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(54) Title: SELECTIVE GLYCOSIDASE INHIBITORS AND USES THEREOF

(57) Abstract: The invention is directed to compounds for selectively inhibiting glycosidases, uses of the compounds and pharmaceutical compositions including 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.

TITLE OF THE INVENTION
SELECTIVE GLYCOSIDASE INHIBITORS AND USES THEREOF

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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]

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.

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]

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.

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]

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]

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 healthy individuals as well as patients suffering from AD or related neurodegenerative diseases.

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]

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] .

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]

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.

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 (αβ), a heterodimeric isozyme, is composed of an α- and a β-subunit. Hexosaminidase B (ββ), a homodimeric isozyme, is

composed of two β-subunits. The two subunits, α- and β-, 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]

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.

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 β-N-acetylglucosaminidases, many compounds that act to block O-GlcNAcase function are non-specific and act potently to inhibit the lysosomal β-hexosaminidases.

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]

STZ has long been used as a diabetogenic compound because it has a particularly detrimental effect on β-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 β-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]

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.

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]

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.

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

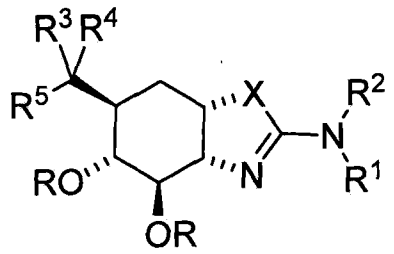
2010; and PCT/CA2009/001302, filed 16 September 2009, published under WO 2010/037207 on 8 April 2010, describe selective inhibitors of O-GlcNAcase.

SUMMARY OF THE INVENTION

The invention is directed to compounds for selectively inhibiting glycosidases, uses of the compounds and pharmaceutical compositions including 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.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula (I) or a pharmaceutically acceptable salt thereof:

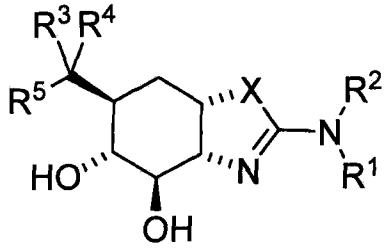


(I)

wherein: X is O or S; each R is independently H or $C(O)CH_3$; R^1 and R^2 are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_n$-cyclopropyl and $-(CH_2)_n$-cyclobutyl wherein n is 0, 1, 2, 3 or 4; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine, pyrrolidine or piperidine, said C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_n$-cyclopropyl, $-(CH_2)_n$-cyclobutyl, azetidine, pyrrolidine or piperidine optionally substituted from one up to the maximum number of substituents with fluoro and methyl; R^3 is selected from the group consisting of: C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-6}cycloalkyl, aryl and heteroaryl, each optionally substituted from one up to the maximum number of substituents with fluoro and OH; R^4 is selected from the group consisting of: H, F, C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkynyl, each excluding hydrogen and fluoro, optionally substituted from one up to the maximum number of substituents with fluoro and OH; or R^3 and R^4 and the carbon atom to which they are attached may join together to form vinyl or a 3 to 7-membered carbocyclic or heterocyclic ring, said 3 to 7-membered carbocyclic or heterocyclic ring optionally containing a double bond and optionally substituted from one up to the maximum number of substituents with fluoro and OH; and R^5 is selected from H, F, OH and $OC(O)CH_3$; with the proviso that when R^4 is F then R^5 is other than OH and $OC(O)CH_3$.

In an embodiment of the invention, X is O. In another embodiment of the invention X is S.

The invention also encompasses a genus of compounds of Formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein X is O or S; R^1 and R^2 are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_n$-cyclopropyl and $-(CH_2)_n$-cyclobutyl wherein n is 0, 1, 2, 3 or 4; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine, pyrrolidine or piperidine, said C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_n$-cyclopropyl, $-(CH_2)_n$-cyclobutyl, azetidine, pyrrolidine or piperidine optionally substituted from one up to the maximum number of substituents with fluoro and methyl; R^3 is selected from the group consisting of: C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-6}cycloalkyl, aryl and heteroaryl, each optionally substituted from one up to the maximum number of substituents with fluoro and OH; R^4 is selected from the group consisting of: H, F, C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkynyl, each excluding hydrogen and fluoro, optionally substituted from one up to the maximum number of substituents with fluoro and OH; or R^3 and R^4 and the carbon atom to which they are attached may join together to form vinyl or a 3 to 7-membered carbocyclic or heterocyclic ring, said 3 to 7-membered carbocyclic or heterocyclic ring optionally containing a double bond and optionally substituted from one up to the maximum number of substituents with fluoro and OH; and R^5 is selected from H, F and OH; with the proviso that when R^4 is F then R^5 is other than OH.

Within the genus, the invention encompasses a first sub-genus of compounds of Formula (Ia) wherein: R^1 and R^2 are independently selected from H, C_{1-4}alkyl and C_{1-4}alkoxy; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine or pyrrolidine; R^3 is C_{1-6}alkyl, optionally substituted from one up to the maximum number of substituents with fluoro; R^4 is selected from the group consisting of: H and C_{1-6}alkyl; and R^5 is OH. Within the first sub-genus, the invention further encompasses compounds of Formula (Ia) wherein: R^1 is methyl, ethyl or propyl; R^2 is H or methyl; R^3 is methyl; and R^4 is H or methyl. In an embodiment of the foregoing, X is O. In another embodiment of the foregoing, X is S.

Also within the genus, the invention encompasses a second sub-genus of compounds of Formula (Ia) wherein: R^3 and R^4 and the carbon atom to which they are attached may join together to form a 3 to 7-membered carbocyclic or heterocyclic ring, said 3 to 7-membered carbocyclic or heterocyclic ring optionally containing a double bond and optionally substituted from one up to the maximum number of substituents with fluoro and OH.

Also within the genus, the invention encompasses a third sub-genus of compounds of Formula (Ia) wherein: R^1 and R^2 are independently selected from the group consisting of: H, C_{1-6}alkyl and C_{1-6}alkoxy; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine or pyrrolidine, said C_{1-6}alkyl, C_{1-6}alkoxy, azetidine or pyrrolidine optionally substituted with 1 to 3 substituents selected from fluoro and methyl; R^3 is selected from the group consisting of: C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{3-6}cycloalkyl, each optionally substituted with 1 to 3 substituents selected from fluoro and OH; and R^4 is selected from the group consisting of: H, F, C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkynyl, each excluding hydrogen and fluoro, optionally substituted with 1 to 3 substituents selected from fluoro and OH; or R^3 and R^4 and the carbon atom to which they are attached may join together to form a 3- to 6-membered carbocyclic ring optionally containing a double bond and optionally substituted with 1 to 3 substituents selected from fluoro and OH.

Also within the genus, the invention encompasses a fourth sub-genus of compounds of Formula (Ia) wherein R^3 is CF_3, R^4 is H and R^5 is OH.

The invention also encompasses the compounds that follow or pharmaceutically acceptable salts thereof.

The invention also encompasses a pharmaceutical composition comprising the compound of Formula (I) or (Ia) in combination with a pharmaceutically acceptable carrier.

The invention also encompasses a method of selectively inhibiting O-GlcNAcase in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt thereof.

The invention also encompasses a method of elevating the level of O-GlcNAc in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt thereof.

The invention also encompasses a method of treating a condition that is modulated by O-GlcNAcase, in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt thereof. An aspect of the invention encompasses this method wherein the condition may include an inflammatory disease, an allergy, asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, atherosclerosis, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing

spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis, systemic anaphylaxis or hypersensitivity response, drug allergy, insect sting allergy, autoimmune disease, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Guillain-Barré syndrome, systemic lupus erythematosus, myastenia gravis, glomerulonephritis, autoimmune thyroiditis, graft rejection, allograft rejection, graft-versus-host disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, spondyloarthropathy, scleroderma, psoriasis, T-cell mediated psoriasis, inflammatory dermatosis, dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, vasculitis, necrotizing, cutaneous, and hypersensitivity vasculitis, eosinphilic myotis, eosiniphilic fasciitis, solid organ transplant rejection, heart transplant rejection, lung transplant rejection, liver transplant rejection, kidney transplant rejection, pancreas transplant rejection, kidney allograft, lung allograft, epilepsy, pain, fibromyalgia, stroke, neuroprotection.

The invention also encompasses a method of treating a condition wherein the condition may be a neurodegenerative disease, e.g., a tauopathy, cancer and stress, in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt thereof. An aspect of the invention encompasses this method wherein the condition may 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, Huntington's disease, Parkinson's disease, Schizophrenia, Mild Cognitive Impairment (MCI), Neuropathy (including peripheral neuropathy, autonomic neuropathy, neuritis, and diabetic neuropathy), or Glaucoma. Another aspect of the invention encompasses this method wherein the stress may be a cardiac disorder. In another aspect, the cardiac disorder may include ischemia; hemorrhage; hypovolemic shock; myocardial infarction; an interventional cardiology procedure; cardiac bypass surgery; fibrinolytic therapy; angioplasty; and stent placement.

The compounds of the invention 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. In

some embodiments, the β-hexosaminidase is a mammalian β-hexosaminidase, such as a rat, mouse or human β-hexosaminidase.

Compounds of the invention selectively inhibit the activity of a mammalian O-GlcNAcase over a mammalian 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.

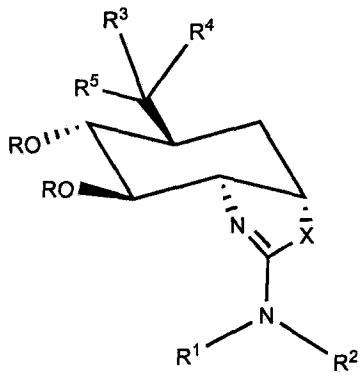
One or more of the compounds of the present invention elevate O-GlcNAc levels on O-GlcNAc-modified polypeptides or proteins *in vivo* specifically via interaction with an O-GlcNAcase enzyme, and are effective in treating conditions which require or respond to inhibition of O-GlcNAcase activity.

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 may therefore be useful to treat Alzheimer's disease and related tauopathies. In some embodiments, one or more of the compounds may be 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 may therefore be useful for treatment of disorders responsive to such increases in O-GlcNAc modification; these disorders may 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.

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.

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



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.

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.

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.

"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.

"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.

"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.

"Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms, including for example, 6-14 members. Examples of aryl include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, dihydrobenzopyranyl, 1,4-benzodioxanyl, and the like. Unless stated otherwise specifically herein, the term "aryl" is meant to include aryl groups optionally substituted by one or more substituents as described herein.

"Heteroaryl" refers to a single or fused aromatic ring group containing one or more heteroatoms in the ring, for example N, O, S, including for example, 5-14 members, such as 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 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, benzimidazole, benzoxazole, benzothiazole, indolizine, indole, isoindole, benzofuran, benzothiophene, 1H-indazole, purine, 4H-quinolizine,

quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine. Unless stated otherwise specifically herein, the term "heteroaryl" is meant to include heteroaryl groups optionally substituted by one or more substituents as described herein.

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

"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.

The term "3 to 7-membered carbocyclic or heterocyclic ring" means a monocylic carbon ring of 3 to 7 atoms or a monocyclic ring of 3 to 7 atoms containing one or more heterotaoms selected from O, N and S.

"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 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. 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

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 may 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 may 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.

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 may 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.

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. Accordingly, a compound of the invention may be used to study and treat AD and other tauopathies.

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) or (Ia). 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 may 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.

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]

Tauopathies that may be treated with the compounds 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.

One or more of the compounds of this invention may also be 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.

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]

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.

In addition, compounds that affect 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.

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 an 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

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) or (Ia) are provided.

The compounds of Formula (I) or (Ia) and their pharmaceutically acceptable salts, stereoisomers, 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.

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

-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.

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).

In alternative embodiments, a compound may be supplied as "prodrugs" 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.

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 wherein 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.

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.

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.

"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.

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) or (Ia) 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.

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.

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.

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.

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.

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.

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.

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 a 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.

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.

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.

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.

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

In the compounds of generic Formula (I) or (Ia), 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) or (Ia). 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) or (Ia) 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

A compound of Formula (I) or (Ia) 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) or (Ia) 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) or (Ia).

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 (Ia) 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.

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.

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) or (Ia), 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.

In some embodiments, one or more of the compounds may be 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 may include neurodegenerative diseases, including Alzheimer's disease, and cancer.

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.

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

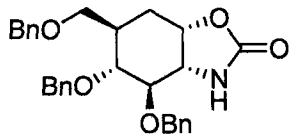
INTERMEDIATE EXAMPLES

Abbreviations

DCM	=	dichloromethane
DIAD	=	diisopropyl azodicarbonate
DMSO	=	dimethylsulfoxide

DMP	=	Dess-Martin periodinane
NBS	=	N-bromosuccinimide
TFA	=	2,2,2-trifluoroacetic acid
THF	=	tetrahydrofuran

Intermediate 1 rac-(3aS,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-hexahydrobenzo[d]oxazol-2(3H)- one



Step 1.

To a solution of rac-((((1R,2R,6R)-6-((benzyloxy)methyl)cyclohex-3-ene-1,2-diyl)bis-(oxy))bis(methylene))dibenzene (*Carb. Res.*, **1990**, *204*, 51-64; *Carb. Res.*, **1990**, *206*, 352-60) (3.71 g, 9.02 mmol) in DMSO (40 mL) and water (0.487 mL, 27.1 mmol) at 10°C was added freshly recrystallised NBS (3.21 g, 18.04 mmol) in one portion. The mixture (which slowly became a yellow solution) was stirred at room temperature for 2.5 h. The reaction was diluted with aqueous saturated $NaHCO_3$ (300 mL) and extracted with EtOAc (2 × 150 mL). The combined extracts were washed with brine and dried over $MgSO_4$. Solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 20-30% EtOAc in hexanes to give a mixture of rac-(1S,2R,3S,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-2-bromocyclohexanol and a diastereomeric side-product in a 9:1 ratio, respectively (4.35 g, 95%). An NMR sample was obtained by a second silica gel column eluted with 20% EtOAc in hexanes. The major product exhibited ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 15H), 4.68 (d, J = 11.2 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 12.1 Hz, 1H), 4.39 (d, J = 12.1 Hz, 1H), 4.33 (dd, J = 6.0, 3.5 Hz, 1H), 4.12 (m, 1H), 3.87 (dd, J = 6.8, 3.5 Hz, 1H), 3.77 (t, J = 6.8 Hz, 1H), 3.58- 3.53 (m, 2H), 2.31- 2.23 (m, 1H), 2.20 (ddd, J = 13.6, 8.8, 3.6 Hz, 1H), 1.82 (dt, J = 14.0, 5.4 Hz, 1H).

Step 2.

To a solution of the mixture obtained above (3.82 g, 7.47 mmol) in dry DCM (26 mL) at 0°C was added a solution of benzoylisocyanate (90%, 1.19 g, 8.01 mmol) in dry DCM (6 mL) dropwise. The mixture was stirred at room temperature for 1.5 h. Solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 40-50% Et_2O in hexanes to give the product rac-(1S,2R,3S, 4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-2-bromocyclohexyl benzoyl-carbamate (4.20 g, 85%) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.79 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.49

(t, J = 7.6 Hz, 2H), 7.38-7.23 (m, 15H), 5.34 (q, J = 4.0 Hz, 1H), 4.86 (d, J = 11.2 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.55 (m, 1H), 4.52 (d, J = 10.8 Hz, 1H), 4.46 (s, 2H), 3.84 (t, J = 8.4 Hz, 1H), 3.79 (dd, J = 8.4, 3.6 Hz, 1H), 3.60 (dd, J = 9.2, 6.0 Hz, 1H), 3.52 (dd, J = 9.2, 3.6 Hz, 1H), 2.43 (ddd, J = 14.8, 11.6, 2.8 Hz, 1H), 2.18-2.09 (m, 1H), 2.00 (dtd, J = 14.8, 4.0, 1.2 Hz, 1H).

