(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2024 (12.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/254440 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *C07D 498/18* (2006.01)
C07D 405/14 (2006.01) *A61P 25/28* (2006.01)
C07D 493/08 (2006.01) *A61P 29/00* (2006.01)
A61K 31/4155 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4439 (2006.01)

(21) International Application Number:
PCT/US2024/032992

(22) International Filing Date:
07 June 2024 (07.06.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/472,202 09 June 2023 (09.06.2023) US
63/540,141 25 September 2023 (25.09.2023) US

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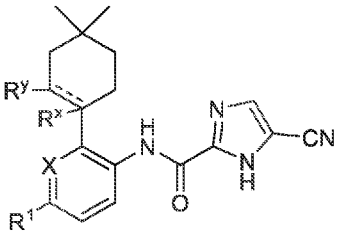
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: 5-CYANO-1H-IMIDAZOLE-2-CARBOXAMIDE COMPOUNDS AS CSF1R INHIBITORS



(I)

(57) Abstract: The invention provides a compound of formula (I): or a prodrug or a salt thereof, wherein R^1, R^x, R^y, and X have any of the values described in the specification, as well as compositions comprising a compound of formula (I). The compounds are useful as kinase inhibitors.

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THERAPEUTIC COMPOUNDS AND METHODS

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority from United States Provisional Patent Application Number 63/472,202 filed 09 June 2023 and from United States Provisional Patent Application Number 63/540,141 filed 25 September 2023. The entire content of each of these United States Provisional Patent Applications is hereby incorporated by reference herein.

BACKGROUND

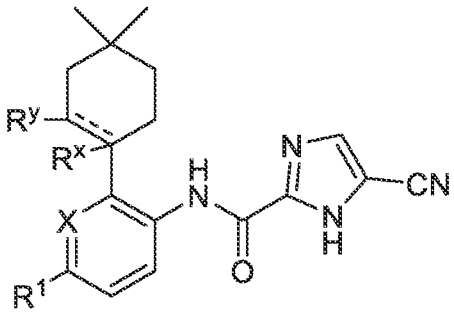
Colony stimulating factor 1 receptor (CSF1R), also known as macrophage colony-stimulating factor receptor (M-CSFR), and CD115 (Cluster of Differentiation 115), is a cell-surface protein encoded by the human *CSF1R* gene (known also as c-FMS). CSF1R is a receptor that can be activated by two ligands: colony stimulating factor 1 (CSF-1) and interleukin-34 (IL-34). CSF1R is highly expressed in myeloid cells. CSF1R signaling is necessary for the survival, proliferation, and differentiation of many myeloid cell types *in vivo* and *in vitro*. CSF1R signaling is involved in many diseases and is targeted in therapies for cancer, neurodegeneration, and inflammatory bone diseases.

WO 2009/052237 describes compounds that inhibit protein kinases, especially c-fms kinase. The compounds are reported to be useful for treating certain cancers, metastasis of certain cancers, pain, and certain autoimmune diseases. One compound, 4-cyano-1H-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(2,2,6,6-tetramethyl-tetrahydro-pyran-4-yl)-pyridin-3-yl]-amide (Example 15, page 83 therein), a selective inhibitor of colony-stimulating factor-1 (CSF-1, c-fms) receptor kinase that acts to inhibit macrophage survival, proliferation, and differentiation in patients with active rheumatoid arthritis, advanced to Phase II clinical trials as JNJ-40346527 (Genovese, M.C., et al (2015) *Journal of Rheumatology*, 42:10).

Currently there is a need for therapeutic agents operating as kinase inhibitors to treat disease and mitigate or delay progression of many disease conditions. In particular, there is a need for inhibitors of c-fms kinase with more precise and predictable selective target coverage in a tissue relevant manner which is driven by more potency, better selectivity over off-targets which cause side effects and limit dose, and therefore, higher exposure of the active molecule in the brain, less brain homogenate binding providing more free fraction in the brain, longer off-rate from CSF1R resulting in enhanced pharmacodynamics as well as a differentiating metabolism that provides higher levels of active drug (and/or active metabolites).

SUMMARY

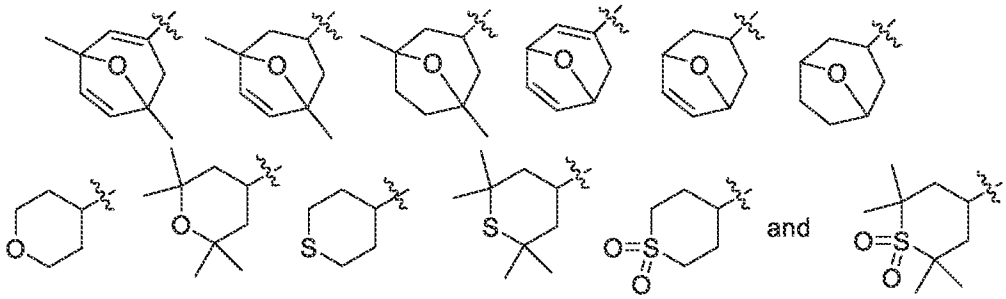
In one embodiment, the invention provides a compound of formula (I):



or a prodrug or a salt thereof, wherein:

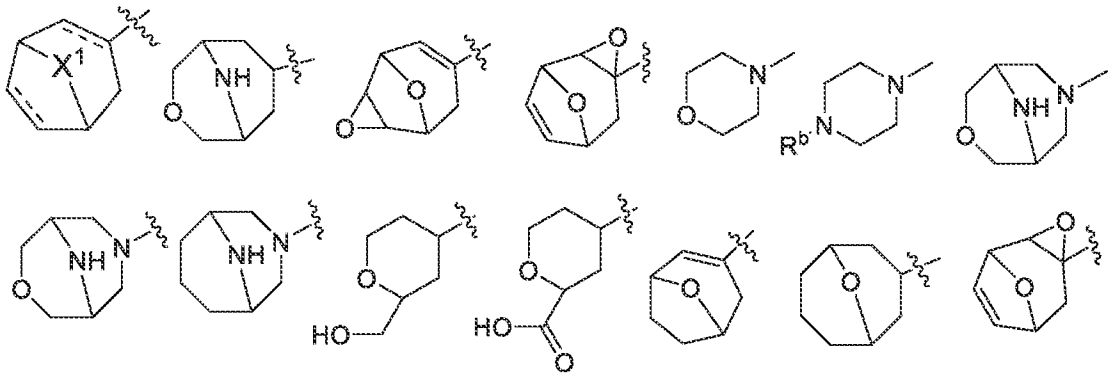
X is N, NR^e, or CH;

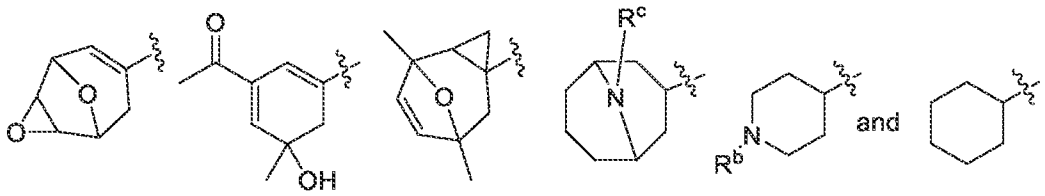
R^1 is selected from the group consisting of:



wherein R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro; or R^1 is R^2 or R^3;

R^2 is:





and is optionally substituted with one or more groups independently selected from D, Cl, F, OH, and (C_1-C_8)alkyl, where (C_1-C_8)alkyl is optionally substituted with one or more groups independently selected from D, Cl, F, OH;

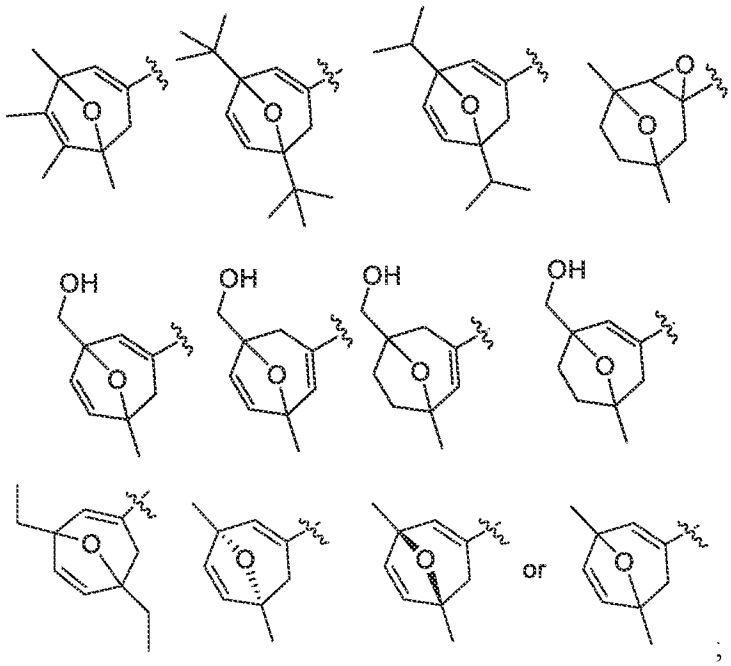
X^1 is NR^a or S;

R^a is selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, and C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^3 is:



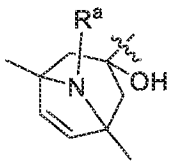
;

R^x and R^y are independently selected from H and D; or R^x and R^y taken together form a double bond;

R^e forms an ammonium oxide with the nitrogen to which it is attached; and

each ------ is independently a single or double bond;

provided that R^2 is not:



wherein R^a is C_1-C_6)alkoxycarbonyl.

The invention also provides a pharmaceutical composition comprising a compound of formula I or a prodrug or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition provides blood-brain barrier (BBB) permeability.

The invention also provides a method of treating a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating a disease initiated or progressed due to myeloid cell immune activation including but not limited to Monocyte, macrophage and microglia.

The invention also provides a method of treating a disease or disorder selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (SARS-CoV-2), neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive, Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy , Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, age-related loss of motor units, muscular dystrophy and Alzheimer's dementia in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating pain in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof. In one embodiment, the pain is skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, or neurogenic pain.

The invention also provides a method of treating cancer in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof. In one embodiment the cancer is selected from the group consisting of

ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia.

The invention also provides a method of treating or preventing cancer metastasis in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof. In one embodiment the cancer is selected from the group consisting of ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia.

The invention also provides a method of treating an autoimmune disease in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof. In one embodiment, the autoimmune disease is selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, and uveitis

The invention also provides a method for inhibiting the activity of c-fms kinase, comprising contacting the c-fms kinase a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof. In one embodiment, the c-fms kinase is contacted with the compound or the salt *in vitro*. In one embodiment, the c-fms kinase is contacted with the compound of formula (I) or a pharmaceutically acceptable salt thereof *in vivo*. In one embodiment, the invention provides inhibitors of c-fms kinase that are not converted to biologically active metabolites *in vivo*.

The invention also provides a method of treating atherosclerosis in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating a disease selected from the group consisting of ALS, FTD, C9 related disease, Alzheimers, Parkinsons, MS, Huntington's Disease, Giant Tenosynovial Carcinoma, and Epilepsy in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, bladder cancer, pancreatic cancer, glioblastoma, melanoma, lymphoma, leukemia, or hairy cell leukemia in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, Giant Tenosynovial

Carcinoma, brain cancer and tumor metastasis to brain or bone in an animal, any advanced solid tumors and cancer tumor metastasis (especially to the brain, CNS, bone, or lymph nodes) in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a method of treating a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (*SARS-CoV-2)*, Hepatitis, neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy, Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System disorders, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, tauopathies, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar dementia, epilepsy, any disorder caused by C9ORF72 mutation, age-related loss of motor units, muscular dystrophy and any other form of dementia, radiation induced cognitive impairment, and Crohn's disease in an animal, comprising administering to the animal a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for use in medical therapy.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (SARS-CoV-2), neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor

related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive, Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy , Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, age-related loss of motor units, muscular dystrophy and Alzheimer's dementia.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of pain. In one embodiment, the pain is skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, or neurogenic pain. In one embodiment, the cancer is selected from the group consisting of ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for treating or preventing cancer metastasis. In one embodiment, the cancer is selected from the group consisting of ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, and hairy cell leukemia.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment an autoimmune disease. In one embodiment, the autoimmune disease is selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, and uveitis.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for inhibiting the activity of c-fms kinase.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the treatment of athlerosclerosis.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the treatment of a disease selected from the group consisting of ALS, FTD, C9 related disease, Alzheimers, Parkinsons, MS, Huntington's Disease, Giant Tenosynovial Carcinoma, and Epilepsy.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the treatment of ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, bladder cancer, pancreatic cancer, glioblastoma, melanoma, lymphoma, leukemia, or hairy cell leukemia.

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the treatment of a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, Giant Tenosynovial Carcinoma, brain cancer and tumor metastasis to brain or bone in an animal, any advanced solid tumors and cancer tumor metastasis (especially to the brain, CNS, bone, or lymph nodes).

The invention also provides a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof for the treatment of a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (*SARS-CoV-2)*, Hepatitis, neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy, Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System disorders, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, tauopathies, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar dementia, epilepsy, any disorder caused by C9ORF72 mutation, age-related loss of motor units, muscular dystrophy and any other form of dementia, radiation induced cognitive impairment, and Crohn's .

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, and tumor metastasis to bone in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a

disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (SARS-CoV-2), neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive, Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy , Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, age-related loss of motor units, muscular dystrophy and Alzheimer's dementia in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating pain in an animal. In one embodiment, the pain is skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, or neurogenic pain.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating cancer in an animal. In one embodiment, the cancer is ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, or hairy cell leukemia.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating or preventing cancer metastasis in an animal. In one embodiment, the cancer is ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, or hairy cell leukemia.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a formulation which optimizes exposure and other pharmacodynamic properties of the compound.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating an autoimmune disease in an animal. In one embodiment, the autoimmune disease selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, and uveitis.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for inhibiting the activity of a c-fms kinase in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating athlerosclerosis in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of ALS, FTD, C9 related disease, Alzheimers, Parkinsons, MS, Huntington's Disease, Giant Tenosynovial Carcinoma, and Epilepsy in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, bladder cancer, pancreatic cancer, glioblastoma, melanoma, lymphoma, leukemia, or hairy cell leukemia in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, Giant Tenosynovial Carcinoma, brain cancer and tumor metastasis to brain or bone in an animal, any advanced solid tumors and cancer tumor metastasis (especially to the brain, CNS, bone, or lymph nodes) in an animal.

The invention also provides the use of a compound of formula (I) or a prodrug or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (*SARS-CoV-2)*, Hepatitis, neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy, Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System

disorders, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, tauopathies, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar dementia, epilepsy, any disorder caused by C9ORF72 mutation, age-related loss of motor units, muscular dystrophy and any other form of dementia, radiation induced cognitive impairment, and Crohn's disease in an animal.

The invention also provides processes and intermediates disclosed herein that are useful for preparing a compound of formula I or a salt thereof.

Certain compounds are deuterated, chlorinated, or fluorinated in the group R^1. Deuteration, chlorination, or fluorination in the group R^1 may improve metabolic stability, potency, and/or *in vivo* efficacy relative to similar compounds with different R^1 substituents.

Certain compounds exhibit higher metabolic stabilities than the corresponding non-deuterated compounds.

Certain compounds exhibit superior *in vivo* pharmacokinetics than the corresponding non-deuterated compounds.

Certain compounds exhibit superior *in vitro* efficacies than the corresponding non-deuterated compounds.

Certain compounds exhibit higher metabolic stabilities than the corresponding non-fluorinated compounds.

Certain compounds exhibit superior *in vivo* pharmacokinetics than the corresponding non-fluorinated compounds.

Certain compounds exhibit superior *in vitro* efficacies than the corresponding non-fluorinated compounds.

Certain compounds exhibit higher metabolic stabilities than the corresponding non-chlorinated compounds.

Certain compounds exhibit superior *in vivo* pharmacokinetics than the corresponding non- chlorinated compounds.

Certain compounds exhibit superior *in vitro* efficacies than the corresponding non-chlorinated compounds.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to certain embodiments of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated embodiments, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is

intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the invention as defined by the claims.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The invention is in no way limited to the methods and materials described.

DEFINITIONS

The following definitions are used, unless otherwise described: halo or halogen is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such as propyl embraces only the straight chain radical, a branched chain isomer such as isopropyl being specifically referred to.

The term "alkyl", by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical, having the number of carbon atoms designated (i.e., C_{1-6} means one to six carbons). Examples of alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, and n-hexyl.

Specifically, (C_1-C_6)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl.

The term "alkoxy" refers to an alkyl groups attached to the remainder of the molecule via an oxygen atom ("oxy").

The term "alkoxycarbonyl" as used herein refers to a group (alkyl)-O-C(=O)-, wherein the term alkyl has the meaning defined herein. The term (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, or hexyloxycarbonyl.

The term "alkanoyl" as used herein refers to a group (alkyl)-C(=O)-, wherein the term alkyl has the meaning defined herein.

As used herein, the term "protecting group" refers to a substituent that is commonly employed to block or protect a particular functional group on a compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, t-butoxycarbonyl (BOC), benzyloxycarbonyl (CBZ) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include phenylsulfonylethyl, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfenyl)ethyl, 2-

(diphenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see P.G.M. Wuts and T.W. Greene, Greene's Protective Groups in Organic Synthesis 4th edition, Wiley-Interscience, New York, 2006.

As used herein a wavy line " ∿ " that intersects a bond in a chemical structure indicates the point of attachment of the bond that the wavy bond intersects in the chemical structure to the remainder of a molecule.

The terms "treat", "treatment", or "treating" to the extent it relates to a disease or condition includes inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition. The terms "treat", "treatment", or "treating" also refer to both therapeutic treatment and/or prophylactic treatment or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as, for example, the development or spread of cancer. For example, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease or disorder, stabilized (i.e., not worsening) state of disease or disorder, delay or slowing of disease progression, amelioration or palliation of the disease state or disorder, and remission (whether partial or total), whether detectable or undetectable. "Treat", "treatment", or "treating," can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the disease or disorder as well as those prone to have the disease or disorder or those in which the disease or disorder is to be prevented. In one embodiment "treat", "treatment", or "treating" does not include preventing or prevention,

The phrase "therapeutically effective amount" or "effective amount" includes but is not limited to an amount of a compound of the that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The term "mammal" as used herein refers to humans, higher non-human primates, rodents, domestic, cows, horses, pigs, sheep, dogs and cats. In one embodiment, the mammal is a human. The term "patient" as used herein refers to any animal including mammals. In one embodiment, the patient is a mammalian patient. In one embodiment, the patient is a human patient.

The disclosure also includes "deuterated analogs" of compounds described herein in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds exhibit increased resistance to metabolism and are thus useful for increasing the half-life of any compound when administered

to a mammal, particularly a human. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism," *Trends Pharmacol. Sci.* 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium. Deuterium labeled or substituted therapeutic compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life, reduced dosage requirements and/or an improvement in therapeutic index. An ^{18}F, ^{3}H, or ^{11}C labeled compound may be useful for PET or SPECT or other imaging studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in a compound described herein. The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

When a compound is substituted with one or more deuterium, it is understood that the compound is enriched in deuterium at a given position above the natural abundance of deuterium. In one embodiment the compound may be enriched by at least 2-times the natural abundance of deuterium. In one embodiment the compound may be enriched by at least 10-times the natural abundance of deuterium. In one embodiment the compound may be enriched by at least 100-times the natural abundance of deuterium. In one embodiment the compound may be enriched by at least 1000-times the natural abundance of deuterium.

The compounds disclosed herein can also exist as tautomeric isomers in certain cases. Although only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention.

It is understood by one skilled in the art that this invention also includes any compound claimed that may be enriched at any or all atoms above naturally occurring isotopic ratios with one or more isotopes such as, but not limited to, deuterium (^{2}H or D). As a non-limiting example, a $-CH_3$ group may be substituted with $-CD_3$.

The pharmaceutical compositions of the invention can comprise one or more excipients. When used in combination with the pharmaceutical compositions of the invention the term "excipients" refers generally to an additional ingredient that is combined with the compound of formula (I) or the pharmaceutically acceptable salt thereof to provide a corresponding composition. For example, when used in combination with the pharmaceutical compositions of the invention the term "excipients" includes, but is not limited to: carriers, binders, disintegrating agents, lubricants, sweetening agents, flavoring agents, coatings, preservatives, and dyes.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention can contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or R and S, are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which can occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

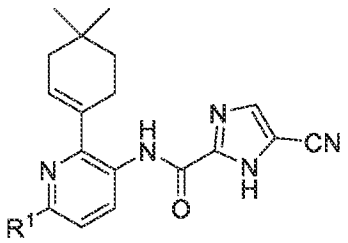
It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of

the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase.

When a bond in a compound formula herein is drawn in a non-stereochemical manner (e.g. flat), the atom to which the bond is attached includes all stereochemical possibilities. When a bond in a compound formula herein is drawn in a defined stereochemical manner (e.g. bold, bold-wedge, dashed or dashed-wedge), it is to be understood that the atom to which the stereochemical bond is attached is enriched in the diastereomer depicted unless otherwise noted. In one embodiment, the compound may be at least 51% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 60% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 80% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 90% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 95 the absolute stereoisomer depicted. In another embodiment, the compound may be at least 99% the absolute stereoisomer depicted.

Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents. It is to be understood that two or more values may be combined. It is also to be understood that the values listed herein below (or subsets thereof) can be excluded.

