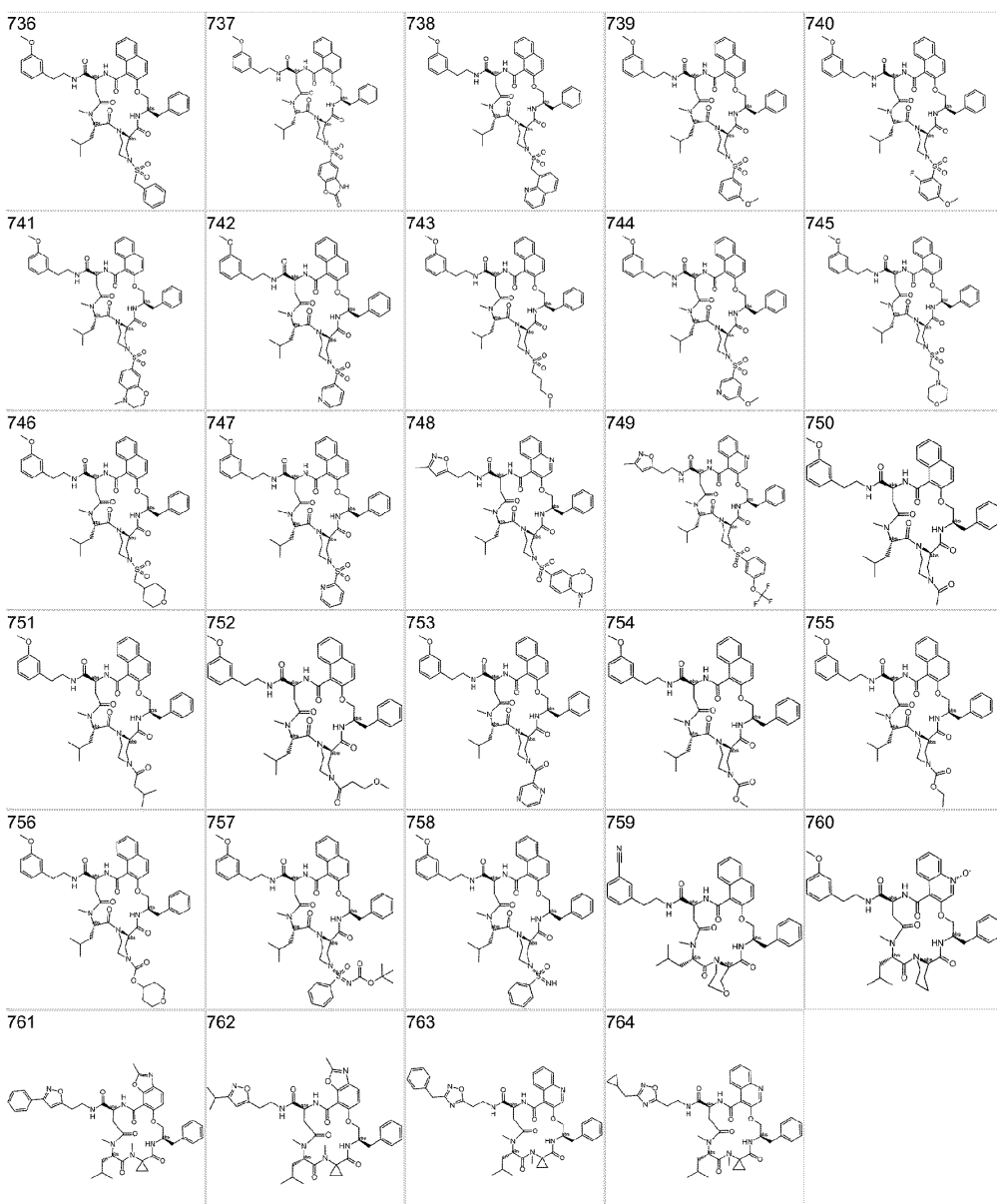


Table 4: Structures of compounds of Example 765 to 829

765	766	767	768	769
770	771	772	773	774
775	776	777	778	779
780	781	782	783	784
785	786	787	788	789
790	791	792	793	794
795	796	797	798	799