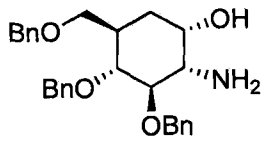
Step 3.

To a solution of above product (390 mg, 0.593 mmol) in dry THF (10 mL) at 0°C was added NaH (60%, 45 mg, 1.13 mmol) After stirring at room temperature for 1.5 h, the mixture was heated at reflux for 20 h. Solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 20-50% EtOAc in hexanes to give rac-(3aS,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-hexahydrobenzo[d]oxazol-2(3H)- one as a white solid (rac-**Intermediate Example 1**) (110 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.39-7.17 (m, 15H), 7.08 (d, J = 8.0 Hz, 2H), 4.99-4.93 (m, 2H), 4.67 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 12.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.27 (d, J = 11.2 Hz, 1H), 4.24 (t, J = 2.4 Hz, 1H), 3.71 (dt, J = 5.6, 1.6 Hz, 1H), 3.52-3.47 (m, 2H), 2.32-2.24 (m, 1H), 2.12-2.03 (m, 2H).

Step 4.

rac-(3aS,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-hexahydrobenzo[d]oxazol-2(3H)-one was resolved by preparative chiral HPLC using a Chiralpak IA column (4.6*15cm, 5um), eluting with Hexane:EtOH 70:30 to give optically pure (>99.9% ee) (3aS,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-hexahydrobenzo[d]oxazol-2(3H)-one (first eluting, $[\alpha]_D$ = +110.33°, DCM as solvent) and (3aR,4S,5S,6S,7aR)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)hexahydrobenzo[d]oxazol-2(3H)-one (second eluting, $[\alpha]_D$ = -112.67°, DCM as solvent). Unless otherwise noted, these chirally pure intermediates were used for the synthesis of chirally pure final compounds following the procedures described herein.

Intermediate 2 rac-(1R,2R,3S,4S,5S)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol

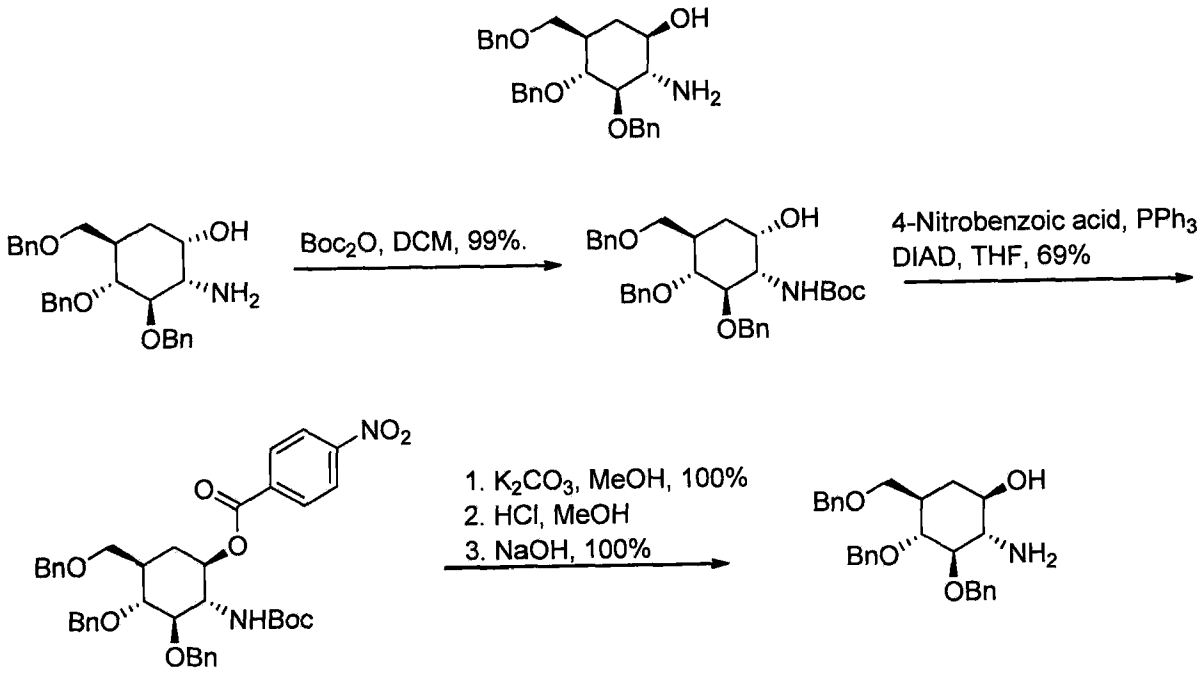


To a mixture of rac-(3aS,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-hexahydrobenzo[d]oxazol-2(3H)-one (280 mg, 0.592 mmol) in ethanol (2 mL) was added 2 N

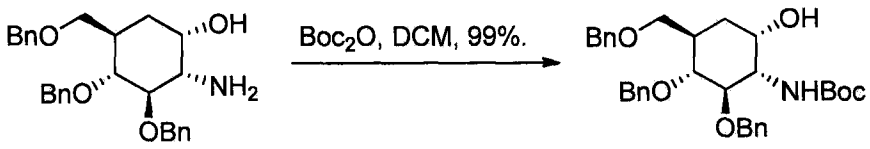
NaOH (10 mL). The mixture was heated at reflux for 16 h. After cooling to room temperature, the mixture was extracted with DCM (3 × 15 mL). The combined extracts were washed with brine and dried over Na_2SO_4. Solvents were evaporated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with 5% MeOH in DCM and 94:4:2 DCM-MeOH-NH_4OH(28% aqueous) to give rac-(1R,2R,3S,4S,5S)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol (Intermediate Example 2) (227 mg, 86%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 15H), 5.01 (d, J = 11.5 Hz, 1H), 4.84 (d, J = 10.9 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 10.9 Hz, 1H), 4.47 (s, 2H), 3.86 (q, J = 2.8 Hz, 1H), 3.79 (dd, J = 9.0, 4.2 Hz, 1H), 3.58-3.53 (m, 2H), 3.44 (dd, J = 9.0, 2.5 Hz, 1H), 2.85 (d, J = 6.7 Hz, 1H), 2.27- 2.15 (m, 1H), 1.94 (dt, J = 14.5, 3.5 Hz, 1H), 1.67 (ddd, J = 14.8, 12.6 Hz, 2.4, 1H).

The individual enantiomers of Intermediate Example 2 (1S,2S,3R,4R,5R)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol and (1R,2R,3S,4S,5S)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol were obtained by a similar procedure as described above but starting with the individual enantiomers of Intermediate Example 1.

Intermediate 3 (1R,2S,3R,4R,5R)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol

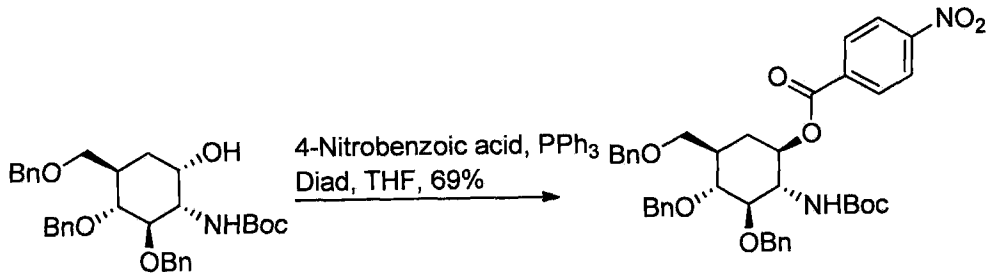


Step 1 *tert*-Butyl((1S,2R,3R,4R,6S)-2,3-bis(benzyloxy)-4-((benzyloxy)methyl)-6-hydroxycyclohexyl)carbamate



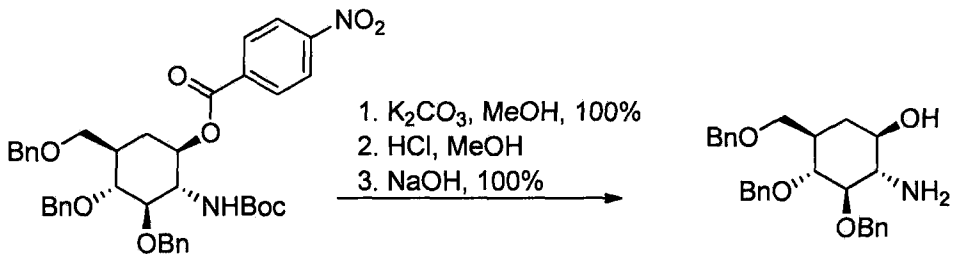
A mixture of (1S,2S,3R,4R,5R)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol (2.60 g, 5.80 mmol) and di-*tert*-butyl dicarbonate (2.60 g, 120 mmol) in DCM (50 mL) was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:10 to 2:3), affording the title compound as a white solid (3.20 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 15H), 4.86 – 4.81 (m, 3H), 4.66 (d, J = 11.3 Hz, 1H), 4.55 (d, J = 10.5 Hz, 1H), 4.45 (s, 2H), 4.14 (s, broad, 1H), 3.69 – 3.66 (m, 2H), 3.57 – 3.52 (m, 2H), 3.48 – 3.46 (m, 1H), 2.20 – 2.15 (m, 2H), 1.89 – 1.84 (m, 1H), 1.72 – 1.68 (m, 1H), 1.43 (s, 9H).

Step 2. (1R,2S,3R,4R,5R)-3,4-Bis(benzyloxy)-5-((benzyloxy)methyl)-2-((tert-butoxycarbonyl)amino)cyclohexyl 4-nitrobenzoate



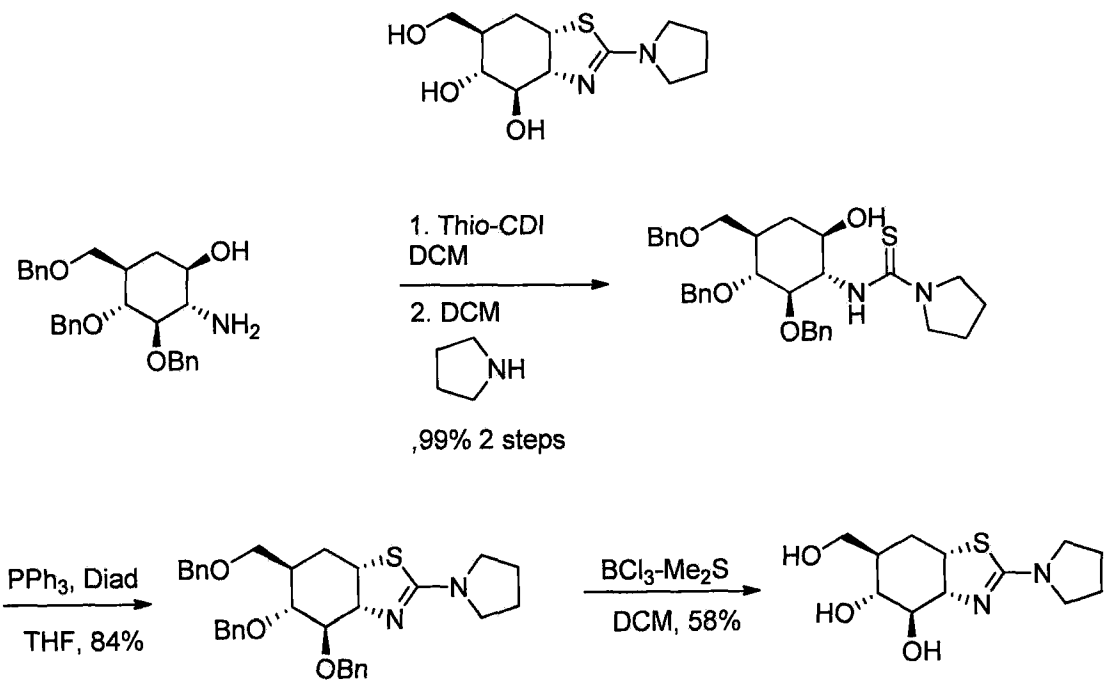
To a solution of *tert*-butyl ((1S,2R,3R,4R,6S)-2,3-bis(benzyloxy)-4-((benzyloxy)methyl)- 6-hydroxycyclohexyl)carbamate (3.20 g, 5.85 mmol), triphenylphosphine (1.92 g, 7.31 mmol) and 4-nitrobenzoic acid (1.37 g, 8.19 mmol) in anhydrous THF (50 mL), at 0°C, was added DIAD (1.42 g, 7.02 mmol) slowly. After addition the mixture was stirred at room temperature for 3 h. The solvent were evaporated under reduced pressure, and the residue was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), affording the title compound as a white solid (2.80 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 4H), 7.33 – 7.25 (m, 15H), 4.90 – 4.86 (m, 3H), 4.71 (d, J = 11.3 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.45 (s, 2H), 4.24 (d, J = 9.7 Hz, 1H), 3.97 – 3.93 (m, 1H), 3.68 – 3.63 (m, 2H), 3.49 (dd, J = 2.0, 8.8 Hz, 1H), 3.38 (t, J = 10.1 Hz , 1H), 2.22 – 2.17 (m, 1H), 1.84 – 1.76 (m, 2H), 1.28 (s, 9H).

Step 3. (1R,2S,3R,4R,5R)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol

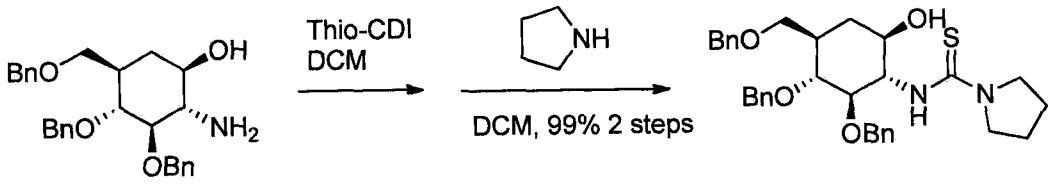


A suspension of (1R,2S,3R,4R,5R)-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)-2- ((tert-butoxycarbonyl)amino)cyclohexyl 4-nitrobenzoate (2.80 g, 4.02 mmol) and anhydrous K_2CO_3 (0.70 g, 0.51 mmol) in MeOH (100 mL) was stirred at room temperature for 2 h. The resulted clear solution was concentrated, and DCM (80 mL) was added. The mixture was washed with saturated aqueous $NaHCO_3$ (60 mL), and 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 purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:3 to 1:1), affording a white solid. The solid was dissolved in mixed MeOH and EtOAc (30 mL, 2::1). HCl (g) was bubbled into the solution for 30 sec, and the mixture was stirred at room temperature for 2 h. The solvent was then removed, water (30 mL) was added and the mixture was basified with diluted aqueous NaOH solution. Extraction with DCM (2 × 40 mL) was performed, and the combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure, affording the title compound as an off-white solid (1.54 g, 94%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 15H), 4.98 (d, J = 11.3 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 10.8 Hz, 1H), 4.47 (s, 2H), 3.64 (dd, J = 4.9, 8.9 Hz, 1H), 3.54 – 3.48 (m, 2H), 3.34 – 3.30 (m, 1H), 3.19 (t, J = 9.4 Hz; 1H), 2.53 – 2.50 (m, 1H), 2.08 – 2.02 (m, 1H), 1.75 – 1.72 (m, 1H), 1.59 – 1.52 (m, 1H).

