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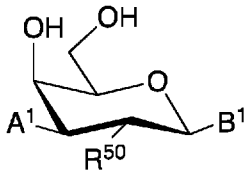

(I)

(57) Abstract: The present invention relates to beta D-galactopyranose compound of formula (I). Wherein the pyranose ring is β-D-galactopyranose, and these compounds are high affinity galectin-3 inhibitors for use in treatment of inflammation; fibrosis, such as pulmonary fibrosis, liver fibrosis, kidney fibrosis, ophthalmological fibrosis and fibrosis of the skin and heart; scarring; keloid formation; aberrant scar formation; surgical adhesions; scleroderma; systemic sclerosis; septic shock; cancer, such as carcinomas, sarcomas, leukemias and lymphomas, such as T-cell lymphomas; metastasising cancers; autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, intestinal fibrosis, ankylosing spondylitis, systemic lupus erythematosus; metabolic disorders; heart disease; heart failure; aortic stenosis, atherosclerosis, pathological angiogenesis, such as ocular angiogenesis or a disease or condition associated with ocular angiogenesis, e.g. neovascularization related to cancer; and eye diseases, such as age-related macular degeneration and corneal neovascularization; atherosclerosis; metabolic diseases such as diabetes; type 2 diabetes; insulin resistance; obesity; Diastolic HF; asthma and other interstitial lung diseases, including Hermansky-Pudlak syndrome, pulmonary arterial hypertension, RA-ILD, SSc-ILD, Lung disease with fibrosis such as COPD and asthma. Otosclerosis, mesothelioma; liver disorders, such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease, Liver cirrhosis of various origins, such as alcoholic and non-alcoholic, autoimmune cirrhosis such as primary biliary cirrhosis and sclerosing cholangitis, virally induced cirrhosis, cirrhosis induced by genetic disease. Liver cancer, cholangiocarcinoma, biliary tract cancer; neurodegenerative disorders such as Parkinsons disease, Alzheimers disease, cognitive impairment, cerebrovascular diseases such as stroke, traumatic brain injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, peripheral nephropathy.

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NOVEL GALACTOSIDE INHIBITOR OF GALECTINS

Technical field

The present invention relates to novel compounds, the use of said compounds as medicament and for the manufacture of a medicament for the treatment of diseases or disorders such as but not limited to cancers; fibrosis; scarring; keloid formation; aberrant scar formation; surgical adhesions; pathological angiogenesis; eye diseases; HIV-1 diseases; inflammation or transplant rejection in mammals. The invention also relates to pharmaceutical compositions comprising said novel compounds.

Background Art

Galectins are proteins with a characteristic carbohydrate recognition domain (CRD). This is a tightly folded β-sandwich of about 130 amino acids (about 15 kDa) with the two defining features 1) a β -galactose binding site and 2) sufficient similarity in a sequence motif of about seven amino acids, most of which (about six residues) make up the β-galactose binding site. Galectins are synthesized as cytosolic proteins from where they can be targeted to the nucleus, specific cytososlic sites, or secreted to engage in mechanisms effecting physiological functions such as inflammation, immune responses, cell-migration and autophagy. (Johannes et. al 2018) There are now over 9319 publications on galectins in PubMed, with most, as mentioned above, about galectins-1 (>1989) and -3 (>4791). Evidence from literature suggests roles for galectins in e.g. fibrosis, inflammation and cancer (Dings et. al., Dubé-Delarosbil et. al 2017)

Galectin-1 is widely expressed in many cell types and tissues (www.proteinatlas.org) being involved in mechanisms such as apoptosis, adhesion and migration, cell transformation, invasion and metastasis immune escape and angiogenesis. Upregulation of galectin 1 has also been associated with cancer (Dings et. al. 2018), inflammation (Sundblad et. al., 2017) fibrotic disease (Kathiriya et. al 2017, Wu et. al. 2019 and Bennet et. al 2019) and diabetes (Drake et. al. 2022). Example of small molecule ligands including β-D-galactopyranoside were recently reviewed and examplified in Blanchard et. al 2016 and Sethi et. al 2021).

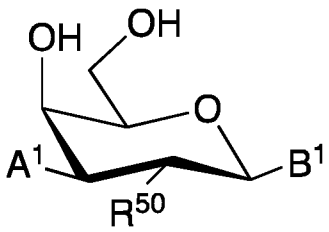
Galectin-3 is widely expressed in many cell types and tissues (www.proteinatlas.org) being involved in mechanisms such as apoptosis, adhesion and migration, cell transformation, invasion and metastasis immune escape and angiogenesis. Upregulation of galectin 3 has also been associated with cancer,

inflammation, neurodegenerative disease, fibrotic disease and diabetes (Dings et. al. 2018, Slack et. al. 2020, Li et. al. 2016) Example of small molecule ligands including β-D-galactopyranoside were recently reviewed and examplified in Blanchard et. al 2014 and Sethi et. al 2021.

Summary of the invention

The compounds of the present invention are novel β-D-galactopyranose compounds that unexpectedly have shown high affinity for galectin-1 and/or galectin-3 and are considered novel potent drug candidates.

In broad first aspect the present invention concerns a β-D-galactopyranose compound of formula (1)



wherein

the pyranose ring is β-D-galactopyranose,

A^1 is $(R^1)_n$-Z^{1a},

wherein

Z^{1a} is a five membered heterocycle having at least one heteroatom selected from O, S, and N, except 1,2,3-triazole and is attached to the β-D-galactopyranose;

n is 1 or 2;

each R^1 is independently selected from

a) C_{1-6} alkyl optionally substituted with a halogen; C_{1-6} alkyl substituted with a OH; halogen; CN; C_2-alkynyl; OH; OC_{1-6} alkyl optionally substituted with a halogen; C_{3-6} cycloalkyl optionally substituted with a halogen; SH; SC_{1-6} alkyl optionally substituted with a halogen; NR^2R^3, wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, C_{3-6} cycloalkyl optionally substituted with a halogen, $C(O)C_{1-6}$ alkyl optionally substituted with a halogen, and $S(O_2)C_{1-6}$ alkyl optionally substituted with a halogen, or R^2 and R^3 taken together with the nitrogen to which they are attached form a heterocycloalkyl, optionally substituted with a group selected from a halogen; a spiro heterocycle, such as N-(2-oxa)-6-azaspiro[3.3]heptanyl; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen;

$S(O_2)C_{3-6}$ cycloalkyl optionally substituted with a halogen; C_{1-6} alkenyl optionally substituted with a halogen; $C(O)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; COOH; $C(O)OC_{1-6}$ alkyl optionally substituted with a halogen; $C(O)OC_{3-6}$ cycloalkyl optionally substituted with a halogen; $C(O)NR^6R^7$, wherein R^6 and R^7 are independently selected from H, C_{1-3} alkyl optionally substituted with a halogen or an aryl, such as a phenyl, cyclopropyl optionally substituted with a halogen; and $S(O_2)NR^8R^9$ wherein R^8 and R^9 are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen;

b) an aryl, such as phenyl or naphthyl, optionally substituted with a group selected from a halogen; CN; a spiro heterocycle; -COOH; $-CONR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{10} and R^{11} together with the nitrogen may form a heterocycloalkyl; C_{1-3} alkyl, optionally substituted with a F; cyclopropyl, optionally substituted with a F; OC_{1-3} alkyl, optionally substituted with a F; O-cyclopropyl, optionally substituted with a F; $NR^{12}R^{13}$, wherein R^{12} and R^{13} are independently selected from H, C_{1-3} alkyl and cyclopropyl; $C(=O)$-R^{14}, wherein R^{14} is selected from H and C_{1-3} alkyl; OH; and R^{15}-CONH- wherein R^{15} is selected from C_{1-3} alkyl and cyclopropyl;

c) a heterocycle, such as heteroaryl or heterocycloalkyl, optionally substituted with a group selected from a halogen; a spiro heterocycle; CN; -COOH; $-CONR^{16}R^{17}$, wherein R^{16} and R^{17} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{16} and R^{17} together with the nitrogen may form a heterocycloalkyl; C_{1-3} alkyl, optionally substituted with a F; cyclopropyl, optionally substituted with a F; OC_{1-3} alkyl, optionally substituted with a F; O-cyclopropyl, optionally substituted with a F; $NR^{18}R^{19}$, wherein R^{18} and R^{19} are independently selected from H, C_{1-3} alkyl, and cyclopropyl; $C(=O)$-R^{20}, wherein R^{20} is selected from H and C_{1-3} alkyl; OH; and R^{21}-CONH- wherein R^{21} is selected from C_{1-3} alkyl and cyclopropyl;

d) phenyl, naphthalinyl, biphenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, quinoxainyl, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzoxazolyl, benzothiazolyl, benzodioxolyl, dihydrobenzodioxinyl, dihydroquinolinonyl, dihydrobenzothiophene-2,2-dioxide, pyrrolyl, furanyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, or thiadiazolyl; optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl optionally

substituted with a halogen; halogen; CN; C_2-alkynyl; OH; OC_{1-6} alkyl optionally substituted with a halogen; C_{3-6} cycloalkyl optionally substituted with a halogen; SH; SC_{1-6} alkyl optionally substituted with a halogen; $NR^{22}R^{23}$, wherein R^{22} and R^{23} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, C_{3-6} cycloalkyl optionally substituted with a halogen, $C(O)C_{1-6}$ alkyl optionally substituted with a halogen, and $S(O_2)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; $S(O_2)C_{3-6}$ cycloalkyl optionally substituted with a halogen; C_{1-6} alkenyl optionally substituted with a halogen; $C(O)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; COOH; $C(O)OC_{1-6}$ alkyl optionally substituted with a halogen; $C(O)OC_{3-6}$ cycloalkyl optionally substituted with a halogen; $C(O)NR^{24}R^{25}$, wherein R^{24} and R^{25} are independently selected from H, C_{1-3} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen; and $S(O_2)NR^{26}R^{27}$ wherein R^{26} and R^{27} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen;

e) Y^1-Z^2 wherein

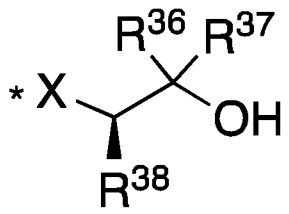
Y^1 is linked to Z^{1a} and is selected from the group consisting of S, Se, SO, SO_2, O, C=O, and $CR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen, OH, or halogen;

Z^2 is selected from the group consisting of phenyl, naphthalinyl, biphenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, quinoxainyl, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzoxazolyl, benzothiazolyl, benzodioxolyl, dihydrobenzodioxinyl, dihydroquinolinonyl, dihydrobenzothiophene-2,2-dioxide, pyrrolyl, furanyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, or thiadiazolyl; optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl optionally substituted with a halogen; halogen; CN; C_2-alkynyl; OH; OC_{1-6} alkyl optionally substituted with a halogen; C_{3-6} cycloalkyl optionally substituted with a halogen; SH; SC_{1-6} alkyl optionally substituted with a halogen; $NR^{30}R^{31}$, wherein R^{30} and R^{31} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, C_{3-6} cycloalkyl optionally substituted with a halogen, $C(O)C_{1-6}$ alkyl optionally substituted with a halogen, and $S(O_2)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with

a halogen; $S(O_2)C_{3-6}$ cycloalkyl optionally substituted with a halogen; C_{1-6} alkenyl optionally substituted with a halogen; $C(O)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; COOH; $C(O)OC_{1-6}$ alkyl optionally substituted with a halogen; $C(O)OC_{3-6}$ cycloalkyl optionally substituted with a halogen; $C(O)NR^{32}R^{33}$, wherein R^{32} and R^{33} are independently selected from H, C_{1-3} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen; and $S(O_2)NR^{34}R^{35}$ wherein R^{34} and R^{35} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen; and

f) hydrogen (H);

B^1 is a)



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wherein the asterix on the X is linked to D-galactopyranose and is in the beta anomeric conformation,

X is selected from S, SO, SO_2, O, C=O, and $CR^{2a}R^{3a}$ wherein R^{2a} and R^{3a} are independently selected from hydrogen, OH, or halogen;

R^{36} is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, C_{1-6} alkyl substituted with a phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl;

R^{37} is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, C_{1-6} alkyl substituted with a phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl;

or R^{36} and R^{37} together with the carbon atom to which they are attached form a non-aromatic 3-6-membered ring optionally containing 1 or 2 nitrogen, 1 or 2 oxygen and/or 1 or 2 sulphur, optionally substituted with a group selected from one or more halogen, hydroxy, CN, C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, C_{3-6} cycloalkyl, SO_2-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2-C_{3-6} cycloalkyl, CO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CO-C_{3-6}

cycloalkyl, COO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, COO-C_{3-6} cycloalkyl, CONH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CONH-C_{3-6} cycloalkyl, SO_2NH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2NH-C_{3-6} cycloalkyl, and a spiroheterocycle optionally substituted with a group selected from a halogen and a C_{1-6} alkyl;

R^{38} is selected from

i) aryl optionally substituted with a group selected from C_{1-6} alkyl, C_{1-6} alkyl substituted with a halogen, OH, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{42}R^{43}$, wherein R^{42} and R^{43} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, and aryl optionally substituted with a group selected from halogen or C_{1-3} alkyl;

ii) heteroaryl optionally substituted with a group selected from C_{1-6} alkyl, C_{1-6} alkyl substituted with a halogen, OH, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{44}R^{45}$, wherein R^{44} and R^{45} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, and aryl optionally substituted with a group selected from halogen or C_{1-3} alkyl;

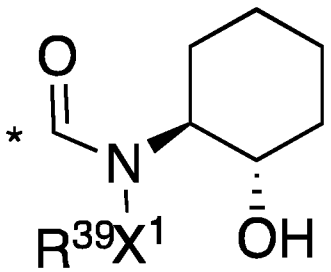
iii) C=O-$NR^{40}R^{41}$ wherein R^{40} and R^{41} are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl substituted with a C_{1-6} alkoxy, C_{1-6} alkyl substituted with a halogen, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{46}R^{47}$, wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a

4-6 membered heterocycloalkyl, such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, C_{1-2}-alkylene-R^{48}, wherein R^{48} represents phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, phenyl optionally substituted with a C_{1-3} alkyl, 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, and


;

or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a 4-6 membered heterocycloalkyl, such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, optionally substituted with a halogen or C_{1-3} alkyl, a partially aromatic bicyclic ring consisting of a pyrrolidine-1-yl or a piperidine-1-yl, wherein said pyrrolidine or piperidine is fused to a phenyl ring;

b)



Wherein the asterix on the carbonyl carbon is linked to D-galactopyranose and is in the beta anomeric conformation,

X^1 is selected from C_{1-6} alkyl or X^1 is absent and R^{39} is linked to N;

R^{39} is attached to N or X^1 and is selected from aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, CN, C_{1-6} alkyl, SO_2C_{1-3} alkyl, C_{1-6} alkyl substituted with a halogen, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, amino, ethynyl, heterocycloalkyl;

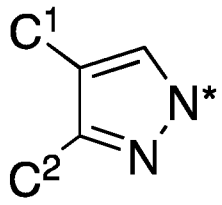
R^{50} is selected from the group consisting of a) H, b) OH, c) OC_{1-6} alkyl optionally substituted with one or more halogen, phenyl, phenyl substituted with one

or more groups selected from OH and halogen, CN, OR^{49}, $NR^{51}R^{52}$, $CONH_2$, and $CONR^{53}R^{54}$, wherein R^{53} and R^{54} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{53} and R^{54} together with the nitrogen may form a heterocycloalkyl optionally substituted with a group selected from OH, wherein R^{49} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{55}-CONH- wherein R^{55} is selected from C_{1-3} alkyl and cyclopropyl, R^{51} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{56}-CONH- wherein R^{56} is selected from C_{1-3} alkyl and cyclopropyl, and R^{52} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{57}-CONH- wherein R^{57} is selected from C_{1-3} alkyl and cyclopropyl, d) branched OC_{3-6} alkyl optionally substituted with one or more halogen, CN, OR^{58}, $NR^{59}R^{60}$, $CONH_2$, and $CONR^{61}R^{62}$, wherein R^{61} and R^{62} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{61} and R^{62} together with the nitrogen may form a heterocycloalkyl optionally substituted with a group selected from OH, wherein R^{58} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{63}-CONH- wherein R^{63} is selected from C_{1-3} alkyl and cyclopropyl, R^{59} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{64}-CONH- wherein R^{64} is selected from C_{1-3} alkyl and cyclopropyl, and R^{60} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{65}-CONH- wherein R^{65} is selected from C_{1-3} alkyl and cyclopropyl , and e) cyclic OC_{3-6} alkyl optionally substituted with one or more halogen, CN, OR^{66}, $NR^{67}R^{68}$, $CONH_2$, and $CONR^{69}R^{70}$, wherein R^{69} and R^{70} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{69} and R^{70} together with the nitrogen may form a heterocycloalkyl optionally substituted with a group selected from OH, wherein R^{66} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{71}-CONH- wherein R^{71} is selected from C_{1-3} alkyl and cyclopropyl, R^{67} is

selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{72}-CONH- wherein R^{72} is selected from C_{1-3} alkyl and cyclopropyl, and R^{68} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{73}-CONH- wherein R^{73} is selected from C_{1-3} alkyl and cyclopropyl; or a pharmaceutically acceptable salt or solvate thereof.

In an embodiment Z^{1a} is selected from 1,2,4-triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, dioxolyl, dithiolyl, thiazolyl, isothiazolyl, furanyl, thiophen, pyrrolyl, imidazolyl, or pyrazolyl. Preferably, Z^{1a} is a pyrazolyl.

When Z^{1a} is a pyrazolyl the preferred embodiment is



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wherein C^1 and C^2 are independently selected from R^1 (when one of C^1 and C^2 is a hydrogen then n is 1 in $(R^1)_n$-Z^{1a}, and when n is 2 then none of C^1 and C^2 is a hydrogen)

wherein the asterix * indicates the nitrogen atom of the pyrazole ring that is covalently attached to the galactopyranose.

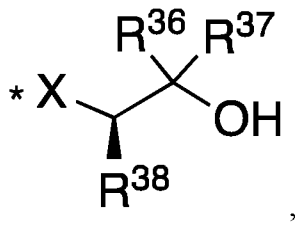
In one embodiment n is 1 and C^1 is selected from R^1 and C^2 is hydrogen.

In a further embodiment C^1 is selected from a phenyl optionally substituted with one, two or three substitutents selected from the group consisting of a halogen, a CN, cyclopropyl optionally substituted with a F, isopropyl optionally substituted with a F, OC_{1-3} alkyl optionally substituted with a F, O-cyclopropyl optionally substituted with a F, O-isopropyl optionally substituted with a F, and a C_{1-3} alkyl optionally substituted with a F; and C^2 is hydrogen. Typically, C^1 is selected from a phenyl substituted with one, two or three substitutents selected from the group consisting of Cl, F, Br and I, such as three F. In another embodiment C^1 is selected from a phenyl substituted with three substitutents selected from the group consisting of Cl and F, such as one Cl and two F. When there are three substituents such substituents are connected to the ortho, meta and para positions of the phenyl. Typically, meta and para

positions of the phenyl. In another embodiment the three substitunets are connected to the ortho, meta and para positions of the phenyl.

In a further embodiment C^1 is selected from a thiazolyl optionally substituted with one, two or three substitutents selected from the group consisting of a halogen, a CN, cyclopropyl optionally substituted with a F, isopropyl optionally substituted with a F, OC_{1-3} alkyl optionally substituted with a F, O-cyclopropyl optionally substituted with a F, O-isopropyl optionally substituted with a F, and a C_{1-3} alkyl optionally substituted with a F; and C^2 is hydrogen. Preferably, C^1 is selected from a thiazol substituted with a halogen, such as one halogen, e.g., one Cl.

In a still further embodiment B^1 is



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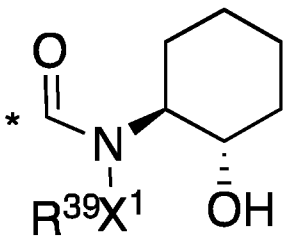
wherein the asterix on the X is linked to D-galactopyranose and is in the beta anomeric conformation, and X, R^{36}, R^{37}, and R^{38} are as defined in above under the compound of formula (1). Preferably, X is S.

In a further embodiment R^{36} and R^{37} together with the carbon atom to which they are attached form a non-aromatic 5-6-membered ring optionally containing 1 nitrogen and/or 1 oxygen, optionally substituted with a group selected from one or more halogen, hydroxy, CN, C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, C_{3-6} cycloalkyl, SO_2-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2-C_{3-6} cycloalkyl, CO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CO-C_{3-6} cycloalkyl, COO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, COO-C_{3-6} cycloalkyl, CONH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CONH-C_{3-6} cycloalkyl, SO_2NH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2NH-C_{3-6} cycloalkyl, and a spiroheterocycle optionally substituted with a group selected from a halogen and a C_{1-6} alkyl. Typically, R^{36} and R^{37} together with the carbon atom to which they are attached form a non-aromatic 5-6-membered ring optionally containing 1 nitrogen and/or 1 oxygen, optionally substituted with a group selected from halogen, C_{1-6} alkyl and SO_2-C_{1-6} alkyl, such as two F, one methyl or one SO_2CH_3.