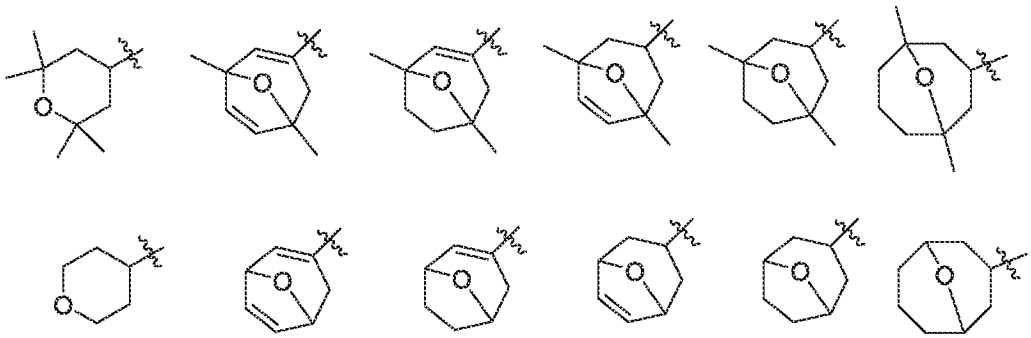
In one aspect, provided is a compound of formula (III):

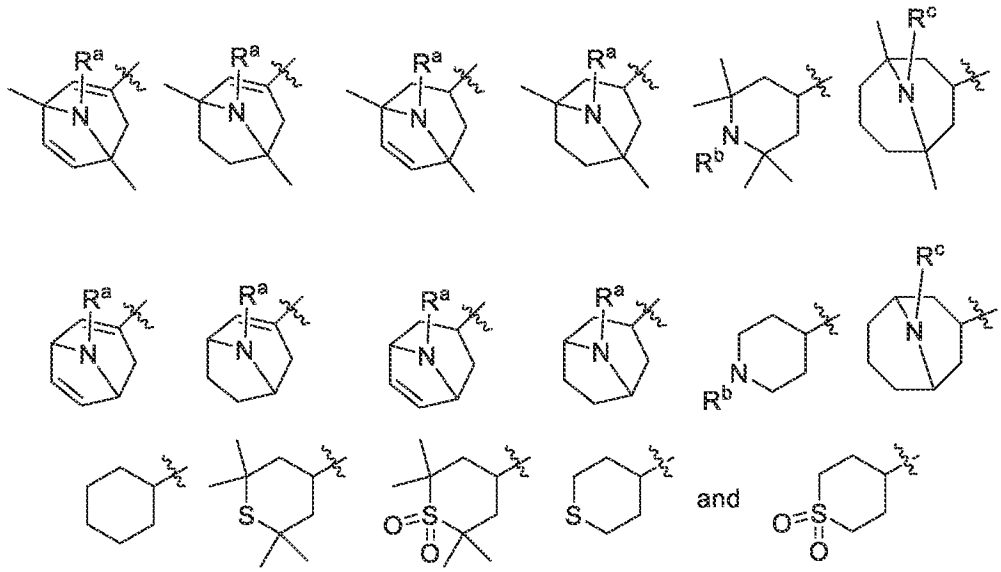


(III)

or a salt thereof, wherein:

R^1 is selected from the group consisting of:





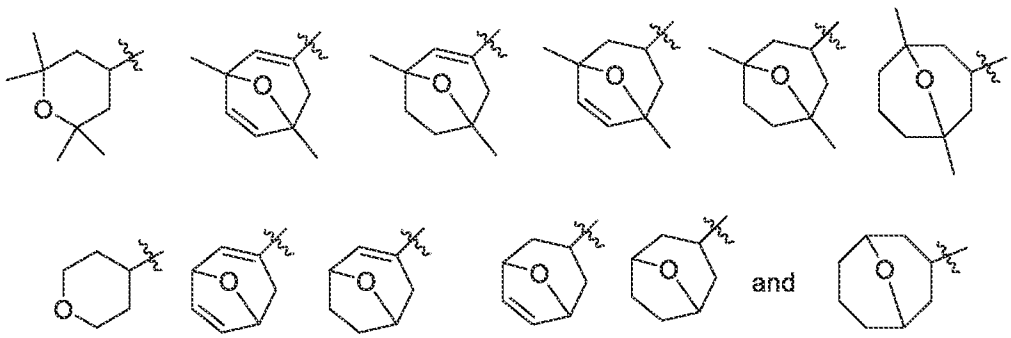
wherein R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro;

R^a is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl; and

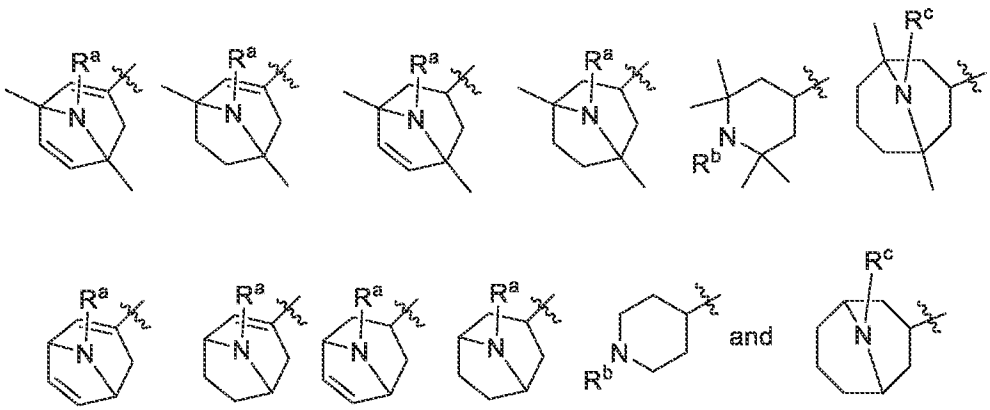
R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl.

A specific value for R^1 is selected from the structures:



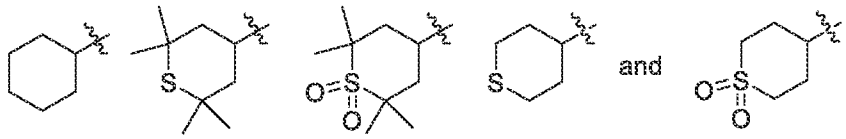
wherein R^1 is optionally substituted with one or more OH and wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

A specific value for R^1 is selected from the structures:



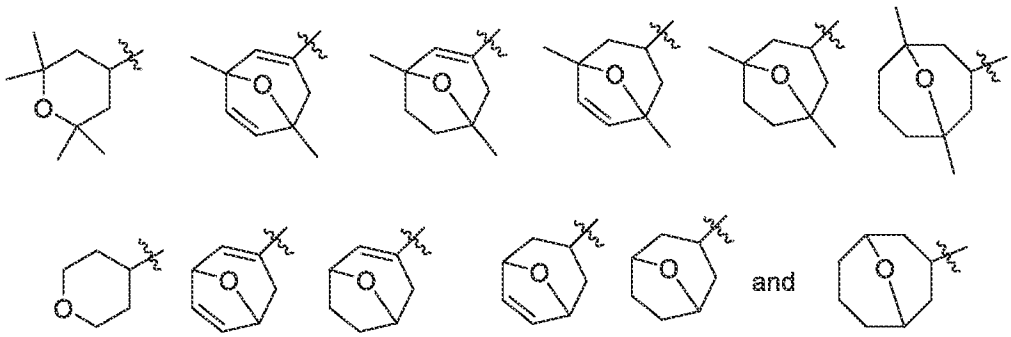
wherein R^1 is optionally substituted with one or more OH and wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

A specific value for R^1 is selected from the structures:



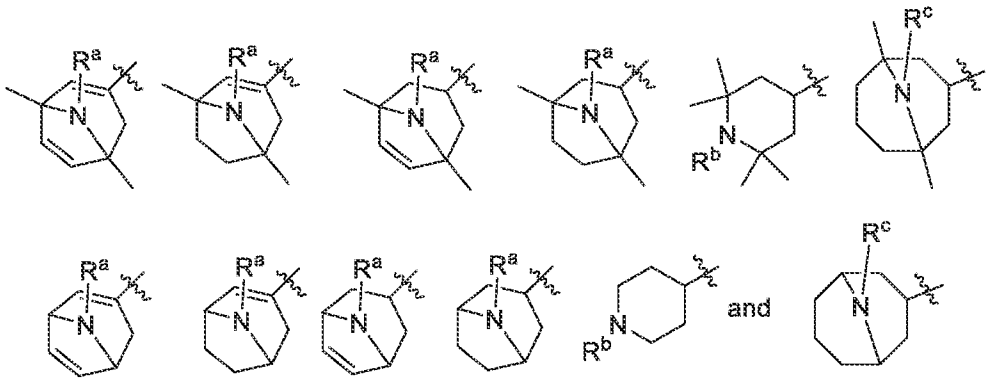
wherein R^1 is optionally substituted with one or more OH and wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

A specific value for R^1 is selected from the structures:



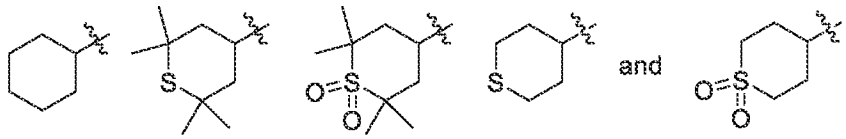
wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

A specific value for R^1 is selected from the structures:



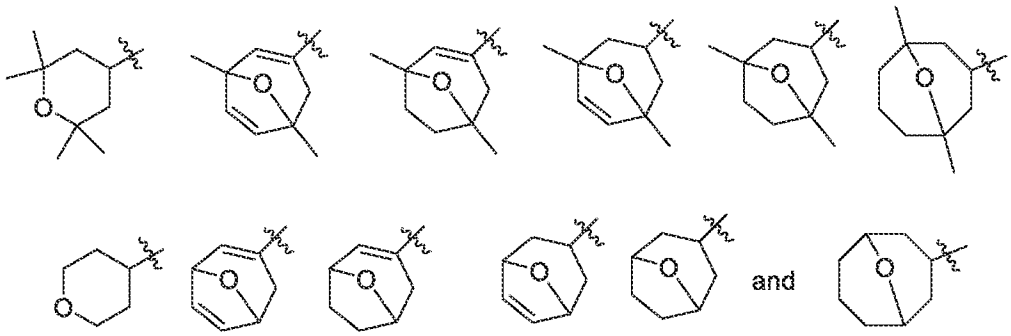
wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

A specific value for R^1 is selected from the structures:



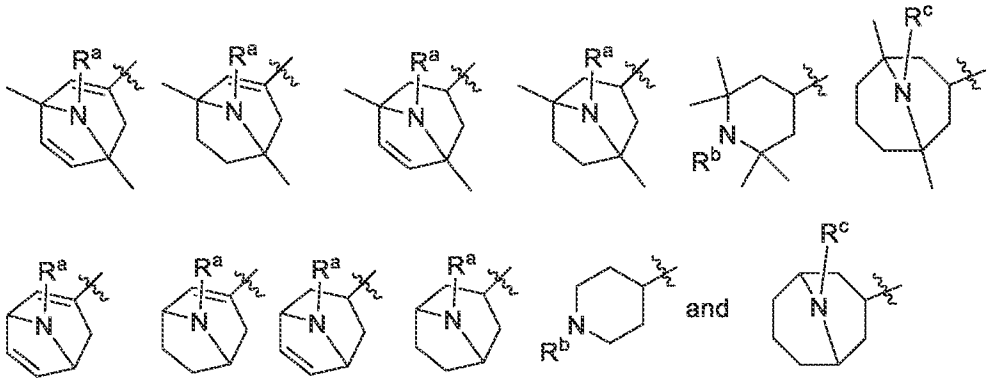
wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

A specific value for R^1 is selected from the structures:



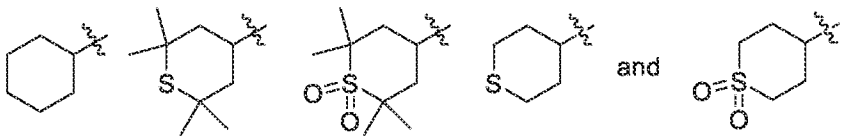
wherein R^1 is substituted with one or more deuterium.

A specific value for R^1 is selected from the structures:



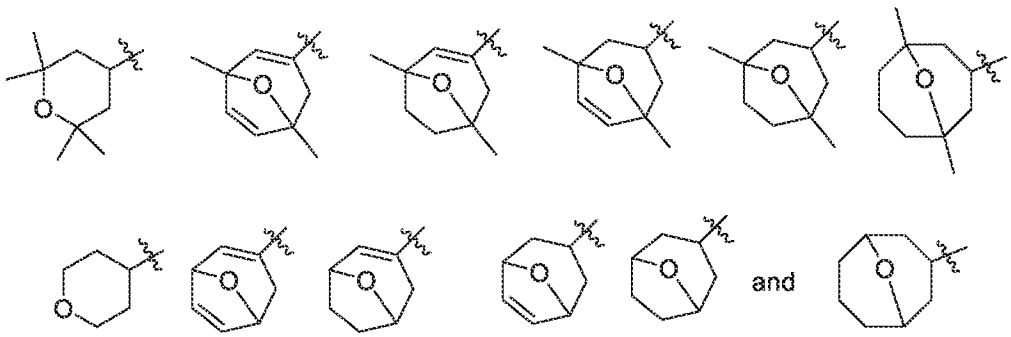
wherein R^1 is substituted with one or more deuterium.

A specific value for R^1 is selected from the structures:



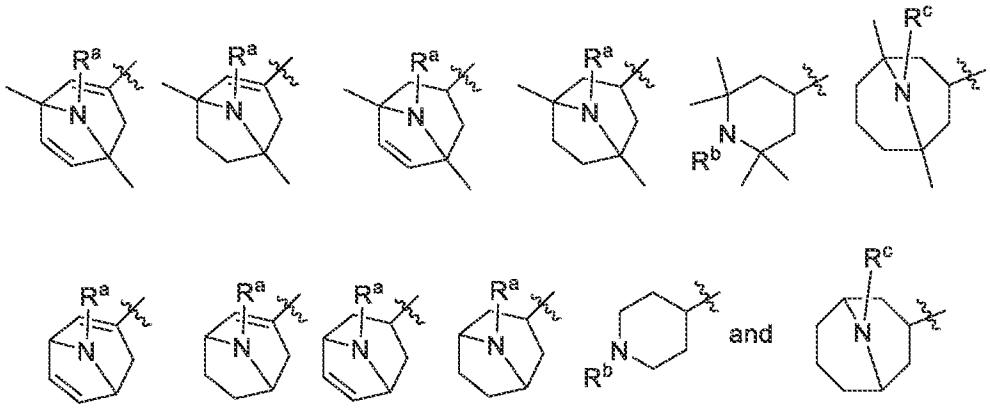
wherein R^1 is substituted with one or more deuterium.

A specific value for R^1 is selected from the structures:



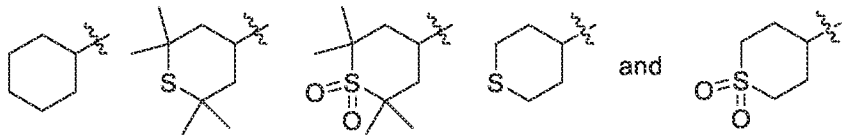
wherein R^1 is substituted with one or more groups independently selected from chloro and fluoro.

A specific value for R^1 is selected from the structures:



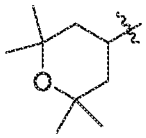
wherein R^1 is substituted with one or more groups independently selected from chloro and fluoro.

A specific value for R^1 is selected from the structures:



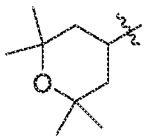
wherein R^1 is substituted with one or more groups independently selected from chloro and fluoro.

A specific value for R^1 has the structure:



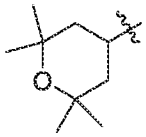
wherein R^1 is substituted with two or more deuterium.

A specific value for R^1 has the structure:



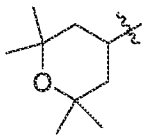
wherein R^1 is substituted with three or more deuterium.

A specific value for R^1 has the structure:



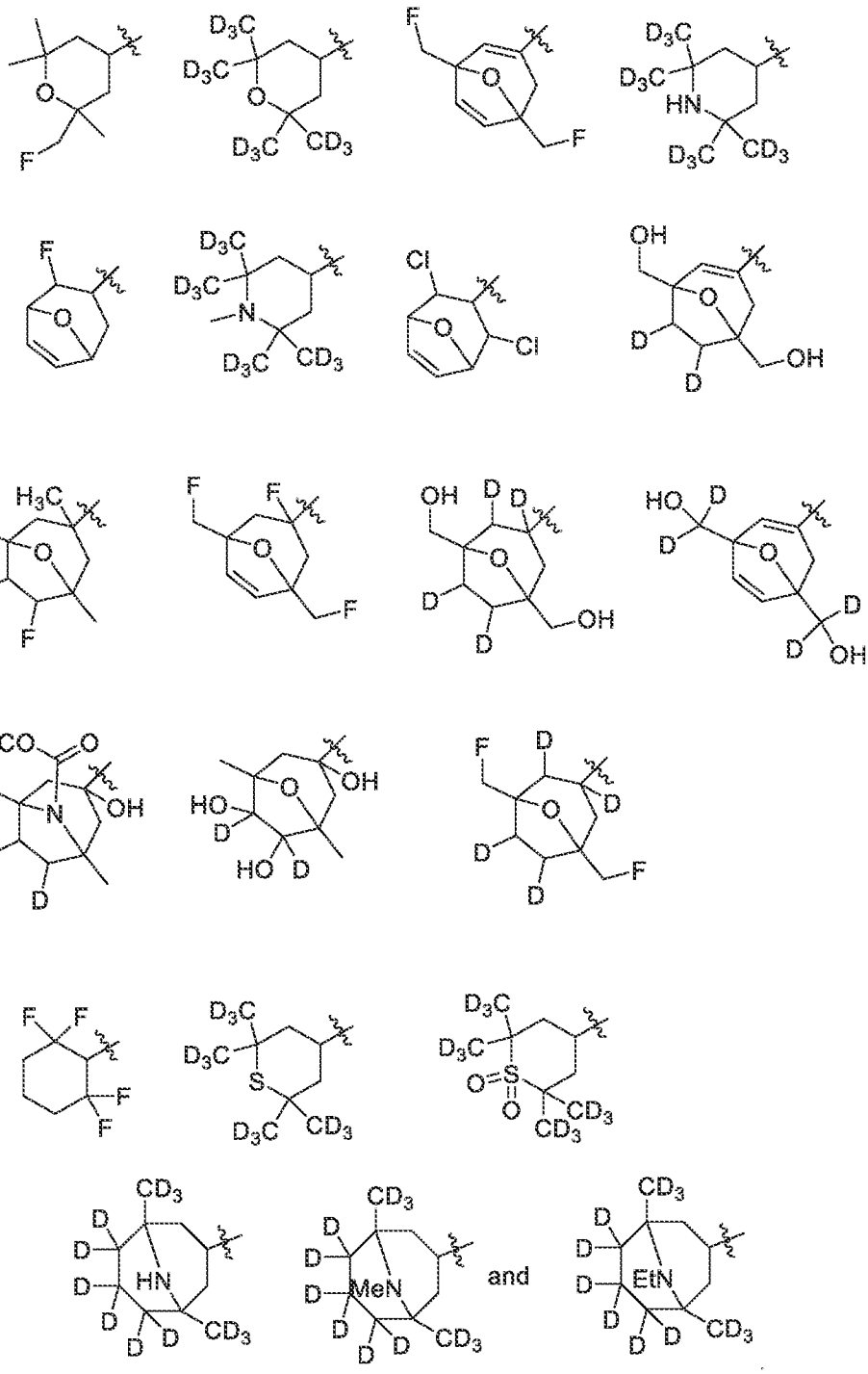
wherein R^1 is substituted with six or more deuterium.

