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(54) **Title**: SELECTIVE GLYCOSIDASE INHIBITORS AND USES THEREOF

(57) **Abstract**: The invention provides compounds with enhanced permeability for selectively inhibiting glycosidases, prodrugs of the compounds, and pharmaceutical compositions including the compounds or prodrugs of the compounds. The invention also provides methods of treating diseases and disorders related to deficiency or overexpression of O-GlcNAcase, accumulation or deficiency of O-GlcNAc.

SELECTIVE GLYCOSIDASE INHIBITORS AND USES THEREOF

FIELD OF THE INVENTION

[0001] This application relates to compounds which selectively inhibit glycosidases and uses thereof.

BACKGROUND OF THE INVENTION

[0002] A wide range of cellular proteins, both nuclear and cytoplasmic, are post-translationally modified by the addition of the monosaccharide 2-acetamido-2-deoxy-ß-D-glucopyranoside (β-N-acetylglucosamine) which is attached via an O-glycosidic linkage.[1] This modification is generally referred to as O-linked N-acetylglucosamine or O-GlcNAc. The enzyme responsible for post-translationally linking β-N-acetylglucosamine (GlcNAc) to specific serine and threonine residues of numerous nucleocytoplasmic proteins is O-GlcNAc transferase (OGT).[2-5] A second enzyme, known as glycoprotein 2-acetamido-2-deoxy-β-D-glucopyranosidase (O-GlcNAcase)[6,7] removes this post-translational modification to liberate proteins making the O-GlcNAc-modification a dynamic cycle occurring several times during the lifetime of a protein.[8]

[0003] O-GlcNAc-modified proteins regulate a wide range of vital cellular functions including, for example, transcription,[9-12] proteasomal degradation,[13] and cellular signaling.[14] O-GlcNAc is also found on many structural proteins.[15-17] For example, it has been found on a number of cytoskeletal proteins, including neurofilament proteins,[18,19] synapsins,[6,20] synapsin-specific clathrin assembly protein AP-3,[7] and ankyrinG.[14] O-GlcNAc modification has been found to be abundant in the brain.[21,22] It has also been found on proteins clearly implicated in the etiology of several diseases including Alzheimer's disease (AD) and cancer.

[0004] For example, it is well established that AD and a number of related tauopathies including Downs' syndrome, Pick's disease, Niemann-Pick Type C disease, and amyotrophic lateral sclerosis (ALS) are characterized, in part, by the development of neurofibrillary tangles (NFTs). These NFTs are aggregates of paired helical filaments (PHFs) and are composed of an abnormal form of the cytoskeletal protein "tau". Normally tau stabilizes a key cellular network of microtubules that is essential for distributing proteins and nutrients within neurons. In AD patients, however, tau becomes hyperphosphorylated, disrupting its

normal functions, forming PHFs and ultimately aggregating to form NFTs. Six isoforms of tau are found in the human brain. In AD patients, all six isoforms of tau are found in NFTs, and all are markedly hyperphosphorylated.[23,24] Tau in healthy brain tissue bears only 2 or 3 phosphate groups, whereas those found in the brains of AD patients bear, on average, 8 phosphate groups.[25,26] A clear parallel between NFT levels in the brains of AD patients and the severity of dementia strongly supports a key role for tau dysfunction in AD.[27,28] The precise causes of this hyperphosphorylation of tau remain elusive. Accordingly, considerable effort has been dedicated toward: a) elucidating the molecular physiological basis of tau hyperphosphorylation;[29] and b) identifying strategies that could limit tau hyperphosphorylation in the hope that these might halt, or even reverse, the progression of Alzheimer's disease[30-33] Thus far, several lines of evidence suggest that up-regulation of a number of kinases may be involved in hyperphosphorylation of tau,[21,34,35] although very recently, an alternative basis for this hyperphosphorylation has been advanced.[21]

[0005] In particular, it has emerged that phosphate levels of tau are regulated by the levels of O-GlcNAc on tau. The presence of O-GlcNAc on tau has stimulated studies that correlate O-GlcNAc levels with tau phosphorylation levels. The interest in this field stems from the observation that O-GlcNAc modification has been found to occur on many proteins at amino acid residues that are also known to be phosphorylated.[36-38] Consistent with this observation, it has been found that increases in phosphorylation levels result in decreased O-GlcNAc levels and conversely, increased O-GlcNAc levels correlate with decreased phosphorylation levels.[39] This reciprocal relationship between O-GlcNAc and phosphorylation has been termed the "Yin-Yang hypothesis"[40] and has gained strong biochemical support by the discovery that the enzyme OGT[4] forms a functional complex with phosphatases that act to remove phosphate groups from proteins.[41] Like phosphorylation, O-GlcNAc is a dynamic modification that can be removed and reinstalled several times during the lifespan of a protein. Suggestively, the gene encoding O-GlcNAcase has been mapped to a chromosomal locus that is linked to AD.[7,42] Hyperphosphorylated tau in human AD brains has markedly lower levels of O-GlcNAc than are found in healthy human brains.[21] It has been shown that O-GlcNAc levels of soluble tau protein from human brains affected with AD are markedly lower than those from healthy brain.[21] Furthermore, PHF from diseased brain was suggested to lack completely any O-GlcNAc modification whatsoever.[21] The molecular basis of this hypoglycosylation of tau is not known, although it may stem from increased activity of kinases and/or dysfunction of one of the enzymes involved in processing O-GlcNAc.

Supporting this latter view, in both PC-12 neuronal cells and in brain tissue sections from mice, a nonselective N-acetylglucosamindase inhibitor was used to increase tau O-GlcNAc levels, whereupon it was observed that phosphorylation levels decreased.[21] The implication of these collective results is that by maintaining healthy O-GlcNAc levels in AD patients, such as by inhibiting the action of O-GlcNAcase, one should be able to block hyperphosphorylation of tau and all of the associated effects of tau hyperphosphorylation, including the formation of NFTs and downstream effects. However, because the proper functioning of the β-hexosaminidases is critical, any potential therapeutic intervention for the treatment of AD that blocks the action of O-GlcNAcase would have to avoid the concomitant inhibition of both hexosaminidases A and B.

[0006] Neurons do not store glucose and therefore the brain relies on glucose supplied by blood to maintain its essential metabolic functions. Notably, it has been shown that within brain, glucose uptake and metabolism decreases with aging.[43] Within the brains of AD patients marked decreases in glucose utilization occur and are thought to be a potential cause of neurodegeneration.[44] The basis for this decreased glucose supply in AD brain[45-47] is thought to stem from any of decreased glucose transport,[48,49] impaired insulin signaling,[50,51] and decreased blood flow.[52]

[0007] In light of this impaired glucose metabolism, it is worth noting that of all glucose entering into cells, 2-5% is shunted into the hexosamine biosynthetic pathway, thereby regulating cellular concentrations of the end product of this pathway, uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc).[53] UDP-GlcNAc is a substrate of the nucleocytoplasmic enzyme O-GlcNAc transferase (OGT),[2-5] which acts to post-translationally add GlcNAc to specific serine and threonine residues of numerous nucleocytoplasmic proteins. OGT recognizes many of its substrates[54,55] and binding partners[41,56] through its tetratricopeptide repeat (TPR) domains.[57,58] As described above, O-GlcNAcase[6,7] removes this post-translational modification to liberate proteins making the O-GlcNAc-modification a dynamic cycle occurring several times during the lifetime of a protein.[8] O-GlcNAc has been found in several proteins on known phosphorylation sites,[10,37,38,59] including tau and neurofilaments.[60] Additionally, OGT shows unusual kinetic behaviour making it exquisitely sensitive to intracellular UDP-GlcNAc substrate concentrations and therefore glucose supply.[41]

[0008] Consistent with the known properties of the hexosamine biosynthetic pathway, the enzymatic properties of OGT, and the reciprocal relationship between O-GlcNAc and phosphorylation, it has been shown that decreased glucose availability in brain leads to tau

hyperphosphorylation.[44] Therefore the gradual impairment of glucose transport and metabolism, whatever its causes, leads to decreased O-GlcNAc and hyperphosphorylation of tau (and other proteins). Accordingly, the inhibition of O-GlcNAcase should compensate for the age related impairment of glucose metabolism within the brains of health individuals as well as patients suffering from AD or related neurodegenerative diseases.

[0009] These results suggest that a malfunction in the mechanisms regulating tau O-GlcNAc levels may be vitally important in the formation of NFTs and associated neurodegeneration. Good support for blocking tau hyperphosphorylation as a therapeutically useful intervention[61] comes from recent studies showing that when transgenic mice harbouring human tau are treated with kinase inhibitors, they do not develop typical motor defects[33] and, in another case,[32] show decreased levels of insoluble tau. These studies provide a clear link between lowering tau phosphorylation levels and alleviating AD-like behavioural symptoms in a murine model of this disease. Indeed, pharmacological modulation of tau hyperphosphorylation is widely recognized as a valid therapeutic strategy for treating AD and other neurodegenerative disorders.[62]

[0010] Small-molecule O-GlcNAcase inhibitors, to limit tau hyperphosphorylation, have been considered for treatment of AD and related tauopathies.[63] Specifically, the O-GlcNAcase inhibitor thiamet-G has been implicated in the reduction of tau phosphorylation in cultured PC-12 cells at pathologically relevant sites.[63] Moreover, oral administration of thiamet-G to healthy Sprague-Dawley rats has been implicated in reduced phosphorylation of tau at Thr231, Ser396 and Ser422 in both rat cortex and hippocampus.[63]

[0011] There is also a large body of evidence indicating that increased levels of O-GlcNAc protein modification provides protection against pathogenic effects of stress in cardiac tissue, including stress caused by ischemia, hemorrhage, hypervolemic shock, and calcium paradox. For example, activation of the hexosamine biosynthetic pathway (HBP) by administration of glucosamine has been demonstrated to exert a protective effect in animals models of ischemia/reperfusion,[64-70] trauma hemorrhage,[71-73] hypervolemic shock,[74] and calcium paradox.[64,75] Moreover, strong evidence indicates that these cardioprotective effects are mediated by elevated levels of protein O-GlcNAc modification.[64,65,67,70,72,75-78] There is also evidence that the O-GlcNAc modification plays a role in a variety of neurodegenerative diseases, including Parkinson's disease and Huntington's disease.[79]

[0012] Humans have three genes encoding enzymes that cleave terminal β-N-acetyl-glucosamine residues from glycoconjugates. The first of these encodes O-GlcNAcase. O-GlcNAcase is a member of family 84 of glycoside hydrolases that includes enzymes from organisms as diverse as prokaryotic pathogens to humans (for the family classification of glycoside hydrolases see Coutinho, P.M. & Henrissat, B. (1999) Carbohydrate-Active Enzymes server at URL: http://afmb.cnrs-mrs.fr/CAZY/.[27,28] O-GlcNAcase acts to hydrolyse O-GlcNAc off of serine and threonine residues of post-translationally modified proteins.[1,6,7,80,81] Consistent with the presence of O-GlcNAc on many intracellular proteins, the enzyme O-GlcNAcase appears to have a role in the etiology of several diseases including type II diabetes,[14,82] AD,[16,21,83] and cancer.[22,84] Although O-GlcNAcase was likely isolated earlier on,[18,19] about 20 years elapsed before its biochemical role in acting to cleave O-GlcNAc from serine and threonine residues of proteins was understood.[6] More recently O-GlcNAcase has been cloned,[7] partially characterized,[20] and suggested to have additional activity as a histone acetyltransferase.[20] However, little was known about the catalytic mechanism of this enzyme.

[0013] The other two genes, HEXA and HEXB, encode enzymes catalyzing the hydrolytic cleavage of terminal β-N-acetylglucosamine residues from glycoconjugates. The gene products of HEXA and HEXB predominantly yield two dimeric isozymes, hexosaminidase A and hexosaminidase B, respectively. Hexosaminidase A (αß), a heterodimeric isozyme, is composed of an α- and a ß-subunit. Hexosaminidase B (ßß), a homodimeric isozyme, is composed of two ß-subunits. The two subunits, α- and ß-, bear a high level of sequence identity. Both of these enzymes are classified as members of family 20 of glycoside hydrolases and are normally localized within lysosomes. The proper functioning of these lysosomal β-hexosaminidases is critical for human development, a fact that is underscored by the tragic genetic illnesses, Tay-Sach's and Sandhoff diseases which stem from a dysfunction in, respectively, hexosaminidase A and hexosaminidase B.[85] These enzymatic deficiencies cause an accumulation of glycolipids and glycoconjugates in the lysosomes resulting in neurological impairment and deformation. The deleterious effects of accumulation of gangliosides at the organismal level are still being uncovered.[86]

[0014] As a result of the biological importance of these β-*N*-acetyl-glucosaminidases, small molecule inhibitors of glycosidases[87-90] have received a great deal of attention,[91] both as tools for elucidating the role of these enzymes in biological processes and in developing potential therapeutic applications. The control of glycosidase function using small molecules

offers several advantages over genetic knockout studies including the ability to rapidly vary doses or to entirely withdraw treatment.

[0015] However, a major challenge in developing inhibitors for blocking the function of mammalian glycosidases, including O-GlcNAcase, is the large number of functionally related enzymes present in tissues of higher eukaryotes. Accordingly, the use of non-selective inhibitors in studying the cellular and organismal physiological role of one particular enzyme is complicated because complex phenotypes arise from the concomitant inhibition of such functionally related enzymes. In the case of ß-N-acetylglucosaminidases, many compounds that act to block O-GlcNAcase function are non-specific and act potently to inhibit the lysosomal β-hexosaminidases.

[0016] A few of the better characterized inhibitors of β-*N*-acetyl-glucosaminidases which have been used in studies of O-GlcNAc post-translational modification within both cells and tissues are streptozotocin (STZ), 2′-methyl-α-D-glucopyrano-[2,1-*d*]-Δ2′-thiazoline (NAG-thiazoline) and *O*-(2-acetamido-2-deoxy-D-glucopyranosylidene)amino *N*-phenylcarbamate (PUGNAc).[14,92-95]

[0017] STZ has long been used as a diabetogenic compound because it has a particularly detrimental effect on ß-islet cells.[96] STZ exerts its cytotoxic effects through both the alkylation of cellular DNA[96,97] as well as the generation of radical species including nitric oxide.[98] The resulting DNA strand breakage promotes the activation of poly(ADP-ribose) polymerase (PARP)[99] with the net effect of depleting cellular NAD+ levels and, ultimately, leading to cell death.[100,101] Other investigators have proposed instead that STZ toxicity is a consequence of the irreversible inhibition of O-GlcNAcase, which is highly expressed within ß-islet cells.[92,102] This hypothesis has, however, been brought into question by two independent research groups.[103,104] Because cellular O-GlcNAc levels on proteins increase in response to many forms of cellular stress[105] it seems possible that STZ results in increased O-GlcNAc-modification levels on proteins by inducing cellular stress rather than through any specific and direct action on O-GlcNAcase. Indeed, Hanover and coworkers have shown that STZ functions as a poor and somewhat selective inhibitor of O-GlcNAcase[106] and although it has been proposed by others that STZ acts to irreversibly inhibit O-GlcNAcase,[107] there has been no clear demonstration of this mode of action. More recently, it has been shown that STZ does not irreversibly inhibit O-GlcNAcase.[108]

[0018] NAG-thiazoline has been found to be a potent inhibitor of family 20 hexosaminidases,[90,109] and more recently, the family 84 O-GlcNAcases.[108] Despite its potency, a downside to using NAG-thiazoline in a complex biological context is that it lacks selectivity and therefore perturbs multiple cellular processes.

[0019] PUGNAc is another compound that suffers from the same problem of lack of selectivity, yet has enjoyed use as an inhibitor of both human O-GlcNAcase[6,110] and the family 20 human β-hexosaminidases.[111] This molecule, developed by Vasella and coworkers, was found to be a potent competitive inhibitor of the β-*N*-acetyl-glucosaminidases from *Canavalia ensiformis*, *Mucor rouxii*, and the β-hexosaminidase from bovine kidney.[88] It has been demonstrated that administration of PUGNAc in a rat model of trauma hemorrhage decreases circulating levels of the pro-inflammatory cytokines TNF-α and IL-6.[112] It has also been shown that administration of PUGNAc in a cell-based model of lymphocyte activation decreases production of the cytokine IL-2.[113] Subsequent studies have indicated that PUGNAc can be used in an animal model to reduce myocardial infarct size after left coronary artery occlusions.[114] Of particular significance is the fact that elevation of O-GlcNAc levels by administration of PUGNAc, an inhibitor of O-GlcNAcase, in a rat model of trauma hemorrhage improves cardiac function.[112,115] In addition, elevation of O-GlcNAc levels by treatment with PUGNAc in a cellular model of ischemia/reperfusion injury using neonatal rat ventricular myocytes improved cell viability and reduced necrosis and apoptosis compared to untreated cells.[116]

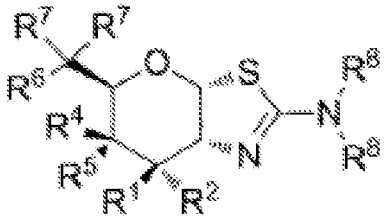
[0020] More recently, it has been suggested that the selective O-GlcNAcase inhibitor NButGT exhibits protective activity in cell-based models of ischemia/reperfusion and cellular stresses, including oxidative stress.[117] This study suggests the use of O-GlcNAcase inhibitors to elevate protein O-GlcNAc levels and thereby prevent the pathogenic effects of stress in cardiac tissue.

[0021] International patent applications PCT/CA2006/000300, filed 1 March 2006, published under No. W0 2006/092049 on 8 September 2006; PCT/CA2007/001554, filed 31 August 2007, published under No. WO 2008/025170 on 6 March 2008; PCT/CA2009/001087, filed 31 July 2009, published under No. WO 2010/012106 on 4 Februrary 2010; PCT/CA2009/001088, filed 31 July 2009, published under WO 2010/012107 on 4 Februrary 2010; and PCT/CA2009/001302, filed 16 September 2009, published under WO 2010/037207 on 8 April 2010, describe selective inhibitors of O-GlcNAcase.

SUMMARY OF THE INVENTION

[0022] The invention provides, in part, compounds for selectively inhibiting glycosidases, prodrugs of the compounds, uses of the compounds and the prodrugs, pharmaceutical compositions including the compounds or prodrugs of the compounds, and methods of treating diseases and disorders related to deficiency or overexpression of O-GlcNAcase, and/or accumulation or deficiency of O-GlcNAc.

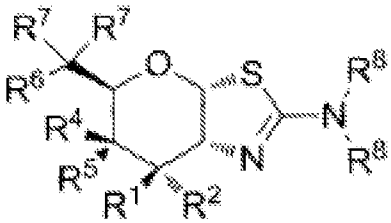
[0023] Thus, herein disclosed is a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

where R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 may be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3.

[0024] Also herein disclosed is a compound of Formula (I) or a pharmaceutically acceptable salt thereof:

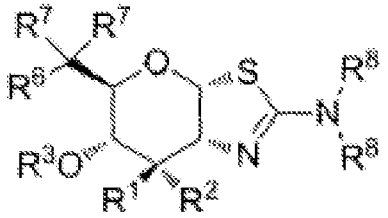


(I)

where R^1 and R^2 may be H and R^6 may be H, F or OR^3; or R^1 may be H and R^2 may be F and R^6 may be H, F or OR^3; or R^1 may be F and R^2 may be H and R^6 may be H, F or OR^3; or R^1 may be OR^3 and R^2 may be H and R^6 may be H or F; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3; or R^4 may be OR^3 and R^5 may be H; each R^7 may be independently H or F; each R^8 may be independently selected from

the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H.

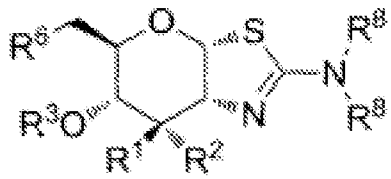
[0025] Also herein disclosed is a compound of Formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

where R^1 and R^2 may be H and R^6 may be F; or R^1 may be H and R^2 may be F and R^6 may be H, F or OR^3; or R^1 may be F and R^2 may be H and R^6 may be H, F or OR^3; or R^1 may be OR^3 and R^2 may be H and R^6 may be F; each R^3 may be independently H or C_{1-6} acyl; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H.

[0026] Also herein disclosed is a compound of Formula (Ib) or a pharmaceutically acceptable salt thereof:

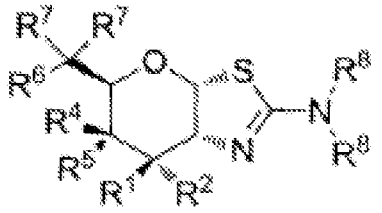


(Ib)

where R^1 and R^2 may be H and R^6 may be H or OR^3; or R^1 may be OR^3 and R^2 may be H and R^6 may be H; each R^3 may be independently H or C_{1-6} acyl; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen

atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl.

[0027] Also herein disclosed is a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

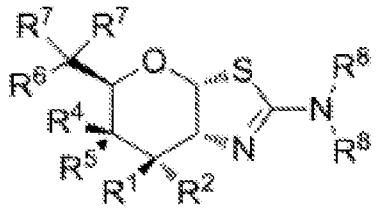
where R^1 may be H, F or OR^3; R^2 may be H or F; each R^3 may be independently H or C acyl; R^4 may be H; R^5 may be OR^3; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^1 is OR^3, R^2 is H; and with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3; and with the proviso that either R^1 or R^2 is other than F.

[0028] The compound may be a prodrug; the compound may selectively inhibit an O-glycoprotein 2-acetamido-2-deoxy-β-D-glucopyranosidase (O-GlcNAcase); the compound may selectively bind an O-GlcNAcase (e.g., a mammalian O- GlcNAcase); the compound may selectively inhibit the cleavage of a 2-acetamido-2-deoxy-β-D-glucopyranoside (O-GlcNAc); the compound may not substantially inhibit a mammalian β-hexosaminidase.

[0029] A compound according to Formula (Ia) or Formula (Ib) may have enhanced permeability.

[0030] Also herein disclosed is a pharmaceutical composition including a compound according to the invention, in combination with a pharmaceutically acceptable carrier.

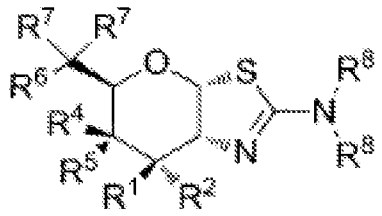
[0031] Also herein disclosed are methods of selectively inhibiting an O-GlcNAcase, or of inhibiting an O-GlcNAcase in a subject in need thereof, or of increasing the level of O-GlcNAc, or of treating a neurodegenerative disease, a tauopathy, cancer or stress, in a subject in need thereof, by administering to the subject an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

where R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3. The condition may be Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), Amyotrophic lateral sclerosis with cognitive impairment (ALSci), Argyrophilic grain dementia, Bluit disease, Corticobasal degeneration (CBD), Dementia pugilistica, Diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Gerstmann-Straussler-Scheinker disease, Guadeloupean parkinsonism, Hallevorden-Spatz disease (neurodegeneration with brain iron accumulation type 1), Multiple system atrophy, Myotonic dystrophy, Niemann-Pick disease (type C), Pallido-ponto-nigral degeneration, Parkinsonism-dementia complex of Guam, Pick's disease (PiD), Post-encephalitic parkinsonism (PEP), Prion diseases (including Creutzfeldt-Jakob Disease (CJD), Variant Creutzfeldt-Jakob Disease (vCJD), Fatal Familial Insomnia, and Kuru), Progressive supercortical gliosis, Progressive supranuclear palsy (PSP), Richardson's syndrome, Subacute sclerosing panencephalitis, Tangle-only dementia, Huntington's disease, Parkinson's disease, Schizophrenia, Mild Cognitive Impairment (MCI), Neuropathy (including peripheral neuropathy, autonomic neuropathy, neuritis, and diabetic neuropathy), or Glaucoma. The stress may be a cardiac disorder, e.g., ischemia; hemorrhage; hypovolemic shock; myocardial infarction; an interventional cardiology procedure; cardiac bypass surgery; fibrinolytic therapy; angioplasty; or stent placement.

[0032] Also herein disclosed is a method of treating an O-GlcNAcase-mediated condition that excludes a neurodegenerative disease, a tauopathy, cancer or stress, in a subject in need thereof, by administering to the subject an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



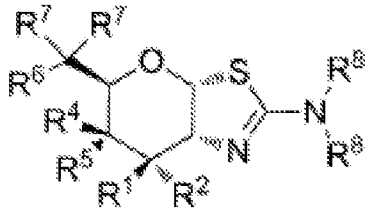
(I)

where R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 may be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3. In some embodiments, the condition may be inflammatory or allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, atherosclerosis, interstitial lung disease (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Guillain-Barré syndrome, systemic lupus erythematosus, myastenia gravis, glomerulonephritis, autoimmune thyroiditis, graft rejection, including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myotis, and eosiniphilic fasciitis; graft rejection, in particular but not limited to solid organ transplants, such as heart, lung, liver, kidney, and pancreas transplants (e.g. kidney and lung allografts); epilepsy; pain; fibromyalgia; stroke, e.g., neuroprotection following a stroke.

[0033] In alternative embodiments, R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 may be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl,

and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3. The administering may increase the level of O-GlcNAc in the subject. The subject may be a human.

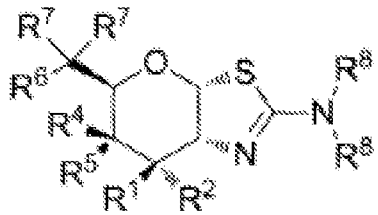
[0034] Also herein disclosed is the use of a compound of an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

where R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 may be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3, in the preparation of a medicament. The medicament may be for selectively inhibiting an O-GlcNAcase, for increasing the level of O-GlcNAc, for treating a condition modulated by an O-GlcNAcase, for treating a neurodegenerative disease, a tauopathy, a cancer, or stress.

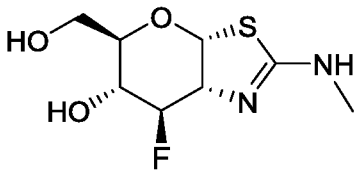
[0035] Also herein disclosed is a method for screening for a selective inhibitor of an O-GlcNAcase, by a) contacting a first sample with a test compound; b) contacting a second sample with a compound of Formula (I)



(I)

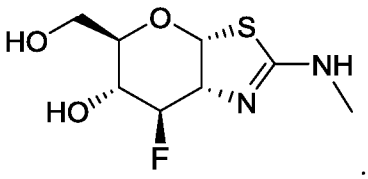
where R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 may be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3; c) determining the level of inhibition of the O-GIcNAcase in the first and second samples, where the test compound is a selective inhibitor of a O-GlcNAcase if the test compound exhibits the same or greater inhibition of the O-GlcNAcase when compared to the compound of Formula (I).

[0035a] According to a first embodiment of the present invention there is provided a compound which is



or a pharmaceutically acceptable salt thereof.

[0035b] According to a second embodiment of the present invention there is provided a compound which is



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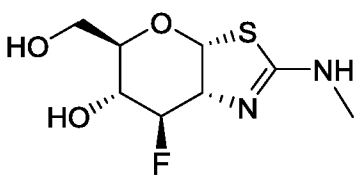
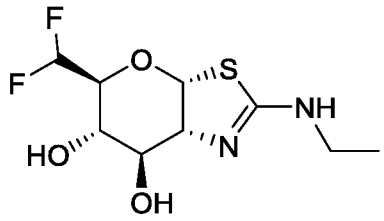
[0035c] According to a third embodiment of the present invention there is provided a compound which is



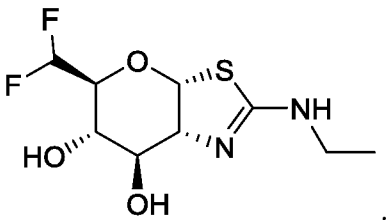
in the form of a pharmaceutically acceptable salt thereof.

[0035d] According to a fourth embodiment of the present invention there is provided a compound which is

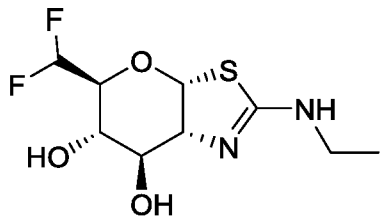


or a pharmaceutically acceptable salt thereof.

[0035e] According to a fifth embodiment of the present invention there is provided a compound which is

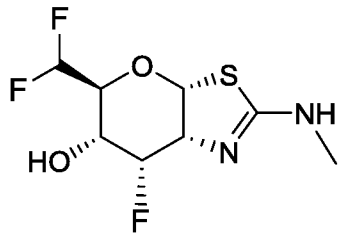


[0035f] According to a sixth embodiment of the present invention there is provided a compound which is



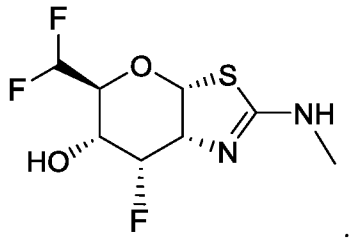
in the form of a pharmaceutically acceptable salt thereof.

[0035g] According to a seventh embodiment of the present invention there is provided a compound which is

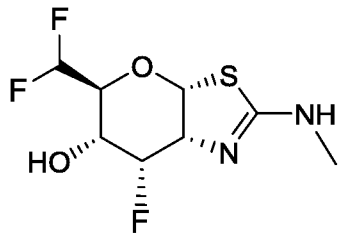


or a pharmaceutically acceptable salt thereof.

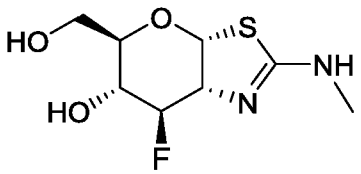
[0035h] According to an eighth embodiment of the present invention there is provided a compound which is



[0035i] According to a ninth embodiment of the present invention there is provided a compound which is

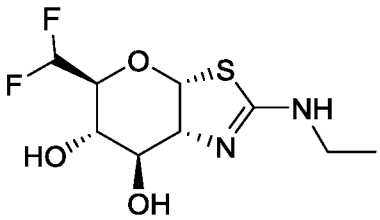


in the form of a pharmaceutically acceptable salt thereof.[0035j] According to a tenth embodiment of the present invention there is provided a pharmaceutical composition comprising a compound which is



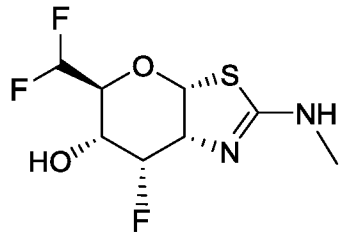
or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0035k] According to an eleventh embodiment of the present invention there is provided a pharmaceutical composition comprising a compound which is



or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0035l] According to a twelfth embodiment of the present invention there is provided a pharmaceutical composition comprising a compound which is



or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

[0035m] According to a thirteenth embodiment of the present invention there is provided a method of treating Alzheimer's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the first to third embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the first to third embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Alzheimer's disease in a human patient in need thereof.