In a still further embodiment R^{38} is heteroaryl optionally substituted with a group selected from C_{1-6} alkyl, C_{1-6} alkyl substituted with a halogen, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{44}R^{45}$, wherein R^{44} and R^{45} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, and aryl optionally substituted with a group selected from halogen or C_{1-3} alkyl. Typically, R^{38} is pyridinyl substituted with a group selected from C_{1-6} alkyl substituted with a halogen and C_{3-6} cycloalkyl, such as one CF_3 or one cyclopropyl. In another embodiment R^{38} is pyridinyl substituted with a C_{1-6} alkyl, such as a methyl, typically one methyl. In a further embodiment R^{38} is pyridinyl substituted with a halogen, such as a Cl, typically one Cl. Alternatively, R^{38} is C=O-$NR^{40}R^{41}$ wherein R^{40} and R^{41} are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} cyclic ether, and a 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl. Preferably, R^{38} is C=O-$NR^{40}R^{41}$ wherein R^{40} is selected from C_{1-6} alkyl and R^{41} is selected from C_{1-6} alkyl, C_{3-4} cycloalkyl, morpholinyl, and pyridinyl.

In a still further embodiment B^1 is



Wherein the asterix on the carbonyl carbon is linked to D-galactopyranose and is in the beta anomeric conformation, and X^1 and R^{39} are as defined in above under the compound of formula (1).

In an embodiment X^1 is selected from C_{1-6} alkyl and R^{39} is selected from aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, CN, C_{1-6} alkyl, SO_2C_{1-3} alkyl, C_{1-6} alkyl substituted with a halogen, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, amino, ethynyl, heterocycloalkyl. In another embodiment X^1 is absent and R^{39} is linked to N and is

selected from phenyl substituted with one or more halogen and CN. In a further embodiment R^{39} is phenyl substituted with one or two selected from Cl and CN.

In a still further embodiment R^{50} is selected from H, OH, OC_{1-4} alkyl, such as O-methyl, O-ethyl, or O-isopropyl, or OC_{1-4} alkyl substituted with one $CONR^{53}R^{54}$, wherein R^{53} and R^{54} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{53} and R^{54} together with the nitrogen form a heterocycloalkyl optionally substituted with a group selected from OH. In an embodiment R^{50} is selected from OH. In another embodiment R^{50} is selected from OC_{1-4} alkyl such as O-methyl, substituted with one $CONR^{53}R^{54}$, wherein R^{53} and R^{54} together with the nitrogen form a heterocycloalkyl optionally substituted with a group selected from OH.

In a further aspect the present invention concerns a β-D-galactopyranose compound of formula (1) selected from any one of the group consisting of:

(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(1-piperidinylcarbonyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

2-Ethylmethylamino-(S)-1-[4-hydroxy-1-(methylsulfonyl)piperidin-4-yl]-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

2-Cyclobutylmethylamino-(S)-1-(1-hydroxycyclopentyl)-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(S)-1-(4-Hydroxypyran-4-yl)-2-methyl(pyridin-2-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-2-methyl(pyran-4-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-2-*O*-methyl-1-thio-β-D-galactopyranoside,

(R)-1-[3-(Trifluoromethyl)pyridin-2-yl]-1-(4-hydroxy-1-methylpiperidin-4-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(3-Cyclopropylpyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

2,6-Anhydro-*N*-(3-chloro-5-cyanophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide,

2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide,

2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-(2-morpholino-2-oxoethyl)-D-glycero-L-manno-heptonamide,

2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-{2-[(S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-D-glycero-L-manno-heptonamide,

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chlorothiazol-2-yl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-2-O-methyl-1-thio-β-D-galactopyranoside, and

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-2-O-methyl-1-thio-β-D-galactopyranoside; or a pharmaceutically acceptable salt or solvat thereof.

In a further aspect the present invention relates to a compound of formula (1) for use as a medicine.

In a still further aspect, the present invention relates to a pharmaceutical composition comprising the compound of any one of the previous claims and optionally a pharmaceutically acceptable additive, such as a carrier and/or excipient.

In a further aspect the present invention relates to a compound of formula (1) of the present invention for use in a method for treating a disorder relating to the binding of a galectin-3 to a ligand in a mammal, such as a human. In a further embodiment the disease or disorder is selected from the group consisting of inflammation; fibrosis, such as pulmonary fibrosis, liver fibrosis, kidney fibrosis, ophthalmological fibrosis and fibrosis of the skin and heart; scarring; keloid formation; aberrant scar formation; surgical adhesions; scleroderma; systemic sclerosis; septic shock; cancer, such as carcinomas, sarcomas, leukemias and lymphomas, such as T-cell lymphomas; metastasising cancers; autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, intestinal fibrosis, ankylosing spondylitis, systemic lupus erythematosus; metabolic disorders; heart disease; heart failure; aortic stenosis, atherosclerosis, pathological angiogenesis, such as ocular angiogenesis or a disease or condition associated with ocular angiogenesis, e.g. neovascularization related to cancer; and eye diseases, such as age-related macular degeneration and corneal neovascularization; atherosclerosis; metabolic diseases such as diabetes; type 2 diabetes; insulin resistance; obesity; Diastolic HF; asthma and other interstitial lung diseases, including Hermansky-Pudlak syndrome, pulmonary arterial hypertension, RA-ILD, SSc-ILD, Lung disease with fibrosis such as COPD and asthma. Otosclerosis, mesothelioma; liver disorders, such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease, Liver cirrhosis of various origins, such as alcoholic and non-alcoholic, autoimmune cirrhosis such as primary biliary cirrhosis and sclerosing cholangitis, virally induced cirrhosis, cirrhosis induced by genetic disease. Liver cancer, cholangiocarcinoma,

biliary tract cancer; neurodegenerative disorders such as Parkinsons disease, Alzheimers disease, cognitive impairment, cerebrovascular diseases such as stroke, traumatic brain injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, peripheral nephropathy.

In a still further aspect the present invention relates to a method for treatment of a disease or disorder relating to the binding of a galectin-3 to a ligand in a mammal, such as a human, wherein a therapeutically effective amount of at least one compound of formula (1) of the present invention is administered to a mammal in need of said treatment.

In a further embodiment the disease or disorder is selected from the group consisting of inflammation; fibrosis, such as pulmonary fibrosis, liver fibrosis, kidney fibrosis, ophthalmological fibrosis and fibrosis of the skin and heart; scarring; keloid formation; aberrant scar formation; surgical adhesions; scleroderma; systemic sclerosis; septic shock; cancer, such as carcinomas, sarcomas, leukemias and lymphomas, such as T-cell lymphomas; metastasising cancers; autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, intestinal fibrosis, ankylosing spondylitis, systemic lupus erythematosus; metabolic disorders; heart disease; heart failure; aortic stenosis, atherosclerosis, pathological angiogenesis, such as ocular angiogenesis or a disease or condition associated with ocular angiogenesis, e.g. neovascularization related to cancer; and eye diseases, such as age-related macular degeneration and corneal neovascularization; atherosclerosis; metabolic diseases such as diabetes; type 2 diabetes; insulin resistance; obesity; Diastolic HF; asthma and other interstitial lung diseases, including Hermansky-Pudlak syndrome, pulmonary arterial hypertension, RA-ILD, SSc-ILD, Lung disease with fibrosis such as COPD and asthma. Otosclerosis, mesothelioma; liver disorders, such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease, Liver cirrhosis of various origins, such as alcoholic and non-alcoholic, autoimmune cirrhosis such as primary biliary cirrhosis and sclerosing cholangitis, virally induced cirrhosis, cirrhosis induced by genetic disease. Liver cancer, cholangiocarcinoma, biliary tract cancer; neurodegenerative disorders such as Parkinsons disease, Alzheimers disease, cognitive impairment, cerebrovascular diseases such as stroke, traumatic brain injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, peripheral nephropathy

Another aspect of the present invention concerns combination therapy involving administering a compound of formula (1) of the present invention together with a therapeutically active compound different from the compound of formula (1) (interchangeable with "a different therapeutically active compound"). In one embodiment the present invention relates to a combination of a compound of formula (1) and a different therapeutically active compound for use in treatment of a disorder relating to the binding of a galectin-3 to a ligand in a mammal. Such disorders are disclosed below.

In an embodiment of the present invention, a therapeutically effective amount of at least one compound of formula (1) of the present invention is administered to a mammal in need thereof in combination with a different therapeutically active compound. In a further embodiment, said combination of a compound of formula (1) together with a different therapeutically active compound is administered to a mammal suffering from a disorder selected from the group consisting of inflammation; fibrosis, such as pulmonary fibrosis, liver fibrosis, kidney fibrosis, ophthalmological fibrosis and fibrosis of the skin and heart; scarring; keloid formation; aberrant scar formation; surgical adhesions; septic shock; cancer, such as carcinomas, sarcomas, leukemias and lymphomas, such as T-cell lymphomas; metastasising cancers; autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, systemic lupus erythematosus; metabolic disorders; heart disease; heart failure; pathological angiogenesis, such as ocular angiogenesis or a disease or condition associated with ocular angiogenesis, e.g. neovascularization related to cancer; and eye diseases, such as age-related macular degeneration and corneal neovascularization; atherosclerosis; metabolic diseases such as diabetes; type 2 diabetes; insulin resistens; obesity; Diastolic HF; asthma and other interstitial lung diseases, including Hermansky-Pudlak syndrome, mesothelioma; liver disorders, such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease.

A non-limiting group of cancers given as examples of cancers that may be treated, managed and/or prevented by administration of a compound of formula (1) in combination with a different therapeutically active compound is selected from: colon carcinoma, breast cancer, pancreatic cancer, ovarian cancer, prostate cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma,

chordoma, angiosarcoma, endotheliosarcoma, lymphangeosarcoma, lymphangeoendothelia sarcoma, synovioma, mesothelioma, Ewing's sarcoma, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystandeocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioblastomas, neuronomas, craniopharingiomas, schwannomas, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroama, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias and lymphomas, acute lymphocytic leukemia and acute myelocytic polycythemia vera, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, Hodgkin's Disease, non-Hodgkin's lymphomas, rectum cancer, urinary cancers, uterine cancers, oral cancers, skin cancers, stomach cancer, brain tumors, liver cancer, laryngeal cancer, esophageal cancer, mammary tumors, childhood-null acute lymphoid leukemia (ALL), thymic ALL, B-cell ALL, acute myeloid leukemia, myelomonocytoid leukemia, acute megakaryocytoid leukemia, Burkitt's lymphoma, acute myeloid leukemia, chronic myeloid leukemia, and T cell leukemia, small and large non-small cell lung carcinoma, acute granulocytic leukemia, germ cell tumors, endometrial cancer, gastric cancer, cancer of the head and neck, chronic lymphoid leukemia, hairy cell leukemia and thyroid cancer.

In some aspects of the present invention, the administration of at least one compound of formula (1) of the present invention and at least one additional therapeutic agent demonstrates therapeutic synergy. In some aspects of the methods of the present invention, a measurement of response to treatment observed after administering both at least one compound of formula (1) of the present invention and the additional therapeutic agent is improved over the same measurement of response to treatment observed after administering either the at least one compound of formula (1) of the present invention or the additional therapeutic agent alone.

A further aspect of the present invention concerns combination therapy involving administering a compound of formula (1) of the present invention together with an anti-fibrotic compound different form the compound of formula (1) to a mammal in need thereof. In a further embodiment, such anti-fibrotic compound may be selected from the following non-limiting group of anti-fibrotic compounds: pirfenidone, nintedanib, simtuzumab (GS-6624, AB0024), BG00011 (STX100), PRM-151, PRM-167, PEG-FGF21, BMS-986020, FG-3019, MN-001, IW001, SAR156597, GSK2126458, PAT-1251 and PBI-4050.

A still further aspect of the present invention concerns combination therapy involving administering a compound of formula (1) in combination with a further conventional cancer treatment such as chemotherapy or radiotherapy, or treatment with immunostimulating substances, gene therapy, treatment with antibodies and treatment using dendritic cells, to a mammal in need thereof.

In an embodiment the compound of formula (1) is administered together with at least one additional therapeutic agent selected from an antineoplastic chemotherapy agent. In a further embodiment, the antineoplastic chemotherapeutic agent is selected from: all-trans retinoic acid, Actimide, Azacitidine, Azathioprine, Bleomycin, Carboplatin, Capecitabine, Cisplatin, Chlorambucil, Cyclophosphamide, Cytarabine, Daunorubicin, Docetaxel, Doxifluridine, Doxorubicin, Epirubicin, Etoposide, Fludarabine, Fluorouracil, Gemcitabine, Hydroxyurea, Idarubicin, Irinotecan, Lenalidomide, Leucovorin, Mechlorethamine, Melphalan, Mercaptopurine, Methotrexate, Mitoxantrone, Oxaliplatin, Paclitaxel, Pemetrexed, Revlimid, Temozolomide, Teniposide, Thioguanine, Valrubicin, Vinblastine, Vincristine, Vindesine and Vinorelbine. In one embodiment, a chemotherapeutic agent for use in the combination of the present agent may, itself, be a combination of different chemotherapeutic agents. Suitable combinations include FOLFOX and IFL. FOLFOX is a combination which includes 5-fluorouracil (5-FU), leucovorin, and oxaliplatin. IFL treatment includes irinotecan, 5-FU, and leucovorin.

In a further embodiment of the present invention, the further conventional cancer treatment includes radiation therapy. In some embodiments, radiation therapy includes localized radiation therapy delivered to the tumor. In some embodiments, radiation therapy includes total body irradiation.

In other embodiments of the present invention the further cancer treatment is selected from the group of immunostimulating substances e.g. cytokines and

antibodies. Such cytokines may be selected from the group consisting of, but not limited to: GM-CSF, type I IFN, interleukin 21, interleukin 2, interleukin 12 and interleukin 15. The antibody is preferably an immunostimulating antibody such as anti-CD40 or anti-CTLA-4 antibodies. The immunostimulatory substance may also be a substance capable of depletion of immune inhibitory cells (e.g. regulatory T-cells) or factors, said substance may for example be E3 ubiquitin ligases. E3 ubiquitin ligases (the HECT, RING and U-box proteins) have emerged as key molecular regulators of immune cell function, and each may be involved in the regulation of immune responses during infection by targeting specific inhibitory molecules for proteolytic destruction. Several HECT and RING E3 proteins have now also been linked to the induction and maintenance of immune self-tolerance: c-Cbl, Cbl-b, GRAIL, Itch and Nedd4 each negatively regulate T cell growth factor production and proliferation.

In some embodiments of the present invention the compound of formula (1) is administered together with at least one additional therapeutic agent selected from a checkpoint inhibitor. In some embodiments of the invention, the checkpoint inhibitor is acting on one or more of the following, non-limiting group of targets: CEACAM1, galectin-9, TIM3, CD80, CTLA4, PD-1, PD-L1, HVEM, BTLA, CD160, VISTA, B7-H4, B7-2, CD155, CD226, TIGIT, CD96, LAG3, GITF, OX40, CD137, CD40, IDO, and TDO. These are known targets and some of these targets are described in Melero et al., Nature Reviews Cancer (2015). Examples of check point inhibitors administered together with the compound of formula (1) are Anti-PD-1: Nivolumab, Pembrolizumab, Cemiplimab. Anti-PD-L1: Atezolizumab, Avelumab, Durvalumab and one Anti-CTLA-4: Ipilimumab. Each one of these check point inhibitors can be made the subject of an embodiment in combination with any one of the compounds of formula (1).

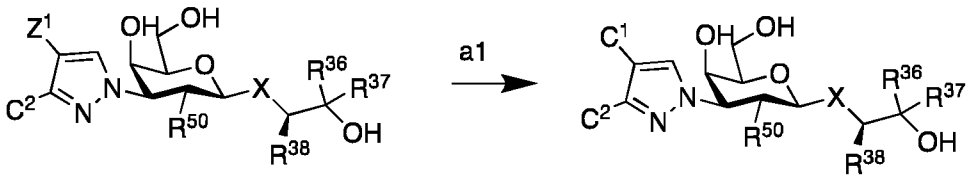
In some embodiments of the present invention the compound of formula (1) is administered together with at least one additional therapeutic agent selected from an inhibitor of indoleamine-2,3-dioxygenase (IDO).

In some embodiments of the present invention the compound of formula (1) is administered together with at least one additional therapeutic agent selected from one or more inhibitors of the CTLA4 pathway. In some embodiments, the inhibitor of the CTLA4 pathway is selected from one or more antibodies against CTLA4.

In some embodiments of the present invention the compound of formula (1) is administered together with at least one additional therapeutic agent selected from one or more inhibitors of the PD-1/PD-L pathway.

In some embodiments, the one or more inhibitors of the PD-1/PD-L pathway are selected from one or more antibodies or antibody fragments against PD-1, PD-L1, and/or PD-L2, or other ways by which an anti-PD1 antibodies can be induced such as mRNA based introduction of genetic material which sets forth in-body production of anti-PD1 or anti-PDL1 antibodies or fragments of such antibodies.

In a still further aspect the present invention relates to a process of preparing a compound of formula II or a pharmaceutically acceptable salt or solvate thereof comprising the step a1 where C^1, C^2, X, R^{36}, R^{37}, R^{38} and R^{50} are defined as above under formula 1;

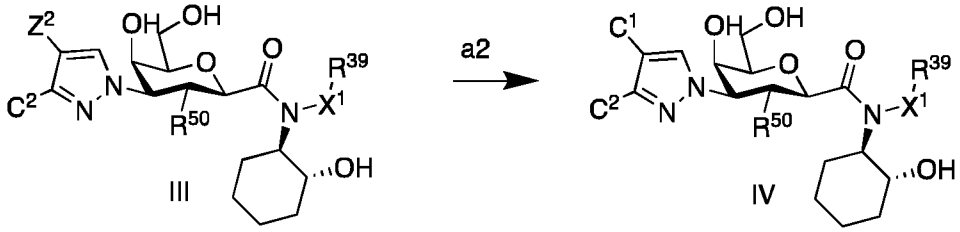


I II

a1) Reacting a compound of formula I wherein Z^1 is a halide such as bromine or iodine with a compound of formula C^1-Y^1, wherein Y^1 is defined as a boronic acid, borinatester, tinalkyl or zincalkyl suitable for cross-coupling reactions such as Suzuki, Stille or Negishi couplings in the presence of a catalyst such as palladium tetrakis or $Pd(dppf)Cl_2$ in a suitable solvent such as 1,4-dioxane/water or acetonitrile optionally in the presence of a base such as K_2CO_3, optionally in the presence of a cupper salt such as CuI, optionally at elevated temperatures to give a compound of formula II; alternatively, reacting a compound of formula I wherein Z^1 is defined as a boronic acid, borinatester, tinalkyl or zincalkyl suitable for cross-coupling reactions such as Suzuki, Stille or Negishi couplings with a compound of formula C^1-Y^2 wherein Y^2 is defined as a halide such as bromine or iodine in the presence of a catalyst such as palladium tetrakis or $Pd(dppf)Cl_2$ and a base such as K_2CO_3 in a suitable solvent such as 1,4-dioxane/water optionally at elevated temperatures to give a compound of formula II.