A specific value for R^1 has the structure:

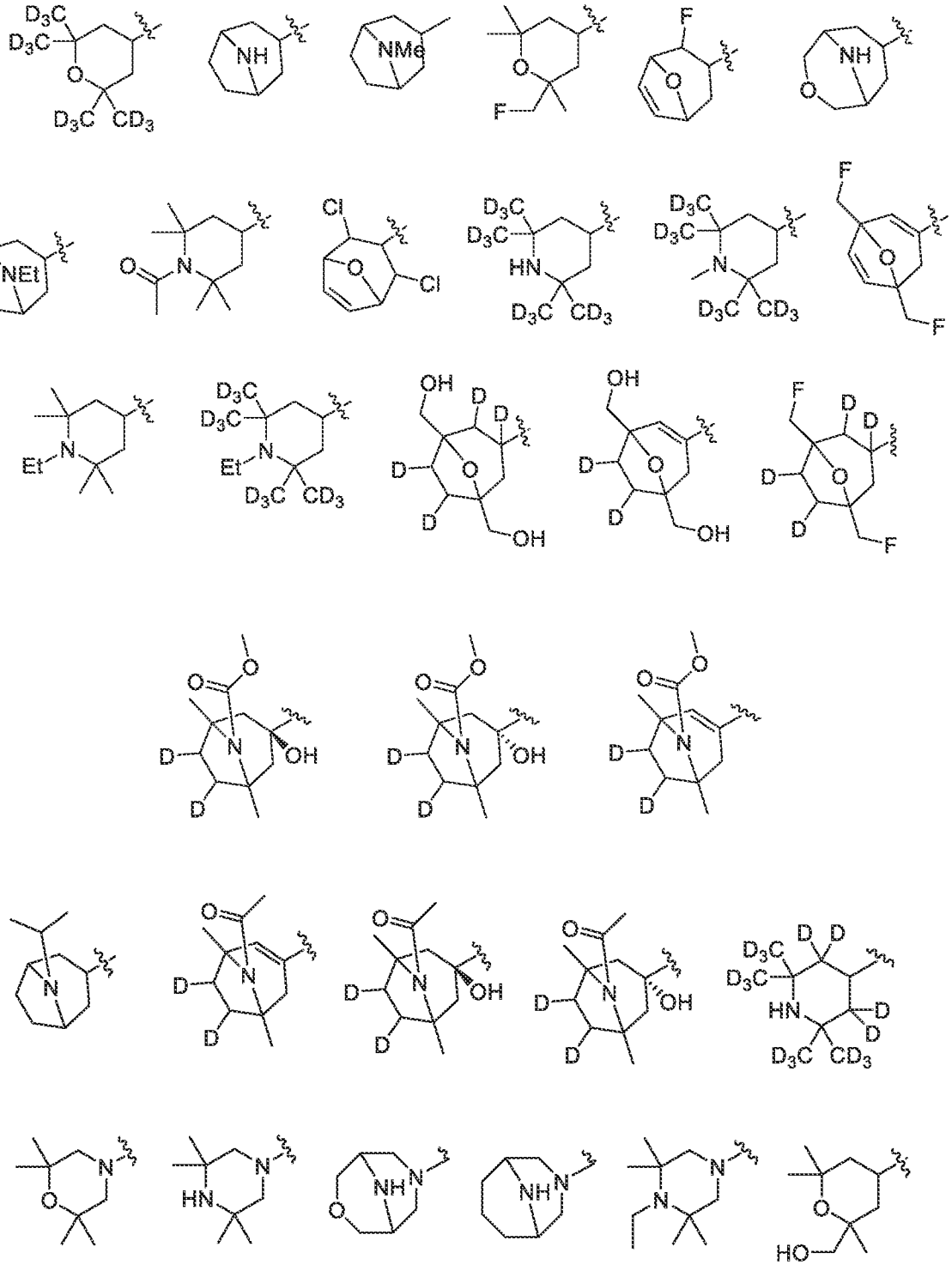


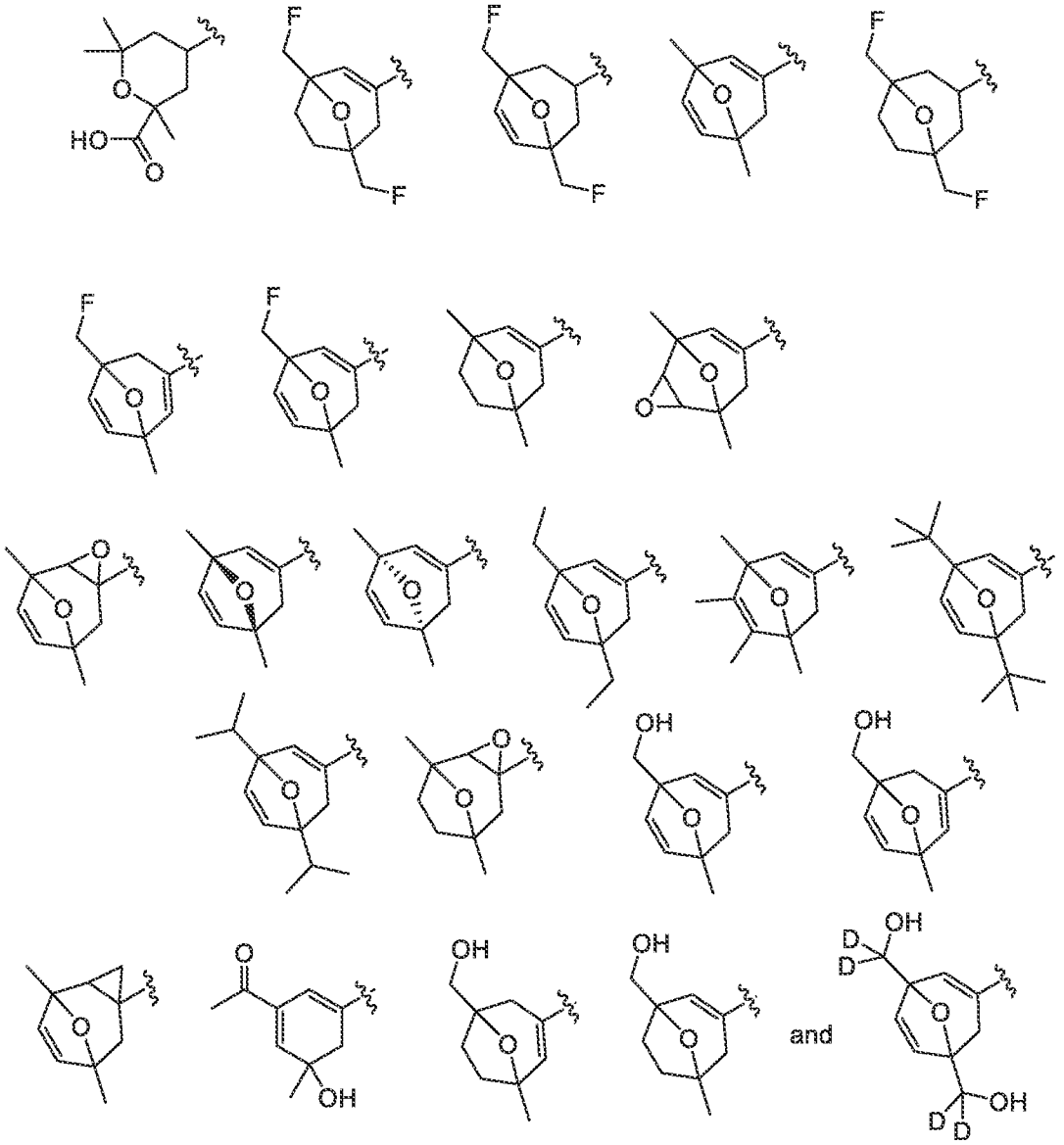
wherein R^1 is substituted with twelve or more deuterium.

A specific value for R^1 is selected from the group consisting of:

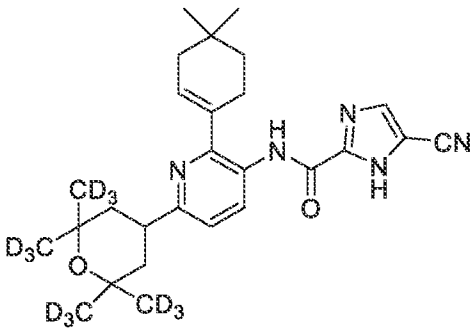


A specific value for R^1 is selected from the group consisting of:



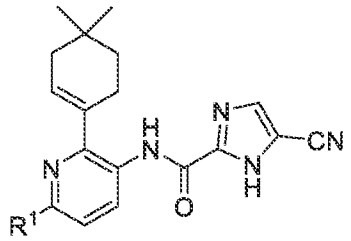


A specific compound, prodrug, or salt is:



or a prodrug or a salt thereof.

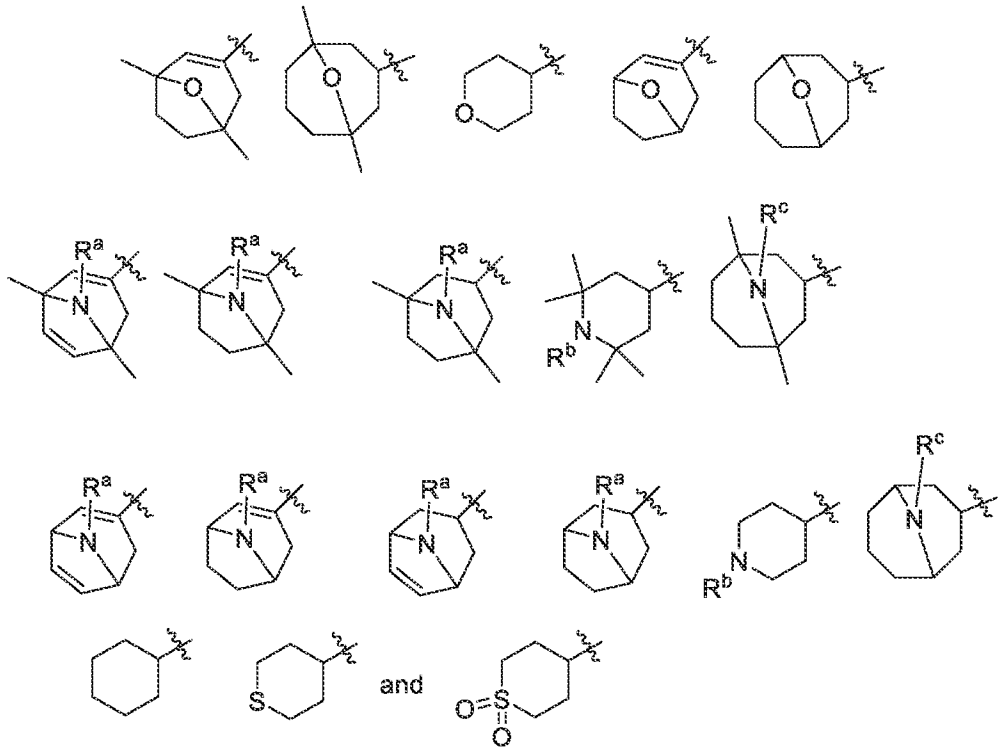
A specific compound, prodrug, or salt is a compound of formula (III):



(III)

or a prodrug or a salt thereof, wherein:

R^1 is selected from the group consisting of:



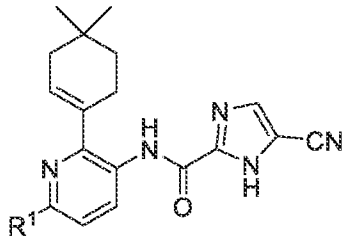
wherein R^1 is optionally substituted with one or more groups independently selected from OH deuterium, chloro, and fluoro;

R^a is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl; and

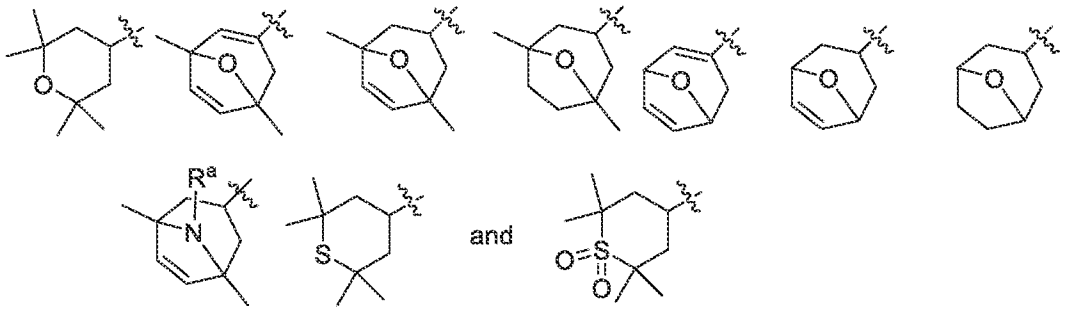
R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl.

A specific compound, prodrug, or salt is a compound of formula (I):



or a prodrug or a salt thereof, wherein:

R^1 is selected from the group consisting of:



wherein R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro;

R^a is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl; and

R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl.

In one embodiment, R^a is methoxycarbonyl.

In one embodiment, R^a is H.

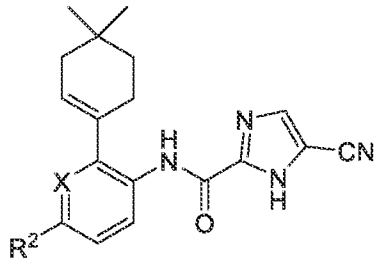
In one embodiment, R^b is H or methyl.

In one embodiment, R^c is H, methyl, or ethyl.

In one embodiment, X is N.

In one embodiment, X is CH.

In one aspect, provided is a compound of formula (II):

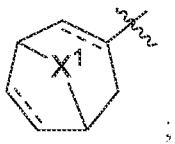


(II)

or a prodrug or a salt thereof, wherein:

X is N or CH;

R^2 is:



;

X^1 is NR^a, O, or S;

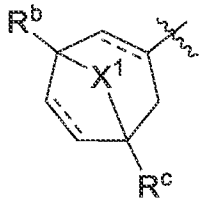
R^a is selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, and (C_1-C_6)alkoxycarbonyl;

------ is a single or double bond; and

R^2 is optionally substituted with one or more groups independently selected from D, Cl, F, OH,

and (C_1-C_6)alkyl, where (C_1-C_6)alkyl is optionally substituted with one or more groups independently selected from D, Cl, F, OH.

A specific value for R^2 is:

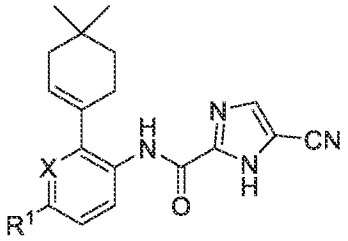


;

where R^b and R^c are independently selected from D, Cl, F, OH, and (C_1-C_6)alkyl, where (C_1-C_6)alkyl is optionally substituted with one or more groups independently selected from D, Cl, F,

A specific value for R^b and R^c is independently selected from CH_3, CH_2F, and CH_2OH.

In one embodiment, the invention provides a compound of formula (III):

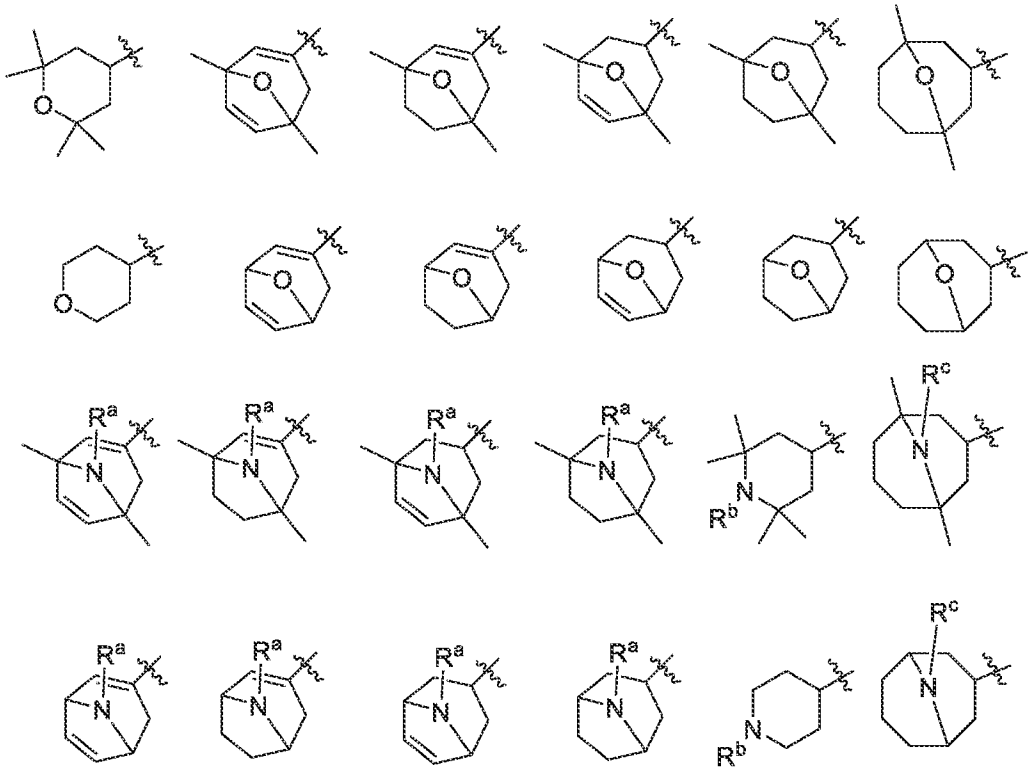


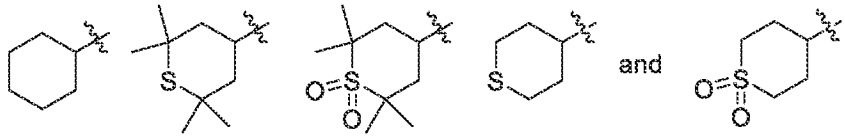
(III)

or a prodrug or a salt thereof, wherein:

X is N or CH;

R^1 is selected from the group consisting of:





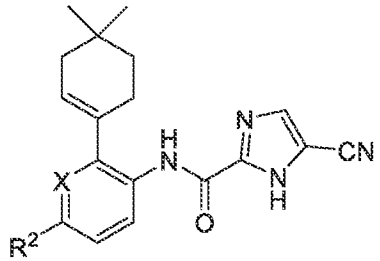
wherein R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro;

R^a is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl; and

R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl.

In one embodiment, the invention provides a compound of formula (I) or a prodrug or a salt thereof that is a compound of formula (II):

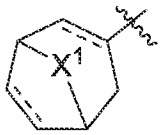


(II)

or a prodrug or a salt thereof, wherein:

X is N or CH;

R^2 is:



;

X^1 is NR^a, O, or S;

R^a is selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, and (C_1-C_6)alkoxycarbonyl;

------ is a single or double bond; and

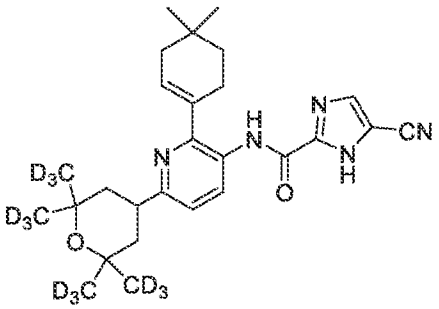
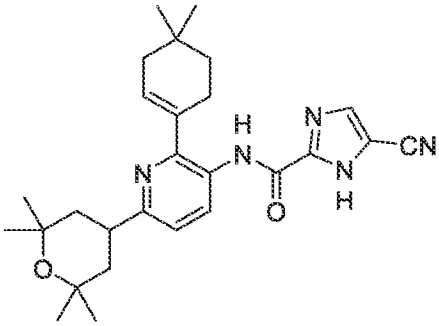
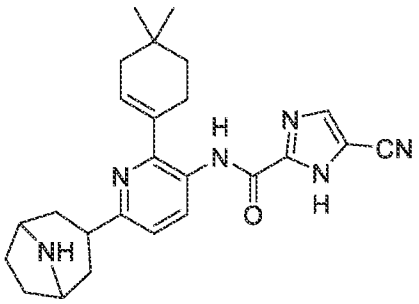
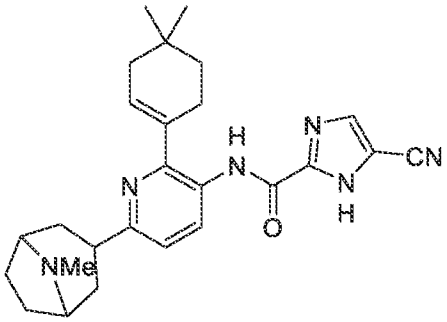
R^2 is optionally substituted with one or more groups independently selected from D, Cl, F, OH, and (C_1-C_6) alkyl, where (C_1-C_6)alkyl is optionally substituted with one or more groups independently selected from D, Cl, F, OH.

Certain Compounds (e.g., certain compounds of formula (I) wherein R^1 includes a bridged bicyclic ring or certain compounds of formula (II)) have improved kinase selectivity, potency, stability, pharmacokinetics, pharmacodynamics, penetration of the blood-brain barrier, chirality, and/or improvements in the activity of metabolites. Certain compounds may also elicit a unique microglia transcriptomic state that is beneficial.