[0035n] According to a fourteenth embodiment of the present invention there is provided a method of treating Alzheimer's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the fourth to sixth embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the fourth to sixth embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Alzheimer's disease in a human patient in need thereof.

[0035o] According to a fifteenth embodiment of the present invention there is provided a method of treating Alzheimer's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the seventh to ninth embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the seventh to ninth embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Alzheimer's disease in a human patient in need thereof.

[0035p] According to a sixteenth embodiment of the present invention there is provided a method of treating Parkinson's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the first to third embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the first to third embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Parkinson's disease in a human patient in need thereof.

[0035q] According to a seventeenth embodiment of the present invention there is provided a method of treating Parkinson's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of

the fourth to sixth embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the fourth to sixth embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Parkinson's disease in a human patient in need thereof.

[0035r] According to an eighteenth embodiment of the present invention there is provided a method of treating Parkinson's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the seventh to ninth embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the seventh to ninth embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Parkinson's disease in a human patient in need thereof.

[0035s] According to a nineteenth embodiment of the present invention there is provided a method of treating Progressive supranuclear palsy in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the first to third embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the first to third embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Progressive supranuclear palsy in a human patient in need thereof.

[0035t] According to a twentieth embodiment of the present invention there is provided a method of treating Progressive supranuclear palsy in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the fourth to sixth embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the fourth to sixth embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Progressive supranuclear palsy in a human patient in need thereof.

[0035u] According to a twenty-first embodiment of the present invention there is provided a method of treating Progressive supranuclear palsy in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of the seventh to ninth embodiments. According to a related embodiment, there is provided the use of a therapeutically effective amount of the compound of any one of the seventh to ninth embodiments or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Progressive supranuclear palsy in a human patient in need thereof.

[0036] This summary of the invention does not necessarily describe all features of the invention.

DETAILED DESCRIPTION

[0037] The invention provides, in part, novel compounds that are capable of inhibiting an O-glycoprotein 2-acetamido-2-deoxy-β-D-glucopyranosidase (O-GlcNAcase). In some embodiments, the O-GlcNAcase is a mammalian O-GlcNAcase, such as a rat, mouse or human O-GlcNAcase.

[0038] In some embodiments, one or more of the compounds according to the invention exhibit enhanced permeability. Permeability can be assessed using a variety of standard experimental techniques, including without limitation in situ perfusion, ex vivo tissue diffusion, in vitro cell monolayers (e.g. Caco-2 cells, MDCK cells, LLC-PK1 cells), and artificial cell membranes (e.g. PAMPA assay); suitable techniques for measuring effective permeability (P_{eff}) or apparent peameability (P_{app}) are reviewed for example by Volpe in *The AAPS Journal*, **2010**, *12(4)*, 670-678. In some embodiments, one or more of the compounds according to the invention show enhanced permeability when tested in one or more of these assays for determining P_{eff} or P_{app}. In some embodiments, a compound that exhibits enhanced permeability exhibits greater oral absorption. In some embodiments, a compound that exhibits enhanced permeability exhibits greater brain penetrance when administered in vivo. In some embodiments, a compound that exhibits enhanced permeability achieves higher brain concentrations when administered in vivo. In some embodiments, a compound that exhibits enhanced permeability exhibits a higher brain/plasma concentration ratio when administered in vivo. In some embodiments, "enhanced permeability" means an increase in measured P_{eff} or P_{app} by any value between 10% and 100%, or of any integer value between 10% and 100%, for example, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or over 100%, or an increase by 1-fold, 2-fold, or 3-fold, or more, as compared to a suitable reference compound disclosed in for example WO 2006/092049 or WO 2008/025170. A suitable reference compound may be, for example, (3aR,5R,6S,7R,7aR)-5-(hydroxymethyl)-2-propyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol, or (3aR,5R,6S,7R,7aR)-2-(ethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol, or (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol. In some embodiments, "enhanced permeability" means a measurable P_{app} value (i.e. a value greater than zero) in the assay described below for determination of P_{app} in LLC-PK1 cells. In some embodiments, "enhanced permeability" means a P_{app} value greater than 2×10^{-6} cm/s in the assay described below for determination of P_{app} in LLC-PK1 cells. In some embodiments, "enhanced permeability" means a P_{app}

value greater than 1 x 10^{-6} cm/s in the assay described below for determination of P_{app} in LLC-PK1 cells. In alternative embodiments, "enhanced permeability" means a P_{app} value in the range 2 x 10^{-6} cm/s to 30 x 10^{-6} cm/s in the assay described below for determination of P_{app} in LLC-PK1 cells.

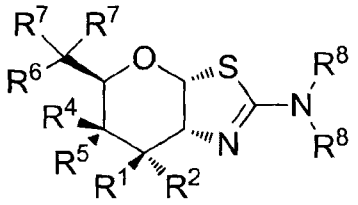
[0039] In some embodiments, a compound according to the invention exhibits superior selectivity in inhibiting an O-GlcNAcase. In some embodiments, one or more of the compounds according to the invention are more selective for an O-GlcNAcase over a β-hexosaminidase. In some embodiments, one or more of the compounds selectively inhibit the activity of a mammalian O-GlcNAcase over a mammalian β-hexosaminidase. In some embodiments, a selective inhibitor of an O-GlcNAcase does not substantially inhibit a β-hexosaminidase. In some embodiments, the β-hexosaminidase is a mammalian β-hexosaminidase, such as a rat, mouse or human β-hexosaminidase. A compound that "selectively" inhibits an O-GlcNAcase is a compound that inhibits the activity or biological function of an O-GlcNAcase, but does not substantially inhibit the activity or biological function of a β-hexosaminidase. For example, in some embodiments, a selective inhibitor of an O-GlcNAcase selectively inhibits the cleavage of 2-acetamido-2-deoxy-β-D-glucopyranoside (O-GlcNAc) from polypeptides. In some embodiments, a selective inhibitor of an O-GlcNAcase selectively binds to an O-GlcNAcase. In some embodiments, a selective inhibitor of an O-GlcNAcase inhibits hyperphosphorylation of a tau protein and/or inhibits formations of NFTs. By "inhibits," "inhibition" or "inhibiting" means a decrease by any value between 10% and 90%, or of any integer value between 30% and 60%, or over 100%, or a decrease by 1-fold, 2-fold, 5-fold, 10-fold or more. It is to be understood that the inhibiting does not require full inhibition. In some embodiments, a selective inhibitor of an O-GlcNAcase elevates or enhances O-GlcNAc levels e.g., O-GlcNAc-modified polypeptide or protein levels, in cells, tissues, or organs (e.g., in brain, muscle, or heart (cardiac) tissue) and in animals. By "elevating" or "enhancing" is meant an increase by any value between 10% and 90%, or of any integer value between 30% and 60%, or over 100%, or an increase by 1-fold, 2-fold, 5-fold, 10-fold, 15-fold, 25-fold, 50-fold, 100-fold or more. In some embodiments, a selective inhibitor of an O-GlcNAcase exhibits a selectivity ratio, as described herein, in the range 10 to 100000, or in the range 100 to 100000, or in the range 1000 to 100000, or at least 10, 20, 50, 100, 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 6000, 7000, 10,000, 25,000, 50,000, 75,000, or any value within or about the described range.

[0040] One or more of the compounds of the present invention elevate O-GlcNAc levels on O-GlcNAc-modified polypeptides or proteins *in vivo* specifically via interaction with an O-GlcNAcase enzyme, and are effective in treating conditions which require or respond to inhibition of O-GlcNAcase activity.

[0041] In some embodiments, one or more of the compounds of the present invention are useful as agents that produce a decrease in tau phosphorylation and NFT formation. In some embodiments, one or more of the compounds are therefore useful to treat Alzheimer's disease and related tauopathies. In some embodiments, one or more of the compounds are thus capable of treating Alzheimer's disease and related tauopathies by lowering tau phosphorylation and reducing NFT formation as a result of increasing tau O-GlcNAc levels. In some embodiments, one or more of the compounds produce an increase in levels of O-GlcNAc modification on O-GlcNAc-modified polypeptides or proteins, and are therefore useful for treatment of disorders responsive to such increases in O-GlcNAc modification; these disorders include without limitation neurodegenerative, inflammatory, cardiovascular, and immunoregulatory diseases. In some embodiments, a compound is also useful as a result of other biological activites related to their ability to inhibit the activity of glycosidase enzymes. In alternative embodiments, one or more of the compounds of the invention are valuable tools in studying the physiological role of O-GlcNAc at the cellular and organismal level.

[0042] In alternative embodiments, the invention provides methods of enhancing or elevating levels of protein O-GlcNAc modification in animal subjects, such as, veterinary and human subjects. In alternative embodiments, the invention provides methods of selectively inhibiting an O-GlcNAcase enzyme in animal subjects, such as, veterinary and human subjects. In alternative embodiments, the invention provides methods of inhibiting phosphorylation of tau polypeptides, or inhibiting formation of NFTs, in animal subjects, such as, veterinary and human subjects.

[0043] In specific embodiments, the invention provides compounds described generally by Formula (I) and the salts, prodrugs, and enantiomeric forms thereof:



(I)

[0044] As set forth in Formula (I): R^1 and R^2 may be H, or R^1 may be H and R^2 may be F, or R^1 may be F and R^2 may be H, or R^1 may be OR^3 and R^2 may be H; each R^3 may be independently H or C_{1-6} acyl; R^4 may be H and R^5 may be OR^3, or R^4 may be OR^3 and R^5 may be H; R^6 may be H, F, or OR^3; each R^7 may be independently H or F; each R^8 may be independently selected from the group consisting of: H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl, or the two R^8 groups may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl; with the proviso that when R^6 is OR^3, each R^7 is H; and with the proviso that either R^1 or R^6 is other than OR^3.

[0045] In some embodiments, R^1 as set forth in Formula (I) may be H, F, OH, or $OC(O)R^9$, where R^9 may be H, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, R^1 may be H, F or OH.

[0046] In some embodiments, R^2 as set forth in Formula (I) may be H or F.

[0047] In some embodiments, R^3 as set forth in Formula (I) may be H or $C(O)R^9$, where R^9 may be H, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, R^3 may be H.

[0048] In some embodiments, R^4 as set forth in Formula (I) may be H, OH, or $OC(O)R^9$, where R^9 may be H, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, R^4 may be H or OH.

[0049] In some embodiments, R^5 as set forth in Formula (I) may be H, OH, or $OC(O)R^9$, where R^9 may be H, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, R^5 may be H or OH.

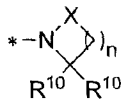
[0050] In some embodiments, R^6 as set forth in Formula (I) may be H, F, OH, or $OC(O)R^9$, where R^9 may be H, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In some embodiments, R^6 may be H, F, or OH.

[0051] In some embodiments, each R^7 as set forth in Formula (I) may be independently H or F.

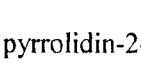
[0052] In some embodiments, each R^8 as set forth in Formula (I) may be independently H, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy, where the C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl. In some embodiments, each R^8 may be independently H, CH_3, CH_2CH_3, $(CH_2)_2CH_3$, $CH_2CH{=}CH_2$, or $CH_2C{\equiv}CH$.

[0053] In some embodiments, the two R^8 groups as set forth in Formula (I) may be connected together with the nitrogen atom to which they are attached to form a ring, said ring optionally independently substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl.

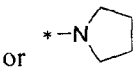
[0054] In some embodiments, NR^8_2 as set forth in Formula (I), may be optionally substituted



, where X may be CR^{10}_2, NR^{10}, O, C=O, O(C=O), (C=O)O, NR^{10}(C=O), or $(C{=}O)NR^{10}$; where each R^{10} may be independently H or C_{1-4} alkyl; and n may be an integer between 0 and 3. In some embodiments, NR^8_2 may be optionally substituted 1-aziridinyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidinyl, morpholin-4-yl, 1-piperizinyl, azetidin-2-one-1-yl, pyrrolidin-2-one-1-yl, or piperid-2-one-1-yl. In some embodiments, NR^8_2 may be



or



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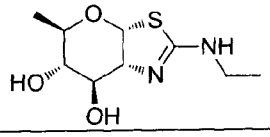
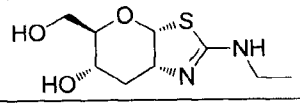
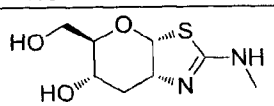
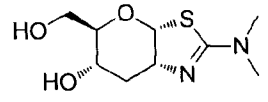
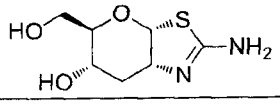
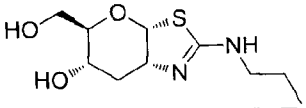
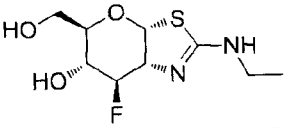
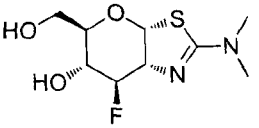
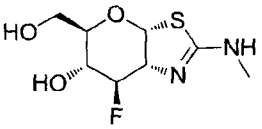
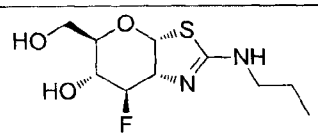
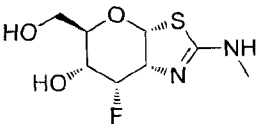
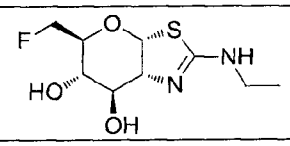
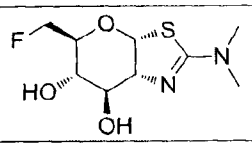
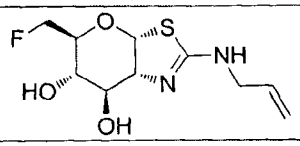
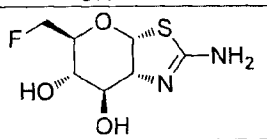
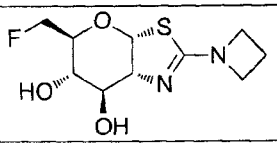
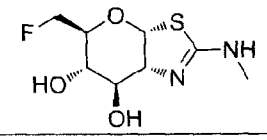
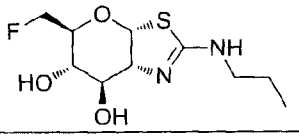
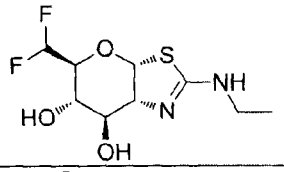
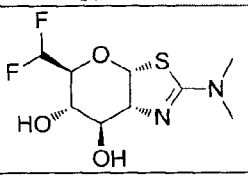
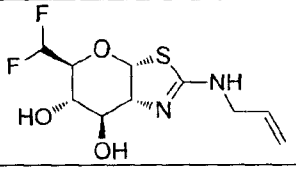
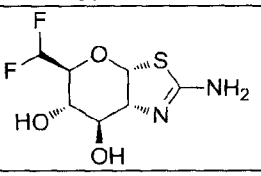
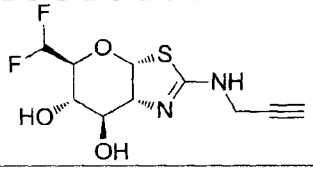
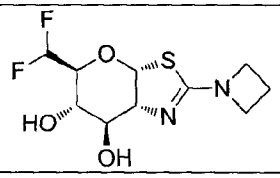
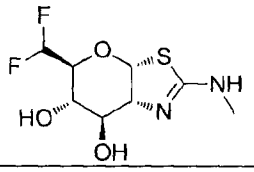
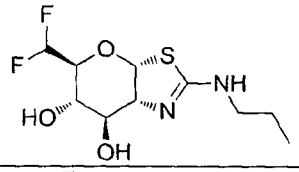
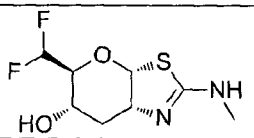
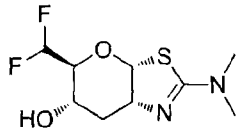
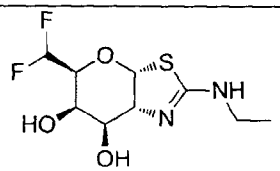
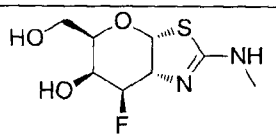
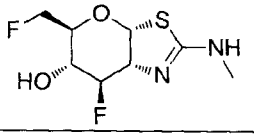
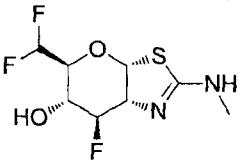
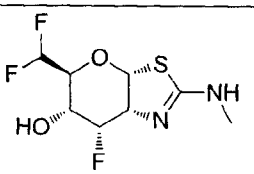
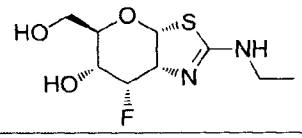
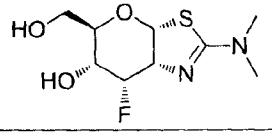
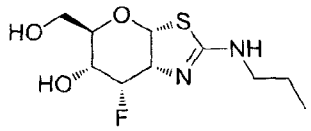
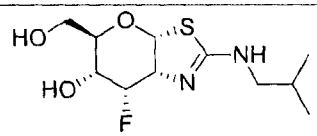
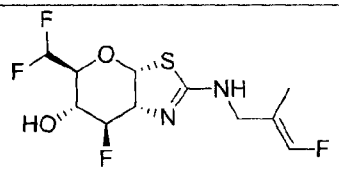
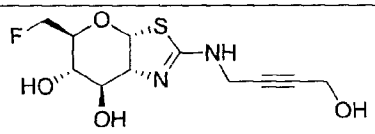
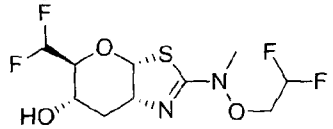
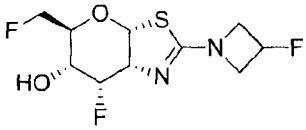
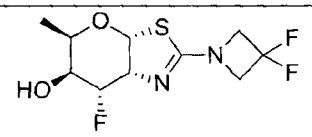
[0055] In specific embodiments of the invention, compounds according to Formula (I) include the compounds described in Table 1.

Table 1

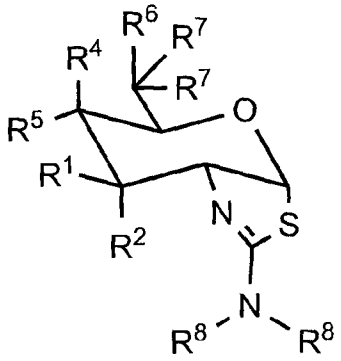
Example	Name	Structure
1	(3aR,5R,6S,7R,7aR)-2-(ethylamino)-5-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
2	(3aR,5R,6S,7aR)-2-(ethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
3	(3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
4	(3aR,5R,6S,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
5	(3aR,5R,6S,7aR)-2-amino-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
6	(3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
7	(3aR,5R,6R,7R,7aR)-2-(ethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
8	(3aR,5R,6R,7R,7aR)-2-(dimethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
9	(3aR,5R,6R,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
10	(3aR,5R,6R,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
11	(3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
12	(3aR,5S,6S,7R,7aR)-2-(ethylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	

Example	Name	Structure
13	(3aR,5S,6S,7R,7aR)-2-(dimethylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
14	(3aR,5S,6S,7R,7aR)-2-(allylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
15	(3aR,5S,6S,7R,7aR)-2-amino-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
16	(3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
17	(3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
18	(3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
19	(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
20	(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
21	(3aR,5S,6S,7R,7aR)-2-(allylamino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
22	(3aR,5S,6S,7R,7aR)-2-amino-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
23	(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(prop-2-yn-1-ylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	

Example	Name	Structure
24	(3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
25	(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
26	(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
27	(3aR,5S,6S,7aR)-5-(difluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
28	(3aR,5S,6S,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
29	(3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
30	(3aR,5R,6S,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
31	(3aR,5S,6R,7R,7aR)-7-fluoro-5-(fluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
32	(3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-7-fluoro-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
33	(3aR,5S,6R,7S,7aR)-5-(difluoromethyl)-7-fluoro-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	

Example	Name	Structure
34	(3aR,5R,6R,7S,7aR)-2-(ethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
35	(3aR,5R,6R,7S,7aR)-2-(dimethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
36	(3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
37	(3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(isobutylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
38	(3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-7-fluoro-2-(((E)-3-fluoro-2-methylallyl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
39	(3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-2-((4-hydroxybut-2-yn-1-yl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol	
40	(3aR,5S,6S,7aR)-2-((2,2-difluoroethoxy)(methyl)amino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
41	(3aR,5S,6R,7S,7aR)-7-fluoro-2-(3-fluoroazetidin-1-yl)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	
42	(3aR,5R,6S,7S,7aR)-2-(3,3-difluoroazetidin-1-yl)-7-fluoro-5-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol	

[0056] As will be appreciated by a person skilled in the art, Formula (I) above may also be represented alternatively as follows:



[0057] As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. For example, "a compound" refers to one or more of such compounds, while "the enzyme" includes a particular enzyme as well as other family members and equivalents thereof as known to those skilled in the art.

[0058] Throughout this application, it is contemplated that the term "compound" or "compounds" refers to the compounds discussed herein and includes precursors and derivatives of the compounds, including acyl-protected derivatives, and pharmaceutically acceptable salts of the compounds, precursors, and derivatives. The invention also includes prodrugs of the compounds, pharmaceutical compositions including the compounds and a pharmaceutically acceptable carrier, and pharmaceutical compositions including prodrugs of the compounds and a pharmaceutically acceptable carrier.

[0059] The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. Any formulas, structures or names of compounds described in this specification that do not specify a particular stereochemistry are meant to encompass any and all existing isomers as described above and mixtures thereof in any proportion. When stereochemistry is specified, the invention is meant to encompass that particular isomer in pure form or as part of a mixture with other isomers in any proportion.

[0060] Certain groups may be optionally substituted as described herein. Suitable substituents include: H, alkyl (C_{1-6}), alkenyl (C_{2-6}), or alkynyl (C_{2-6}) each of which may

optionally contain one or more heteroatoms selected from O, S, P, N, F, Cl, Br, I, or B, and each of which may be further substituted, for example, by =O; or optionally substituted forms of acyl, alkyl- alkenyl-, or alkynyl- and forms thereof which contain heteroatoms in the alkyl, alkenyl, or alkynyl moieties. Other suitable substituents include =O, =NR, halo, CN, CF_3, CHF_2, NO_2, OR, SR, NR_2, N_3, COOR, and $CONR_2$, where R is H or alkyl, cycloalkyl, alkenyl, or alkynyl. Where the substituted atom is C, the substituents may include, in addition to the substituents listed above, halo, OOCR, NROCR, where R is H or a substituent set forth above.

[0061] For example, in the above Formula (I), each C_{1-6} acyl, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy group may be independently optionally substituted with one or more substituents. In some embodiments, each C_{1-6} acyl, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy group in Formula (I) may be substituted with one or more inorganic substituents; phosphoryl; halo; =O; $=NR^9$; OR; C_{1-6} alkyl or C_{2-6} alkenyl optionally containing one or more P, N, O, S, N, F, Cl, Br, I, or B, and optionally substituted with halo; CN; optionally substituted carbonyl; $NR^9{}_2$; $C=NR^9$; an optionally substituted carbocyclic or heterocyclic ring, where R^9 may be H, C_{1-6} alkyl, or C_{3-6} cycloalkyl. In alternative embodiments, each C_{1-6} acyl, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, or C_{1-6} alkoxy group may be optionally substituted from one up to the maximum number of substituents with one or more of fluoro, OH, or methyl. In alternative embodiments, each optionally substituted C_{1-6} acyl, C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-6} alkynyl, and C_{1-6} alkoxy group in Formula (I) may independently include one or more heteroatoms selected from P, O, S, N, F, Cl, Br, I, or B.

[0062] "Alkyl" refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing no unsaturation and including, for example, from one to ten carbon atoms, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, and which is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, the alkyl group may be optionally substituted by one or more substituents as described herein. Unless stated otherwise specifically herein, it is understood that the substitution can occur on any carbon of the alkyl group.

[0063] "Alkenyl" refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one double bond and including, for example, from two to ten carbon atoms, such as 2, 3, 4, 5, 6, 7, 8, 9, or 10 carbon atoms, and which is attached to the rest of the molecule by a single bond or a double bond. Unless stated otherwise specifically in the specification, the alkenyl group may be optionally substituted by

one or more substituents as described herein. Unless stated otherwise specifically herein, it is understood that the substitution can occur on any carbon of the alkenyl group.

[0064] "Alkynyl" refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one triple bond and including, for example, from two to ten carbon atoms. Unless stated otherwise specifically in the specification, the alkenyl group may be optionally substituted by one or more substituents as described herein.

[0065] "Aryl" refers to a phenyl group, an aromatic ring including 6 carbon atoms. Unless stated otherwise specifically herein, the term "aryl" is meant to include aryl groups optionally substituted by one or more substituents as described herein.

[0066] "Heteroaryl" refers to a single aromatic ring group containing one or more heteroatoms in the ring, for example N, O, S, including for example, 5-6 members, such as 5 or 6 members. Examples of heteroaryl groups include furan, thiophene, pyrrole, oxazole, thiazole, imidazole, pyrazole, isoxazole, isothiazole, 1,2,3-oxadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-triazine, imidazole. Unless stated otherwise specifically herein, the term "heteroaryl" is meant to include heteroaryl groups optionally substituted by one or more substituents as described herein.

[0067] "Acyl" refers to a group of the formula $-C(O)R_a$, where R_a is a C_{1-10} alkyl or C_{3-15} cycloalkyl group as described herein. The alkyl or cycloalkyl group(s) may be optionally substituted as described herein.

[0068] "Alkoxy" refers to a group of the formula $-OR_b$, where R_b is a C_{1-10} alkyl group as described herein. The alkyl group(s) may be optionally substituted as described herein.

[0069] "Cycloalkyl" refers to a stable monovalent monocyclic, bicyclic or tricyclic hydrocarbon group consisting solely of carbon and hydrogen atoms, having for example from 3 to 15 carbon atoms, and which is saturated and attached to the rest of the molecule by a single bond. Unless otherwise stated specifically herein, the term "cycloalkyl" is meant to include cycloalkyl groups which are optionally substituted as described herein.

[0070] "Halo" refers to bromo, chloro, fluoro, iodo, etc. In some embodiments, suitable halogens include fluorine or chlorine.

[0071] In some embodiments, two R^8 groups as set forth in Formula (I) may be connected together with the nitrogen atom to which they are attached to form a ring. In these

embodiments, "ring" refers to a stable nitrogen-containing monocyclic group having 3 to 6 members that may be saturated or monounsaturated. In alternative embodiments, the ring may include C, H and N atoms. In other embodiments, the ring may include heteroatoms, for example O and S. Examples of a ring in these embodiments include 1-aziridinyl, 1-azetidinyl, 1-pyrrolidinyl, 2,5-dihydro-1H-pyrrol-1-yl, 1-piperidinyl, 1,2,3,6-tetrahydropyridin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 1-piperizinyl, azetidin-2-one-1-yl, pyrrolidin-2-one-1-yl, piperid-2-one-1-yl, 1,2-oxazetidin-2-yl , isoxazolidin-2-yl, and 1,2-oxazinan-2-yl. The ring in these embodiments may be optionally substituted as described herein.

[0072] "Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs one or more times and instances in which it does not. For example, "optionally substituted alkyl" means that the alkyl group may or may not be substituted and that the description includes both substituted alkyl groups and alkyl groups having no substitution, and that said alkyl groups may be substituted one or more times. Examples of optionally substituted alkyl groups include, without limitation, methyl, ethyl, propyl, etc. and including cycloalkyls such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.; examples of optionally substituted alkenyl groups include allyl, crotyl, 2-pentenyl, 3-hexenyl, 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc. In some embodiments, optionally substituted alkyl and alkenyl groups include C_{1-6} alkyls or alkenyls.

Therapeutic Indications

[0073] The invention provides methods of treating conditions that are modulated, directly or indirectly, by an O-GlcNAcase enzyme or by O-GlcNAc-modified protein levels, for example, a condition that is benefited by inhibition of an O-GlcNAcase enzyme or by an elevation of O-GlcNAc-modified protein levels. Such conditions include, without limitation, Glaucoma, Schizophrenia, tauopathies, such as Alzheimer's disease, neurodegenerative diseases, cardiovascular diseases, diseases associated with inflammation, diseases associated with immunosuppression and cancers. One or more of the compounds of the invention are also useful in the treatment of diseases or disorders related to deficiency or over-expression of O-GlcNAcase or accumulation or depletion of O-GlcNAc, or any disease or disorder

responsive to glycosidase inhibition therapy. Such diseases and disorders include, but are not limited to, Glaucoma, Schizophrenia, neurodegenerative disorders, such as Alzheimer's disease (AD), or cancer. Such diseases and disorders may also include diseases or disorders related to the accumulation or deficiency in the enzyme OGT. Also included is a method of protecting or treating target cells expressing proteins that are modified by O-GlcNAc residues, the dysregulation of which modification results in disease or pathology. The term "treating" as used herein includes treatment, prevention, and amelioration.

[0074] In alternative embodiments, the invention provides methods of enhancing or elevating levels of protein O-GlcNAc modification in animal subjects, such as, veterinary and human subjects. This elevation of O-GlcNAc levels can be useful for the prevention or treatment of Alzheimer's disease; prevention or treatment of other neurodegenerative diseases (e.g. Parkinson's disease, Huntington's disease); providing neuroprotective effects; preventing damage to cardiac tissue; and treating diseases associated with inflammation or immunosuppression.

[0075] In alternative embodiments, the invention provides methods of selectively inhibiting an O-GlcNAcase enzyme in animal subjects, such as veterinary and human subjects.

[0076] In alternative embodiments, the invention provides methods of inhibiting phosphorylation of tau polypeptides, or inhibiting formation of NFTs, in animal subjects, such as, veterinary and human subjects. Accordingly, a compound of the invention may be used to study and treat AD and other tauopathies.

[0077] In general, the methods of the invention are effected by administering a compound according to the invention to a subject in need thereof, or by contacting a cell or a sample with a compound according to the invention, for example, a pharmaceutical composition comprising a therapeutically effective amount of the compound according to Formula (I). More particularly, they are useful in the treatment of a disorder in which the regulation of O-GlcNAc protein modification is implicated, or any condition as described herein. Disease states of interest include Alzheimer's disease (AD) and related neurodegenerative tauopathies, in which abnormal hyperphosphorylation of the microtubule-associated protein tau is involved in disease pathogenesis. In some embodiments, a compound may be used to block hyperphosphorylation of tau by maintaining elevated levels of O-GlcNAc on tau, thereby providing therapeutic benefit.