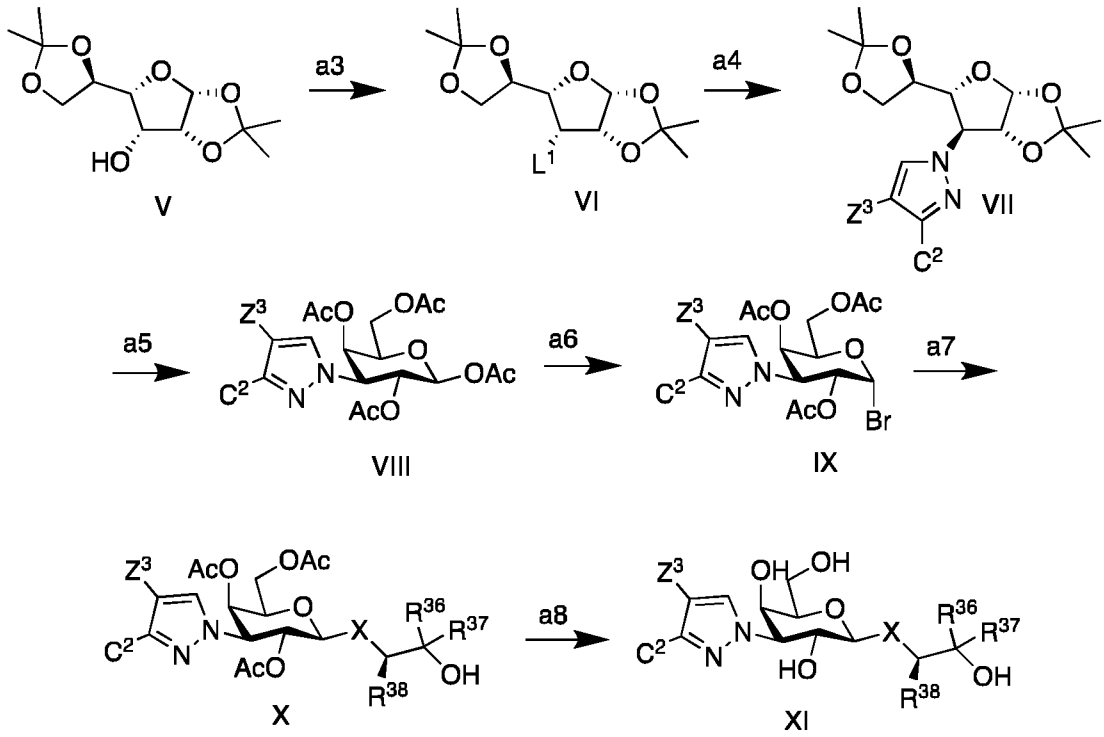
In a still further aspect the present invention relates to a process of preparing a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof

comprising the step a2 where C^1, C^2, X^1, R^{39} and R^{50} are defined as above under formula 1;



a2) Reacting a compound of formula III wherein Z^2 is a halide such as bromine or iodine with a compound of formula C^1-Y^3, wherein Y^3 is defined as a boronic acid, borinatester, tinalkyl or zincalkyl suitable for cross-coupling reactions such as Suzuki, Stille or Negishi couplings in the presence of a catalyst such as palladium tetrakis or $Pd(dppf)Cl_2$ in a suitable solvent such as 1,4-dioxane/water optionally in the presence of a base such as K_2CO_3, optionally at elevated temperatures to give a compound of formula IV; alternatively, reacting a compound of formula III wherein Z^2 is defined as a boronic acid, borinatester, tinalkyl or zincalkyl suitable for cross-coupling reactions such as Suzuki, Stille or Negishi couplings with a compound of formula C^1-Y^4 wherein Y^4 is defined as a halide such as bromine or iodine in the presence of a catalyst such as palladium tetrakis or $Pd(dppf)Cl_2$ and a base such as K_2CO_3 in a suitable solvent such as 1,4-dioxane/water optionally at elevated temperatures to give a compound of formula IV.

In a still further aspect the present invention relates to a process of preparing a compound of formula XI or a pharmaceutically acceptable salt or solvate thereof comprising the steps a3-a8 where C^2, X, R^{36}, R^{37} and R^{38} are defined as above under formula 1;



a3) Reacting a compound of formula V with a reagent such as trifluoromethanesulphonic anhydride in the presence of a base such as pyridine in a suitable solvent such as DCM to give a compound of formula VI wherein L^1 is a leaving group such as a triflate.

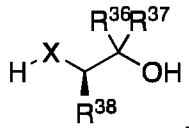
a4) Reacting a compound of formula VI with a compound of formula Z^3-W^1, such as

wherein Z^3 is defined as a hydrogen or a halide such as bromine or iodine, in the presence of a base such as Cs_2CO_3 in a suitable solvent such as DMF to give a compound of formula VII.

a5) Reacting a compound of formula VII with an acid such as TFA and water while removing the water by azeotropic distillation to give a product which is further reacted with acetic anhydride, an organic base such as triethylamine in a solvent such as ethyl acetate to give a compound of formula VIII.

a6) Reacting a compound of formula VIII with HBr in glacial acetic acid to give a compound of formula IX.

a7) Reacting a compound of formula IX with a compound of formula H-B^1 wherein B^1 is defined as above under formula 1, such as

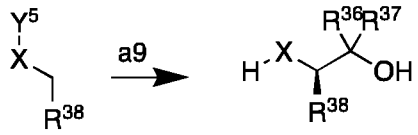


, in the presence of a

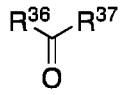
base such as Cs_2CO_3 in an inert solvent such as DMF to give a compound of formula X.

a8) Reacting a compound of formula X with a base such as sodium methoxide in a solvent such as methanol to give a compound of formula XI.

In a still further aspect the present invention relates to a process of preparing a compound of formula XIII or a pharmaceutically acceptable salt or solvate thereof comprising the step a9 where X, R^{36}, R^{37} and R^{38} are defined as above under formula 1;

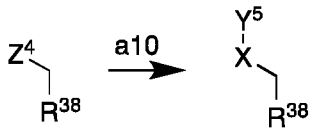


XII XIII

a9) Reacting a compound of formula XII wherein Y^5 is a protecting group such as quinoline with a carbonyl compound such as 

in the presence of a strong base such as LDA or BuLi in a suitable solvent such as THF to give an intermediate where the protective group Y^5 is cleaved, in the case of quinoline, by reacting it with sodium cyanoborohydride in acetic acid to give a compound of formula XIII.

In a still further aspect the present invention relates to a process of preparing a compound of formula XII or a pharmaceutically acceptable salt or solvate thereof comprising the step a10 where X and R^{38} are defined as above under formula 1;

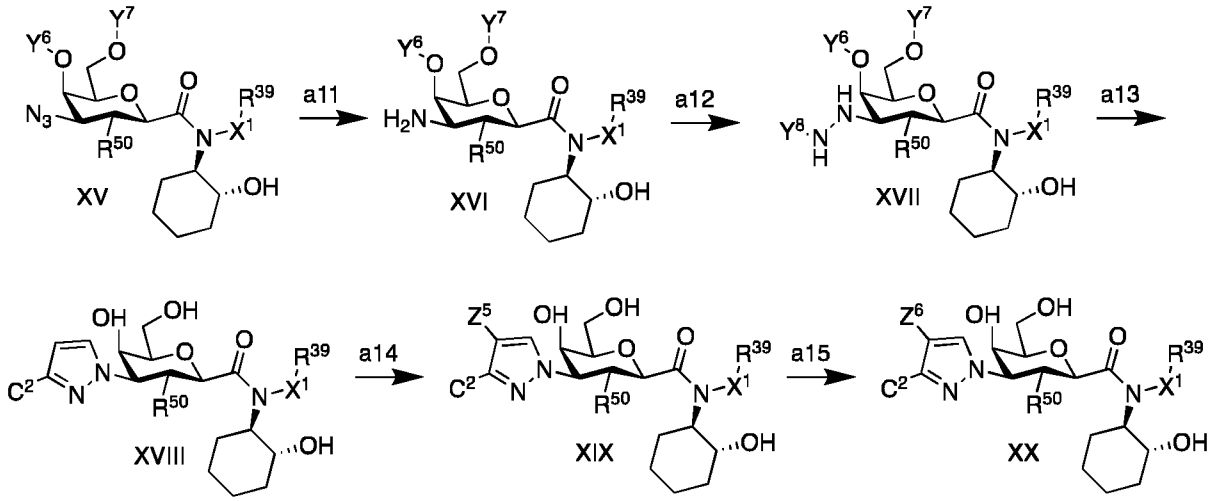


XIV XII

a10) Reacting a compound of formula XIV wherein Z^4 is a halide such as bromine with a compound of formula X-Y^5 wherein Y^5 is a protective group such as quinoline in the presence of a base such as Cs_2CO_3 in a suitable solvent such as DMF to give a compound of formula XII.

In a still further aspect the present invention relates to a process of preparing a compound of formula XX or a pharmaceutically acceptable salt or solvate thereof comprising the steps a11-a15 where C^2, X^1, R^{39} and R^{50} are defined as above under

formula 1; Y^6 and Y^7 together form a protective group such as benzylidene, Y^8 is a protective group such as a boc-group, Z^5 is defined as a halogen such as iodine or bromine and Z^6 is defined as a boronic acid or a borinate.



a11) Reacting a compound of formula XV with a reducing agent such as triphenylphosphine in an inert solvent such as THF and water optionally at elevated temperatures to give a compound of formula XVI.

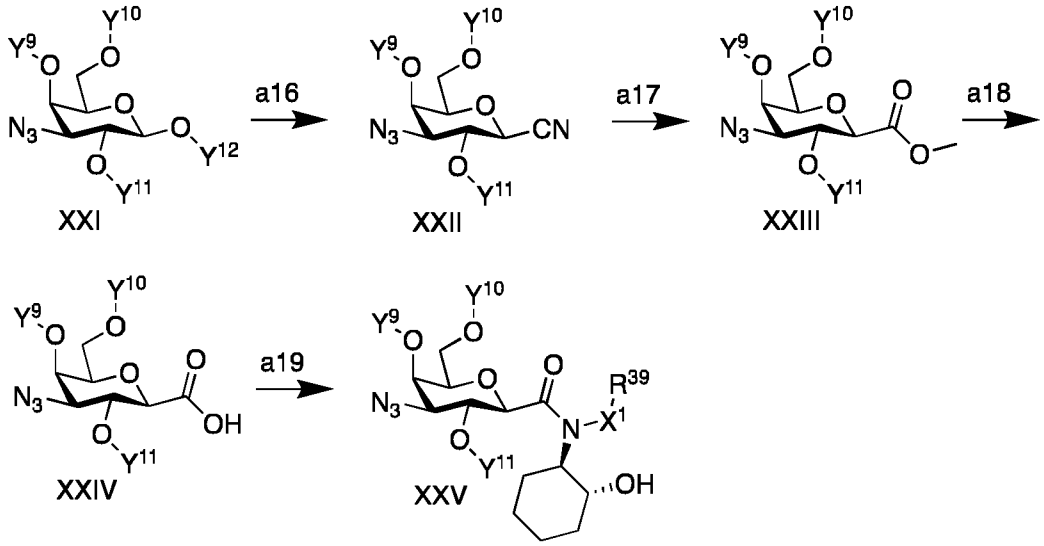
a12) Reacting a compound of formula XVI with *N-tert*-butyloxycarbonyl-3-(4-cyanophenyl)oxaziridine in an inert solvent such as DCM to give a compound of formula XVII.

a13) Reacting a compound of formula XVII with a deprotecting agent such as TFA in an inert solvent such as DCM to give an intermediate which is further reacted with 1,1,3,3-tetraethoxypropane and HCl to give a compound of formula XVIII.

a14) Reacting a compound of the formula XVIII with a halogenating agent such as *N*-bromosuccinimide or *N*-iodosuccinimide in an inert solvent such as DCM to give a compound of formula XIX.

a15) Reacting compound of formula XIX with bis(pinacolato)diboron in the presence of a catalyst such as $Pd(dppf)Cl_2$ and a base such as potassium acetate in an inert solvent such as DMSO optionally at elevated temperatures to give a compound of formula XX.

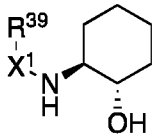
In a still further aspect the present invention relates to a process of preparing a compound of formula XXV or a pharmaceutically acceptable salt or solvate thereof comprising the steps a16-a19 where X^1 and R^{39} are defined as above under formula 1;



a16) Reacting a compound of formula XXI wherein Y^9-Y^{12} is a protective group such as acetate, with a cyanide reagent such as trimethylsilyl cyanide in the presence of a reagent such as boron trifluoride diethyl etherate in an inert solvent such as nitromethane at 0 °C to give a compound of the formula XXII.

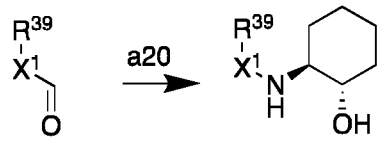
a17) Reacting a compound of formula XXII wherein Y^9-Y^{11} is a protective group such as acetate with acetyl chloride in methanol optionally at elevated temperatures giving a product which is further reacted with benzaldehyde dimethylacetal in the presence of D(+)-10-camphorsulfonic acid to give a compound of formula XXIII, wherein Y^9 and Y^{10} together form a protective group such as benzylidene and Y^{11} is a hydrogen. Optionally the compound of formula XXIII, wherein Y^9 and Y^{10} together form a protective group such as benzylidene and Y^{11} is a hydrogen could be reacted with a reagent of formula Z^7-Y^{11} wherein Z^7 is a halide such as iodine or bromine in the presence of a base such as Cs_2CO_3 in a solvent such as DMF to give another compound of formula XXIII wherein Y^9 and Y^{10} together form a protective group such as benzylidene and Y^{11} is selected from c), d) or e) under R^{50} under formula 1.

a18) Reacting a compound of formula XXIII with a base such as sodium hydroxide in a suitable solvent such as ethanol and water optionally at elevated temperatures to give a compound of formula XXIV.

a19) Reacting a compound of formula XXIV with an amine, such as  , under standard peptide coupling conditions such as EDC and HOBT in the presence

of a base such as triethylamine in a suitable solvent such as DMF optionally at elevated temperatures to give a compound of formula XXV.

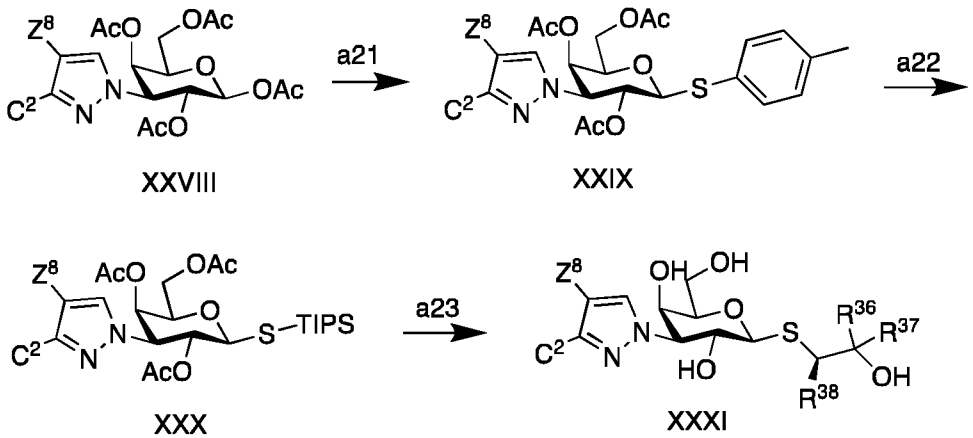
In a still further aspect the present invention relates to a process of preparing a compound of formula XXVII or a pharmaceutically acceptable salt or solvate thereof comprising the step a20 where X^1 and R^{39} are defined as above under formula 1;



XXVI XXVII

a20) Reacting a compound of formula XXVI with (1S,2S)-trans-2-aminocyclohexanol in the presence of a reducing agent such as sodium cyanoborohydride in a suitable solvent such as DMF to give a compound of formula XXVII.

In a still further aspect the present invention relates to a process of preparing a compound of formula XXX or a pharmaceutically acceptable salt or solvate thereof comprising the steps a21-a23 where C^2, R^{36}, R^{37} and R^{38} are defined as above under formula 1;



XXVIII XXIX

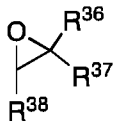
XXX XXXI

a21) Reacting a compound of formula XXVIII wherein Z^8 is a halide such as iodine with hydrogen bromide in acetic acid, in a suitable solvent such as DCM to give an intermediate, which is reacted with 4-methylbenzenethiol in the presence of a base such as K_2CO_3 in a suitable solvent such as DMF to give a compound of formula XXIX.

a22) Reacting a compound of formula XXIX with bromine in a suitable solvent such as DCM to give an intermediate, which is reacted with triisopropylsilanethiol in the

presence of a base such as K_2CO_3 in a suitable solvent such as acetonitrile to give a compound of formula XXX.

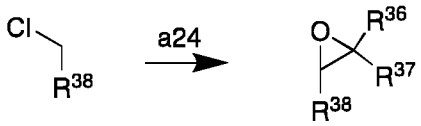
a23) Reacting a compound of formula XXX with a compound of the formula XXXII



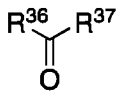
XXXII

in the presence of tetrabutylammonium fluoride trihydrate in a suitable solvent such as acetonitrile to give an intermediate, which is further reacted with a base, such as sodium methoxide, in a suitable solvent such as methanol to give a compound of formula XXXI.

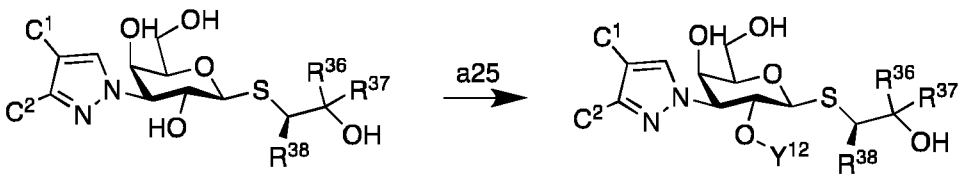
In a still further aspect the present invention relates to a process of preparing a compound of formula XXXII or a pharmaceutically acceptable salt or solvate thereof comprising the step a24 where R^{36}, R^{37} and R^{38} are defined as above under formula 1;



XXXIII XXXII

a24) Reacting a compound of formula XXXIII with a base such as lithium diisopropylamide in a suitable solvent such as THF at -78 °C followed by treatment with a compound of the formula  to give a compound of formula XXXII.

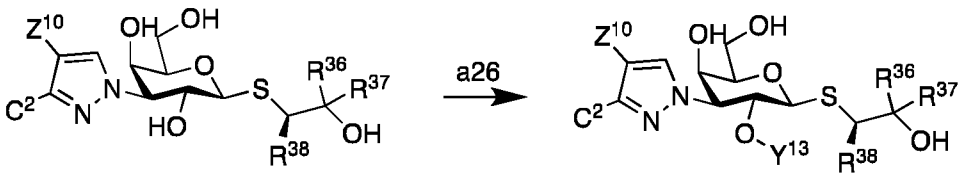
In a still further aspect the present invention relates to a process of preparing a compound of formula XXXV or a pharmaceutically acceptable salt or solvate thereof comprising the step a25 where C^1, C^2, R^{36}, R^{37} and R^{38} are defined as above under formula 1 and Y^{12} is selected from c), d) or e) under R^{50} under formula 1;



XXXIV XXXV

a25) Reacting a compound of formula XXXIV with benzaldehyde dimethylacetal in the presence of an acid, such as *p*-toluenesulfonic acid, in a suitable solvent such as acetonitrile to give an intermediate, which is reacted with a reagent of formula Z^9-Y^{12} wherein Z^9 is a halide in the presence of a base, such as lithium *tert*-butoxide, in a suitable solvent such as DMF to give an intermediate, which is reacted with TFA in water to give a compound of formula XXXV.

In a still further aspect the present invention relates to a process of preparing a compound of formula XXXVII or a pharmaceutically acceptable salt or solvate thereof comprising the step a26 where C^2, R^{36}, R^{37} and R^{38} are defined as above under formula 1 and Y^{13} is selected from c), d) or e) under R^{50} under formula 1;



XXXVI XXXVII

a26) Reacting a compound of formula XXXVI wherein Z^{10} is a halide such as iodine with benzaldehyde dimethylacetal in the presence of an acid, such as *p*-toluenesulfonic acid, in a suitable solvent such as acetonitrile to give an intermediate, which is reacted with a reagent of formula Z^{11}-Y^{13} wherein Z^{11} is a halide in the presence of a base, such as lithium *tert*-butoxide, in a suitable solvent such as DMF to give an intermediate, which is reacted with TFA in water to give a compound of formula XXXVII.

Detailed Description of the invention

In a further aspect the present invention concerns a β-D-galactopyranose compound of formula (1) selected from any one of the exemplified compounds of examples 1-11 or a pharmaceutically acceptable salt thereof.

In a still further aspect the present invention concerns a β-D-galactopyranose compound of formula (1) selected from any one of the exemplified compounds of examples 12-20 or a pharmaceutically acceptable salt thereof.

The skilled person will understand that it may be necessary to adjust or change the order of steps in the processes a1-a26, and such change of order is encompassed

by the aspects of the process as described above in the reaction schemes and accompanying description of the process steps.

Furthermore, the skilled person will understand that the processes described above and hereinafter the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include optionally substituted and/or unsaturated alkyl groups (e.g. methyl, allyl, benzyl or tert-butyl), trialkyl silyl or diarylalkylsilyl groups (e.g. t-butyldimethylsilyl, t-butyldipheylsilyl or trimethylsilyl), AcO(acetoxy), TBS(t-butyldimethylsilyl), TMS(trimethylsilyl), PMB (p-methoxybenzyl), and tetrahydropyranyl. Suitable proteting groups for carboxylic acid include (C_{1-6})-alkyl or benzyl esters. Suitable protecting groups for amino include t-butyloxycarbonyl, benzyloxycarbonyl, 2-(trimethylsilyl)-ethoxy-methyl or 2-trimethylsilylethoxycarbonyl (Teoc). Suitable protecting groups for S include S-C(=N)NH_2, TIPS.

The protection and deprotection of functional groups may take place before or after any reaction in the above-mentioned processes.