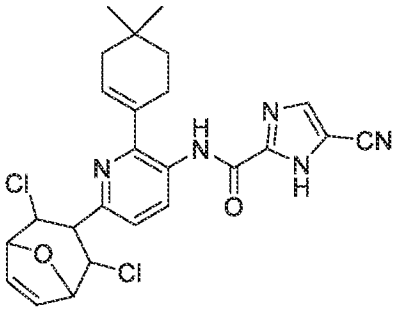
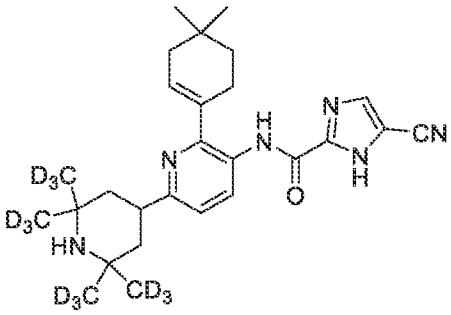
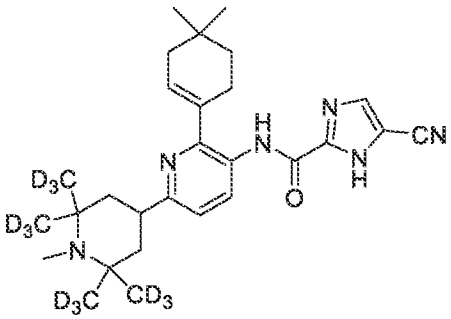
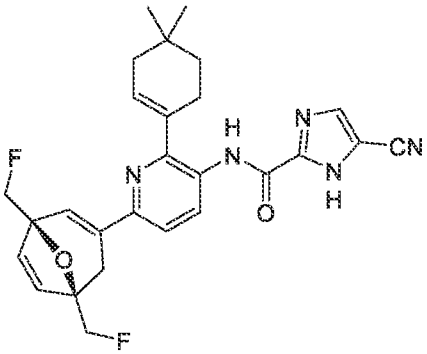
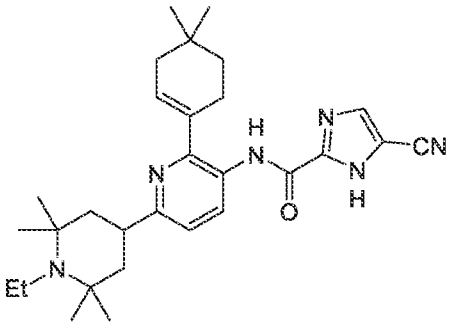
All of the exemplary compounds of Table 1 were prepared, characterized by LCMS $[M+H]^+$ (liquid chromatography mass spectroscopy) with detection of parent ion, and tested

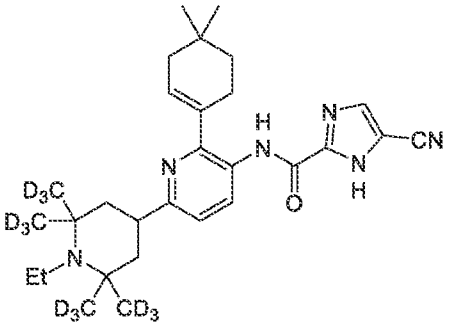
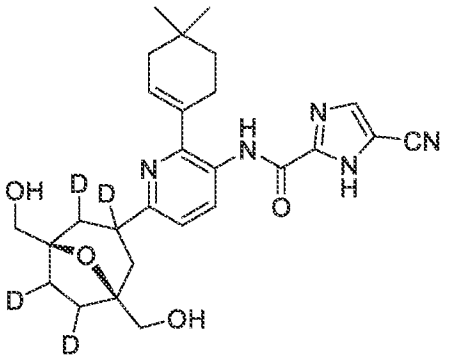
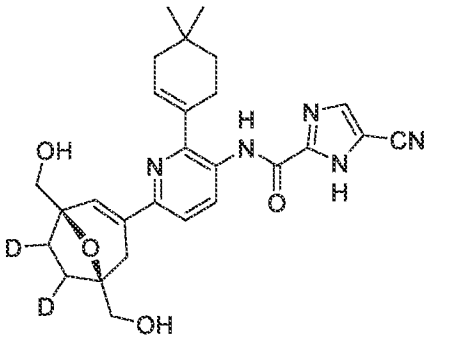
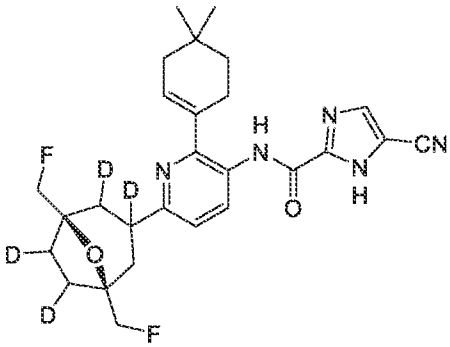
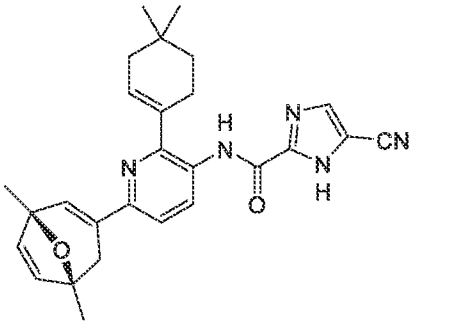
according to the assay described in Example 24. Exemplary Formula I compounds have assay activity IC_{50} values with the following ranges: more than seven compounds had an IC_{50} < 10 nM; more than eleven compounds had an IC_{50} between 10nM and 100nM. Certain exemplary compounds demonstrate blood-brain barrier (BBB) permeability. Exemplary formula I compounds are shown in Table 1.

Table 1 Exemplary compounds of formula (I)

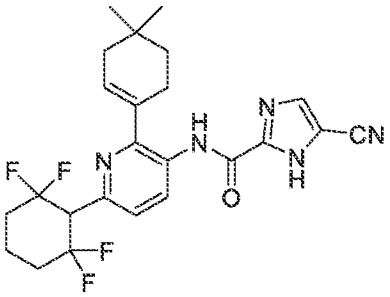
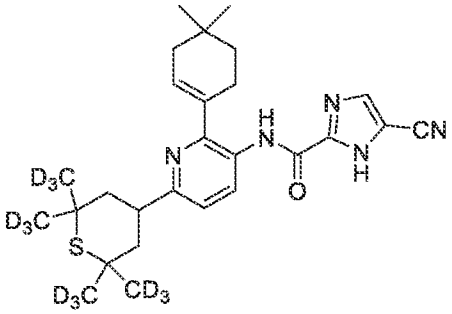
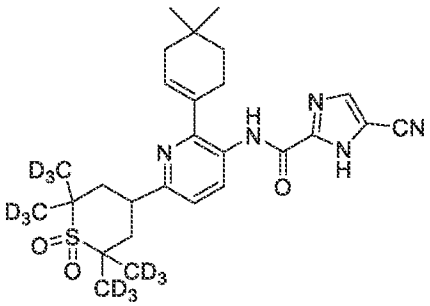
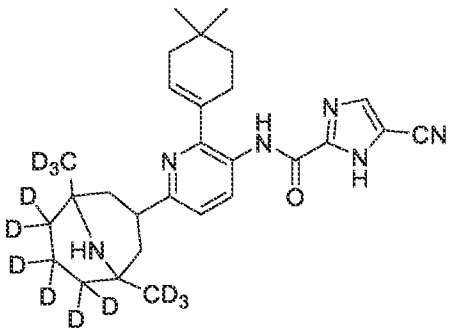
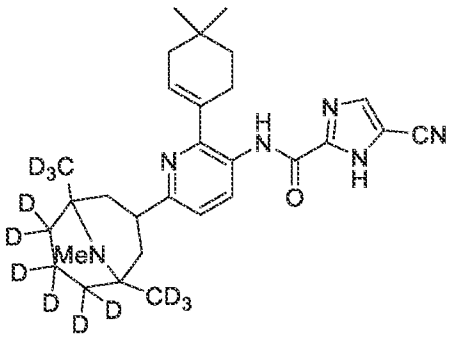
Structure	Name	MW
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2,2,6,6-tetrakis(methyl-d3)tetrahydro-2H-pyran-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	473.7
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2,2,6,6-tetramethyltetrahydro-2H-pyran-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	461.6
	N-(6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	430.6
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	444.6

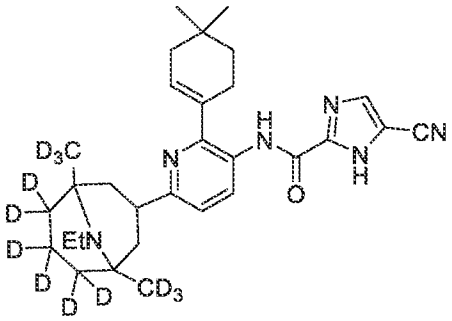
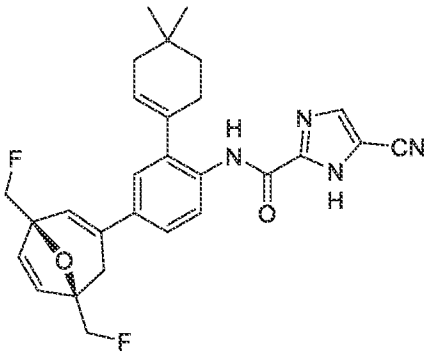
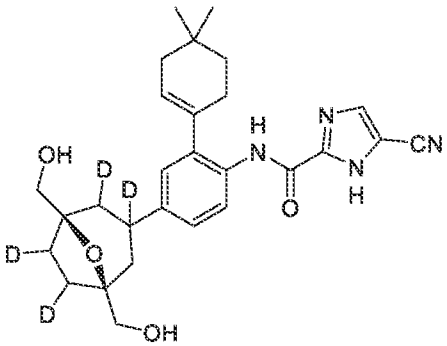
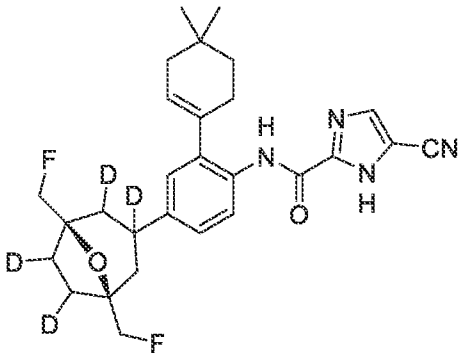
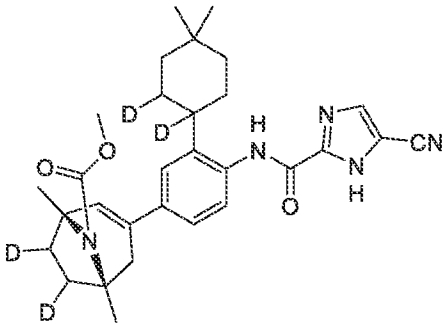
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2-(fluoromethyl)-2,6,6-trimethyltetrahydro-2H-pyran-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	479.6
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-((1R,5R)-2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl)pyridine-3-yl)-1H-imidazole-2-carboxamide	447.5
	N-(6-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	446.6
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	458.6
	N-(6-(1-acetyl-2,2,6,6-tetramethylpiperidin-4-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	502.7

	5-cyano-N-(6-(2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	498.4
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2,2,6,6-tetrakis(methyl-d3)piperidin-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	472.7
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(1-methyl-2,2,6,6-tetrakis(methyl-d3)piperidin-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	486.7
	N-(6-((1R,5R)-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	491.5
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(1-ethyl-2,2,6,6-tetramethylpiperidin-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	488.7

	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(1-ethyl-2,2,6,6-tetrakis(methyl-d3)piperidin-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	500.8
	N-(6-((1R,5S)-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl-2,3,6,7-d4)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	495.6
	N-(6-((1R,5S)-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl-6,7-d2)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	491.6
	N-(6-((1R,5S)-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl-2,3,6,7-d4)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	499.6
	5-cyano-N-(6-((1R,5R)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	455.6

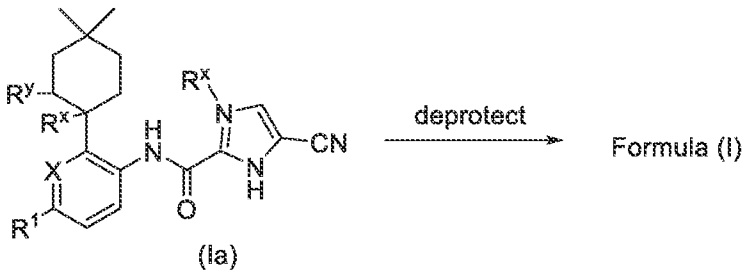
	5-cyano-N-(6-(6,7-difluoro-1,3,5-trimethyl-8-oxabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	509.6
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(3-fluoro-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	511.5
	N-(6-(1,5-bis(hydroxymethyl-d2)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	491.6
	methyl 3-(5-(5-cyano-1H-imidazole-2-carboxamido)-6-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-2-yl)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate-6,7-d2	534.7
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(3,6,7-trihydroxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl-6,7-d2)pyridin-3-yl)-1H-imidazole-2-carboxamide	509.6

	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2,2,6,6-tetrafluorocyclohexyl)pyridin-3-yl)-1H-imidazole-2-carboxamide	475.5
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2,2,6,6-tetrakis(methyl-d3)tetrahydro-2H-thiopyran-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	489.7
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(2,2,6,6-tetrakis(methyl-d3)-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)pyridin-3-yl)-1H-imidazole-2-carboxamide	521.7
	N-(6-(1,5-bis(methyl-d3)-9-azabicyclo[3.3.1]nonan-3-yl-6,6,7,7,8,8-d6)-2-(4,4-dimethylcyclohex-1-en-1-yl)pyridin-3-yl)-5-cyano-1H-imidazole-2-carboxamide	484.7
	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(9-methyl-1,5-bis(methyl-d3)-9-azabicyclo[3.3.1]nonan-3-yl-6,6,7,7,8,8-d6)pyridin-3-yl)-1H-imidazole-2-carboxamide	498.7

	5-cyano-N-(2-(4,4-dimethylcyclohex-1-en-1-yl)-6-(9-ethyl-1,5-bis(methyl-d3)-9-azabicyclo[3.3.1]nonan-3-yl-6,6,7,7,8,8-d6)pyridin-3-yl)-1H-imidazole-2-carboxamide	512.8
	N-(5-((1R,5R)-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)-4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-cyano-1H-imidazole-2-carboxamide	490.6
	N-(5-((1R,5S)-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl-2,3,6,7-d4)-4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-cyano-1H-imidazole-2-carboxamide	494.6
	N-(5-((1R,5S)-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl-2,3,6,7-d4)-4',4'-dimethyl-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-yl)-5-cyano-1H-imidazole-2-carboxamide	498.6
	methyl (1R,5S)-3-(4-(5-cyano-1H-imidazole-2-carboxamido)-3-(4,4-dimethylcyclohexyl-1,2-d2)phenyl)-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate-6,7-d2	519.7

	methyl (1R,3r,5S)-3-(4-(5-cyano-1H-imidazole-2-carboxamido)-3-(4,4-dimethylcyclohexyl-1,2-d2)phenyl)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate-6,7-d2	537.7
	methyl (1R,3s,5S)-3-(4-(5-cyano-1H-imidazole-2-carboxamido)-3-(4,4-dimethylcyclohexyl-1,2-d2)phenyl)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate-6,7-d2	537.7

Processes and intermediates that are useful for preparing compounds of formula (I) are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified.



A compound of formula (Ia), wherein R^x is a protecting group can be converted to a corresponding compound of formula (I) by deprotecting the compound of formula (Ia) to provide the corresponding compound of formula (I). Accordingly, the invention provides a method to prepare a compound of formula (I) comprising deprotecting a corresponding compound of formula (Ia), wherein R^x is a protecting group to provide the compound of formula (I). The invention also provides a compound of formula (Ia) wherein R^x is a suitable protecting group. In one embodiment, R^x is a trimethtlsilylethoxymethyl (SEM) group. In one embodiment, invention provides a method to prepare a compound of formula (I) comprising treating a corresponding compound of formula (Ia), wherein R^x is a is a trimethtlsilylethoxymethyl (SEM) protecting group, with a fluoride source (e.g., tetrabutylammonium fluoride) to provide the compound of formula (I).

In cases where compounds are sufficiently basic or acidic, a salt of a compound of formula I can be useful as an intermediate for isolating or purifying a compound of formula I. Additionally, administration of a compound of formula I as a pharmaceutically acceptable acid or base salt may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartrate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. As used herein the term "prodrug" refers to those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Prodrugs of the invention include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of a compound of the present invention.

Additional types of prodrugs are also encompassed. For instance, a free carboxyl group of a compound of the invention can be derivatized as an amide or alkyl ester. As another example, compounds of this invention comprising free hydroxy groups can be derivatized as prodrugs by converting the hydroxy group into a group such as, but not limited to, a phosphate ester, hemisuccinate, dimethylaminoacetate, or phosphoryloxymethyloxycarbonyl group, as outlined in Fleisher, D. et al., (1996) Improved oral drug delivery: solubility limitations overcome by the use of prodrugs *Advanced Drug Delivery Reviews*, 19:115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group can be an alkyl ester optionally substituted with groups including, but not limited to, ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also

encompassed. Prodrugs of this type are described in *J. Med. Chem.*, (1996), 39:10. More specific examples include replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkanoyloxymethyl, 1-((C_{1-6})alkanoyloxy)ethyl, 1-methyl-1-((C_{1-6})alkanoyloxy)ethyl, (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkanoyl, alpha-amino(C_{1-4})alkanoyl, arylacyl and alpha-aminoacyl, or alpha-aminoacyl-alpha-aminoacyl, where each alpha-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -$P(O)(O(C_{1-6})alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

For additional examples of prodrug derivatives, see, for example, a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs," by H. Bundgaard p. 113-191 (1991); c) H. Bundgaard, *Advanced Drug Delivery Reviews*, 8:1-38 (1992); d) H. Bundgaard, et al., *Journal of Pharmaceutical Sciences*, 77:285 (1988); and e) N. Kakeya, et al., *Chem. Pharm. Bull.*, 32:692 (1984), each of which is specifically incorporated herein by reference.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or

a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the

preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

Compounds of the invention can also be administered in combination with other therapeutic agents, for example, checkpoint inhibitors, cholinesterase inhibitors, antibodies that target disease RNA and protein species, including but not limited to Amyloid beta, gene therapies, including, but not limited to, ASOs, siRNA, shRNA, AAV-based approaches, cell therapies, including, but not limited to, CRISPR, TALEN and ZFN), and compounds that modulate autophagy, ferroptosis, DNA damage repair, mis-folded protein, protein aggregation, apoptosis, mitochondria function, biogenesis, fusion/fission or the inflammasome.

The invention will now be illustrated by the following non-limiting Examples.

EXAMPLES

As used herein, the following abbreviations have the indicated meanings.

ACN: acetonitrile

AIBN: azobisisobutyronitrile

Boc: *tert*-butoxycarbonyl

$CDCl_3$: chloroform-d

C Phos Pd G3: [(2-dicyclohexylphosphino-2′,6′-bis(*N*,*N*-dimethylamino) -1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate

DAPI: 4',6-diamidino-2-phenylindole

DCM: dichloromethane

DIEA: *N*,*N*-diisopropylethylamine

DIPEA: diisopropylethylamine

DMA: *N*,*N*-dimethylacetamide

DMAP: 4-dimethylaminopyridine

DMF: dimethylformamide

DMSO: dimethylsulfoxide

DMSO-d6: dimethylsulfoxide-d6

Dppf: diphenylphosphino

Dtbbpy: 4,4′-di-tert-butyl-2,2′-dipyridyl

Eq.: equivalent(s)

EtOAc: ethyl acetate

EtOH: ethanol

Glyme: dimethoxyethane

HPLC: high performance liquid chromatography

IPA: *iso*-propyl alcohol

iPrOAc: *iso*-propyl acetate

i-Pr: *iso*-propyl

KOAc: potassium acetate

LC/MS: liquid chromatography / mass spectrometry

LDA: lithium diisopropylamide

LED: light emitting diode

LiHMDS: lithium bis(triomethylsilyl)amide

m/z: mass to charge ratio.

m-CPBA: *meta*-chloroperoxybenzoic acid

MeCN: acetonitrile

MeOD: methanol-d1

MeOH: methanol

MeOH-d4: methanol-d4

MS: mass spectrometry

MTBE: *tert*-butyl methyl ether

NBS: *N*-bromosuccinimde

NFSI: *N*-fluorobenzenesulfonimide

NHC-1: 5,7-di-*tert*-butyl-3-phenylbenzo[d]oxazol-3-ium tetrafluoroborate

Pet. Et.: petroleum ether

Pin_2B_2: 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane

PPTS: pyridinium *p*-toluenesulfonate

PyBroP: bromo-tris-pyrrolidino-phosphonium hexafluorophosphate

R_t: retention time

SEM: 2-(trimethylsilyl)ethoxymethyl

SPhos Pd G3: (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) [2-(2′-amino-1,1′-biphenyl)]palladium(II) methanesulfonate

TEA: triethylamine

TEBAC: benzyltriethylammonium chloride

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

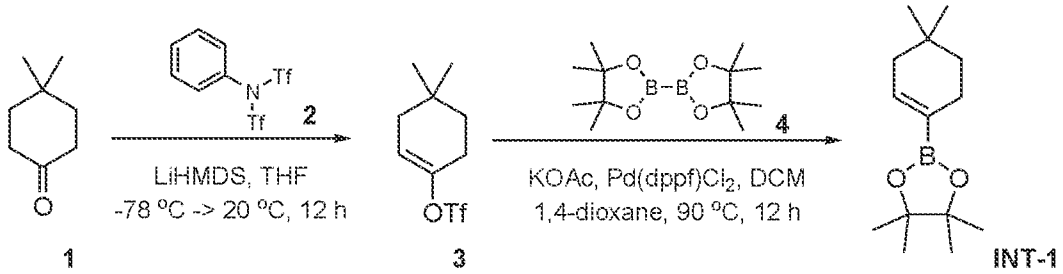
General Methods

LC/MS were performed with appropriate conditions for each compound tested on a Shimadzu LC-20ADXR system. ^{1}H NMR were performed with a Bruker 400MHz Avance system. Selected purifications were performed with either a) an ISCO® SEPAFLASH® silica column system, or b) an appropriate preparative HPLC system, using appropriate conditions for each compound. It is readily understood by one skilled in the art that other systems for analyzing and/or purifying compounds and intermediates could achieve similar results.

Synthetic Intermediates

The following is a description of synthetic intermediates (**INT-1 to INT-6**) useful for making representative compounds of the invention.