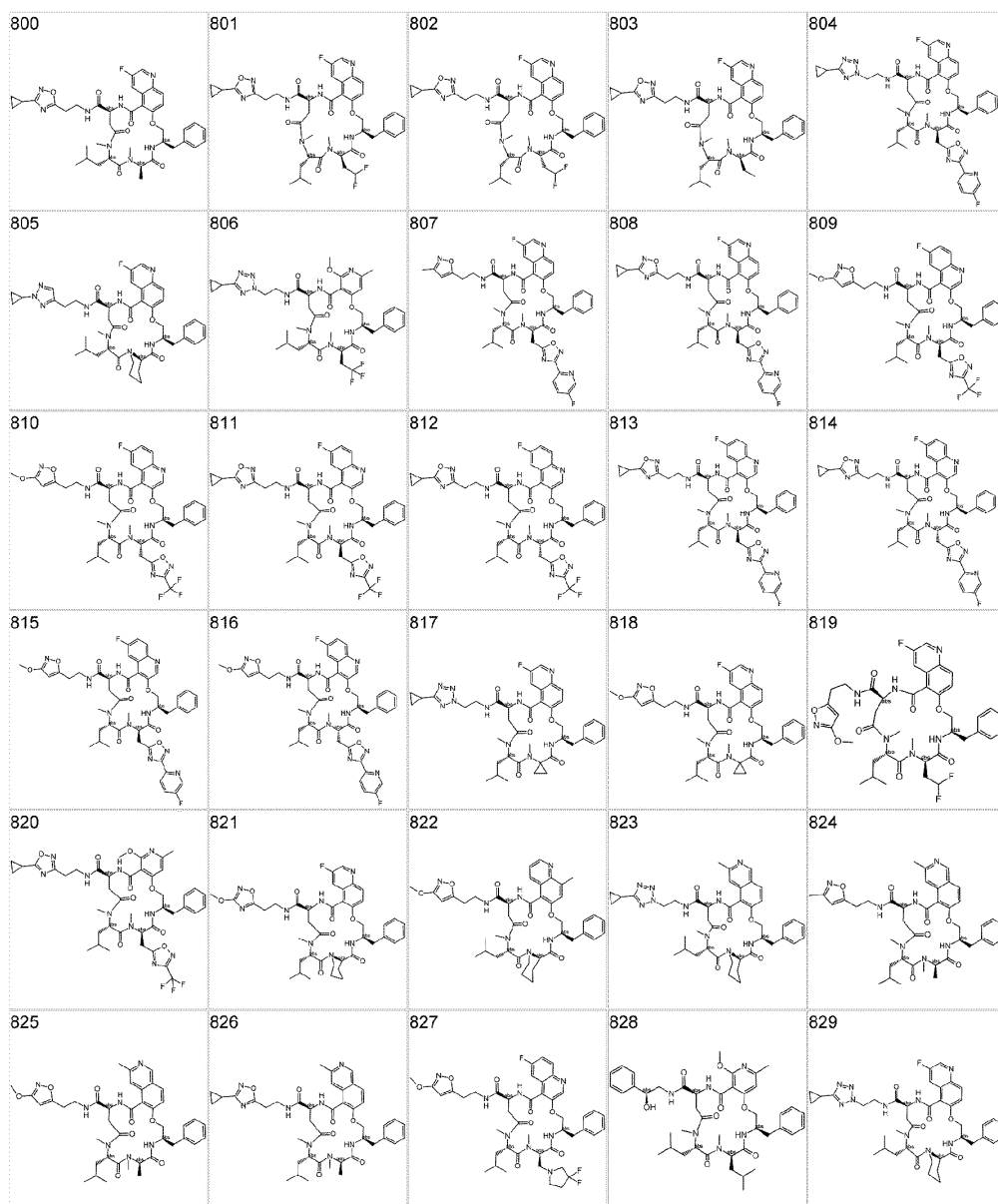
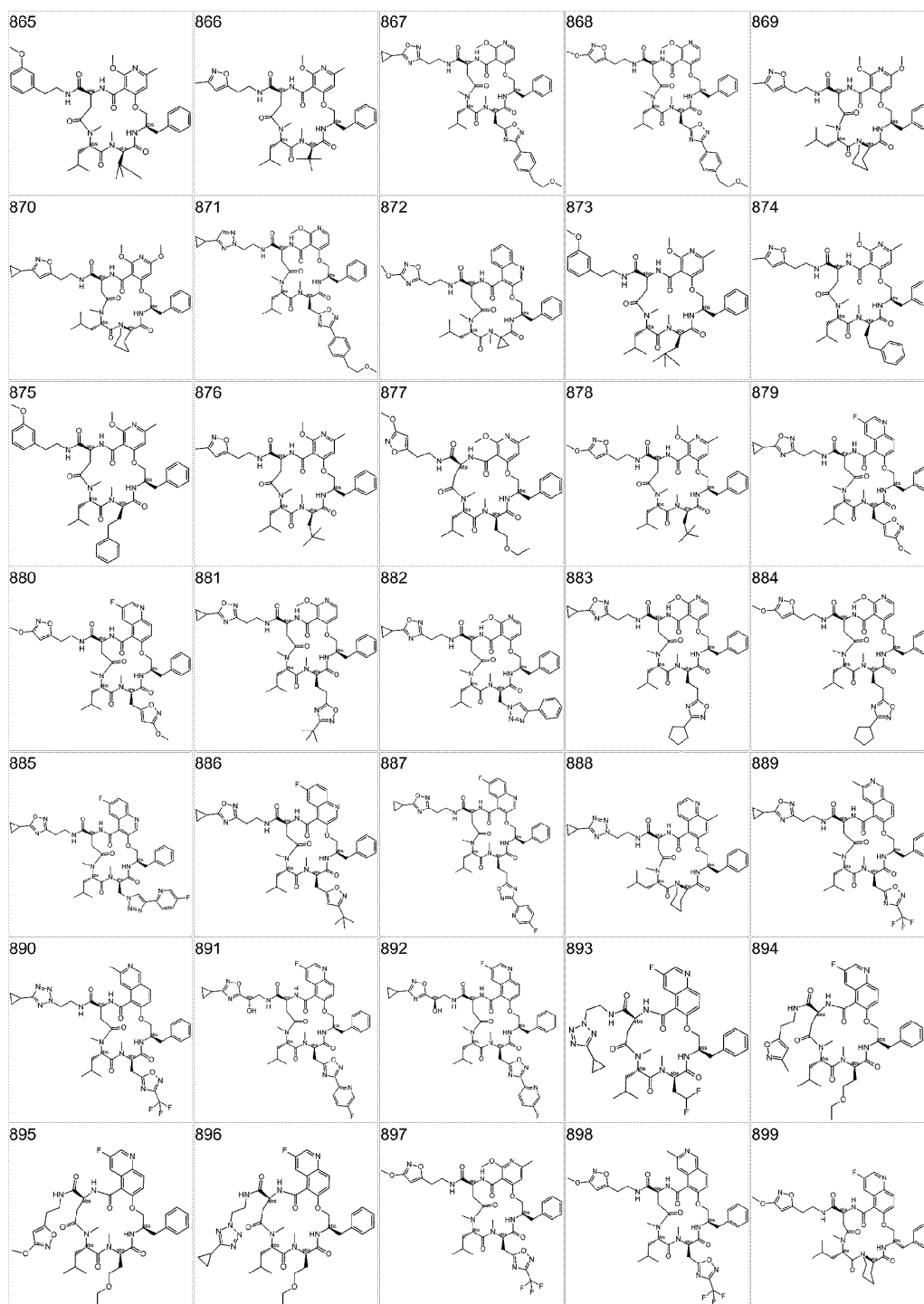
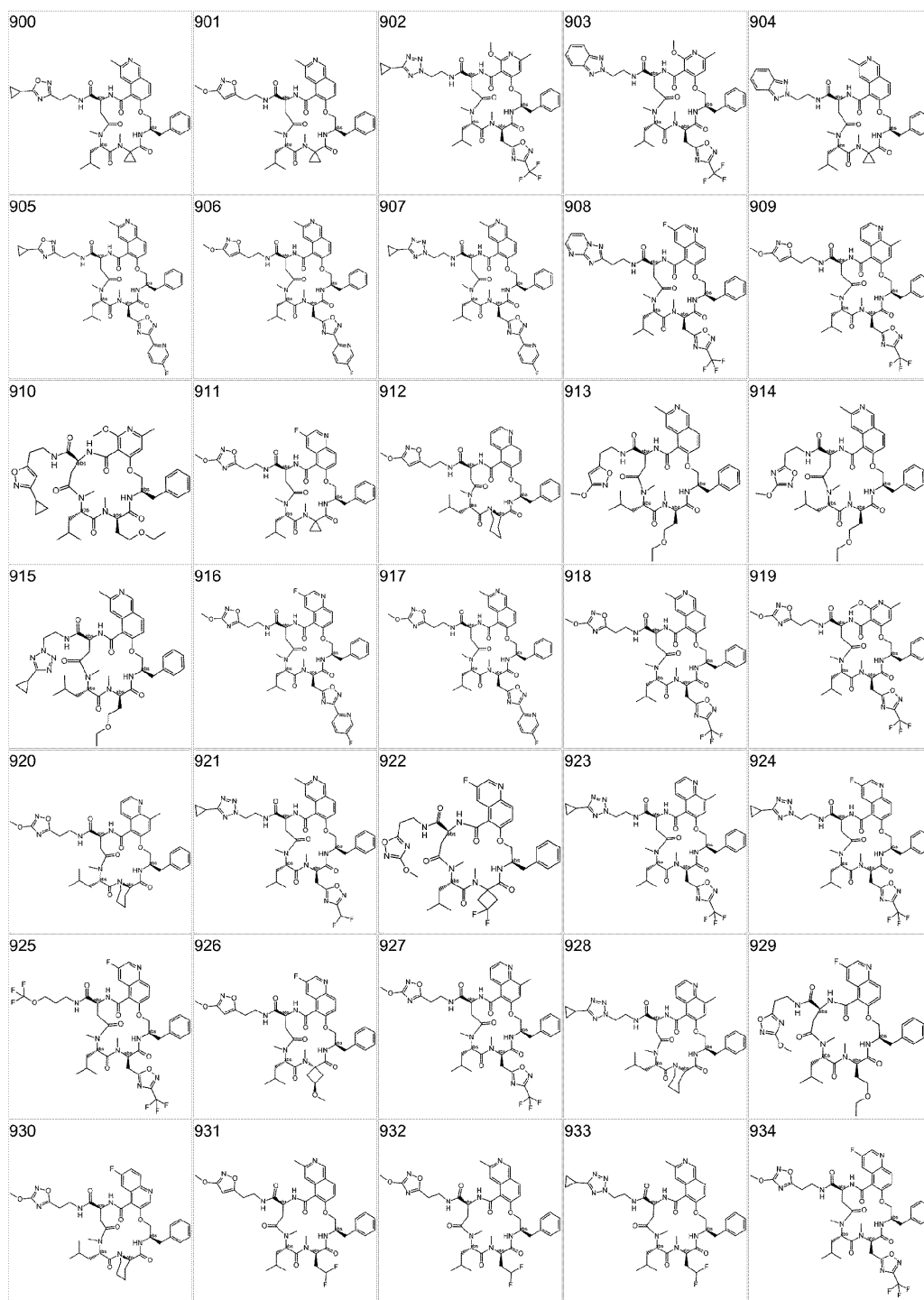
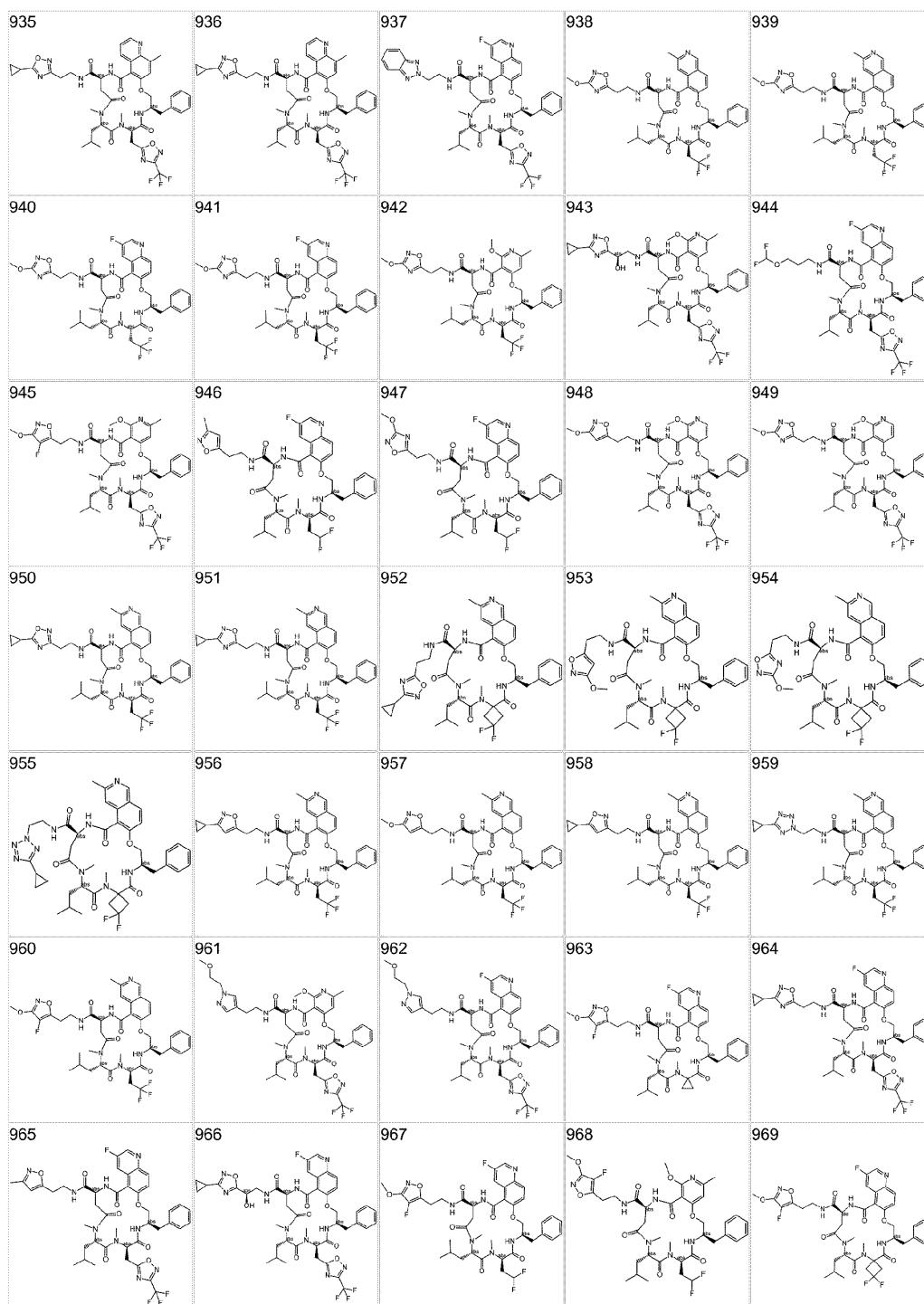


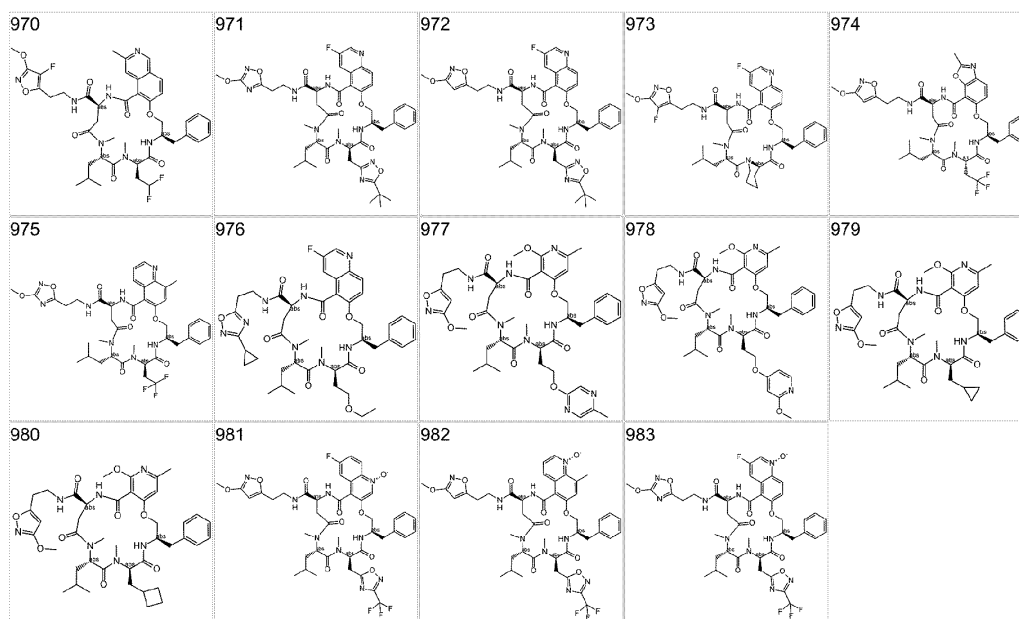
Table 5: Structures of compounds of Example 830 to 983

830	831	832	833	834
835	836	837	838	839
840	841	842	843	844
845	846	847	848	849
850	851	852	853	854
855	856	857	858	859
860	861	862	863	864









In Tables 3, 4 and 5 above, a stereogenic or asymmetric center indicated in the structures as “abs” represents said stereogenic or asymmetric center in the respective enantiomerically enriched absolute (*R*)- or (*S*)-configuration as depicted. A stereogenic or asymmetric center indicated in the structures as “&1” represents said stereogenic or asymmetric center in the respective (*RS*)-configuration, i.e. comprising the respective enantiomerically enriched (*R*)-configuration, or enantiomerically enriched (*S*)-configuration, or any mixture of epimers at such center.