Intermediate 4 8(3aR,4R,5R,6R,7aS)-6-(hydroxymethyl)-2-(pyrrolidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

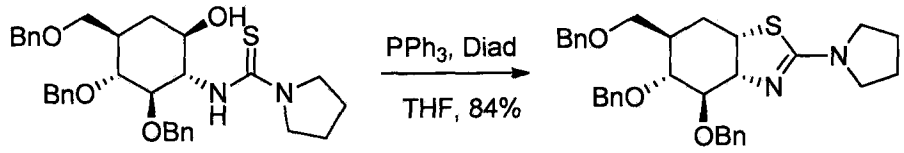


Step 1. *N*-((1S,2R,3R,4R,6R)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)-6-hydroxycyclohexyl)pyrrolidine-1-carbothioamide



A mixture of (1R,2S,3R,4R,5R)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol (0.210 g, 0.469 mmol), 1,1-thiocarbonyldiimidazole (Thio-CDI) (0.125 g, 0.704 mmol) in DCM (10 mL) was stirred at room temperature for 3 h. Pyrrolidine (0.10 mL) was then added, and the mixture was further stirred for 1 h. The solvent was removed under reduced pressure, and the residue was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 2::3 to 4::1), affording the product as a pale yellow solid (0.26 g, 99%). ^{1}H NMR (400 MHz, CDCl3) δ 7.29 – 7.16 (m, 15H), 5.06 (d, J = 7.5 Hz, 1H), 4.77 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 10.8 Hz, 1H), 4.70 – 4.66 (m, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 10.8 Hz, 1H), 4.42 (s, 2H), 4.19 (s, broad, 1H), 3.65 (t, J = 8.8 Hz, 1H), 3.56 (dd, J = 4.5, 8.8 Hz, 1H), 3.51 – 3.40 (m, 3H), 2.07 – 2.02 (m, 1H), 1.76 – 1.62 (m, 6H).

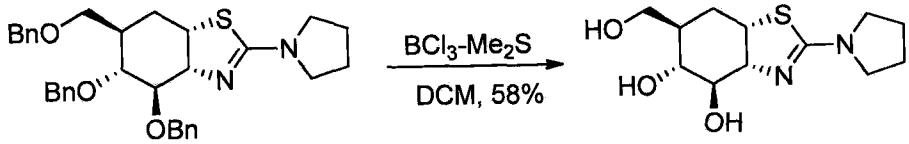
Step 2 (3aR,4R,5R,6R,7aS)-4,5-Bis(benzyloxy)-6-((benzyloxy)methyl)-2-(pyrrolidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole



To a solution of *N*-((1S,2R,3R,4R,6R)-2,3-bis(benzyloxy)-4-((benzyloxy)methyl)-6-hydroxycyclohexyl)pyrrolidine-1-carbothioamide (0.260 g, 0.464 mmol) and triphenylphosphine (0.183 g, 0.700 mmol) in anhydrous THF (6.0 mL) was added DIAD (0.131 g, 0.650 mmol). After addition the mixture was stirred at room temperature for 60 h. The solvent was evaporated under reduced pressure, and the residue was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:10 to 1:4), affording as a colorless oil (0.21 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.42 (m, 2H), 7.34 – 7.23 (m, 13H), 4.95 (d, J = 11.6 Hz, 1H), 4.86 (d, J = 11.0 Hz, 1H), 4.76 (d, J = 11.6 Hz, 1H), 4.56 (d, J = 11.0 Hz, 1H), 4.50 – 4.43 (m, 2H), 3.80 (d, J = 7.6 Hz, 1H), 3.78 – 3.76 (m, 2H), 3.68 (dd, J = 4.0, 9.0 Hz, 1H), 3.57 – 3.43 (m, 4H), 3.13 (d, J = 6.2 Hz, 1H), 2.89 – 2.88 (m, 1H), 2.28 – 2.23 (m, 1H), 2.05 – 2.02 (m, 1H), 2.00 – 1.90 (m, 4H), 1.87 – 1.82 (m, 1H).

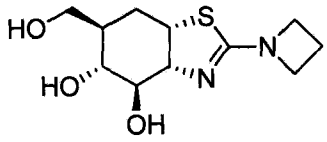
Step 3.

(3aR,4R,5R,6R,7aS)-6-(hydroxymethyl)-2-(pyrrolidin-1-yl)-3a,4,5,6,7,7a- hexahydrobenzo[d]thiazole-4,5-diol

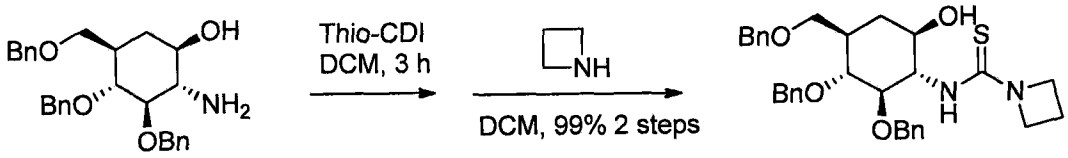


To a solution of (3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-2-(pyrrolidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole (0.200 g, 0.369 mmol) was added excess boron trichloride-methyl sulfide complex (1.70 g, 9.48 mmol). The mixture was stirred at room temperature for 4 days, and then quenched with MeOH at 0°C. The quenched solution was stirred for 10 min, and then concentrated under reduced pressure to dryness. The residue was purified on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/CH_2Cl_2, 1: 4), affording (3aR,4R,5R,6R,7aS)-6-(hydroxymethyl)-2-(pyrrolidin-1-yl)-3a,4,5,6,7,7a- hexahydrobenzo[d]thiazole-4,5-diol an off-white solid (0.058 g, 58%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.35 – 4.33 (m, 1H), 3.79 (dd, J = 4.1, 10.4 Hz, 1H), 4.74 (dd, J = 6.1, 8.6 Hz, 1H), 3.63 (dd, J = 6.1, 10.4 Hz, 1H), 3.50 – 3.46 (m, 2H), 3.44 – 3.30 (m, 3H), 3.22 (t, J = 10.4, 1H), 2.23 – 2.18 (m, 1H), 1.98 – 1.91 (m, 5H), 1.78 – 1.61 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 164.62, 78.45, 76.43, 74.37, 64.12, 54.72, 50.27, 40.73, 26.90, 26.44; MS, m/z = 273 (M + 1).

Intermediate 5 (3aR,4R,5R,6R,7aS)-2-(azetidin-1-yl)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

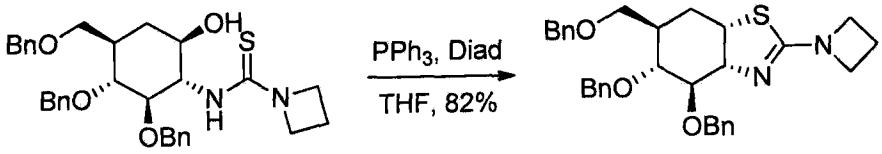


Step 1. *N*-((1S,2R,3R,4R,6R)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)-6-hydroxycyclohexyl)azetidine-1-carbothioamide



The title compound was prepared via a synthetic procedure as described above for Intermediate Example 4 Step 1 from **(1R,2S,3R,4R,5R)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol** (0.230 g, 0.515 mmol), using a DCM solution of azetidine free base, which was obtained from azetidine hydrochloride salt by basification with saturated aqueous Na_2CO_3 solution and subsequent extraction with DCM. After purification on silica gel by automatic flash column chromatography (EtOAc/hexanes, 3:2 to 10:1), The title compound was isolated as a pale yellow solid (0.28 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 15H), 4.80 (s, broad, 1H), 4.85 (d, J = 12.0 Hz, 1H), 4.80 (d, J = 10.8 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 10.8 Hz, 1H), 4.50 (s, broad, 1H), 4.48 (s, 2H), 3.96 (s, broad, 2H), 3.69 (t, J = 8.8 Hz, 1H), 3.63 (dd, J = 4.5, 8.8 Hz, 1H), 3.62 – 3.46 (m, 3H), 2.15 – 2.09 (m, 2H), 1.76 – 1.66 (m, 3H).

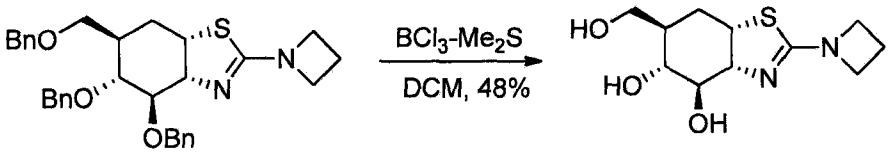
Step 2. (3aR,4R,5R,6R,7aS)-2-(Azetidin-1-yl)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole



Prepared by a Mitsunobu reaction via a procedure as described above in Intermediate Example 4, Step 2 from *N*-((1S,2R,3R,4R,6R)-2,3-Bis(benzyloxy)-4-((benzyloxy)methyl)-6-hydroxycyclohexyl) azetidine- 1-carbothioamide (0.280 g, 0.512 mmol). After purification on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), the product was obtained as a colorless oil (0.22 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.41 (m, 2H), 7.35 – 7.23 (m, 13H), 4.92 (d, J = 11.5 Hz, 1H), 4.84 (d, J = 11.0 Hz, 1H), 4.76 (d, J = 11.5

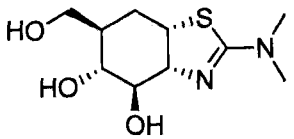
Hz, 1H), 4.55 (d, J = 11.0 Hz, 1H), 4.49 – 4.42 (m, 2H), 4.23 – 4.18 (m, 2H), 4.13 – 4.06 (m, 2H), 3.78 (d, J = 7.6 Hz, 1H), 3.67 (dd, J = 4.9, 9.0 Hz, 1H), 3.47 – 3.42 (m, 2H), 2.97 (d, J = 6.2 Hz, 1H), 2.84 – 2.83 (m, 1H), 1.81 (quint, J = 7.2 Hz, 2H), 2.21 – 2.18 (m, 1H), 2.05 – 1.98 (m, 1H), 1.82 – 1.80 (m, 1H).

Step 3 (3aR,4R,5R,6R,7aS)-2-(azetidin-1-yl)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

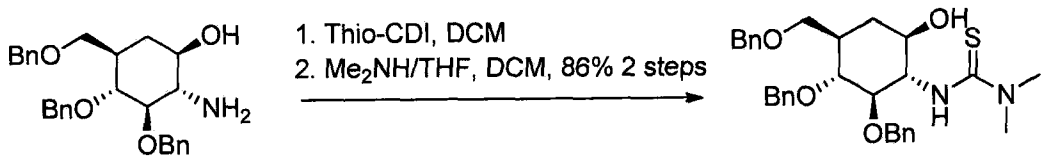


This compound was prepared by boron trichloride-methyl sulfide de-benzylation via a procedure as described above in Example 4, Step 3 from (3aR,4R,5R,6R,7aS)-2-(Azetidin-1-yl)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole (0.220 g, 0.417 mmol). Purification on silica gel by flash column chromatography (1.0 M NH_3 in $MeOH/CH_2Cl_2$, 1: 4), afforded the title compound as an off-white solid (0.052 g, 48%). ^1H NMR (400 MHz, CD_3OD) δ 4.37 – 4.33 (m, 1H), 4.08 – 3.98 (m, 4H), 3.80 – 3.75 (m, 2H), 3.62 (dd, J = 6.3, 10.8 Hz, 1H), 3.40 (t, J = 9.1, 1H), 3.32 (t, J = 9.8 Hz, 1H), 2.35 (quint, J = 7.6, 2H), 2.22 – 2.17 (m, 1H), 1.96 – 1.89 (m, 1H), 1.78 – 1.70 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.63, 78.24, 76.76, 74.30, 64.03, 55.10, 53.30, 40.73, 26.99, 17.58; MS, m/z = 281 (M + 23).

Intermediate 6 (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



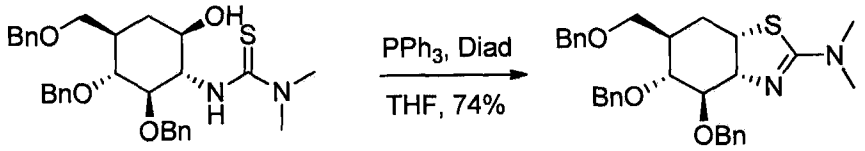
Step 1. (3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-N,N-dimethyl-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazol-2-amine



The title compound was prepared via a synthetic procedure as described above in Intermediate Example 4, Step 1 from (1R,2S,3R,4R,5R)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol (0.380 g, 0.850 mmol), using Me_2NH in THF (2.0 M). After

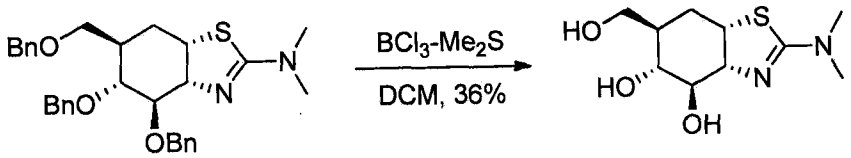
purification on silica gel by automatic flash column chromatography (EtOAc/hexanes, 3:2 to 2:1), The product was obtained as an pale yellow solid (0.39 g, 86%).

Step 2. (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-4,5-bisbenzyloxy-6-(benzyloxyoxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole



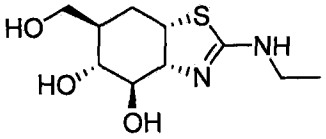
Prepared by a Mitsunobu reaction via a procedure as described in Example 4, Step 2 from (3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-N,N-dimethyl-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazol-2-amine (0.39 g, 0.73 mmol). After purification on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), The product was obtained as a colorless oil (0.28 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.42 (m, 2H), 7.34 – 7.22 (m, 13H), 4.96 (d, J = 11.5 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.0 Hz, 1H), 4.45 – 4.42 (m, 2H), 3.81 (d, J = 7.9 Hz, 1H), 3.67 (dd, J = 5.0, 9.0 Hz, 1H), 3.50 – 3.44 (m, 2H),3.42 (s, 3H), 3.23 (s, 3H), 3.18 (d, J = 6.3 Hz, 1H), 2.85 – 2.83 (m, 1H), 2.31 – 2.26 (m, 1H), 2.06 – 1.99 (m, 1H), 1.87 – 1.82 (m, 1H).