Intermediate **INT-1**



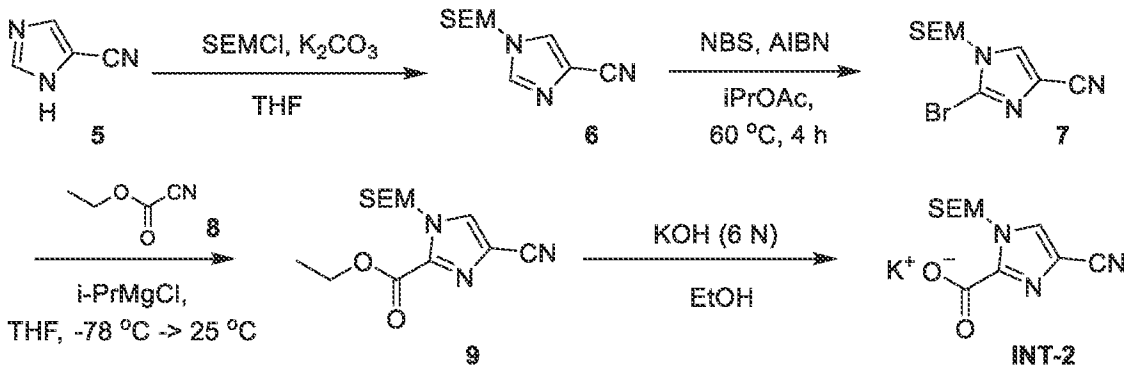
2-(4,4-Dimethylcyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (INT-1)

To a solution of LiHMDS (1 M, 475.45 mL, 1.2 eq) in THF (900 mL) was added dropwise a solution of 4,4-dimethylcyclohexanone (**1**, 50 g, 396.21 mmol, 1 eq) in THF (300 mL) at -70 °C. The mixture was further stirred at -70 °C for 2 h. Then 1,1,1-trifluoro-*N*-phenyl-*N*-(trifluoromethylsulfonyl)methanesulfonamide (**2**, 148.62 g, 416.0 mmol, 1.05 eq) was added at -70 °C. The mixture was stirred at 20 °C for 10 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc= 10:1) until it indicated the reaction had completed. The reaction mixture was quenched by NH_4Cl (aqueous, 1000 mL) and extracted with EtOAc (1000 mL x 3). The organic layers were combined, washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 1/0 to 10/1, gradient) to afford (4,4-dimethylcyclohexen-1-yl) trifluoromethanesulfonate (3, 79 g, 305.9 mmol, 77.2 % yield) as a yellow solid, and was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.68-5.66 (m, 1H), 2.35 - 2.32 (m, 2H), 1.99-1.97 (m, 2H), 1.54 (t, J = 6.4 Hz, 2H), 0.97 (s, 6H).

To a solution of (4,4-dimethylcyclohexen-1-yl) trifluoromethanesulfonate (**3**, 79 g, 305.90 mmol, 1 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4**, 85.45 g, 336.49 mmol, 1.1 eq) in dioxane (1000 mL) was added

dropwise a solution of KOAc (90.06 g, 917.7 mmol, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (7.49 g, 9.18 mmol, 0.03 *eq*). The mixture was stirred at 90 °C for 12 h under N_2. The reaction was monitored with TLC (Pet. Et.: EtOAc = 10:1) until it indicated the reaction had completed. The reaction mixture was quenched by H_2O (1000 mL) and extracted with EtOAc (1000 mL x 3). The organic layers were combined, washed with brine (1000 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1 gradient) to afford 2-(4,4-dimethylcyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**INT-1**, 38 g, 160.9 mmol, 52.6 % yield) as a yellow solid, and was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.51-6.46 (m, 1H), 2.13 - 2.10 (m, 2H), 1.85-1.84 (m, 2H), 1.32 (t, *J* = 6.4 Hz, 2H), 1.20 (s, 12H), 0.86 (s, 6H).

Intermediate **INT-2**



[4-Cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (INT-2)

To a solution of 1*H*-imidazole-5-carbonitrile (**5**, 45 g, 483.42 mmol, 1 eq) in THF (500 mL) was added 2-(chloromethoxy)ethyl-trimethyl-silane (96.72 g, 580.10 mmol, 102.67 mL, 1.2 eq) and K_2CO_3 (133.62 g, 966.8 mmol, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (300 mL) and extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SEPAFLASH® Silica Flash Column, Eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min). 1-(2-trimethylsilylethoxymethyl)imidazole-4-carbonitrile (6, 92 g, 411.9 mmol, 85.2 % yield) was obtained as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 294 K) δ (ppm) = 7.79 - 7.59 (m, 2H), 5.44 - 5.30 (m, 2H), 3.64 - 3.43 (m, 2H), 0.99 - 0.86 (m, 2H), -0.01 (s, 9H).

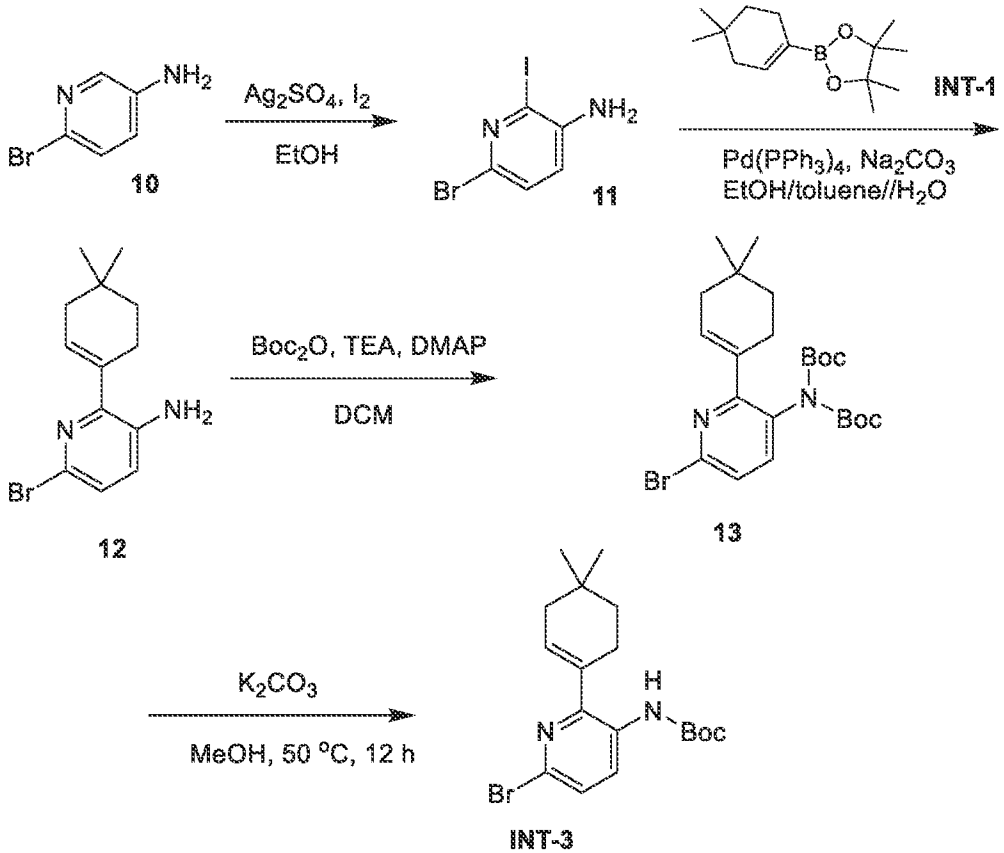
To a solution of 1-(2-trimethylsilylethoxymethyl)imidazole-4-carbonitrile (**6**, 92 g, 411.92 mmol, 1 eq) in isopropyl acetate (900 mL) was added NBS (80.65 g, 453.11 mmol, 1.1 eq) and AIBN (6.76 g, 41.19 mmol, 0.1 eq). The mixture was stirred at 60 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1) until it indicated the starting material had been completely consumed. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (80 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SEPAFLASH® Silica Flash Column, using an eluent of 0 ~ 50 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min). 2-bromo-1-(2-trimethylsilylethoxymethyl)imidazole-4-carbonitrile (**7**, 90 g, 297.77 mmol, 72.3 % yield) was obtained as a yellow oil and used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.65 (s, 1H), 5.32 (s, 2H), 3.61 - 3.52 (m, 2H), 1.00 - 0.90 (m, 2H), 0.02 (s, 9H).

To a solution of 2-bromo-1-(2-trimethylsilylethoxymethyl)imidazole-4-carbonitrile (**7**, 90 g, 297.77 mmol, 1 eq) in THF (200 mL) was added dropwise *i*-PrMgCl (2 M, 163.78 mL, 1.1 eq) at -40 °C. The mixture was stirred at -40 °C for 0.5 hr. Then ethyl cyanoformate (**8**, 59.01 g, 595.6 mmol, 58.37 mL, 2 eq) was added at -78 °C. The mixture was allowed to warm and further stirred at 25 °C for 2.5 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3:1) until it indicated the starting material had been completely consumed. The reaction mixture was diluted with water (300 mL) and extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SEPAFLASH® Silica Flash Column, using an eluent of 0 ~ 50 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min). Ethyl 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylate (**9**, 60 g, 203.1 mmol, 68.2 % yield) was obtained as a yellow oil and used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 295 K) δ (ppm) = 7.79 (s, 1H), 5.80 (s, 2H), 4.46 (q, J = 7.1 Hz, 2H), 3.61 (dd, J = 7.9, 8.7 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 0.98 - 0.93 (m, 2H), 0.00 (s, 9H).

To a solution of ethyl 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylate (**9**, 5.00 g, 16.93 mmol, 1 eq) in EtOH (40 mL) was added KOH (949.63 mg, 16.93 mmol, 1 eq). The mixture was stirred at 25 °C for 10 min. The reaction was monitored by TLC (Pet. Et. : EtOAc = 3:1) until it indicated that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to afford a residue of [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 5 g, 16.4 mmol, 96.7

% yield) that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4, 298 K) δ (ppm) = 7.96 (s, 1H), 5.88 (s, 2H), 3.62 - 3.58 (m, 2H), 0.94 - 0.88 (m, 2H), -0.01 (s, 9H).

Intermediate **INT-3**



***tert*-Butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (INT-3)**

To a solution of 6-bromopyridin-3-amine (**10**, 20 g, 115.60 mmol, 1 eq) in EtOH (300 mL) was added Ag_2SO_4 (36.04 g, 115.60 mmol, 19.59 mL, 1 eq) and I_2 (29.34 g, 115.60 mmol, 23.29 mL, 1 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). The organic layers were combined, washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford 6-bromo-2-iodo-pyridin-3-amine (**11**, 22 g, 73.60 mmol, 63.7 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, CDCl3, 300 K) δ (ppm) = 7.19 (d, *J* = 8.3 Hz, 1H), 6.81 (d, *J* = 8.3 Hz, 1H), 4.29 - 3.01 (m, 2H).

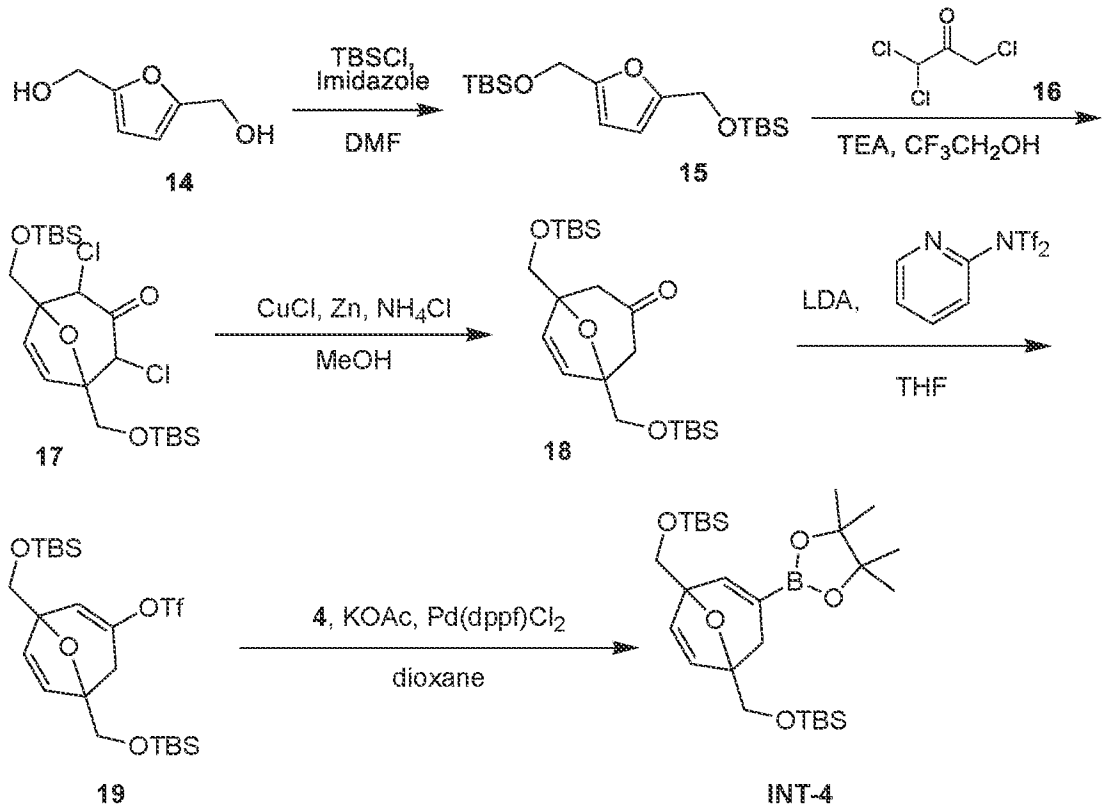
To a solution of 6-bromo-2-iodo-pyridin-3-amine (**11**, 10 g, 33.46 mmol, 1 eq) in toluene (500 mL) and EtOH (250 mL) was added 2-(4,4-dimethylcyclohexen-1-yl)-4,4,5,5-tetramethyl-

1,3,2-dioxaborolane (**INT-1**, 10.27 g, 43.49 mmol, 1.3 eq) and Na_2CO_3 (2 M, 133.82 mL, 8 eq) and $Pd(PPh_3)_4$ (1.93 g, 1.67 mmol, 0.05 eq). The mixture was stirred at 80 °C for 12 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc= 5:1) until it indicated the reaction had completed. The reaction mixture was quenched by H_2O (500 mL) and extracted with EtOAc (500 mL x 3). The organic layers were combined, washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1 gradient) to afford 6-bromo-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**12**, 25 g, 88.91 mmol, 88.6 % yield) as yellow solid that was used further as is.

To a solution of 6-bromo-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**12**, 25 g, 88.91 mmol, 1 eq) in DCM (250 mL) was added Boc_2O (58.21 g, 266.72 mmol, 61.28 mL, 3 eq), TEA (26.99 g, 266.72 mmol, 37.12 mL, 3 eq) and DMAP (2.17 g, 17. 8 mmol, 0.2 eq) The mixture was stirred at 20 °C for 12 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc= 5:1) until it indicated the reaction had completed. The reaction mixture was quenched by H_2O (250 mL) and extracted with DCM (250 mL x 3). The organic layers were combined, washed with brine (250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1 gradient) to afford *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-*N*-*tert*-butoxycarbonyl-carbamate (**13**, 29 g, 60.24 mmol, 67.8 % yield) as yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-*N*-*tert*-butoxycarbonyl-carbamate (**13**, 29 g, 60.24 mmol, 1 eq) in MeOH (290 mL) was added K_2CO_3 (24.98 g, 180.7 mmol, 3 eq). The mixture was stirred at 50 °C for 12 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it indicated the reaction had completed. The reaction mixture was quenched by H_2O (190 mL) and extracted with EtOAc (190 mL x 3). The organic layers were combined, washed with brine (190 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1) to afford *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 19 g, 49.83 mmol, 82.7 % yield) as yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is. MS (LC/MS) *m/z* observed 381.1, expected 381.1 [M+H].

Intermediate **INT-4**



tert-Butyl-[[5-[[_tert_-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]-dimethyl-silane (INT-4)

To a solution of [5-(hydroxymethyl)-2-furyl]methanol (**14**, 50 g, 390.24 mmol, 1 eq) in DMF (500 mL) was added TBSCl (147.04 g, 975.61 mmol, 119.55 mL, 2.5 eq) and imidazole (79.70 g, 1.17 mol, 3 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (500 mL) and extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford _tert_-butyl-[[5-[[_tert_-butyl(dimethyl)silyl]oxymethyl]-2-furyl]methoxy]-dimethyl-silane (**15**, 110 g, 308.43 mmol, 79.0 % yield) as a yellow oil, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.16 (s, 2H), 4.62 (s, 4H), 0.91 (s, 18H), 0.09 (s, 12H).

To a solution of _tert_-butyl-[[5-[[_tert_-butyl(dimethyl)silyl]oxymethyl]-2-furyl]methoxy]-dimethyl-silane (**15**, 30 g, 84.12 mmol, 1 eq) in CF_3CH_2OH (300 mL) was added _N,N_-diethylethanamine (34.05 g, 336.47 mmol, 46.83 mL, 4 eq), and 1,1,3-trichloropropan-2-one (**16**, 40.73 g, 252.35 mmol, 3 eq) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting

material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification. 1,5-Bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**17**, 60 g, 49.83 mmol, 59.2 % yield, 40 % purity) was obtained without further characterization, as a crude yellow oil, that was used further as is.

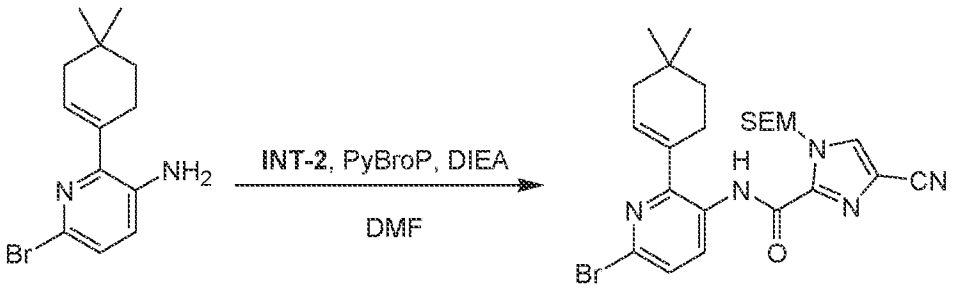
To a mixture of CuCl (6.17 g, 62.29 mmol, 1.49 mL, 0.5 eq), NH_4Cl (46.65 g, 872.09 mmol, 7 eq) and zinc (40.73 g, 622.92 mmol, 5 *eq*) in MeOH (600 mL) was added a solution of 1,5-bis[[tertbutyl(dimethyl)silyl]oxymethyl]-2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**17**, 60 g, 124.58 mmol, 1 eq) in MeOH (30 mL) dropwise at 25 °C and further stirred at 25 °C for 16 hours. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered through CELITE™ pad. The filtrate was diluted with water (200 mL) and extracted with EtOAc(150 mL x 2). Precipitate was dissolved by addition of HCl (2 N). The organic layers were combined, washed with brine, dried over MgSO4, and evaporated to obtain a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 50 mL/min) to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**, 12 g, 29.08 mmol, 23.3 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.10 (s, 2H), 3.80 (d, J = 1.4 Hz, 4H), 2.64 - 2.55 (m, 2H), 2.46 - 2.37 (m, 2H), 0.90 (s, 17H), 0.08 (s, 12H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**, 10 g, 24.23 mmol, 1 eq) in THF (100 mL) was added dropwise LDA (2 M, 24.23 mL, 2 eq) at -78 °C. After 0.5 h, a solution of 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (13.02 g, 36.35 mmol, 1.5 eq) in THF (20 mL) was added dropwise at -78 °C. The mixture was allowed to warm and further stirred at 25 °C for 2.5 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (saturated, aqueous, 20 mL) and extracted with EtOAc(10 mL x 2). The organic layers were combined, washed with brine (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient with a flow rate of 80 mL/min) to afford [1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]trifluoromethanesulfonate (**19**, 10 g, 18.36 mmol, 75.8 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) =

6.42 (d, J = 5.9 Hz, 1H), 6.29 (s, 1H), 5.92 (d, J = 5.8 Hz, 1H), 3.81 (s, 4H), 2.82 (dd, J = 1.8, 17.6 Hz, 1H), 2.13 (dd, J = 1.1, 17.6 Hz, 1H), 0.91 (s, 18H), 0.12 - 0.06 (m, 12H).

To a solution of [1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**19**, 5 g, 9.18 mmol, 1 eq) in dioxane (60 mL) was added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4**, 4.66 g, 18.36 mmol, 2 eq), KOAc (2.70 g, 27.53 mmol, 3 eq) and Pd(dppf)Cl_2 (671.57 mg, 917.82 μmol, 0.1 eq). The mixture was stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The organic layers were combined, washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]-dimethyl-silane (**INT-4**, 4.6 g, 8.80 mmol, 95.9 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.96 (t, J = 2.0 Hz, 1H), 6.34 (d, J = 5.8 Hz, 1H), 5.84 (d, J = 5.8 Hz, 1H), 3.80 - 3.75 (m, 4H), 2.47 (dd, J = 2.3, 18.7 Hz, 1H), 1.92 (dd, J = 1.9, 18.6 Hz, 1H), 1.24 (s, 12H), 0.91 (s, 12H), 0.09 - 0.06 (m, 18H).