[0078] The effectiveness of a compound in treating pathology associated with the accumulation of toxic tau species (for example, Alzheimer's disease and other tauopathies) may be confirmed by testing the ability of a compound to block the formation of toxic tau species in established cellular[118-120] and/or transgenic animal models of disease.[32,33]

[0079] Tauopathies that may be treated with a compound of the invention include: Alzheimer's disease, Amyotrophic lateral sclerosis (ALS), Amyotrophic lateral sclerosis with cognitive impairment (ALSci), Argyrophilic grain dementia, Bluit disease, Corticobasal degeneration (CBD), Dementia pugilistica, Diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, Frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), Gerstmann-Straussler-Scheinker disease, Guadeloupean parkinsonism, Hallevorden-Spatz disease (neurodegeneration with brain iron accumulation type 1), Multiple system atrophy, Myotonic dystrophy, Niemann-Pick disease (type C), Pallido-ponto-nigral degeneration, Parkinsonism-dementia complex of Guam, Pick's disease (PiD), Post-encephalitic parkinsonism (PEP), Prion diseases (including Creutzfeldt-Jakob Disease (CJD), Variant Creutzfeldt-Jakob Disease (vCJD), Fatal Familial Insomnia, and Kuru), Progressive supercortical gliosis, Progressive supranuclear palsy (PSP), Richardson's syndrome, Subacute sclerosing panencephalitis, Tangle-only dementia, and Glaucoma.

[0080] One or more of the compounds of this invention are also useful in the treatment of conditions associate with tissue damage or stress, stimulating cells, or promoting differentiation of cells. Accordingly, in some embodiments, a compound of this invention may be used to provide therapeutic benefit in a variety of conditions or medical procedures involving stress in cardiac tissue, including but not limited to: ischemia; hemorrhage; hypovolemic shock; myocardial infarction; an interventional cardiology procedure; cardiac bypass surgery; fibrinolytic therapy; angioplasty; and stent placement.

[0081] The effectiveness of a compound in treating pathology associated with cellular stress (including ischemia, hemorrhage, hypovolemic shock, myocardial infarction, and other cardiovascular disorders) may be confirmed by testing the ability of a compound to prevent cellular damage in established cellular stress assays,[105,116,117] and to prevent tissue damage and promote functional recovery in animal models of ischemia-reperfusion,[70,114] and trauma-hemorrhage.[72,112,115]

[0082] Compounds that selectively inhibit O-GlcNAcase activity may be used for the treatment of diseases that are associated with inflammation, including but not limited to, inflammatory or allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, atherosclerosis, interstitial lung disease (ILD) (*e.g.*, idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies; autoimmune diseases, such as rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Guillain-Barré syndrome, systemic lupus erythematosus, myastenia gravis, glomerulonephritis, autoimmune thyroiditis, graft rejection, including allograft rejection or graft-versus-host disease; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (*e.g.*, necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myotis, eosiniphilic fasciitis; and cancers.

[0083] In addition, compounds that affects levels of protein O-GlcNAc modification may be used for the treatment of diseases associated with immunosuppression, such as in individuals undergoing chemotherapy, radiation therapy, enhanced wound healing and burn treatment, therapy for autoimmune disease or other drug therapy (*e.g.*, corticosteroid therapy) or combination of conventional drugs used in the treatment of autoimmune diseases and graft/transplantation rejection, which causes immunosuppression; or immunosuppression due to congenital deficiency in receptor function or other causes.

[0084] One or more of the compounds of the invention may be useful for treatment of neurodegenerative diseases, including Parkinson's disease and Huntington's disease. Other conditions that may be treated are those triggered, affected, or in any other way correlated with levels of O-GlcNAc post-translational protein modification. It is expected that one or more of the compounds of this invention may be useful for the treatment of such conditions and in particular, but not limited to, the following for which a association with O-GlcNAc levels on proteins has been established: graft rejection, in particular but not limited to solid organ transplants, such as heart, lung, liver, kidney, and pancreas transplants (e.g. kidney and lung allografts); cancer, in particular but not limited to cancer of the breast, lung, prostate, pancreas, colon, rectum, bladder, kidney, ovary; as well as non-Hodgkin's lymphoma and

melanoma; epilepsy, pain, fibromyalgia, or stroke, e.g., for neuroprotection following a stroke.

Pharmaceutical & Veterinary Compositions, Dosages, And Administration

[0085] Pharmaceutical compositions including compounds according to the invention, or for use according to the invention, are contemplated as being within the scope of the invention. In some embodiments, pharmaceutical compositions including an effective amount of a compound of Formula (I) are provided.

[0086] The compounds of Formula (I) and their pharmaceutically acceptable salts, enantiomers, solvates, and derivatives are useful because they have pharmacological activity in animals, including humans. In some embodiments, one or more of the compounds according to the invention are stable in plasma, when administered to a subject.

[0087] In some embodiments, a compound according to the invention, or for use according to the invention, may be provided in combination with any other active agents or pharmaceutical compositions where such combined therapy is useful to modulate O-GlcNAcase activity, for example, to treat neurodegenerative, inflammatory, cardiovascular, or immunoregulatory diseases, or any condition described herein. In some embodiments, a compound according to the invention, or for use according to the invention, may be provided in combination with one or more agents useful in the prevention or treatment of Alzheimer's disease. Examples of such agents include, without limitation,

- acetylcholine esterase inhibitors (AChEIs) such as Aricept® (Donepezil), Exelon® (Rivastigmine), Razadyne® (Razadyne ER®, Reminyl®, Nivalin®, Galantamine), Cognex® (Tacrine), Dimebon, Huperzine A, Phenserine, Debio-9902 SR (ZT-1 SR), Zanapezil (TAK0147), ganstigmine, NP7557, etc.;
- NMDA receptor antagonists such as Namenda® (Axura®, Akatinol®, Ebixa®, Memantine), Dimebon, SGS-742, Neramexane, Debio-9902 SR (ZT-1 SR), etc.;
- gamma-secretase inhibitors and/or modulators such as Flurizan™ (Tarenflurbil, MPC-7869, R-flurbiprofen), LY450139, MK 0752, E2101, BMS-289948, BMS-299897, BMS-433796, LY-411575, GSI-136, etc.;
- beta-secretase inhibitors such as ATG-Z1, CTS-21166, etc.;
- alpha-secretase activators, such as NGX267, etc;

- amyloid-β aggregation and/or fibrillization inhibitors such as Alzhemed™ (3APS, Tramiprosate, 3-amino-1-propanesulfonic acid), AL-108, AL-208, AZD-103, PBT2, Cereact, ONO-2506PO, PPI-558, etc.;
- tau aggregation inhibitors such as methylene blue, etc.;
- microtubule stabilizers such as AL-108, AL-208, paclitaxel, etc.;
- RAGE inhibitors, such as TTP488, etc.;
- 5-HT1a receptor antagonists, such as Xaliproden, Lecozotan, etc.;
- 5-HT4 receptor antagonists, such as PRX-03410, etc.;
- kinase inhibitors such as SRN-003-556, amfurindamide, LiCl, AZD1080, NP031112, SAR-502250, etc.;
- humanized monoclonal anti-Aβ antibodies such as Bapineuzumab (AAB-001), LY2062430, RN1219, ACU-5A5, etc.;
- amyloid vaccines such as AN-1792, ACC-001, etc.;
- neuroprotective agents such as Cerebrolysin, AL-108, AL-208, Huperzine A, etc.;
- L-type calcium channel antagonists such as MEM-1003, etc.;
- nicotinic receptor antagonists, such as AZD3480, GTS-21, etc.;
- nicotinic receptor agonists, such as MEM 3454, Nefiracetam, etc.;
- peroxisome proliferator-activated receptor (PPAR) gamma agonists such as Avandia® (Rosglitazone), etc.;
- phosphodiesterase IV (PDE4) inhibitors, such as MK-0952, etc.;
- hormone replacement therapy such as estrogen (Premarin), etc.;
- monoamine oxidase (MAO) inhibitors such as NS2330, Rasagiline (Azilect®), TVP-1012, etc.;
- AMPA receptor modulators such as Ampalex (CX 516), etc.;
- nerve growth factors or NGF potentiators, such as CERE-110 (AAV-NGF), T-588, T-817MA, etc.;
- agents that prevent the release of luteinizing hormone (LH) by the pituitary gland, such as leuoprolide (VP-4896), etc.;
- GABA receptor modulators such as AC-3933, NGD 97-1, CP-457920, etc.;
- benzodiazepine receptor inverse agonists such as SB-737552 (S-8510), AC-3933, etc.;
- noradrenaline-releasing agents such as T-588, T-817MA, etc.

[0088] It is to be understood that combination of compounds according to the invention, or for use according to the invention, with Alzheimer's agents is not limited to the examples described herein, but includes combination with any agent useful for the treatment of Alzheimer's disease. Combination of compounds according to the invention, or for use according to the invention, and other Alzheimer's agents may be administered separately or in conjunction. The administration of one agent may be prior to, concurrent to, or subsequent to the administration of other agent(s).

[0089] In alternative embodiments, a compound may be supplied as a "prodrug" or protected forms, which release the compound after administration to a subject. For example, a compound may carry a protective group which is split off by hydrolysis in body fluids, *e.g.*, in the bloodstream, thus releasing the active compound or is oxidized or reduced in body fluids to release the compound. Accordingly, a "prodrug" is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound of the invention. Thus, the term "prodrug" refers to a metabolic precursor of a compound of the invention that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject in need thereof, but is converted in vivo to an active compound of the invention. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound of the invention, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a subject.

[0090] The term "prodrug" is also meant to include any covalently bonded carriers which release the active compound of the invention *in vivo* when such prodrug is administered to a subject. Prodrugs of a compound of the invention may be prepared by modifying functional groups present in the compound of the invention in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound of the invention. Prodrugs include compounds of the invention where a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound of the invention is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and acetamide, formamide, and benzamide derivatives of amine functional groups in one or more of the compounds of the invention and the like.

[0091] A discussion of prodrugs may be found in "Smith and Williams' Introduction to the Principles of Drug Design," H.J. Smith, Wright, Second Edition, London (1988); Bundgard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam); The Practice of

Medicinal Chemistry, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996); A Textbook of Drug Design and Development, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5, pgs 113 191 (Harwood Academic Publishers, 1991); Higuchi, T., *et al.*, "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14; or in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, all of which are incorporated in full by reference herein.

[0092] Suitable prodrug forms of one or more of the compounds of the invention include embodiments in which one or more R^3 as set forth in Formula (I) is (CO)R, where R is optionally substituted alkyl, alkenyl, alkynyl, aryl, or heteroaryl. In these cases the ester groups may be hydrolyzed in vivo (e.g. in bodily fluids), releasing the active compounds in which each R^3 is H. Preferred prodrug embodiments of the invention include compounds of Formula (I) where one or more R^3 is $C(O)CH_3$.

[0093] Compounds according to the invention, or for use according to the invention, can be provided alone or in combination with other compounds in the presence of a liposome, an adjuvant, or any pharmaceutically acceptable carrier, diluent or excipient, in a form suitable for administration to a subject such as a mammal, for example, humans, cattle, sheep, etc. If desired, treatment with a compound according to the invention may be combined with more traditional and existing therapies for the therapeutic indications described herein. Compounds according to the invention may be provided chronically or intermittently. "Chronic" administration refers to administration of the compound(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature. The terms "administration," "administrable," or "administering" as used herein should be understood to mean providing a compound of the invention to the subject in need of treatment.

[0094] "Pharmaceutically acceptable carrier, diluent or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier that has been approved, for example, by the United States Food and Drug Administration or other governmental agency as being acceptable for use in humans or domestic animals.

[0095] A compound of the present invention may be administered in the form of a pharmaceutically acceptable salt. In such cases, pharmaceutical compositions in accordance with this invention may comprise a salt of such a compound, preferably a physiologically acceptable salt, which are known in the art. In some embodiments, the term "pharmaceutically acceptable salt" as used herein means an active ingredient comprising compounds of Formula I used in the form of a salt thereof, particularly where the salt form confers on the active ingredient improved pharmacokinetic properties as compared to the free form of the active ingredient or other previously disclosed salt form.

[0096] A "pharmaceutically acceptable salt" includes both acid and base addition salts. A "pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like.

[0097] A "pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine,methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

[0098] Thus, the term "pharmaceutically acceptable salt" encompasses all acceptable salts including but not limited to acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartarate, mesylate, borate, methylbromide, bromide, methylnitrite, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutame, stearate, glycollylarsanilate, sulfate, hexylresorcinate, subacetate, hydradamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, panoate, valerate, and the like.

[0099] Pharmaceutically acceptable salts of a compound of the present invention can be used as a dosage for modifying solubility or hydrolysis characteristics, or can be used in sustained release or prodrug formulations. Also, pharmaceutically acceptable salts of a compound of this invention may include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylene-diamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethyl-amine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

[00100] Pharmaceutical formulations will typically include one or more carriers acceptable for the mode of administration of the preparation, be it by injection, inhalation, topical administration, lavage, or other modes suitable for the selected treatment. Suitable carriers are those known in the art for use in such modes of administration.

[00101] Suitable pharmaceutical compositions may be formulated by means known in the art and their mode of administration and dose determined by the skilled practitioner. For parenteral administration, a compound may be dissolved in sterile water or saline or a pharmaceutically acceptable vehicle used for administration of non-water soluble compounds such as those used for vitamin K. For enteral administration, the compound may be administered in a tablet, capsule or dissolved in liquid form. The table or capsule may be enteric coated, or in a formulation for sustained release. Many suitable formulations are known, including, polymeric or protein microparticles encapsulating a compound to be released, ointments, gels, hydrogels, or solutions which can be used topically or locally to administer a compound. A sustained release patch or implant may be employed to provide

release over a prolonged period of time. Many techniques known to skilled practitioners are described in *Remington: the Science & Practice of Pharmacy* by Alfonso Gennaro, 20th ed., Williams & Wilkins, (2000). Formulations for parenteral administration may, for example, contain excipients, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of a compound. Other potentially useful parenteral delivery systems for modulatory compounds include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

[00102] A compound or a pharmaceutical composition according to the present invention may be administered by oral or non-oral, e.g., intramuscular, intraperitoneal, intravenous, intracisternal injection or infusion, subcutaneous injection, transdermal or transmucosal routes. In some embodiments, a compound or pharmaceutical composition in accordance with this invention or for use in this invention may be administered by means of a medical device or appliance such as an implant, graft, prosthesis, stent, etc. Implants may be devised which are intended to contain and release such compounds or compositions. An example would be an implant made of a polymeric material adapted to release the compound over a period of time. A compound may be administered alone or as a mixture with a pharmaceutically acceptable carrier *e.g.,* as solid formulations such as tablets, capsules, granules, powders, etc.; liquid formulations such as syrups, injections, etc.; injections, drops, suppositories, pessaryies. In some embodiments, compounds or pharmaceutical compositions in accordance with this invention or for use in this invention may be administered by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

[00103] A compound of the invention may be used to treat animals, including mice, rats, horses, cattle, sheep, dogs, cats, and monkeys. However, a compound of the invention can also be used in other organisms, such as avian species (*e.g.*, chickens). One or more of the compounds of the invention may also be effective for use in humans. The term "subject" or

alternatively referred to herein as "patient" is intended to be referred to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. However, one or more of the compounds, methods and pharmaceutical compositions of the present invention may be used in the treatment of animals. Accordingly, as used herein, a "subject" may be a human, non-human primate, rat, mouse, cow, horse, pig, sheep, goat, dog, cat, etc. The subject may be suspected of having or at risk for having a condition requiring modulation of O-GlcNAcase activity.

[00104] An "effective amount" of a compound according to the invention includes a therapeutically effective amount or a prophylactically effective amount. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result, such as inhibition of an O-GlcNAcase, elevation of O-GlcNAc levels, inhibition of tau phosphorylation, or any condition described herein. A therapeutically effective amount of a compound may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the compound to elicit a desired response in the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. A therapeutically effective amount is also one in which any toxic or detrimental effects of the compound are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result, such as inhibition of an O-GlcNAcase, elevation of O-GlcNAc levels, inhibition of tau phosphorylation, or any condition described herein. Typically, a prophylactic dose is used in subjects prior to or at an earlier stage of disease, so that a prophylactically effective amount may be less than a therapeutically effective amount. A suitable range for therapeutically or prophylactically effective amounts of a compound may be any integer from 0.1 nM-0.1 M, 0.1 nM-0.05 M, 0.05 nM-15 μM or 0.01 nM-10 μM.

[00105] In alternative embodiments, in the treatment or prevention of conditions which require modulation of O-GlcNAcase activity, an appropriate dosage level will generally be about 0.01 to 500 mg per kg subject body weight per day, and can be administered in singe or multiple doses. In some embodiments, the dosage level will be about 0.1 to about 250 mg/kg per day. It will be understood that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound used, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration,

rate of excretion, drug combination, the severity of the particular condition, and the patient undergoing therapy.

[00106] It is to be noted that dosage values may vary with the severity of the condition to be alleviated. For any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgement of the person administering or supervising the administration of the compositions. Dosage ranges set forth herein are exemplary only and do not limit the dosage ranges that may be selected by medical practitioners. The amount of active compound(s) in the composition may vary according to factors such as the disease state, age, sex, and weight of the subject. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It may be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. In general, compounds of the invention should be used without causing substantial toxicity, and as described herein, one or more of the compounds exhibit a suitable safety profile for therapeutic use. Toxicity of a compound of the invention can be determined using standard techniques, for example, by testing in cell cultures or experimental animals and determining the therapeutic index, i.e., the ratio between the LD50 (the dose lethal to 50% of the population) and the LD100 (the dose lethal to 100% of the population). In some circumstances however, such as in severe disease conditions, it may be necessary to administer substantial excesses of the compositions.

[00107] In the compounds of generic Formula (I), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula (I). For example, different isotopic forms of hydrogen (H) include protium (^{1}H), deuterium (^{2}H) and tritium (^{3}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula (I) can be prepared without undue experimentation by conventional techniques well

known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Other Uses and Assays

[00108] A compound of Formula (I) may be used in screening assays for compounds which modulate the activity of glycosidase enzymes, preferably the O-GlcNAcase enzyme. The ability of a test compound to inhibit O-GlcNAcase-dependent cleavage of O-GlcNAc from a model substrate may be measured using any assays, as described herein or known to one of ordinary skill in the art. For example, a fluoresence or UV-based assay known in the art may be used. A "test compound" is any naturally-occurring or artificially-derived chemical compound. Test compounds may include, without limitation, peptides, polypeptides, synthesised organic molecules, naturally occurring organic molecules, and nucleic acid molecules. A test compound can "compete" with a known compound such as a compound of Formula (I) by, for example, interfering with inhibition of O-GlcNAcase-dependent cleavage of O-GlcNAc or by interfering with any biological response induced by a compound of Formula (I).

[00109] Generally, a test compound can exhibit any value between 10% and 200%, or over 500%, modulation when compared to a compound of Formula (I) or other reference compound. For example, a test compound may exhibit at least any positive or negative integer from 10% to 200% modulation, or at least any positive or negative integer from 30% to 150% modulation, or at least any positive or negative integer from 60% to 100% modulation, or any positive or negative integer over 100% modulation. A compound that is a negative modulator will in general decrease modulation relative to a known compound, while a compound that is a positive modulator will in general increase modulation relative to a known compound.

[00110] In general, test compounds are identified from large libraries of both natural products or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the method(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or

animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova (Slough, UK), Harbor Branch Oceanographic Institute (Ft. Pierce, FL, USA), and PharmaMar, MA, USA. In addition, natural and synthetically produced libraries are produced, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

[00111] When a crude extract is found to modulate inhibition of O-GlcNAcase-dependent cleavage of O-GlcNAc, or any biological response induced by a compound of Formula (I), further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and identification of a chemical entity within the crude extract having O-GlcNAcase- inhibitory activities. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogeneous extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic, prophylactic, diagnostic, or other value may be subsequently analyzed using a suitable animal model, as described herein on known in the art.

[00112] In some embodiments, one or more of the compounds are useful in the development of animal models for studying diseases or disorders related to deficiencies in O-GlcNAcase, over-expression of O-GlcNAcase, accumulation of O-GlcNAc, depletion of O-GlcNAc, and for studying treatment of diseases and disorders related to deficiency or over-expression of O-GlcNAcase, or accumulation or depletion of O-GlcNAc. Such diseases and disorders include neurodegenerative diseases, including Alzheimer's disease, and cancer.

[00113] Various alternative embodiments and examples of the invention are described herein. These embodiments and examples are illustrative and should not be construed as limiting the scope of the invention.

EXAMPLES

[00114] The following examples are intended to illustrate embodiments of the invention and are not intended to be construed in a limiting manner.

Abbreviations

ABCN = 1,1'-azobis(cyclohexane-carbonitrile)

AcCl = acetyl chloride

AcOH = acetic acid

BCl_3 = boron trichloride

BnBr = benzyl bromide

Boc_2O = di-*tert*-butyl dicarbonate

BzCl = benzoyl chloride

DAST = diethylaminosulfur trifluoride

DCM = dichloromethane

DIPEA = diisopropylethylamine

DMAP = 4-dimethylaminopyridine

DMF = *N*,*N*-dimethylformamide

DMP = Dess-Martin periodinane

Et_3N = triethylamine

Et_2O = diethyl ether

TBDMSCl = *tert*-butyldimethylsilyl chloride

TBAF = tetra-*n*-butylammonium fluoride

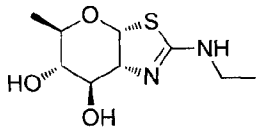
TFA = 2,2,2-trifluoroacetic acid

THF = tetrahydrofuran

thio-CDI = 1,1'-thiocarbonyl diimidazole

Example 1

(3aR,5R,6S,7R,7aR)-2-(ethylamino)-5-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00115] To a suspension of (3aR,5R,6S,7R,7aR)-2-(ethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (35.0 g, 141 mmol) in DMF (300 mL) cooled at 15°C, was added DIPEA (6.0 mL), Boc_2O (61.5 g, 282 mmol) and MeOH (6.0 mL). The mixture was stirred at room temperature for 16 h, and then MeOH (50 mL) was added. The reaction mixture was concentrated under reduced pressure at ~35°C. The residue was purified on silica gel by flash column chromatography (EtOAc/hexanes 1:1, then MeOH/DCM, 1:5), followed by recrystallization from EtOAc/hexanes, to afford tert-butyl ((3aR,5R,6S,7R,7aR)-6,7-dihydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate as a white solid (31.5 g, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, J = 6.8 Hz, 1H), 4.23-4.22 (m, 1H), 4.17-4.14 (m, 1H), 3.91-3.86 (m, 2H), 3.81-3.77 (m, 3H), 3.59-3.55 (m, 1H), 3.17-3.16 (m, 1H, OH), 1.53 (s, 9H), 1.16 (t, J = 7.0 Hz, 3H).

[00116] To a solution of the above material (5.0 g, 14.4 mmol) in DMF (25 mL) was added imidazole (1.57g, 23.1 mmol) and TBDMSCl (2.82g, 18.7 mmol). The reaction mixture stirred at room temperature for 30 h was diluted with EtOAc (100 mL). Organics were washed with satd. NH_4Cl, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:1), affording tert-butyl ((3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate as a white solid (5.08 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d, J = 6.7 Hz, 1H), 4.25 (t, J = 6.2 Hz, 1H), 4.16 (t, J = 6.4 Hz, 1H), 4.10-4.04 (m, 2H), 3.91-3.85 (m, 3H), 3.65-3.62 (m, 1H), 1.55 (s, 9H), 1.26 (t, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H).

[00117] To a solution of the above material (1.15 g, 2.5 mmol), tetrabutyl ammonium iodide (0.092 g, 0.25 mmol) in DMF (25 mL) at 0°C was added NaH (60%, 0.3g, 7.5 mmol) followed by *p*-methoxybenzyl chloride (1.02 mL, 7.5 mmol). The reaction mixture was then

stirred at room temperature for 6 h, diluted with Et_2O (50 mL) and quenched with water (5 mL). The ether layer was further washed with satd. NH_4Cl, brine, dried over anhydrous Na_2SO_4 and concentrated. A mixture of two products, tert-butyl ((3aR,5R,6S,7R,7aR)-6-((tert-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-5-((4-methoxyphenoxy)methyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate and tert-butyl ((3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6,7-bis((4-methoxybenzyl)oxy)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate was isolated (1.6 g, 66%) in a 1:2 ratio, respectively, as indicated by ^1H NMR.

[00118] To a solution of the above mixture (1.58 g, 2.26 mmol) in THF (15 mL) was added 1M TBAF solution (4.0 mL, 4 mmol) at 0°C and the mixture was then stirred at room temperature for 2 h. Diluted with EtOAc (50 mL), the organic layer was washed with satd. NH_4Cl, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:2), affording tert-butyl ethyl((3aR,5R,6S,7R,7aR)-5-(hydroxymethyl)-6,7-bis((4-methoxybenzyl)oxy)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate (0.75 g, 56%) as a gummy solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.6, 2H), 7.15 (d, J = 8.6, 2H), 6.88-6.80 (m, 4H), 6.01 (d, J = 6.9 Hz, 1H), 4.64 (d, J = 11.8 Hz, 1H), 4.59 (d, J = 11.8 Hz, 1H), 4.48-4.45 (m, 1H), 4.37-4.34 (ddd, J = 6.8, 3.6, 1.28 Hz, 1H), 4.27 (d, J = 11.2, 1H), 4.24-4.23 (dd, J = 1.8, 1.76 Hz, 1H), 3.87-3.80 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.70-3.65 (m, 1H), 3.59-3.56 (dt, J = 9.0, 1.44 Hz, 1H), 3.55-3.49 (m, 1H), 3.41-3.37 (ddd, J = 8.5, 5.3, 2.8 Hz, 1H), 1.78 (t, J = 6.4 Hz, 1H), 1.50 (s, 9H), 1.18 (t, J = 6.9 Hz, 3H).

[00119] To a solution of triphenyl phosphine (0.179g, 0.68 mmol) in dry toluene (5 mL) was added iodine (0.145g, 0.57 mmol), pyridine (0.1 mL, 1.2 mmol) and a solution of the above material (0.210 g, 0.357 mmol) pre-dissolved in toluene (3 mL). The reaction mixture was stirred at 65°C for 3.5 h. Insoluble yellowish material was filtered off and filtrate diluted with EtOAc (50 mL) was washed with 1N HCl (20 mL), satd. $NaHCO_3$ (20 mL) and brine. EtOAc layer was separated, dried over Na_2SO_4 and concentrated to crude product which was purified on silica gel by flash column chromatography (EtOAc/hexanes, 3:7), affording tert-butyl ethyl((3aR,5S,6S,7R,7aR)-5-(iodomethyl)-6,7-bis((4-methoxybenzyl)oxy)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate as a white solid (0.23 g, 92.4%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.4, 2H), 7.18 (d, J = 8.4, 2H), 6.89-6.82 (m, 4H), 6.07 (d, J = 7 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.54-4.51 (m, 1H), 4.36-4.31 (m, 2H), 4.19 (t, J = 2.64 Hz, 1H), 3.87 (d, J = 6.9 Hz, 1H), 3.83 (d, J = 6.9

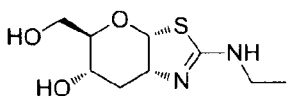
Hz, 1H), 3.77 (s, 6H), 3.50-3.48 (dd, J = 6.8, 1.3 Hz, 1H), 3.37-3.34 (m, 1H), 3.23-3.20 (m, 2H), 1.51 (s, 9H), 1.10 (t, J = 6.9 Hz, 3H).

[00120] To a solution of the above material (0.120 g, 0.172 mmol) in ethanol (4 mL) and Et_3N (0.1 mL) was added Pd/C (10% Wt, 0.060 g). The mixture was hydrogenated at 50 psi and at room temperature for 24 h. Catalyst was removed by filtration and solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 3:7 EtOAc/hexanes to give tert-butyl ((3aR,5R,6R,7R,7aR)-6,7-bis((4-methoxybenzyl)oxy)-5-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate (0.077 g, 78.4%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 6.8, 2H), 7.17 (d, J = 6.8, 2H), 6.87-6.81 (m, 4H), 6.07 (d, J = 5.6 Hz, 1H), 4.67 (d, J = 9.4 Hz, 1H), 4.58 (d, J = 9.4 Hz, 1H), 4.50 (d, J = 8.9 Hz, 1H), 4.34 (m, 1H), 4.27 (d, J = 8.9 Hz, 1H), 4.23-4.17 (m, 1H), 3.87-3.84 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.44-3.39 (m, 1H), 3.30-3.28 (m, 1H), 1.50 (s, 9H), 1.18 (d, J = 4.9 Hz, 3H), 1.10 (t, J = 5.5 Hz, 3H).

[00121] The above material (0.075 g, 0.131 mmol) was dissolved in 30% TFA/DCM solution (10 mL) and stirred at room temperature for 2.5 h. The reaction mixture was concentrated and co-evaporated with Et_2O (20 mL). To the residue was added 2M NH_3/MeOH solution (3 mL) and concentrated under reduced pressure. The product obtained was purified on silica gel by flash column chromatography eluted with 5% MeOH in DCM and 94:4:2 DCM-MeOH-NH_4OH (28% aqueous) to give (3aR,5R,6S,7R,7aR)-2-(ethylamino)-5-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (0.021 g, 68.7%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.60 (d, J = 6.5 Hz, 1H), 4.08 (t, J = 7.04 Hz, 1H), 3.77 (t. J = 7.2 Hz, 1H), 3.75-3.72 (m, 1H), 3.44-3.38 (ddd, J = 14.6, 7.28, 2.08 Hz, 2H), 3.25-3.20 (dd, J = 7.7, 1.12 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 160. 40, 90.08, 75.69, 75.66, 74.21, 66.27, 55.65, 18.91, 14.51; MS, m/z = 233 (M + 1).

Example 2

(3aR,5R,6S,7aR)-2-(ethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00122] To a solution of *tert*-butyl ((3aR,5R,6S,7R,7aR)-6,7-dihydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate (1.64 g, 4.73 mmol),

DIPEA (1.34 g, 10.4 mmol) and DMAP (0.010 g, 0.082 mmol) in DCM (50 mL), at 0°C, was added BzCl (1.33 g, 9.50 mmol) slowly. After addition the mixture was stirred at room temperature overnight. Satd. aqueous NH_4Cl solution (50 mL) was added, and the organic layer was collected. The aqueous layer was further extracted with DCM (2 × 40 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was separated on silica gel by flash column chromatography (EtOAc/hexanes, 1:4 to 1:2), affording ((3aR,5R,6S,7R,7aR)-6-(benzoyloxy)-2-((*tert*-butoxycarbonyl)(ethyl)amino)-7-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate as a white solid (0.67 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.1 Hz, 4H), 7.57-7.35 (m, 6H), 6.19 (d, J = 7.1 Hz, 1H), 5.21 (dd, J = 2.8, 9.2 Hz, 1H), 4.56-4.51 (m, 2H), 4.47-4.42 (m, 2H), 4.14-4.10 (m, 1H), 3.99-3.92 (m, 2H), 1.55 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H).