Furthermore the skilled person will appreciate, that, in order to obtain compounds of the invention in an alternative, and on some occasions more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

In a still further embodiment the compound (1) is on free form. “On free form” as used herein means a compound of formula (1), either an acid form or base form, or as a neutral compound, depending on the substitutents. The free form does not have any acid salt or base salt in addition. In one embodiment the free form is an anhydrate. In another embodiment the free form is a solvate, such as a hydrate.

In a further embodiment the compound of formula (1) is a crystalline form. The skilled person may carry out tests in order to find polymorphs, and such polymorphs are intended to be encompassed by the term "crystalline form" as used herein.

Whenever a "compound of formula (1)" is used herein it means the compound of formula (1) in any form incl the free form or as a salt thereof, such as a pharmaceutically acceptable salt thereof, unless otherwise indicated herein or clearly contradicted by context.

When the compounds and pharmaceutical compositions herein disclosed are used for the above treatment, a therapeutically effective amount of at least one compound is administered to a mammal in need of said treatment.

The term "C_{1-x} alkyl" as used herein means a straight or branched alkyl group containing 1-x carbon atoms, e.g. C_{1-5} or C_{1-6}, such as methyl, ethyl, isopropyl, propyl, butyl, pentyl or hexyl.

The term "branched C_{3-x} alkyl" as used herein means a branched alkyl group containing 3-x carbon atoms e.g. C_{3-5} or C_{3-6}, such as isopropyl, isobutyl, tert-butyl, isopentyl, 3-methylbutyl, 2,2-dimethylpropyl, n-hexyl, 2-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl.

The term "OC_{1-x} alkyl" as used herein means an alkoxy group containing 1-x carbon atoms, e.g. C_{1-5} or C_{1-6}, such as methoxy, ethoxy, propoxy, butyloxy, pentyloxy or hexyloxy.

The term "SC_{1-x} alkyl" as used herein means an alkylthio group containing 1-x carbon atoms, e.g. C_{1-5} or C_{1-6}, such as thiomethyl or thioethyl.

The term "C_{3-x} cycloalkyl" as used herein means a cyclic alkyl group containing 3-x carbon atoms, e.g. C_{3-6} or C_{3-7}, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and 1-methylcyclopropyl.

The term "OC_{3-x} cycloalkyl" as used herein means a cyclic alkoxy group containing 3-x carbon atoms, e.g. C_{3-6} or C_{3-7}, such as cyclopropoxy, cyclobutoxy, and cyclopentyloxy.

The term "$C(O)C_{1-6}$ alkyl" as used herein means a carbonyl group whereto is attached a C_{1-6} alkyl.

The term "$C(O)C_{3-6}$ cycloalkyl as used herein means a carbonyl group whereto is attached a C_{3-6} cycloalkyl.

The term "$C(O)OC_{1-6}$ alkyl" as used herein means a carbonyl group whereto is attached a C_{1-6} alkoxy.

The term "$C(O)OC_{3-6}$ cycloalkyl" as used herein means a carbonyl group whereto is attached a C_{3-6} cycloalkoxy.

The term "$S(O_2)C_{3-6}$ cycloalkyl" as used herein means a sulphonyl group whereto is attached a C_{3-6} cycloalkyl.

The term "$S(O_2)C_{1-6}$ alkyl" as used herein means a sulphonyl group whereto is attached a C_{1-6} alkyl.

The term "C_{2-6} alkenyl" as used herein means a straight or branched hydrocarbon chain containing one double bond.

The term "C_{5-7} cycloalkyl" as used herein means a cyclic alkyl group containing 5-7 carbon atoms, such as cyclopentyl, cyclohexyl, or cycloheptyl.

The term "Oxo" as used herein means an oxygen atom with double bonds, also indicated as =O.

The term "CN" as used herein means a cyano group.

The term "halogen" as used herein means Cl, F, Br or I.

The term "C_{1-6} alkoxy" as used herein means an oxygen linked to a C_{1-6} alkyl, such as methoxy or ethoxy.

The term "C_{1-6} alkylthio" as used herein means a sulphur linked to a C_{1-6} alkyl, such as thiomethoxy or thioethoxy.

The term "C_{1-6} alkoxycarbonyl" as used herein means a C_{1-6} alkoxy linked to a carbonyl, such as methoxycarbonyl ($CH_2OC(=O)$).

The term "C_2-alkynyl" as used herein means C(triple bond)CH.

The term "a five or six membered heteroaromatic ring" as used herein means one five membered heteroaromatic ring or one six membered heteroaromatic ring. The five membered heteroaromatic ring contains 5 ring atoms of which one to four are heteroatoms selected from N, O, and S. The six membered heteroaromatic ring contains 6 ring atoms of which one to five are heteroatoms selected from N, O and S. Examples include thiophene, furan, pyran, pyrrole, imidazole, pyrazole, isothiazole, isooxazole, pyridine, pyrazine, pyrimidine and pyridazine. When such heteroaromatic rings are substituents they are termed thiophenyl, furanyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isooxazolyl, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl. Also included are oxazoyl, thiazoyl, thiadiazoly, oxadiazoyl, and pyridonyl.

The term “an aryl” as used herein means an aromatic ring having at least 6 carbonatoms and includes phenyl and naphthyl.

The term “a heterocycle, such as heteroaryl or heterocycloalkyl” as used herein means a heterocycle consisting of one or more 3-7 membered ring systems containing one or more heteroatoms and wherein such ring systems may optionally be aromatic. The term “a heteroaryl” as used herein means a mono or bicyclic aromatic ringsystem containing one or more heteroatoms, such as 1-10, e.g. 1-6, selected from O, S, and N, including but not limited to oxazolyl, oxadiazolyl, thiophenyl, thiadiazolyl, thiazolyl, pyridyl, pyrimidinyl, pyridonyl, pyrimidonyl, quinolinyl, azaquionolyl, isoquinolinyl, azaisoquinolyl, quinazolinyl, azaquinazolinyl, bensozazoyl, azabensoxazoyl, bensothiazoyl, or azabensothiazoyl. The term “a heterocycloalkyl” as used herein means a mono or bicyclic 3-7 membered alifatic heterocycle containing one or more heteroatoms, such as 1-7, e.g. 1-5, selected from O, S, and N, including but not limited to piperidinyl, tetrahydropyranyl, tetrahydrothipyranyl, or piperidonyl.

The term “a spiro heterocycle” as used herein means a two-ring system connected by a common carbon atom, and containing from 5 to 12 ring members wherein from 2 to 11 are carbon atoms and at least one is a heteroatom, such as a hetero atom selected from one or more N, S, O; one example is N-(2-oxa)-6-azaspiro[3.3]heptanyl.

The term “treatment” and “treating” as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. The treatment may either be performed in an acute or in a chronic way. The patient to be treated is preferably a mammal; in particular, a human being, but it may also include animals, such as dogs, cats, cows, sheep and pigs.

The term "a therapeutically effective amount" of a compound of formula (1) of the present invention as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

In a still further aspect, the present invention relates to a pharmaceutical composition comprising the compound of formula (1) and optionally a pharmaceutically acceptable additive, such as a carrier or an excipient.

As used herein “pharmaceutically acceptable additive” is intended without limitation to include carriers, excipients, diluents, adjuvant, colorings, aroma, preservatives etc. that the skilled person would consider using when formulating a compound of the present invention in order to make a pharmaceutical composition.

The adjuvants, diluents, excipients and/or carriers that may be used in the composition of the invention must be pharmaceutically acceptable in the sense of being compatible with the compound of formula (1) and the other ingredients of the pharmaceutical composition, and not deleterious to the recipient thereof. It is preferred that the compositions shall not contain any material that may cause an adverse reaction, such as an allergic reaction. The adjuvants, diluents, excipients and carriers that may be used in the pharmaceutical composition of the invention are well known to a person skilled within the art.

As mentioned above, the compositions and particularly pharmaceutical compositions as herein disclosed may, in addition to the compounds herein disclosed, further comprise at least one pharmaceutically acceptable adjuvant, diluent, excipient and/or carrier. In some embodiments, the pharmaceutical compositions comprise from 1 to 99 % by weight of said at least one pharmaceutically acceptable adjuvant, diluent, excipient and/or carrier and from 1 to 99 % by weight of a compound as herein disclosed. The combined amount of the active ingredient and of the pharmaceutically acceptable adjuvant, diluent, excipient and/or carrier may not constitute more than 100% by weight of the composition, particularly the pharmaceutical composition.

In some embodiments, only one compound as herein disclosed is used for the purposes discussed above.

In some embodiments, two or more of the compounds as herein disclosed are used in combination for the purposes discussed above.

The composition, particularly pharmaceutical composition comprising a compound set forth herein may be adapted for oral, intravenous, topical, intraperitoneal, nasal, buccal, sublingual, or subcutaneous administration, or for administration via the respiratory tract in the form of, for example, an aerosol or an air-suspended fine powder. Therefore, the pharmaceutical composition may be in the form of, for example, tablets, capsules, powders, nanoparticles, crystals, amorphous substances, solutions, transdermal patches or suppositories.

Further embodiments of the process are described in the experimental section herein, and each individual process as well as each starting material constitutes embodiments that may form part of embodiments.

The above embodiments should be seen as referring to any one of the aspects (such as 'method for treatment', 'pharmaceutical composition', 'compound for use as a medicament', or 'compound for use in a method') described herein as well as any one of the embodiments described herein unless it is specified that an embodiment relates to a certain aspect or aspects of the present invention.

All references, including publications, patent applications and patents, cited herein are hereby incorporated by reference to the same extent as if each reference was individually and specifically indicated to be incorporated by reference and was set forth in its entirety herein.

All headings and sub-headings are used herein for convenience only and should not be construed as limiting the invention in any way.

Any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

The terms "a" and "an" and "the" and similar referents as used in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into

the specification as if it were individually recited herein. Unless otherwise stated, all exact values provided herein are representative of corresponding approximate values (*e.g.*, all exact exemplary values provided with respect to a particular factor or measurement can be considered to also pro-vide a corresponding approximate measurement, modified by "about," where appropriate).

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of any and all examples, or exemplary language (*e.g.*, "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise indicated. No language in the specification should be construed as indicating any element is essential to the practice of the invention unless as much is explicitly stated.

The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability and/or enforceability of such patent documents.

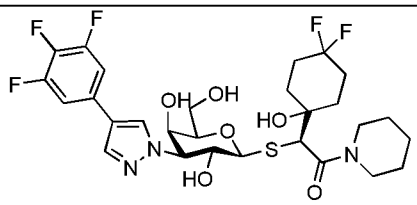
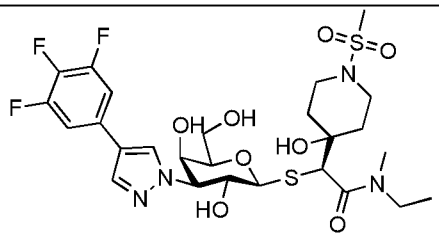
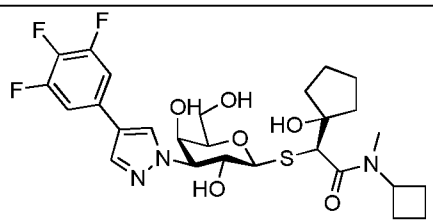
The term "and/or" as used herein is intended to mean both alternatives as well as each of the alternatives individually. For instance, the expression "xxx and/or yyy" means "xxx and yyy"; "xxx"; or "yyy", all three alternatives are subject to individual embodiments.

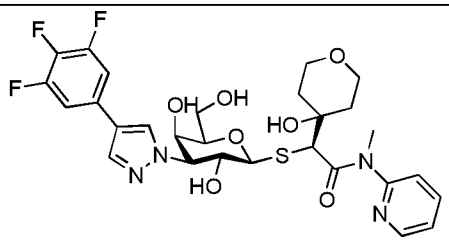
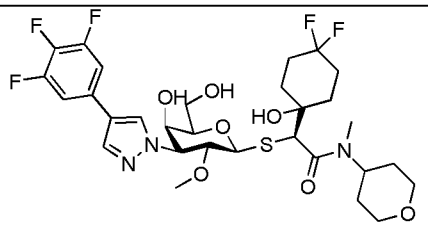
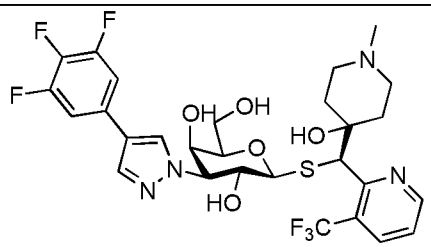
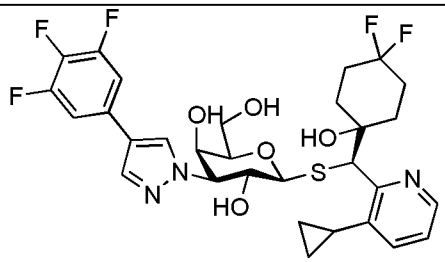
The description herein of any aspect or embodiment of the invention using terms such as "comprising", "having", "including" or "containing" with reference to an element or elements is intended to provide support for a similar aspect or embodiment of the invention that "consists of", "consists essentially of", or "substantially comprises" that particular element or elements, unless otherwise stated or clearly contradicted by context (*e.g.*, a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

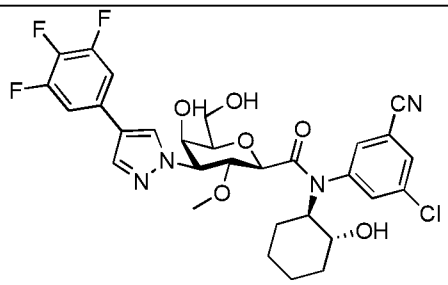
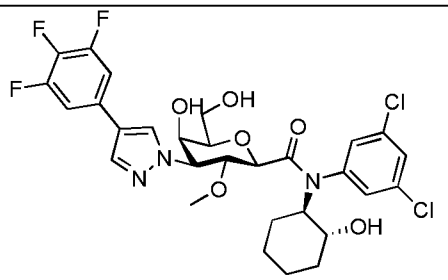
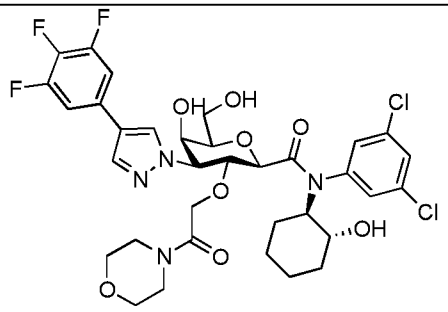
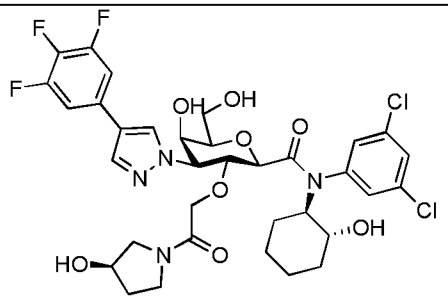
The present invention is further illustrated by the following examples that, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention indiverse forms thereof.

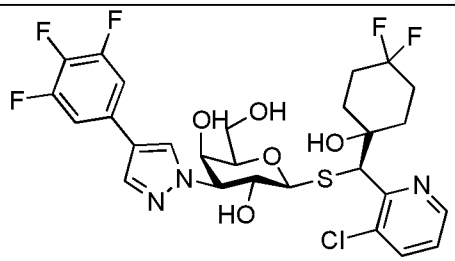
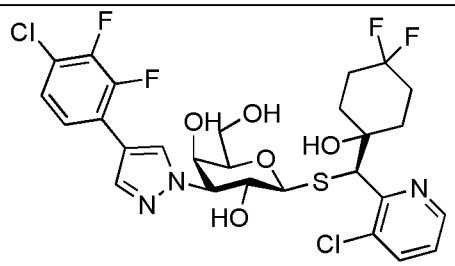
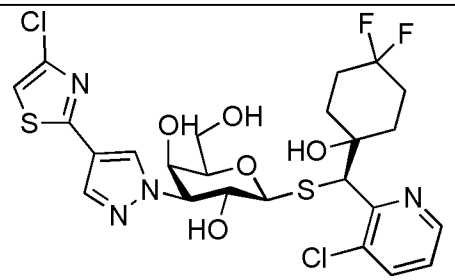
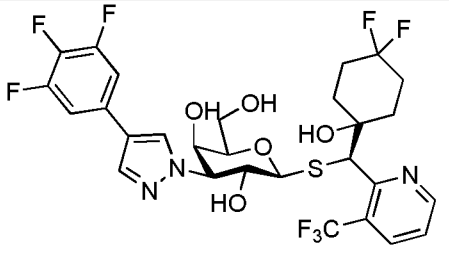
Experimental procedures (Evaluation of Kd values)

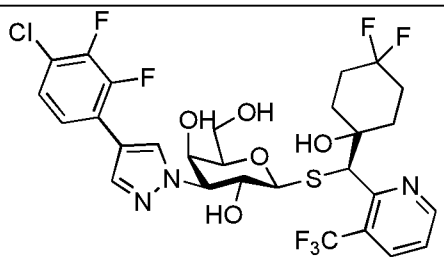
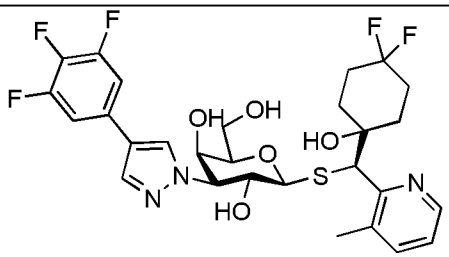
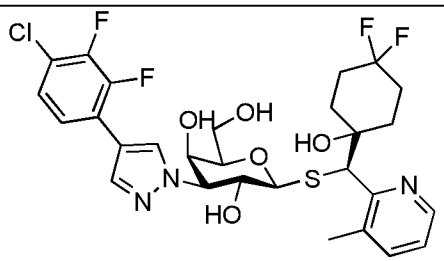
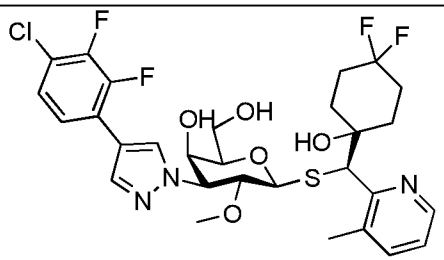
The affinity of Example 1-20 for galectins were determined by a fluorescence anisotropy assay where the compound was used as an inhibitor of the interaction between galectin and a fluorescein tagged saccharide probe as described Sörme, P., Kahl-Knutsson, B., Huflejt, M., Nilsson, U. J., and Leffler H. (2004) Fluorescence polarization as an analytical tool to evaluate galectin-ligand interactions. Anal. Biochem. 334: 36-47, (Sörme et al., 2004) and Monovalent interactions of Galectin-1 By Salomonsson, Emma; Larumbe, Amaia; Tejler, Johan; Tullberg, Erik; Rydberg, Hanna; Sundin, Anders; Khabut, Areej; Frejd, Torbjorn; Lobsanov, Yuri D.; Rini, James M.; et al, From Biochemistry (2010), 49(44), 9518-9532, (Salomonsson et al., 2010).

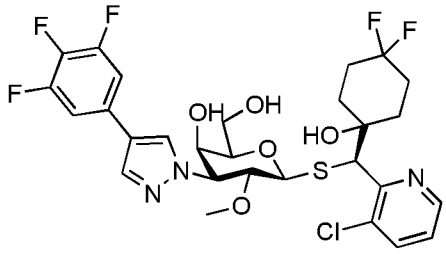
Example	Name	Structure	Gal-1 Kd (µM)	Gal-3 Kd (µM)
1	**(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(1-piperidinylcarbonyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside**			
2	**2-Ethylmethylamino-(S)-1-[4-hydroxy-1-(methylsulfonyl)piperidin-4-yl]-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside**			
3	**2-Cyclobutylmethylamino-(S)-1-(1-hydroxycyclopentyl)-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-**			

	1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside			
4	(S)-1-(4-Hydroxypyran-4-yl)-2-methyl(pyridin-2-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside			
5	(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-2-methyl(pyran-4-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-2-*O*-methyl-1-thio-β-D-galactopyranoside			
6	(R)-1-[3-(Trifluoromethyl)pyridin-2-yl]-1-(4-hydroxy-1-methylpiperidin-4-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside			
7	(R)-1-(3-Cyclopropylpyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside			

8	2,6-Anhydro-*N*-(3-chloro-5-cyanophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide			
9	2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide			
10	2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-(2-morpholino-2-oxoethyl)-D-glycero-L-manno-heptonamide			
11	2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-{2-[(S)-3-hydroxypyrrolidin-			

	1-yl]-2-oxoethyl}-D-glycero-L-manno-heptonamide			
12	**(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside**		6.4	0.021
13	**(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside**		37	0.006
14	**(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chlorothiazol-2-yl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside**		0.32	0.50
15	**(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside**		2.3	0.009

16	**(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside**		8.9	0.009
17	**(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside**		3.3	0.009
18	**(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside**		32	0.15
19	**(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-2-*O*-methyl-1-thio-β-D-galactopyranoside**		9.7	0.037

20	**(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-2-*O*-methyl-1-thio-β-D-galactopyranoside**		9.2	0.036

Synthesis of Examples and intermediates

General experimental:

Nuclear Magnetic Resonance (NMR) spectra were recorded on a 400 MHz Bruker AVANCE III 500 instrument or a Varian instrument at 400 MHz, at 25 °C. Chemical shifts are reported in ppm (d) using the residual solvent as internal standard. Peak multiplicities are expressed as follow: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplet; q, quartet; m, multiplet; br s, broad singlet. LC-MS were acquired on an Agilent 1200 HPLC coupled with an Agilent MSD mass spectrometer operating in ES (+) ionization mode. Column: XBridge C18 (4.6 × 50 mm,3.5 µm) or SunFire C18 (4.6 × 50 mm, 3.5 µm). Solvent A water + 0.1% TFA and solvent B Acetonitrile + 0.1% TFA or solvent A water (10 mM Ammonium hydrogen carbonate) and solvent B Acetonitrile. Wavelength: 254 nM. Alternatively, LC-MS were acquired on an Agilent 1100 HPLC coupled with an Agilent MSD mass spectrometer operating in ES (+) ionization mode. Column: Waters symmetry 2.1 x 30 mm C18 or Chromolith RP-18 2 x 50 mm. Solvent A water + 0.1% TFA and solvent B Acetonitrile + 0.1% TFA. Wavelength 254 nm.