Intermediate **INT-5**



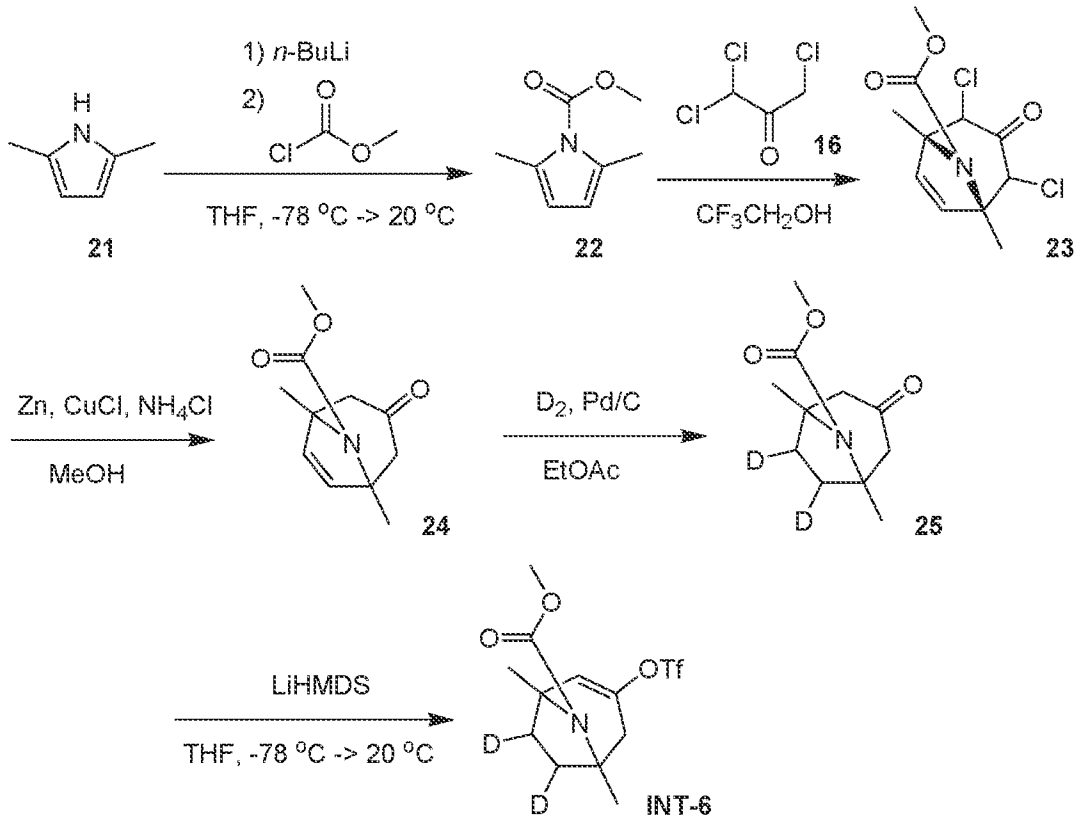
20 **INT-5**

***N*-[6-Bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (INT-5)**

To a solution of 6-bromo-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**20**, 2 g, 7.11 mmol, 1 *eq*) in DMF (20 mL) was added [5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 3.91 g, 12.80 mmol, 1.8 eq) , PyBroP (4.97 g, 10.67 mmol, 1.5 eq) and DIEA (2.76 g, 21.34 mmol, 3.72 mL, 3 *eq*). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 1.438 min, M+H = 530.2) until it showed reactant had been completely consumed. The reaction mixture was diluted with water (30 mL) and

extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 3.4 g, 6.41 mmol, 90.1 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.91 (s, 1H), 8.64 (d, *J* = 8.7 Hz, 1H), 7.78 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.00 (td, *J* = 2.0, 3.5 Hz, 1H), 5.92 (s, 2H), 3.70 - 3.62 (m, 2H), 2.51 - 2.42 (m, 2H), 2.13 (br d, *J* = 3.4 Hz, 2H), 1.63 - 1.60 (m, 3H), 1.12 (s, 6H), 1.01 - 0.95 (m, 2H), 0.01 (s, 8H), MS (LC/MS) *m/z* observed 530.2, expected 530.2 [M+H].

Intermediate **INT-6**



Methyl 6,7-dideuterio-1,5-dimethyl-3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (INT-6)

To a solution of 2,5-dimethyl-1*H*-pyrrole (**21**, 45 g, 472.98 mmol, 48.13 mL, 1 eq) in THF (500 mL) was added *n*-BuLi (2.5 M, 227.03 mL, 1.2 eq) at -78 °C. The mixture was further stirred at -78 °C for 0.5 h under N_2. Methyl carbonochloridate (53.63 g, 567.57 mmol, 43.85 mL, 1.2 eq) was then added at -78 °C. The mixture was allowed to warm and further stirred at 20 °C for 11.5 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it

showed that the reaction had completed. Two separate reactions were combined for the workup. The reaction mixture was quenched by addition of NH_4Cl (sat. aqueous, 1000 mL) and extracted with EtOAc (1000 mL x 3). The organic layers were combined, washed with brine (1500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 1/0 to 1/1 gradient) to afford methyl 2,5-dimethylpyrrole-1-carboxylate (**22**, 115 g, 750.76 mmol, 79.37% yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of methyl 2,5-dimethylpyrrole-1-carboxylate (**22**, 20 g, 130.57 mmol, 1 eq) and 1,1,3-trichloropropan-2-one (63.23 g, 391.70 mmol, 3 eq) in CF_3CH_2OH (40 mL) was added TEA (39.64 g, 391.70 mmol, 54.52 mL, 3 eq). The mixture was stirred at 20 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 L x 3). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification to afford methyl 2,4-dichloro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**23**, 30 g, 107.86 mmol, 82.6 % yield) as a white solid and used further as is, without further characterization.

To a solution of CuCl (5.34 g, 53.93 mmol, 1.29 mL, 0.5 eq), NH_4Cl (40.39 g, 755.04 mmol, 7 eq) and Zn (35.27 g, 539.31 mmol, 5 eq) in MeOH (300 mL) was added a solution of methyl 2,4-dichloro-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**23**, 30 g, 107.86 mmol, 1 eq) in MeOH (50 mL). The mixture was stirred at 20 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was filtered through a CELITE™ pad and the filtrate was diluted with water (400 mL) and extracted with EtOAc (200 mL x 3). The organic layers were combined, washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Welch Xtimate C18 250 x 70 mm, 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; gradient: 20 % - 50 % B% over 18.0 min) to afford methyl 1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**24**, 6 g, 28.68 mmol, 26.6 % yield) as yellow oil, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of methyl 1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylate (**24**, 4.9 g, 23.42 mmol, 1 eq) in EtOAc (30 mL) was added Pd/C (1.96 g, 1.84 mmol, 10 % purity, 0.079 eq). The mixture was stirred at 20 °C for 3 h under D_2 (15 psi) atmosphere. The

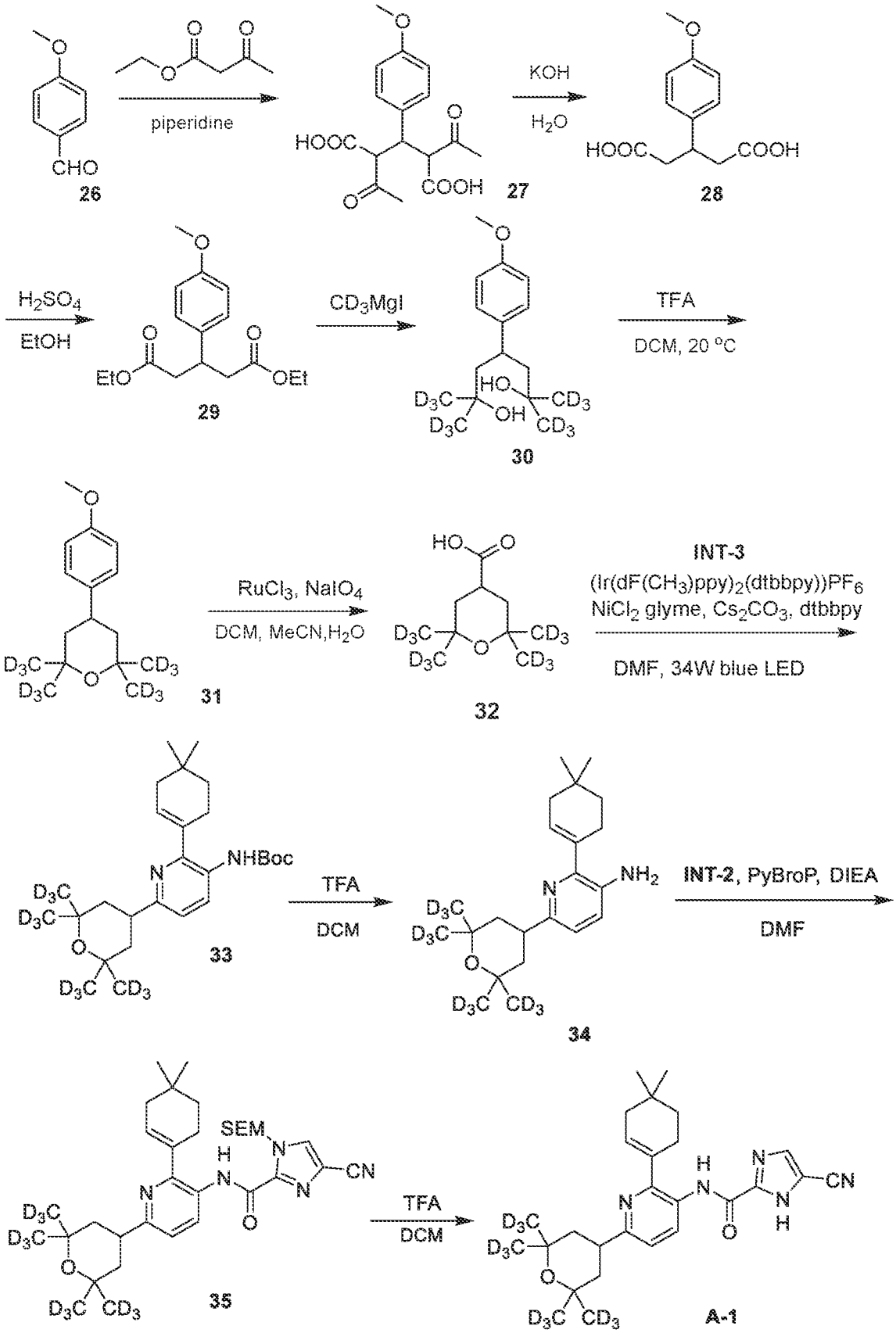
reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1) until it showed that the reaction had completed. The reaction mixture was filtered and concentrated under reduced pressure to remove MeOD, without further purification, to afford methyl 6,7-dideuterio-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**25**, 4.5 g, 21.10 mmol, 90.1 % yield) as yellow oil, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of LiHMDS (1 M, 23.21 mL, 1.1 eq) in THF (10 mL) was added dropwise, a solution of methyl 6,7-dideuterio-1,5-dimethyl-3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**25**, 4.5 g, 21.10 mmol, 1 eq) in THF (50 mL) at -70 °C. The mixture was allowed to warm and stirred further at 20 °C for 0.5 h. A solution of 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (8.31 g, 23.21 mmol, 1.1 eq) in THF (10 mL) was then added at -70 °C. The reaction mixture was allowed to warm and further stirred at 20 °C for 2.5 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. : EtOAc = 5/1) until it showed that the reaction had completed. The reaction mixture was quenched by NH_4Cl (sat. aqueous, 40 mL) and extracted with EtOAc (40 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO2, Pet. Et. / EtOAc = 1/0 to 5/1) to afford methyl 6,7-dideuterio-1,5-dimethyl-3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**INT-6**, 4 g, 11.58 mmol, 54.9 % yield) as yellow oil, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

The following is a description of the preparation of representative compounds of the invention.

EXAMPLE 1

4-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-1



To a solution of 4-methoxybenzaldehyde (**26**, 15 g, 110.17 mmol, 13.39 mL, 1 eq) in ethyl 3-oxobutanoate (43.01 g, 330.52 mmol, 41.76 mL, 3 eq) was added piperidine (1.29 g, 15.19 mmol, 1.50 mL, 0.14 eq). The mixture was stirred at 25 °C for 48 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was filtered and concentrated under reduced pressure, without further purification to afford diethyl 2,4-diacetyl-3-(4-methoxyphenyl)pentanedioate (**27**, 30 g, 79.3 mmol, 72.0 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

A mixture of diethyl 2,4-diacetyl-3-(4-methoxyphenyl)pentanedioate (**27**, 30 g, 79.28 mmol, 1 eq) and KOH (20 M, 150.00 mL, 37.8 eq) was stirred at 80 °C for 2 h. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was diluted with ice water (100 mL) and extracted with EtOAc (100 mL x 3). The aqueous phase was adjusted pH to 6 with HCl (conc.) and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine (100 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure, without further purification or characterization, to afford 3-(4-methoxyphenyl)pentanedioic acid (**28**, 15 g, 63.0 mmol, 79.4 % yield) as a white solid that was used further as is.

To a solution of 3-(4-methoxyphenyl)pentanedioic acid (**28**, 15 g, 63.0 mmol, 1 eq) in EtOH (60 mL) was added H_2SO_4 (3.68 g, 37.52 mmol, 2 mL, 0.6 eq). The mixture was stirred at 90 °C for 5 h. The reaction was monitored by TLC (Pet. Et.: EtOAc = 3:1) until it showed that the reaction had completed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1) to afford diethyl 3-(4-methoxyphenyl)pentanedioate (**29**, 15 g, 51.0 mmol, 80.9 % yield) as a yellow oil, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of diethyl 3-(4-methoxyphenyl)pentanedioate (**29**, 5 g, 16.99 mmol, 1 eq) was added a solution of iodo(trideuteriomethyl)magnesium (1 M, 108.72 mL, 6.40 eq) in THF (10 mL) at 0 °C. The mixture was allowed to warm and then stirred at 20 °C for 12 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 1:1) until it showed that the reaction had completed. The reaction mixture was quenched by addition of NH_4Cl (saturated, aqueous, 50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1) to afford 1,1,1,7,7,7-hexadeuterio-4-(4-methoxyphenyl)-2,6-bis(trideuteriomethyl)heptane-2,6-diol (**30**, 3 g, 10.77 mmol, 63.4 % yield) as a white solid,

where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of 1,1,1,7,7,7-hexadeuterio-4-(4-methoxyphenyl)-2,6-bis(trideuteriomethyl)heptane-2,6-diol (**30**, 3 g, 10.77 mmol, 1 eq) in DCM (30 mL) was added TFA (4.62 g, 40.52 mmol, 3.00 mL, 3.76 eq). The mixture was stirred at 20 °C for 12 h. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was diluted with $NaHCO_3$ (saturated, aqueous, 10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (SiO_2, Pet. Et.: EtOAc = 1:0 to 1:1) to afford 4-(4-methoxyphenyl)-2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran (**31**, 1.8 g, 6.91 mmol, 64.2 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of 4-(4-methoxyphenyl)-2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran (**31**, 1.8 g, 6.91 mmol, 1 eq) in DCM (10 mL) and MeCN (10 mL) and H_2O (15 mL) was added $NaHCO_3$ (290.32 mg, 3.46 mmol, 134.41 µL, 0.5 eq), $NaIO_4$ (14.78 g, 69.12 mmol, 3.83 mL, 10 eq) and $RuCl_3$ (143.37 mg, 691.15 µmol, 46.10 µL, 0.1 eq) at 0 °C. The mixture was stirred at 0 °C for 2 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 1:1) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purification by column chromatography (SiO_2, Pet. Et.: EtOAc = 1:0 to 1:1) to afford 2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-carboxylic acid (**32**, 0.7 g, 3.53 mmol, 51.1 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 0.35 g, 917.90 µmol, 1 eq) and 2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-carboxylic acid (233.01 mg, 1.17 mmol, 1.28 eq) in DMF (10 mL) was added dichloronickel;1,2-dimethoxyethane (20.17 mg, 91.8 µmol, 0.1 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (**32**, 36.95 mg, 137.68 µmol, 0.15 eq), Cs_2CO_3 (598.14 mg, 1.84 mmol, 2 *eq*) and $(IR(dF(CH_3)ppy)_2(dtbbpy))PF_6$ (9.31 mg, 9.18 µmol, 0.01 eq). The mixture was stirred at 20 °C for 12 h under N_2 atmosphere under 34w blue LED lights. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (20 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4,

filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc=1/0 to 10/1) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]-3-pyridyl]carbamate (**33**, 0.4 g, 879.69 μmol, 31.95 % yield) as yellow oil, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]-3-pyridyl]carbamate (**33**, 0.4 g, 879.7 μmol, 1 eq) in DCM (5 mL) was added TFA (2.40 g, 21.04 mmol, 1.56 mL, 23.9 eq). The mixture was stirred at 20 °C for 1 h. The reaction was monitored by HPLC (R_t = 3.076 min) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to remove DCM. The resulting residue was purified by Prep-HPLC (column: Waters Xbridge BEH C18 100 x 30 mm x 10 μm; mobile phase:[water (NH_4HCO_3) - ACN]; B%: gradient 50 %-90 %, 8 min) to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]pyridin-3-amine (**34**, 0.2 g, 564.03 μmol, 64.12 % yield) as a white solid that was used further as is.

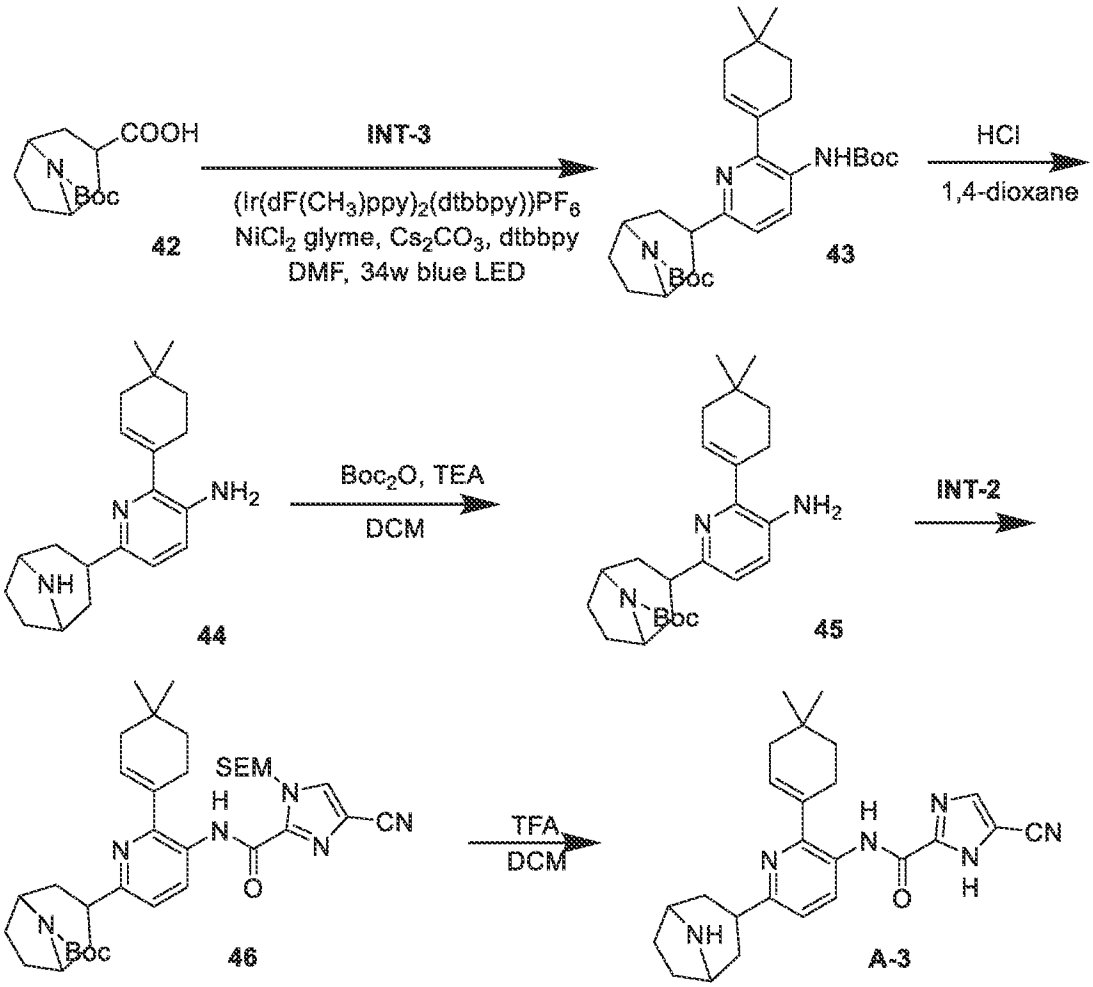
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]pyridin-3-amine (**34**, 0.2 g, 564.03 μmol, 1 eq) and 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylic acid (**INT-2**, 345.70 mg, 1.13 mmol, 2 eq) in DMF (5 mL) was added PyBroP (394.41 mg, 846.04 μmol, 1.5 eq), and DIEA (218.69 mg, 1.69 mmol, 294.72 μL, 3 eq). The mixture was stirred at 20 °C for 12 h under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (20 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / Ethyl acetate = 1/0 to 10/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**35**, 0.25 g, 413.95 μmol, 73.4 % yield) as yellow oil that was used further as is. MS (LC/MS) *m/z* observed 604.7, expected 604.5 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**35**, 0.25 g, 413.95 μmol, 1 eq) in DCM (1 mL) was added TFA (7.33 g, 64.28 mmol, 4.77 mL, 155.28 *eq*). The mixture was stirred at 20 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS until it showed that the reaction was complete. The reaction mixture was concentrated under reduced pressure to remove

DCM. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [water (TFA)-ACN]; gradient: 40 %-70 % B over 8 min) to afford title compound, 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-1**) as a white solid (112.9 mg, 238.4 μmol, 57.6 % yield). ^{1}H NMR (400 MHz, MeOH-d4) δ = 9.03 - 8.94 (m, 1H), 8.07 (s, 1H), 7.80 - 7.66 (m, 1H), 6.22 (br s, 1H), 3.67 - 3.51 (m, 1H), 2.53 - 2.42 (m, 2H), 2.17 (br d, *J* = 3.5 Hz, 2H), 1.89 (br d, *J* = 12.9 Hz, 2H), 1.71 - 1.61 (m, 4H), 1.13 (s, 6H), MS (LC/MS) *m/z* observed 474.5, expected 474.4 [M+H].