II. Biological Assays

Compounds of the present invention may be further characterized with regard to their general pharmacokinetic and pharmacological properties using conventional assays well known in the art for example relating to their bioavailability in different species (such as rat or dog); or for their properties with regard to drug safety and/or toxicological properties using conventional assays well known in the art, for example relating to cytochrome P450 enzyme inhibition and time dependent inhibition, pregnane X receptor (PXR) activation, glutathione binding, or phototoxic behavior.

Biological in vitro Assays

Evaluation of compound EC₅₀ and E_{max} values

The corrector activities of the compounds of formula (I) on CFTR are determined in accordance with the following experimental method. The method measures the effect of over-night compound incubation on F508del-CFTR cell surface expression in a recombinant U2OS cell line (DiscoverRx, #93-0987C3). This cell line is engineered to co-express (i) human F508del-CFTR tagged with a Prolink (PK =short β -galactosidase fragment) and (ii) the remainder of the β -galactosidase enzyme (Enzyme Acceptor; EA) localized to the plasma membrane. Incubation with compounds

that increase PK-tagged F508del-CFTR at the plasma membrane will lead to complementation of the EA fragment to form a functional β -galactosidase enzyme which is quantified by a chemiluminescence reaction.

Briefly, the cells are seeded at 3500cells/well into 384-well low volume plates (Corning, #3826) in 20 μ l of full medium (Mc Coy's 5a (#36600-021, Gibco) + 10% FBS Gibco + penicillin/streptomycin). The cells are incubated for 5h in the incubator before the addition of 5 μ l/well of compound dilution series (5x working stocks in full medium). Final DMSO concentration in the assay is 0.25%. The cells are co-incubated with the compounds for 16h in the incubator at 37°C, 5% CO₂. The next day, the cell plates are incubated for 2h at RT in the dark. Then, 10 μ l/well of Flash detection reagent (DiscoverX, #93-0247) is added, the plate is incubated for another 30min at RT in the dark and chemiluminescence is measured. Concentration-response curves are generated using compound-intrinsic maximal efficacy as upper plateau, and from these CRCs compound-intrinsic EC₅₀ values are determined. Compound-specific E_{max} values are calculated in relation to the E_{max} of the corrector lumacaftor (E_{max} lumacaftor = 100%).

The calculated EC₅₀ values may fluctuate depending on the daily assay performance. Fluctuations of this kind are known to those skilled in the art. EC₅₀ values from several measurements are given as geomean values. The calculated E_{max} values may fluctuate depending on the daily assay performance. Fluctuations of this kind are known to those skilled in the art. E_{max} values from several measurements are given as arithmetic mean values.

References

Elborn JS. (2016) Cystic fibrosis. Lancet 388:2519-2531. Dalemans W, Barbry P, Champigny G, Jallat S, Dott K, Dreyer D, Crystal RG, Pavirani A, Lecocq JP, Lazdunski M (1991) Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. Nature 354: 526-8.

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Table of Biological Data:

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
1	56	105
2	110	150
3	816	151
4	673	195
5	369	109
6	420	112
7	398	118
8	887	210
9	360	130
10	82	123
11	182	132
12	270	184
13	268	153
14	160	185
15	187	240
16	269	137
17	466	180

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
18	388	117
19	743	125
20	721	102
21	350	108
22	600	104
23	991	115
24	823	131
25	547	142
26	299	111
27	474	114
28	603	106
29	439	140
30	275	113
31	463	111
32	318	146
33	255	141
34	260	121

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
35	262	109
36	306	120
37	122	205
38	299	191
39	415	450
40	897	147
41	280	215
42	353	419
43	862	137
44	571	247
45	682	324
46	679	137
47	213	247
48	409	151
49	347	136
50	558	256
51	352	187

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
52	348	176
53	596	404
54	558	373
55	945	245
56	764	256
57	414	315
58	759	175
59	772	237
60	662	228
61	421	202
62	809	222
63	418	250
64	441	143
65	647	282
66	587	169
67	615	236
68	448	331
69	454	262
70	754	202
71	338	326
72	142	335
73	214	253
74	128	271
75	255	191
76	196	283
77	231	237
78	544	277
79	327	296
80	170	308
81	233	232
82	598	246
83	731	309
84	274	299
85	260	244
86	314	157
87	162	190
88	230	112
89	132	262
90	364	129
91	466	210
92	289	256
93	777	189
94	257	201
95	250	178
96	425	206
97	146	285
98	311	326
99	205	254
100	184	273
101	201	163

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
102	225	332
103	499	256
104	211	204
105	173	351
106	864	308
107	794	257
108	581	222
109	231	321
110	478	261
111	392	242
112	817	200
113	369	158
114	924	220
115	380	250
116	554	253
117	776	237
118	329	265
119	328	248
120	331	212
121	615	354
122	324	292
123	873	280
124	382	347
125	271	229
126	261	230
127	107	311
128	190	292
129	406	264
130	1000	264
131	127	320
132	110	313
133	149	213
134	506	150
135	177	255
136	270	271
137	254	311
138	538	292
139	463	381
140	142	318
141	313	331
142	194	381
143	922	320
144	211	327
145	309	107
146	247	318
147	270	339
148	811	198
149	191	259
150	151	130
151	759	106

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
152	668	133
153	460	115
154	398	102
155	260	144
156	647	123
157	395	121
158	315	169
159	385	100
160	224	116
161	250	137
162	472	132
163	377	185
164	519	167
165	287	149
166	624	111
167	822	238
168	338	193
169	334	170
170	329	267
171	144	301
172	324	213
173	455	212
174	954	194
175	229	179
176	821	245
177	647	248
178	680	237
179	731	251
180	388	257
181	718	251
182	406	270
183	621	237
184	410	205
185	379	275
186	644	209
187	645	267
188	586	275
189	453	270
190	334	310
191	474	295
192	316	107
193	521	118
194	613	178
195	889	202
196	425	106
197	579	132
198	195	243
199	230	214
200	210	270
201	222	109

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
202	187	160
203	183	134
204	198	173
205	175	229
206	272	164
207	317	138
208	277	188
209	392	118
210	352	108
211	309	146
212	292	130
213	292	100
214	292	221
215	214	172
216	420	102
217	202	135
218	353	143
219	206	182
220	258	103
221	833	229
222	216	249
223	388	141
224	340	144
225	191	110
226	520	213
227	290	103
228	460	190
229	279	117
230	482	103
231	592	173
232	526	105
233	610	92
234	471	110
235	825	117
236	435	126
237	300	128
238	375	153
239	514	142
240	1260	77
241	1660	92
242	177	232
243	181	232
244	177	239
245	260	174
246	140	105
247	146	111
248	106	191
249	116	175
250	86	160
251	83	159

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
252	888	111
253	88	136
254	102	152
255	183	299
256	147	319
257	249	116
258	424	117
259	428	136
260	783	243
261	327	215
262	339	231
263	448	140
264	442	117
265	266	106
266	357	136
267	107	275
268	100	273
269	350	251
270	423	172
271	266	185
272	374	176
273	365	169
274	288	186
275	148	333
276	91	333
277	830	134
278	709	167
279	643	112
280	297	188
281	110	361
282	114	360
283	272	231
284	337	136
285	239	118
286	177	144
287	207	154
288	147	175
289	186	160
290	188	260
291	109	210
292	114	191
293	340	137
294	265	138
295	202	174
296	158	144
297	193	225
298	220	186
299	109	136
300	103	210
301	112	202

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
302	106	193
303	180	275
304	581	193
305	533	123
306	923	139
307	423	113
308	469	103
309	456	113
310	788	202
311	454	127
312	727	111
313	313	119
314	469	111
315	115	349
316	55	343
317	661	89
318	679	295
319	574	296
320	363	297
321	816	266
322	504	197
323	742	258
324	666	247
325	187	237
326	276	273
327	461	225
328	987	228
329	796	198
330	418	138
331	121	240
332	309	183
333	345	182
334	323	232
335	270	262
336	207	212
337	452	116
338	292	173
339	195	237
340	278	139
341	144	237
342	464	128
343	332	270
344	126	284
345	95	268
346	106	282
347	131	282
348	340	155
349	597	258
350	546	299
351	756	127

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
352	297	262
353	513	177
354	231	321
355	87	307
356	167	353
357	475	124
358	411	171
359	318	144
360	184	224
361	264	183
362	153	247
363	252	230
364	264	201
365	398	387
366	265	172
367	249	321
368	918	147
369	107	243
370	388	229
371	226	180
372	72	360
373	200	149
374	102	333
375	461	316
376	156	284
377	704	111
378	45	138
379	76	312
380	65	325
381	68	322
382	44	264
383	65	317
384	54	282
385	191	326
386	393	149
387	342	215
388	310	163
389	115	320
390	269	188
391	70	319
392	327	144
393	118	314
394	262	151
395	110	316
396	241	190
397	262	207
398	125	280
399	506	146
400	164	292
401	559	189

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
402	305	314
403	550	179
404	157	254
405	343	171
406	409	173
407	684	123
408	241	134
409	214	144
410	129	269
411	138	250
412	377	291
413	557	129
414	372	251
415	840	274
416	526	345
417	437	343
418	276	259
419	358	243
420	437	231
421	391	320
422	192	193
423	278	239
424	831	235
425	348	364
426	269	217
427	248	274
428	614	218
429	606	224
430	964	194
431	208	281
432	474	413
433	167	344
434	664	327
435	895	119
436	458	300
437	844	159
438	474	422
439	253	345
440	788	296
441	815	326
442	443	154
443	316	275
444	1050	199
445	958	194
446	900	248
447	447	220
448	961	109
449	543	165
450	379	107
451	257	307

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
452	886	292
453	417	251
454	234	236
455	677	211
456	250	185
457	326	144
458	209	238
459	726	390
460	310	398
461	444	262
462	345	130
463	278	269
464	319	109
465	800	387
466	548	328
467	936	152
468	504	361
469	381	110
470	662	169
471	981	278
472	284	239
473	585	119
474	478	359
475	992	314
476	333	344
477	754	327
478	168	337
479	480	253
480	201	276
481	448	225
482	414	247
483	517	311
484	251	117
485	238	204
486	201	303
487	1340	147
488	910	270
489	625	273
490	222	181
491	209	178
492	305	168
493	687	253
494	260	295
495	296	207
496	523	317
497	535	171
498	198	313
499	189	321
500	553	199
501	198	308