Step 3. (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole- 4,5-diol

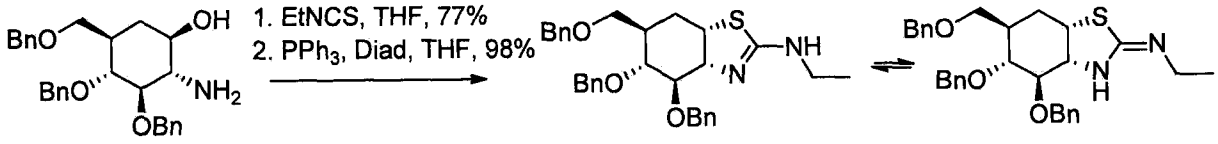


Prepared by boron trichloride-methyl sulfide de-benzylation via a procedure as described above in Intermediate Example 4 Step 3 from (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-4,5-bisbenzyloxy-6-(benzyloxyoxymethyl)- 3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole (0.270 g, 0.523 mmol). Purification on silica gel by flash column chromatography (1.0 M NH_3 in $MeOH/CH_2Cl_2$, 1: 4), afforded the product as an off-white solid (0.048 g, 36%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.36 – 4.33 (m, 1H), 3.81 – 3.76 (m, 2H), 3.63 (dd, J = 6.3, 10.8 Hz, 1H), 3.41 (t, J = 9.1 Hz, 1H), 3.31 (t, J = 9.8 Hz, 1H), 3.02 (s, 6H), 2.24 – 2.19 (m, 1H), 1.97 – 1.93 (m, 1H), 1.79 – 1.71 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.90, 77.01, 73.49, 70.83, 63.54, 52.60, 41.98, 40.84, 26.53; MS, m/z = 269 (M + 23).

Intermediate 7 (3aR,4R,5R,6R,7aS)-2-(ethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

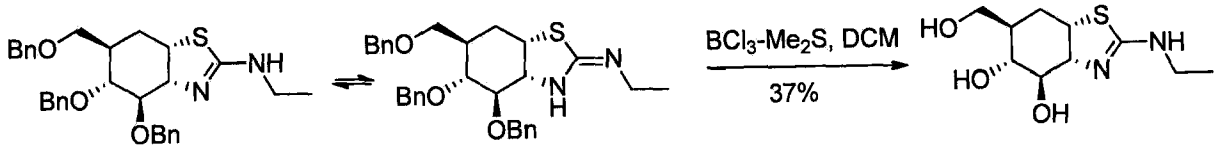


Step 1. (3aR,4R,5R,6R,7aS)-2-(ethylamino)-4,5- bisbenzyloxy-6-(benzyloxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole



To a solution of (1R,2S,3R,4R,5R)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol (0.380 g, 0.850 mmol) was added ethyl isothiocyanate (EtNCS) (0.096 g, 1.1 mmol), and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was purified on silica gel by flash column chromatography (EtOAc/hexanes, 2:1), affording the thiourea as a white solid (0.35 g,77%). To a solution of the white solid (0.350 g, 0.655 mmol) and triphenylphosphine (0.314 g, 1.20 mmol) in anhydrous THF (10 mL) was added DIAD (0.202 g, 1.00 mmol) at 0°C. After addition the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:10 to 1:3), affording (3aR,4R,5R,6R,7aS)-2-(ethylamino)-4,5- bisbenzyloxy-6-(benzyloxymethyl)- 3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole as a colorless oil (0.33 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) spectrum was very complicated due to the presence of two tautomeric isomers.

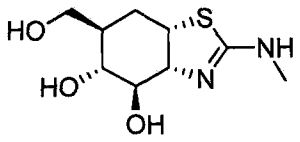
Step 2. (3aR,4R,5R,6R,7aS)-2-(ethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



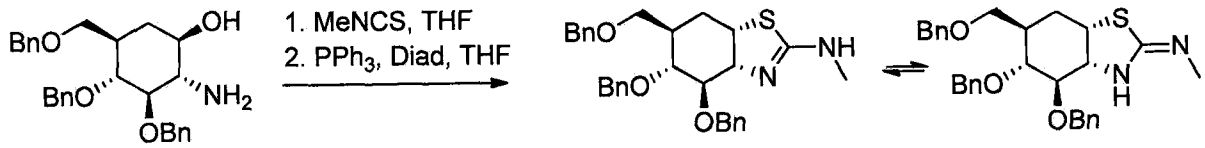
The title compound was prepared by boron trichloride-methyl sulfide de-benzylation via a procedure as described above for Example 4, Step 3 (0.330 g, 0.639 mmol). Purification on silica gel by flash column chromatography (1.0 M NH_3 in MeOH/CH_2Cl_2, 1: 4), afforded the product as an off-white solid (0.059 g, 37%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.29 – 4.25 (m,

1H), 3.77 (dd, J = 4.0, 10.8 Hz, 1H), 3.70 (dd, J = 6.4, 8.6 Hz, 1H), 3.61 (dd, J = 6.4, 10.8 Hz, 1H), 3.42 (t, J = 9.0, 1H), 3.28 – 3.18 (m, 3H), 2.19 – 2.13 (m, 1H), 1.97 – 1.92 (m, 1H), 1.78 – 1.69 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.13, 78.21, 75.34, 74.53, 64.15, 53.00, 40.67, 40.49, 27.04, 15.05; MS, m/z = 269 (M + 23).

Intermediate 8 (3aR,4R,5R,6R,7aS)-2-(methylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

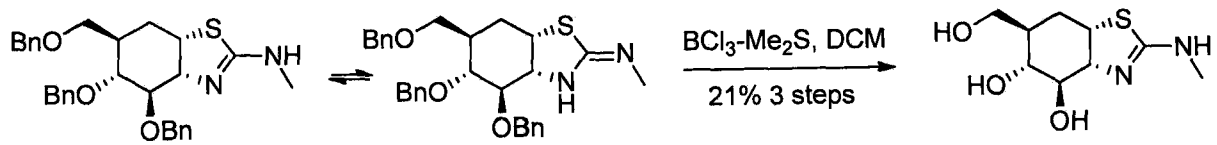


Step 1. (3aR,4R,5R,6R,7aS)-2-(methylamino)-4,5- bisbenzyloxy-6-(benzyloxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole



The title compound was prepared via a synthetic sequence as described above Intermediate Example 7, starting form (1R,2S,3R,4R,5R)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol (0.150 g, 0.336 mmol) and methyl isothiocyanate (MeNCS) (0.049 g, 0.67 mmol). The crude product was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:20 to 1:3), affording (3aR,4R,5R,6R,7aS)-2-(mthylamino)-4,5- bisbenzyloxy-6-(benzyloxymethyl)- 3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole as a colorless oil (0.16 g, impure).

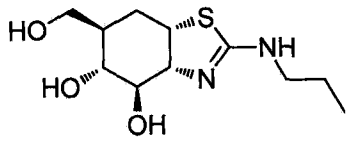
Step 2. (3aR,4R,5R,6R,7aS)-2-(methylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



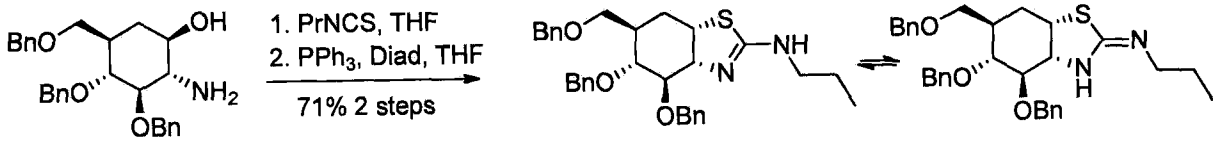
The title compound was prepared by boron trichloride-methyl sulfide de-benzylation via a procedure as described above for Intermediate Example 7 Step 2 from the product of step 1 (0.16 g, impure). Purification on silica gel by flash column chromatography (1.0 M NH_3 in $MeOH/CH_2Cl_2$, 1: 3), afforded the title compound an off-white solid (0.023 g, 21% overall). ^{1}H NMR (400 MHz, CD_3OD) δ 4.38 – 4.35 (m, 1H), 3.81 – 3.75 (m, 2H), 3.63 (dd, J = 6.2, 10.8 Hz, 1H), 3.46 (t, J = 9.1 Hz, 1H), 3.23 (t, J = 9.8 Hz, 1H), 2.89 (s, 3H), 2.21 – 2.15 (m, 1H), 1.96

– 1.90 (m, 1H), 1.82 – 1.74 (m 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 167.45, 77.90, 74.26, 74.15, 63.99, 52.99, 40.72, 31.40, 26.93; MS, m/z = 255 (M + 23).

Intermediate 9 (3aR,4R,5R,6R,7aS)-2-(propylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

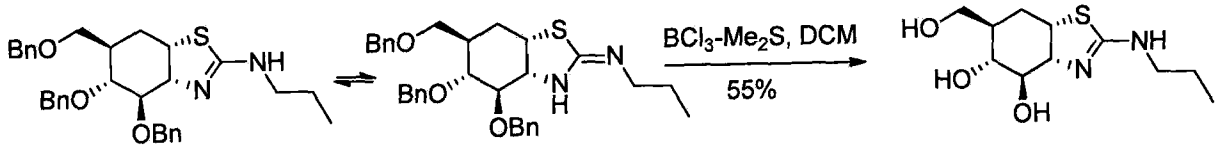


Step 1. (3aR,4R,5R,6R,7aS)-2-(porpylamino)-4,5- bisbenzyloxy-6-(benzyloxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole



(3aR,4R,5R,6R,7aS)-2-(porpylamino)-4,5- bisbenzyloxy-6-(benzyloxymethyl)- 3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole was prepared via a synthetic sequence as described for Intermediate Example 7 starting from (1R,2S,3R,4R,5R)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol (0.150 g, 0.336 mmol) and propyl isothiocyanate (PrNCS) (0.067 g, 0.67 mmol). The product was purified on silica gel by automatic flash column chromatography (EtOAc/hexanes, 1:20 to 1:3), affording the product as a colorless oil (0.13 g, 71%).

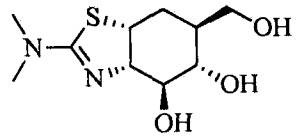
Step 2. (3aR,4R,5R,6R,7aS)-2-(propylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



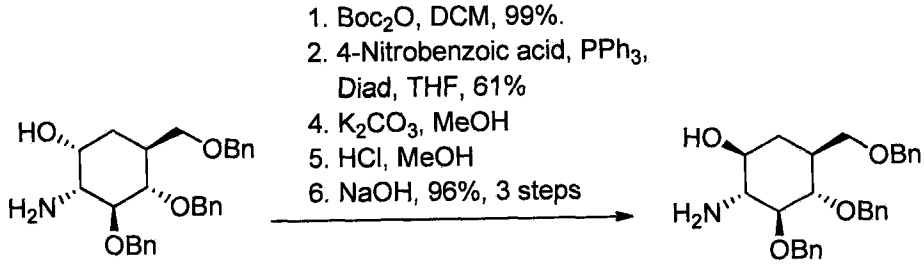
The title compound was prepared by boron trichloride-methyl sulfide de-benzylation via a procedure as described for Intermediate Example 7 from the product of Step 1 above (0.126 g, impure). Purification on silica gel by flash column chromatography (1.0 M NH_3 in $MeOH/CH_2Cl_2$, 1: 4), afforded (3aR,4R,5R,6R,7aS)-2-(propylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a- hexahydrobenzo[d]thiazole-4,5-diol as an off-white solid (0.033 g, 55%). ^1H NMR (400 MHz, CD_3OD) δ 4.33 – 4.29 (m, 1H), 3.78 (dd, J = 4.0, 10.8 Hz, 1H), 3.73 (dd, J = 6.3, 8.6 Hz, 1H), 3.63 (dd, J = 6.3, 10.8 Hz, 1H), 3.45 (t, J = 9.0, 1H), 3.27 – 3.15 (m, 3H), 2.21 – 2.15 (m, 1H), 1.96 – 1.90 (m, 1H), 1.81 – 1.73 (m, 1H), 1.63 – 1.54 (m, 2H), 0.94 (t, J = 7.4

Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.11, 78.04, 74.41, 66.92, 64.06, 52.65, 47.90, 40.68, 26.99, 23.72, 11.74; MS, m/z = 283 (M + 23).

Intermediate 10 (3aS,4S,5S,6S,7aR)-2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

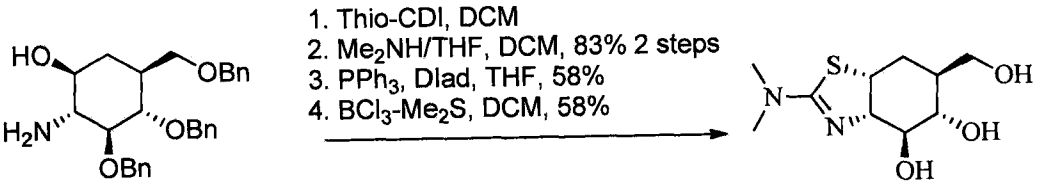


Step 1. (1S,2R,3S,4S,5S)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol



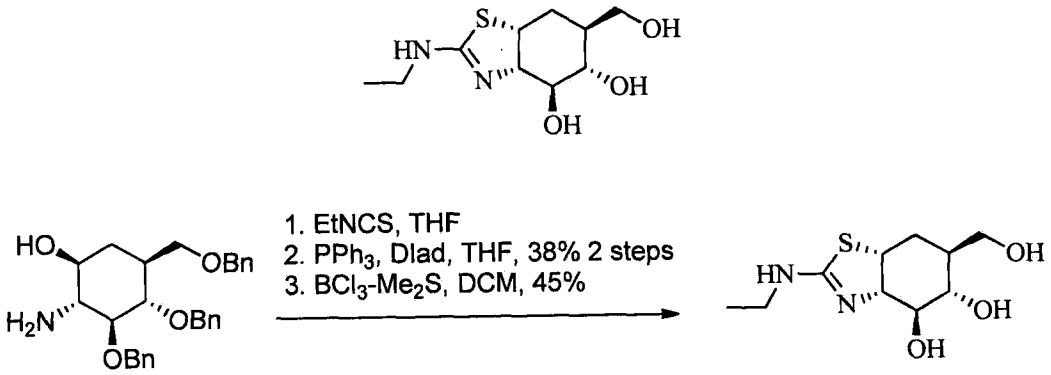
The product of step 1 was an enantiomeric isomer of (1R,2S,3R,4R,5R)-2-amino-3,4-bis(benzyloxy)-5- ((benzyloxy)methyl)cyclohexanol described above in Intermediate Example 3, Step 3. It was prepared via a synthetic sequence substantially identical to that described above for Intermediate Example 3 Steps 1-3, starting from the enantiomeric (1R,2R,3S,4S,5S)-2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol. The purification conditions for each step reaction were also the same as described, (1S,2R,3S,4S,5S)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol was obtained as a white solid with overall yield 58% employing procedures substantially as described for the Intermediate Example 3. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 15H), 4.98 (d, J = 11.3 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 10.8 Hz, 1H), 4.47 (s, 2H), 3.64 (dd, J = 4.9, 8.9 Hz, 1H), 3.54 – 3.48 (m, 2H), 3.30 – 3.26 (m, 1H), 3.16 (t, J = 9.4 Hz, 1H), 2.52 – 2.50 (m, 1H), 2.08 – 2.03 (m, 1H), 1.76 – 1.72 (m, 1H), 1.58 – 1.52 (m, 1H).