EXAMPLE 2

_N_-[6-(8-Azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1_H_-imidazole-2-carboxamide A-3



To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 0.5 g, 1.31 mmol, 1 eq) and 8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octane-3-carboxylic acid (**42**, 334.78 mg, 1.31 mmol, 1 eq)in DMF (5 mL) was added dichloronickel;1,2-dimethoxyethane (28.81 mg, 131.13 μmol, 0.1 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (52.79 mg, 196.69 μmol, 0.15 eq), Cs_2CO_3 (854.48 mg, 2.62 mmol,

2 eq) and ($Ir(dF(CH_3)ppy)_2(dtbbpy))PF_6$ (13.30 mg, 13.11 μmol, 0.01 eq). The mixture was stirred at 20 °C for 12 h under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc=1/0 to 10/1) to afford *tert*-butyl 3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**43**, 0.8 g, 1.56 mmol, 39.7 % yield) as yellow oil, without further characterization, that was used further as is.

To a solution of *tert*-butyl 3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**43**, 0.8 g, 1.56 mmol, 1 eq) in dioxane (4 mL) was added HCl/dioxane (4 M, 4 mL, 10.23 eq). The mixture was stirred at 20 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t=0.444 min, [M+H] = 312.4) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to remove dioxane, without further purification to afford 6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**44**, 0.5 g, 1.44 mmol, 91.9 % yield) as an HCl salt, as a yellow oil, that was used further as is. MS (LC/MS) *m/z* observed 312.4, expected 312.2 [M+H].

To a solution of 6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine, hydrochloride salt (**44**, 0.5 g, 1.44 mmol, 1 eq) in DCM (1 mL) was added Boc_2O (313.65 mg, 1.44 mmol, 330.15 uL, 1 eq) and TEA (159.96 mg, 1.58 mmol, 220.03 uL, 1.1 eq). The mixture was stirred at 20 °C for 1 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et.: EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc= 1/0 to 10/1 gradient) to afford *tert*-butyl 3-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**45**, 0.35 g, 850.4 μmol, 59.2 % yield) as a white solid, where the ^1H NMR was consistent with the expected structure and the product was used further as is. MS (LC/MS) *m/z* observed 412.3, expected 412.3 [M+H].

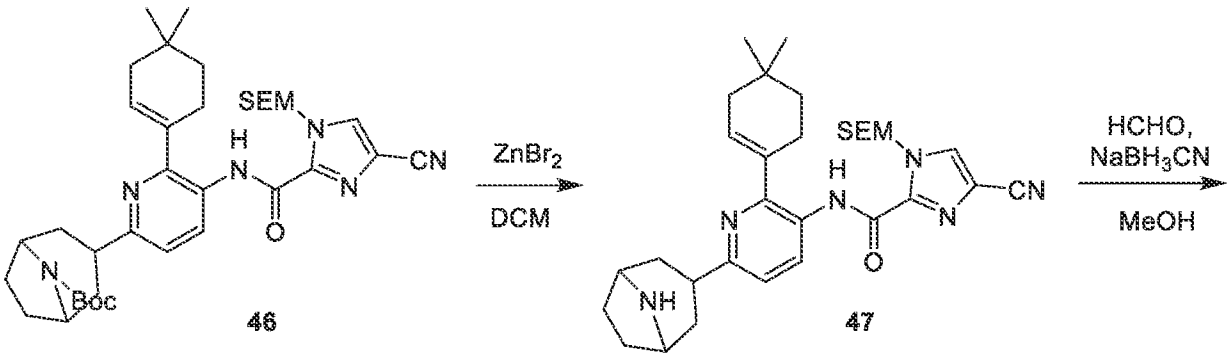
To a solution of *tert*-butyl 3-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**45**, 0.3 g, 728.90 μmol, 1 eq) and 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylic acid (**INT-2**, 379.74 mg, 1.24 mmol, 1.7 eq) in DMF (2 mL) was added DIEA (282.61 mg, 2.19 mmol, 380.9 uL, 3 eq) and PyBroP (509.70

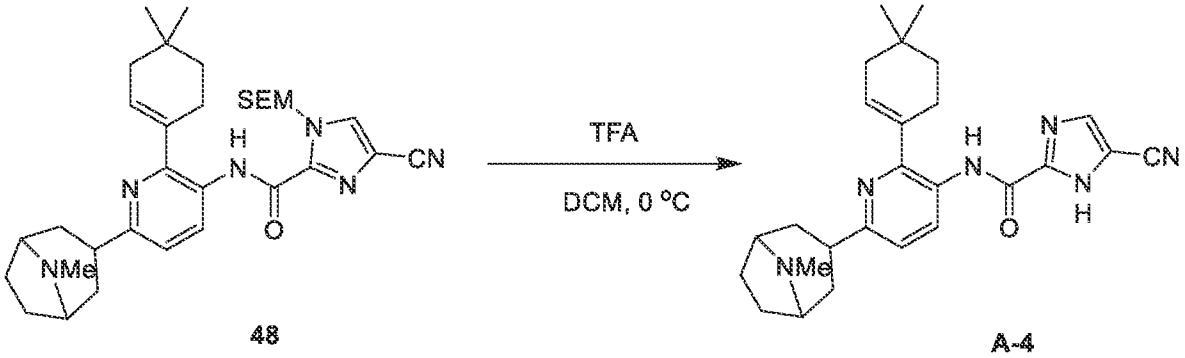
mg, 1.09 mmol, 1.5 eq). The mixture was stirred at 20 °C for 12 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10:0) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (1 mL) and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 1/0 to 10/1 gradient) to afford *tert*-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**46**, 0.2 g, 302.6 μmol, 41.5 % yield) as a white solid that was used further as is, without further characterization.

To a solution of *tert*-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4- dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**46** 0.05 g, 75.65 μmol, 1 eq) in DCM (1 mL) was added TFA (770.00 mg, 6.75 mmol, 500.00 uL, 89.27 eq). The mixture was stirred at 0 °C for 2 h under an N_2 atmosphere. The reaction was monitored by HPLC (R_t=1.12 min, [M+H] = 431.4) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 x 30 mm x 10 μm; mobile phase : [water (NH_4HCO_3) - ACN]; B%: 15 % - 55 % gradient, 8 min) to afford title compound, *N*-[6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-3**, 19.60 mg, 45.52 μmol, 60.2 % yield) as yellow oil. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.01 (s, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 7.55 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 5.87 (br s, 1H), 4.03 (br s, 2H), 3.21 - 3.17 (m, 1H), 2.38 (br s, 2H), 2.13 - 1.95 (m, 8H), 1.91 - 1.82 (m, 2H), 1.50 (br t, *J* = 6.3 Hz, 2H), 1.09 - 1.01 (m, 6H), MS (LC/MS) *m/z* observed 431.4, expected 431.3

EXAMPLE 3

4-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-4





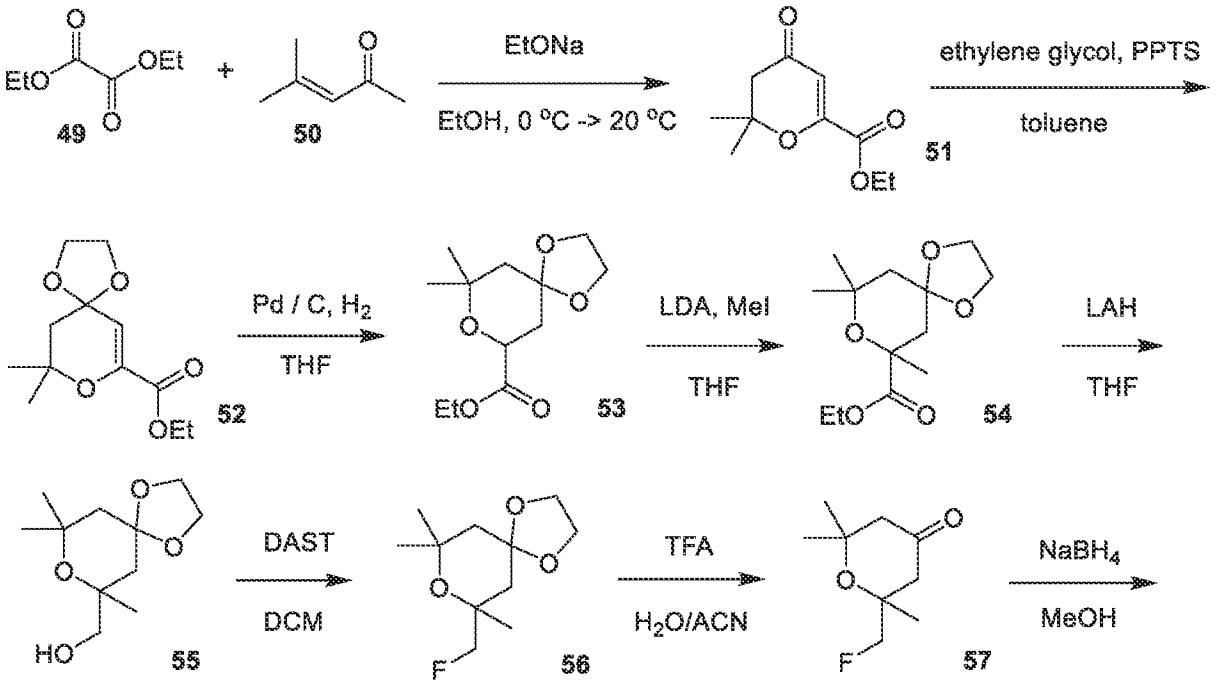
To a solution of *tert*-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**46**, 0.15 g, 226.96 μmol, 1 eq) in DCM (5 mL) was added $ZnBr_2$ (408.89 mg, 1.82 mmol, 90.86 uL, 8 eq). The mixture was stirred at 20 °C for 12 h under an N_2 atmosphere. The reaction was monitored by LCMS (R_t= 1.196 min, [M+H] = 561.4) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (5 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Phenomenex C18 80 x 40 mm x 3 μm; mobile phase:[water(NH_4HCO_3) -ACN]; B %: 25 % - 55 % gradient, 8 min) to afford *N*-[6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**47**, 0.02 g, 35.66 μmol, 15.7 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is. MS (LC/MS) *m/z* observed 561.4, expected 561.3 [M+H].

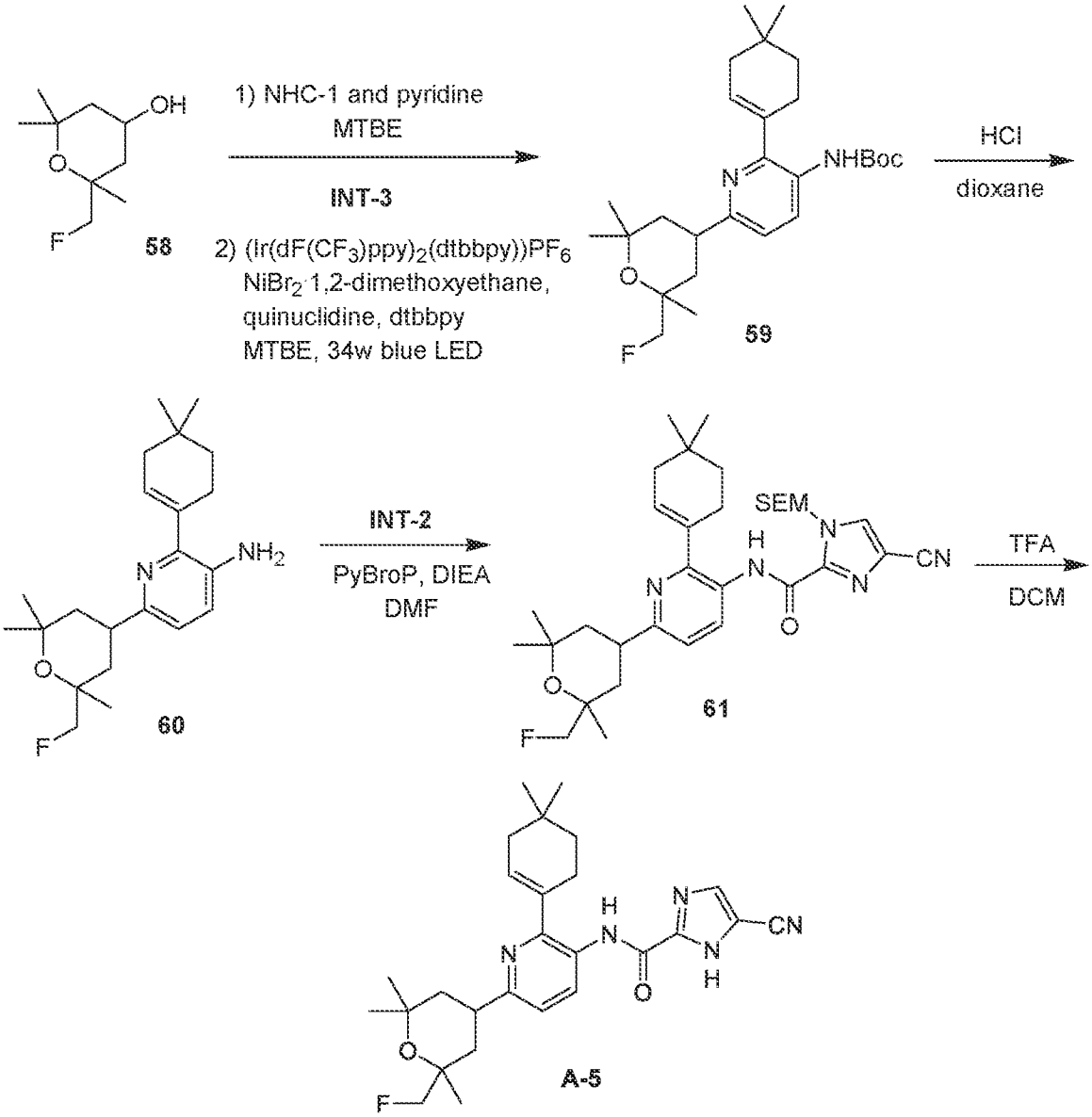
To a solution of *N*-[6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**47**, 0.02 g, 35.66 μmol, 1 eq) in MeOH (2 mL) was added formaldehyde (14.47 mg, 178.32 μmol, 13.28 uL, 37 % purity, 5 eq). The mixture was stirred at 0 °C for 0.5 h under an N_2 atmosphere and then $NaBH_3CN$ (5.60 mg, 89.16 μmol, 2.5 eq) was added. The mixture was stirred at 20 °C for a further 11.5 h under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t= 0.892 min, [M+H] = 575.5) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, washed with brine (5 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give, without further purification, 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**48**, 0.015 g, 26.09 μmol, 73.2 % yield) as a white solid, which was used further as is. MS (LC/MS) *m/z* observed 575.5, expected 575.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**48**, 0.015 g, 26.09 μmol, 1 eq) in DCM (1 mL) was added TFA (462.00 mg, 4.05 mmol, 0.3 mL, 155.28 eq). The mixture was stirred at 20 °C for 2 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t= 0.709 min, [M+H] = 445.3) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, washed with brine (5 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Waters Xbridge BEH C18 100 x 30 mm x 10 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 20 % - 55 % gradient, 8 min) to afford title compound, 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-4**, 0.0032 g, 7.2 μmol, 27.6 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.04 (s, 1H), 8.38 - 8.25 (m, 1H), 8.13 - 7.92 (m, 1H), 7.32 - 7.15 (m, 1H), 5.99 - 5.81 (m, 1H), 3.88 (br d, *J* = 1.6 Hz, 2H), 2.67 (s, 3H), 2.45 - 2.40 (m, 2H), 2.34 - 2.11 (m, 5H), 2.10 - 2.00 (m, 2H), 1.99 - 1.86 (m, 4H), 1.52 - 1.44 (m, 2H), 1.00 (s, 6H), MS (LC/MS) m/z observed 445.4, expected 445.3 [M+H].

EXAMPLE 4

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-5





To a solution of diethyl oxalate (**49**, 50 g, 342.14 mmol, 46.73 mL, 1 eq) in EtOH (400 mL) was added 4-methylpent-3-en-2-one (**50**, 33.58 g, 342.14 mmol, 39.50 mL, 1 eq) at 0 °C. The mixture was added a solution of EtONa (151.34 g, 444.78 mmol, 20 % purity, 1.3 eq). The mixture was stirred at 20 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. To the reaction mixture was added H_2SO_4 (300 mL) at 25 °C and stirred for 16 hr. The organic layers were combined, washed with H_2O (400 mL x 3), extracted with EtOAc (500 mL x 3) and washed with brine(300 mL). The organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 3/1 gradient) to afford ethyl 2,2-dimethyl-4-oxo-3*H*-pyran-6-carboxylate (**51**, 30 g, 151.35 mmol, 44.2 % yield) as a yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of ethyl 2,2-dimethyl-4-oxo-3*H*-pyran-6-carboxylate (**51**, 22.8 g, 115.03 mmol, 1 eq) in toluene (230 mL) was added ethylene glycol (71.39 g, 1.15 mol, 64.32 mL, 10 eq) and PPTS (2.89 g, 11.50 mmol, 0.1 eq). The mixture was stirred at 135 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. : EtOAc= 5:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (180 mL), extracted with EtOAc (350mL x 3) and washed with brine(400 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 3/1 gradient) to afford ethyl 9,9-dimethyl-1,4,8-trioxaspiro[4.5]dec-6-ene-7-carboxylate (**52**, 10 g, 41.28 mmol, 35.9 % yield) as a yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of ethyl 9,9-dimethyl-1,4,8-trioxaspiro[4.5]dec-6-ene-7-carboxylate (**52**, 20 g, 82.55 mmol, 1 eq) in THF (200 mL) was added Pd/C (10 g, 5 % purity). The mixture was stirred at 25 °C for 2 hr under H_2 (50 psi). The reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1) until it showed that the starting material had been completely consumed. The mixture was filtered and concentrated under reduced pressure to give a residue without further purification to afford ethyl 7,7-dimethyl-1,4,8-trioxaspiro[4.5]decane-9-carboxylate (**53**, 20 g, 81.87 mmol, 99.2 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 4.38 (dd, J = 2.4, 12.3 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.05 - 3.99 (m, 2H), 3.97 - 3.90 (m, 2H), 1.99 (td, J = 2.4, 13.0 Hz, 1H), 1.74 - 1.63 (m, 3H), 1.34 (s, 6H), 1.29 (t, J = 7.2 Hz, 3H).

To a solution of ethyl 7,7-dimethyl-1,4,8-trioxaspiro[4.5]decane-9-carboxylate (**53**, 7 g, 28.66 mmol, 1 eq) in THF (100 mL), at -78 °C , was added LDA (2 M, 15.76 mL, 1.1 eq). After 2 hrs, MeI (6.10 g, 42.98 mmol, 2.68 mL, 1.5 eq) was added. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with NH_4Cl (aqueous, 100 mL) and extracted with EtOAc (100 mL x 2). The organic layers were combined, washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford ethyl 7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decane-7-carboxylate (**54**, 5.7 g, 22.1 mmol, 77. % yield) as a yellow solid, that was used further as is and without further characterization.

To a solution of ethyl 7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decane-7-carboxylate (**54**, 5.7 g, 22.07 mmol, 1 eq) in THF (60 mL) was added LAH (1.00 g, 26.48 mmol, 1.2 eq) at 0 °C. The

mixture was stirred at 25 °C for 4 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (1.0 mL) and NaOH (1.0 mL, 15 %). The reaction mixture was filtered and concentrated under reduced pressure to give, without further purification, (7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decan-7-yl)methanol (**55**, 4 g, 18.5 mmol, 83.8 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 4.04 - 3.97 (m, 2H), 3.97 - 3.88 (m, 2H), 3.41 - 3.33 (m, 1H), 3.32 - 3.25 (m, 1H), 1.96 (d, *J* = 13.8 Hz, 1H), 1.76 (dd, *J* = 1.8, 13.7 Hz, 1H), 1.66 - 1.58 (m, 1H), 1.54 (dd, *J* = 1.8, 13.8 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H).

To a solution of (7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decan-7-yl)methanol (**55**, 4 g, 18.50 mmol, 1 eq) in DCM (50 mL), was added DAST (5.96 g, 36.99 mmol, 4.89 mL, 2 eq) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (30 mL) and extracted with DCM (30 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 5 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford 7-(fluoromethyl)-7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decane (**56**, 4 g, 18.33 mmol, 99.1 % yield) as a yellow oil, that was used further as is. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 3.90 - 3.75 (m, 4H), 3.66 - 3.53 (m, 2H), 2.21 (dd, *J* = 13.7, 16.9, Hz, 1H), 2.02 - 1.92 (m, 1H), 1.91 - 1.82 (m, 2H), 1.34 - 1.25 (m, 3H), 1.19 (s, 3H), 1.15 (s, 3H).

To a solution of 7-(fluoromethyl)-7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decane (**56**, 4 g, 18.33 mmol, 1 eq) in H_2O (30 mL) and ACN (30 mL) was added TFA (4.18 g, 36.65 mmol, 2.71 mL, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (30 mL) and extracted with DCM (30 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 5 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford 2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-one (**57**, 2.3 g, 13.20 mmol, 72.0 % yield) as a yellow oil, that was used further as is. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 3.90 - 3.75 (m, 4H), 3.66 - 3.53 (m, 2H), 2.21 (dd, *J* = 13.7, 16.9 Hz, 1H), 2.02 - 1.92 (m, 1H), 1.91 - 1.82 (m, 2H), 1.34 - 1.25 (m, 3H), 1.19 (s, 3H), 1.15 (s, 3H).