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
502	752	295
503	772	137
504	149	298
505	229	330
506	318	211
507	469	337
508	382	378
509	75	327
510	108	256
511	624	314
512	300	316
513	815	169
514	170	304
515	518	140
516	494	155
517	986	222
518	655	189
519	184	332
520	345	155
521	433	191
522	204	237
523	483	352
524	60	339
525	56	288
526	394	167
527	151	318
528	321	337
529	947	206
530	334	353
531	265	336
532	397	375
533	221	352
534	273	394
535	407	424
536	175	358
537	384	294
538	80	340
539	95	391
540	269	256
541	185	357
542	368	334
543	785	399
544	774	398
545	349	385
546	350	411
547	281	330
548	106	326
549	166	167
550	687	129
551	222	317

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
552	413	358
553	287	304
554	324	310
555	219	309
556	327	322
557	594	253
558	167	355
559	155	236
560	114	249
561	437	215
562	444	282
563	125	330
564	49	298
565	338	254
566	703	278
567	384	307
568	391	238
569	108	270
570	374	323
571	47	347
572	701	200
573	423	306
574	308	319
575	411	273
576	523	268
577	600	268
578	53	319
579	399	131
580	198	319
581	300	303
582	116	279
583	339	90
584	575	156
585	176	168
586	221	165
587	414	106
588	650	102
589	298	160
590	362	201
591	341	259
592	881	119
593	614	190
594	810	171
595	332	233
596	167	195
597	168	211
598	759	312
599	151	299
600	97	286
601	589	138

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
602	286	299
603	205	301
604	354	103
605	637	257
606	521	150
607	121	283
608	804	267
609	574	320
610	89	311
611	344	251
612	148	298
613	82	312
614	484	317
615	465	170
616	581	92
617	75	318
618	80	309
619	155	322
620	316	266
621	339	288
622	199	296
623	248	349
624	921	171
625	781	186
626	163	253
627	786	395
628	363	355
629	521	215
630	261	175
631	898	133
632	927	326
633	652	316
634	173	178
635	404	112
636	91	276
637	106	300
638	182	297
639	173	305
640	132	339
641	87	305
642	168	366
643	220	270
644	277	270
645	289	211
646	158	201
647	820	182
648	748	159
649	908	149
650	596	214
651	375	127

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
652	593	155
653	332	140
654	290	330
655	150	318
656	357	327
657	347	291
658	283	300
659	359	325
660	91	358
661	421	247
662	124	297
663	801	210
664	231	291
665	119	323
666	484	311
667	764	149
668	160	330
669	856	230
670	353	167
671	235	179
672	103	312
673	67	314
674	262	133
675	194	159
676	62	267
677	37	283
678	355	296
679	869	277
680	448	340
681	447	313
682	110	351
683	362	262
684	986	235
685	500	234
686	436	332
687	794	107
688	458	104
689	245	390
690	478	401
691	201	364
692	104	301
693	40	401
694	241	213
695	201	237
696	14	252
697	27	306
698	199	313
699	299	338
700	188	186
701	165	268

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
702	295	162
703	316	167
704	398	156
705	305	193
706	707	162
707	502	305
708	874	195
709	47	284
710	149	280
711	778	301
712	187	211
713	31	432
714	36	410
715	64	283
716	144	313
717	69	348
718	359	272
719	124	313
720	881	244
721	142	328
722	101	347
723	512	160
724	93	345
725	1370	200
726	624	234
727	5050	138
728	235	232
729	100	258
730	593	248
731	381	248
732	64	239
733	349	235
734	299	325
735	314	176
736	153	286
737	665	298
738	110	256
739	101	297
740	111	280
741	116	294
742	214	246
743	207	217
744	178	239
745	693	206
746	211	213
747	234	213
748	529	295
749	153	301
750	784	267
751	217	213

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
752	706	200
753	430	264
754	219	279
755	168	270
756	311	252
757	145	280
758	334	266
759	296	131
760	723	333
761	676	202
762	929	333
763	264	181
764	374	315
765	300	323
766	154	393
767	212	390
768	497	292
769	140	346
770	1001	228
771	597	299
772	514	343
773	841	339
774	751	345
775	875	359
776	325	360
777	875	216
778	141	302
779	811	213
780	116	280
781	124	296
782	859	439
783	889	410
784	311	391
785	210	365
786	156	337
787	190	323
788	549	344
789	675	358
790	650	350
791	80	345
792	628	261
793	235	105
794	83	354
795	141	384
796	156	321
797	399	308
798	197	324
799	258	335
800	266	352
801	149	330

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
802	723	200
803	248	355
804	115	360
805	191	276
806	233	394
807	206	358
808	116	399
809	10	391
810	161	285
811	19	333
812	127	280
813	110	346
814	631	242
815	128	413
816	741	286
817	420	375
818	385	359
819	276	431
820	49	461
821	200	392
822	131	363
823	241	366
824	674	354
825	353	388
826	283	340
827	54	379
828	299	317
829	142	320
830	1040	310
831	491	231
832	518	367
833	615	411
834	240	300
835	363	326
836	967	257
837	198	358
838	118	358
839	123	336
840	128	363
841	120	271
842	495	305
843	114	368
844	1040	356
845	453	308
846	165	261
847	186	340
848	225	364
849	46	465
850	1150	224
851	148	310

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
852	163	249
853	92	322
854	136	326
855	80	341
856	35	357
857	407	337
858	95	308
859	36	342
860	578	288
861	722	384
862	921	335
863	587	326
864	617	385
865	103	356
866	337	324
867	31	413
868	18	397
869	358	305
870	201	316
871	32	378
872	535	318
873	41	336
874	66	332
875	21	333
876	113	317
877	186	361
878	27	336
879	63	360
880	59	359
881	309	337
882	473	367
883	111	344
884	96	385
885	78	328
886	15	359
887	111	340
888	170	410
889	34	403
890	34	409
891	1490	402
892	467	442
893	216	394
894	339	431
895	136	409
896	188	427
897	32	454
898	22	440
899	819	294
900	831	374
901	736	390

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
902	55	453
903	51	414
904	722	365
905	311	415
906	294	433
907	425	454
908	94	401
909	17	430
910	477	423
911	531	341
912	272	332
913	294	390
914	368	358
915	334	361
916	196	470
917	487	398
918	42	462
919	104	443
920	175	380
921	231	393
922	302	396
923	26	500
924	33	409
925	92	286
926	759	416
927	27	492
928	971	247
929	306	513
930	142	460
931	298	507
932	373	491
933	399	485
934	37	528
935	24	496
936	26	469
937	59	460
938	245	498
939	737	288
940	673	298
941	135	459
942	194	460
943	240	471
944	77	336
945	33	502
946	447	404
947	281	458
948	61	501
949	113	518
950	201	464
951	165	405

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
952	339	438
953	268	394
954	382	383
955	381	394
956	508	412
957	192	451
958	338	439
959	222	413
960	85	507
961	353	453
962	103	453
963	267	447
964	21	418

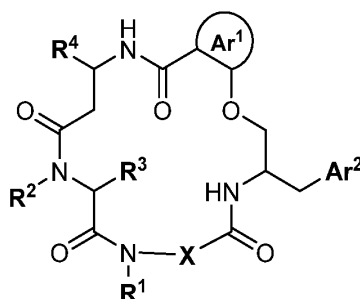
Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
965	32	453
966	82	404
967	92	472
968	226	478
969	142	452
970	109	463
971	163	482
972	128	436
973	117	446
974	703	440
975	119	497
976	179	348
977	281	410

Ex.	EC ₅₀ [nmol/l]	E _{max} [%]
978	129	457
979	209	394
980	53	435
981	133	448
982	236	530
983	270	506

- 5 **Reference Compound 1: Apicidin** was purchased from Sigma-Aldrich and evaluated in the above DiscoverX assay under the same conditions; the compound showed an EC₅₀: >20000 nmol/l.

Claims

1. A compound of Formula (I)



Formula (I)

5 wherein

❖ X represents -CR^{X1}R^{X2}, wherein

➤ R^{X1} and R^{X2} together with the carbon atom to which they are attached form a ring which is:

- C₃₋₆-cycloalkan-1,1-diyl;
- C₅₋₆-cycloalkan-1,1-diyl which is fused to a benzene ring;
- 10 ▪ C₃₋₆-cycloalkan-1,1-diyl, wherein said C₃₋₆-cycloalkan-1,1-diyl group independently is mono-substituted with C₁₋₃-alkoxy, fluoro, or hydroxy; or di-substituted with fluoro;
- C₄₋₆-heterocycloalkan-diyl, wherein said C₄₋₆-heterocycloalkan-diyl contains one ring nitrogen atom, wherein said nitrogen when having a free valency is unsubstituted or mono-substituted wherein the substituents are independently selected from C₁₋₄-alkyl, and -COO-
- 15 C₁₋₃-alkyl; or
- C₄₋₆-heterocycloalkan-diyl, wherein said C₄₋₆-heterocycloalkan-diyl contains one ring oxygen atom;

➤ R^{X1} and R^{X2} both independently represent C₁₋₄-alkyl; or

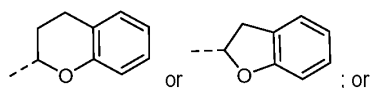
➤ R^{X1} represents hydrogen, and

20 R^{X2} represents

- hydrogen;
- C₁₋₆-alkyl;
- C₁₋₄-fluoroalkyl;
- C₃₋₆-cycloalkyl;
- 25 ▪ C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with
 - hydroxy;
 - C₁₋₄-alkoxy;
 - -L^{X1}-C₃₋₆-cycloalkyl wherein said C₃₋₆-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein L^{X1} independently represents a direct bond or oxygen;

5

- C₄₋₆-heterocycloalkyl wherein said C₄₋₆-heterocycloalkyl contains one ring oxygen atom;
- -NR^{N1}R^{N2} wherein R^{N1} and R^{N2} together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom, wherein said ring is mono- or di-substituted with fluoro;
- a partially aromatic bicyclic ring, which is



10

▪ -L^{X2}-Ar^{X2} wherein -

- L^{X2} independently represents a direct bond, C₁₋₃-alkylene, -C₁₋₃-alkylene-O-*, or -C₁₋₃-alkylene-O-C₁₋₂-alkylene-*, wherein the asterisks indicate the bond that is attached to the group Ar^{X2}; and
- Ar^{X2} independently represents aryl, or 5- to 10-membered heteroaryl; wherein said group Ar^{X2} independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - C₃₋₆-cycloalkyl;
 - C₁₋₃-fluoroalkyl; and
 - Ar^{X3} wherein Ar^{X3} independently represents phenyl, or 5- or 6-membered heteroaryl; wherein said group Ar^{X3} independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C₁₋₃-alkyl, C₁₋₃-alkoxy, C₁₋₃-alkoxy-C₂₋₃-alkyl, C₃₋₅-cycloalkyl, C₁₋₃-fluoroalkyl, and halogen;