Preparative HPLC was performed on a Gilson 215. Flow: 25 mL/min Column: XBrige prep C18 10 µm OBD (19 × 250 mm) column. Wavelength: 254 nM. Solvent A water (10 mM Ammonium hydrogen carbonate) and solvent B Acetonitrile. Alternatively, preparative HPLC were acquired on a Gilson system. Flow: 15 ml/min Column: kromasil 100-5-C18 column. Wavelength: 220 nm. Solvent A water + 0.1% TFA and solvent B Acetonitrile + 0.1% TFA.

The following abbreviations are used

aq: aqueous

Calcd: Calculated

MeCN: Acetonitrile

CuI: Copper Iodide

DCM: Dichloromethane

DIPEA: Diisopropylethylamine

DMF: N,N-dimethylformamide

ESI-MS: Electrospray ionization mass spectrometry

EtOAc or EA: Ethylacetate

Et_3N: Triethylamine

h: hour(s)

HPLC: High performance liquid chromatography

LC: Liquid Chromatography

mL: milliliter

MeOH: Methanol

MeOD: Deuterated methanol

mm: millimeter

mM: millimolar

MS: Mass spectroscopy

nm: nanometer

NaOMe: Sodium methoxide

N_2: Nitrogen gas

NMR: Nuclear magnetic resonance

$Pd(dppf)Cl_2$: [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)

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

PE: petroleum ether

pH: acidity

Prep: preparative

rt: room temperature

TFA: trifluoroacetic acid

THF: Tetrahydrofuran

TMS: Trimethylsilyl

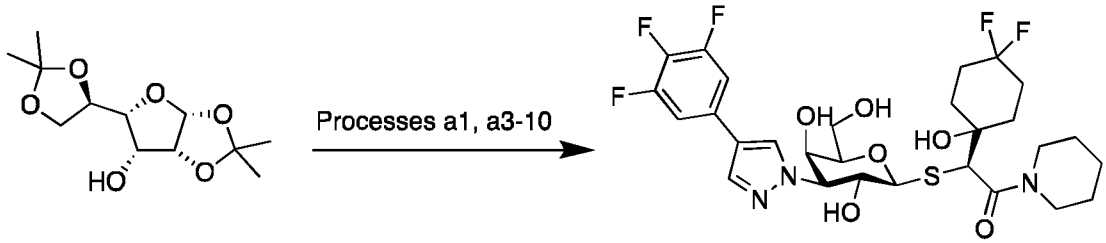
UV: Ultraviolet

Å: Ångström

Synthesis of example 1-20 from their respective starting materials and intermediates 12-20.

Example 1

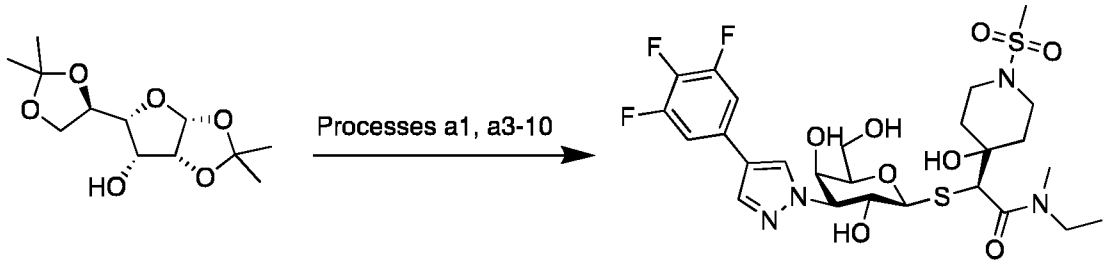
(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(1-piperidinylcarbonyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



Example 1 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1 and a3-10 described above.

Example 2

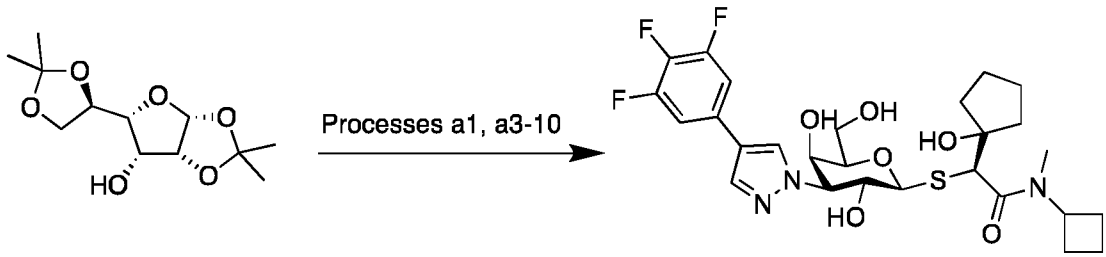
2-Ethylmethylamino-(S)-1-[4-hydroxy-1-(methylsulfonyl)piperidin-4-yl]-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



Example 2 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1 and a3-10 described above.

Example 3

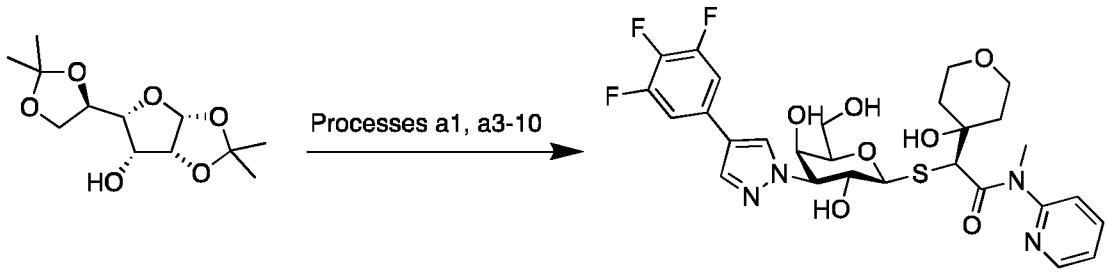
2-Cyclobutylmethylamino-(S)-1-(1-hydroxycyclopentyl)-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



Example 3 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1 and a3-10 described above.

Example 4

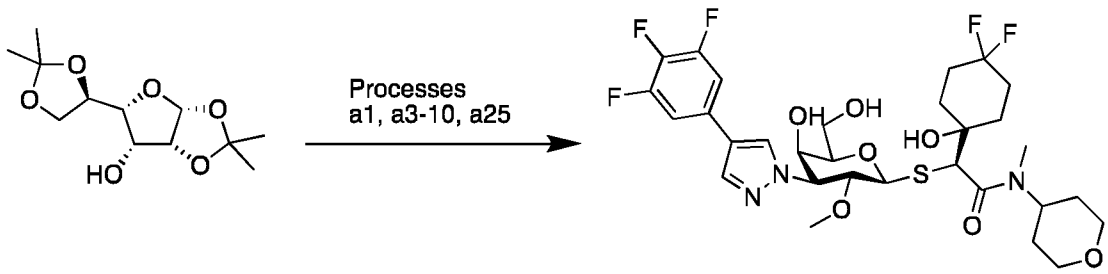
(S)-1-(4-Hydroxypyran-4-yl)-2-methyl(pyridin-2-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



Example 4 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1 and a3-10 described above.

Example 5

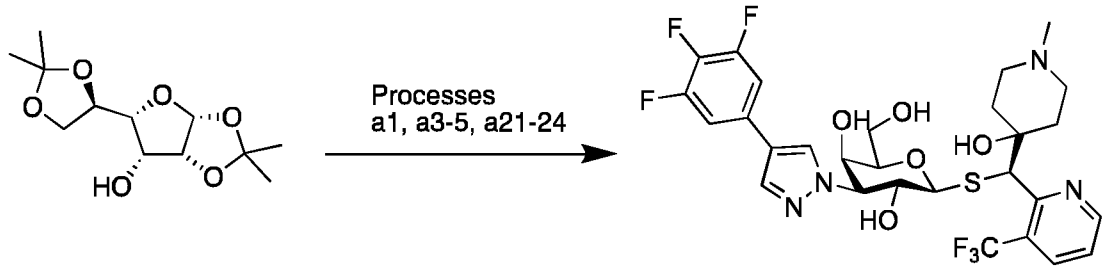
(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-2-methyl(pyran-4-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-2-*O*-methyl-1-thio-β-D-galactopyranoside



Example 5 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1, a3-10 and a25 described above.

Example 6

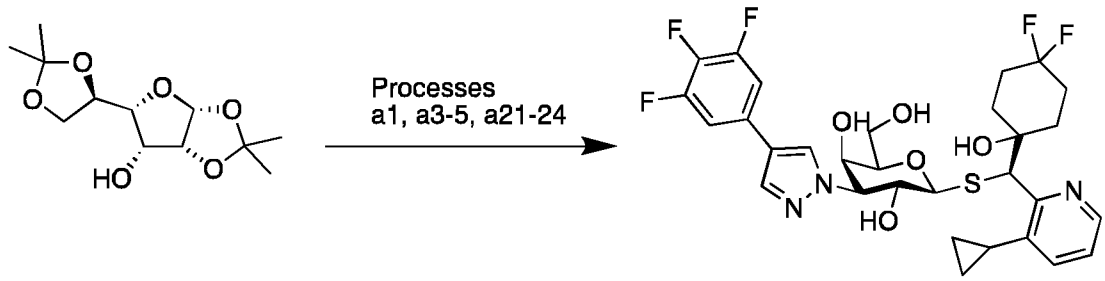
(R)-1-[3-(Trifluoromethyl)pyridin-2-yl]-1-(4-hydroxy-1-methylpiperidin-4-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



Example 6 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1, a3-5 and a21-24 described above.

Example 7

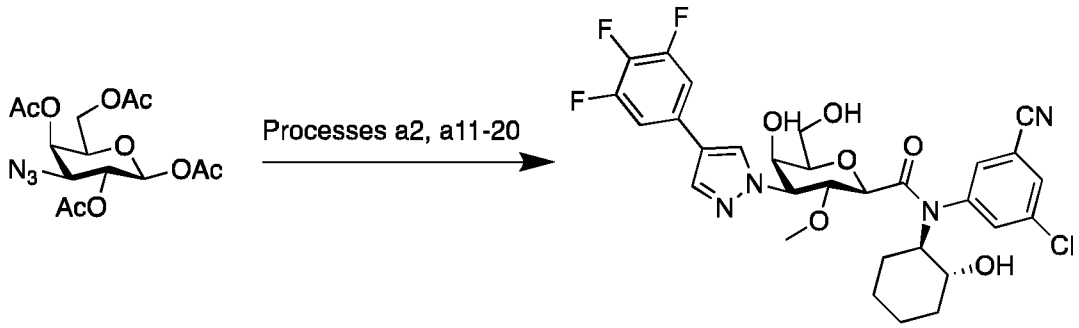
(R)-1-(3-Cyclopropylpyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



Example 7 is made, starting from 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose, by following the processes a1, a3-5 and a21-24 described above.

Example 8

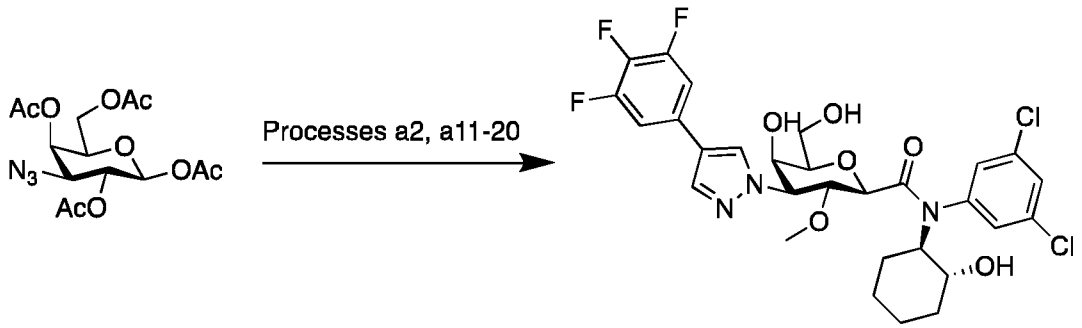
2,6-Anhydro-*N*-(3-chloro-5-cyanophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide



Example 8 is made, starting from 1,2,4,6-tetra-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranoside, by following the processes a2 and a11-20 described above. In process a17 the optional step is performed using iodomethane.

Example 9

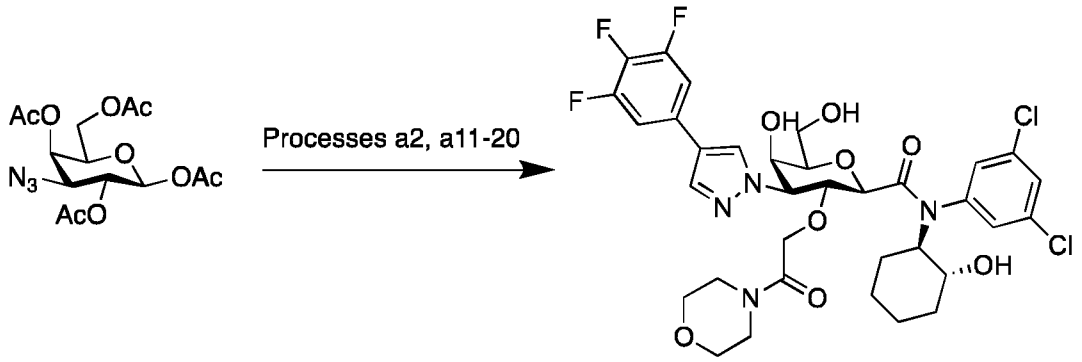
2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide



Example 9 is made, starting from 1,2,4,6-tetra-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranoside, by following the processes a2 and a11-20 described above. In process a17 the optional step is performed using iodomethane.

Example 10

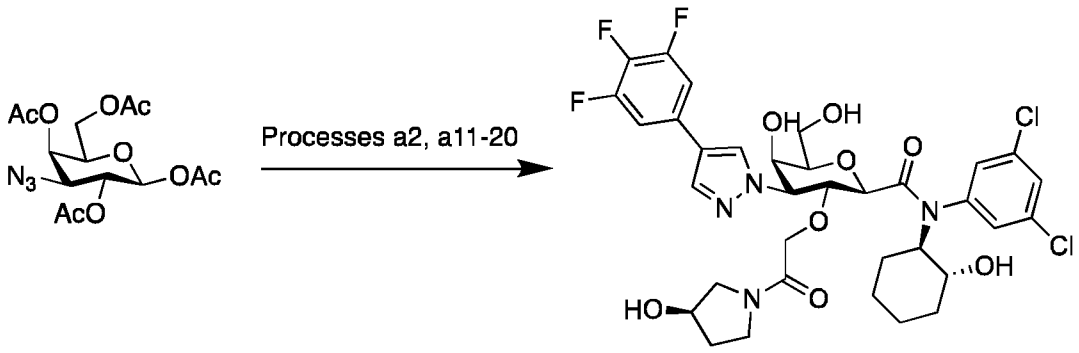
2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-(2-morpholino-2-oxoethyl)-D-glycero-L-manno-heptonamide



Example 10 is made, starting from 1,2,4,6-tetra-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranoside, by following the processes a2 and a11-20 described above. In process a17 the optional step is performed using 4-(bromoacetyl)morphiline.

Example 11

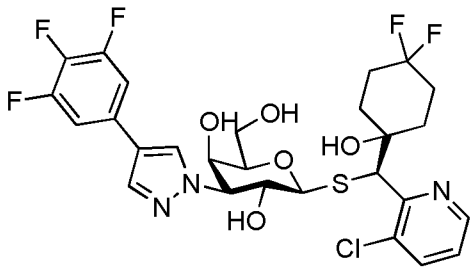
2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-{2-[(S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-D-glycero-L-manno-heptonamide



Example 11 is made, starting from 1,2,4,6-tetra-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranoside, by following the processes a2 and a11-20 described above. In process a17 the optional step is performed using 2-bromo-1-[(3S)-3-hydroxy-1-pyrrolidinyl]ethanone.

Example 12

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside

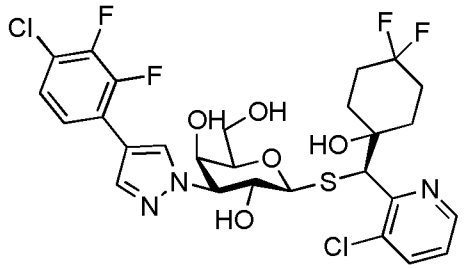


A suspension of (R)-1-(3-chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (15 mg, 0.024 mmol), (3,4,5-trifluorophenyl)boronic acid (6.3 mg, 0.036 mmol), K_2CO_3 (16 mg, 0.12 mmol) and $Pd(dppf)Cl_2$ (2.6 mg, 0.04 mmol) in dioxane/water (2:1, 0.15 mL) was stirred 40 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (4.2 mg, 28 %). ESI-MS *m/z* calcd for $[C_{27}H_{27}ClF_5N_3O_5S]$ $[M+H]^+$: 636.1; found: 636.0. ^1H NMR (400 MHz, Methanol-d_4) δ 8.56 (dd, *J* = 4.6, 1.3 Hz, 1H), 8.11 (s, 1H), 8.01 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.88 (s, 1H), 7.41 (dd, *J* = 8.2, 4.7 Hz, 1H), 7.34 (dd, *J*

= 9.2, 6.7 Hz, 2H), 5.06 (s, 1H), 4.48 (d, *J* = 9.3 Hz, 1H), 4.28 (dd, *J* = 10.6, 3.0 Hz, 1H), 4.20 – 4.11 (m, 1H), 4.10 (d, *J* = 2.6 Hz, 1H), 3.74 – 3.64 (m, 3H), 2.38 (d, *J* = 15.7 Hz, 1H), 2.19 – 1.91 (m, 3H), 1.90 – 1.76 (m, 3H), 1.50 (d, *J* = 14.3 Hz, 1H).

Example 13

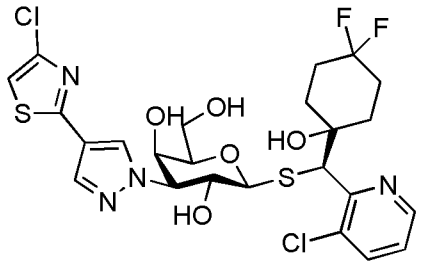
(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside



A suspension of (R)-1-(3-chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (15 mg, 0.024 mmol), (4-chloro-2,3-difluorophenyl)boronic acid (6.9 mg, 0.036 mmol), K_2CO_3 (16 mg, 0.12 mmol) and Pd(dppf)Cl_2 (2.6 mg, 0.04 mmol) in dioxane/water (2:1, 0.15 mL) was stirred 40 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (5.4 mg, 35 %). ESI-MS *m/z* calcd for $[C_{27}H_{27}Cl_2F_4N_3O_5S]$ $[M+H]^+$: 652.1; found: 651.8. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.56 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.21 – 8.14 (m, 1H), 8.01 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.95 (s, 1H), 7.47 (td, *J* = 8.1, 7.3, 2.0 Hz, 1H), 7.41 (dd, *J* = 8.2, 4.8 Hz, 1H), 7.27 (ddd, *J* = 8.7, 6.9, 1.8 Hz, 1H), 5.07 (s, 1H), 4.48 (d, *J* = 9.4 Hz, 1H), 4.33 (dd, *J* = 10.5, 2.8 Hz, 1H), 4.21 – 4.13 (m, 1H), 4.12 (d, *J* = 2.7 Hz, 1H), 3.76 – 3.63 (m, 3H), 2.38 (d, *J* = 13.9 Hz, 1H), 2.23 – 1.91 (m, 3H), 1.90 – 1.75 (m, 3H), 1.51 (d, *J* = 13.7 Hz, 1H).