Step 2. (3aS,4S,5S,6S,7aR)-2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



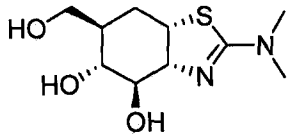
(3aS,4S,5S,6S,7aR)-2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol was an enantiomeric isomer of (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol. It was prepared via a synthetic sequence similar to that described in Intermediate Example 6, but starting with the product of Step 1 above. The purification conditions for each step reaction were also the same as described for the and (3aS,4S,5S,6S,7aR)-2-(dimethylamino)-6-(hydroxymethyl)- 3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol was obtained as a white solid with overall yield 28%. ^{1}H NMR (400 MHz, CD_3OD) δ 4.44 – 4.41 (m, 1H), 3.83 (dd, J = 6.5, 9.1 Hz, 1H), 3.79 (dd, J = 3.9, 10.8 Hz, 1H), 3.64 (dd, J = 6.3, 10.8 Hz, 1H), 3.45 (t, J = 9.1 Hz, 1H), 3.23 (t, J = 9.8 Hz, 1H), 3.09 (s, 6H), 2.25 – 2.20 (m, 1H), 1.95 – 1.90 (m, 1H), 1.83 – 1.75 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.71, 77.78, 74.03, 73.99, 63.86, 53.78, 41.09, 40.78, 26.71; MS, m/z = 269 (M + 23).

Intermediate 11 (3aS,4S,5S,6S,7aR)-2-(ethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole- 4,5-diol



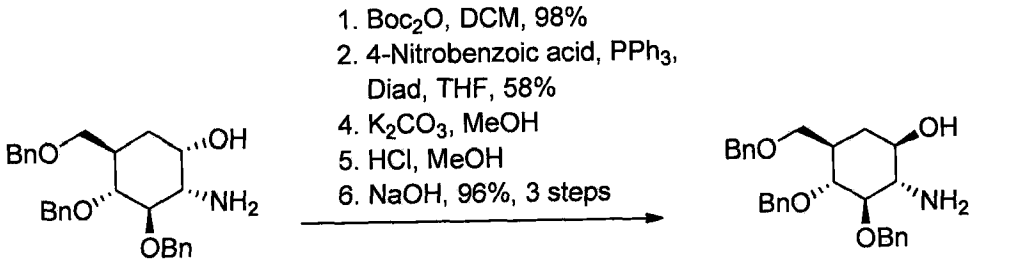
(3aS,4S,5S,6S,7aR)-2-(ethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d] thiazole-4,5-diol was an enantiomeric isomer of (3aR,4R,5R,6R,7aS)-2-(ethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol. It was prepared from (1S,2R,3S,4S,5S)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol via a synthetic sequence substantially as described in Intermediate Example 7. The purification conditions for each step reaction were also the same and (3aS,4S,5S,6S,7aR)-2-(ethylamino)-6-(hydroxymethyl)- 3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole -4,5-diol was obtained as a white solid with overall yield 17%. ^{1}H NMR (400 MHz, CD_3OD) δ 4.62 – 4.60 (m, 1H), 3.97 (dd, J = 6.7, 9.0 Hz, 1H), 3.89 (dd, J = 3.5, 10.9 Hz, 1H), 3.67 (dd, J = 5.7, 10.9 Hz, 1H), 3.57 (t, J = 9.0, 1H), 3.47 – 3.41 (m, 2H), 3.28 (t, J = 9.7 Hz, 1H), 2.21 – 2.17 (m, 1H), 1.94 – 1.88 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.21, 76.44, 73.25, 67.85, 63.33, 50.65, 41.36, 40.86, 26.42, 13.71; MS, m/z = 269 (M + 23).

Intermediate 12 Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



(Racemate)

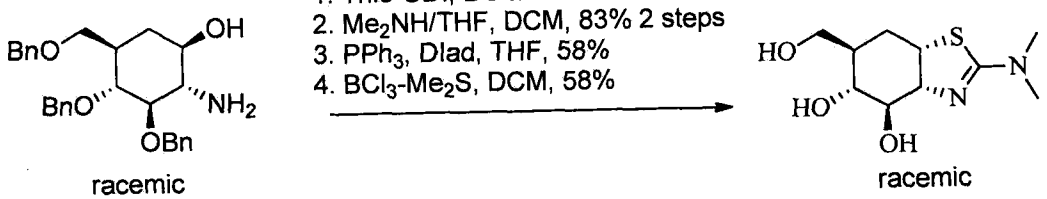
Step 1. Rac-(1R,2S,3R,4R,5R)/(1S,2R,3S,4S,5S)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl)cyclohexanol



(Racemate)

Rac-(1R,2S,3R,4R,5R)/(1S,2R,3S,4S,5S)-2-Amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol was a racemate of the product of Intermediate 3. It was prepared via a synthetic sequence as described for Intermediate 3, starting from racemic Intermediate Example 2 (Rac-(1R,2R,3S,4S,5S) /(1S,2R,3S,4S,5S) -2-amino-3,4-bis(benzyloxy)-5-((benzyloxy)methyl) cyclohexanol. The purification conditions for each step reaction were also the same as described, and compound was obtained as a white solid with overall yield 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 15H), 4.98 (d, J = 11.3 Hz, 1H), 4.84 (d, J = 10.8 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 10.8 Hz, 1H), 4.47 (s, 2H), 3.64 (dd, J = 4.9, 8.9 Hz, 1H), 3.54 – 3.50 (m, 2H), 3.32 – 3.26 (m, 1H), 3.16 (t, J = 9.4 Hz, 1H), 2.51 – 2.49 (m, 1H), 2.09 – 2.04 (m, 1H), 1.79 – 1.72 (m, 1H), 1.58 – 1.49 (m, 1H), 1.27 (d, J = 6.2 Hz, 1H).

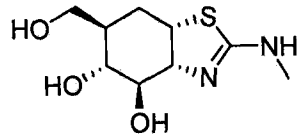
Step 2. Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



racemic racemic

Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol was a racemic mixture. It was prepared via a synthetic sequence as described above for Intermediate Example 10. The purification conditions for each step reaction were also the same as described and compound Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2- (dimethylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 4.65 – 4.63 (m, 1H), 3.98 (dd, J = 6.5, 8.8 Hz, 1H), 3.79 (dd, J = 3.2, 10.8 1H), 3.67 (dd, J = 5.5, 10.8 Hz, 1H), 3.49 (t, J = 9.1 Hz, 1H), 3.30 – 3.25 (m, 1H),3.28 (s, 6H), 2.25 – 2.20 (m, 1H), 1.935 – 1.89 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.47, 76.43, 73.14, 68.54, 63.32, 51.76, 40.88, 26.40; MS, m/z = 269 (M + 23).

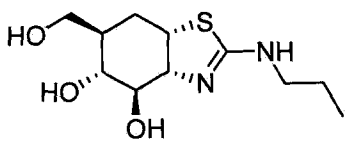
Intermediate 13 Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(methylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



(Racemate)

Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(methylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a- hexahydrobenzo[d]thiazole-4,5-diol was a racemate version of Intermediate Example 8. It was prepared via a synthetic sequence as described for Intermediate Example 8 starting from the racemic Intermediate Example 2. The purification conditions for each step reaction were also the same as described, and the product was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 4.42 – 4.29 (m, 1H), 3.78 (dd, J = 4.0, 10.8 Hz, 1H), 3.72 (dd, J = 6.4, 8.5 Hz, 1H), 3.62 (dd, J = 6.4, 10.8 Hz, 1H), 3.43 (t, J = 9.1 Hz, 1H), 3.22 (t, J = 9.8 Hz, 1H), 2.85 (s, 3H), 2.21 – 2.15 (m, 1H), 1.98 – 1.90 (m, 1H), 1.79 – 1.71 (m 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.05, 78.23, 75.63, 74.51, 64.14, 53.46, 40.69, 31.20, 27.03; MS, m/z = 255 (M + 23).

Intermediate 14. Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(propylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

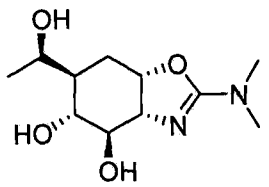


(Racemate)

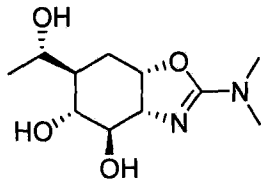
Rac-(3aR,4R,5R,6R,7aS)/(3aS,4S,5S,6S,7aR)--2-(propylamino)-6-(hydroxymethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol was a racemate version of Intermediate Example 9. It was prepared via a synthetic sequence as described for Intermediate Example 9, starting from the racemic Intermediate Example 2. The purification conditions for each step reaction were also the same as described and the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 4.62 – 4.59 (m, 1H), 3.98 – 3.95 (m, 1H), 3.79 (dd, J = 3.3, 10.9 Hz, 1H), 3.69 – 3.65 (m, 1H), 3.56 (t, J = 9.2 Hz, 1H), 3.38 – 3.25 (m, 3H), 2.22 – 2.19 (m, 1H), 1.94 – 1.88 (m, 2H), 1.71 – 1.64 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.76, 76.46, 73.27, 67.83, 63.30, 50.57, 47.95, 40.84, 26.40, 22.66, 11.40; MS, m/z = 283 (M + 23).

EXAMPLES 1 AND 2

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-2-(Dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol (Example 1 and (3a*R*,4*R*,5*R*,6*R*,7a*S*)-2-(Dimethylamino)-6-((*S*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol (Example 2

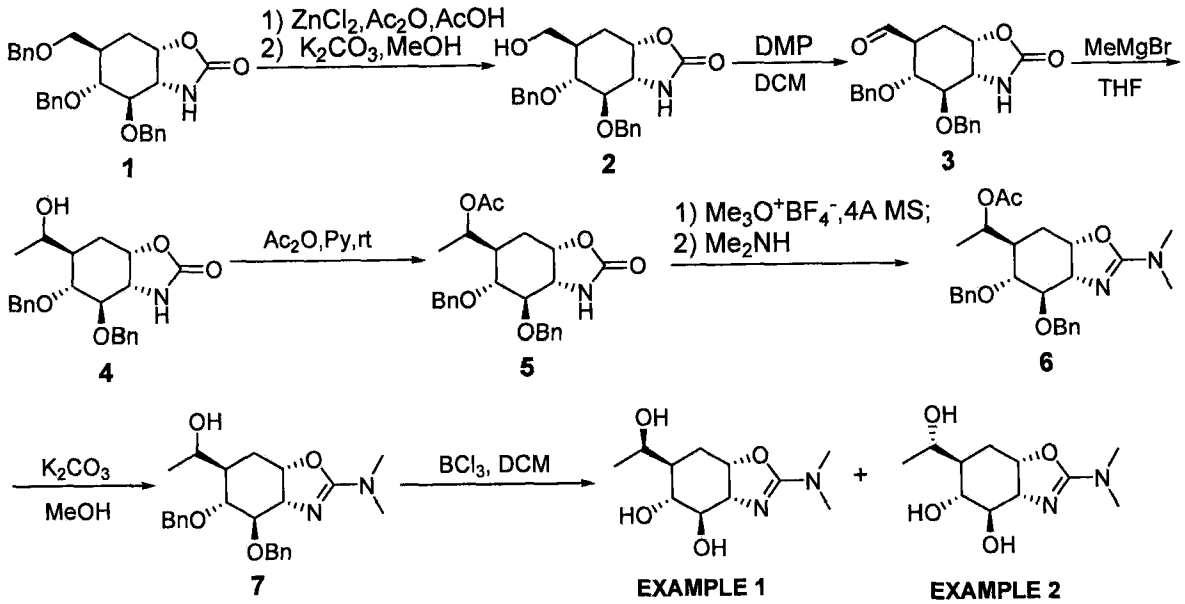


Example 1

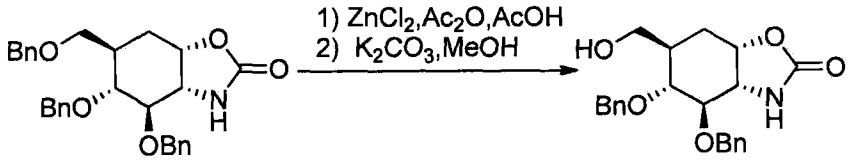


Example 2

Scheme I



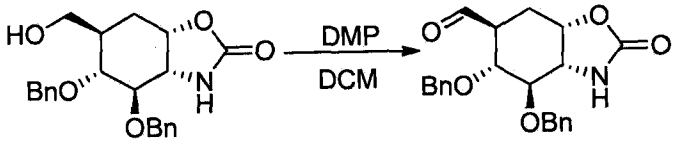
Step 1. (3a*S*,4*R*,5*R*,6*R*,7a*S*)-4,5-Bis(benzyloxy)-6-(hydroxymethyl)-hexahydrobenzo[d]oxazol-2(3H)-one (2):



1 2

To a solution of **1** (3.0 g, 6.3 mmol) in acetic anhydride (30 mL) and acetic acid (3 mL) was added zinc(II) chloride (7.4 g, 54 mmol). After stirring for 30 min at room temperature, the mixture was poured into water (100 mL). The pH value was adjusted to 7-8 with Na_2CO_3 and the solution was extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated to give a residue, which was dissolved into MeOH (50 mL). The solution was treated with K_2CO_3 (1.0 g, 7.2 mmol) for 2 h at room temperature, and was neutralized by acetic acid. Removal of solvents provided a crude product, which was purified by a silica gel column, eluted with 10% MeOH in DCM to give **2** as a white solid (1.4 g, 57 %). (ES, *m/z*): $[M+H]^+$ 383.9; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 - 7.46 (m, 10H), 4.89 - 5.00 (m, 2H), 4.59 - 4.73 (m, 4H), 3.75 - 3.79 (m, 1H), 3.38 - 3.58 (m, 3H), 2.10 - 2.17 (m, 1H), 1.73 - 1.97 (m, 2H).

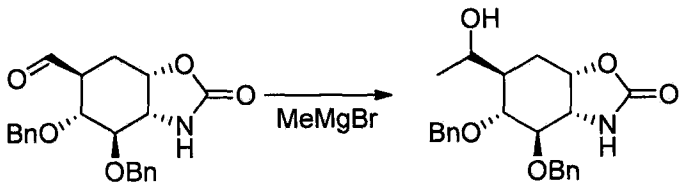
Step 2. (3a*S*,4*R*,5*R*,6*S*,7a*S*)-4,5-Bis(benzyloxy)-2-oxo-octahydrobenzo[d]oxazole-6-carbaldehyde (3):



2 3

A solution of compound **2** (1.4 g, 3.6 mmol) in DCM (25 mL) was treated with DMP (3.1 g, 7.3 mmol) for 3 h at room temperature. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL) and extracted with DCM (4 x 20 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the crude aldehyde **3** (1.4 g, yellow oil), which was used in the next step without further purification. (ES, *m/z*): $[M+H]^+$ 382.0; ^1H NMR (300 MHz, $CDCl_3$), δ: 9.74 (s, 1H), 7.28 - 7.46 (m, 10H), 4.54 - 4.85 (m, 5H), 3.85 - 3.90 (m, 1H), 3.69 - 3.74 (m, 1H), 3.60 - 3.65 (m, 1H), 2.94 - 2.96 (m, 1H), 2.19 - 2.27 (m, 1H), 1.94 - 2.00 (m, 1H).