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25 and

R¹ independently represents

- hydrogen;
- -C₁₋₈-alkyl;
- -C₂₋₆-alkyl wherein said C₂₋₆-alkyl is mono-substituted with hydroxy, or C₁₋₄-alkoxy;
- -C₁₋₆-alkyl wherein said C₁₋₆-alkyl is mono-substituted with R¹¹; wherein R¹¹ independently represents
 - a saturated 5- or 6-membered heterocycloalkyl containing one or two ring heteroatoms wherein said heteroatoms are independently selected from nitrogen and oxygen, wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono-

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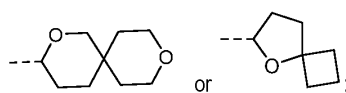
or di-substituted, wherein the substituents independently are selected from C₁₋₄-alkyl, halogen, and benzyl;

➤ C₃₋₆-cycloalkyl, wherein said C₃₋₆-cycloalkyl is unsubstituted or mono-substituted with C₁₋₄-alkoxy;

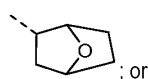
5 ➤ phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen, cyano, and morpholin-4-yl;

➤ benzyloxy;

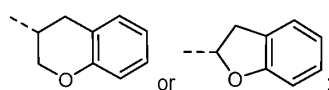
10 ➤ a spirocyclic fragment, which is



➤ a saturated bicyclic ring, which is

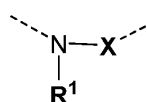


➤ a partially aromatic bicyclic ring, which is

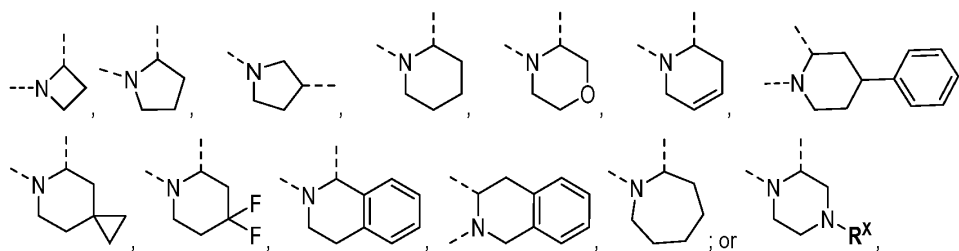


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❖ or the fragment



represents a heterocyclic ring which is

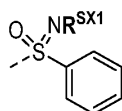


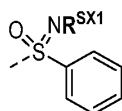
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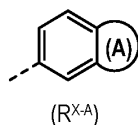
wherein R^x represents

- hydrogen;
- C₁₋₄-alkyl;
- C₃₋₆-cycloalkyl;
- 25 • C₁₋₄-alkyl, wherein said C₁₋₄-alkyl is mono-substituted with C₃₋₄-cycloalkyl;

- C₂₋₄-alkyl, wherein said C₂₋₄-alkyl is mono-substituted with hydroxy or C₁₋₃-alkoxy;
- phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₃-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen;



- 5
- , wherein **R^{SX1}** represents hydrogen or -CO-O-C₁₋₄-alkyl;
 - -CO-R^{OX1}, or -SO₂-R^{OX1}; wherein **R^{OX1}** independently represents
 - C₁₋₄-alkyl;
 - C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with C₁₋₃-alkoxy, tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl, or -NR^{ONX1}R^{ONX2} wherein **R^{ONX1}** and **R^{ONX2}** independently represent hydrogen or C₁₋₃-alkyl;
 - tetrahydropyranyl;
 - phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C₁₋₄-alkyl, C₁₋₃-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen; or
 - a group of the structure (R^{X-A}):
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wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substituents independently are selected from oxo and C₁₋₃-alkyl; or

- -CO-O-R^{OX2}; wherein **R^{OX2}** represents
 - C₁₋₄-alkyl;
 - 2,2,2-trichloroethyl; or
 - tetrahydropyranyl;
- 25

R² represents C₁₋₄-alkyl;

R³ represents hydrogen; C₁₋₆-alkyl; -CH₂-C₃₋₆-cycloalkyl; or C₂₋₄-alkynyl;

R⁴ represents a group -CO-NH-R⁴¹; wherein **R⁴¹** represents

- 30
- C₂₋₆-alkyl, which is mono-substituted with C₁₋₄-alkoxy, C₁₋₄-fluoroalkoxy, or hydroxy;
 - C₁₋₃-alkoxy-C₂₋₃-alkylene-O-CH₂-CH₂-;

- $-\text{CH}_2\text{CH}_2\text{C}_{5-6}\text{-heterocycloalkyl}$, wherein said $\text{C}_{5-6}\text{-heterocycloalkyl}$ contains one ring oxygen atom, wherein said $\text{C}_{5-6}\text{-heterocyclyl}$ is unsubstituted, mono- or di-substituted with $\text{C}_{1-4}\text{-alkyl}$;
- $-\text{L}^1\text{-aryl}$; wherein L^1 represents $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-^*$, $-\text{CH}_2\text{CF}_2^*$, $-\text{CH}_2\text{-(cyclopropan-1,1-diyl)}^*$, $-\text{CH}(\text{CH}_2\text{OH})\text{CH}_2^*$, or $-\text{CH}_2\text{CH}(\text{OH})^*$; wherein asterisks indicate the bond with which L^1 is attached to the aryl; wherein aryl represents phenyl or naphthyl; wherein said aryl is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkoxy}$, $\text{C}_{1-3}\text{-fluoroalkyl}$, $\text{C}_{1-3}\text{-fluoroalkoxy}$, halogen, cyano, $\text{C}_{3-6}\text{-cycloalkyl}$, $\text{C}_{3-6}\text{-cycloalkyl-methyl}$, $\text{C}_{1-3}\text{-alkoxy-C}_{1-3}\text{-alkyl}$, hydroxy- $\text{C}_{1-3}\text{-alkyl}$, $\text{C}_{2-3}\text{-alkynyl}$, morpholin-4-yl, $\text{C}_{1-3}\text{-alkyl-SO}_2$, 5- or 6-membered heteroaryl, or $-\text{NR}^{\text{N41}}\text{R}^{\text{N42}}$, wherein independently R^{N41} is hydrogen or $\text{C}_{1-4}\text{-alkyl}$, and R^{N42} is hydrogen or $\text{C}_{1-4}\text{-alkyl}$;
- $-\text{L}^2\text{-HET}$; wherein L^2 represents $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{O}-^*$, $-\text{CH}_2\text{CF}_2^*$, $-\text{CH}_2\text{-(cyclopropan-1,1-diyl)}^*$, $-\text{CH}(\text{CH}_2\text{OH})\text{CH}_2^*$, or $-\text{CH}_2\text{CH}(\text{OH})^*$; wherein asterisks indicate the bond with which L^2 is attached to HET; wherein HET represents 5- to 10-membered heteroaryl, wherein said HET is independently unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkoxy}$, $\text{C}_{1-3}\text{-fluoroalkyl}$, $\text{C}_{1-3}\text{-fluoroalkoxy}$, halogen, cyano, $\text{C}_{3-6}\text{-cycloalkyl}$, $\text{C}_{3-6}\text{-cycloalkyl-methyl}$, $\text{C}_{1-3}\text{-alkoxy-C}_{1-3}\text{-alkyl}$, hydroxy- $\text{C}_{1-3}\text{-alkyl}$, $\text{C}_{2-3}\text{-alkynyl}$, benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkoxy}$, or $\text{C}_{1-4}\text{-fluoroalkoxy}$;
- $-\text{CH}_2\text{CH}_2\text{-HCy}^1$, wherein HCy^1 represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with $\text{C}_{1-4}\text{-alkyl}$; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkoxy}$, $\text{C}_{1-3}\text{-fluoroalkyl}$, $\text{C}_{1-3}\text{-fluoroalkoxy}$, halogen, or cyano;
- $-\text{CH}_2\text{CH}_2\text{-HCy}^2$, wherein HCy^2 represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring; or
- $-\text{L}^3\text{-HCy}^3$, wherein L^3 represents a direct bond, or $-\text{CH}_2-$; wherein HCy^3 represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one oxygen atom; wherein L^3 is attached to said group HCy^3 at a carbon atom which is part of said 5- to 7-membered saturated heterocyclic ring; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, or mono-substituted with $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkoxy}$, $\text{C}_{1-3}\text{-fluoroalkyl}$, $\text{C}_{1-3}\text{-fluoroalkoxy}$, halogen, or cyano;

Ar^1 represents

- 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted;
- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently selected from $\text{C}_{1-4}\text{-alkyl}$, $\text{C}_{1-4}\text{-alkoxy}$, $\text{C}_{1-3}\text{-fluoroalkyl}$, $\text{C}_{1-3}\text{-fluoroalkoxy}$, cyano, and halogen;

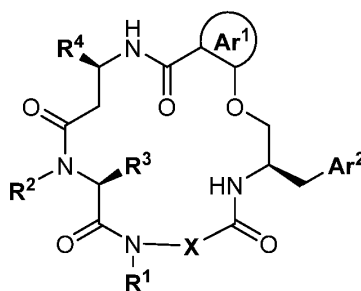
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or
- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₃-fluoroalkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkoxy, cyano, and halogen; or
- quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted, or said quinoline-diyl N-oxide is mono-substituted with methyl or fluoro;

and

Ar² represents

- phenyl or naphthyl, wherein said phenyl or naphthyl independently is unsubstituted, mono- or di-substituted wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₃-fluoroalkyl, halogen, cyano, C₁₋₆-alkoxy, and C₁₋₃-fluoroalkoxy;
 - 5- or 6-membered heteroaryl, wherein said 5- or 6-membered heteroaryl independently is unsubstituted or mono-substituted wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₃-fluoroalkyl, halogen, cyano, C₁₋₆-alkoxy, and C₁₋₃-fluoroalkoxy; or
 - 9- or 10-membered heteroaryl;
- or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I) as defined for claim 1, wherein the compounds are also compounds of Formula (I_E):



Formula (I_E);