Example 14

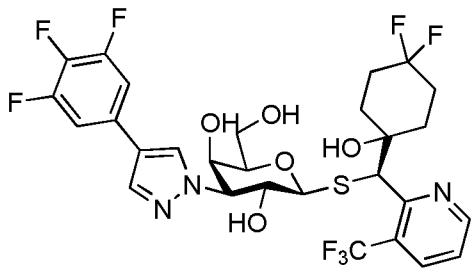
(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chlorothiazol-2-yl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside



A solution of tributyl-(4-chlorothiazol-2-yl)stannane (13.7 mg, 0.029 mmol) in anhydrous MeCN (140 µL, degassed) was added to (R)-1-(3-chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (15 mg, 0.024 mmol), CuI (0.9 mg, 0.0048 mmol) and $Pd(PPh_3)_4$ (2.7 mg, 0.0024 mmol) and the mixture was stirred 20 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (6.1 mg, 41%). ESI-MS *m/z* calcd for $[C_{24}H_{26}Cl_2F_2N_4O_5S_2]$ $[M+H]^+$: 623.1; found: 622.9. ^1H NMR (400 MHz, Methanol-d_4) δ 8.55 (d, *J* = 4.7 Hz, 1H), 8.27 (s, 1H), 8.01 – 7.93 (m, 2H), 7.38 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.29 (s, 1H), 5.05 (s, 1H), 4.48 (d, *J* = 9.4 Hz, 1H), 4.34 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.15 (t, *J* = 10.0 Hz, 1H), 4.11 (d, *J* = 2.5 Hz, 1H), 3.75 – 3.63 (m, 3H), 2.38 (d, *J* = 13.1 Hz, 1H), 2.20 – 1.90 (m, 3H), 1.90 – 1.72 (m, 3H), 1.51 (d, *J* = 15.5 Hz, 1H).

Example 15

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside

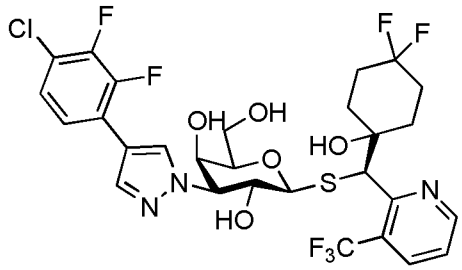


A suspension of (R)-1-(4,4-difluoro-1-hydroxycyclohexyl)-1-(3-(trifluoromethyl)pyridin-2-yl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (16 mg, 0.024 mmol), (3,4,5-trifluorophenyl)boronic acid (6.3 mg, 0.036 mmol), K_2CO_3 (16 mg, 0.12 mmol) and $Pd(dppf)Cl_2$ (2.6 mg, 0.04 mmol) in dioxane/water (2:1, 0.15 mL) was stirred 40 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue

was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (1.4 mg, 9 %). ESI-MS *m/z* calcd for $[C_{28}H_{27}F_8N_3O_5S]$ $[M+H]^+$: 670.2; found: 670.0. ^1H NMR (400 MHz, Methanol-d_4) δ 8.82 (d, *J* = 4.2 Hz, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.51 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.38 – 7.30 (m, 2H), 4.56 (s, 1H), 4.52 (d, *J* = 9.3 Hz, 1H), 4.29 (dd, *J* = 10.5, 2.7 Hz, 1H), 4.15 – 4.06 (m, 2H), 3.75 – 3.69 (m, 2H), 3.64 (t, *J* = 6.2 Hz, 1H), 2.53 (d, *J* = 13.3 Hz, 1H), 2.22 – 1.99 (m, 2H), 1.98 – 1.74 (m, 3H), 1.62 (td, *J* = 14.1, 4.2 Hz, 1H), 1.38 (d, *J* = 12.9 Hz, 1H).

Example 16

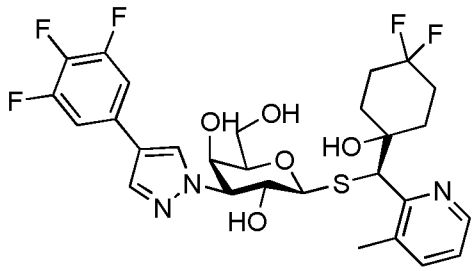
(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside



A suspension of (R)-1-(4,4-difluoro-1-hydroxycyclohexyl)-1-(3-(trifluoromethyl)pyridin-2-yl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (16 mg, 0.024 mmol), (4-chloro-2,3-difluorophenyl)boronic acid (6.9 mg, 0.036 mmol), K_2CO_3 (16 mg, 0.12 mmol) and Pd(dppf)Cl_2 (2.6 mg, 0.04 mmol) in dioxane/water (2:1, 0.15 mL) was stirred 40 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (0.7 mg, 4 %). ESI-MS *m/z* calcd for $[C_{28}H_{27}ClF_7N_3O_5S]$ $[M+H]^+$: 686.1; found: 685.9. ^1H NMR (400 MHz, Methanol-d_4) δ 8.81 (d, *J* = 4.5 Hz, 1H), 8.18 (d, *J* = 4.6 Hz, 2H), 7.94 (s, 1H), 7.55 – 7.42 (m, 2H), 7.32 – 7.22 (m, 1H), 4.58 – 4.50 (m, 2H), 4.34 (dd, *J* = 10.5, 2.8 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.76 – 3.69 (m, 2H), 3.65 (t, *J* = 6.2 Hz, 1H), 2.54 (s, 1H), 2.20 – 2.00 (m, 2H), 1.98 – 1.77 (m, 3H), 1.68 – 1.56 (m, 1H), 1.36 (s, 1H).

Example 17

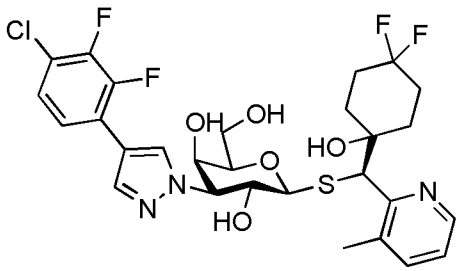
(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside



A suspension of (R)-1-(4,4-difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (15 mg, 0.025 mmol), (3,4,5-trifluorophenyl)boronic acid (6.5 mg, 0.037 mmol), K_2CO_3 (17 mg, 0.12 mmol) and Pd(dppf)Cl_2 (2.7 mg, 0.037 mmol) in dioxane/water (2:1, 0.30 mL) was stirred 40 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (0.2 mg, 1 %). ESI-MS *m/z* calcd for $[C_{28}H_{30}F_5N_3O_5S]$ $[M+H]^+$: 616.2; found: 616.2. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.39 (d, *J* = 4.5 Hz, 1H), 8.11 (s, 1H), 7.87 (s, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.34 (dd, *J* = 9.0, 6.7 Hz, 2H), 7.22 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.63 (s, 1H), 4.36 (d, *J* = 9.3 Hz, 1H), 4.27 (dd, *J* = 10.4, 2.9 Hz, 1H), 4.14 (t, *J* = 10.0 Hz, 1H), 4.07 (d, *J* = 2.5 Hz, 1H), 3.76 – 3.64 (m, 2H), 3.60 (dd, *J* = 11.1, 5.2 Hz, 1H), 2.46 (s, 3H), 2.22 – 2.00 (m, 2H), 2.00 – 1.86 (m, 1H), 1.87 – 1.68 (m, 3H), 1.44 (d, *J* = 15.8 Hz, 1H), 1.30 (d, *J* = 7.5 Hz, 1H).

Example 18

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside

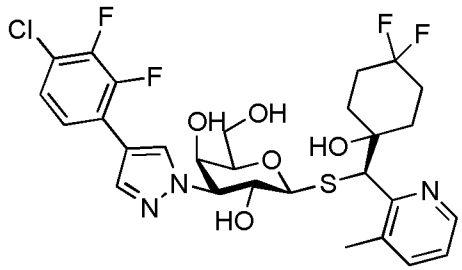


A suspension of (R)-1-(4,4-difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (30

mg, 0.049 mmol), (4-chloro-2,3-difluorophenyl)boronic acid (14 mg, 0.074 mmol), K_2CO_3 (34 mg, 0.25 mmol) and $Pd(dppf)Cl_2$ (5.4 mg, 0.074 mmol) in dioxane/water (2:1, 0.30 mL) was stirred 1 h at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (16 mg, 52 %). ESI-MS *m/z* calcd for $[C_{28}H_{30}ClF_4N_3O_5S]$ $[M+H]^+$: 632.2; found: 631.9. ^1H NMR (400 MHz, 400 MHz, Methanol-d_4) δ 8.64 – 8.46 (m, 1H), 8.20 (s, 1H), 8.17 – 7.99 (m, 1H), 7.96 (s, 1H), 7.83 – 7.51 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 4.79 (s, 1H), 4.37 – 4.30 (m, 2H), 4.23 (d, *J* = 9.9 Hz, 1H), 4.07 (s, 1H), 3.60 (d, *J* = 11.2 Hz, 3H), 2.72 – 2.55 (m, 3H), 2.47 (d, *J* = 13.3 Hz, 1H), 2.29 – 1.67 (m, 6H), 1.42 – 1.25 (m, 1H).

Example 19

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-2-*O*-methyl-1-thio-β-D-galactopyranoside

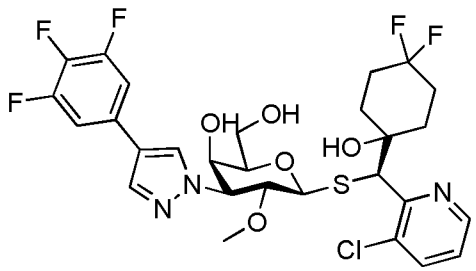


To a solution of (R)-1-(4,4-difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1*H*-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside (13 mg, 0.021 mmol) in MeCN (0.25 mL) benzaldehyde dimethyl acetal (6.3 µL, 0.042 mmol) and *p*-toluenesulfonic acid monohydrate (1.2 mg, 0.006 mmol) were added and the mixture was stirred 3 h at rt. Additional benzaldehyde dimethyl acetal (6.3 µL, 0.042 mmol) was added and the mixture was stirred overnight at rt. Then additional benzaldehyde dimethyl acetal (6.3 µL, 0.042 mmol) was added and the mixture was stirred 3 h at rt. The mixture was concentrated and added to a silica plug. The impurities were eluted with PE while the remaining material was eluted with EtOAc and concentrated. The residue was dissolved in DMF (0.25 mL) and iodomethane (3.9 µL, 0.063 mmol) and lithium *tert*-butoxide (1.7 mg, 0.021 mmol) were added. The mixture was stirred 30 min at rt, then additional lithium *tert*-butoxide (1.7 mg, 0.021 mmol) was added. The mixture was stirred 30 min

at rt and then additional lithium *tert*-butoxide (0.9 mg, 0.011 mmol) was added. The mixture was stirred 30 min and was then diluted with EtOAc (2.0 mL). The solution was washed with water (5 x 2.0 mL), dried, concentrated, and dissolved in TFA/H_2O (4:1, 150 µL). The mixture was stirred 15 min at rt before ice was added. The mixture was made basic with aq NaOH (5 M) and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried, concentrated, and purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (3.0 mg, 22 %). ESI-MS *m/z* calcd for $[C_{29}H_{32}ClF_4N_3O_5S]$ $[M+H]^+$: 646.2; found: 646.2. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.60 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 2H), 7.99 (s, 1H), 7.81 – 7.72 (m, 1H), 7.49 (t, *J* = 7.1 Hz, 1H), 7.30 (t, *J* = 7.1 Hz, 1H), 4.89 (s, 1H), 4.38 (dd, *J* = 10.3, 2.4 Hz, 1H), 4.33 (d, *J* = 9.3 Hz, 1H), 4.04 (d, *J* = 2.1 Hz, 1H), 3.99 (t, *J* = 9.7 Hz, 1H), 3.62 – 3.50 (m, 3H), 3.13 (s, 3H), 2.67 (s, 3H), 2.50 (d, *J* = 12.2 Hz, 1H), 2.22 – 1.94 (m, 4H), 1.84 (t, *J* = 11.8 Hz, 2H), 1.33 – 1.23 (m, 1H).

Example 20

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-2-*O*-methyl-1-thio-β-D-galactopyranoside

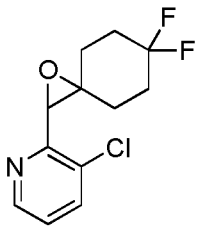


A suspension of (R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-2-*O*-methyl-1-thio-β-D-galactopyranoside (19 mg, 0.030 mmol), (3,4,5-trifluorophenyl)boronic acid (7.9 mg, 0.045 mmol), K_2CO_3 (21 mg, 0.15 mmol) and Pd(dppf)Cl_2 (3.3 mg, 0.045 mmol) in dioxane/water (2:1, 0.30 mL) was stirred 40 min at 60 °C. The mixture was cooled to rt, filtered through a C_{18}-plug (3 g, eluting with MeCN) and concentrated. The residue was purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the title compound (1.6 mg, 8 %). ESI-MS *m/z* calcd for $[C_{28}H_{29}ClF_5N_3O_5S]$ $[M+H]^+$: 650.2; found: 650.2. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.57 (d, *J* = 4.8 Hz, 1H), 8.23 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.91 (s, 1H), 7.43 (dd, *J* = 8.2, 4.8 Hz, 1H), 7.37 (dd, *J* = 9.1, 6.6 Hz, 2H), 5.06 (s, 1H), 4.47 (d, *J* = 9.5 Hz, 1H), 4.34 (dd, *J* = 10.3, 2.7 Hz,

1H), 4.08 (d, *J* = 2.5 Hz, 1H), 3.85 (q, *J* = 8.6 Hz, 1H), 3.70 (d, *J* = 5.7 Hz, 2H), 3.63 (t, *J* = 6.0 Hz, 1H), 3.07 (d, *J* = 3.8 Hz, 3H), 2.40 (d, *J* = 13.6 Hz, 1H), 2.06 (d, *J* = 16.0 Hz, 3H), 1.86 – 1.76 (m, 3H), 1.48 (d, *J* = 13.7 Hz, 1H).

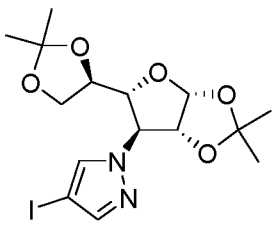
Intermediate 12

3-Chloro-2-(6,6-difluoro-1-oxaspiro[2.5]octan-2-yl)pyridine



To a cooled (-78 °C) solution of lithium diisopropylamide (3.7 mL, 2M in THF, 7.41 mmol) in anhydrous THF (10 mL) 3-chloro-2-(chloromethyl)pyridine (1.0 g, 6.17 mmol) was added followed by a solution of 4,4-difluorocyclohexanone (993 mg, 7.41 mmol) in anhydrous THF (3 mL). The mixture was stirred 1 h at -78 °C. The mixture was allowed to reach rt and saturated aq NH_4Cl (1.0 mL) was added. The mixture was extracted with EtOAc (3 x 1.0 mL). The combined organic phases were dried, concentrated, and purified by chromatography (SiO_2, PE/EtOAc) to afford the product (533 mg, 33 %). ESI-MS *m/z* calcd for $[C_{12}H_{12}ClF_2NO]$ $[M+H]^+$: 260.1; found: 260.6. ^1H NMR (400 MHz, Chloroform-d) δ 8.57 (d, *J* = 4.7 Hz, 1H), 7.72 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.25 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.22 (s, 1H), 2.29 – 2.03 (m, 4H), 1.95 – 1.86 (m, 2H), 1.68 – 1.58 (m, 2H).

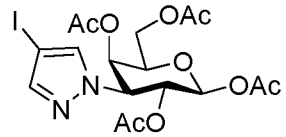
3-Deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose



A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-gulofuranose (12.54 g, 48.2 mmol) in DCM (150 mL) and pyridine (7.8 mL, 96.4 mmol) was cooled to 0 °C and trifluoromethanesulphonic anhydride (9.8 mL, 57.9 mmol) in DCM (30 mL) was added dropwise. After stirring 1 h at 10 °C the mixture was quenched by adding crushed ice. The mixture was partitioned between DCM and HCl (1 M), the organic phase was

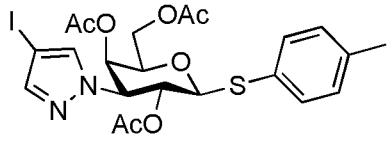
washed with saturated aq $NaHCO_3$, dried and concentrated. To a solution of the crude and Cs_2CO_3 (15.7 g, 48.2 mmol) in DMF (150 mL) 4-iodopyrazole (13.36 g, 67.5 mmol) was added. After stirring 2 h at rt ice was added to the mixture, the solids were filtered off and washed with 33 % aq MeOH, then dried to afford the product (23.9 g, quantitative yield). ESI-MS *m/z* calcd for $[C_{15}H_{21}IN_2O_5]$ $[M+H]^+$: 437.1; found: 436.9. ^1H NMR (400 MHz, Chloroform-d) δ 7.58 (s, 1H), 7.54 (s, 1H), 5.98 (d, *J* = 4.0 Hz, 1H), 4.89 (dd, *J* = 3.9, 2.3 Hz, 1H), 4.71 (dd, *J* = 6.7, 2.1 Hz, 1H), 4.31 (dd, *J* = 6.7, 4.4 Hz, 1H), 4.29 – 4.22 (m, 1H), 4.05 (dd, *J* = 8.3, 6.8 Hz, 1H), 3.88 (dd, *J* = 8.3, 6.8 Hz, 1H), 1.64 (s, 3H), 1.45 (s, 3H), 1.38 (s, 6H).

1,2,4,6-Tetra-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-β-D-galactopyranoside



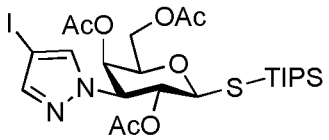
3-Deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-galactofuranose (6.00 g, 15.4 mmol) was dissolved in TFA (40 mL) and water (100 mL) and stirred 1 h at rt. The mixture was evaporated using MeCN for azeotropic removal of water and TFA and finally treated in vacuum. The crude was dissolved in EtOAc (105 mL), Et_3N (105 mL) and acetic anhydride (53 mL, 560 mmol) were added, and the mixture was stirred 20 h at rt. The mixture was cooled to 0 °C and EtOAc (200 mL) followed by HCl (280 mL, 2 M) were added slowly. The mixture was stirred 20 min, then filtered through celite. The organic phase was separated, washed with saturated aq $NaHCO_3$ and brine, dried and evaporated. The residue was filtered through silica using EtOAc/PE (1:1) and concentrated. The obtained syrup was dissolved in EtOAc (50 mL), and PE (80 mL) was added slowly, which resulted in crystallization. The crystals were isolated by filtration to afford the product (9.68 g, 58 % purity, 38 %). The filtrate was evaporated to afford more of the product (15.8 g, 65 % purity, 62 %). ESI-MS *m/z* calcd for $[C_{17}H_{21}IN_2O_9]$ $[M+H]^+$: 525.0; found: 524.8. ^1H NMR (400 MHz, Chloroform-d) δ 7.52 (s, 1H), 7.50 (s, 1H), 5.82 – 5.75 (m, 2H), 5.47 (d, *J* = 3.1 Hz, 1H), 4.79 (m, 1H), 4.16 – 4.07 (m, 3H), 2.15 (s, 3H), 2.04 (s, 6H), 1.93 (s, 3H).

4-Methylphenyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside



To a solution of 1,2,4,6-tetra-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-β-D-galactopyranoside (3.19 g, 5.5 mmol) in DCM (20 mL) HBr (3.58 mL, 5.1 M in acetic acid, 18.2 mmol) was added and the mixture was stirred 4 h at rt. The mixture was washed with cold saturated aq $NaHCO_3$ and the organic phase was dried and evaporated. The residue was dissolved in EtOAc and evaporated to dryness. The obtained material, 4-methylbenzenethiol (912 mg, 7.2 mmol), and K_2CO_3 (325 mesh, 2.3 g, 16.5 mmol) were dissolved in DMF (20 mL) and stirred 24 h at rt. The mixture was partitioned between EtOAc and brine. The organic phase was separated, evaporated, and the residue was triturated using MeOH. The crystalline precipitate was isolated by filtration to afford the product (1.23 g, 40 %). ESI-MS *m/z* calcd for $[C_{22}H_{25}IN_2O_7S]$ $[M+H]^+$: 589.0; found: 588.8. ^1H NMR (400 MHz, Chloroform-d) δ 7.51 (s, 1H), 7.48 (s, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.66 (dd, *J* = 10.9, 9.8 Hz, 1H), 5.46 (d, *J* = 2.4 Hz, 1H), 4.75 (m, 2H), 4.16 (dd, *J* = 11.4, 7.2 Hz, 1H), 4.11 (dd, *J* = 11.4, 6.0 Hz, 1H), 4.01 (t, *J* = 6.6 Hz, 1H), 2.37 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H).