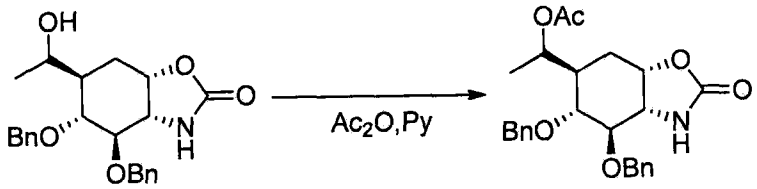
Step 3. (3a*S*,4*R*,5*R*,6*R*,7a*S*)-4,5-Bis(benzyloxy)-6-(1-hydroxyethyl)-hexahydrobenzo[d]oxazol-2(3H)-one (4):



3 4

To a solution of the above crude **3** (1.4 g, 3.6 mmol) in THF (10 mL) was added methylmagnesium chloride (7.0 mL, 2.5M in THF, 17.5 mmol) at -78°C. After 1 hour, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with DCM (4 x 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give a residue, which was purified by a silica gel column, eluted with 10% MeOH in DCM to give **4** as a white solid (1.0 g, 68 % in two steps, the ratio of diastereomers is 1:3 by ^1H NMR). (ES, m/z): $[M+H]^+$ 397.9; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 - 7.45 (m, 10H), 4.91 - 4.96 (m, 2H), 4.70 - 4.87 (m, 2H), 4.50 - 4.69 (m, 2H), 3.74 - 3.79 (m, 2H), 3.47 - 3.58 (m, 2H), 1.50 - 1.76 (m, 2H), 1.15 (d, J = 6.6 Hz, 3H).

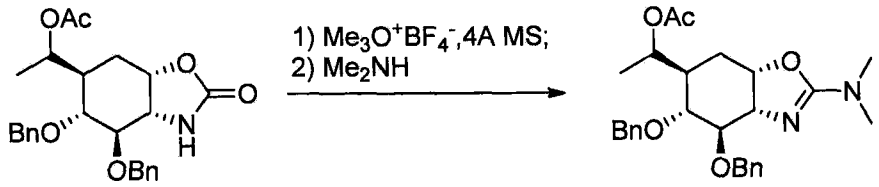
Step 4. 1-((3a*S*,4*R*,5*R*,6*R*,7a*S*)-4,5-Bis(benzyloxy)-2-oxo-octahydrobenzo[d]oxazol-6-yl)ethyl acetate (5):



4 5

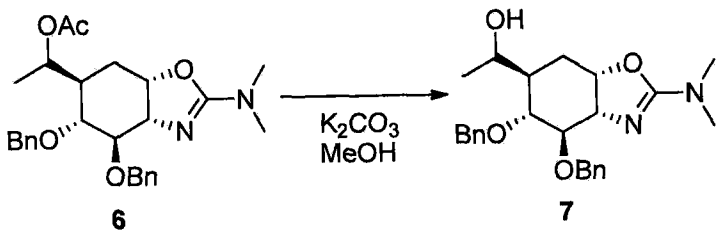
Acetic anhydride (3.3 g, 32 mmol) was added to a solution of **4** (1.0 g, 2.5 mmol) in pyridine (60 mL) and the solution was stirred overnight at room temperature. The mixture was concentrated *in vacuo* to give a residue, which was purified by a silica gel column, eluted with 2% MeOH in DCM to give **5** as yellow oil (900 mg, 81%, the ratio of diastereomers is 1:3 by ^1H NMR). (ES, m/z): $[M+H]^+$ 457.1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 - 7.43 (m, 10H), 4.91 - 4.95 (m, 1H), 4.72 - 4.78 (m, 3H), 4.56 - 4.66 (m, 2H), 4.47 - 4.50 (m, 1H), 3.61 - 3.63 (m, 1H), 3.49 - 3.54 (m, 1H), 3.32 - 3.35 (m, 1H), 2.03 (s, 3H), 1.51 - 1.76 (m, 2H), 1.27 (d, J = 6.3 Hz, 3H).

Step 5. 1-((3a*S*,4*R*,5*R*,6*R*,7a*S*)-4,5-Bis(benzyloxy)-2-(dimethylamino)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazol-6-yl)ethyl acetate (6):



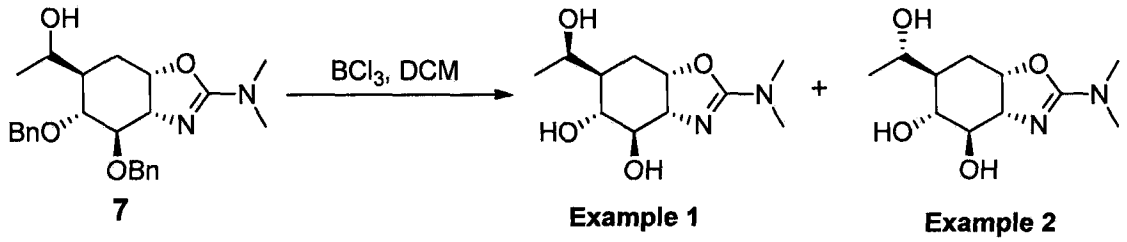
A mixture of compound **5** (0.90 g, 2.0 mmol), trimethyloxonium tetrafluoroborate (1.5 g, 10 mmol) and 4Å Molecular sieves (0.5 g) in DCM (5 mL) was stirred overnight at room temperature, followed by addition of dimethylamine (20 mL, 1 M in THF, 20 mmol). The reaction mixture was stirred for 12 h at room temperature, then quenched with saturated aqueous $NaHCO_3$ (20 mL), extracted with DCM (4 x 50 mL). The organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give crude product **6**, which was used in the next step directly. (ES, m/z): $[M+H]^+$ 467.1.

Step 6. 1-((3a*S*,4*R*,5*R*,6*R*,7a*S*)-4,5-Bis(benzyloxy)-2-(dimethylamino)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazol-6-yl)ethanol (7):



A mixture of the crude **6** and potassium carbonate (142 mg, 1.0 mmol) in MeOH (10 mL) was stirred for 2 h at room temperature. The solution was neutralized with acetic acid and concentrated *in vacuo* to give a residue, which was purified by a silica gel column, eluted with 3% MeOH and 1% ammonia (conc.) in EtOAc to give **7** as yellow oil (200 mg, 23 % in 2 steps). (ES, m/z): $[M+H]^+$ 425.1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.41 (m, 10H), 4.86 - 4.90 (m, 1H), 4.72 - 4.80 (m, 2H), 4.35 - 4.40 (m, 2H), 4.10 - 4.20 (m, 1H), 3.91 - 3.95 (m, 1H), 3.71 - 3.52 (m, 1H), 3.55 - 3.57 (m, 2H), 2.85 (s, 3H), 2.89 (s, 3H), 1.72 - 1.87 (m, 2H), 1.26 - 1.28 (m, 3H).

Step 7. (3a*R*,4*R*,5*R*,6*R*,7a*S*)-2-(Dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol (Example 1) and (3a*R*,4*R*,5*R*,6*R*,7a*S*)-2-(Dimethylamino)-6-((*S*)-1-hydroxyethyl)- 3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol (Example 2)



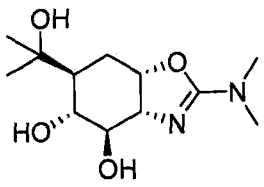
To a solution of compound 7 (200 mg, 0.47 mmol) in DCM (5 mL) was added trichloroborane (4 mL, 1 M in DCM, 4 mmol) at -78°C. The reaction mixture was warmed up and stirred for 1 hour at 0°C, then quenched with MeOH (2 mL) at -30°C. Removal of solvents provided a residue, which was neutralized by NH_4OH and purified by Prep-HPLC under the following conditions: [(Agilent 1200 Prep-HPLC): Column, X-Bridge Prep C18, 19 * 150 mm; mobile phase, water with 0.05% TFA and CH_3CN (5% - 25% in 6.5 mins); Detector, UV 200nm] to give two isomers.

Example 1, the faster eluting isomer as white solid (10.7 mg, 9.3%). (ES, m/z): $[M+H]^+$ 245.0; ^1H NMR (300 MHz, D_2O) δ 4.60 - 4.70 (m, 1H), 4.05 - 4.13 (m, 1H), 3.52 - 3.57 (m, 1H), 3.21 - 3.29 (m, 2H), 2.86 (s, 6H), 2.14 - 2.21 (m, 1H), 1.64 - 1.81 (m, 2H), 1.10 (d, J = 6.3 Hz, 3H).

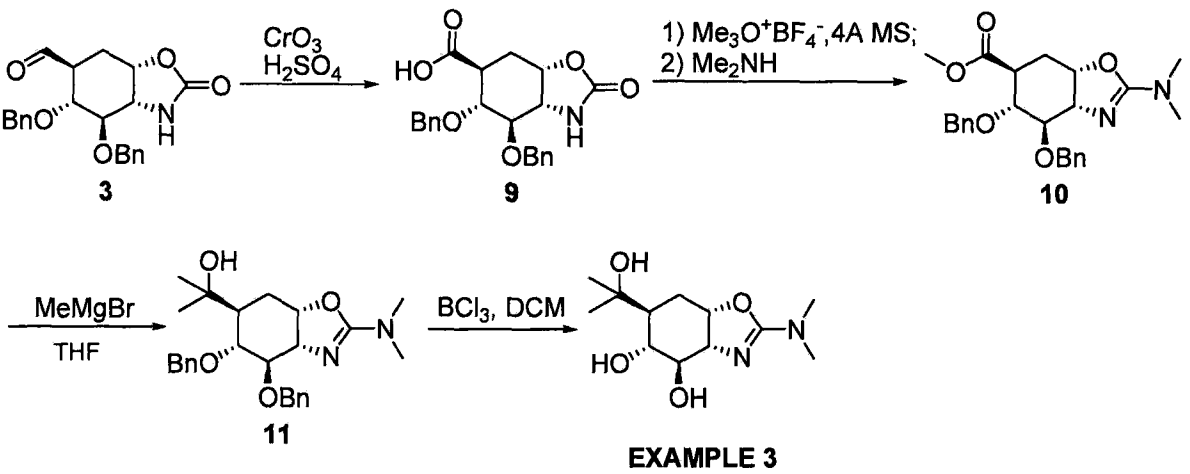
Example 2, the slower eluting isomer as a white solid (32.7 mg, 28.4%). (ES, m/z): $[M+H]^+$ 245.0; ^1H NMR (300 MHz, D_2O) δ 4.60 - 4.69 (m, 1H), 4.14 - 4.21 (m, 1H), 3.46 - 3.51 (m, 1H), 3.19 -3.31 (m, 2H), 2.83 (s, 6H), 2.14 - 2.21 (m, 1H), 1.54 - 1.70 (m, 2H), 1.13 (d, J = 6.3 Hz, 3H).

EXAMPLE 3

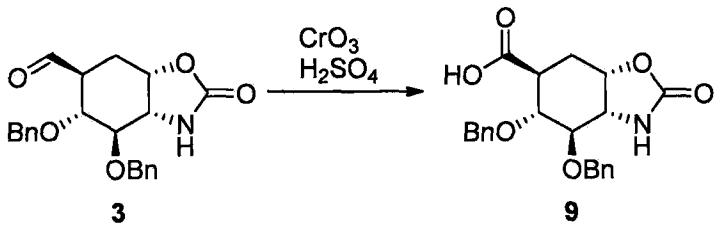
(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(Dimethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol (Example 3



Scheme II

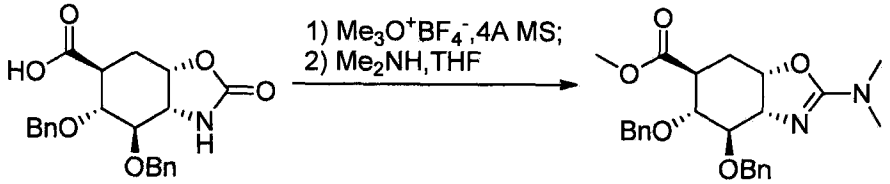


Step 1. (3a*S*,4*R*,5*R*,6*S*,7a*S*)-4,5-Bis(benzyloxy)-2-oxo-octahydrobenzo[d]oxazole-6-carboxylic acid (9):



A solution of compound **3** (2.2 g, 5.8 mmol) in acetone (20 mL) was treated with freshly prepared Jones reagent (6 mL) for 1 hour at room temperature, then quenched with water (30 mL), extracted with DCM (4 x 50 mL). The combined organic layer was washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a residue, which was purified by a silica gel column, eluted with MeOH (1% - 10%) in DCM to give **9** as a yellow solid (1.7 g, 74 %). (ES, *m/z*): $[M+H]^+$ 397.8; ^1H NMR (300 MHz, CD_3OD) δ 8.05 - 8.10 (m, 1H), 7.28 - 7.35 (m, 10H), 4.64 - 4.86 (m, 5H), 3.90 - 3.98 (m, 2H), 3.62 - 3.69 (m, 1H), 2.76 - 2.82 (m, 1H), 2.16 - 2.27 (m, 2H).

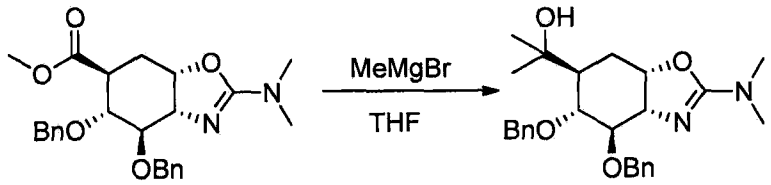
Step 2. (3a*S*,4*R*,5*R*,6*S*,7a*S*)-Methyl-4,5-bis(benzyloxy)-2-(dimethylamino)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-6-carboxylate (10):



9 **10**

A mixture of compound **9** (400 mg, 1.0 mmol), trimethyloxonium tetrafluoroborate (2.4 g, 16 mmol) and 4A MS (500 mg) in DCM (10 mL) was stirred for 40 h at room temperature, followed by addition of dimethylamine (20 mL, 1 M in THF, 20 mmol). After additional 12 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), extracted with DCM (4 x 30 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a residue, which was purified by a silica gel column, eluted with 3% MeOH and 1% ammonia (conc.) in EtOAc to give **10** as yellow oil (200 mg, 57 %). (ES, *m/z*): $[M+H]^+$ 439.1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.40 (m, 10H), 4.51 - 4.89 (m, 5H), 3.65 - 3.72 (m, 4H), 2.78 - 3.05 (m, 8H), 2.53 - 2.66 (m, 1H), 1.45 - 1.80 (m, 2H).

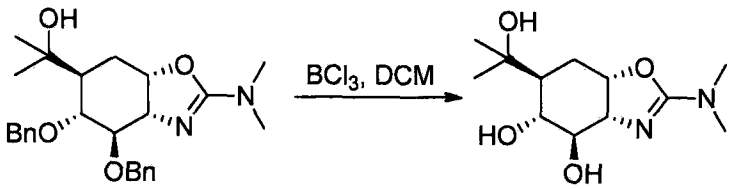
Step 3. 2-((3a*S*,4*R*,5*R*,6*S*,7a*S*)-4,5-Bis(benzyloxy)-2-(dimethylamino)-3a,4,5,6,7,7a-hexahydrobenzo-[d]oxazol-6-yl)propan-2-ol (11):



10 **11**

To a solution of compound **10** (200 mg, 0.46 mmol) in THF (10 mL) was added methylmagnesium chloride (1.9 mL, 2.5 M in THF, 4.6 mmol) at -70°C. After additional 1 hour, the reaction was quenched with saturated aqueous NH_4Cl (10 mL), extracted with DCM (4 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give a residue, which was purified by a silica gel column, eluted with 3% MeOH and 1% ammonia (conc.) in EtOAc to give **11** as a yellow oil (150 mg, 75 %). (ES, *m/z*): $[M+H]^+$ 439.1; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.39 (m, 10H), 4.82 - 4.87 (m, 3H), 4.67 - 4.70 (m, 1H), 4.43 - 4.57 (m, 1H), 3.64 - 3.73 (m, 3H), 2.88 (s, 6H), 2.03 - 2.06 (m, 1H), 1.56 - 1.70 (m, 2H), 1.18 - 1.30 (m, 6H).