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2; wherein

❖ **X** represents -CR^{x1}R^{x2}, wherein

- **R^{X1}** and **R^{X2}** together with the carbon atom to which they are attached form a ring which is:
 - C₃₋₆-cycloalkan-1,1-diyl-;
 - C₅₋₆-cycloalkan-1,1-diyl- which is fused to a benzene ring; or
 - C₃₋₆-cycloalkan-1,1-diyl-, wherein said C₃₋₆-cycloalkan-1,1-diyl group is mono-substituted with C₁₋₃-alkoxy, or di-substituted with fluoro;
- **R^{X1}** and **R^{X2}** both independently represent C₁₋₄-alkyl; or
- **R^{X1}** represents hydrogen, and **R^{X2}** represents
 - hydrogen;
 - C₁₋₆-alkyl;
 - C₁₋₄-fluoroalkyl;
 - C₃₋₆-cycloalkyl;
 - C₁₋₃-alkyl wherein said C₁₋₃-alkyl is mono-substituted with
 - hydroxy;
 - C₁₋₄-alkoxy;
 - -**L^{X1}**-C₃₋₆-cycloalkyl wherein said C₃₋₆-cycloalkyl is unsubstituted or di-substituted with fluoro; and wherein **L^{X1}** independently represents a direct bond or oxygen;
 - C₄₋₆-heterocycloalkyl wherein said C₄₋₆-heterocycloalkyl contains one ring oxygen atom;
 - -**NR^{N1}R^{N2}** wherein **R^{N1}** and **R^{N2}** together with the nitrogen form a 4- to 6-membered carbocyclic ring comprising the nitrogen atom, wherein said ring is mono- or di-substituted with fluoro;
 - -**L^{X2}-Ar^{X2}** wherein -
 - **L^{X2}** independently represents a direct bond, C₁₋₃-alkylene, -C₁₋₃-alkylene-O-*, or -C₁₋₃-alkylene-O-C₁₋₂-alkylene-*, wherein the asterisks indicate the bond that is attached to the group **Ar^{X2}**; and
 - **Ar^{X2}** independently represents aryl, or 5- to 10-membered heteroaryl; wherein said group **Ar^{X2}** independently is unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from
 - C₁₋₄-alkyl;
 - C₁₋₃-alkoxy;
 - halogen;
 - cyano;
 - C₃₋₆-cycloalkyl;
 - C₁₋₃-fluoroalkyl; and

- $\text{Ar}^{\text{X}3}$ wherein $\text{Ar}^{\text{X}3}$ independently represents phenyl, or 5- or 6-membered heteroaryl; wherein said group $\text{Ar}^{\text{X}3}$ independently is unsubstituted, or mono-, or di-substituted wherein the substituents independently are selected from C_{1-3} -alkyl, C_{1-3} -alkoxy, C_{1-3} -alkoxy- C_{2-3} -alkyl, C_{3-5} -cycloalkyl, C_{1-3} -fluoroalkyl, and halogen;

and

R^1 independently represents hydrogen or -C_{1-3} -alkyl; or

❖ X represents $\text{-CR}^{\text{X}1}\text{R}^{\text{X}2}$, wherein

➤ $\text{R}^{\text{X}1}$ represents hydrogen, and

$\text{R}^{\text{X}2}$ represents hydrogen, or methyl; or

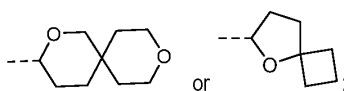
➤ $\text{R}^{\text{X}1}$ and $\text{R}^{\text{X}2}$ together with the carbon atom to which they are attached form a ring which is C_{3-5} -cycloalkan-1,1-diyl-;

and

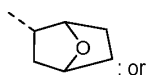
R^1 independently represents

- -C_{4-6} -alkyl;
- -C_{2-6} -alkyl, wherein said C_{2-6} -alkyl is mono-substituted with C_{1-4} -alkoxy;
- -C_{3-6} -alkyl, wherein said C_{3-6} -alkyl is mono-substituted with phenyl, or benzyloxy;
- $\text{-(CH}_2\text{)}_m\text{-R}^{11}$ wherein m represents the integer 1 or 2; and R^{11} independently represents
 - a saturated 5- or 6-membered heterocycloalkyl containing one or two ring oxygen atoms, wherein said 5- or 6-membered heterocycloalkyl is independently unsubstituted, mono- or di-substituted with C_{1-4} -alkyl;
 - C_{3-6} -cycloalkyl, wherein said C_{3-6} -cycloalkyl is unsubstituted or mono-substituted with C_{1-4} -alkoxy;
 - phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4} -alkyl, C_{1-4} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano or halogen;

➤ a spirocyclic fragment, which is

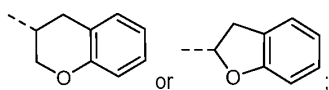


➤ a saturated bicyclic ring, which is

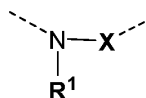


➤ a partially aromatic bicyclic ring, which is

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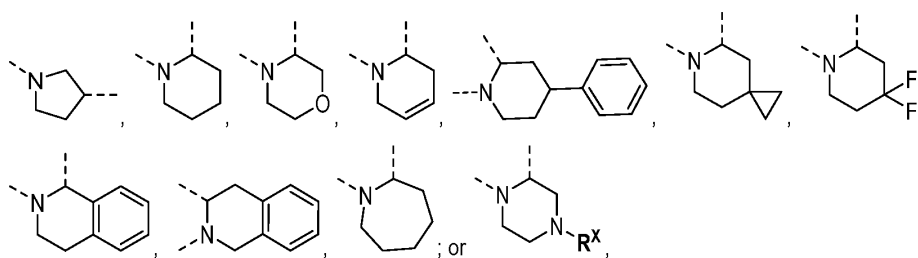


❖ or the fragment



represents a heterocyclic ring which is

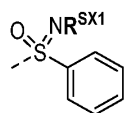
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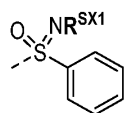
wherein R^x represents

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- hydrogen;
- C_{1-4} -alkyl;
- C_{3-4} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with C_{3-4} -cycloalkyl;
- C_{2-4} -alkyl, wherein said C_{2-4} -alkyl is mono-substituted with hydroxy, or C_{1-3} -alkoxy;
- phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the substituents independently are selected from C_{1-4} -alkyl, C_{1-3} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano or halogen;

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- , wherein R^{sx1} represents hydrogen or $-CO-O-C_{1-4}$ -alkyl;
- $-CO-R^{ox1}$, or $-SO_2-R^{ox1}$; wherein R^{ox1} independently represents
 - C_{1-4} -alkyl;
 - C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with C_{1-3} -alkoxy, tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl, or $-NR^{onx1}R^{onx2}$ wherein R^{onx1} and R^{onx2} independently represent hydrogen or C_{1-3} -alkyl;
 - tetrahydropyranyl;
 - phenyl or 5- or 6-membered heteroaryl, wherein said phenyl or 5- or 6-membered heteroaryl independently is unsubstituted, mono- or di-substituted wherein the

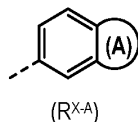
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substituents independently are selected from C₁₋₄-alkyl, C₁₋₃-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, cyano or halogen; or

- a group of the structure (R^{X-A}):



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wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group, wherein ring (A) comprises two heteroatoms independently selected from oxygen and nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted wherein the substituents independently are selected from oxo and C₁₋₃-alkyl; or

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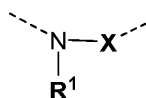
- -CO-O-R^{ox2}; wherein R^{ox2} represents

- C₁₋₄-alkyl;
- 2,2,2-trichloroethyl; or
- tetrahydropyranyl;

or a pharmaceutically acceptable salt thereof.

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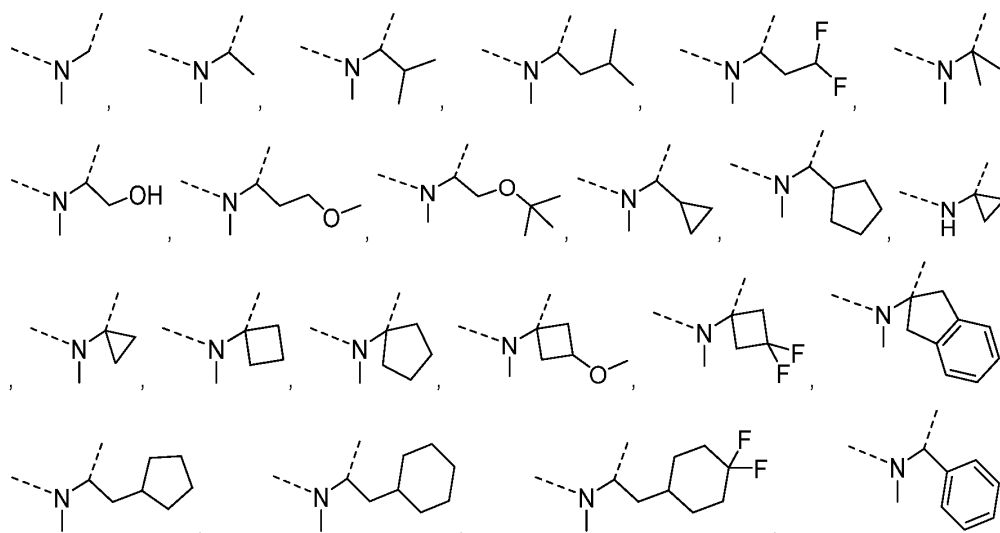
4. A compound according to claim 1 or 2; wherein the fragment



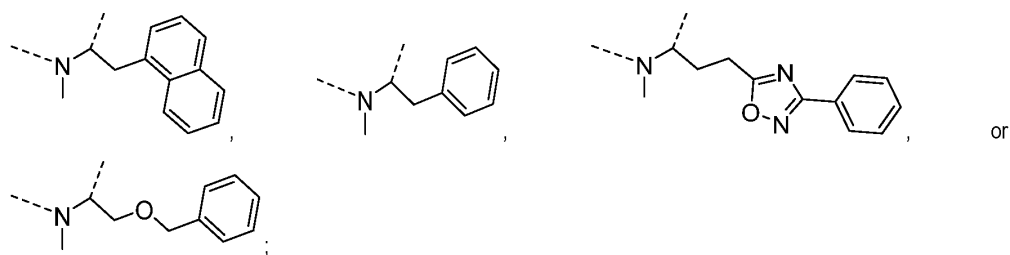
represents a group selected from:

A)