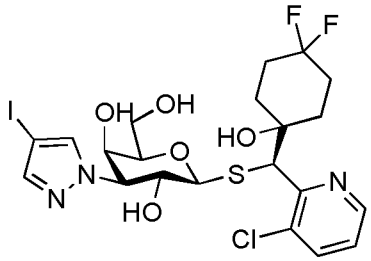
Triisopropylsilyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside



To a solution of 4-methylphenyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (1000 mg, 1.70 mmol) in DCM (10 mL) bromine (84 µL, 1.70 mmol) was added and the mixture was stirred 20 min at rt. The mixture was washed with aq Na_2SO_3 (0.6 M). The organic phase was dried, evaporated and purified by chromatography (SiO_2, PE/EtOAc). The obtained material was dissolved together with K_2CO_3 (325 mesh, 387 mg, 2.80 mmol) and triisopropylsilanethiol (0.40 mL, 1.82 mmol) in MeCN (7.0 mL) and the mixture was stirred 90 min at rt. The mixture was partitioned between EtOAc and brine. The organic phase was evaporated, and purified by chromatography (SiO_2, PE/EtOAc) to afford the product (677 mg, 61 %). ESI-MS *m/z* calcd for $[C_{24}H_{39}IN_2O_7SSi]$ $[M+H]^+$: 655.1; found: 655.0. ^1H NMR

(400 MHz, Chloroform-d) δ 7.53 (s, 1H), 7.51 (s, 1H), 5.65 (dd, *J* = 11.1, 9.3 Hz, 1H), 5.46 (d, *J* = 2.6 Hz, 1H), 4.74 (d, *J* = 9.3 Hz, 1H), 4.73 (dd, *J* = 11.1, 3.2 Hz, 1H), 4.13 (dd, *J* = 11.5, 5.9 Hz, 1H), 4.06 (dd, *J* = 11.4, 6.8 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 1H), 2.04 (s, 6H), 1.96 (s, 3H), 1.29 (m, 3H), 1.15 (d, *J* = 7.2 Hz, 18H).

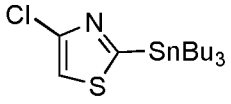
(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside



To a solution of 3-chloro-2-(6,6-difluoro-1-oxaspiro[2.5]octan-2-yl)pyridine (116 mg, 0.45 mmol) and triisopropylsilyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (293 mg, 0.45 mmol) in MeCN (2.1 mL) tetrabutylammonium fluoride trihydrate (0.45 mL, 1 M in THF, 0.45 mmol) was added and the mixture was stirred overnight at rt. The mixture was concentrated and purified by chromatography (SiO_2, PE/EtOAc). The obtained material was dissolved in anhydrous MeOH (1 mL) and NaOMe (0.20 mL, 1 M) was added, and the mixture was stirred 90 min at rt. The mixture was neutralized with acetic acid, concentrated, and purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the product (78.3 mg, 28 %). ESI-MS *m/z* calcd for $[C_{21}H_{25}ClF_2IN_3O_5S]$ $[M+H]^+$: 632.0; found: 631.8. ^1H NMR (400 MHz, Methanol-d_4) δ 8.55 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.99 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.80 (s, 1H), 7.52 (s, 1H), 7.40 (dd, *J* = 8.2, 4.8 Hz, 1H), 5.04 (s, 1H), 4.44 (d, *J* = 9.4 Hz, 1H), 4.28 (dd, *J* = 10.5, 2.8 Hz, 1H), 4.13 – 4.03 (m, 1H), 4.04 (d, *J* = 2.6 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.66 – 3.60 (m, 1H), 2.37 (d, *J* = 12.9 Hz, 1H), 2.20 – 1.89 (m, 3H), 1.89 – 1.74 (m, 3H), 1.50 (d, *J* = 14.3 Hz, 1H).

Intermediate 14

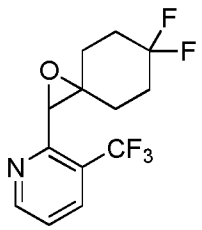
Tributyl-(4-chlorothiazol-2-yl)stannane



To a cooled (-78 °C) solution of 2-bromo-4-chloro-thiazole (200 mg, 1.0 mmol) in diethyl ether (3.3 mL) *n*-butyl lithium (443 µL, 2.5 M in hexanes, 1.11 mmol) was added and the mixture was stirred 25 min at -78 °C. Tributyltin chloride (364 µL, 1.21 mmol) was added and the mixture was slowly allowed to reach rt. The reaction was quenched with water (3 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 x 3 mL). The combined organic phases were washed with brine, dried, filtered and concentrated to afford the product (486 mg, purity 85 %, quantitative yield). ESI-MS *m/z* calcd for $[C_{15}H_{28}ClNSSn]$ $[M+H]^+$: 410.1; found: 410.1. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.27 (s, 1H), 1.66 – 1.55 (m, 6H), 1.39 – 1.30 (m, 6H), 1.26 – 1.20 (m, 6H), 0.90 (t, *J* = 7.3 Hz, 9H).

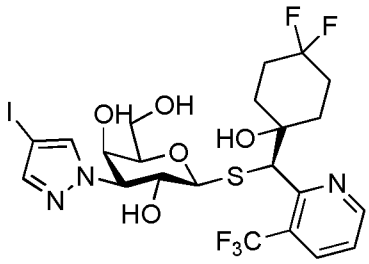
Intermediate 15

3-(Trifluoromethyl)-2-(6,6-difluoro-1-oxaspiro[2.5]octan-2-yl)pyridine



To a cooled (-78 °C) solution of lithium diisopropylamide (1.53 mL, 2 M in THF, 3.07 mmol) in anhydrous THF (10 mL) a solution of 2-(chloromethyl)-3-(trifluoromethyl)pyridine (500 mg, 2.56 mmol) in anhydrous THF (2.0 mL) was added followed by a solution of 4,4-difluorocyclohexanone (441 mg, 3.07 mmol) in anhydrous THF (2.0 mL). The mixture was stirred 1 h at -78 °C. The mixture was allowed to reach rt and saturated aq NH_4Cl (1.0 mL) was added, and the mixture was extracted with EtOAc (3 x 1.0 mL). The combined organic phases were dried, concentrated, and purified by chromatography (SiO_2, PE/EtOAc) to afford the product (587 mg, 78 %). ESI-MS *m/z* calcd for $[C_{13}H_{12}F_5NO]$ $[M+H]^+$: 294.1; found: 293.8. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.84 (d, *J* = 4.7 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.41 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.29 (d, *J* = 1.8 Hz, 1H), 2.31 – 1.88 (m, 4H), 1.69 (td, *J* = 13.0, 4.7 Hz, 1H), 1.48 – 1.37 (m, 1H), 1.22 (s, 1H), 0.91 (td, *J* = 13.2, 7.4 Hz, 1H).

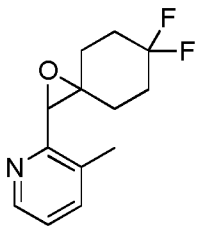
(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside



To a solution of 3-(trifluoromethyl)-2-(6,6-difluoro-1-oxaspiro[2.5]octan-2-yl)pyridine (164 mg, 0.56 mmol) and triisopropylsilyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (366 mg, 0.56 mmol) in MeCN (2.1 mL) tetrabutylammonium fluoride trihydrate (0.56 mL, 1 M in THF, 0.56 mmol) was added and the mixture was stirred overnight at rt. The mixture was concentrated and purified by chromatography (SiO_2, PE/EtOAc). The obtained material was dissolved in anhydrous MeOH (2.0 mL) and NaOMe (40 µL, 5 M) was added. The mixture was stirred 90 min at rt. The mixture was neutralized with acetic acid, concentrated, and purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the product (32 mg, 9 %). ESI-MS *m/z* calcd for $[C_{22}H_{25}F_5IN_3O_5S]$ $[M+H]^+$: 666.1; found: 666.0. ^1H NMR (400 MHz, Methanol-d_4) δ 8.81 (d, *J* = 4.2 Hz, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.79 (s, 1H), 7.53 – 7.49 (m, 2H), 4.54 (s, 1H), 4.49 (d, *J* = 9.5 Hz, 1H), 4.29 (dd, *J* = 10.5, 2.5 Hz, 1H), 4.08 – 3.98 (m, 2H), 3.70 (d, *J* = 5.6 Hz, 2H), 3.61 (t, *J* = 6.3 Hz, 1H), 2.51 (d, *J* = 13.4 Hz, 1H), 2.21 – 1.98 (m, 2H), 1.96 – 1.75 (m, 3H), 1.61 (td, *J* = 13.7, 3.3 Hz, 1H), 1.36 (d, *J* = 12.9 Hz, 1H).

Intermediate 17

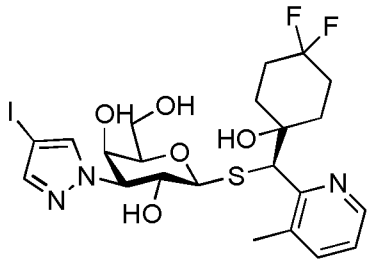
2-(6,6-Difluoro-1-oxaspiro[2.5]octan-2-yl)-3-methylpyridine



A solution of 2-(chloromethyl)-3-methylpyridine hydrochloride (1.0 g, 5.6 mmol) in DCM was washed with saturated aq $NaHCO_3$. The organic phase was dried, concentrated and redissolved in anhydrous THF (2.0 mL). The solution was added dropwise to a cooled (-78 °C) solution of lithium diisopropylamide (3.37 mL, 2 M in THF, 6.7 mmol) in anhydrous THF (10 mL), followed by the addition of a solution of 4,4-difluorocyclohexanone (904 mg, 6.7 mmol) in anhydrous THF (3.0 mL). The

resulting mixture was stirred 1 h at -78 °C. The mixture was allowed to reach rt and the solvent was reduced (to approximately 5 mL) by evaporation. Saturated aq NH_4Cl (4.0 mL) was added, and the mixture was extracted with EtOAc (3 x 3.0 mL). The combined organic phases were dried, concentrated, and purified by chromatography (SiO_2, PE/EtOAc) to afford the product (511 mg, 38 %). ^1H NMR (400 MHz, Methanol-d_4) δ 8.34 (d, *J* = 4.3 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.28 (dd, *J* = 7.7, 4.9 Hz, 1H), 4.19 (s, 1H), 2.42 (s, 3H), 2.25 – 2.12 (m, 3H), 2.11 – 1.84 (m, 2H), 1.80 (dd, *J* = 6.6, 4.5 Hz, 1H), 1.61 (ddd, *J* = 14.9, 10.7, 4.9 Hz, 1H), 1.36 – 1.26 (m, 1H).

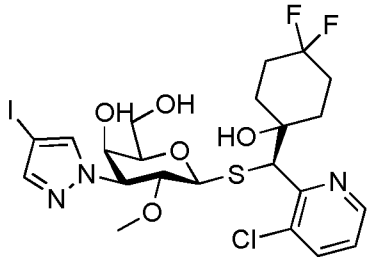
(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside



To a solution of 2-(6,6-difluoro-1-oxaspiro[2.5]octan-2-yl)-3-methylpyridine (272 mg, 1.02 mmol) and triisopropylsilyl 2,4,6-tri-*O*-acetyl-3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (670 mg, 1.02 mmol) in MeCN (2.1 mL) tetrabutylammonium fluoride trihydrate (1.02 mL, 1 M in THF, 1.02 mmol) was added and the mixture was stirred 5 h at rt. The mixture was concentrated and purified by chromatography (SiO_2, PE/EtOAc). The obtained material was dissolved in anhydrous MeOH (2.0 mL) and NaOMe (50 µL, 5 M) was added. The mixture was stirred 2 h at rt. The mixture was neutralized with acetic acid, concentrated, and purified by prep HPLC (C_{18}, H_2O/MeCN/0.1 % TFA) to afford the product (75 mg, 12 %). ^1H NMR (400 MHz, Methanol-d_4) δ 8.58 (d, *J* = 5.5 Hz, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.84 (s, 1H), 7.78 – 7.68 (m, 1H), 7.54 (s, 1H), 4.86 (s, 1H), 4.28 (dd, *J* = 9.8, 2.6 Hz, 2H), 4.24 – 4.12 (m, 1H), 3.98 (s, 1H), 3.63 – 3.46 (m, 3H), 2.64 (s, 3H), 2.45 (d, *J* = 13.0 Hz, 1H), 2.21 – 1.91 (m, 4H), 1.84 (t, *J* = 11.6 Hz, 2H), 1.28 (d, *J* = 10.9 Hz, 1H).

Intermediate 20

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-2-*O*-methyl-1-thio-β-D-galactopyranoside



To a solution of (R)-1-(3-chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-(4-iodo-1*H*-1,2-pyrazol-1-yl)-1-thio-β-D-galactopyranoside (40 mg, 0.063 mmol) in MeCN (0.5 mL) benzaldehyde dimethyl acetal (48 µL, 0.32 mmol) and *p*-toluenesulfonic acid hydrate (41 mg, 0.22 mmol) were added and the mixture was stirred overnight at rt. Additional benzaldehyde dimethyl acetal (19 µL, 0.13 mmol) was added and the mixture was stirred 90 min at rt. The reaction mixture was quenched with Et_3N (40 µL) and concentrated. The residue was dissolved in water and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried, concentrated, and dissolved in DMF (750 µL). Iodomethane (12 µL, 0.19 mmol) and lithium *tert*-butoxide (5.0 mg, 0.063 mmol) were added, and the mixture was stirred 15 min at rt. Additional lithium *tert*-butoxide (2.5 mg, 0.032 mmol) was added, and the mixture was stirred 15 min at rt. The mixture was diluted with EtOAc, washed with H_2O, dried, and concentrated. The residue was dissolved in H_2O/TFA (1:4, v/v, 400 µL) and stirred 15 min at rt. Ice was added and the mixture was made basic using aq NaOH (5 M) and extracted with EtOAc (3 x 2 mL). The combined organic phases were dried, concentrated, and purified by chromatography (SiO_2, PE/EtOAc) to afford the product (19 mg, 47 %). ESI-MS *m/z* calcd for $[C_{22}H_{27}ClF_2IN_3O_5S]$ $[M+H]^+$: 646.0; found: 646.0. ^1H NMR (400 MHz, Methanol-d_4) δ 8.53 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.93 – 7.88 (m, 2H), 7.54 (s, 1H), 7.34 (dd, *J* = 8.2, 4.6 Hz, 1H), 5.02 (s, 1H), 4.44 (d, *J* = 9.5 Hz, 1H), 4.34 (dd, *J* = 10.4, 2.8 Hz, 1H), 4.03 (d, *J* = 2.1 Hz, 1H), 3.78 – 3.72 (m, 1H), 3.72 – 3.68 (m, 2H), 3.60 (t, *J* = 6.2 Hz, 1H), 3.01 (s, 3H), 2.38 (d, *J* = 14.0 Hz, 1H), 2.19 – 1.89 (m, 3H), 1.88 – 1.72 (m, 3H), 1.55 – 1.47 (m, 1H).

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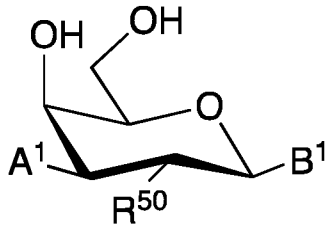
We Claim:

1. A D-galactopyranose compound of formula (1)



wherein

the pyranose ring is β-D-galactopyranose,

A^1 is $(R^1)_n$-Z^{1a},

wherein

Z^{1a} is a five membered heterocycle having at least one heteroatom selected from O, S, and N, except 1,2,3-triazole and is attached to the β-D-galactopyranose;

n is 1 or 2;

each R^1 is independently selected from

a) C_{1-6} alkyl optionally substituted with a halogen; C_{1-6} alkyl substituted with a OH; halogen; CN; C_2-alkynyl; OH; OC_{1-6} alkyl optionally substituted with a halogen; C_{3-6} cycloalkyl optionally substituted with a halogen; SH; SC_{1-6} alkyl optionally substituted with a halogen; NR^2R^3, wherein R^2 and R^3 are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, C_{3-6} cycloalkyl optionally substituted with a halogen, $C(O)C_{1-6}$ alkyl optionally substituted with a halogen, and $S(O_2)C_{1-6}$ alkyl optionally substituted with a halogen, or R^2 and R^3 taken together with the nitrogen to which they are attached form a heterocycloalkyl, optionally substituted with a group selected from a halogen; a spiro heterocycle, such as N-(2-oxa)-6-azaspiro[3.3]heptanyl; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; $S(O_2)C_{3-6}$ cycloalkyl optionally substituted with a halogen; C_{1-6} alkenyl optionally substituted with a halogen; $C(O)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; COOH; $C(O)OC_{1-6}$ alkyl optionally substituted with a halogen; $C(O)OC_{3-6}$ cycloalkyl optionally substituted with a halogen; $C(O)NR^6R^7$, wherein R^6 and R^7 are independently selected from H, C_{1-3} alkyl optionally substituted with a halogen or an aryl, such as a phenyl, cyclopropyl optionally substituted with a halogen; and $S(O_2)NR^8R^9$ wherein R^8 and R^9

are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen;

b) an aryl, such as phenyl or naphthyl, optionally substituted with a group selected from a halogen; CN; a spiro heterocycle; -COOH; -$CONR^{10}R^{11}$, wherein R^{10} and R^{11} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{10} and R^{11} together with the nitrogen may form a heterocycloalkyl; C_{1-3} alkyl, optionally substituted with a F; cyclopropyl, optionally substituted with a F; OC_{1-3} alkyl, optionally substituted with a F; O-cyclopropyl, optionally substituted with a F; $NR^{12}R^{13}$, wherein R^{12} and R^{13} are independently selected from H, C_{1-3} alkyl and cyclopropyl; C(=O)-R^{14}, wherein R^{14} is selected from H and C_{1-3} alkyl; OH; and R^{15}-CONH- wherein R^{15} is selected from C_{1-3} alkyl and cyclopropyl;

c) a heterocycle, such as heteroaryl or heterocycloalkyl, optionally substituted with a group selected from a halogen; a spiro heterocycle; CN; -COOH; -$CONR^{16}R^{17}$, wherein R^{16} and R^{17} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{16} and R^{17} together with the nitrogen may form a heterocycloalkyl; C_{1-3} alkyl, optionally substituted with a F; cyclopropyl, optionally substituted with a F; OC_{1-3} alkyl, optionally substituted with a F; O-cyclopropyl, optionally substituted with a F; $NR^{18}R^{19}$, wherein R^{18} and R^{19} are independently selected from H, C_{1-3} alkyl, and cyclopropyl; C(=O)-R^{20}, wherein R^{20} is selected from H and C_{1-3} alkyl; OH; and R^{21}-CONH- wherein R^{21} is selected from C_{1-3} alkyl and cyclopropyl;

d) phenyl, naphthalinyl, biphenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, quinoxainyl, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzoxazolyl, benzothiazolyl, benzodioxolyl, dihydrobenzodioxinyl, dihydroquinolinonyl, dihydrobenzothiophene-2,2-dioxide, pyrrolyl, furanyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, or thiadiazolyl; optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl optionally substituted with a halogen; halogen; CN; C_2-alkynyl; OH; OC_{1-6} alkyl optionally substituted with a halogen; C_{3-6} cycloalkyl optionally substituted with a halogen; SH; SC_{1-6} alkyl optionally substituted with a halogen; $NR^{22}R^{23}$, wherein R^{22} and R^{23} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, C_{3-6} cycloalkyl optionally substituted with a halogen, $C(O)C_{1-6}$ alkyl optionally substituted with a halogen, and $S(O_2)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; $S(O_2)C_{3-6}$ cycloalkyl optionally

substituted with a halogen; C_{1-6} alkenyl optionally substituted with a halogen; $C(O)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; COOH; $C(O)OC_{1-6}$ alkyl optionally substituted with a halogen; $C(O)OC_{3-6}$ cycloalkyl optionally substituted with a halogen; $C(O)NR^{24}R^{25}$, wherein R^{24} and R^{25} are independently selected from H, C_{1-3} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen; and $S(O_2)NR^{26}R^{27}$ wherein R^{26} and R^{27} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen;

e) Y^1-Z^2 wherein

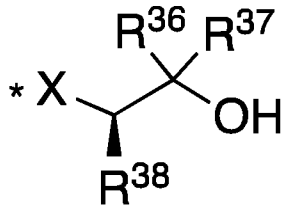
Y^1 is linked to Z^{1a} and is selected from the group consisting of S, Se, SO, SO_2, O, C=O, and $CR^{28}R^{29}$ wherein R^{28} and R^{29} are independently selected from hydrogen, OH, or halogen;