Step 4. (3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(Dimethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol (Example 3):

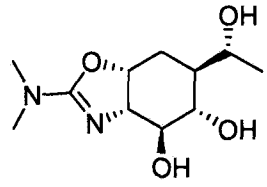
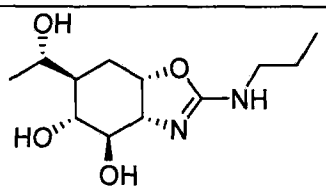
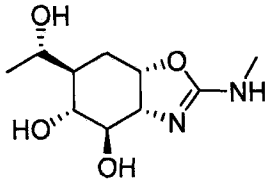


11

To a solution of compound **11** (150 mg, 0.34 mmol) in DCM (5 mL) was added trichloroborane (3.5 mL, 1 M in DCM, 3.5 mmol) at -78°C. After stirring for 1 hour at 0°C, the reaction mixture was quenched with MeOH (2 mL) at -30°C and concentrated *in vacuo* to give a residue, which was neutralized and purified by Prep-HPLC under the following conditions: [Column, 19 x 150 mm; mobile phase, water with 0.05%TFA and CH_3CN (10% - 45% in 10 min); Detector, 220] to give (3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(Dimethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol (**Example 3**) as a white solid (26.9 mg, 30 %). (ES, *m/z*): $[M+H]^+$ 259.0; ^1H NMR (300 MHz, D_2O) δ 4.62 - 4.66 (m, 1H), 3.44 - 3.55 (m, 2H), 3.28 (t, J = 8.1 Hz, 1H), 2.82 (s, 6H), 2.11 - 2.17 (m, 1H), 1.50 - 1.69 (m, 2H), 1.19 (s, 3H), 1.15 (s, 3H).

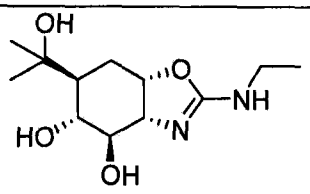
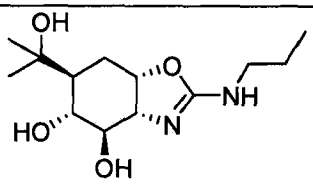
The following compounds in Table 1 were made following procedures analagous to Examples 1 and 2.

Table 1

Example	Structure	Name	MH+
4		(3a*S*,4*S*,5*S*,6*S*,7a*R*)-2-(dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol(Slower eluting isomer by HPLC)	245.0
5		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(propylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol	259.0
6		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(methylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol	231.0

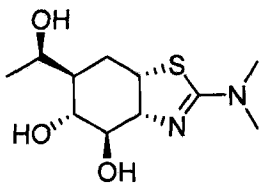
The following compounds in Table 2 were made following procedures analagous to Example 3.

Table 2

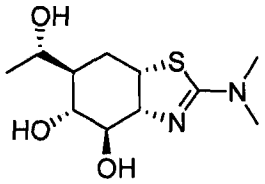
Example	Structure	Name	MH+
7		(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(ethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol	259.0
8		(3a*R*,4*R*,5*R*,6*S*,7a*S*)-6-(2-hydroxypropan-2-yl)-2-(propylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol	273.0

EXAMPLES 9 AND 10

(3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-((R)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol (Example 9) and (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-((S)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol (Example 10)

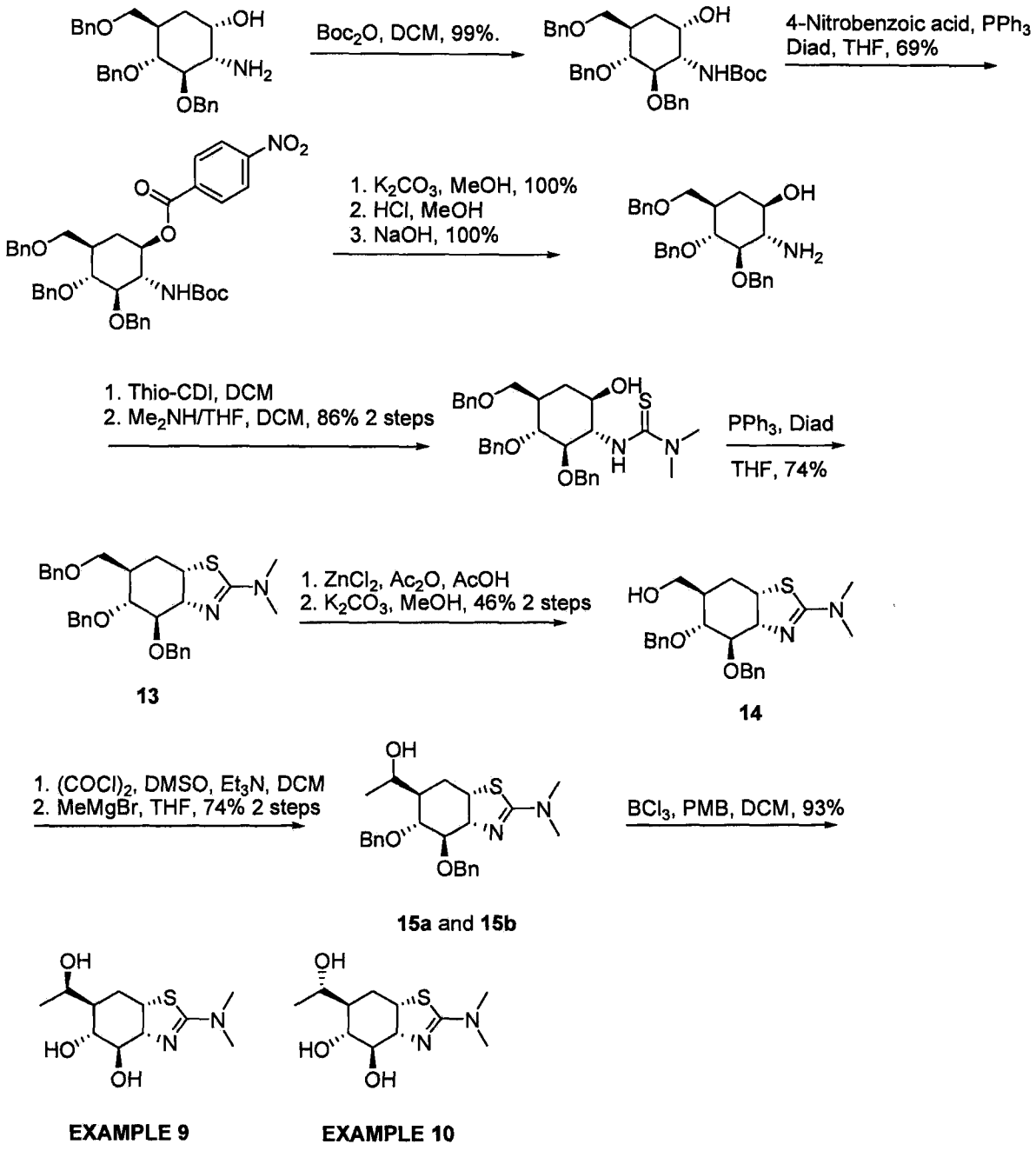


Example 9

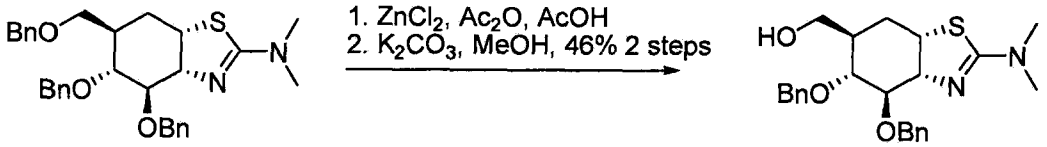


Example 10

Scheme III



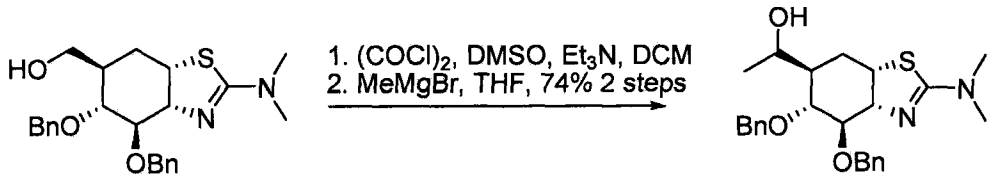
Step 1. ((3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-2-(dimethylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazol-6-yl)methanol (14)



13 **14**

At 15°C, to a solution of (3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-6-((benzyloxy)methyl)-N,N-dimethyl-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazol-2-amine **(13)** (0.950 g, 1.84 mmol) in mixed Ac_2O/AcOH (10 mL/2 mL) was added anhydrous $ZnCl_2$ (2.5 g, 18 mmol). The mixture was stirred at room temperature for 2 h and concentrated under vacuum at room temperature. The residue was diluted with DCM (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The mixture was stirred for 30 min, and the solid was filtered off over a Celite 521 cake. The organic layer was collected from the filtrate, and the aqueous was extracted with DCM (3 × 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 dissolved in MeOH (15 mL). Anhydrous K_2CO_3 (0.47 g, 3.4 mmol) was added, and the mixture was stirred at room temperature for 2 h. AcOH (0.5 mL) was added and the reaction mixture was concentrated under reduced pressure at room temperature. The residue was diluted with saturated aqueous $NaHCO_3$ (30 mL), and then extracted with DCM (3 × 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, then MeOH/DCM, 1:10), affording **14** as a sticky pale yellow foam (0.36 g, 46%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.41 (m, 2H), 7.36 – 7.24 (m, 8H), 5.02 (d, J = 11.0 Hz, 1H), 4.95 (d, J = 11.2 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.31 – 4.28 (m, 1H), 4.11 (t, J = 7.3 Hz, 1H), 3.70 (t, J = 8.4 Hz, 1H), 3.64 – 3.62 (m, 2H), 3.35 (dd, J = 8.9, 10.2 Hz, 1H), 3.00 (s, 6H), 2.23 (s, br. 1H), 2.24 – 2.16 (m, 1H), 2.07 – 2.02 (m, 1H), 1.72 – 1.64 (m, 1H).

Step 2. (R &S)-1-((3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-2-(dimethylamino)- 3a,4,5,6,7,7a-hexahydrobenzo-[d]thiazol-6-yl)ethanol (mixed 15a and 15b)

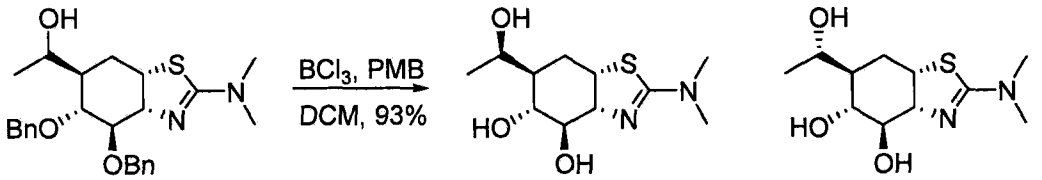


14 **15a and 15b**

To a solution of DMSO (0.193 g, 2.46 mmol) in anhydrous DCM (10 mL) at –78°C under N_2 was added oxalyl chloride (0.268 g, 2.11 mmol) slowly, and the mixture was stirred at –30°C for 45 min. The mixture was then cooled at –78°C, and a solution of ((3aR,4R,5R,6R,7aS)-4,5-

bis(benzyloxy)- 2-(dimethylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazol-6-yl)methanol (**14**) (0.330 g, 0.704 mmol) in anhydrous DCM (5 mL) was added slowly. After stirring at –30°C for 2 h the reaction mixture was cooled back at –78°C, and triethylamine (0.50 g, 5.0 mmol) was added. The mixture was stirred at –30°C for another 30 min, and then quenched with water (30 mL). The organic layer was collected, and the aqueous was extracted with DCM (3 × 20 mL). The combined extract was dried over anhydrous Na_2SO_4. After filtration the solvent was evaporated under reduced pressure to give a sticky pale yellow foam. Under N_2 the pale yellow foam was dissolved in anhydrous THF (15 mL), and MeMgBr (1.4 M in THF/toluene, 1.5 mL, 2.1 mmol) was added. After addition the mixture was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL), and then extracted with DCM (3 × 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), affording mixed **15a & 15b** as a sticky pale yellow foam (0.23 g, 74%) with a ratio of **15a**:**15b** = 1:3 based on ^1H NMR.

Step 3. (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-((R)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol and (3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-((S)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol



15a and 15b **Example 9** **Example 10**

To (R & S)-1-((3aR,4R,5R,6R,7aS)-4,5-bis(benzyloxy)-2-(dimethylamino)-3a,4,5,6,7,7a-hexahydrobenzo [d]thiazol-6-yl)ethanol (**15a and 15b**) (0.230 g, 0.522 mmol) and pentamethylbenzene (0.75 g, 5.1 mmol) in anhydrous DCM (10 mL) at –78°C under N_2, was added BCl_3 (1.0 M in DCM, 3.0 mL, 3.0 mmol). The mixture was stirred for ~3 h during the period of time 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 and separated on silica gel by flash column chromatography (1.0 M NH_3 in $MeOH/CH_2Cl_2$, 1: 6), affording **Example 9** (0.031 g, 23%) and **Example 10** (0.094 g, 69%) both as white solids.

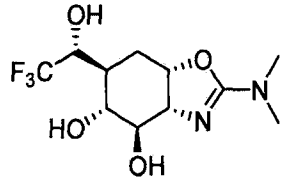
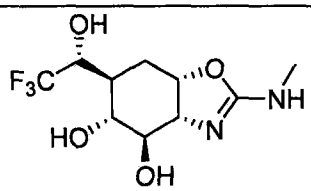
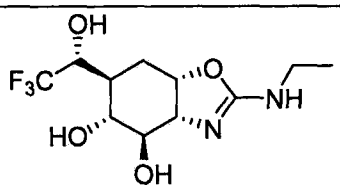
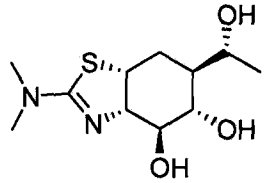
Example 9, Characterization data: ^1H NMR (400 MHz, CD_3OD) δ 4.36 – 4.32 (m, 1H), 4.15 – 4.09 (m, 1H), 3.76 (dd, J = 6.5, 8.6 Hz, 1H), 3.39 (t, J = 8.9 Hz, 1H), 3.23 (dd, J = 9.3, 10.4 Hz, 1H), 3.01 (s, 6H), 2.19 – 2.13 (m, 1H), 2.02 – 1.96 (m, 1H), 1.68 – 1.60 (m, 1H), 1.14 (d, J = 6.4

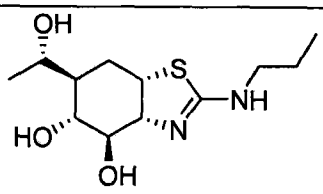
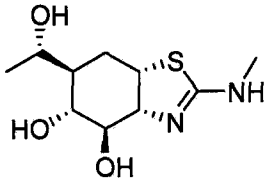
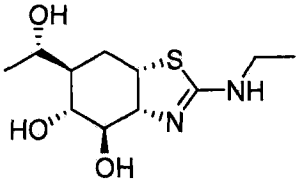
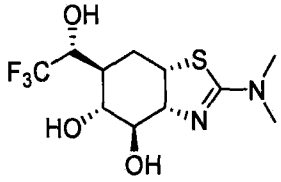
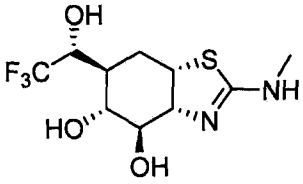
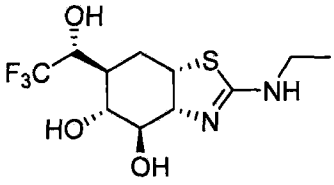
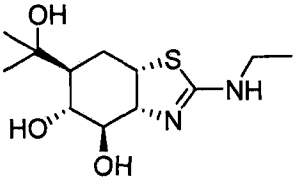
Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.14, 78.60, 76.48, 76.11, 69.49, 54.85, 44.02, 40.57, 24.01, 18.71; MS, (ES, *m/z*) $[M+H]^+$ 261.1.