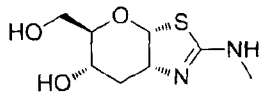
[00123] A mixture of the above material (0.346 g, 0.623 mmol) and thio-CDI (90% tech, 0.20 g, 1.0 mmol) in anhydrous toluene (10 mL) was stirred at 95°C for 4 h. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 2:3), affording (3aR,5R,6S,7R,7aR)-7-((1H-Imidazole-1-carbonothioyl)oxy)-5-((benzoyloxy)methyl)-2-((tert-butoxycarbonyl)(ethyl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-yl benzoate as a yellow solid (0.343 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.08-7.94 (m, 4H), 7.70 (s, 1H), 7.57-7.37 (m, 6H), 7.18 (s, 1H), 6.36 (dd, J = 1.9, 3.7 Hz, 1H), 6.17 (d, J = 7.1 Hz, 1H), 5.54 (td, J = 1.2, 9.2 Hz, 1H), 4.70-4.67 (m, 1H), 4.60 (dd, J = 3.2, 12.1 Hz, 1H), 4.42 (dd, J = 5.1, 12.2 Hz, 1H), 4.11-4.08 (m, 1H), 4.05-3.97 (m, 2H), 1.56 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H).

[00124] A mixture of the above material (0.343 g, 0.515 mmol), Bu_3SnH (0.291 g, 1.00 mmol) and ABCN (8.0 mg, 0.033 mmol) in anhydrous toluene (10 mL) was stirred at 90°C for 3 h. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:4), affording ((3aR,5R,6S,7aR)-6-(benzoyloxy)-2-((*tert*-butoxycarbonyl)(ethyl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate as a white solid (0.141 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.94 (m, 4H), 7.57-7.52 (m, 2H), 7.44-7.35 (m, 4H), 6.07 (d, J = 7.2 Hz, 1H), 5.44-5.40 (m, 1H), 4.52-4.41 (m, 3H), 4.06-3.96 (m, 3H), 2.70-2.64 (m, 1H), 2.47-2.40 (m, 1H), 1.56 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H).

[00125] A mixture of the above material (0.140 g, 0.260 mmol) and K_2CO_3 (0.030 g, 0.22 mmol) in anhydrous MeOH (6 mL) was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc), affording a white solid. The solid was dissolved in MeOH (3 mL), into which HCl (g) was bubbled for 30 sec. The solution was then stirred at room temperature for 3 h. The solvent was removed, and the residue was neutralized with 1.0 M NH_3 in MeOH and subsequently purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1:8), affording (3aR,5R,6S,7aR)-2-(ethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as an off-white solid (0.044 g, 73%). ^{1}H NMR (500 MHz, CD_3OD) δ 6.20 (d, J = 7.1Hz, 1H), 4.28-4.25 (m, 1H), 3.75 (dd, J = 2.6, 14.4 Hz, 1H), 3.73-3.69 (m, 1H), 3.61 (dd, J = 6.4, 14.4 Hz, 1H), 3.54-3.51 (m, 1H), 3.30-3.22 (m, 2H), 2.16-2.11 (m, 1H), 2.06-2.00 (m, 1H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 163.24, 91.35, 77.13, 69.15, 65.79, 63.36, 39.60, 34.75, 14.87; MS, m/z = 233 (M + 1).

Example 3

(3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00126] To a suspension of (3aR,5R,6S,7R,7aR)-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (1.50 g, 6.40 mmol) and $NaHCO_3$ (1.01 g, 12.0 mmol) in THF/water (40 mL, 1 :3) was added benzyl chloroformate (1.70 g, 10.0 mmol). The mixture was stirred at room temperature for 4 days. The organic solvent was removed under reduced pressure to result in a precipitate. The precipitated solid was collected by filtration, washed with Et_2O and dried under vacuum, affording benzyl ((3aR,5R,6S,7R,7aR)-6,7-dihydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (1.72 g, 73%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.44-7.32 (m, 5H), 6.13 (d, J = 6.9 Hz, 1H), 5.27-5.20 (m, 2H), 4.14 (t, J = 6.1 Hz, 1H), 4.02 (t, J = 4.9 Hz, 1H), 3.74 (dd, J = 2.4, 12.0 Hz, 1H), 3.63 (dd, J = 6.1, 12.0 Hz, 1H), 3.53 (dd, J = 4.5, 9.2 Hz, 1H), 3.47-3.43 (m, 1H), 3.39 (s, 3H).

[00127] A mixture of the above material (1.50 g, 4.08 mmol), benzaldehyde dimethyl acetal (3 mL) and *p*-toluenesulfonic acid monohydrate (0.058 g, 0.30 mmol) in DMF (10 mL) was

stirred at 50°C under a slight vacuum overnight. After cooling the solution was neutralized with solid $NaHCO_3$, and then concentrated under reduced pressure. The residue was purified on silica gel by flash column chromatography (EtOAc/DCM/hexanes, 2:4:1), affording benzyl ((3aR,4aR,8aS,9R,9aR)-9-hydroxy-7-phenyl-3a,4a,5,8a,9,9a-hexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (0.91 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.40-7.35 (m, 8H), 6.28 (d, J = 7.5 Hz, 1H), 5.78 (s, 1H), 5.29-5.21 (m, 2H), 4.34 (dd, J = 5.1, 10.4 Hz, 1H), 4.15-4.06 (m, 2H), 3.89-3.84 (m, 1H), 3.76 (t, J = 10.4 Hz, 1H), 3.58 (t, J = 9.4, 1H), 3.38 (s, 3H), 2.62 (d, J = 2.4 Hz, 1H).

[00128] A mixture of the above material (0.700 g, 1.54 mmol) and thio-CDI (90% tech, 0.80 g, 4.04 mmol) in anhydrous DMF (20 mL) was stirred at 90°C overnight. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/DCM, 2:1), affording O-((3aR,4aR,8aS,9R,9aR)-2-(((benzyloxy)carbonyl)(methyl)amino)-7-phenyl-3a,4a,5,8a,9,9a-hexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,2-d]thiazol-9-yl) 1H-imidazole-1-carbothioate as a yellow solid (0.71 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.66 (s, 1H), 7.42-7.37 (m, 7H), 7.35-7.32 (m, 3H), 7.03 (s, 1H), 6.28 (d, J = 7.2 Hz, 1H), 6.20 (dd, J = 7.1, 8.6 Hz, 1H), 5.56 (s, 1H), 5.26 (s, 2H), 4.43 (t, J = 7.1 Hz, 1H), 4.39 (dd, J = 5.1, 10.4 Hz, 1H), 4.19-4.13 (m, 1H), 3.93 (t, J = 9.0 Hz, 1H), 3.79 (t, J = 10.4 Hz, 1H), 3.32 (s, 3H).

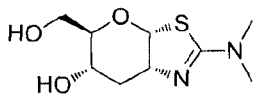
[00129] A mixture of the above material (0.560 g, 1.00 mmol), Bu_3SnH (0.87 g, 3.0 mmol) and ABCN (24 mg, 0.10 mmol) in anhydrous THF (20 mL) was stirred at reflux for 3 h. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes/DCM, 1:3:1), affording benzyl methyl((3aR,4aR,8aS,9aR)-7-phenyl-3a,4a,5,8a,9,9a-hexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,2-d]thiazol-2-yl)carbamate as a white solid (0.32 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.47 (m, 2H), 7.39-7.33 (m, 8H), 6.21 (d, J = 6.5 Hz, 1H), 5.56 (s, 1H), 5.29-5.20 (m, 2H), 4.52-4.25 (m, 2H), 4.08-4.02 (m, 1H), 3.72 (t, J = 10.3 Hz, 1H), 3.61-3.54 (m, 1H), 3.33 (s, 3H), 2.41-2.35 (m, 1H), 1.76-1.68 (m, 1H).

[00130] To a solution of the above material (0.20 g, 0.45 mmol) in anhydrous DCM (10 mL), cooled at -78°C under N_2, was added boron trichloride in DCM (1.0 M, 2.0 mL, 2.0 mmol). The mixture was stirred for 3 h while the reaction temperature was gradually brought to ~ 0°C. The mixture was then cooled at -78°C again, and MeOH (5 mL) was added carefully. After stirred at room temperature for 30 min the mixture was concentrated under

reduced pressure. The residue was neutralized with 1.0 M NH_3 in MeOH, and subsequently purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH:DCM, 1:7), affording (3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as an off-white solid (0.070 g, 72%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.20 (d, J = 6.4 Hz, 1H), 4.27-4.23 (m, 1H), 3.74 (dd, J = 2.5, 12.0 Hz, 1H), 3.71-3.67 (m, 1H), 3.63 (dd, J = 6.2, 12.0 Hz, 1H), 3.54-3.49 (m, 1H), 2.83 (s, 3H), 2.16-2.10 (m, 1H), 2.04-1.97 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.99, 91.81, 77.11, 69.31, 65.82, 63.32, 34.93, 30.49; MS, m/z = 219 (M + 1).

Example 4

(3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



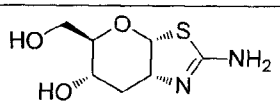
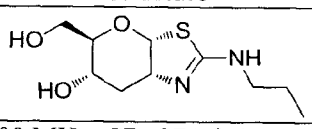
[00131] A suspension of (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (0.800 g, 3.23 mmol) and anhydrous $ZnCl_2$ (1.00 g, 7.35 mmol) in benzaldehyde (5 mL) was stirred at room temperature overnight. DCM (50 mL) and satd. aqueous $NaHCO_3$ (50 mL) was added, and mixture was stirred for 20 min. The solid was filtered off, and the organic layer was collected from the filtrate. The aqueous layer was extracted with DCM (2 × 50 mL), and the combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 3:100), affording (3aR,4aR,8aS,9R,9aR)-2-(dimethylamino)-7-phenyl-3a,4a,5,8a,9,9a-hexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,2-d]thiazol-9-ol as a pale yellow solid (0.76 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.40-7.34 (m, 3H), 6.39 (d, J = 6.6 Hz, 1H), 5.58 (s, 1H), 4.31 (dd, J = 5.1, 10.4 Hz, 1H), 4.10-4.03 (m, 2H), 3.86 (dd, J = 8.2, 9.5 Hz, 1H), 3.76 (t, J = 10.4 Hz, 1H), 3.59 (t, J = 9.5 Hz, 1H), 3.00 (s, 6H).

[00132] A mixture of the above material (0.67 g, 2.0 mmol) and thio-CDI (90% tech, 1.6 g, 8.0 mmol) in anhydrous DMF (20 mL) was stirred at 95°C overnight. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (MeOH/DCM, 1:100 to 5:100), affording a mixture containing O-((3aR,4aR,8aS,9R,9aR)-2-(dimethylamino)-7-phenyl-3a,4a,5,8a,9,9a-hexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,2-d]thiazol-9-yl) 1H-imidazole-1-carbothioate. This mixture

was dissolved in anhydrous THF (30 mL), and Bu_3SnH (1.0 g, 3.4 mmol) and ABCN (0.060 mg, 0.24 mmol) was added, and the mixture was stirred at reflux overnight. The solvent was then removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH:DCM, 3:100), affording an pale yellow solid containing (3aR,4aR,8aS,9aR)-N,N-dimethyl-7-phenyl-3a,4a,5,8a,9,9a-hexahydro-[1,3]dioxino[4',5':5,6]pyrano[3,2-d]thiazol-2-amine (0.17 g, impure). The solid was treated with 2% HCl in MeOH (10 mL) at room temperature for 2 h, and then the solvent was removed under reduced pressure. The residue was neutralized with 1.0 M NH_3 in MeOH, and subsequently purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH:DCM, 1:10), affording pure (3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as an off-white solid (0.050 g, 11% overall yield). ^{1}H NMR (400 MHz, CD_3OD) δ 6.23 (d, J = 6.4 Hz, 1H), 4.28-4.24 (m, 1H), 3.74 (dd, J = 2.5, 12.0 Hz, 1H), 3.70-3.65 (m, 1H), 3.59 (dd, J = 6.2, 12.0 Hz, 1H), 3.53-3.48 (m, 1H), 2.99 (s, 6H), 2.14-2.08 (m, 1H), 2.02-1.95 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.60, 92.43, 77.19, 69.67, 65.79, 63.27, 40.15, 34.93; MS, m/z = 255 (M + 23).

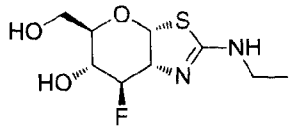
[00133] The following examples were synthesized according to procedures analogous to the schemes and examples outlined above.

Table 2

Example	Structure	Name
5		(3aR,5R,6S,7aR)-2-amino-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
^{1}H NMR (400 MHz, CD_3OD) δ 6.44 (d, J = 6.9 Hz, 1H), 4.56-4.52 (m, 1H), 3.90-3.85 (m, 1H), 3.77 (dd, J = 2.5, 12.1 Hz, 1H), 3.63 (dd, J = 6.4, 12.1 Hz, 1H), 3.54-3.50 (m, 1H), 2.18-2.10 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.80, 87.98, 77.53, 63.91, 63.25, 59.96, 32.33; MS, m/z = 205 (M + 1).		
Example	Structure	Name
6		(3aR,5R,6S,7aR)-5-(hydroxymethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
^{1}H NMR (400 MHz, CD_3OD) δ 6.18 (d, J = 6.3 Hz, 1H), 4.26-4.22 (m, 1H), 3.74 (dd, J = 2.1, 11.8 Hz, 1H), 3.71-3.66 (m, 1H), 3.59 (dd, J = 6.3, 11.8 Hz, 1H), 3.54-3.49 (m, 1H), 3.21-3.12 (m, 2H), 2.14-2.08 (m, 1H), 2.04-1.99 (m, 1H), 1.59-1.53 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.32, 91.40, 77.17, 69.28, 65.94, 63.36, 46.81, 34.81, 23.67, 11.72; MS, m/z = 269 (M + 23).		

Example 7

(3aR,5R,6R,7R,7aR)-2-(ethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol

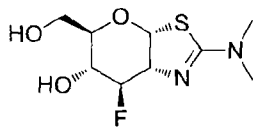


[00134] To a solution of ((3aR,5R,6S,7R,7aR)-6-(benzoyloxy)-2-((*tert*-butoxycarbonyl)(ethyl)amino)-7-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate (0.49 g, 0.88 mmol) in anhydrous DCM (3 mL), at -40°C under N_2, was added DAST (1.0 g, 6.2 mmol). After addition the mixture was stirred at room temperature overnight. After the reaction mixture was again cooled at -40°C, it was diluted with DCM (20 mL), and then quenched by adding satd. aqueous $NaHCO_3$ dropwise. The organic layer was collected, and the aqueous was extracted with DCM (2 × 15 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:5 to 2:7), affording ((3aR,5R,6R,7R,7aR)-6-(benzoyloxy)-2-((tert-butoxycarbonyl)(ethyl)amino)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate as a white solid (0.14 g, impure, ~28%).

[00135] Conversion of the above material to the title compound was accomplished by removal of benzoate and Boc protection groups using K_2CO_3 in MeOH and satd. HCl in MeOH respectively, via procedures as described for Example 2. After purification on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1:7), (3aR,5R,6R,7R,7aR)-2-(ethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol was obtained as an off-white solid (0.051 g, 23% overall). ^{1}H NMR (400 MHz, CD_3OD) δ 6.33 (d, J = 6.6 Hz, 1H), 4.77 (td, J = 5.0, 48.2 Hz, 1H), 4.34-4.27 (m, 1H), 3.81 (dd, J = 2.0, 12.0 Hz, 1H), 3.77-3.72 (m, 1H), 3.68 (dd, J = 5.7, 12.0 Hz, 1H), 3.63-3.59 (m, 1H), 3.31-3.23 (m, 2H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.40, 96.25 (d, J = 177.7 Hz), 90.55 (d, J = 3.9 Hz), 75.26 (d, J = 4.6 Hz), 73.58 (d, J = 24.5 Hz), 68.91 (d, J = 22.8 Hz), 62.85, 39.54, 14.82; MS, m/z = 251 (M + 1).

Example 8

(3aR,5R,6R,7R,7aR)-2-(dimethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00136] To a solution of (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (5.20 g, 21.0 mmol) and imidazole (12.0 g, 176 mmol) in DMF (60 mL) was added TBDMSCl (15.0 g, 99.5 mmol). The mixture was stirred at room temperature for 24 h, and then diluted with brine (200 mL). The mixture was extracted with Et_2O ((3 × 100 mL). The combined extract was washed with brine (100 mL) and water (100 mL), and then dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure. The residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:4 to 1:1), affording (3aR,5R,6R,7R,7aR)-7-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as a white solid (5.95 g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, J = 5.8 Hz, 1H), 4.34-4.33 (m, 1H), 4.20 (t, J = 5.0 Hz, 1H), 3.80-3.72 (m, 2H), 3.48 (s, br., 2H), 3.01 (s, 6H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), 0.07 (s, 6H).

[00137] To a solution of the above material (5.95 g, 12.5 mmol) and DMAP (0.12 g, 0.98 mmol) in pyridine (50 mL), at 0°C, was added BzCl (3.00 g, 21.3 mmol) slowly. After addition the mixture was stirred at room temperature for 24 h. Satd. aqueous $NaHCO_3$ solution (100 mL) was added, and the mixture extracted with EtOAc (3 × 100 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:9 to 1:3), affording (3aR,5R,6R,7R,7aR)-7-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-yl benzoate as a clear oil (6.85 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.02 (m, 2H), 7.56-7.52 (m, 1H), 7.43-7.39 (m, 2H), 6.26 (d, J = 6.4 Hz, 1H), 5.06-5.03 (m, 1H), 4.40 (dd, J = 2.2, 3.8 Hz, 1H), 3.81-3.78 (m, 1H), 3.71-3.70 (m, 2H), 3.03 (s, 6H), 0.88 (s, 9H), 0.85 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H), 0.02 (s, 3H), 0.00 (3H).

[00138] To a solution of the above material (9.30 g, 16.8 mmol) in dry MeOH (100 mL), was bubbled HCl for 2 min, and the mixture was then stirred at room temperature for 2 h. After concentrated under reduced pressure the mixture was treated with satd. aqueous $NaHCO_3$ solution (150 mL), and then extracted with EtOAc (6 × 80 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, affording (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-7-hydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-yl benzoate as a white crystalline solid (5.40 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.58-7.53 (m, 1H), 7.44-7.39 (m, 2H), 6.37 (d, J = 4.5 Hz, 1H), 5.12-5.09 (m, 1H), 4.41-4.37 (m, 2H), 3.94-3.85 (m, 1H), 3.78-3.74 (m, 1H), 3.67 (dd, J = 4.9, 12.5 Hz, 1H), 3.00 (s, 6H).

[00139] To a solution of the above material (5.35 g, 15.2 mmol) and DMAP (0.050 g, 0.41 mmol) in pyridine (50 mL), at 0°C, was added BzCl (2.22 g, 15.8 mmol) slowly. After addition the mixture was stirred at room temperature for 4 h. Satd. aqueous $NaHCO_3$ solution (100 mL) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:1 to 10:1), affording ((3aR,5R,6S,7R,7aR)-6-(benzoyloxy)-2-(dimethylamino)-7-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate as a white solid (4.45 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.00 (m, 4H), 7.58-7.51 (m, 2H), 7.44-7.37 (m, 4H), 6.38 (d, J = 6.6 Hz, 1H), 5.23-5.20 (m, 1H), 4.55 (dd, J = 3.2, 12.0 Hz, 1H) 4.48-4.40 (m, 3H), 4.27-4.22 (m, 1H), 3.00 (s, 6H).

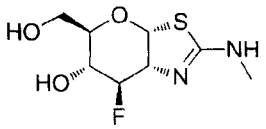
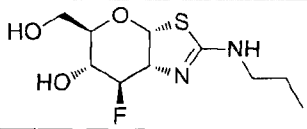
[00140] To a solution of the above material (0.410 g, 0.898 mmol) in anhydrous DCM (6 mL), at -78°C under N_2, was added DAST (0.87 g, 5.4 mmol). After addition the mixture was stirred at room temperature for 16 h. The reaction mixture was then cooled at -78°C, diluted with DCM (20 mL), and quenched by adding satd. aqueous $NaHCO_3$ (20 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 30 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:3 to 1:2), affording ((3aR,5R,6R,7R,7aR)-6-(benzoyloxy)-2-(dimethylamino)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate) as a white solid (0.380 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.00 (m, 4H), 7.58-7.55 (m, 1H), 7.54-7.51 (m, 1H), 7.44-7.41 (m, 2H), 7.39-7.36 (m, 2H), 6.35 (d, J = 5.4 Hz, 1H), 5.47 (dd, J = 7.3, 16.3 Hz, 1H), 5.23 (ddd, J = 1.1, 2.8, 35.2 Hz,

1H), 4.70-4.66 (m, 1H), 4.52 (dd, J = 2.8, 9.6 Hz), 4.40 (dd, J = 4.7, 9.6 Hz, 1H), 4.14-4.10 (m, 1H), 3.05 (s, 6H).

[00141] A mixture of the above material (0.375 g, 0.818 mmol) and K_2CO_3 (0.113 g, 0.818 mmol) in anhydrous MeOH (8 mL) was stirred at room temperature for 2 h. The reaction mixture was neutralized with dry ice, and the solvent was then removed under reduced pressure. The residue was purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1:12), affording (3aR,5R,6R,7R,7aR)-2-(dimethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as a white solid (0.190 g, 93%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.35 (d, J = 6.7 Hz, 1H), 4.74 (dt, J = 48.1, 5.0 Hz, 1H), 4.31 (dt, J = 13.8, 6.0 Hz, 1H), 3.79 (dd, J = 2.0, 12.0 Hz, 1H), 3.76-3.69 (m, 1H), 3.66 (dd, J = 5.8, 12.0 Hz), 3.61-3.57 (m, 1H), 3.01 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.25, 96.36 (d, J = 176.8 Hz), 91.60 (d, J = 3.9 Hz), 75.45 (d, J = 4.6 Hz), 73.99 (d, J = 24.7 Hz), 68.98 (d, J = 22.9 Hz), 62.91, 40.33; MS, (ES, *m/z*) $[M+H]^+$ 251.1.

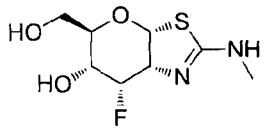
[00142] The following examples were synthesized according to procedures analogous to the schemes and examples outlined above.

Table 3

Example	Structure	Name
9		(3aR,5R,6R,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
^{1}H NMR (400 MHz, CD_3OD) δ 6.33 (d, J = 6.5 Hz, 1H), 4.75 (dt, J = 48.2, 5.1 Hz, 1H), 4.29 (dt, J = 13.9, 5.9 Hz, 1H), 3.81-3.64 (m, 3H), 3.62-3.57 (m, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.66, 96.42 (d, J = 177.8 Hz), 91.17 (d, J = 4.0 Hz), 75.37 (d, J = 4.6 Hz), 73.68 (d, J = 24.5 Hz), 69.02 (d, J = 22.8 Hz), 62.92, 30.53. (ES, *m/z*) $[M+H]^+$: 237.1.		
Example	Structure	Name
10		(3aR,5R,6R,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
^{1}H NMR (400 MHz, CD_3OD) δ 6.31 (d, J = 6.4 Hz, 1H), 4.74 (dt, J = 48.2, 4.9 Hz, 1H), 4.31-4.24 (m, 1H), 3.81-3.58 (m, 4H), 324-3.15 (m, 2H), 1.60-1.53 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.93, 96.41 (d, J = 177.7 Hz), 90.64 (d, J = 4.0 Hz), 75.38 (d, J = 4.5 Hz), 73.63 (d, J = 24.4 Hz), 69.03 (d, J = 22.8 Hz), 62.96, 46.72, 23.66, 11.53. (ES, *m/z*) $[M+H]^+$: 265.2.		

Example 11

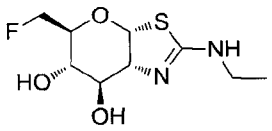
(3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00143] To a solution of tert-butyl ((3aR,5R,6R,7S,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate (0.200 g, 0.444 mmol) in dry MeOH (6 mL) was bubbled HCl gas for 30 sec. The mixture was stirred at room temperature for 5 h. After the solvent was evaporated under reduced pressure, the residue was neutralized with 1.0 M NH_3 in MeOH and purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1:8) followed by recrystallization from MeOH/Et_2O, affording (3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as a white solid (0.093 g, 89%). ^1H NMR (400 MHz, CD_3OD) δ 6.62 (d, J = 6.5 Hz, 1H), 4.89 (td, J = 3.5 Hz, 51.0 Hz, 1H), 4.54 (ddd, J = 3.5, 6.5, 20.6, 1H), 3.98-3.94 (m, 1H), 3.90-3.84 (m, 1H), 3.83-3.81 (m, 1H), 3.75 (dd, J = 5.4, 12.2 Hz, 1H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 90.63 (d, J = 181.3 Hz), 88.53 (d, J = 2.3 Hz), 73.60 (d, J = 4.3 Hz), 66.02 (d, J = 17.3 Hz), 64.80-64.50 (m), 62.44, 31.38; MS, (ES, *m/z*) $[M+H]^+$ 237.1.

Example 12

(3aR,5S,6S,7R,7aR)-2-(ethylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00144] Methanesulfonyl chloride (0.038 mL, 0.495 mmol) was added in portions to a stirred solution of tert-butyl ethyl((3aR,5R,6S,7R,7aR)-5-(hydroxymethyl)-6,7-bis((4-methoxybenzyl)oxy)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate (0.190g, 0.323 mmol) in dry pyridine (5 mL) at -20°C. After 3 h, the reaction mixture was diluted with DCM (20 mL) and the DCM extract was washed with satd. $NaHCO_3$, brine, dried over

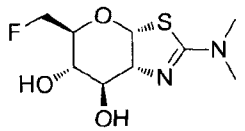
Na_2SO_4 and concentrated. Residual pyridine was removed by co-evaporation with hexanes. The crude product was purified by silica gel column chromatography (3:7 EtOAc/hexanes) to give ((3aR,5R,6S,7R,7aR)-2-((tert-butoxycarbonyl)(ethyl)amino)-6,7-bis((4-methoxybenzyl) oxy) -5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl methanesulfonate (0.215g, 99.6%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 6.91-6.83 (m, 4H), 6.01 (d, J =6.88 Hz, 1H), 4.66 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.1 Hz, 1H), 4.42-4.36 (m, 2H), 4.27-4.23 (m, 3H), 3.96-3.84 (m, 2H), 3.8 (s, 3H), 3.79 (s, 3H), 3.55 (m, 2H), 2.98 (s, 3H), 1.52 (s, 9H), 1.20 (t, J = 6.9 Hz, 3H).

[00145] To a solution of the above material (0.520 g, 0.78 mmol) in CH_3CN (6 mL) was added a solution of tetraethylammonium fluoride (0.640 g, 4.28 mmol) in CH_3CN (4 mL) and the mixture was heated to reflux for 2.5 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography (1:1 EtOAc/hexanes) to provide tert-butyl ethyl((3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-6,7-bis((4-methoxybenzyl)oxy)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate (0.335 g, 72.7%) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 6.93-6.86 (m, 4H), 6.08 (d, J = 6.88 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.52-4.51(m, 1H), 4.41- 4.38 (m, 2H), 4.33 (d, J = 11.6 Hz, 1H), 4.26 (t, J = 2.88 Hz, 1H), 3.93-3.87 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.69-3.66 (m, 1H), 3.61-3.50 (m, 1H), 1.55 (s, 9H), 1.15 (t, J = 6.9 Hz, 3H).

[00146] The above material (0.115g, 0.195 mmol) dissolved in 30% TFA/DCM at 0° C was stirred for 3h at room temperature. TFA/DCM was then evaporated completely and the resulting residue suspended in 2M NH_3/MeOH (3 mL). Methanolic ammonia solution was again concentrated and crude residue was purified by silica gel column chromatography using 10% MeOH in DCM to give (3aR,5S,6S,7R,7aR)-2-(ethylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a light yellowish solid (0.035g, 72.8%). ^{1}H NMR (400 MHz, CD_3OD) 6.49 (d, J = 6.48 Hz, 1H), 4.66-4.52 (dt, J = 47.6, 10.5, 4.3 Hz, 2H), 4.12 (t, J = 6.6 Hz, 1H), 3.90 (t, J = 6.9 Hz, 1H), 3.80- 3.73 (m, 2H), 3.55 (dd, J = 6.3, 3.2 Hz, 1H), 3.4-3.3 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 163.78, 89.63, 83.90 (d, $J_{C6,F}$ 171.7Hz, C-6), 76.83 (d, $J_{C5,F}$ 17.8Hz, C-5), 75.43, 69.51 (d, $J_{C4,F}$ 7.0Hz, C-4), 67.71, 42.13, 14.74. ES/MS: 251.0 [M +1].

Example 13

(3aR,5S,6S,7R,7aR)-2-(dimethylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00147] To a stirred solution of (3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (1.19 g, 3.3 mmol) in DMF (18 mL) at 0°C was added NaH (60%, 0.5g, 13 mmol) in small portions. After 20 min, BnBr (1.17 mL, 9.9 mmol) was added and the reaction mixture was then stirred at room temperature overnight. Reaction was diluted with DCM (100 mL) and DCM extract was washed with satd. $NaHCO_3$, brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:1), affording (3aR,5R,6S,7R,7aR)-6,7-bis(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-N,N-dimethyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-amine methanol as a gummy solid (0.805 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.16 (m, 10H), 6.19 (d, J = 6.7 Hz, 1H), 4.72 (d, J = 12 Hz, 1H), 4.60 (d, J = 12 Hz, 1H), 4.57 (d, J = 11.4 Hz, 1H), 4.37-4.32 (m, 2H), 4.06-4.00 (m, 1H), 3.69-3.62 (m, 2H), 3.60-3.52 (m, 2H), 2.89 (s, 6H), 0.80 (s, 9H), 0.04 (s, 6H).

[00148] To a solution of the above material (0.80 g, 1.48 mmol) in THF (6 mL) was added 1M TBAF solution (2.25 mL, 2.25 mmol) at 0°C and the mixture was then stirred at room temperature overnight. Diluted with EtOAc (50 mL), the organic layer was washed with satd. NH_4Cl, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified on silica gel by flash column chromatography (100% EtOAc), affording ((3aR,5R,6S,7R,7aR)-6,7-bis(benzyloxy)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methanol (0.57g, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.38-7.28 (m, 10H), 6.29 (d, J = 6.9 Hz, 1H), 4.79 (d, J = 12.1 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.55-4.53 (m, 1H), 4.43 (d, J = 11.5 Hz, 1H), 4.24 (m, 1H), 3.77 (d, J = 12.1 Hz, 1H), 3.69-3.59 (m, 3H), 3.00 (s, 6H).