Z^2 is selected from the group consisting of phenyl, naphthalinyl, biphenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, quinoxainyl, indolyl, indazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzoxazolyl, benzothiazolyl, benzodioxolyl, dihydrobenzodioxinyl, dihydroquinolinonyl, dihydrobenzothiophene-2,2-dioxide, pyrrolyl, furanyl, thienyl, pyrazolyl, isoxazolyl, isothiazolyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, oxadiazolyl, or thiadiazolyl; optionally substituted with one or more substituents selected from the group consisting of C_{1-6} alkyl optionally substituted with a halogen; halogen; CN; C_2-alkynyl; OH; OC_{1-6} alkyl optionally substituted with a halogen; C_{3-6} cycloalkyl optionally substituted with a halogen; SH; SC_{1-6} alkyl optionally substituted with a halogen; $NR^{30}R^{31}$, wherein R^{30} and R^{31} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, C_{3-6} cycloalkyl optionally substituted with a halogen, $C(O)C_{1-6}$ alkyl optionally substituted with a halogen, and $S(O_2)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; $S(O_2)C_{3-6}$ cycloalkyl optionally substituted with a halogen; C_{1-6} alkenyl optionally substituted with a halogen; $C(O)C_{1-6}$ alkyl optionally substituted with a halogen; $C(O)C_{3-6}$ cycloalkyl optionally substituted with a halogen; COOH; $C(O)OC_{1-6}$ alkyl optionally substituted with a halogen; $C(O)OC_{3-6}$ cycloalkyl optionally substituted with a halogen; $C(O)NR^{32}R^{33}$, wherein R^{32} and R^{33} are independently selected from H, C_{1-3} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen; and $S(O_2)NR^{34}R^{35}$ wherein R^{34} and

R^{35} are independently selected from H, C_{1-6} alkyl optionally substituted with a halogen, and cyclopropyl optionally substituted with a halogen; and

f) hydrogen (H);

B^1 is a)



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wherein the asterix on the X is linked to D-galactopyranose and is in the beta anomeric conformation,

X is selected from S, SO, SO_2, O, C=O, and $CR^{2a}R^{3a}$ wherein R^{2a} and R^{3a} are independently selected from hydrogen, OH, or halogen;

R^{36} is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, C_{1-6} alkyl substituted with a phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl;

R^{37} is selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, C_{1-6} alkyl substituted with a phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl;

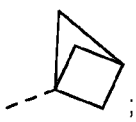
or R^{36} and R^{37} together with the carbon atom to which they are attached form a non-aromatic 3-6-membered ring optionally containing 1 or 2 nitrogen, 1 or 2 oxygen and/or 1 or 2 sulphur, optionally substituted with a group selected from one or more halogen, hydroxy, CN, C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, C_{3-6} cycloalkyl, SO_2-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2-C_{3-6} cycloalkyl, CO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CO-C_{3-6} cycloalkyl, COO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, COO-C_{3-6} cycloalkyl, CONH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CONH-C_{3-6} cycloalkyl, SO_2NH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2NH-C_{3-6} cycloalkyl, and a spiroheterocycle optionally substituted with a group selected from a halogen and a C_{1-6} alkyl;

R^{38} is selected from

i) aryl optionally substituted with a group selected from C_{1-6} alkyl, C_{1-6} alkyl substituted with a halogen, OH, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{42}R^{43}$, wherein R^{42} and R^{43} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, and aryl optionally substituted with a group selected from halogen or C_{1-3} alkyl;

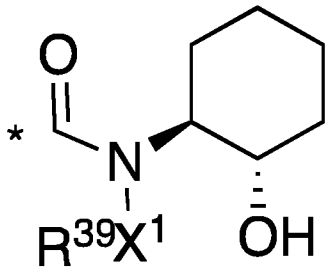
ii) heteroaryl optionally substituted with a group selected from C_{1-6} alkyl, C_{1-6} alkyl substituted with a halogen, OH, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{44}R^{45}$, wherein R^{44} and R^{45} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, and aryl optionally substituted with a group selected from halogen or C_{1-3} alkyl;

iii) C=O-$NR^{40}R^{41}$ wherein R^{40} and R^{41} are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkyl substituted with a C_{1-6} alkoxy, C_{1-6} alkyl substituted with a halogen, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{46}R^{47}$, wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl, such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, C_{1-2}-alkylene-R^{48}, wherein R^{48} represents phenyl optionally substituted with a C_{1-3} alkyl or 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, phenyl optionally substituted with a C_{1-3} alkyl, 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl, and

 ;

or R^{40} and R^{41} taken together with the nitrogen to which they are attached form a 4-6 membered heterocycloalkyl, such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, optionally substituted with a halogen or C_{1-3} alkyl, a partially aromatic bicyclic ring consisting of a pyrrolidine-1-yl or a piperidine-1-yl, wherein said pyrrolidine or piperidine is fused to a phenyl ring;

or B^1 is b)



Wherein the asterix on the carbonyl carbon is linked to D-galactopyranose and is in the beta anomeric conformation,

X^1 is selected from C_{1-6} alkyl or X^1 is absent and R^{39} is linked to N;

R^{39} is attached to N or X^1 and is selected from aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, CN, C_{1-6} alkyl, SO_2C_{1-3} alkyl, C_{1-6} alkyl substituted with a halogen, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, amino, ethynyl, heterocycloalkyl;

R^{50} is selected from the group consisting of a) H, b) OH, c) OC_{1-6} alkyl optionally substituted with one or more halogen, phenyl, phenyl substituted with one or more groups selected from OH and halogen, CN, OR^{49}, $NR^{51}R^{52}$, $CONH_2$, and $CONR^{53}R^{54}$, wherein R^{53} and R^{54} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{53} and R^{54} together with the nitrogen may form a heterocycloalkyl optionally substituted with a group selected from OH, wherein R^{49} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{55}-CONH- wherein R^{55} is selected from C_{1-3} alkyl and cyclopropyl, R^{51} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted

with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{56}-CONH- wherein R^{56} is selected from C_{1-3} alkyl and cyclopropyl, and R^{52} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{57}-CONH- wherein R^{57} is selected from C_{1-3} alkyl and cyclopropyl, d) branched OC_{3-6} alkyl optionally substituted with one or more halogen, CN, OR^{58}, $NR^{59}R^{60}$, $CONH_2$, and $CONR^{61}R^{62}$, wherein R^{61} and R^{62} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{61} and R^{62} together with the nitrogen may form a heterocycloalkyl optionally substituted with a group selected from OH, wherein R^{58} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{63}-CONH- wherein R^{63} is selected from C_{1-3} alkyl and cyclopropyl, R^{59} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{64}-CONH- wherein R^{64} is selected from C_{1-3} alkyl and cyclopropyl, and R^{60} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{65}-CONH- wherein R^{65} is selected from C_{1-3} alkyl and cyclopropyl , and e) cyclic OC_{3-6} alkyl optionally substituted with one or more halogen, CN, OR^{66}, $NR^{67}R^{68}$, $CONH_2$, and $CONR^{69}R^{70}$, wherein R^{69} and R^{70} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{69} and R^{70} together with the nitrogen may form a heterocycloalkyl optionally substituted with a group selected from OH, wherein R^{66} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{71}-CONH- wherein R^{71} is selected from C_{1-3} alkyl and cyclopropyl, R^{67} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{72}-CONH- wherein R^{72} is selected from C_{1-3} alkyl and cyclopropyl, and R^{68} is selected from the group consisting of H, CN, a halogen, methyl optionally substituted with a F, OCH_3 optionally substituted with a F, OCH_2CH_3 optionally substituted with a F, OH, and R^{73}-CONH- wherein R^{73} is selected from C_{1-3} alkyl and cyclopropyl; or

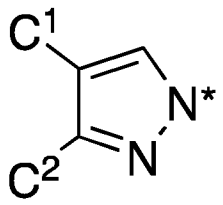
a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1 wherein Z^{1a} is selected from 1,2,4-triazolyl, oxazolyl, isoxazolyl, oxadiazolyl, dioxolyl, dithiolyl, thiazolyl, isothiazolyl, furanyl, thiophen, pyrrolyl, imidazolyl, or pyrazolyl.

3. The compound of claim 1 or 2 wherein Z^{1a} is a pyrazolyl.

4. The compound of any one of claims 1-3 wherein

A^1 is $(R^1)_n$-Z^{1a} is

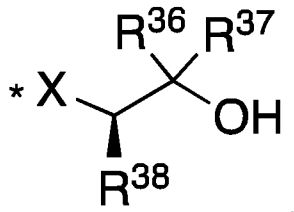


wherein the asterix * indicates the nitrogen atom of the pyrazole ring that is covalently attached to the galactopyranose, and C^1 and C^2 are independently selected from R^1.

5. The compound of claim 4 wherein a) C^1 is selected from a phenyl optionally substituted with one, two or three substitutents selected from the group consisting of a halogen, a CN, cyclopropyl optionally substituted with a F, isopropyl optionally substituted with a F, OC_{1-3} alkyl optionally substituted with a F, O-cyclopropyl optionally substituted with a F, O-isopropyl optionally substituted with a F, and a C_{1-3} alkyl optionally substituted with a F; and C^2 is hydrogen, or b) C^1 is selected from a thiazol optionally substituted with one, two or three substitutents selected from the group consisting of a halogen, a CN, cyclopropyl optionally substituted with a F, isopropyl optionally substituted with a F, OC_{1-3} alkyl optionally substituted with a F, O-cyclopropyl optionally substituted with a F, O-isopropyl optionally substituted with a F, and a C_{1-3} alkyl optionally substituted with a F; and C^2 is hydrogen.

6. The compound of claim 4 or 5 wherein a) C^1 is selected from a phenyl substituted with one, two or three substitutents selected from the group consisting of Cl, F, Br and I, such as three F or b) C^1 is selected from a thiazol substituted with one or two substitutents selected from the group consisting of Cl, F, Br and I, such as one Cl.

7. The compound of any one of claims 1-6 wherein B^1 is



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wherein the asterix on the X is linked to D-galactopyranose and is in the beta anomeric conformation, and X, R^{36}, R^{37}, and R^{38} are as defined in claim 1.

8. The compound of claim 7 wherein X is S.

9. The compound of claim 7 or 8 wherein R^{36} and R^{37} together with the carbon atom to which they are attached form a non-aromatic 5-6-membered ring optionally containing 1 nitrogen and/or 1 oxygen, optionally substituted with a group selected from one or more halogen, hydroxy, CN, C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, C_{3-6} cycloalkyl, SO_2-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2-C_{3-6} cycloalkyl, CO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CO-C_{3-6} cycloalkyl, COO-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, COO-C_{3-6} cycloalkyl, CONH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, CONH-C_{3-6} cycloalkyl, SO_2NH-C_{1-6} alkyl optionally substituted with a C_{3-6} cycloalkyl, SO_2NH-C_{3-6} cycloalkyl, and a spiroheterocycle optionally substituted with a group selected from a halogen and a C_{1-6} alkyl.

10. The compound of claim 9 wherein R^{36} and R^{37} together with the carbon atom to which they are attached form a non-aromatic 5-6-membered ring optionally containing 1 nitrogen and/or 1 oxygen, optionally substituted with a group selected from halogen, C_{1-6} alkyl and SO_2-C_{1-6} alkyl, such as two F, one methyl or one SO_2CH_3.

11. The compound of any one of claims 7-10 wherein R^{38} is heteroaryl optionally substituted with a group selected from halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with a halogen, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a

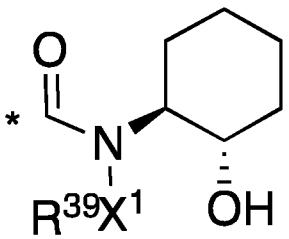
halogen, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, $(CH_2)_{0-1}$-C_{3-6} cycloalkyl optionally substituted with a group selected from halogen or C_{1-3} alkyl, C_{4-6} cyclic ether, CH_2-C_{4-6} cyclic ether, CH_2CH_2-C_{4-6} cyclic ether, CH_2-CH_2-$NR^{44}R^{45}$, wherein R^{44} and R^{45} together with the nitrogen atom to which they are attached form a 4-6 membered heterocycloalkyl such as selected from azetidine-1-yl, pyrrolidine-1-yl, piperidine-1-yl, and morpholin-4-yl, and aryl optionally substituted with a group selected from halogen or C_{1-3} alkyl.

12. The compound of claim 11 wherein R^{38} is pyridinyl substituted with a group selected from halogen, a C_{1-6} alkyl substituted with a halogen and C_{3-6} cycloalkyl, such as one CF_3 or one cyclopropyl.

13. The compound of any one of claims 7-10 wherein R^{38} is C=O-$NR^{40}R^{41}$ wherein R^{40} and R^{41} are independently selected from H, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{4-6} cyclic ether, and a 5- or 6-membered heteroaryl optionally substituted with a C_{1-3} alkyl.

14. The compound of claim 13 wherein R^{38} is C=O-$NR^{40}R^{41}$ wherein R^{40} is selected from C_{1-6} alkyl and R^{41} is selected from C_{1-6} alkyl, C_{3-4} cycloalkyl, morpholinyl, and pyridinyl.

15. The compound of any one of claims 1-6 wherein B^1 is



Wherein the asterix on the carbonyl carbon is linked to D-galactopyranose and is in the beta anomeric conformation, and X^1 and R^{39} are as defined in claim 1.

16. The compound of claim 15 wherein X^1 is selected from C_{1-6} alkyl and R^{39} is selected from aryl or heteroaryl optionally substituted with one or more halogen, hydroxy, CN, C_{1-6} alkyl, SO_2C_{1-3} alkyl, C_{1-6} alkyl substituted with a halogen, C_{1-6} alkyl substituted with a hydroxy, C_{1-6} alkoxy substituted with a halogen, C_{3-6} cycloalkyl, C_{3-}

$_{6}$ cycloalkyl substituted with a group selected from halogen or C_{1-3} alkyl, amino, ethynyl, heterocycloalkyl.

17. The compound of claim 15 wherein X^1 is absent and R^{39} is linked to N and is selected from phenyl substituted with one or more halogen and CN.

18. The compound of claim 16 or 17 wherein R^{39} is phenyl substituted with one or two selected from Cl and CN.

19. The compound of any one of claims 1-18 wherein R^{50} is selected from H, OH, OC_{1-4} alkyl, such as O-methyl, O-ethyl, or O-isopropyl, or OC_{1-4} alkyl substituted with one $CONR^{53}R^{54}$, wherein R^{53} and R^{54} are independently selected from H, C_{1-3} alkyl, and cyclopropyl, or R^{53} and R^{54} together with the nitrogen form a heterocycloalkyl optionally substituted with a group selected from OH.

20. The compound of any one of claims 1-19 wherein R^{50} is selected from OH.

21. The compound of any one of claims 1-19 wherein R^{50} is selected from OC_{1-4} alkyl such as O-methyl, substituted with one $CONR^{53}R^{54}$, wherein R^{53} and R^{54} together with the nitrogen form a heterocycloalkyl optionally substituted with a group selected from OH.

22. The compound of claim 1 selected from any one of the group consisting of:

(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(1-piperidinylcarbonyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

2-Ethylmethylamino-(S)-1-[4-hydroxy-1-(methylsulfonyl)piperidin-4-yl]-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

2-Cyclobutylmethylamino-(S)-1-(1-hydroxycyclopentyl)-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(S)-1-(4-Hydroxypyran-4-yl)-2-methyl(pyridin-2-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(S)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-2-methyl(pyran-4-yl)amino-2-oxoethyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-2-*O*-methyl-1-thio-β-D-galactopyranoside,

(R)-1-[3-(Trifluoromethyl)pyridin-2-yl]-1-(4-hydroxy-1-methylpiperidin-4-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(3-Cyclopropylpyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

2,6-Anhydro-*N*-(3-chloro-5-cyanophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide,

2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-methyl-D-glycero-L-manno-heptonamide,

2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-(2-morpholino-2-oxoethyl)-D-glycero-L-manno-heptonamide,

2,6-Anhydro-*N*-(3,5-dichlorophenyl)-4-deoxy-4-[4-(3,4,5-trifluorophenyl)-1*H*-1,2-pyrazol-1-yl]-*N*-[(1S,2S)-2-hydroxycyclohexyl]-3-*O*-{2-[(S)-3-hydroxypyrrolidin-1-yl]-2-oxoethyl}-D-glycero-L-manno-heptonamide,

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-[4-(4-chlorothiazol-2-yl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-[3-(trifluoromethyl)pyridin-2-yl]methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-1-thio-β-D-galactopyranoside,

(R)-1-(4,4-Difluoro-1-hydroxycyclohexyl)-1-(3-methylpyridin-2-yl)methyl 3-[4-(4-chloro-2,3-difluorophenyl)-1H-1,2-pyrazol-1-yl]-3-deoxy-2-O-methyl-1-thio-β-D-galactopyranoside, and

(R)-1-(3-Chloropyridin-2-yl)-1-(4,4-difluoro-1-hydroxycyclohexyl)methyl 3-deoxy-3-[4-(3,4,5-trifluorophenyl)-1H-1,2-pyrazol-1-yl]-2-O-methyl-1-thio-β-D-galactopyranoside; or a pharmaceutically acceptable salt or solvat thereof.

23. The compound of any one of claims 1-22 for use as a medicine.

24. A pharmaceutical composition comprising the compound of any one of the previous claims and optionally a pharmaceutically acceptable additive.

25. The compound of any one of the claims 1-22 for use in a method for treating a disorder relating to the binding of a galectin-3 to a ligand in a mammal, such as a human, wherein said disorder is selected from the group consisting of inflammation; fibrosis, such as pulmonary fibrosis, liver fibrosis, kidney fibrosis, ophthalmological fibrosis and fibrosis of the skin and heart; scarring; keloid formation; aberrant scar formation; surgical adhesions; scleroderma; systemic sclerosis; septic shock; cancer, such as carcinomas, sarcomas, leukemias and lymphomas, such as T-cell lymphomas; metastasising cancers; autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, intestinal fibrosis, ankylosing spondylitis, systemic lupus erythematosus; metabolic disorders; heart disease; heart failure; aortic stenosis,

atherosclerosis, pathological angiogenesis, such as ocular angiogenesis or a disease or condition associated with ocular angiogenesis, e.g. neovascularization related to cancer; and eye diseases, such as age-related macular degeneration and corneal neovascularization; atherosclerosis; metabolic diseases such as diabetes; type 2 diabetes; insulin resistance; obesity; Diastolic HF; asthma and other interstitial lung diseases, including Hermansky-Pudlak syndrome, pulmonary arterial hypertension, RA-ILD, SSc-ILD, Lung disease with fibrosis such as COPD and asthma. Otosclerosis, mesothelioma; liver disorders, such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease, Liver cirrhosis of various origins, such as alcoholic and non-alcoholic, autoimmune cirrhosis such as primary biliary cirrhosis and sclerosing cholangitis, virally induced cirrhosis, cirrhosis induced by genetic disease. Liver cancer, cholangiocarcinoma, biliary tract cancer; neurodegenerative disorders such as Parkinsons disease, Alzheimers disease, cognitive impairment, cerebrovascular diseases such as stroke, traumatic brain injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, peripheral nephropathy.

26. A method for treatment of a disorder relating to the binding of a galectin-3 to a ligand in a mammal, such as a human, wherein a therapeutically effective amount of at least one compound according to any one of the claims 1-22 is administered to a mammal in need of said treatment.

27. The method of claim 26, wherein said disorder is selected from the group consisting ofinflammation; fibrosis, such as pulmonary fibrosis, liver fibrosis, kidney fibrosis, ophthalmological fibrosis and fibrosis of the skin and heart; scarring; keloid formation; aberrant scar formation; surgical adhesions; scleroderma; systemic sclerosis; septic shock; cancer, such as carcinomas, sarcomas, leukemias and lymphomas, such as T-cell lymphomas; metastasising cancers; autoimmune diseases, such as psoriasis, rheumatoid arthritis, Crohn’s disease, ulcerative colitis, intestinal fibrosis, ankylosing spondylitis, systemic lupus erythematosus; metabolic disorders; heart disease; heart failure; aortic stenosis, atherosclerosis, pathological angiogenesis, such as ocular angiogenesis or a disease or condition associated with ocular angiogenesis, e.g. neovascularization related to cancer; and eye diseases, such as age-related macular degeneration and corneal neovascularization; atherosclerosis; metabolic diseases such as diabetes; type 2 diabetes; insulin resistance; obesity;

Diastolic HF; asthma and other interstitial lung diseases, including Hermansky-Pudlak syndrome, pulmonary arterial hypertension, RA-ILD, SSc-ILD, Lung disease with fibrosis such as COPD and asthma. Otosclerosis, mesothelioma; liver disorders, such as non-alcoholic steatohepatitis or non-alcoholic fatty liver disease, Liver cirrhosis of various origins, such as alcoholic and non-alcoholic, autoimmune cirrhosis such as primary biliary cirrhosis and sclerosing cholangitis, virally induced cirrhosis, cirrhosis induced by genetic disease. Liver cancer, cholangiocarcinoma, biliary tract cancer; neurodegenerative disorders such as Parkinsons disease, Alzheimers disease, cognitive impairment, cerebrovascular diseases such as stroke, traumatic brain injury, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, peripheral nephropathy.