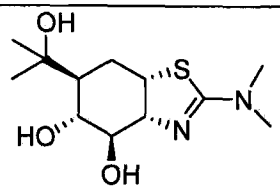
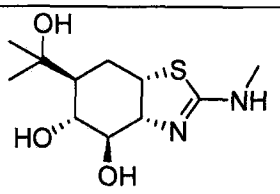
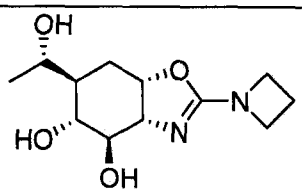
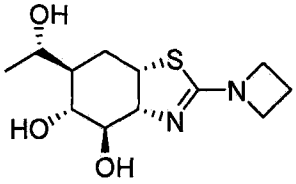
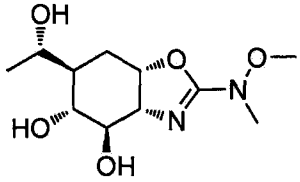
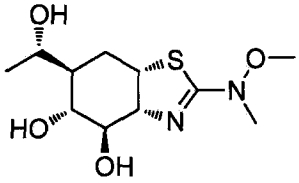
Example 10, Characterization data: ^{1}H NMR (400 MHz, CD_3OD) δ 4.36 – 4.33 (m, 1H), 4.28 – 4.23 (m, 1H), 3.76 (dd, J = 6.7, 8.0 Hz, 1H), 3.43 – 3.37 (m, 2H), 3.01 (s, 6H), 2.09 – 2.03 (m, 1H), 1.83 – 1.74 (m, 2H), 1.18 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.02, 78.73, 76.45, 73.61, 66.53, 54.74, 44.25, 40.59, 22.98, 20.78; MS, (ES, *m/z*) $[M+H]^+$ 261.1.

The following compounds in Table 3 are prepared in a manner similar to Examples 1 through 10 above.

Table 3

Example	Structure	Name
11		(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzoxazole-4,5-diol
12		(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzoxazole-4,5-diol
13		(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(ethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzoxazole-4,5-diol
14		(3a*S*,4*S*,5*S*,6*S*,7a*R*)-2-(dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]othiazole-4,5-diol(Slower eluting isomer by HPLC)

15		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(propylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiaazole-4,5-diol
16		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(methylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol
17		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(ethylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol
18		(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazole-4,5-diol
19		(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazole-4,5-diol
20		(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(ethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazole-4,5-diol
21		(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(ethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

22		(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(dimethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol
23		(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(methylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol
24		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(azetidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol
25		(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(azetidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol
26		(3aR,4R,5R,6R,7aS)-6-((S)-1-hydroxyethyl)-2-(methoxy(methyl)amino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol
27		(3aR,4R,5R,6R,7aS)-6-((S)-1-hydroxyethyl)-2-(methoxy(methyl)amino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol

Biological Activity

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

Experimental procedure for kinetic analyses

Enzymatic reactions are 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 is 0.7 nM. Test compound of varying concentrations is added to the enzyme prior to initiation of the reaction. The reaction is performed at room temperature in a 96-well plate and is initiated with the addition of substrate. The production of fluorescent product is 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 is 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 are determined.

K_I values are determined using the Cheng-Prusoff equation; the Km of O-GlcNacase for substrate is 0.2 mM.

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

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

Experimental procedure for kinetic analyses

Enzymatic reactions are 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 ddH2O, as a substrate. The amount of purified human β-hexosaminidase enzyme used in the reaction is 24 nM. Test compound of varying concentrations is added to the enzyme prior to initiation of the reaction. The reaction is performed at room temperature in a 96-well plate and is initiated with the addition of substrate. The production of fluorescent product is 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 is 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 are determined.

$K_I$values are determined using the Cheng-Prusoff equation..

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 μM.

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

KI (β-hexosaminidase)/KI (O-GlcNAcase)

In general, the compounds described herein exhibit 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

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.

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. Cells are plated in 96-well plates with approximately 10,000 cells / well. Compounds to be tested are 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 are 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 are used to determine a concentration response curve. To prepare a cell lysate, the media from compound treated cells is removed, the cells are 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 is collected and transferred to a new plate, which is 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 is determined using 20 μL of the sample using the BCA method.

The ELISA portion of the assay is performed in a black Maxisorp 96-well plate that is 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 are washed 3 times with 300 μL /well of Wash buffer (Tris-buffered saline with 0.1% Tween 20). The wells are blocked with 100 μL /well Blocking buffer (Tris buffered saline w/0.05% Tween 20 and 2.5% Bovine serum albumin). Each well is then washed two times with 300 ul/well of wash buffer. The anti O-GlcNAc antibody RL-2 (Abcam, Cambridge, MA), diluted 1:1000 in blocking buffer, is added at 100 ul/well. The plate is sealed and incubated at 37°C for 2 hr with gentle shaking. The wells are then washed 3-times with 300 ul/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) is added at100 μL /well. The plate is incubated for 60 min at 37°C with gentle shaking. Each well is then washed 3-times with

300 μL/well wash buffer. The detection reagent is 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 is incubated for 15 minutes at room temperature and then read with excitation at 530 nm and emission at 590 nm.

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

Representative data from the binding and cell-based assays described above are shown in the following table.

Example #	Cell-based ELISA EC50 (nM)	Fluorescence-based hOGA Ki (nM)
1A	nd	4.5
2	83	0.26
3	nd	54
4	nd	437
5	572	7.1
6	84	0.26

Example #	Cell-based ELISA EC50 (nM)	Fluorescence-based hOGA Ki (nM)
7	nd	93
8	nd	1674
9	nd	14
10	1	0.14

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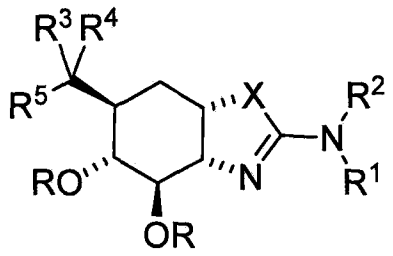
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WHAT IS CLAIMED:

1. A compound of Formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

X is O or S;

each R is independently H or C(O)CH_3;

R^1 and R^2 are independently selected from the group consisting of: H, C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_n$-cyclopropyl and $-(CH_2)_n$-cyclobutyl wherein n is 0, 1, 2, 3 or 4; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine, pyrrolidine or piperidine, said C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_n$-cyclopropyl, $-(CH_2)_n$-cyclobutyl, azetidine, pyrrolidine or piperidine optionally substituted from one up to the maximum number of substituents with fluoro and methyl;

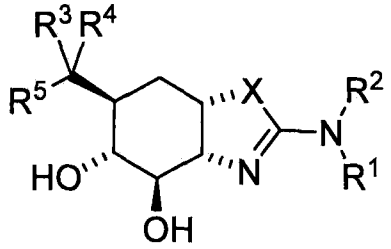
R^3 is selected from the group consisting of: C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-6}cycloalkyl, aryl and heteroaryl, each optionally substituted from one up to the maximum number of substituents with fluoro and OH;

R^4 is selected from the group consisting of: H, F, C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkynyl, each excluding hydrogen and fluoro, optionally substituted from one up to the maximum number of substituents with fluoro and OH; or R^3 and R^4 and the carbon atom to which they are attached may join together to form vinyl or a 3 to 7-membered carbocyclic or heterocyclic ring, said 3 to 7-membered carbocyclic or heterocyclic ring optionally containing a double bond and optionally substituted from one up to the maximum number of substituents with fluoro and OH; and

R^5 is selected from H, F, OH and OC(O)CH_3;

with the proviso that when R^4 is F then R^5 is other than OH and $OC(O)CH_3$.

2. The compound according to Claim 1 of Formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein R^5 is selected from H, F and OH, with the proviso that when R^4 is F then R^5 is other than OH.

3. The compound according to claim 2 wherein:

R^1 and R^2 are independently selected from H, C_{1-4}alkyl and C_{1-4}alkoxy; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine or pyrrolidine;

R^3 is C_{1-6}alkyl, optionally substituted from one up to the maximum number of substituents with fluoro;

R^4 is selected from the group consisting of: H and C_{1-6}alkyl; and

R^5 is OH.

4. The compound according to Claim 3 wherein:

R^1 is methyl, ethyl or propyl;

R^2 is H or methyl;

R^3 is methyl; and

R^4 is H or methyl.

5. The compound according to Claim 2 wherein R^3 and R^4 and the carbon atom to which they are attached may join together to form a 3 to 7-membered carbocyclic or heterocyclic ring, said 3 to 7-membered carbocyclic or heterocyclic ring optionally containing a double bond and optionally substituted from one up to the maximum number of substituents with fluoro and OH.

6. The compound according to Claim 2, wherein:

R^1 and R^2 are independently selected from the group consisting of: H, C_{1-6}alkyl and C_{1-6}alkoxy; or R^1 and R^2 may be joined together with the nitrogen atom to which they are attached to form azetidine or pyrrolidine, said C_{1-6}alkyl, C_{1-6}alkoxy, azetidine or pyrrolidine optionally substituted with 1 to 3 substituents selected from fluoro and methyl;

R^3 is selected from the group consisting of: C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl and C_{3-6}cycloalkyl, each optionally substituted with 1 to 3 substituents selected from fluoro and OH; and

R^4 is selected from the group consisting of: H, F, C_{1-8}alkyl, C_{2-8}alkenyl and C_{2-8}alkynyl, each excluding hydrogen and fluoro, optionally substituted with 1 to 3 substituents selected from fluoro and OH; or R^3 and R^4 and the carbon atom to which they are attached may join together to form a 5-membered carbocyclic ring optionally containing a double bond and optionally substituted with 1 to 3 substituents selected from fluoro and OH.

7. The compound according to Claim 2 wherein R^3 is CF_3, R^4 is H and R^5 is OH.

8. A compound selected from the following group:

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-2-(Dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-2-(Dimethylamino)-6-((*S*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(Dimethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydro-benzo[d]oxazole-4,5-diol;

(3a*S*,4*S*,5*S*,6*S*,7a*R*)-2-(dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(propylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(methylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(ethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*S*,7a*S*)-6-(2-hydroxypropan-2-yl)-2-(propylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-((R)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3aR,4R,5R,6R,7aS)-2-(dimethylamino)-6-((S)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzoxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzoxazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(ethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzoxazole-4,5-diol;

(3a*S*,4*S*,5*S*,6*S*,7a*R*)-2-(dimethylamino)-6-((*R*)-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydrobenzo[d]othiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(propylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiaazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(methylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(ethylamino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(dimethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)- 2-(ethylamino)-6-(2,2,2-trifluoro-1-hydroxyethyl)-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(ethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(dimethylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*S*,7a*S*)-2-(methylamino)-6-(2-hydroxypropan-2-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(azetidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol; and

(3a*R*,4*R*,5*R*,6*R*,7a*S*)-6-((*S*)-1-hydroxyethyl)-2-(azetidin-1-yl)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

(3aR,4R,5R,6R,7aS)-6-((S)-1-hydroxyethyl)-2-(methoxy(methyl)amino)-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole-4,5-diol;

(3aR,4R,5R,6R,7aS)-6-((S)-1-hydroxyethyl)-2-(methoxy(methyl)amino)-3a,4,5,6,7,7a-hexahydrobenzo[d]thiazole-4,5-diol;

or a pharmaceutically acceptable salt of any of the foregoing compounds.

9. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

10. A method of selectively inhibiting O-GlcNAcase in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

11. A method of elevating the level of O-GlcNAc in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

12. A method of treating a condition that is modulated by O-GlcNAcase, in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

13. The method of claim 12 wherein the condition is selected from one or more of the group consisting of an inflammatory disease, an allergy, asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias, delayed-type hypersensitivity, atherosclerosis, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis, systemic anaphylaxis or hypersensitivity response, drug allergy, insect sting allergy, autoimmune disease, rheumatoid arthritis, psoriatic arthritis, multiple sclerosis, Guillain-Barré syndrome, systemic lupus erythematosus, myastenia gravis, glomerulonephritis, autoimmune thyroiditis, graft rejection, allograft rejection, graft-versus-host disease, inflammatory bowel disease, Crohn's disease, ulcerative colitis, spondyloarthropathy, scleroderma, psoriasis, T-cell mediated psoriasis, inflammatory dermatosis, dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, vasculitis, necrotizing, cutaneous, and hypersensitivity vasculitis, eosinphilic myotis, eosiniphilic fasciitis, solid organ transplant rejection, heart transplant rejection, lung transplant rejection, liver transplant rejection, kidney transplant rejection, pancreas transplant rejection, kidney allograft, lung allograft, epilepsy, pain, fibromyalgia, stroke, neuroprotection.

14. A method of treating a condition selected from the group consisting of a neurodegenerative disease, a tauopathy, cancer and stress, in a subject in need thereof, the

method comprising administering to the subject an effective amount of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

15. The method of claim 14 wherein the condition is selected from one or more of the group consisting of 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.

16. The method of claim 14 wherein the stress is a cardiac disorder.

17. The method of claim 16 wherein the cardiac disorder is selected from one or more of the group consisting of ischemia; hemorrhage; hypovolemic shock; myocardial infarction; an interventional cardiology procedure; cardiac bypass surgery; fibrinolytic therapy; angioplasty; and stent placement.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/50225

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/76; A61K 31/42 (2012.01)
USPC - 514/374-377
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC-514/374-377

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC-514/365, 367, 369-370 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Thomson Innovation, Google, Google Scholar, WIPO, PUBCHEM, ChemSpider, Selective glycosidase inhibitors, hexahydrobenzene, hexahydrobenzyl, hexahydrobenzo, oxazole, benzoxazole, diol, thiazole

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2008/0287375 A1 (Vocadlo et al.) 20 November 2008 (20.11.2008) para [0013], [0019], [0047], [0051]-[0057], [0061], [0163], [0165]	1, 9-12, 14-16 --- 1-8, 13, 17
Y	Corbet et al. The Synthesis of Pseudo-sugars Related to Allosamizoline. Tetrahedron Letters, 1993, Vol 34, No 9, pp 1525-1528; pg 1525	1-8
Y	US 2010/0016386 A1 (Vocadlo et al.) 21 January 2010 (21.01.2010) para [0029]-[0030], [0068]-[0069], [0085]	7, 13, 17
P/X	WO 2011/140640 A1 (Li et al.) 17 November 2011 (17.11.2011) entire document	1-17
Y	WO 2006/092049 A1 (Vocadlo et al.) 08 September 2006 (08.09.2006) entire document	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 September 2012 (20.09.2012)	10 OCT 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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