[00149] Methanesulfonyl chloride (0.180 mL, 2.32 mmol) was added in portions to a stirred solution of the above material (0.673 g, 1.57 mmol) in dry pyridine (8 mL) at -20°C. After 3h, reaction mixture was diluted with DCM (20 mL) and DCM extract was washed with satd.

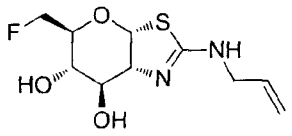
$NaHCO_3$ (30 mL), brine, dried over Na_2SO_4 and concentrated. Residual pyridine was removed by co-evaporation with hexanes. The crude product was purified by silica gel column chromatography, eluted with 100% EtOAc to give ((3aR,5R,6S,7R,7aR)-6,7-bis(benzyloxy)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl methanesulfonate (0.610 g, 76.4%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) 7.32-7.18 (m, 10H), 6.15 (d, J = 6.48 Hz, 1H), 4.68 (d, J = 12 Hz, 1H), 4.57 (d, J = 12 Hz, 1H), 4.53 (d, J = 11.5 Hz, 1H), 4.48-4.45 (dd, J = 3.8, 2.0 Hz, 1H), 4.29 (d, J = 11.4 Hz, 1H), 4.24-4.16 (m, 3H), 3.73-3.69 (m, 1H), 3.53-3.50 (dt, J = 8.9, 1.7 Hz, 1H), 2.91 (s, 6H), 2.90 (s, 3H).

[00150] To a solution of the above material (0.7 g, 1.38 mmol) in CH_3CN (15 mL) was added a solution of TBAF (1.13 g, 7.59 mmol) in CH_3CN (5 mL) and the mixture was heated to reflux for 2.5 h. After evaporation of the solvent, the residue was purified by silica gel column chromatography (7:3 EtOAc/hexanes) to provide (3aR,5S,6S,7R,7aR)-6,7-bis(benzyloxy)-5 -(fluoromethyl)-N,N-dimethyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-amine (0.567 g, 95%) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) 7.33-7.18 (m, 10H), 6.20 (d, J = 6.5 Hz, 1H), 4.72 (d, J = 12 Hz, 1H), 4.60 (d, J = 12.6 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.46-4.41 (m, 2H), 4.34-4.30 (m, 2H), 4.14 (t, J = 3 Hz, 1H), 3.74-3.64 (m, 1H), 3.59-3.55 (m, 1H), 2.91 (s, 6H).

[00151] To a solution of the above material (0.56 g, 1.3 mmol) in dry DCM (8 mL) at -78 ℃ was added a solution of BCl_3 (1.0 M in DCM, 6.5 mL, 6.5 mmol) dropwise. The mixture was stirred at -78 ℃ to 0 ℃ for 3 h. The reaction was then quenched by adding a solution of 1:1 DCM-MeOH (5 mL) at -78 ℃. The mixture was slowly warmed to room temperature. Solvents were evaporated under reduced pressure. 1.3M NH_3/MeOH solution (10 mL) was added to the residue and evaporated. This was repeated for one more time. The residue was purified by silica gel column chromatography, eluted with 90:10 DCM-1.3M NH_3-MeOH soln. to give (3aR,5S,6S,7R,7aR)-2-(dimethylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (0.25 g, 76.7%). ^{1}H NMR (400 MHz, CD_3OD) 6.31 (d, J = 6.44 Hz, 1H), 4.63-4.50 (dd, J = 44.4, 3.4 Hz, 2H), 4.09 (t, J = 6.0 Hz, 1H), 3.92 (t, J = 6.9 Hz, 1H), 3.79- 3.69 (m, 1H), 3.55-3.51 (dd, J = 5.4, 4.04 Hz, 1H), 3.01 (s, 6H). ^{13}C NMR (100 MHz, MeOD) δ 166.34, 92.58, 84.50 (d, $J_{C6,F}$ 171.2 Hz, C-6), 77.09, 76.56, 76.55, 75.72 (d, $J_{C5,F}$ 17.7 Hz, C-5), 70.73 (d, $J_{C4,F}$ 7.12 Hz, C-4), 40.97. ES/MS: 251.6 [M +1].

Example 14

(3aR,5S,6S,7R,7aR)-2-(allylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00152] A solution of (3aR,5R,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (1.7 g, 3.0 mmol) in DCM (40 mL) was treated with DAST (2.5 g, 15.4 mmol) for 30 min at -78°C. After stirred overnight at room temperature, the reaction was quenched with satd. aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by a silica gel column with 5%-10% EtOAc in petroleum ether to give (3aR,5S,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a white solid (580 mg, 32%). (ES, *m/z*): $[M+H]^+$ 571.0; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 7.5 Hz, 4H), 7.60 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.8 Hz, 4H), 6.27 (d, J = 6.3 Hz, 1H), 6.08 (s, 1H), 5.86-5.92 (m, 1H), 5.40 (d, J = 9.6 Hz, 1H), 5.12 (d, J = 9.3 Hz, 2H), 4.81-4.89 (dd, J = 10.0, 2.8 Hz, 1H), 4.63-4.69 (m, 2H), 4.50-4.54 (m, 2H), 3.82-3.98 (m, 1H), 1.63 (s, 9H).

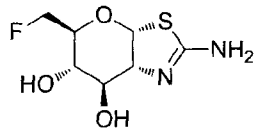
[00153] A solution of the above material (540 mg, 0.94 mmol) in MeOH (10 mL) was treated with K_2CO_3 (26 mg, 0.18 mmol) for 2 h at room temperature, then neutralized with AcOH. Volatiles were removed to give a residue, which was purified by a silica gel column, eluted with 5% MeOH in DCM to give tert-butyl allyl((3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate as a white solid (310 mg, 86%). (ES, *m/z*): $[M+H]^+$ 363.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (d, J = 6.9Hz, 1H), 5.85-5.96 (m, 1H), 5.11-5.18 (m, 2H), 4.61 (d, J = 2.4 Hz, 1H), 4.43-4.58 (m, 3H), 4.13-4.16 (m, 1H), 4.04-4.07 (m, 1H), 3.53-3.63 (m, 2H), 1.53 (s, 9H).

[00154] A solution of the above material (100 mg, 0.27 mmol) in MeOH (6 mL) was bubbled with dry HCl gas at room temperature until saturated. After additional 4 h, volatiles were removed to give a residue, which was re-dissolved into MeOH (5 mL) and neutralized with conc. NH_4OH, concentrated and purified by a silica gel column, eluted with 5%-10%

MeOH in DCM to give (3aR,5S,6S,7R,7aR)-2-(allylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as white solid (42.7 mg, 58%). (ES, *m/z*): $[M+H]^+$ 263.0; ^{1}H NMR (300 MHz, D_2O) δ 6.29 (d, *J* = 6.3 Hz, 1H), 5.85-5.96 (m, 1H), 5.19-5.26 (m, 1H), 5.09-5.14 (m, 1H), 4.63 (d, *J* = 3.3 Hz, 1H), 4.47 (d, *J* = 3.6 Hz, 1H), 4.07-4.11 (m, 1H), 3.95-3.99 (m, 1H), 3.86-3.89 (m, 2H), 3.68-3.79 (m, 1H), 3.51-3.56 (m, 1H).

Example 15

(3aR,5S,6S,7R,7aR)-2-amino-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



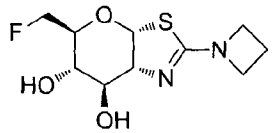
[00155] To a solution of (3aR,5S,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (500 mg, 0.88 mmol) in 1,4-dioxane (30 mL) was added $Pd(PPh_3)_4$ (200 mg, 0.17 mmol), HCO_2H (84 mg, 1.76 mmol) and Et_3N (177 mg, 1.76 mmol) at room temperature under N_2 atmosphere. After 20 min at 60°C, additional HCO_2H (404 mg, 8.8 mmol) was added into the reaction mixture. The reaction was stirred for additional 2 h at 60 °C, and then quenched by H_2O (40 mL), neutralized by $NaHCO_3$, extracted with DCM (3 x 50 mL). The combined organic layer was concentrated and purified by a silica gel column, eluted with 10% EtOAc in petroleum ether to give (3aR,5S,6S,7R,7aR)-2-(tert-butoxycarbonylamino)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as white syrup (330 mg, 71%). (ES, *m/z*): $[M+H]^+$ 531.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.2 Hz, 2H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.46-7.66 (m, 5H), 6.46 (d, *J* = 7.5 Hz, 1H), 5.85 (s, 1H), 5.53 (d, *J* = 6.6 Hz, 1H), 4.71-4.79 (m, 2H), 4.62 (t, *J* = 2.1 Hz, 1H), 3.95-4.03 (m, 1H), 1.57 (s, 9H).

[00156] A solution of the above material (330 mg, 0.62 mmol) in MeOH (10 mL) was treated with K_2CO_3 (24 mg, 0.17 mmol) for 2 h at room temperature, then neutralized by AcOH. Volatiles were removed to give a residue, which was purified by a silica gel column, eluted with 2%-5% MeOH in DCM to afford tert-butyl (3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-ylcarbamate as white solid (170 mg, 85%). (ES, *m/z*): $[M+H]^+$ 323.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.22 (d, *J* = 6.6 Hz, 1H), 4.67-4.79 (m, 1H), 4.57-4.66 (m, 2H), 3.84-3.96 (m, 2H), 3.70 (t, *J* = 8.4 Hz, 1H), 1.52 (s, 9H).

[00157] A solution of the above material (110 mg, 0.34 mmol) in MeOH (5 mL) was bubbled with dry HCl gas until saturated at room temperature. After additional 3 h, volatiles were removed to give a residue, which was neutralized with conc. NH_4OH and purified by a silica gel column, eluted with 10%-20% MeOH in DCM to give (3aR,5S,6S,7R,7aR)-2-amino-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as white solid (15 mg, 20%). (ES, *m/z*): $[M+H]^+$ 222.9; ^1H NMR (300 MHz, D_2O) δ 6.31 (d, J = 6.3 Hz, 1H), 4.63 (d, J = 3.3 Hz, 1H), 4.47 (d, J = 3.6 Hz, 1H), 4.07 (t, J = 5.7 Hz, 1H), 3.93 (t, J = 4.8 Hz, 1H), 3.66-3.80 (m, 2H), 3.51-3.58 (m, 1H).

Example 16

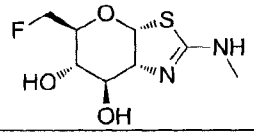
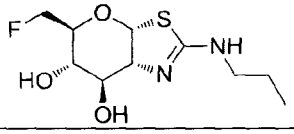
(3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00158] A solution of (3aR,5R,6S,7R,7aR)-2-(azetidin-1-yl)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (100 mg, 0.2 mmol) in DCM (10 mL) was treated with DAST (137 mg, 0.8 mmol) for 30 min at -78 °C. After stirring overnight at room temperature, the reaction was quenched with satd. aqueous $NaHCO_3$ (10 mL), extracted with DCM (3 x 10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product as a white syrup (80 mg), which was dissolved into MeOH (5 mL) and treated with K_2CO_3 (10 mg, 0.07 mmol) for 3 h at room temperature. The reaction mixture was neutralized by AcOH and concentrated. The residue was purified by a silica gel column, eluted with 5%-10% MeOH in DCM to give (3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as white solid (10 mg, 17%, two steps). (ES, *m/z*): $[M+H]^+$ 263.0; ^1H NMR (300 MHz, D_2O) δ 6.30 (d, J = 6.3 Hz, 1H), 4.49-4.69 (dd, J = 57, 3.3 Hz, 1H), 4.11-4.15 (m, 1H), 3.93-4.01 (m, 5H), 3.70-3.82 (m, 1H), 3.59-3.69 (m, 1H), 2.24-2.34 (m, 2H).

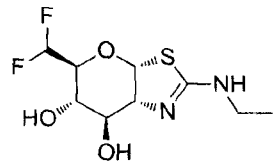
[00159] The following examples were synthesized according to procedures analogous to the schemes and examples outlined above.

Table 4

Example	Structure	Name
17		(3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol
^{1}H NMR (400 MHz, CD_3OD) 6.52 (d, J = 6.48 Hz, 1H), 4.66-4.52 (dt, J = 47.6, 10.4, 4.2 Hz, 2H), 4.15 (t, J = 6.5 Hz, 1H), 3.93 (t, J = 6.9 Hz, 1H), 3.87- 3.76 (m, 1H), 3.59-3.55 (dd, J = 6.4, 3.12 Hz, 1H), 2.99 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 169.32, 90.48, 84.10 (d, $J_{C6,F}$ 171.5 Hz, C-6), 76.45 (d, $J_{C5,F}$ 17.8 Hz, C-5), 69.86 (d, $J_{C4,F}$ 6.6 Hz, C-4), 55.67, 46.07, 32.11. (ES, *m/z*): $[M+H]^+$: 237.6.		
Example	Structure	Name
18		(3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol
^{1}H NMR (400 MHz, CD_3OD) 6.44 (d, J = 6.44 Hz, 1H), 4.67-4.49 (dt, J = 47.5, 10.4, 4.2 Hz, 2H), 4.11 (t, J = 6.4 Hz, 1H), 3.91 (t, J = 6.1 Hz, 1H), 3.82- 3.72 (m, 1H), 3.52-3.55 (dd, J = 6.0, 3.4 Hz, 1H), 3.27-3.21 (m, 2H), 1.66-1.57 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 167.82, 90.26, 84.10 (d, $J_{C6,F}$ 171.5 Hz, C-6), 76.34 (d, $J_{C5,F}$ 17.7 Hz, C-5), 75.80, 75.79, 70.05 (d, $J_{C4,F}$ 6.9 Hz, C-4), 55.67, 23.98, 12.38. (ES, *m/z*): $[M+H]^+$: 265.4.		

Example 19

(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00160] To a solution of tert-butyl ((3aR,5R,6S,7R,7aR)-6,7-dihydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate (5.01g, 14.4 mmol) in DMF (25 mL) was added imidazole (1.57g, 23.1 mmol) and TBDMSCl (2.82g, 21.7 mmol). The reaction mixture stirred at room temperature for 30h was diluted with EtOAc (100 mL). Organics were washed with satd. NH_4Cl, brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:1), affording tert-butyl ((3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate as a white solid (5.08 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (d,

J = 6.7 Hz, 1H), 4.25 (t, J = 6.2 Hz, 1H), 4.16 (t, J = 6.4 Hz, 1H), 4.10-4.04 (m, 2H), 3.91-3.85 (m, 3H), 3.65-3.62 (m, 1H), 1.55 (s, 9H), 1.26 (t, J = 7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H).

[00161] To a solution of the above material (1.0 g, 2.2 mmol) in pyridine (20 mL), at 0°C was added DMAP (0.024 g, 0.20 mmol) followed by BzCl (2.0 mL, 17.6 mmol) slowly. The mixture was warmed to room temperature and stirred overnight. The reaction was diluted with EtOAc (50 mL), washed with satd. $NaHCO_3$ solution and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual pyridine was co-evaporated with hexanes and the crude residue was separated on silica gel by flash column chromatography (EtOAc/hexanes, 1:5) to give (3aR,5R,6S,7R,7aR)-2-((tert-butoxycarbonyl)(ethyl)amino)-5-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (1.05 g, 71.3%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m , 2H), 7.99 (m, 2H), 7.61-7.52 (m, 2H), 7.47-7.38 (m, 4H), 6.12 (d, J = 5.6 Hz, 1H), 5.89 (dd, J = 1.5, 1.4 Hz, 1H), 5.39 (m, 1H), 4.46 (ddd, J = 5.5, 2.9, 0.96 Hz, 1H), 3.96 (m, 2H), 3.80 (m, 1H), 3.75-3.70 (m, 2H), 1.54 (s, 9H), 1.18 (t, J = 5.5 Hz, 3H), 0.83 (s, 9H), 0.01 (s, 3H), 0.03 (s, 3H).

[00162] To a solution of the above material (3.2 g, 4.8 mmol) in dry MeOH (30 mL) was added AcCl (0.07 mL, 1.0 mmol) at 0°C. The reaction mixture was stirred at this temperature for 30 min and then at room temperature overnight. The reaction mixture was diluted with DCM (30 mL) and neutralized with 10% aq. $NaHCO_3$ solution. DCM layer was further washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was residue was purified by silica gel column chromatography (EtOAc/hexanes, 3:7) to provide (3aR,5R,6S,7R,7aR)-2-((tert-butoxycarbonyl)(ethyl)amino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (2.4 g, 90%) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m , 2H), 8.01 (m, 2H), 7.58-7.53 (m, 2H), 7.47-7.39 (m, 4H), 6.14 (d, J = 7.0 Hz, 1H), 5.93 (dd, J = 1.9, 1.8 Hz, 1H), 5.34 (m, 1H), 4.49 (ddd, J = 6.8, 3.6, 0.96 Hz, 1H), 4.03-3.92 (m, 2H), 3.80-3.65 (m, 3H), 1.53 (s, 9H), 1.19 (t, J = 6.9 Hz, 3H).

[00163] To a solution of the above material (1.0 g, 1.8 mmol) in dry DCM (25 mL) at 0° C was added dry pyridine (0.30 mL, 3.7 mmol), followed by DMP (1.14 g, 2.69 mmol). The reaction was stirred at 0° C for 10 min and at room temperature for next 1.5 h. The reaction mixture was diluted with 1M $Na_2S_2O_3$ / satd. $NaHCO_3$ (30 mL, 1:1) and stirred for 10 min. DCM layer was separated, dried over anhydrous Na_2SO_4 and concentrated to yield crude

foamy solid (3aR,5S,6S,7R,7aR)-2-((tert-butoxycarbonyl)(ethyl)amino)-5-formyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (1.0 g crude). The product was carried forward for the next reaction without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.04 (m , 4H), 7.58 (m, 2H), 7.47-7.39 (m, 4H), 6.14 (d, J = 6.24 Hz, 1H), 6.01 (dd, J = 1.8, 1.3 Hz, 1H), 5.53-5.51 (m, 1H), 4.38 (ddd, J = 6.2, 3.2, 1.2 Hz, 1H), 4.27 (d, J = 7.3 Hz, 1H), 4.0-3.9 (m, 2H), 1.53 (s, 9H), 1.15 (t, J = 6.8 Hz, 3H).

[00164] The above material (1.0 g, crude) was taken in DCM (30 mL) and cooled to -78° C. DAST (1 mL, 7.7 mmol) was added dropwise while stirring at -78°C. After the addition, cooling bath was removed and reaction mixture stirred at room temperature overnight. The reaction was diluted with satd. $NaHCO_3$ solution (15 mL). DCM layer was separated, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:4) to provide (3aR,5S,6S,7R,7aR)-2-((tert-butoxycarbonyl)(ethyl)amino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (0.413 g, 40%) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m , 2H), 8.0 (m, 2H), 7.60-7.53 (m, 2H), 7.46-7.39 (m, 4H), 6.13 (d, J = 7.0 Hz, 1H), 5.94 (m, 1H), 5.93 (td, J = 54.08, 2.9 Hz, 1H), 5.59-5.56 (m, 1H), 4.55-4.52 (ddd, J = 7.0, 3.4, 1.3 Hz, 1H), 3.98-3.86 (m, 3H), 1.55 (s, 9H), 1.17 (t, J = 6.9 Hz, 3H).

[00165] To a stirred solution of the above material (0.41 g, 0.71 mmol) in dry MeOH (20 mL) was added K_2CO_3 (0.050 g, 0.36 mmol) at 0°C. The reaction mixture was warmed to room temperature and stirred 1.5 h. AcOH (0.5 mL) was added to the reaction mixture and contents were concentrated. The crude residue was was purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to provide tert-butyl ((3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate (0.24 g, 91.6%) as a foamy solid. ^{1}H NMR (400 MHz, MeOD) δ 6.03 (d, J = 6.6 Hz, 1H), 5.93 (td, J = 54.5, 2.6 Hz, 1H), 4.19 (m, 1H), 4.11 (t, J = 4.3 Hz, 1H), 3.96-3.87 (m, 2H), 3.82 (dd, J = 4.7, 4.4 Hz, 1H), 3.56-3.47 (m, 1H), 1.53 (s, 9H), 1.16 (t, J = 6.9 Hz, 3H).

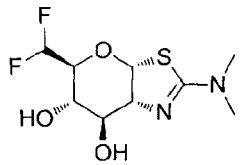
[00166] The above material (0.24 g, 0.65 mmol) was taken in 30% TFA/DCM (10 mL) at 0°C and stirred at this temperature for 1 h and slowly warming to room temperature for next 1 h. The reaction mixture was evaporated to dryness. The residue was neutralized with 2M NH_3/MeOH (5 mL) solution and purified by silica gel column chromatography (DCM/MeOH, 95:5) to provide (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (0.166 g, 95.2%). ^{1}H

NMR (400 MHz, MeOD) δ 6.41 (d, J = 6.4 Hz, 1H), 6.00 (td, J = 54.4, 1.9 Hz, 1H), 4.22 (t, J = 5.9 Hz, 1H), 4.01 (t, J = 4.6 Hz, 1H), 3.76-3.70 (m, 2H), 3.37-3.33 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H).). ^{13}C NMR (100 MHz, MeOD) δ 167.35, 116.25 (t, $J_{C6,F}$ 242.0 Hz, C-6), 89.10, 75.42 (t, J = 21.0 Hz), 74.74, 71.24, 69.96 (t, J = 4.0 Hz, C-4), 41.61, 15.09. ES/MS: 269.1 [M +1].

[00167] A sample of the above material (13.0 g, 48.5 mmol, 97% pure by LCMS with UV detection at 220 nm) was dissolved into boiling EtOAc (70 mL) then hexane (about 20 mL) was added dropwise until some solids appeared. The resulting solution was allowed to cool to room temperature. Solids were collected to give (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (10.6 g, 98.3% pure by LCMS with UV detection at 220 nm). This material exhibited spectral characteristics identical to those described above for this compound.

Example 20

(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00168] To a solution of (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (0.944 g, 3.8 mmol) in DMF (5 mL) was added imidazole (0.8 g, 12 mmol) and TBDMSCl (0.75 g, 4.97 mmol). The reaction mixture was stirred at room temperature for 18 h and concentrated using high vacuum. The crude residue was purified on silica gel by flash column chromatography (DCM/MeOH, 95:5), affording (3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (0.76 g, 55.2%). ^{1}H NMR (400 MHz, MeOD) δ 6.31 (d, J = 6.4 Hz, 1H), 4.06 (t, J = 6.1 Hz, 1H), 3.92-3.88 (m, 2H), 3.81-3.76 (dd, J = 11.4, 5.7 Hz, 1H), 3.62-3.58 (m, 1H), 3.52-3.48 (dd, J = 9.3, 5.5 Hz, 1H), 3.02 (s, 6H), 0.93 (s, 9H), 0.10 (s, 6H).

[00169] To a solution of the above material (0.84 g, 2.31 mmol) in pyridine (10 mL), at 0°C was added DMAP (0.028 g, 0.23 mmol) followed by BzCl (1.6 mL, 13.8 mmol) slowly. The mixture was warmed to room temperature and stirred overnight. The reaction was diluted

with EtOAc (50 mL), washed with satd. $NaHCO_3$ solution and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residual pyridine was co-evaporated with hexanes and the crude residue was separated on silica gel by flash column chromatography (EtOAc/hexanes, 2:3) to give (3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (0.9 g, 68.4%) as a foamy white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.01 (m , 4H), 7.53-7.47 (m, 2H), 7.40-7.32 (m, 4H), 6.36 (d, J = 5.2 Hz, 1H), 5.81 (t, J = 2.4 Hz, 1H), 5.35-5.33 (dd, J = 7.1, 0.9 Hz, 1H), 4.59 (t, J = 4.2 Hz, 1H), 3.92-3.89 (m, 1H), 3.80-3.73 (m, 2H), 3.05 (s, 6H), 0.83 (s, 9H), 0.01 (s, 6H).

[00170] To a solution of the above material (0.88 g, 1.54 mmol) in dry MeOH (6 mL) was added AcCl (0.054 mL, 0.77 mmol) at 0°C. The reaction mixture was stirred at this temperature for 30 min and then at room temperature overnight. The reaction mixture was diluted with DCM (30 mL) and neutralized with 10% aq. $NaHCO_3$ solution. DCM layer was further washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude residue was residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:1) to provide (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano-[3,2-d]thiazole-6,7-diyl dibenzoate (0.57 g, 81%) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m , 4H), 7.55-7.49 (m, 2H), 7.41-7.37 (m, 4H), 6.36 (d, J = 6.5 Hz, 1H), 5.84-5.83 (dd, J = 4.3, 3.0 Hz, 1H), 5.32-5.28 (m, 1H), 4.57 (t, J = 5.2 Hz, 1H), 3.92-3.88 (m, 1H), 3.78-3.75 (dd, J = 12.4, 2.5 Hz, 1H), 3.70-3.65 (dd, J = 12.4, 5.4 Hz, 1H), 3.03 (s, 6H).

[00171] To a solution of the above material (0.57 g, 1.25 mmol) in dry DCM (10 mL) at 0° C was added DMP (0.8 g, 1.88 mmol). The reaction was stirred at 0° C for 10 min and at room temperature for next 1.5 h when the starting material was completely consumed. The reaction mixture was diluted 1:1 1M $Na_2S_2O_3$: Satd. $NaHCO_3$ (30 mL) and stirred for 10 min. DCM layer was separated, dried over anhydrous Na_2SO_4 and concentrated to yield crude foamy solid containing (3aR,5S,6S,7R,7aR)-2-(dimethylamino)-5-formyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (0.56 g crude). The crude product was carried forward for the next reaction without any further purification.

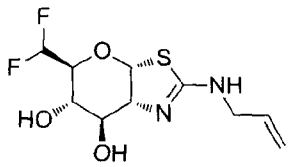
[00172] The above material (0.56 g, crude) was taken in DCM (10 mL) and cooled to -78° C. DAST (0.72 mL, 5.5 mmol) was added dropwise while stirring at -78° C. After the addition, cooling bath was removed and reaction mixture stirred at room temperature overnight. The reaction was diluted with satd. $NaHCO_3$ solution (15 mL). DCM layer was separated, dried

over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by silica gel column chromatography (EtOAc/hexanes, 1:4) to provide (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (0.330 g, 55.2% over 2 steps) as a foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.01 (m , 4H), 7.57-7.53 (m, 2H), 7.44-7.39 (m, 4H), 6.38 (d, J = 5.3 Hz, 1H), 5.99-5.77 (m, 1H), 5.85 (m, 1H), 5.54 (d, J = 6.8 Hz, 1H), 4.66-4.64 (m, 1H), 4.06-4.01 (m, 1H), 3.06 (s, 6H).

[00173] To a stirred solution of the above material (0.33 g, 0.69 mmol) in dry MeOH (8 mL) was added K_2CO_3 (0.073 g, 0.53 mmol) at 0°C. The reaction mixture was warmed to room temperature and stirred 1.5 h. AcOH (0.5 mL) was added to the reaction mixture and contents were concentrated. The AcOH salt thus obtained was treated with 2M NH_3/MeOH solution (8 mL) and again concentrated. The residue was was purified by silica gel column chromatography (DCM/MeOH, 9:1) to provide (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a foamy solid (0.1 g, 54%). ^{1}H NMR (400 MHz, MeOD) δ 6.31 (d, J = 6.4 Hz, 1H), 5.98 (td, J = 54.1, 2.0 Hz, 1H), 4.20 (t, J = 5.6 Hz, 1H), 4.04 (t, J = 4.7 Hz, 1H), 3.78-3.66 (m, 2H), 3.03 (s, 6H). ^{13}C NMR (100 MHz, MeOD) δ 166.20, 116.56 (t, $J_{C6,F}$ 241.2 Hz, C-6), 91.41, 77.21, 75.57, 75.04 (t, J = 21.0 Hz), 70.68 (t, J = 3.3 Hz, C-4), 41.17. ES/MS: 269.1 [M +1].

Example 21

(3aR,5S,6S,7R,7aR)-2-(allylamino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00174] A mixture of prop-2-en-1-amine (9.2 g, 0.16 mol) and (2S,3R,4R,5S,6R)-6-(acetoxymethyl)-3-isothiocyanatotetrahydro-2H-pyran-2,4,5-triyl triacetate (60 g, 0.154 mol) in DCM (300 mL) was stirred for 1 h at room temperature, followed by addition of TFA (88 g, 0.77 mol). The resulting solution was stirred overnight at room temperature, and was quenched with aqueous $NaHCO_3$ to pH at 8, and extracted with DCM (3 x 300 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and condensed to give a residue, which was purified by a silica gel column with 1%~2% MeOH in DCM to give

(3aR,5R,6S,7R,7aR)-5-(acetoxymethyl)-2-(allylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl diacetate as a yellow liquid (58 g, 84%). (ES, *m/z*): $[M+H]^+$ 387.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.33 (d, J = 6.6 Hz, 1H), 5.84-5.96 (m, 1H), 5.32-5.44 (m, 4H), 4.98-5.04 (m, 1H), 4.37 (t, J = 5.7 Hz, 1H), 4.28-4.22 (m, 2H), 3.92-3.95 (m, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H).

[00175] A solution of the above material (50 g, 0.13 mol) in MeOH (300 mL) was treated with K_2CO_3 (3.6 g, 0.26 mol) overnight at room temperature, and followed by addition of Boc_2O (56 g, 0.26 mol) and Et_3N (19.6 g, 0.19 mol). After additional 2 h, the resulting solution was concentrated to give a residue, which was purified by a silica gel column, eluted with 5% MeOH in DCM to give tert-butyl allyl((3aR,5R,6S,7R,7aR)-6,7-dihydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate as an oil (42 g, 90% in two steps). (ES, *m/z*): $[M+H]^+$ 361.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, J = 6.9 Hz, 1H), 5.84-5.96 (m, 1H), 5.22-5.44 (m, 4H), 4.37-4.38 (m, 1H), 4.22-4.28 (m, 2H), 3.92-3.95 (m, 3H), 1.54 (s, 9H).

[00176] A mixture of TBDMSCl (26 g, 0.17 mmol), DMAP (1.4 g, 0.01 mol), Et_3N (23.5 g, 0.23 mmol) and the above material (42 g, 0.12 mol) in DCM (300 mL) was stirred overnight at 40 °C. The reaction mixture was quenched by satd. aqueous $NaHCO_3$ (20 mL), and was condensed to give a residue, which was purified by a silica gel column, eluted with 1%~2% MeOH in DCM to give tert-butyl allyl((3aR,5R,6S,7R,7aR)-5-((tert-butyldimethylsilyloxy)methyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)carbamate as a light yellow syrup (48 g, 87%). (ES, *m/z*): $[M+H]^+$ 474.9; ^1H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J = 6.6 Hz, 1H), 5.84-5.93 (m, 1H), 5.22-5.32 (m, 4H), 4.65-4.67 (m, 1H), 4.26-4.31 (m, 1H), 4.20-4.22 (m, 1H), 3.84-3.88 (m, 3H), 1.54 (s, 9H), 0.93 (s, 9H), 0.09 (s, 6H).