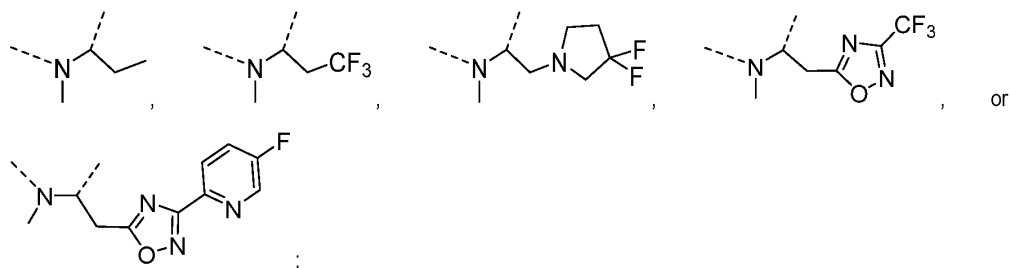
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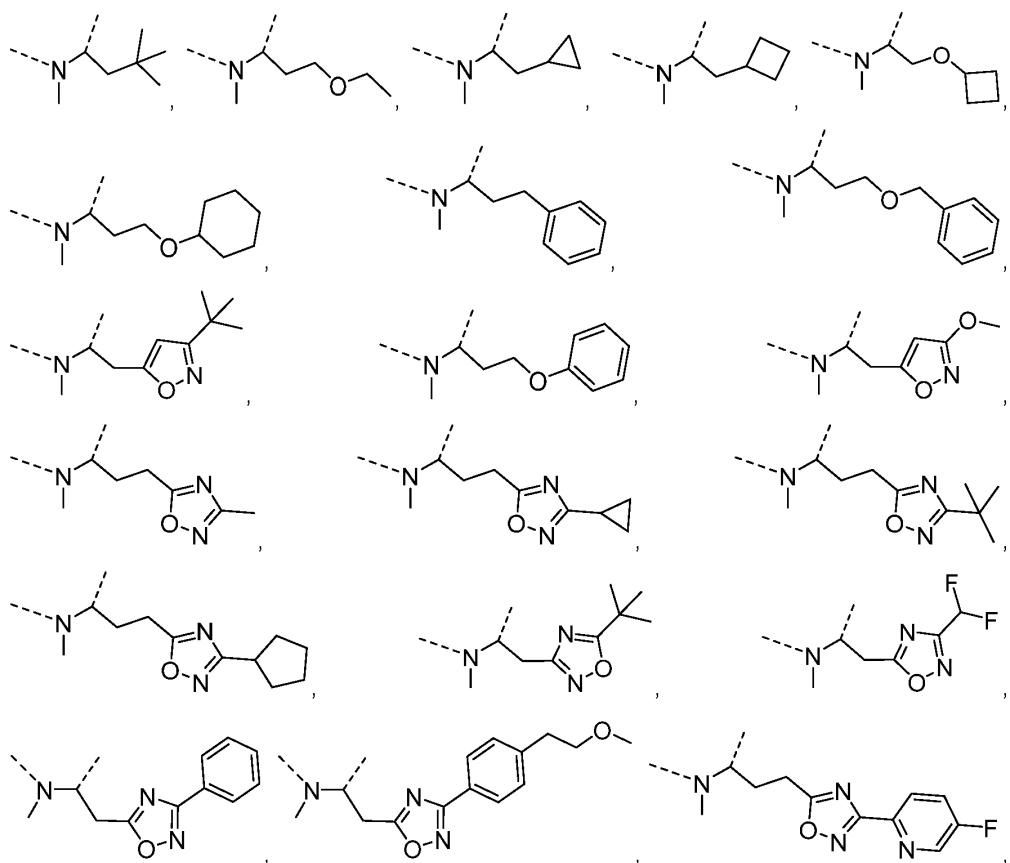


B)



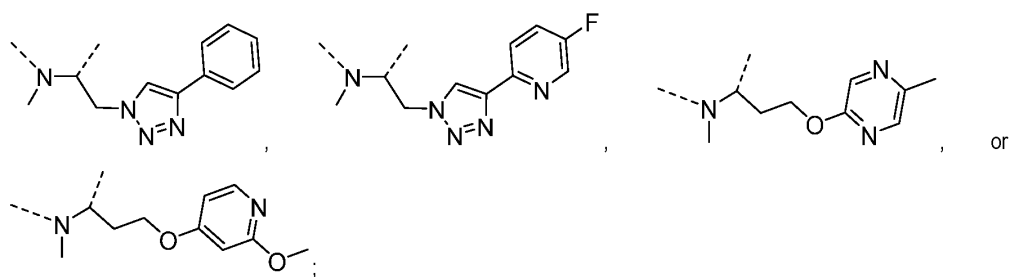
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C)

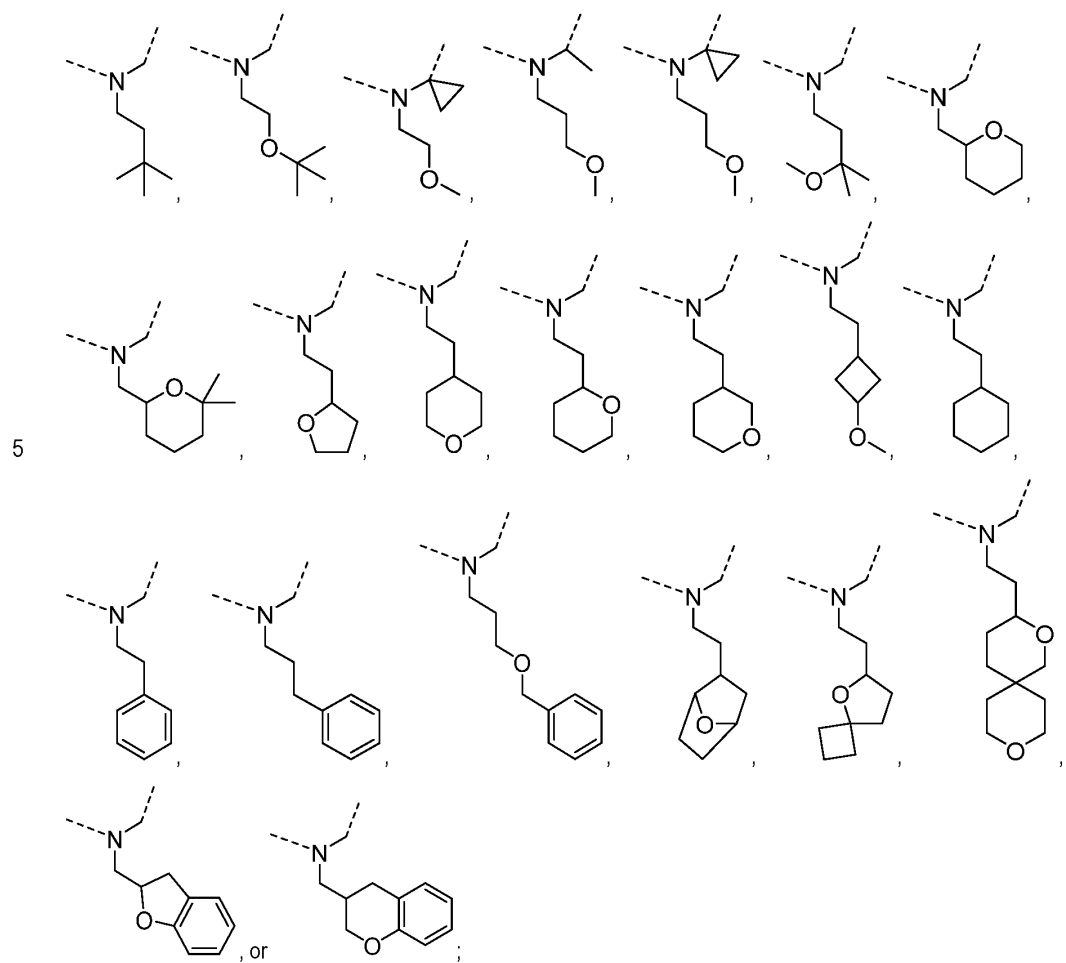


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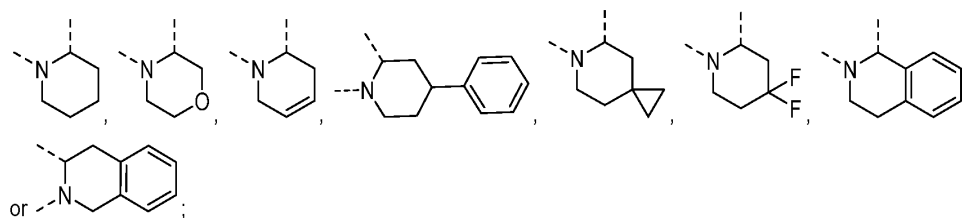


D)

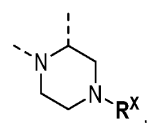


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E)



F)

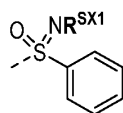


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wherein R^X represents

- C_{1-4} -alkyl;
- C_{3-4} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with C_{3-4} -cycloalkyl;
- C_{1-4} -alkyl, wherein said C_{1-4} -alkyl is mono-substituted with hydroxy, or C_{1-3} -alkoxy;
- phenyl;
- 6-membered heteroaryl, wherein said 6-membered heteroaryl is unsubstituted or mono-substituted with halogen;

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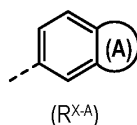
15

- $-CO-R^{SX1}$, wherein R^{SX1} represents $-CO-O-C_{1-4}$ -alkyl;
- $-CO-R^{OX1}$, or $-SO_2-R^{OX1}$; wherein R^{OX1} independently represents
 - C_{1-4} -alkyl;
 - C_{1-3} -alkyl wherein said C_{1-3} -alkyl is mono-substituted with C_{1-3} -alkoxy, tetrahydropyranyl, morpholin-4-yl, phenyl, 10-membered heteroaryl, or $-NR^{ONX1}R^{ONX2}$ wherein R^{ONX1} and R^{ONX2} independently represent hydrogen or C_{1-3} -alkyl;
 - tetrahydropyranyl;
 - phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C_{1-3} -alkoxy, C_{1-3} -fluoroalkoxy or halogen;
 - 5- or 6-membered heteroaryl wherein said 5- or 6-membered heteroaryl is independently unsubstituted or mono-substituted with C_{1-3} -alkoxy; or
 - a group of the structure (R^{X-A}):

20

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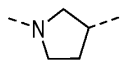


wherein (A) represents a non-aromatic 5- or 6-membered ring fused to the phenyl group,
 wherein ring (A) comprises two heteroatoms independently selected from oxygen and
 nitrogen; wherein said ring (A) independently is unsubstituted or mono-substituted
 wherein the substituents independently are selected from oxo and C₁₋₃-alkyl; or

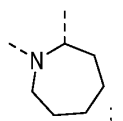
- -CO-O-R^{ox2}; wherein R^{ox2} represents

- C₁₋₄-alkyl;
- 2,2,2-trichloroethyl; or
- tetrahydropyranyl;

G)



or H)



or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 4; wherein R² represents methyl;
 or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5; wherein R³ represents isobutyl;
 or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 6; wherein R⁴ represents a group -CO-NH-R⁴¹; wherein R⁴¹
 represents

- C₂₋₆-alkyl, which is mono-substituted with C₁₋₄-alkoxy, or C₁₋₄-fluoroalkoxy;
- C₁₋₃-alkoxy-C₂₋₃-alkylene-O-CH₂-CH₂-;
- -CH₂-CH₂-C₅₋₆-heterocycloalkyl, wherein said C₅₋₆-heterocycloalkyl contains one ring oxygen atom,
 wherein said C₅₋₆-heterocyclyl is unsubstituted, mono- or di-substituted with C₁₋₄-alkyl;
- -L¹-aryl; wherein L¹ represents -CH₂-CH₂-, -CH₂-CH₂-O-* or -CH₂-CF₂*, -CH₂-(cyclopropan-1,1-diyl)*, -
 CH(CH₂-OH)-CH₂*, or -CH₂-CH(OH)*; wherein asterisks indicate the bond with which L¹ is attached to

the aryl; wherein aryl represents phenyl; wherein said aryl independently is unsubstituted, mono-, di- or tri-substituted, wherein the substituents are independently C₁₋₄-alkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkyl, C₁₋₃-fluoroalkoxy, halogen, cyano, hydroxy-C₁₋₃-alkyl, C₂₋₃-alkynyl, morpholin-4-yl, C₁₋₃-alkyl-SO₂-, 5- or 6-membered heteroaryl, or -NR^{N41}R^{N42}, wherein independently R^{N41} is hydrogen or C₁₋₄-alkyl, and R^{N42} is

5

hydrogen or C₁₋₄-alkyl;

- -L²-HET¹; wherein L² represents -CH₂-CH₂-, -CH₂-CF₂-, -CH₂-(cyclopropan-1,1-diyl)-*, or -CH₂-CH(OH)-*; wherein asterisks indicate the bond with which L² is attached to HET¹; wherein HET¹ represents 5- or 6-membered heteroaryl, wherein said 5- or 6-membered heteroaryl is independently unsubstituted, mono-, or di-substituted, wherein the substituents are independently C₁₋₄-alkyl; C₁₋₄-alkoxy; C₁₋₃-fluoroalkyl; halogen; C₃₋₆-cycloalkyl; C₃₋₆-cycloalkyl-methyl; C₁₋₃-alkoxy-C₁₋₃-alkyl; C₂₋₃-alkynyl, benzyl; or phenyl which is unsubstituted, mono- or di-substituted wherein the substituents independently are C₁₋₄-alkyl, C₁₋₄-alkoxy, or C₁₋₄-fluoroalkoxy;

10

- -CH₂-CH₂-HET², wherein HET² represents 9- or 10-membered bicyclic heteroaryl, wherein said HET² is unsubstituted;

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- -CH₂-CH₂-HCy¹, wherein HCy¹ represents a partially aromatic bicyclic ring system consisting of a phenyl ring which is fused to a 5- to 7-membered saturated heterocyclic ring containing one or two heteroatoms independently selected from oxygen and nitrogen, wherein, if present, said nitrogen when having a free valency is unsubstituted or mono-substituted with C₁₋₄-alkyl; and wherein the phenyl ring of said partially aromatic bicyclic ring system is unsubstituted, mono-, or di-substituted, wherein the substituents are

20

- independently C₁₋₄-alkyl, C₁₋₄-alkoxy, or halogen; or
- -CH₂-CH₂-HCy², wherein HCy² represents a partially aromatic bicyclic ring system consisting of a 5-membered heteroaryl which is fused to a 5- to 7-membered saturated carbocyclic ring;

or a pharmaceutically acceptable salt thereof.

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8. A compound according to any one of claims 1 to 7; wherein Ar² represents phenyl; or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8, wherein Ar¹ represents

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- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₄-alkoxy, and halogen;
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted; or

- a bicyclic aromatic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic aromatic ring independently is unsubstituted, or mono-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl, and halogen;

or a pharmaceutically acceptable salt thereof.

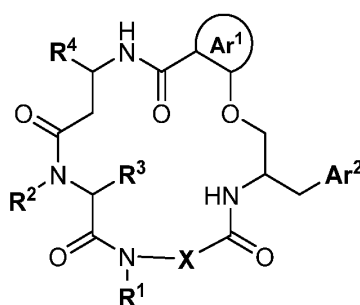
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10 10. A compound according to claim 1 wherein said compound is the compound of example 1; 2; 3; 4; 5; 6; 7; 8; 9; 10; 11; 12; 13; 14; 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 41; 42; 43; 44; 45; 46; 47; 48; 49; 50; 51; 52; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69; 70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81; 82; 83; 84; 85; 86; 87; 88; 89; 90; 91; 92; 93; 94; 95; 96; 97; 98; 99; 100; 101; 102; 103; 104; 105; 106; 107; 108; 109; 110; 111; 112; 113; 114; 115; 116; 117; 118; 119; 120; 121; 122; 123; 124; 125; 126; 127; 128; 129; 130; 131; 132; 133; 134; 135; 136; 137; 138; 139; 140; 141; 142; 143; 144; 145; 146; 147; 148; 149; 150; 151; 152; 153; 154; 155; 156; 157; 158; 159; 160; 161; 162; 163; 164; 165; 166; 167; 168; 169; 170; 171; 172; 173; 174; 175; 176; 177; 178; 179; 180; 181; 182; 183; 184; 185; 186; 187; 188; 189; 190; 191; 192; 193; 194; 195; 196; 197; 198; 199; 200; 201; 202; 203; 204; 205; 206; 207; 208; 209; 210; 211; 212; 213; 214; 15 215; 216; 217; 218; 219; 220; 221; 222; 223; 224; 225; 226; 227; 228; 229; 230; 231; 232; 233; 234; 235; 236; 237; 238; 239; 240; 241; 242; 243; 244; 245; 246; 247; 248; 249; 250; 251; 252; 253; 254; 255; 256; 257; 258; 259; 260; 261; 262; 263; 264; 265; 266; 267; 268; 269; 270; 271; 272; 273; 274; 275; 276; 277; 278; 279; 280; 281; 282; 283; 284; 285; 286; 287; 288; 289; 290; 291; 292; 293; 294; 295; 296; 297; 298; 299; 300; 301; 302; 303; 304; 305; 306; 307; 308; 309; 310; 311; 312; 313; 314; 315; 316; 317; 318; 319; 320; 321; 322; 323; 324; 325; 326; 327; 328; 329; 20 330; 331; 332; 333; 334; 335; 336; 337; 338; 339; 340; 341; 342; 343; 344; 345; 346; 347; 348; 349; 350; 351; 352; 353; 354; 355; 356; 357; 358; 359; 360; 361; 362; 363; 364; 365; 366; 367; 368; 369; 370; 371; 372; 373; 374; 375; 376; 377; 378; 379; 380; 381; 382; 383; 384; 385; 386; 387; 388; 389; 390; 391; 392; 393; 394; 395; 396; 397; 398; 399; 400; 401; 402; 403; 404; 405; 406; 407; 408; 409; 410; 411; 412; 413; 414; 415; 416; 417; 418; 419; 420; 421; 422; 423; 424; 425; 426; 427; 428; 429; 430; 431; 432; 433; 434; 435; 436; 437; 438; 439; 440; 441; 442; 443; 444; 25 445; 446; 447; 448; 449; 450; 451; 452; 453; 454; 455; 456; 457; 458; 459; 460; 461; 462; 463; 464; 465; 466; 467; 468; 469; 470; 471; 472; 473; 474; 475; 476; 477; 478; 479; 480; 481; 482; 483; 484; 485; 486; 487; 488; 489; 490; 491; 492; 493; 494; 495; 496; 497; 498; 499; 500; 501; 502; 503; 504; 505; 506; 507; 508; 509; 510; 511; 512; 513; 514; 515; 516; 517; 518; 519; 520; 521; 522; 523; 524; 525; 526; 527; 528; 529; 530; 531; 532; 533; 534; 535; 536; 537; 538; 539; 540; 541; 542; 543; 544; 545; 546; 547; 548; 549; 550; 551; 552; 553; 554; 555; 556; 557; 558; 559; 30 560; 561; 562; 563; 564; 565; 566; 567; 568; 569; 570; 571; 572; 573; 574; 575; 576; 577; 578; 579; 580; 581; 582; 583; 584; 585; 586; 587; 588; 589; 590; 591; 592; 593; 594; 595; 596; 597; 598; 599; 600; 601; 602; 603; 604; 605; 606; 607; 608; 609; 610; 611; 612; 613; 614; 615; 616; 617; 618; 619; 620; 621; 622; 623; 624; 625; 626; 627; 628; 629; 630; 631; 632; 633; 634; 635; 636; 637; 638; 639; 640; 641; 642; 643; 644; 645; 646; 647; 648; 649; 650; 651; 652; 653; 654; 655; 656; 657; 658; 659; 660; 661; 662; 663; 664; 665; 666; 667; 668; 669; 670; 671; 672; 673; 674; 35 675; 676; 677; 678; 679; 680; 681; 682; 683; 684; 685; 686; 687; 688; 689; 690; 691; 692; 693; 694; 695; 696; 697; 698; 699; 700; 701; 702; 703; 704; 705; 706; 707; 708; 709; 710; 711; 712; 713; 714; 715; 716; 717; 718; 719; 720; 721; 722;

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 5 815; 816; 817; 818; 819; 820; 821; 822; 823; 824; 825; 826; 827; 828; 829; 830; 831; 832; 833; 834; 835; 836; 837;
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 10 930; 931; 932; 933; 934; 935; 936; 937; 938; 939; 940; 941; 942; 943; 944; 945; 946; 947; 948; 949; 950; 951; 952;
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 976; 977; 978; 979; 980; 981; 982; or 983;

or a pharmaceutically acceptable salt thereof.

15 11. A compound of Formula (II)



Formula (II)

for use in the treatment of cystic fibrosis;

wherein X , R^1 , R^2 , R^3 , R^4 , Ar^2 are as defined for the compounds of Formula (I) according to claim 1; and

20 Ar^1 represents

- phenylene wherein said phenylene is unsubstituted;
- 5- or 6-membered heteroarylene wherein said 5- or 6-membered heteroarylene is unsubstituted;
- phenylene, or 5- or 6-membered heteroarylene; wherein said phenylene, or 5- or 6-membered heteroarylene independently is mono-, di- or tri-substituted, wherein the substituents are independently
 25 selected from C_{1-4} -alkyl, C_{1-4} -alkoxy, C_{1-3} -fluoroalkyl, C_{1-3} -fluoroalkoxy, cyano, and halogen;
- phenylene wherein said phenylene is fused to a 5- or 6-membered saturated heterocyclic ring containing one or two oxygen atoms, wherein said 5- or 6-membered saturated heterocyclic ring independently is unsubstituted or di-substituted with fluoro; or

- a bicyclic ring selected from naphthylene and 8- to 10-membered bicyclic heteroarylene; wherein said bicyclic ring independently is unsubstituted, mono-, or di-substituted, wherein the substituents are independently selected from C₁₋₄-alkyl, C₁₋₃-fluoroalkyl, C₁₋₄-alkoxy, C₁₋₃-fluoroalkoxy, cyano, and halogen; or
- 5 • quinoline-diyl, wherein said quinoline-diyl is present in form of the respective N-oxide; wherein said quinoline-diyl N-oxide is unsubstituted, or said quinoline-diyl N-oxide is mono-substituted with methyl or fluoro;

or a pharmaceutically acceptable salt thereof.

- 10 **12.** A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

13. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15

14. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the treatment of CFTR-related diseases and disorders including cystic fibrosis.

- 20 **15.** A method of treatment of CFTR-related diseases and disorders including cystic fibrosis, said method comprising administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 10, or of a pharmaceutically acceptable salt thereof.