[00177] A mixture of BzCl (11.1 g, 79 mmol), DMAP (322 mg, 2.63 mmol), pyridine (20.8 g, 263 mmol) and the above material (12.5 g, 26.3 mmol) in DCM (150 mL) at 0 °C was stirred overnight at room temperature. The reaction mixture was quenched with satd. aqueous $NaHCO_3$ (200 mL), extracted with DCM (3 x 100 mL), washed with brine (3 x 50 mL), dried over anhydrous $MgSO_4$, and condensed to give a residue, which was purified by a silica gel column with 10% EtOAc in petroleum ether to afford (3aR,5R,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-((tert-butyl-dimethylsilyloxy)methyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a white solid (16.5 g, 78%). (ES, *m/z*): $[M+H]^+$ 683.1; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05-8.10 (m, 4H), 7.56-7.61 (m, 2H), 7.42-7.47 (m,

4H), 6.27 (d, J = 7.2 Hz, 1H), 5.99-6.02 (m, 2H), 5.86-5.92 (m, 1H), 5.43-5.46 (m, 1H), 5.10-5.18 (m, 2H), 4.81-4.89 (m, 1H), 4.56-4.62 (m, 2H), 3.76-3.87 (m, 3H), 1.56 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H).

[00178] A solution of the above material (7.0 g, 10.3 mmol) in MeOH (50 mL) was treated with AcCl (0.5 mL, 0.07 mmol) for 3 h at room temperature. The reaction mixture was quench with satd. aqueous $NaHCO_3$ (10 mL) and water (200 mL), extracted with DCM (3 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give a residue, which was purified by a silica gel column with 10% EtOAc in petroleum ether to give (3aR,5R,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a white syrup (1.7 g, 29%). (ES, *m/z*): $[M+H]^+$ 569.0; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06-8.09 (m, 4H), 7.60-7.63 (m, 2H), 7.43-7.58 (m, 4H), 6.26 (d, J = 6.9 Hz, 1H), 6.06-6.27 (m, 2H), 5.37-5.41 (d, J = 8.4 Hz, 1H), 5.11-5.28 (m, 2H), 4.82-4.84 (m, 1H), 4.56-4.62 (m, 2H), 3.71-3.86 (m, 3H), 1.56 (s, 9H).

[00179] A solution of the above material (1.5 g, 2.6 mmol) in DCM (30 mL) was treated with DMP (1.7 g, 4.0 mmol) for 2 h at room temperature. The resulting solution was quenched with satd. aqueous $NaHCO_3$ (10 mL) and satd. aqueous $Na_2S_2O_3$ (10 mL), extracted with DCM (3 x 50 mL), dried over Na_2SO_4, and concentrated under vacuum to give a residue, which was purified by a short silica gel column with 30% EtOAc in petroleum to afford the crude aldehyde (1.3 g), which was dissolved into DCM (20 mL) and treated with DAST (1.5 g, 9.3 mmol) at -78 °C. After stirred overnight at room temperature, the resulting solution was quenched with satd. aqueous $NaHCO_3$ (50 mL), extracted with DCM (3 x 50 mL), dried over Na_2SO_4, and concentrated under vacuum to give a residue, which was purified by a silica gel column with 10% EtOAc in petroleum to give (3aR,5S,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a white solid (650 mg, 43%). (ES, *m/z*): $[M+H]^+$ 589.0; ^1H NMR (300 MHz, $CDCl_3$), δ 8.03-8.13 (m, 4H), 7.56-7.61 (m, 2H), 7.48-7.51 (m, 4H), 6.11-6.14 (d, J = 8.7 Hz, 1H), 5.95-6.09 (td, J = 54.3 Hz, 2.8 Hz, 1H), 5.19-5.25 (m, 2H), 4.44-4.45 (m, 2H), 4.31-4.36 (m, 2H), 4.10-4.18 (m, 2H), 1.53 (s, 9H).

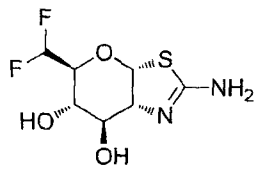
[00180] A solution of the above material (200 mg, 0.34 mmol) in MeOH (15 mL) was treated with K_2CO_3 (10 mg, 0.07 mmol) for 3 h at room temperature. The reaction mixture was neutralized by acetate acid, and was condensed to give a residue, which was purified by a silica gel column, eluted with 1%~2% MeOH in DCM to give tert-butyl allyl((3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-

pyrano[3,2-d]thiazol-2-yl)carbamate as a yellow oil (150 mg, 76%). (ES, *m/z*): $[M+H]^+$ 381.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (d, J = 8.7 Hz, 1H), 5.95-6.09 (m, 1H), 5.19-5.25 (m, 2H), 4.44-4.45 (m, 2H), 4.31-4.36 (m, 2H), 4.10-4.18 (m, 2H), 1.53 (s, 9H).

[00181] A solution of the above material (150 mg, 0.39 mmol) in DCM (18 mL) was treated with TFA (1.8 mL) overnight at room temperature. The reaction mixture was condensed to give a residue, which was neutralized by NH_4OH (0.5 mL, 25%~28%, w/v) for purification by Prep-HPLC under the following conditions [(Agilent 1200 prep HPLC; Column: Sun Fire Prep C18, 19*50mm 5um; mobile phase: Water with 0.03% NH_4OH and CH_3CN (10% CH_3CN up to 45% in 10 min; Detector: UV 220 nm) to give (3aR,5S,6S,7R,7aR)-2-(allylamino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (16.6 mg, 15%). $[M+H]^+$ 281.0; ^1H NMR (300 MHz, D_2O) δ 6.20 (d, J = 6.3 Hz, 1H), 6.14-6.16 (m, 1H), 5.74-5.78 (t, J = 2.7 Hz, 1H), 5.04-5.10 (m, 2H), 4.20-4.24 (t, J = 6.0 Hz, 1H), 4.04-4.07 (t, J = 4.2 Hz, 1H), 3.66-3.86 (m, 4H).

Example 22

3aR,5S,6S,7R,7aR)-2-amino-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00182] To a solution of (3aR,5S,6S,7R,7aR)-2-(allyl(tert-butoxycarbonyl)amino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (900 mg, 1.53 mmol) in 1,4-dioxane (30 mL) was added $Pd(PPh_3)_4$ (347 mg, 0.30 mmol), HCO_2H (384 mg, 8.35 mmol) and Et_3N (846 mg, 8.38 mmol) under N_2 atmosphere at 10 °C. After 20 min at 60 °C, additional HCO_2H (1.4 g, 30.3 mmol) was added. After stirred overnight at 60 °C, the reaction mixture was quenched with satd. aqueous $NaHCO_3$, extracted with DCM (3 x 30 mL), dried by anhydrous $MgSO_4$, and concentrated under reduced pressure to afford a residue, which was purified by a silica gel column, eluted with 10% EtOAc in hexane to give (3aR,5S,6S,7R,7aR)-2-(tert-butoxycarbonylamino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a white syrup (600 mg, 72%). (ES, *m/z*): $[M+H]^+$ 549.0; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07-8.14 (m, 4H), 7.60-7.65 (m, 2H), 7.51-

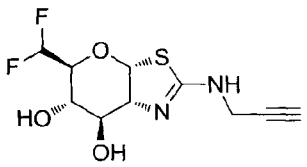
7.59 (m, 4H), 6.34 (d, J = 8.7 Hz, 1H), 5.82-6.20 (td, J = 54.0 Hz, 2.7 Hz, 1H), 5.83-5.85 (m, 1H), 5.61-5.64 (m, 1H), 4.59-4.63 (m, 1H), 4.05-4.18 (m, 1H), 1.53 (s, 9H).

[00183] A solution of the above material (600 mg, 1.1 mmol) in MeOH (50 mL) was treated with K_2CO_3 (45 mg, 0.33 mmol) for 3 h at room temperature. The reaction mixture was neutralized by addition of AcOH, and was condensed to give a residue, which was purified by a silica gel column eluted with 1% ~ 5% MeOH in DCM to give tert-butyl (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-ylcarbamate as a solid (300 mg, 81%). (ES, *m/z*): $[M+H]^+$ 341.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (d, J = 6.6 Hz, 1H), 5.85-6.21 (td, J = 51.6 Hz, 2.7 Hz, 1H), 3.84-4.16 (m, 4H), 1.56 (s, 9H).

[00184] A solution of the above material (135 mg, 0.4 mmol) in DCM (10 mL) was treated with TFA (1mL) overnight at room temperature. Removal of solvents gave a residue, which was dissolved into MeOH (5 mL) and neutralized by conc. NH_4OH (0.5 mL, 25% ~ 28%, w/v). Concentration and purification by Prep-HPLC under the following conditions [(Agilent 1200): Column, X-Bridge C18; mobile phase, 50mmol/L NH_4HCO_3 in water with 0.05% NH_4OH and CH_3CN (CH_3CN 5% up to 20% in 10min); Detector, 220nm UV] afforded (3aR,5S,6S,7R,7aR)-2-amino-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (26.7 mg, 27%). (ES, *m/z*): $[M+H]^+$ 240.9; ^1H NMR (CD_3OD, 300 MHz) δ 6.28 (d, J = 6.3 Hz, 1H), 5.50-6.14 (td, J = 54.3 Hz, 2.1 Hz, 1H), 4.16-4.20 (m, 1H), 4.02-4.05 (t, J = 4.5 Hz, 1H), 3.74-3.80 (m, 1H), 3.63-3.71 (m, 1H).

Example 23

(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(prop-2-ynylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00186] A solution of (3aR,5S,6S,7R,7aR)-2-(tert-butoxycarbonylamino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate (800 mg, 1.46 mmol) and 3-bromoprop-1-yne (538 mg, 4.56 mmol) in DMF (15 mL) was treated with K_2CO_3 (125 mg, 0.91 mmol) overnight at room temperature. The reaction mixture was quenched with satd. aqueous NH_4Cl (30 mL), extracted with DCM (3 x 10 mL), washed with

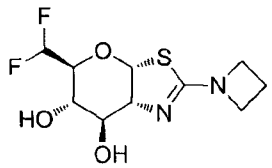
brine (3 x 10 mL), dried over anhydrous $MgSO_4$, and condensed to give a residue, which was purified by a silica gel column with 10% EtOAc in petroleum ether to give a mixture containing (3aR,5S,6S,7R,7aR)-2-(tert-butoxycarbonyl(prop-2-ynyl)amino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a light yellow solid (210 mg), which was used in the next step without further purification. (ES, *m/z*): $[M+H]^+$ 587.0.

[00187] A solution of above mixture (210 mg, 0.36 mmol) in MeOH (10 mL) was treated with K_2CO_3 (14.8 mg, 0.11 mmol) for 2 h at 25 °C, and followed by neutralization with AcOH. Removal of volatiles afforded a residue, which was purified by a silica gel column with 20% EtOAc in petroleum ether to give a mixture containing tert-butyl (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl(prop-2-ynyl)carbamate (125 mg). (ES, *m/z*): $[M+H]^+$ 379.0.

[00188] A solution of above mixture (50 mg, 0.1 mmol) in THF (10 mL) was treated with MeMgCl (0.3 mL, 1 mmol, 3 M in THF) overnight at 10 °C. The reaction was quenched with satd. aqueous $N_{H4}Cl$ (1 mL), and was condensed to give a residue, which was dissolved into 10% MeOH in DCM, and filtered through a short silica gel column. Concentration and purification by Prep-HPLC under the following conditions [(Agilent 1200 prep HPLC): Column, Sun Fire Prep C18*50mm 5um; mobile phase, H_2O with CH_3CN (40%CH_3CN up to 60% in 5 min); Detector, UV, 220nm] afforded (3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(prop-2-ynylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (22 mg, faster moving isomer by HPLC). (ES, *m/z*): $[M+H]^+$ 279.0; ^1H NMR (300 MHz, DMSO) δ 7.37 (broad, 1H), 6.21 (d, J = 6.3 Hz, 1H), 5.76-6.28 (td, J = 53.7 Hz, 2.1 Hz, 1H), 5.27(d, J = 4.5 Hz, 1H), 4.96-4.98(d, J = 6.3 Hz,1H), 4.05-4.09 (m, 1H), 3.85-3.99 (m, 3H), 3.51-3.60 (m, 2H), 3.13 (s, 1H).

Example 24

(3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00190] A mixture of Et_3N (18.7 g, 185 mmol), azetidine hydrochloride (12 g, 129 mmol) and (2S,3R,4R,5S,6R)-6-(acetoxymethyl)-3-isothiocyanatotetrahydro-2H-pyran-2,4,5-triyl

triacetate (48 g, 123 mmol) in DCM (500 mL) was stirred for 2 h at room temperature, and followed by addition of TFA (56 g, 493 mmol). The resulting solution was stirred overnight at room temperature, neutralized by $NaHCO_3$, extracted with DCM (3 x 100 mL), dried over anhydrous Na_2SO_4, and condensed to give a residue, which was purified by a silica gel column, eluted with 30% EtOAc in petroleum to give (3aR,5R,6S,7R,7aR)-5-(acetoxymethyl)-2-(azetidin-1-yl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl diacetate as a light yellow syrup (36 g, 75%). (ES, *m/z*): $[M+H]^+$: 386.9; ^1H NMR (300 MHz, $CDCl_3$) δ 6.29 (d, J = 6.6 Hz, 1H), 5.44-5.47 (m, 1H), 4.95-4.99 (m, 1H), 4.36 (t, J = 5.4 Hz, 1H), 4.05-4.18 (m, 6H), 3.86-3.92 (m, 1H), 2.34-2.44 (m, 2H), 2.07-2.14 (m, 9H).

[00191] A solution of the above material (36 g, 93 mmol) in MeOH (200 mL) was treated with K_2CO_3 (5.14 g, 37 mmol) for 4 h at room temperature. The resulted solution was filtered through a short silica gel column to afford (3aR,5R,6S,7R,7aR)-2-(azetidin-1-yl)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as light yellow syrup (21 g, 87%). (ES, *m/z*): $[M+H]^+$: 261.0; ^1H NMR (300 MHz, DMSO) δ 6.27 (d, J = 6.3 Hz, 1H), 3.94 (t, J = 6.3 Hz, 1H), 3.85 (t, J = 7.5 Hz, 4H), 3.70 (t, J = 4.8 Hz, 1H), 3.55-3.59 (m, 1H), 3.33-3.42 (m, 3H), 2.21-2.51 (m, 2H).

[00192] To a solution of the above material (34 g, 131 mmol), Et_3N (20.2 g, 0.2 mol) and DMAP (0.5 g, 4 mmol) in DCM (200 mL) was added TBDMSCl (21.6 g, 143 mmol). After stirred overnight at 15 °C, the reaction mixture was quenched by addition of satd. aqueous $NaHCO_3$ (200 mL), extracted with DCM (3 x 100 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to give a residue, which was purified on a silica gel column with 2% MeOH in DCM to afford (3aR,5R,6S,7R,7aR)-2-(azetidin-1-yl)-5-((tert-butyldimethylsilyloxy)methyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a solid (32 g, 65%). (ES, *m/z*): $[M+H]^+$: 375.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.38 (d, J = 6.3 Hz, 1H), 4.24 (t, J = 6.3 Hz, 1H), 4.04-4.09 (m, 5H), 3.85 (d, J =3.6 Hz, 2H), 3.70-3.78 (m, 1H), 3.66-3.69 (m, 1H), 2.33-2.43 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

[00193] A solution of the above material (3.0 g, 8.0 mmol) in DMF (40 mL) was treated with NaH (1.5 g, 37.50 mmol) at room temperature for 30 min, and followed by addition of BzCl (3.36 g, 24 mmol). The resulting solution was stirred overnight at 15 °C, quenched with water/ice (100 mL), extracted with DCM (3 x 50 mL), washed with brine (3 x 20 mL), dried over anhydrous Na_2SO_4, and condensed to give a residue, which was purified by a silica gel column with 10% EtOAc in petroleum ether to afford (3aR,5R,6S,7R,7aR)-2-(azetidin-1-yl)-5-((tert-butyldimethylsilyloxy)methyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-

diyl dibenzoate as light yellow oil (1.38 g, 30%). (ES, *m/z*): $[M+H]^+$: 583.0; ^1H NMR (300 MHz, $CDCl_3$)δ 8.05-8.09 (m, 4H), 7.54-7.59 (m, 2H), 7.28-7.39 (m, 4H), 6.43 (d, J = 6.3 Hz, 1H), 5.84-5.96 (m, 1H), 5.37 (dd, J = 2.1, 1.5 Hz, 1H), 4.59-4.61 (m, 1H), 4.04-4.09 (m, 5H), 3.78-3.93 (m, 2H), 2.38-2.43 (m, 2H), 0.91 (s, 9H), 0.09 (s, 6H).

[00194] A solution of the above material (1.3 g, 2.2 mmol) in MeOH (10 mL) was treated with AcCl (1 mL, 0.45 mmol) overnight at 15 °C. The reaction was quenched with satd. aqueous $NaHCO_3$ (20 mL), extracted with DCM (3 x 40 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to give a residue, which was purified by a silica gel column, eluted with 20% EtOAc in petroleum ether to afford (3aR,5R,6S,7R,7aR)-2-(azetidin-1-yl)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as a solid (0.42 g, 40%). (ES, *m/z*): $[M+H]^+$: 469.0; ^1H NMR (300 MHz, $CDCl_3$)δ 8.04-8.11 (m, 4H), 7.55-7.62 (m, 2H), 7.42-7.48 (m, 4H), 6.48 (d, J = 6.6 Hz, 1H), 5.92 (t, J = 3.6 Hz, 1H), 5.35 (dd, J = 8.0, 3.6 Hz, 1H), 4.63 (t, J = 5.4 Hz, 1H), 4.11-4.18 (m, 4H), 3.92-3.96 (m, 1H), 3.80-3.84 (m, 1H), 3.69-3.68 (m, 1H), 2.38-2.48 (m, 2H).

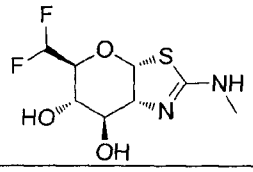
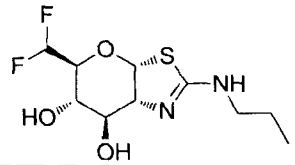
[00195] A solution of the above material (400 mg, 0.85 mmol) in DCM (20 mL) was treated with DMP (600 mg, 1.41 mmol) at 0 °C for 10 min, and additional 2 h at 25 °C. The resulting solution was quenched with satd. aqueous $NaHCO_3$ (10 mL) and satd. aqueous $Na_2S_2O_3$ (10 mL), extracted with DCM (3 x 20 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford a residue, which was dissolved into DCM (20 mL) and treated with DAST (5 mL, 4.48 mmol) at -78°C. The resulted solution was stirred overnight at 15 °C, and was quenched with satd. aqueous $NaHCO_3$ (10 mL). The organic layer was separated and the resulted aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layers was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by a silica gel column with 20% EtOAc in petroleum ether to afford (3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diyl dibenzoate as light yellow oil (240 mg, 46%). (ES, *m/z*): $[M+H]^+$: 488.9; ^1H NMR (300 MHz, $CDCl_3$)δ 8.03-8.13 (m, 4H), 7.56-7.63 (m, 2H), 7.42-7.49 (m, 4H), 6.48 (d, J = 6.6 Hz, 1H), 5.94-5.96 (m, 2H), 5.58 (d, J = 8.7 Hz, 1H), 4.73 (s, 1H), 4.07-4.17 (m, 4H), 2.43-2.51 (m, 2H).

[00196] A solution of the above material (110 mg, 0.23 mmol) in MeOH (10 mL) was treated with K_2CO_3 (20 mg, 0.14 mmol) for 2 h at 25 °C, and then neutralized by AcOH. Removal of volatiles gave a residue, which was purified by a silica gel column with 10% MeOH in DCM to afford (3aR,5S,6S,7R,7aR)-2-(azetidin-1-yl)-5-(difluoromethyl)-5,6,7,7a-

tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (24 mg, 22%). (ES, *m/z*): $[M+H]^+$: 280.9; ^1H NMR (300 MHz, D_2O) δ 6.29 (d, *J* = 6.3 Hz, 1H), 5.82-6.00 (td, *J* = 54.0 Hz, 1.8 Hz, 1H), 4.24 (t, *J* = 5.7 Hz, 1H), 3.97-4.04 (m, 5H), 3.82-3.87 (m, 1H), 3.69-3.80 (m, 1H), 2.29 (m, 2H).

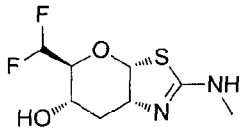
[00197] The following examples were synthesized according to procedures analogous to the schemes and examples outlined above.

Table 5

Example	Structure	Name
25		(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol
^1H NMR (400 MHz, MeOD) δ 6.45 (d, *J* = 6.4 Hz, 1H), 6.01 (td, *J* = 54.2, 2.2 Hz, 1H), 4.23 (t, *J* = 6.0 Hz, 1H), 4.00 (t, *J* = 4.8 Hz, 1H), 3.82-3.73 (m, 2H), 2.95 (s, 3H). ^{13}C NMR (100 MHz, MeOD) δ 168.82, 116.17 (t, $J_{C6,F}$ 241.5 Hz, C-6), 89.26, 75.42 (t, *J* = 21.2 Hz), 74.75, 69.87 (t, *J* = 3.3 Hz, C-4), 55.64, 32.20. (ES, *m/z*): $[M+H]^+$: 255.0.		
Example	Structure	Name
26		(3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol
^1H NMR (400 MHz, MeOD) δ 6.44 (d, *J* = 6.5 Hz, 1H), 6.01 (td, *J* = 54.2, 1.8 Hz, 1H), 4.23 (t, *J* = 5.9 Hz, 1H), 4.03 (t, *J* = 4.6 Hz, 1H), 3.79-3.72 (m, 2H), 3.32-3.23 (m, 2H), 1.69-1.60 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 167.42, 116.25 (t, $J_{C6,F}$ 241.4 Hz, C-6), 89.12, 75.41 (t, *J* = 21.4 Hz), 74.78, 69.99 (t, *J* = 3.2 Hz, C-4), 55.64, 48.47, 23.98, 12.36. (ES, *m/z*): $[M+H]^+$: 283.1.		

Example 27

(3aR,5S,6S,7aR)-5-(difluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00198] A mixture of ((3aR,5R,6S,7R,7aR)-6-(benzoyloxy)-2-((*tert*-butoxycarbonyl)(methyl)amino)-7-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate (5.00 g, 9.24 mmol) and thio-CDI (90% tech, 3.40 g, 19.1 mmol) in

anhydrous DMF (30 mL) was stirred at 95°C for 4 h. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 2:3), affording (3aR,5R,6S,7R,7aR)-7-((1H-imidazole-1-carbonothioyl)oxy)-5-((benzoyloxy)methyl)-2-((tert-butoxycarbonyl)(methyl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-yl benzoate as a pale yellow solid (5.60 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.03-8.01 (m, 2H), 7.97-7.95 (m, 2H), 7.64-7.60 (m, 1H), 7.54 -7.50 (m, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.02 (s, 1H), 6.38-6.37 (m, 1H), 6.15 (d, J = 7.1 Hz, 1H), 5.56 (td, J = 1.2, 9.2 Hz, 1H), 4.70-4.67 (m, 1H), 4.58 (dd, J = 3.2, 12.1 Hz, 1H), 4.42 (dd, J = 5.1, 12.1 Hz, 1H), 4.08-4.03 (m, 1H), 3.43 (s, 3H), 1.56 (s, 9H).

[00199] A mixture of the above material (5.60 g, 8.59 mmol), Bu_3SnH (5.84 g, 17.0 mmol) and ABCN (0.15 g, 0.60 mmol) in mixed anhydrous toluene/THF (50/50 mL) was stirred at 90°C for 16 h. After cooling the solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:2), affording ((3aR,5R,6S,7aR)-6-(benzoyloxy)-2-((tert-butoxycarbonyl)(methyl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate as a white solid (3.20 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.98 (m, 4H), 7.58-7.49 (m, 2H), 7.44-7.40 (m, 4H), 6.08 (d, J = 7.3 Hz, 1H), 5.44-5.40 (m, 1H), 4.49-4.40 (m, 3H), 4.07-4.03 (m, 1H), 3.35 (s, 3H), 2.64-2.59 (m, 1H), 2.44-2.37 (m, 1H), 1.56 (s, 9H).

[00200] Following the procedure described for Example 32, the above material (3.20 g, 6.10 mmol) was benzoyl deprotected using K_2CO_3. After purification on silica gel by flash column chromatography (MeOH/DCM, 1:50 to 1:20), tert-butyl ((3aR,5R,6S,7aR)-6-hydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate was obtained as a white solid (1.82 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (d, J = 6.9 Hz, 1H), 4.36-4.32 (m, 1H), 3.89-3.85 (m, 1H), 3.81-3.75 (m, 1H), 3.65-3.59 (m, 1H), 3.38-3.34 (m, 1H), 3.33 (s, 3H), 2.48-2.43 (m, 1H), 2.32 (d, J = 10.7 Hz, 1H), 2.17-2.11 (m, 1H), 1.84 (t, J = 6.3 Hz, 1H), 1.54 (s, 9H).

[00201] Following the procedure described for Example 32, the above material (1.82 g, 5.74 mmol) was mono-TBDMS protected. After purification on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:2), tert-butyl ((3aR,5R,6S,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate was obtained as a colorless sticky oil (2.30 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, J = 6.8 Hz, 1H), 4.31-4.28 (m, 1H), 3.92-3.90 (m, 1H), 3.73 (d, J =

4.6 Hz, 2H), 3.35-3.31 (m, 1H), 3.33 (s, 3H), 2.41 (d, J = 9.4 Hz, 1H), 2.41-2.36 (m, 1H), 2.18-2.12 (m, 1H), 1.54 (s, 9H), 0.89 (s, 9H), 0.06 (s, 6H).

[00202] Following the procedure described for Example 32, the above material (2.78 g, 6.45 mmol) was benzyl protected using BnBr. After purification on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:4), tert-butyl ((3aR,5R,6S,7aR)-6-(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate was obtained as a colorless sticky oil (2.7 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 6.02 (d, J = 7.1 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.34-4.30 (m, 1H), 3.83-3.78 (m, 1H), 3.77-3.69 (m, 2H), 3.53-3.50 (m, 1H), 3.29 (s, 3H), 2.44-2.39 (m, 1H), 2.14-2.08 (m, 1H), 1.52 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H).

[00203] Following the procedure described for Example 32, the above material (2.70 g, 5.30 mmol) was silyl-deprotected using TBAF. After purification on silica gel by flash column chromatography (EtOAc/hexanes, 1:5 to 1:1), tert-butyl ((3aR,5R,6S,7aR)-6-(benzyloxy)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate was obtained as a colorless sticky foam (2.0 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 6.01 (d, J = 7.2 Hz, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.36-4.34 (m, 1H), 3.77-3.72 (m, 2H), 3.62-3.54 (m, 2H), 3.30 (s, 3H), 2.53-2.48 (m, 1H), 2.09-2.02 (m, 1H), 1.71 (t, J = 6.3 Hz, 1H), 1.53 (s, 9H).

[00204] Following the procedure described for Example 32, the above material (0.663 g, 1.62 mmol) was oxidized to the aldehyde using DMP. After purification on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 2:3), tert-butyl ((3aR,5S,6S,7aR)-6-(benzyloxy)-5-formyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate was obtained as a white foam (0.57 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.36-7.27 (m, 5H), 6.04 (d, J = 4.3 Hz, 1H), 4.69 (d, J = 9.2 Hz, 1H), 4.50 (d, J = 9.2 Hz, 1H), 4.43-4.39 (m, 1H), 4.07 (d, J = 6.4 Hz), 4.02-3.99 (m, 1H), 3.29 (s, 3H), 2.64-2.59 (m, 1H), 2.10-2.03 (m, 1H), 1.53 (s, 9H).

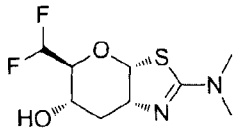
[00205] Following the procedure described for Example 32, the above material (0.550 g, 1.35 mmol) was treated with DAST. After purification on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), tert-butyl ((3aR,5S,6S,7aR)-6-(benzyloxy)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate was obtained as a pale yellow sticky oil (0.48 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27

(m, 5H), 6.04 (d, J = 7.4 Hz, 1H), 5.79 (dt, J = 2.2, 54.7 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.43 (d, J = 11.4 Hz, 1H), 4.43-3.40 (m, 1H), 4.01-3.97 (m, 1H), 3.82-3.73 (m, 1H), 3.27 (s, 3H), 2.59-2.54 (m, 1H), 2.10-2.05 (m, 1H), 1.53 (s, 9H).

[00206] Following the procedure described for Example 32, the above material (0.480 g, 1.12 mmol was deprotected using BCl_3. After purification on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1: 12), (3aR,5S,6S,7aR)-5-(difluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol was obtained as a pale yellow sticky solid (0.24 g, 87%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.17 (d, J = 6.4 Hz, 1H), 5.91 (dt, J = 2.6, 54.4 Hz, 1H), 4.38-4.34 (m, 1H), 4.03-3.98 (m, 1H), 3.64-3.61 (m, 1H), 2.84 (s, 3H), 2.16-2.13 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.35, 116.00 (t, J = 241.0 Hz), 91.12, 74.97 (t, J = 42.7 Hz), 70.00, 64.54 (t, J = 3.6 Hz), 34.19, 30.79; MS, m/z = 239.0 (M + 1).

Example 28

(3aR,5S,6S,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00207] To a solution of (3aR,5R,6R,7R,7aR)-7-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol (4.26 g, 8.95 mmol) in anhydrous DMF (30 mL) was added BnBr (1.68 g, 9.84 mmol) and tetrabutylammonium iodide (0.330 g, 0.895 mmol). At 0°C NaH (60%, 0.430 g, 10.744 mmol) was added in portions and then the reaction was stirred at this temperature for 2 h. The mixture was diluted with water (200 mL), extracted with Et_2O (2 ×100 mL). The combined extract was washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give a mixture containing ~80% (3aR,5R,6R,7R,7aR)-6-(benzyloxy)-7-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-N,N-dimethyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-amine (5.06 g, 100%) which was inseparable on silica gel column. This mixture was directly submitted to next reaction.

[00208] To a solution of the above material (9.89 g, 17.5 mmol) in MeOH (100 mL) at 0°C was added AcCl (6.21 mL, 87.4 mmol). The mixture was stirred at room temperature for 16

h. Solvent was evaporated under reduced pressure. The residue was purified on silica gel column, eluted with 2%-5% 2M NH_3 MeOH solution in DCM to give (3aR,5R,6S,7R,7aR)-6-(benzyloxy)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-7-ol (4.58 g, 78%). MS m/z 339.1 (M+1, 100%).

[00209] To a solution of the above material (4.58 g, 13.6 mmol) and imidazole (2.76 g, 40.7 mmol) in anhydrous DMF (30 mL) at 0°C was added TBDMSCl (2.45 g, 16.3 mmol). The mixture was stirred at room temperature for 21 h. The reaction was diluted with water (200 mL), extracted with Et_2O (2 × 100 mL). The combined extracts were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified on silica gel column, eluted with 1%-3% 2 M NH_3 MeOH solution in DCM to give (3aR,5R,6S,7R,7aR)-6-(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-7-ol (5.80 g, 95%). MS m/z 453.2 (M+1, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.37 (m, 5H), 6.37 (d, J = 6.6 Hz, 1H), 4.88 (d, J = 11.4 Hz, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.22 (t, J = 6.4 Hz, 1H), 4.09-4.13 (m, 1H), 3.80-3.82 (m, 2H), 3.74-3.78 (m, 1H), 3.64 (dd, J = 8.7 Hz, 6.4 Hz, 1H), 2.98 (s, 6H), 0.897 (s, 9H), 0.90 (s, 9H), 0.052 (s, 3H), 0.056 (s, 3H).

[00210] A mixture of the above material (5.80 g, 12.8 mmol) and thio-CDI (90% tech, 4.57 g, 23.1 mmol) in anhydrous DMF (30 mL) was stirred at 90 °C for 2.5 h. After cooling, the mixture was diluted with water (200 mL), extracted with Et_2O (2 × 100 mL). The combined extracts were washed with brine (100 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was purified on silica gel column, eluted with 30%-100% EtOAc in hexanes to give O-((3aR,5R,6S,7R,7aR)-6-(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-7-yl) 1H-imidazole-1-carbothioate (6.51 g, 90%). MS m/z 563.2 (M+1, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.59 (s, 1H), 7.23-7.34 (m, 5H), 7.03 (s, 1H), 6.36 (brs, 1H), 6.31 (d, J = 6.7 Hz, 1H), 4.91 (d, J = 11.6 Hz, 1H), 4.62 (m, 1H), 4.58 (d, J = 11.6 Hz, 1H), 3.85 (d, J = 8.7 Hz, 1H), 3.64-3.74 (m, 3H), 3.03 (s, 6H), 0.82 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H).

[00211] A mixture of the above material (6.51 g, 11.6 mmol), tributyltin hydride (7.47 g, 25.7 mmol) and ABCN (0.313 g, 1.28 mmol) in anhydrous THF (100 mL) was heated at reflux for 17 h. After cooling the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 50%-80% EtOAc in hexanes to give (3aR,5R,6S,7aR)-6-(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-

N,N-dimethyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-amine as a white solid (4.07 g, 81%). MS m/z 437.2 (M+1, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.37 (m, 5H), 6.25 (d, J = 6.6 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.34-4.39 (m, 1H), 3.65-3.80 (m, 4H), 2.99 (s, 6H), 2.25 (brs, 1H), 2.10-2.16 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H).

[00212] To a solution of the above material (4.07 g, 9.33 mmol) in MeOH (50 mL) at 0°C was added AcCl (1.33 mL, 18.7 mmol). The mixture was stirred at room temperature for 16 h. Solvent was evaporated under reduced pressure. The residue was purified on silica gel column, eluted with 3%-5% 2 M NH_3 MeOH solution in DCM to give ((3aR,5R,6S,7aR)-6-(benzyloxy)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methanol (2.78 g, 91%). MS m/z 323.1 (M+1, 100%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.36 (m, 5H), 6.22 (d, J = 6.6 Hz, 1H), 4.70 (d, J = 11.6 Hz, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.32-4.37 (m, 1H), 3.71-3.79 (m, 2H), 3.60-3.67 (m, 2H), 2.97 (s, 6H), 2.19-2.25 (m, 1H), 2.09-2.15 (m, 1H), 1.86 (br s, 1H).

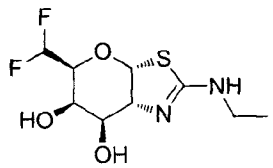
[00213] To a solution of DMSO (0.875 g, 11.2 mmol) in anhydrous DCM (15 mL) at -78°C under N_2 was added oxalyl chloride (1.316 g, 10.36 mmol) dropwise. The mixture was stirred at ~ -30°C for 30 min and cooled to -78°C again. A solution of the above material (1.39 g, 4.32 mmol) in anhydrous DCM (15 mL) was added dropwise. After stirred at ~ -30°C for 2 h the reaction mixture was cooled back to -78°C, and Et_3N (1.74 g, 17.3 mmol) was added. The mixture was stirred at~ -30°C for another 30 min, and then quenched with water (50 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 20 mL). The combined extracts were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude (3aR,5S,6S,7aR)-6-(benzyloxy)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-5-carbaldehyde (1.24 g) as a yellow foam. MS m/z 353.1 (M+23, 100%).

[00214] To a solution of the above crude material (200 mg) in anhydrous DCM (5 mL) at 0 °C was added bis(2-methoxyethyl)aminosulfur trifluoride (0.553 g, 2.50 mmol). The mixture was stirred at room temperature for 27 h. The reaction was quenched with satd. aqueous $NaHCO_3$ (10 mL), and then extracted with EtOAc (2 × 10 mL). The combined extract was dried over anhydrous Na_2SO_4. The solvents were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexanes, 2:1 to 5:1) to afford (3aR,5S,6S,7aR)-6-(benzyloxy)-5-(difluoromethyl)-N,N-dimethyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-amine as a pale yellow foam (0.050 g, 23%, 2 steps). MS m/z 343.1 (M+1, 100%).

[00215] To a solution of the above material (0.049 g, 0.14 mmol) in DCM (2 mL) at -78°C was added a solution of BCl_3 in DCM (1.0 M, 0.19 mL, 0.19 mmol). The mixture was slowly warmed up to room temperature and stirred for 18 h. The reaction was cooled to -78°C again and a 1:1 mixture of MeOH-DCM (2 mL) was added dropwise to quench the reaction. Solvents were evaporated and the residue was treated with MeOH for three more times. The crude product was purified by silica gel column chromatography, eluted with 1%-2% 2 M NH_3 MeOH solution in DCM to give the product (3aR,5S,6S,7aR)-5-(difluoromethyl)-2-(dimethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol (0.0193 g, 53%) as a white solid. MS m/z 253.1 (M+1, 100%); ^{1}H NMR (400 MHz, MeOD) δ 6.22 (d, J = 6.5 Hz, 1H), 5.93 (td, J = 54.4 Hz, 2.6 Hz, 1H), 4.36-4.40 (m, 1H), 3.99-4.03 (m, 1H), 3.59-3.68 (m, 1H), 3.03 (s, 6H), 2.12-2.16 (m, 2H); ^{13}C NMR (100 MHz, MeOD) δ 165.06, 115.86 (t, J = 192.8 Hz), 91.48, 74.91 (t, J = 17.1 Hz), 70.02, 64.40 (t, J = 2.8 Hz), 40.31, 34.09.

Example 29

(3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol



[00216] A solution of tert-butyl ((3aR,5S,6S,7R,7aR)-5-(difluoromethyl)-6,7-dihydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(ethyl)carbamate (500 mg, 1.3 mmol) and imidazole (277 mg, 4 mmol) in DMF (20 mL) was treated with TBDMSCl (611 mg, 4 mmol) for 3 h at 40°C. The resulting solution was then cooled to room temperature, quenched by satd. aqueous $NaHCO_3$ (50 mL) solution, extracted with DCM (3x20 mL), washed with brine (3x10 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give a residue, which was purified by a silica gel column, eluted with 5%-10% EtOAc in petroleum ether to afford tert-butyl(3aR,5S,6R,7R,7aR)-7-(tert-butyldimethylsilyloxy)-5-(difluoromethyl)-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl(ethyl)carbamate as a light yellow syrup (420 mg, 64 %). (ES, *m/z*): $[M+1]^+$ 483.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (d, J = 5.4 Hz, 1H), 5.98 (td, J = 55.2 Hz, 3.6 Hz, 1H), 4.10-3.91 (m, 5H), 3.77-3.70 (m, 1H), 1.56 (s, 9H), 1.21 (t, J = 6.9 Hz, 3H), 0.94 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H).

[00217] A solution of the above material (440 mg, 0.9 mmol) in DCM (20 mL) was treated with DMP (587 mg, 1.4 mmol) for 1 h at room temperature. The reaction mixture was quenched by a mixture of satd. aqueous $NaHCO_3$ (5 mL) and sodium hyposulfite (5 mL). The organic layer was collected and the aqueous layer was extracted with DCM (3x20 ml). The combined organic layer was washed with brine (10 mL) and dried over anhydrous $MgSO_4$. After filtration, the filtrates were concentrated to give a residue, which was purified by a silica gel column, eluted with 5% EtOAc in petroleum ether to afford tert-butyl(3aR,5S,7R,7aR)-7-(tert-butyldimethylsilyloxy)-5-(difluoromethyl)-6-oxo-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl(ethyl)carbamate as white syrup (370 mg, 84 %). (ES, *m/z*): $[M+1]^+$ 481.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 6.9 Hz, 1H), 6.08 (td, J = 52.8 Hz, 1.5 Hz, 1H), 4.69 (d, J = 3.6 Hz, 1H), 4.63 (dd, J = 6.9 Hz, 3.9 Hz, 1H), 4.16-4.09 (m, 1H), 3.98-3.89 (m, 2H), 1.57 (s, 9H), 1.14 (t, J = 6.9 Hz, 3H), 0.93 (s, 9H), 0.20 (s, 3H), 0.13 (s, 3H).

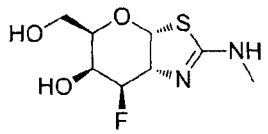
[00218] A solution of the above material (400 mg, 0.8 mmol) in MeOH (5 mL) was treated with $NaBH_4$ (63 mg, 1.7 mmol) for 2 h at room temperature. The reaction mixture was quenched with water (20 mL) and extracted with DCM (3x10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum to give a residue, which was purified by a silica gel column, eluted with 10 % EtOAc in petroleum ether to afford tert-butyl(3aR,5S,6S,7R,7aR)-7-(tert-butyldimethylsilyloxy)-5-(difluoromethyl)-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl(ethyl)carbamate as white syrup (103 mg, 25%). (ES, *m/z*): $[M+1]^+$ 483.0; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, J = 6.3 Hz, 1H), 6.06 (td, J = 70.2 Hz, 6.6 Hz, 1H), 4.37-4.31 (m, 1H), 4.25-4.20 (m, 1H), 4.12-4.06 (m, 1H), 4.01-3.92 (m, 2H), 3.87 (m, 1H), 3.85-3.76 (m, 1H), 1.56 (s, 9H), 1.21 (t, J = 6.9 Hz, 3H), 0.96 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H).

[00219] To a solution of the above material (20 mg, 0.04 mmol) in MeOH (10 mL) was bubbled with dry HCl gas until it was saturated at 0 °C. The resulting solution was stirred for 3 h at room temperature. Removal of volatiles gave a residue, which was dissolved into MeOH (2 mL) and neutralized with concentrated NH_4OH (1 mL). After concentrating under reduced pressure, the crude product was purified by a short silica gel column, eluted with 10% MeOH in DCM to afford (3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-2-(ethylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol as a white solid (10 mg, 90 %). (ES, *m/z*): $[M+1]^+$ 269.0; ^1H NMR (300 MHz, CD_3OD) δ 6.31 (d, J = 6.0 Hz, 1H), 5.97 (td, J =

56.1, 6.3Hz, 1H), 4.12 (t, J = 6.3 Hz, 1H), 4.03 (t, J = 3.0 Hz,1H), 3.95-3.90 (m, 1H), 3.88-3.85 (m, 1H), 3.32-3.21 (m, 2H), 1.17 (t, J = 7.5 Hz, 3H).

Example 30

(3aR,5R,6S,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



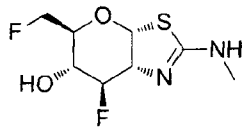
[00220] To a solution of tert-butyl ((3aR,5R,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-oxo-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate (2.57 g, 5.72 mmol) in dry MeOH (50 mL), at 0°C, was added $NaBH_4$ (0.295 g, 7.80 mmol). After the mixture was stirred at 0°C for 20 min a chip of dry ice was added, and the solvent was evaporated. The residue was dissolved in DCM (50 mL) and washed with satd. aqueous $NaHCO_3$ (50 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 30 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), affording tert-butyl ((3aR,5R,6S,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate (0.95 g, 37%), as a sticky oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (d, J = 6.7 Hz, 1H), 4.84 (ddd, J = 3.2, 6.7, 48.2 Hz, 1H), 4.45 (td, J = 6.7, 16.6 Hz, 1H), 4.32-4.29 (m, 1H), 4.00-3.93 (m, 2H), 3.90-3.86 (m, 1H), 3.36 (s, 3H), 3.19 (s, br., 1H, (OH)), 1.53 (s, 9H), 0.90 (s, 9H), 0.093 (s, 3H), 0.087 (s, 3H).

[00221] To a solution of the above material (0.110 g, 0.244 mmol) in dry MeOH (4 mL) was bubbled HCl gas for 30 sec. The mixture was stirred at room temperature for 2 h. After the solvent was evaporated under reduced pressure, the residue was neutralized with 1.0 M NH_3 in MeOH and purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1:9) affording (3aR,5R,6S,7R,7aR)-7-fluoro-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as a white solid (0.043 g, 89%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.38 (dd, J = 1.0, 6.7 Hz, 1H), 4.65 (ddd, J = 3.3, 7.8, 48.2 Hz, 1H), 4.30-4.22 (m, 1H), 4.15-4.11 (m, 1H), 4.01-3.98 (m, 1H), 3.78-3.72 (m, 2H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.87, 94.77 (d, J = 182.5 Hz), 91.73 (d, J =

7.8 Hz), 75.66 (d, J = 5.8 Hz), 69.89 (d, J = 21.0 Hz), 67.01 (d, J = 27.6 Hz), 61.81 (d, J = 3.1 Hz), 30.30; MS, (ES, *m/z*) $[M+H]^+$ 237.1.

Example 31

(3aR,5S,6R,7R,7aR)-7-fluoro-5-(fluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00222] To a suspension of (3aR,5R,6S,7R,7aR)-5-(hydroxymethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (80.00 g, 341.6 mmol) in DMF (500 mL) was added DIPEA (8 mL), MeOH (8 mL) and Boc_2O (100.0 g, 458.7 mmol) in sequence. The suspension was stirred at room temperature for 6 h, and became a clear solution. After the volume of the solution was reduced under reduced pressure at room temperature by around 100 mL to remove MeOH and tert-butanol, the solution was cooled with an ice cooling bath, and imidazole (92.9 g, 1.36 mol), and TBDMSCl (155 g, 1.03 mol) was added in sequence. After stirred at room temperature overnight the mixture was diluted with brine (1.5 L). Extraction was performed with Et_2O three times (500 mL and 2 × 300 mL). The combined ether extract was washed with brine (1 L) and dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue of the two batches was combined and purified on silica gel by flash column chromatography (EtOAc/hexanes, 2:11) to afford tert-butyl ((3aR,5R,6R,7R,7aR)-7-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white crystalline solid (136 g, 71%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (d, J = 6.2 Hz, 1H), 4.29 (s, br. 1H), 4.06-4.05 (m, 1H), 3.81-3.75 (m, 2H), 3.71-3.68 (m, 1H), 3.47-3.43 (m, 1H), 3.36 (s, 3H), 1.54 (s, 9H), 0.915 (s, 9H), 0.893 (s, 9H), 0.161 (s, 3H), 0.149 (s, 3H), 0.068 (s, 6H).

[00223] At 0°C, to a solution of the above material (94.30 g, 167.5 mmol) and DMAP (0.50 g, 4.1 mmol) in pyridine (350 mL) was added BzCl (28.3 g, 201 mmol). The mixture was stirred at room temperature overnight, another portion of BzCl (6.90 g, 49.1 mmol) was added and the mixture was stirred at room temperature for another 3 h. MeOH (20 ml) was added and the mixture was stirred for another 30 min. The mixture was diluted with brine (1 L) and extracted with mixed EtOAc/hexanes three times (1:4; 600 mL, 200 mL and 100 mL).

The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the combined residue of all three batches was treated with 1.5 M HCl in MeOH (1.0 L) at room temperature for 16 h. The solvent was then removed at room temperature under reduced pressure to afford a white solid. To the white solid in DCM (1.6 h) was added DIPEA (100 mL) and Boc_2O (109 g, 500 mmol) in sequence. The mixture was then stirred at room temperature for 4 days. The reaction mixture was washed with satd. aqueous NH_4Cl (1 L) and brine (1 L), and dried over anhydrous Na_2SO_4. (The combined aqueous washing was basified to pH = ~9 with satd. aqueous Na_2CO_3 solution and extracted with DCM (5 × 150 mL). The combined DCM extracts were dried over anhydrous Na_2SO_4. After filtration the solution was treated with Boc_2O (30 g) for 5 h. After washed with satd. aqueous NH_4Cl (1 L) and brine (1 L), and dried over anhydrous Na_2SO_4.). All DCM extracts were combined. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:4 to 3:2) to afford (3aR,5R,6S,7R,7aR)-2-((tert-butoxycarbonyl)(methyl)amino)-7-hydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-yl benzoate as a white solid (56.5 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.98 (m, 2H), 7.59-7.54 (m, 1H), 7.44-7.40 (m, 2H), 6.20 (d, J = 7.0 Hz, 1H), 5.15-5.12 (m, 1H), 4.55-4.50 (m, 1H), 4.41-4.39 (m, 1H), 3.80-3.76 (m, 1H), 3.70-3.66 (m, 1H), 3.49 (s, br., 1H), 3.34 (s, 3H), 1.56 (s, 9H).

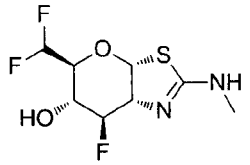
[00224] To a solution of the above material (500 mg, 1.1 mmol) in DCM (15 mL) was added DAST (1.1 g, 6.8 mmol) at -78 °C under nitrogen atmosphere. After stirred overnight at room temperature, the reaction mixture was quenched with satd. aqueous $NaHCO_3$ (30 mL) solution, extracted with DCM (3x15 mL), dried over anhydrous Na_2SO_4, and condensed to give a residue, which was purified by a silica gel column, eluted with 10%-30% EtOAc in petroleum ether to afford (3aR,5S,6R,7R,7aR)-2-(tert-butoxycarbonyl(methyl)amino)-7-fluoro-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-yl benzoate (370 mg, 73%) as light yellow oil. (ES, *m/z*): $[M+H]^+$ 443.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02-8.01 (m, 2H), 7.64-7.62 (m, 1H), 7.59-7.44 (m, 2H), 6.19 (d, J = 7.2 Hz, 1H), 5.44-5.26 (m, 2H), 4.62-4.60 (m, 2H), 4.58-4.46 (m, 1H), 3.90-3.80 (m, 1H), 3.39 (s, 3H), 1.58 (s, 9H).

[00225] A solution of the above material (170 mg, 0.4 mmol) in THF (10 mL) was treated with MeMgCl (3 mmol, 1 ml, 3 M in THF) for 1 h at room temperature. The reaction mixture was quenched with satd. aqueous NH_4Cl (30 mL) solution, extracted with EtOAc (3x20 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, and condensed to give a residue,

which was purified by a silica gel column, eluted with 2%-5% MeOH in DCM to afford (3aR,5S,6R,7R,7aR)-7-fluoro-5-(fluoromethyl)-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as a white solid (35 mg, 38 %). (ES, *m/z*): $[M+H]^+$ 239.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (d, *J* = 6.3 Hz, 1H), 5.14 (td, *J* = 45.6 Hz, 2.1 Hz, 1H), 4.70-4.44 (m, 3H), 3.90-3.79 (m, 1H), 3.73-3.61 (m, 1H), 2.95 (s, 3H).

Example 32

(3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-7-fluoro-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00226] To a suspension of (3aR,5R,6S,7R,7aR)-2-(methylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol (8.50 g, 37.0 mmol) in DMF (60 mL) was added DIPEA (2.0 mL), Boc_2O (23.0 g, 105 mmol) and MeOH (2.0 mL). The mixture was stirred at room temperature for 3 h, and then MeOH (50 mL) was added. The reaction mixture was concentrated under reduced pressure at ~35°C. The residue was purified on silica gel by flash column chromatography (MeOH/DCM, 1:8), followed by re-crystallization from EtOAc/hexanes, to afford tert-butyl ((3aR,5R,6S,7R,7aR)-6,7-dihydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (11.8 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (d, *J* = 6.9 Hz, 1H), 4.20 (d, *J* = 6.4 Hz, 1H), 4.11 (d, *J* = 5.6 Hz, 1H), 3.85-3.70 (m, 2H), 3.63-3.55 (m, 1H), 3.31 (s, 3H), 1.53 (s, 9H).

[00227] To a solution of the above material (11.7 g, 35.1 mmol), DIPEA (10.3 g, 80.0 mmol) and DMAP (0.040 g, 0.33 mmol) in DCM (180 mL), at 0°C, was added BzCl (10.1 g, 72.0 mmol) slowly. After addition the mixture was stirred at room temperature for 5 h. Satd. aqueous NH_4Cl solution (100 mL) was added, and the organic layer was collected. The aqueous layer was further extracted with DCM (3 × 50 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was separated on silica gel by flash column chromatography (EtOAc/hexanes, 1:4 to 1:1), affording ((3aR,5R,6S,7R,7aR)-6-(benzoyloxy)-2-((tert-butoxycarbonyl)(methyl)amino)-7-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-

yl)methyl benzoate as a white solid (4.20 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 4H), 7.60-7.55 (m, 1H), 7.54-7.50 (m, 1H), 7.45-7.41 (m, 2H), 7.37-7.35 (m, 2H), 6.21 (d, J = 7.1 Hz, 1H), 5.23-5.20 (m, 1H), 4.55-4.51 (m, 2H), 4.48-4.42 (m, 2H), 4.15-4.07 (m, 2H), 3.36 (s, 3H), 1.56 (s, 9H).

[00228] To a solution of the above material (7.91 g, 14.6 mmol) in anhydrous DCM (100 mL) at -78°C under N_2, was added DAST (11.8 g, 73.0 mmol). After addition the mixture was stirred at room temperature for 72 h. The reaction mixture was then cooled at -78°C, diluted with DCM (100 mL), and then quenched with satd. aqueous $NaHCO_3$ (150 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 100 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:4), affording ((3aR,5R,6R,7R,7aR)-6-(benzoyloxy)-2-((tert-butoxycarbonyl)(methyl)amino)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-5-yl)methyl benzoate as a white solid (6.10 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.98 (m, 4H), 7.60-7.56 (m, 1H), 7.56-7.52 (m, 1H), 7.45-7.41 (m, 2H), 7.38-7.35 (m, 2H), 6.19 (d, J = 7.2 Hz, 1H), 5.52-5.46 (m, 1H), 5.40-5.28 (m, 1H), 4.61-4.56 (m, 1H), 4.52 (dd, J = 3.6, 12.0 Hz, 1H), 4.43 (dd, J = 5.7, 12.0 Hz, 1H), 4.03-3.99 (m, 1H), 3.36 (s, 3H), 1.56 (s, 9H).

[00229] A mixture of the above material (6.10 g, 11.2 mmol) and K_2CO_3 (1.00 g, 7.25 mmol) in anhydrous MeOH (50 mL) was stirred at room temperature for 3 h. Dry ice was added, and the solvent was removed under reduced pressure. The residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:1 to 10:1), affording tert-butyl ((3aR,5R,6R,7R,7aR)-7-fluoro-6-hydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (3.25 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 6.8 Hz, 1H), 5.15 (ddd, J = 2.4, 4.4, 45.7 Hz, 1H), 4.46-4.41 (m, 1H), 3.96-3.89 (m, 1H), 3.83 (dd, J = 3.2, 11.8 Hz, 1H), 3.73 (dd, J = 5.4, 11.8 Hz, 1H), 3.46-3.42 (m, 1H), 3.32 (s, 3H), 1.54 (s, 9H).

[00230] At 0°C, to a solution of the above material (0.880 g, 2.61 mmol) and imidazole (0.354 g, 5.20 mmol) in anhydrous DMF (15 mL) was added TBDMSCl (0.452 g, 3.00 mmol). The mixture was stirred at room temperature for 72 h and diluted with Et_2O (100 mL) and brine (100 mL). The organic layer was collected, and the aqueous was extracted with Et_2O (50 mL). The combined extract was washed with water (50 mL) and dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and

the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), affording tert-butyl ((3aR,5R,6R,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white foam (1.10 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 6.8 Hz, 1H), 5.19-5.02 (m, 1H), 4.43-4.38 (m, 1H), 3.98-3.93 (m, 1H), 3.85 (dd, J = 5.0, 10.6 Hz, 1H), 3.73 (dd, J = 5.2, 10.6 Hz, 1H), 3.45-3.43 (m, 1H), 3.34 (s, 3H), 1.54 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H).

[00231] At 0°C, to a solution of the above material (1.06 g, 2.35 mmol) and Bu_4NI (0.087 g, 0.24 mmol) in anhydrous DMF (15 mL) was added NaH (60% in mineral oil, 0.118 g, 2.94 mmol). After addition of NaH, to the reaction mixture was added BnBr (0.703 g, 4.11 mmol). The mixture was stirred at room temperature for 16 h and diluted with Et_2O (60 mL) and satd. NH_4Cl (50 mL). The organic layer was collected, and the aqueous was extracted with Et_2O (2 × 30 mL). The combined extract was washed with brine (40 mL) and dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:4), affording tert-butyl ((3aR,5R,6R,7R,7aR)-6-(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a sticky oil (1.22 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 6.10 (d, J = 7.0 Hz, 1H), 5.30-5.16 (m, 1H), 4.80 (d, J = 11.0 Hz, 1H), 4.55 (d, J = 11.0 Hz, 1H), 4.48-4.42 (m, 1H), 3.88-3.80 (m, 1H), 3.78-3.69 (m, 2H), 3.46-3.44 (m, 1H), 3.31 (s, 3H), 1.53 (s, 9H), 0.89 (s, 9H), 0.04 (s, 6H).

[00232] At 0°C, to a solution of the above material (1.22 g, 2.25 mmol) in THF (15 mL) was added TBAF (1.0 M in THF, 5.0 mL, 5.0 mmol). After addition the reaction mixture was stirred at room temperature for 2 h and diluted with EtOAc (20 mL) and brine (50 mL). The organic layer was collected, and the aqueous was extracted with EtOAc (2 × 50 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:5 to 1:2), affording tert-butyl ((3aR,5R,6R,7R,7aR)-6-(benzyloxy)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (0.96 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.29 (m, 5H), 6.09 (d, J = 6.7 Hz, 1H), 5.32 (ddd, J = 1.8, 3.6, 45.4 Hz, 1H), 4.80 (d, J = 11.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.53-4.48 (m, 1H), 3.81-3.72 (m, 2H), 3.61-3.55 (m, 1H), 3.49-3.45 (m, 1H), 3.31 (s, 3H), 1.53 (s, 9H).

[00233] To a solution of the above material (1.50 g, 3.52 mmol) in DCM (40 mL) was added DMP (2.20 g, 5.20 mmol). After stirred at room temperature for 1 h the reaction mixture was diluted with Et_2O (20 mL), and then concentrated to dryness. Satd. aqueous $NaHCO_3$ (30 mL) with $Na_2S_2O_3$ (2 g) was added, and the mixture was extracted with EtOAc (2 × 50 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:5 to 1:2), affording tert-butyl ((3aR,5S,6R,7R,7aR)-6-(benzyloxy)-7-fluoro-5-formyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (1.02 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.35-7.29 (m, 5H), 6.12 (d, J = 7.0 Hz, 1H), 5.39-5.27 (m, 1H), 4.78 (d, J = 11.4 Hz, 1H), 4.66 (d, J = 11.4 Hz, 1H), 4.57-4.51 (m, 1H), 4.00-3.95 (m, 2H), 3.31 (s, 3H), 1.53 (s, 9H).

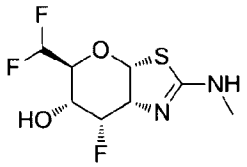
[00234] To a solution of the above material (0.156 g, 0.367 mmol) in anhydrous DCM (6 mL) at -78°C under N_2, was added DAST (0.354 g, 2.20 mmol). After addition the mixture was stirred at room temperature for 16 h. The reaction mixture was then cooled at -78°C, diluted with DCM (10 mL), and then quenched with satd. aqueous $NaHCO_3$ (10 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 15 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:4), affording tert-butyl ((3aR,5S,6R,7R,7aR)-6-(benzyloxy)-5-(difluoromethyl)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a pale yellow oil (0.125 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 6.11 (d, J = 7.2 Hz, 1H), 5.79 (dt, J = 2.4, 54.4 Hz, 1H), 5.37-5.25 (m, 1H), 4.78 (d, J = 11.3 Hz, 1H), 4.59 (d, J = 11.3 Hz, 1H), 4.58-4.53 (m, 1H), 4.00-3.92 (m, 1H), 3.72-3.63 (m, 1H), 3.29 (s, 3H), 1.53 (s, 9H).

[00235] To a solution of the above material (0.240 g, 0.537 mmol) and pentamethylbenzene (0.26 g, 1.7 mmol) in anhydrous DCM (10 mL) at -78°C under N_2, was added BCl_3 (1.0 M in DCM, 1.6 mL, 1.6 mmol). The mixture was stirred at room temperature for ~3 h while the temperature of the cooling trap reached at 0°C. The reaction mixture was cooled at -78°C, quenched with mixed MeOH/DCM, and then concentrated to dryness. The residue was purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/DCM, 1: 15), affording (3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-7-fluoro-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as an off-white solid (0.104 g, 76%). ^{1}H NMR

(400 MHz, CD_3OD) δ 6.30 (d, J = 6.6 Hz, 1H), 5.96 (dt, J = 2.4, 54.1 Hz, 1H), 4.89 (td, J = 3.9, 46.5 Hz, 1H), 4.48-4.42 (m, 1H), 4.02-3.94 (m, 1H), 3.72-3.63 (m, 1H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.08 (d, J = 2.3 Hz), 115.63 (dt, J = 7.9, 241.6 Hz), 94.73 (d, J = 177.6 Hz), 89.90 (d, J = 2.0 Hz), 74.04 (d, J = 26.1 Hz), 72.92 (dt, J = 3.9, 21.3 Hz), 67.87 (td, J = 3.8, 25.0 Hz), 30.74; MS, m/z = 257.0 (M + 1).

Example 33

(3aR,5S,6R,7S,7aR)-5-(difluoromethyl)-7-fluoro-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol



[00236] At 0°C, to a solution of tert-butyl ((3aR,5R,6R,7R,7aR)-7-fluoro-6-hydroxy-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate (18.7 g, 55.5 mmol) and imidazole (11.4 g, 167 mmol) in anhydrous DMF (150 mL) was added TBDMSCl (9.19 g, 61.0 mmol). The mixture was stirred at room temperature for 16 h, diluted with Et_2O (300 mL) and washed with brine (2 × 300 mL). The organic layer was collected, and the aqueous was extracted with Et_2O (2 × 150 mL). The combined extract was washed with brine (100 mL) and dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), affording tert-butyl ((3aR,5R,6R,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white foam (24.1 g, 96%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 6.8 Hz, 1H), 5.19-5.02 (m, 1H), 4.43-4.38 (m, 1H), 3.98-3.93 (m, 1H), 3.85 (dd, J = 5.0, 10.6 Hz, 1H), 3.73 (dd, J = 5.2, 10.6 Hz, 1H), 3.45-3.43 (m, 1H), 3.34 (s, 3H), 1.54 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H).

[00237] To a solution of the above material (9.28 g, 20.6 mmol) in DCM (150 mL) was added DMP (13.1 g, 30.9 mmol). After stirred at room temperature for 1 h the reaction was diluted with Et_2O (400 mL). The resulting suspension was filtered through Celite cake, and the filtrate was concentrated to dryness at room temperature. The residue was loaded onto a layered $NaHCO_3$/silica gel plug, and the product was eluted with (EtOAc/hexanes, 1:4), affording tert-butyl ((3aR,5R,7R,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-

oxo-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white crystalline solid (8.96 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, J = 7.0 Hz, 1H), 5.09 (dd, J = 4.7, 48.4 Hz, 1H), 4.75-4.69 (m, 1H), 4.12-4.05 (m, 2H), 3.96-3.93 (m, 1H), 3.28 (s, 3H), 1.54 (s, 9H), 0.86 (s, 9H), 0.056 (s, 3H), 0.050 (s, 3H).

[00238] To a solution of the above material (8.96 g, 20.0 mmol) in dry MeOH (250 mL) was added NaH (60% in mineral oil, 0.158 g, 3.95 mmol), and the mixture was stirred at room temperature for 15 min. The reaction mixture was then cooled at 0°C, and $NaBH_4$ (1.32 g, 34.9 mmol) was added. After the mixture was stirred at 0°C for 20 min a chip of dry ice was added and the solvent was evaporated. The above residue was dissolved in DCM (100 mL), and washed with satd. aqueous NH_4Cl (100 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 50 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:10 to 2:5), affording tert-butyl ((3aR,5R,6R,7S,7aR)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-6-hydroxy-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white foam (6.84 g, 76% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (d, J = 6.7 Hz, 1H), 5.01 (td, J = 4.3, 46.8 Hz, 1H), 4.49-4.44 (m, 1H), 4.17-4.13 (m, 1H), 3.80-3.79 (m, 2H), 3.66-3.63 (m, 1H), 3.38 (s, 3H), 2.72 (s, br., 1H, (OH)), 1.54 (s, 9H), 0.89 (s, 9H), 0.062 (s, 3H), 0.057 (s, 3H).

[00239] At 0°C, to a solution of the above material (1.30 g, 2.89 mmol) and Bu_4NI (0.107 g, 0.290 mmol) in anhydrous DMF (12 mL) was added NaH (60% in mineral oil, 0.145 g, 3.63 mmol). After addition of NaH, BnBr (0.989 g, 5.78 mmol) was added. After stirred at 0°C for 30 min and then at room temperature overnight the mixture was diluted with Et_2O (100 mL). The mixture was washed with satd. aqueous NH_4Cl (2 × 50 mL). The aqueous was extracted with Et_2O (2 × 40 mL). The combined extract was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:20 to 1:4), affording tert-butyl ((3aR,5R,6R,7S,7aR)-6-(benzyloxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a sticky oil (1.44 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 6.21 (d, J = 7.2 Hz, 1H), 5.30-5.16 (m, 1H), 4.80 (d, J = 11.4 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.50-4.42 (m, 1H), 3.95-3.78 (m, 4H), 3.44 (s, 3H), 1.54 (s, 9H), 0.89 (s, 9H), 0.049 (s, 6H).

[00240] At 0°C, to a solution of the above material (1.44 g, 2.66 mmol) in THF (25 mL) was added TBAF (1.0 M in THF, 3.5 mL, 3.5 mmol). After addition the reaction mixture was stirred at room temperature for 2 h and diluted with brine (50 mL). The mixture was extracted with EtOAc (2 × 40 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:2 to 1:1), affording tert-butyl ((3aR,5R,6R,7S,7aR)-6-(benzyloxy)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white solid (1.08 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 6.18 (d, J = 7.4 Hz, 1H), 5.17-5.04 (m, 1H), 4.84 (d, J = 11.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.50-4.43 (m, 1H), 3.95-3.91 (m, 1H), 3.88 3.82 (m, 1H), 3.79-3.75 (m, 1H), 3.71-3.67 (m, 1H), 3.37 (s, 3H), 1.53 (s, 9H).

[00241] To a solution of the above material (2.57 g, 6.03 mmol) in DCM (60 mL) at 0℃ was added DMP (3.82 g, 9.00 mmol). After stirred at room temperature for 1 h the reaction mixture was diluted with Et_2O (100 mL). The resulting suspension was filtered through a Celite cake, and the filtrate was concentrated to dryness at room temperature. The residue was extracted with EtOAc (3 × 50 mL), and the solid was filtered off. The extract was washed mixed satd. aqueous $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (5 mL). The extract was collected and dried over anhydrous $MgSO_4$. After filtration the solvent was evaporated under reduced pressure to give the crude aldehyde tert-butyl ((3aR,5S,6R,7S,7aR)-6-(benzyloxy)-7-fluoro-5-formyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate. This crude material was used in the next step without further purification. ^{1}H NMR(400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.39-7.29 (m, 5H), 6.04 (d, J = 7.0 Hz, 1H), 5.08 (td, J = 4.2, 46.7 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.55-4.49 (m, 1H), 4.31 (d, J = 7.5 Hz, 1H), 4.19-4.15 (m, 1H), 3.30 (s, 3H), 1.52 (s, 9H).)

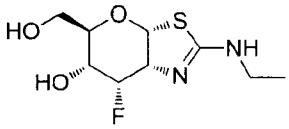
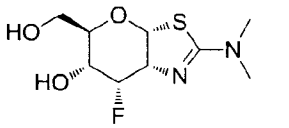
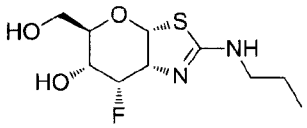
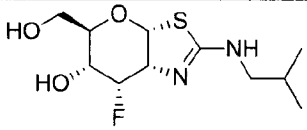
[00242] To a solution of the above material (0.19 g, ~80% pure, ~0.36 mmol) in anhydrous DCM (6 mL) at –78°C under N_2, was added DAST (0.37 g, 2.3 mmol). After addition the mixture was stirred at room temperature for 24 h. The reaction mixture was then cooled at –78°C, and quenched with satd. aqueous $NaHCO_3$ (10 mL). The organic layer was collected, and the aqueous was extracted with DCM (2 × 10 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 1:20 to 1:4), affording tert-butyl ((3aR,5S,6R,7S,7aR)-6-(benzyloxy)-5-(difluoromethyl)-7-fluoro-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-2-yl)(methyl)carbamate as a white foam (0.097

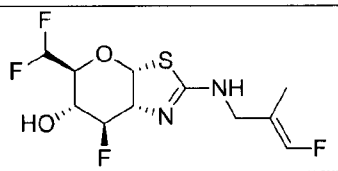
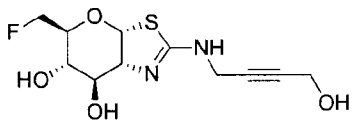
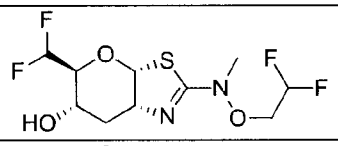
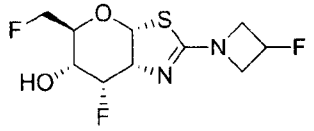
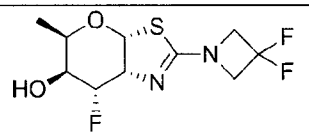
g, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 6.12 (d, J = 6.9 Hz, 1H), 5.85 (dt, J = 1.6, 54.5 Hz, 1H), 5.11 (td, J = 4.0, 47.3 Hz, 1H), 4.83 (d, J = 11.2 Hz, 1H), 4.57 (d, J = 11.2 Hz, 1H), 4.55-4.50 (m, 1H), 4.12-4.04 (m, 2H), 3.28 (s, 3H), 1.52 (s, 9H).

[00243] To a solution of the above material (0.097 g, 0.22 mmol) and pentamethylbenzene (0.050 g, 0.34 mmol) in anhydrous DCM (3 mL) at –78°C under N_2, was added BCl_3 (1.0 M in DCM, 1.0 mL, 1.0 mmol). The mixture was stirred at room temperature for ~5 h while the temperature of the cooling trap reached room temperature. The reaction mixture was cooled at –78°C, quenched with mixed MeOH/DCM, and then concentrated to dryness. The residue was purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/CH_2Cl_2, 1: 12), affording (3aR,5S,6R,7S,7aR)-5-(difluoromethyl)-7-fluoro-2-(methylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol as a white solid (0.041 g, 72%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.37 (d, J = 6.6 Hz, 1H), 6.04 (dt, J = 1.5, 54 .0 Hz, 1H), 4.86 (td, J = 3.3, 50.9 Hz, 1H), 4.39 (ddd, J = 3.8, 6.6, 20.9 Hz, 1H), 4.05-3.95 (m, 2H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.00, 115.89 (t, J = 242.6 Hz), 90.65 (d, J = 185.7 Hz), 90.25 (d, J = 3.5 Hz), 72.22-71.71 (m), 71.71 (d, J = 16.1 Hz), 66.22-65.97 (m), 30.48; MS, m/z = 257.1 (M + 1).

[00244] The following examples may be synthesized according to procedures analogous to the schemes and examples outlined above.

Table 6

Example	Structure	Name
34		(3aR,5R,6R,7S,7aR)-2-(ethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
35		(3aR,5R,6R,7S,7aR)-2-(dimethylamino)-7-fluoro-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
36		(3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(propylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
37		(3aR,5R,6R,7S,7aR)-7-fluoro-5-(hydroxymethyl)-2-(isobutylamino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol

Example	Structure	Name
38		(3aR,5S,6R,7R,7aR)-5-(difluoromethyl)-7-fluoro-2-(((E)-3-fluoro-2-methylallyl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
39		(3aR,5S,6S,7R,7aR)-5-(fluoromethyl)-2-((4-hydroxybut-2-yn-1-yl)amino)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol
40		(3aR,5S,6S,7aR)-2-((2,2-difluoroethoxy)(methyl)amino)-5-(difluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
41		(3aR,5S,6R,7S,7aR)-7-fluoro-2-(3-fluoroazetidin-1-yl)-5-(fluoromethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol
42		(3aR,5R,6S,7S,7aR)-2-(3,3-difluoroazetidin-1-yl)-7-fluoro-5-methyl-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazol-6-ol

Biological Activity

Assay for determination of K_I values for inhibition of O-GlcNAcase activity

[00245] Experimental procedure for kinetic analyses: Enzymatic reactions were carried out in a reaction containing 50 mM NaH_2PO_4, 100 mM NaCl and 0.1% BSA (pH 7.0) using 2 mM 4-Methylumbelliferyl N-acetyl-β-D-glucosaminide dihydrate (Sigma M2133) dissolved in ddH_2O, as a substrate. The amount of purified human O-GlcNAcase enzyme used in the reaction was 0.7 nM. Test compound of varying concentrations was added to the enzyme prior to initiation of the reaction. The reaction was performed at room temperature in a 96-well plate and was initiated with the addition of substrate. The production of fluorescent product was measured every 60 sec for 45 min with a Tecan Infinite M200 plate-reader with excitation at 355 nM and emission detected at 460 nM, with 4-Methylumbelliferone (Sigma M1381) used to produce a standard curve. The slope of product production was determined for each concentration of compound tested and plotted, using standard curve fitting algorithms for sigmoidal dose response curves. The values for a four parameter logistic curve fit of the data were determined.

[00246] K_I values were determined using the Cheng-Prusoff equation; the K_m of O-GlcNAcase for substrate was 0.2 mM.

[00247] Examples 1 to 33 were tested in the above described assay and exhibited K_I values for inhibition of O-GlcNAcase in the range 0.1 nM-10 μM.

Assay for determination of K_I values for inhibition of β-hexosaminidase activity

[00248] Experimental procedure for kinetic analyses: Enzymatic reactions were carried out in a reaction containing 50 mM NaH_2PO_4, 100 mM NaCl and 0.1% BSA (pH 7.0) using 2 mM 4-Methylumbelliferyl N-acetyl-β-D-glucosaminide dihydrate (Sigma M2133) dissolved in ddH_2O, as a substrate. The amount of purified human β-hexosaminidase enzyme used in the reaction was 24 nM. Test compound of varying concentrations was added to the enzyme prior to initiation of the reaction. The reaction was performed at room temperature in a 96-well plate and was initiated with the addition of substrate. The production of fluorescent product was measured every 60 sec for 45 min with a Tecan Infinite M200 plate-reader with excitation at 355 nM and emission detected at 460 nM, with 4-Methylumbelliferone (Sigma M1381) used to produce a standard curve. The slope of product production was determined for each concentration of compound tested and plotted, using standard curve fitting algorithms for sigmoidal dose response curves. The values for a four parameter logistic curve fit of the data were determined.

[00249] K_I values were determined using the Cheng-Prusoff equation.

[00250] When tested in this assay, many of the compounds described herein exhibit K_I values for inhibition of β-hexosaminidase in the range 10 nM to greater than 100 uM.

[00251] The selectivity ratio for inhibition of O-GlcNAcase over β-hexosaminidase is defined here as:

$$K_I \text{ (β-hexosaminidase)}/K_I \text{ (O-GlcNAcase)}$$

[00252] In general, the compounds described herein exhibited a selectivity ratio in the range of about 10 to 100000. Thus, many compounds of the invention exhibit high selectivity for inhibition of O-GlcNAcase over β-hexosaminidase.

Assay for determination of cellular activity for compounds that inhibit O-GlcNAcase activity

[00253] Inhibition of O-GlcNAcase, which removes O-GlcNAc from cellular proteins, results in an increase in the level of O-GlcNAcylated protein in cells. An increase in O-GlcNAcylated protein can be measured by an antibody, such as RL-2, that binds to O-GlcNAcylated protein. The amount of O-GlcNAcylated protein:RL2 antibody interaction can be measured by enzyme linked immunosorbant assay (ELISA) procedures.

[00254] A variety of tissue culture cell lines, expressing endogenous levels of O-GlcNAcase, can be utilized; examples include rat PC-12, and human U-87, or SK-N-SH cells. In this assay,rat PC-12 cells were plated in 96-well plates with approximately 10,000 cells / well. Compounds to be tested were dissolved in DMSO, either 2 or 10 mM stock solution, and then diluted with DMSO and water in a two-step process using a Tecan workstation. Cells were treated with diluted compounds for 24 h (5.4 µL into 200 µL l well volume) to reach a final concentration of inhibitor desired to measure a compound concentration dependent response, typically, ten 3 fold dilution steps, starting at 10 µM were used to determine a concentration response curve. To prepare a cell lysate, the media from compound treated cells was removed, the cells were washed once with phosphate buffered saline (PBS) and then lysed for 5 minutes at room temperature in 50 µL of Phosphosafe reagent (Novagen Inc, Madison, WI) with protease inhibitors and PMSF. The cell lysate was collected and transferred to a new plate, which was then either coated to assay plates directly or frozen -80°C until used in the ELISA procedure. If desired, the total protein concentration of samples was determined using 20 µL of the sample using the BCA method.

[00255] The ELISA portion of the assay was performed in a black Maxisorp 96-well plate that was coated overnight at 4°C with 100 µL /well of the cell lysate (1:10 dilution of the lysate with PBS containing protease inhibitors, phosphatase inhibitors, and PMSF). The following day the wells were washed 3 times with 300 µL /well of Wash buffer (Tris-buffered saline with 0.1% Tween 20). The wells were blocked with 100 µL /well Blocking buffer (Tris buffered saline w/0.05% Tween 20 and 2.5% Bovine serum albumin). Each well was then washed two times with 300 µL/well of wash buffer. The anti O-GlcNAc antibody RL-2 (Abcam, Cambridge, MA), diluted 1:1000 in blocking buffer, was added at 100 µL/well. The plate was sealed and incubated at 37°C for 2 h with gentle shaking. The wells were then washed 3-times with 300 µL/well wash buffer. To detect the amount of RL-2 bound horse-radish peroxidase (HRP) conjugated goat anti-mouse secondary antibody (diluted 1:3000 in blocking buffer) was added at100 µL /well. The plate was incubated for

60 min at 37°C with gentle shaking. Each well was then washed 3-times with 300 µL/well wash buffer. The detection reagent was added, 100 µL /well of Amplex Ultra RED reagent (prepared by adding 30 µL of 10 mM Amplex Ultra Red stock solution to 10 mL PBS with 18 µL 3% hydrogen peroxide, H_2O_2). The detection reaction was incubated for 15 minutes at room temperature and then read with excitation at 530 nm and emission at 590 nm.

[00256] The amount of O-GlcNAcylated protein, as detected by the ELISA assay, was plotted for each concentration of test compound using standard curve fitting algorithms for sigmoidal dose response curves. The values for a four parameter logistic curve fit of the data were determined, with the inflection point of the curve being the potency value for the test compound.

Assay for determination of apparent permeability (P_{app})

[00257] Bi-directional transport was evaluated in LLC-PK1 cells in order to determine apparent permeability (P_{app}). LLC-PK1 cells can form a tight monolayer and therefore can be used to assess vectorial transport of compounds from basolateral to apical (B→A) and from apical to basolateral (A → B).

[00258] To determine P_{app}, LLC-PK1 cells were cultured in 96-well transwell culture plates (Millipore). Solutions containing the test compounds (1 µM) were prepared in Hank's Balanced Salt Solution with 10 mM HEPES. Substrate solution (150 µL) was added to either the apical (A) or the basolateral (B) compartment of the culture plate, and buffer (150 µL) was added to the compartment opposite to that containing the compound. At t = 3 h, 50 µL samples were removed from both sides of monolayers dosed with test compound and placed in 96 well plates, scintillant (200 µL) or internal standard (100 µL labetolol 1µM) was added to the samples and concentration was determined by liquid scintillation counting in a MicroBeta Wallac Trilux scintillation counter (Perkin Elmer Life Sciences, Boston, MA) or by LCMS/MS (Applied Biosystems SCIEX API 5000 triple quadruple mass spectrometer). [^{3}H]Verapamil (1 µM) was used as the positive control. The experiment was performed in triplicate.

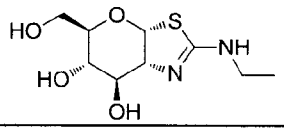
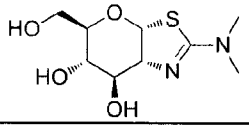
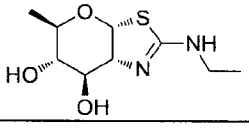
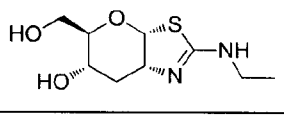
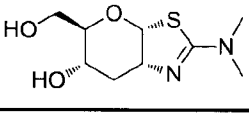
[00259] The apparent permeability, P_{app}, was calculated by the following formula for samples taken at t = 3 h:

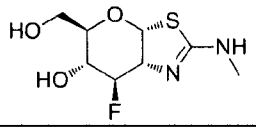
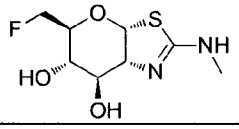
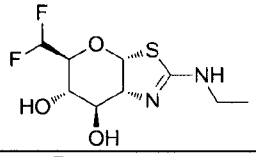
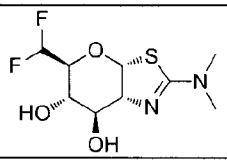
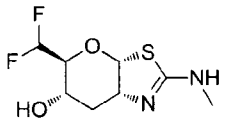
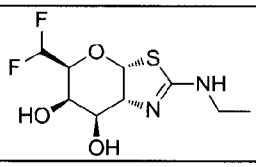
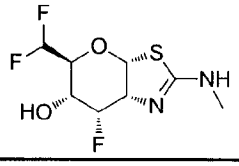
$$P_{app} = \frac{\text{Volume of Receptor Chamber (mL)}}{[\text{Area of membrane (cm}^2)][\text{Initial Concentration } (\mu\text{M})]} x \frac{\Delta \text{ in Concentration } (\mu\text{M})}{\Delta \text{ in Time (s)}}$$

Where: Volume of Receptor Chamber was 0.15 mL; Area of membrane was 0.11 cm^2; the Initial Concentration is the sum of the concentration measured in the donor plus concentration measured in receiver compartments at t = 3 h; Δ in Concentration is concentration in the receiver compartment at 3 h; and Δ in Time is the incubation time (3 x 60 x 60 = 10800 s). P_{app} was expressed as 10^{-6} cm/s. The P_{app} (LLC-PK1 cells) are the average of the P_{app} for transport from A to B and P_{app} for transport from B to A at t = 3 h:

$$P_{app}(\text{LLC}-\text{PK1 Cells}) = \frac{P_{app}(A \rightarrow B) + P_{app}(B \rightarrow A)}{2}$$

Representative data from the binding, cell-based, and permeability assays described above are shown in the following table. Certain compounds of the invention exhibited superior potency or permeability in one or more of these assays as compared to compounds disclosed in WO 2006/092049 and WO 2008/025170. For comparison, the first two table entries show data for compounds (3aR,5R,6S,7R,7aR)-2-(ethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol and (3aR,5R,6S,7R,7aR)-2-(dimethylamino)-5-(hydroxymethyl)-5,6,7,7a-tetrahydro-3aH-pyrano[3,2-d]thiazole-6,7-diol, disclosed in WO 2008/025170.

Example	Structure	Cell-based ELISA EC_{50} (nM)	Fluorescence-based hOGA Ki (nM)	Papp LLC-PK1 cells (10^{-6} cm/s)
N/A		13	0.4	< 1.0
N/A		10	0.3	< 1.0
1		ND	70	ND
2		365	44	3.8
4		358	13	ND

Example	Structure	Cell-based ELISA EC_{50} (nM)	Fluorescence-based hOGA Ki (nM)	Papp LLC-PK1 cells (10^{-6} cm/s)
9		307	1.3	ND
17		34	0.5	7.1
19		53	5.7	6.0
20		6.0	1.4	13.7
27		ND	28	24.0
29		ND	164	ND
33		ND	13	20.1

[00260] The present invention has been described with regard to one or more embodiments. However, it will be apparent to persons skilled in the art that a number of variations and modifications can be made without departing from the scope of the invention as defined in the claims.

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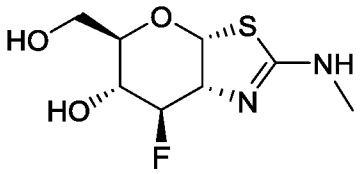
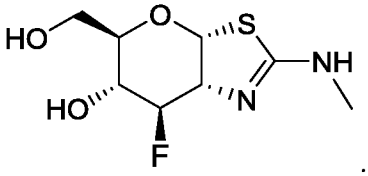
CLAIMS:

1. A compound which is

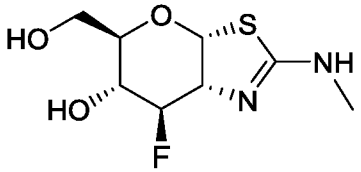


or a pharmaceutically acceptable salt thereof.

2. A compound which is

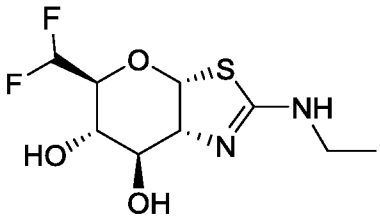


3. A compound which is



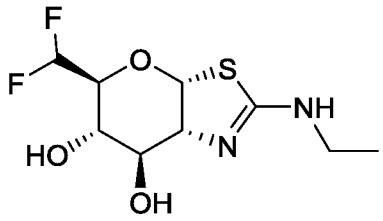
in the form of a pharmaceutically acceptable salt thereof.

4. A compound which is

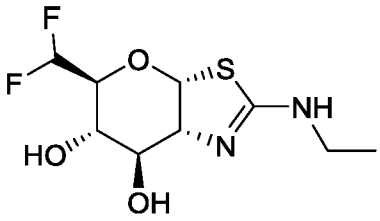


or a pharmaceutically acceptable salt thereof.

5. A compound which is

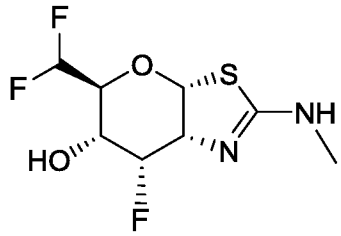


6. A compound which is



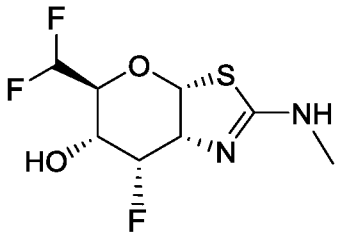
in the form of a pharmaceutically acceptable salt thereof.

7. A compound which is

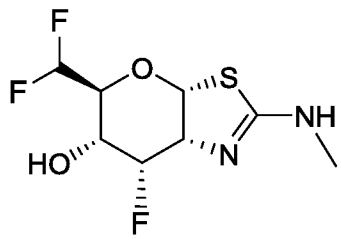


or a pharmaceutically acceptable salt thereof.

8. A compound which is

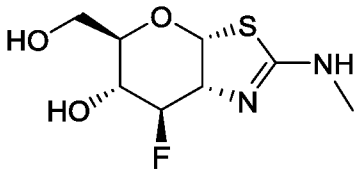


9. A compound which is



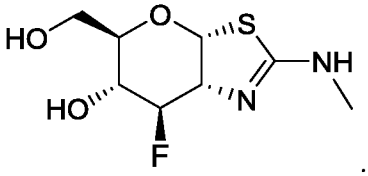
in the form of a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound which is

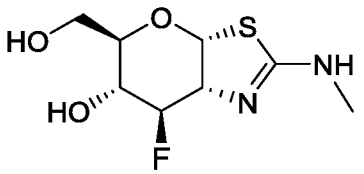


or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of Claim 10 wherein the compound is

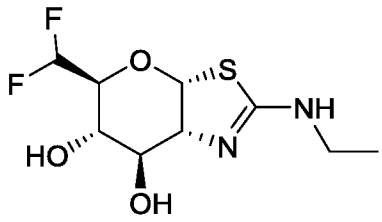


12. The pharmaceutical composition of Claim 10 wherein the compound is



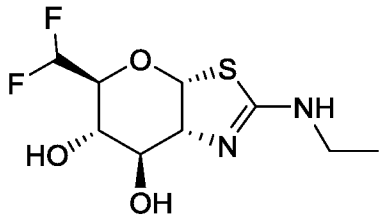
in the form of a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound which is

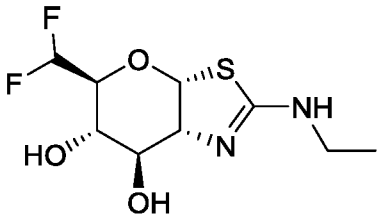


or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of Claim 13 wherein the compound is

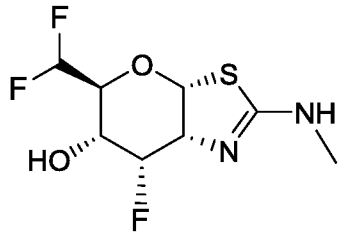


15. The pharmaceutical composition of Claim 13 wherein the compound is



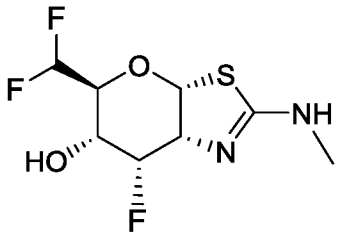
in the form of a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising a compound which is

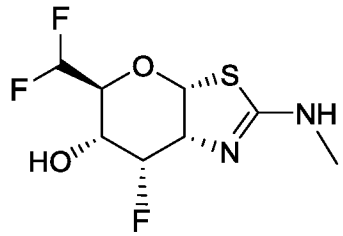


or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition of Claim 16 wherein the compound is



18. The pharmaceutical composition of Claim 16 wherein the compound is



in the form of a pharmaceutically acceptable salt thereof.

19. A method of treating Alzheimer's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 1 to 3 or a pharmaceutically acceptable salt thereof.

20. A method of treating Alzheimer's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 4 to 6 or a pharmaceutically acceptable salt thereof.

21. A method of treating Alzheimer's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 7 to 9 or a pharmaceutically acceptable salt thereof.

22. A method of treating Parkinson's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 1 to 3 or a pharmaceutically acceptable salt thereof.

23. A method of treating Parkinson's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 4 to 6 or a pharmaceutically acceptable salt thereof.

24. A method of treating Parkinson's disease in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 7 to 9 or a pharmaceutically acceptable salt thereof.

25. A method of treating Progressive supranuclear palsy in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound any one of of Claims 1 to 3 or a pharmaceutically acceptable salt thereof.

26. A method of treating Progressive supranuclear palsy in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 4 to 6 or a pharmaceutically acceptable salt thereof.

27. A method of treating Progressive supranuclear palsy in a human patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of any one of Claims 7 to 9 or a pharmaceutically acceptable salt thereof.

28. Use of a therapeutically effective amount of the compound of any one of Claims 1 to 3 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Alzheimer's disease in a human patient in need thereof.

29. Use of a therapeutically effective amount of the compound of any one of Claims 4 to 6 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Alzheimer's disease in a human patient in need thereof.

30. Use of a therapeutically effective amount of the compound of any one of Claims 7 to 9 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Alzheimer's disease in a human patient in need thereof.

31. Use of a therapeutically effective amount of the compound of any one of Claims 1 to 3 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Parkinson's disease in a human patient in need thereof.

32. Use of a therapeutically effective amount of the compound of any one of Claims 4 to 6 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Parkinson's disease in a human patient in need thereof.

33. Use of a therapeutically effective amount of the compound of any one of Claims 7 to 9 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Parkinson's disease in a human patient in need thereof.

34. Use of a therapeutically effective amount of the compound of any one of Claims 1 to 3 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Progressive supranuclear palsy in a human patient in need thereof.

35. Use of a therapeutically effective amount of the compound of any one of Claims 4 to 6 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Progressive supranuclear palsy in a human patient in need thereof.

36. Use of a therapeutically effective amount of the compound of any one of Claims 7 to 9 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for treating Progressive supranuclear palsy in a human patient in need thereof.

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Alectos Therapeutics, Inc.

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