To a solution of 2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-one (**57**, 2.3 g, 13.20 mmol, 1 eq) in MeOH (30 mL) was added $NaBH_4$ (499.47 mg, 13.20 mmol, 1 eq) at 0 °C. The mixture was stirred at 25 °C for 1 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc = 3:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with NH_4Cl (50 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % EtOAc/Pet. Et. gradient at a flow rate of 60 mL/min) to afford 2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-ol (**58**, 1.8 g, 10.21 mmol, 77.4 % yield) as a yellow oil, which was further used as is. ^{1}H NMR (400 MHz, DMSO-d6, 297 K) δ (ppm) = 4.63 (d, J = 4.4 Hz, 1H), 4.53 (d, J = 4.4 Hz, 1H), 3.94 - 3.83 (m, 1H), 3.17 (ddd, J = 2.3, 7.4, 12.2 Hz, 1H), 2.11 - 2.00 (m, 2H), 1.84 (dd, J = 10.3, 14.3 Hz, 1H), 1.73 (br dd, J = 2.3, 4.9 Hz, 2H), 1.37 - 1.29 (m, 3H), 1.10 (d, J = 5.6 Hz, 5H).

To a solution of 2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-ol (**58**, 202.20 mg, 1.15 mmol, 1.75 eq) and NHC-1 (414.62 mg, 1.05 mmol, 1.6 eq) in MTBE (2 mL) was added pyridine (82.98 mg, 1.05 mmol, 84.67 uL, 1.6 eq) in MTBE (1 mL) dropwise over 5 min at 25 °C, after 10 min, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 250 mg, 655.64 μmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (8.99 mg, 9.83 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (10.12 mg, 32.78 μmol, 0.05 eq), dtbbpy (13.20 mg, 49.17 μmol, 0.075 eq), and quinuclidine (127.57 mg, 1.15 mmol, 1.75 *eq*) in DMA (3 mL) under N_2. The mixture was stirred at 25 °C for 3 hr under blue LED lights. The reaction was monitored by LC/MS (R_t = 0.971 min, [M+H] = 461.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase: [water (TFA) - ACN]; B%: 45 % - 70 % gradient, 8 min) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]carbamate (**59**, 100 mg, 217.10 μmol, 33.1 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 8.79 (br d, J = 8.9 Hz, 1H), 7.33 (d, J = 8.9 Hz, 1H), 6.81 (s, 1H), 6.03 (br s, 1H), 3.74 (br dd, J = 3.4, 12.6 Hz, 2H), 3.51 - 3.45 (m, 3H), 2.37 (br s, 3H), 2.25 - 2.12 (m, 2H), 2.11 - 2.07 (m, 3H), 2.05 - 1.91 (m, 2H), 1.84 (br d, J = 14.1 Hz, 1H), 1.59 (br t, J = 6.3 Hz,

3H), 1.50 (d, J = 4.8 Hz, 3H), 1.27 (s, 3H), 1.24 (s, 3H), 1.08 - 1.00 (m, 9H), MS (LC/MS) *m/z* observed 461.4, expected 461.3 [M+H].

A solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]carbamate (**59**, 100 mg, 217.10 μmol, 1 eq) in HCl/dioxane (5 mL) was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 0.778 min, [M+H] = 361.4) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 x 30 mm x 10 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 60 % - 90 % gradient, 8 min) to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]pyridin-3-amine (**60**, 80 mg, 210.81 μmol, 97.1 % yield, 95 % purity) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 6.96 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 5.88 (br s, 1H), 4.71 (s, 2H), 3.73 (d, J = 12.4 Hz, 1H), 3.29 - 3.19 (m, 1H), 2.76 - 2.65 (m, 1H), 2.40 - 2.30 (m, 2H), 2.05 - 1.89 (m, 5H), 1.66 (d, J = 14.8 Hz, 1H), 1.48 - 1.37 (m, 5H), 1.15 (d, J = 5.6 Hz, 6H), 0.97 (s, 6H), MS (LC/MS) *m/z* observed 361.4, expected 361.3 [M+H].

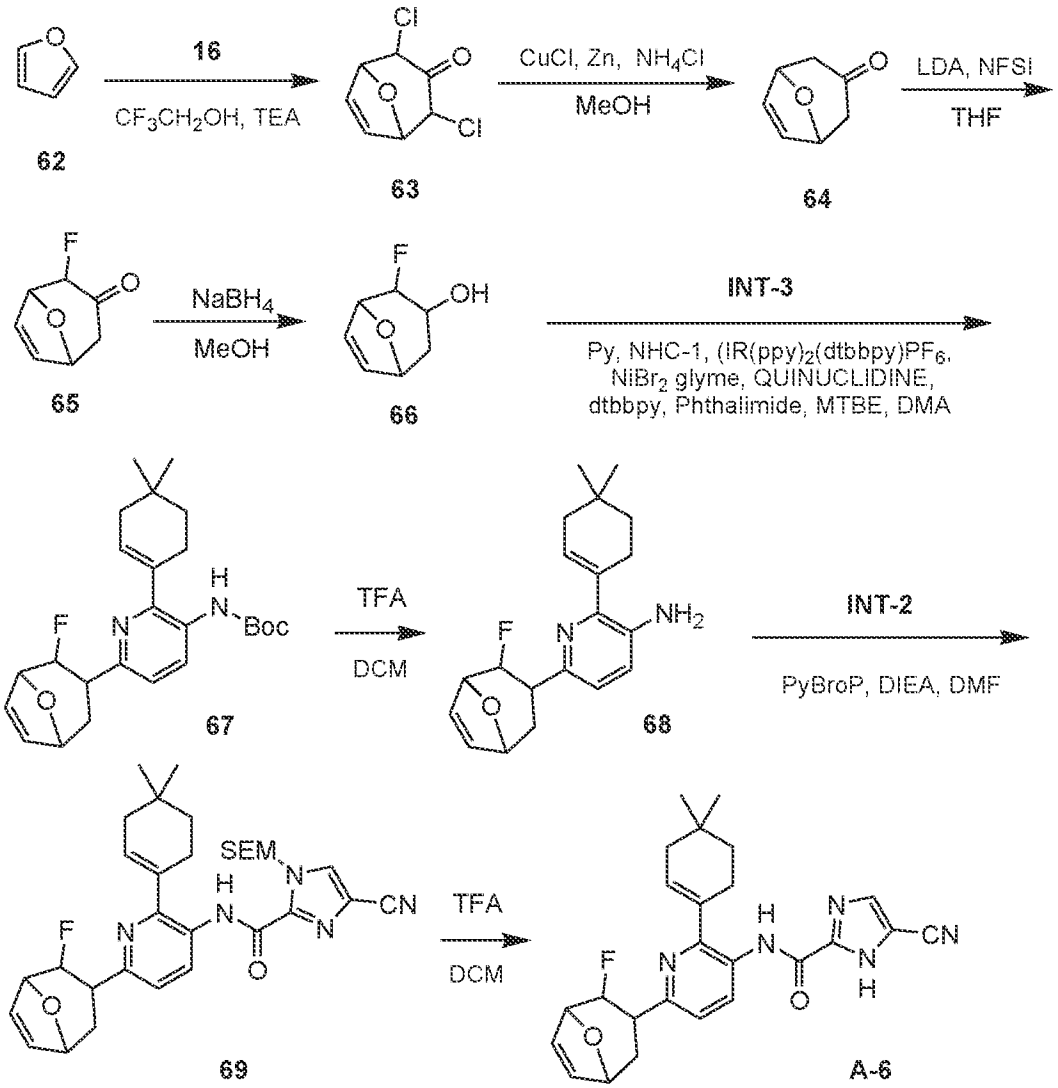
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]pyridin-3-amine (**60**, 70 mg, 194.17 μmol, 1 eq) in DMF (1 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 118.62 mg, 388.34 μmol, 2 eq), PyBroP (135.78 mg, 291.26 μmol, 1.5 eq) and DIEA (75.28 mg, 582.51 μmol, 101.46 uL, 3 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 1.119 min, M+H = 610.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase: [water (TFA) - ACN]; B%: 60 % - 100 % gradient, 8 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**61**, 60 mg, 98.39 μmol, 50.7 % yield) as a yellow solid that was used further as is. MS (LC/MS) *m/z* observed 610.4, expected 610.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**61**, 60 mg, 98.39 μmol, 1 eq) in DCM (5 mL), was added TFA (1 mL). The mixture was stirred at 25 °C for 1 hr. The reaction was monitored by LC/MS (R_t = 0.951 min,

[M+H] = 480.3) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase: [water (TFA) - ACN]; B%: 70 % - 100 % gradient, 8 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-5**, 19.2 mg, 40.0 μmol, 40.7 % yield) a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 295 K) δ (ppm) = 14.27 (br s, 1H), 10.09 (s, 1H), 8.33 (s, 1H), 8.11 (br d, *J* = 8.0 Hz, 1H), 7.26 (br d, *J* = 8.4 Hz, 1H), 5.90 (br s, 1H), 3.78 (br d, *J* = 12.0 Hz, 1H), 3.28 (br dd, *J* = 6.4, 11.6 Hz, 1H), 2.94 (br t, *J* = 10.4 Hz, 1H), 2.40 (br s, 2H), 2.17 - 1.97 (m, 3H), 1.91 (br s, 2H), 1.73 (br d, *J* = 14.8 Hz, 1H), 1.51 - 1.40 (m, 5H), 1.18 (br d, *J* = 8.0 Hz, 6H), 0.96 (s, 6H), MS (LC/MS) *m/z* observed 480.3, expected 480.3 [M+H].

EXAMPLE 5

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(fluoromethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-6



To a solution of furan (**62**, 15 g, 220.35 mmol, 16.03 mL, 1 eq) in CF_3CH_2OH (150 mL) was added *N,N*-diethylethanamine (89.19 g, 881.40 mmol, 122.68 mL, 4 eq), and 1,1,3-trichloropropan-2-one (**16**, 106.70 g, 661.05 mmol, 3 eq) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give, without further purification, 2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**63**, 40 g, 207.22 mmol, 94.0 % yield) as a yellow oil, that was further used as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.53 (s, 2H), 5.15 (d, *J* = 4.8 Hz, 2H), 4.72 (d, *J* = 4.6 Hz, 2H).

To a mixture of CuCl (15.39 g, 155.42 mmol, 3.72 mL, 0.5 eq), NH_4Cl (116.39 g, 2.18 mol, 7 eq) and zinc (101.63 g, 1.55 mol, 5 eq) in MeOH (600 mL) was added a solution of 2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**63**, 60 g, 310.84 mmol, 1 eq) in MeOH (30 mL) dropwise at 25 °C. The mixture was further stirred at 25 °C for 16 hours. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered through CELITE™ pad. The filtrate was diluted with water (200 mL) and extracted with EtOAc (150 mL x 2). Precipitate was dissolved by addition of HCl (2 N). The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 50 mL/min) to afford 8-oxabicyclo[3.2.1]oct-6-en-3-one (**64**, 20 g, 112.78 mmol, 36.3 % yield, 70 % purity) as a yellow oil, that was further used as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 6.28 (s, 2H), 5.05 (d, *J* = 5.0 Hz, 2H), 2.77 (dd, *J* = 5.1, 16.9 Hz, 2H), 2.35 (d, *J* = 16.4 Hz, 2H).

To a solution of 8-oxabicyclo[3.2.1]oct-6-en-3-one (**64**, 18 g, 145.00 mmol, 1 eq) in THF (150 mL) at -78 °C was added LDA (2 M, 290.00 mL, 4 eq). After 2 hrs, NFSI (182.90 g, 580.00 mmol, 4 eq) in THF (150 mL) was added. The mixture was stirred at -78 °C for 3 hrs. The reaction was monitored by TLC (Pet. Et.: EtOAc= 3:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with NH_4Cl (aqueous, 300 mL) and extracted with EtOAc (200 mL x 2). The organic layers were combined, washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford 2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**65**, 5 g, 35.2

mmol, 24.3 % yield) as a yellow oil that was further used as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.51 (br d, *J* = 6.1 Hz, 1H), 6.18 (dd, *J* = 1.7, 5.9 Hz, 1H), 5.09 (d, *J* = 4.8 Hz, 2H), 4.39 - 4.21 (m, 1H), 3.08 (dd, *J* = 5.0, 16.5 Hz, 1H), 2.44 (d, *J* = 16.5 Hz, 1H).

To a solution of 2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**65**, 5 g, 35.18 mmol, 1 eq) in MeOH (60 mL) was added $NaBH_4$ (2.00 g, 52.77 mmol, 1.5 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc= 3:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with NH_4Cl (aqueous, 50 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % EtOAc/Pet. Et. gradient at a flow rate of 60 mL/min) to afford 2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**66**, 1.5 g, 10.4 mmol, 29.6 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 295 K) δ (ppm) = 6.28 (td, *J* = 1.6, 6.1 Hz, 1H), 6.20 (dd, *J* = 1.9, 6.1 Hz, 1H), 4.99 - 4.91 (m, 1H), 4.90 - 4.85 (m, 1H), 4.66 - 4.50 (m, 1H), 4.06 - 3.88 (m, 1H), 2.03 - 1.94 (m, 2H), 1.87 - 1.80 (m, 1H).

To a solution of 2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**66**, 198.46 mg, 1.38 mmol, 1.75 eq) and NHC-1 (497.54 mg, 1.26 mmol, 1.6 eq) in MTBE (4 mL) was added pyridine (99.57 mg, 1.26 mmol, 101.61 μL, 1.6 eq) in MTBE (1 mL) dropwise over 5 mins at 25 °C, after a further 10 min, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 300 mg, 786.77 μmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (10.79 mg, 11.80 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (12.14 mg, 39.34 μmol, 0.05 eq), quinuclidine (153.08 mg, 1.38 mmol, 1.75 eq) ,4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (15.84 mg, 59.01 μmol, 0.075 eq) and isoindoline-1,3-dione (26.05 mg, 177.02 μmol, 0.225 eq) in DMA (4 mL) under N_2. The mixture was stirred at 25 °C for 12 hr under blue LED lights. The reaction was monitored by LC/MS (R_t = 1.144 min, [M+H] =429.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®;4 g, SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % EtOAc/Pet. Et. gradient at a flow rate of 60 mL/min) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-3-pyridyl]carbamate

(**67**, 130 mg, 151.7 μmol, 19.3 % yield, 50 % purity) as a yellow solid, that was sued further as is. MS (LC/MS) *m/z* observed 429.3, expected 429.3 [M+H].

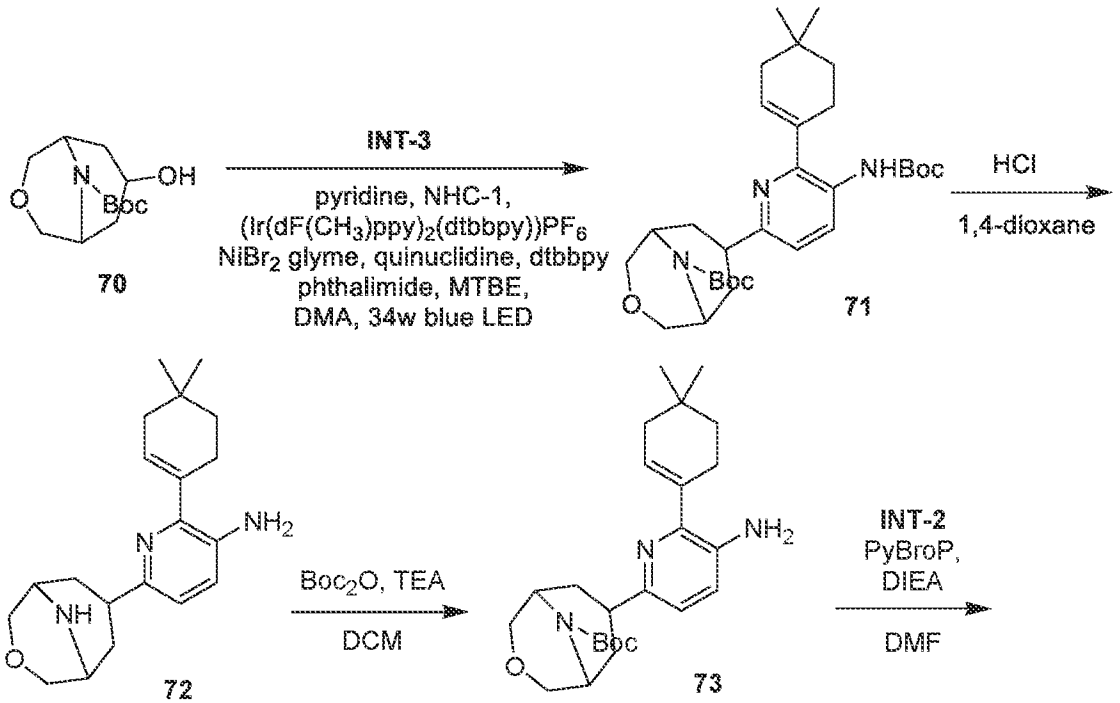
To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-3-pyridyl]carbamate (**67**, 230 mg, 536.71 μmol, 1 eq) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 0.393 min, [M+H] = 329.3) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue to give, without further purification, 2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]pyridin-3-amine (**68**, 230 mg, 389.88 μmol, 72.6 % yield, 75 % purity) as a TFA salt, as a yellow solid, that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4, 299 K) δ (ppm) = 7.72 - 7.67 (m, 1H), 7.64 - 7.59 (m, 1H), 6.48 - 6.45 (m, 1H), 6.44 - 6.39 (m, 1H), 6.14 (td, *J* = 1.9, 3.7 Hz, 1H), 4.97 - 4.94 (m, 1H), 4.62 - 4.46 (m, 1H), 3.92 - 3.75 (m, 1H), 2.44 - 2.38 (m, 1H), 2.37 - 2.33 (m, 2H), 2.15 - 2.08 (m, 2H), 2.02 (s, 1H), 1.71 - 1.65 (m, 1H), 1.62 (t, *J* = 6.2 Hz, 2H), 1.07 (s, 6H), MS (LC/MS) *m/z* observed 329.3, expected 329.3 [M+H].

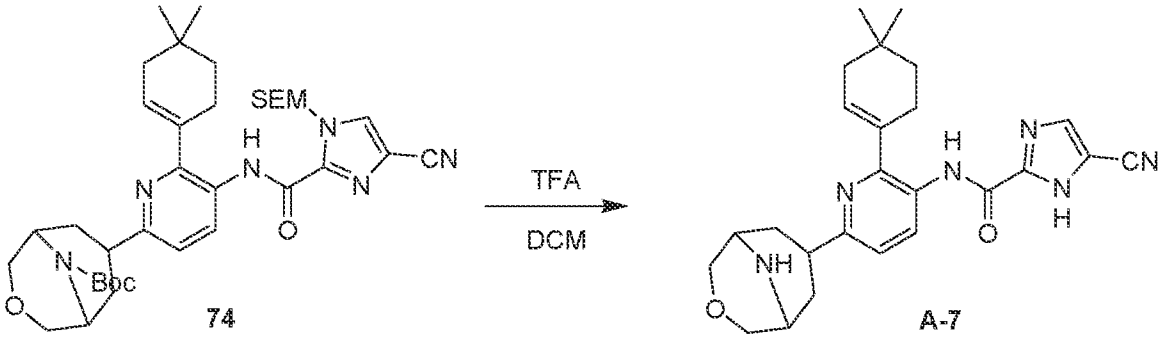
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]pyridin-3-amine (**68**, 230 mg, 700.32 μmol, 1 eq) in DMF (5 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 427.82 mg, 1.40 mmol, 2 eq) , DIEA (271.53 mg, 2.10 mmol, 365.94 μL, 3 eq) and PyBroP (489.71 mg, 1.05 mmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction was monitored by LC/MS (R_t = 2.853 min, [M+H] = 578.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**69**, 260 mg, 315.01 μmol, 45.0 % yield, 70 % purity) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.88 (s, 1H), 8.71 (br d, *J* = 8.7 Hz, 1H), 7.77 (s, 1H), 7.30 (br s, 1H), 6.42 - 6.31 (m, 2H), 6.00 - 5.91 (m, 3H), 5.02 (br s, 1H), 4.93 (br d, *J* = 8.0 Hz, 1H), 4.87 - 4.66 (m, 1H), 3.72 - 3.62 (m, 3H), 2.52 - 2.39 (m, 3H), 2.18 (s, 2H), 2.14 (br d, *J* = 1.9 Hz, 2H), 1.71 (br dd, *J* = 5.9, 13.2 Hz, 1H), 1.36 (br dd, *J* = 5.3, 7.6 Hz, 2H), 1.12 (d, *J* = 4.1 Hz, 6H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 578.3, expected 578.3 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**69**, 260 mg, 450.01 μmol, 1 eq) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t =2.164 min, [M+H] = 448.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-fluoro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-6**, 49.8 mg, 111.3 μmol, 24.7 % yield) as a yellow oil. ^{1}H NMR (400 MHz, MeOH-d4, 298 K) δ (ppm) = 8.82 (d, *J* = 8.8 Hz, 1H), 8.04 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 6.49 - 6.46 (m, 1H), 6.44 - 6.40 (m, 1H), 6.09, (td, *J* = 2.0, 3.5 Hz, 1H), 4.99 - 4.96 (m, 1H), 4.88 (br d, *J* = 2.4 Hz, 1H), 4.76 - 4.61 (m, 1H), 3.85 - 3.67 (m, 1H), 2.52 - 2.47 (m, 1H), 2.47 - 2.41 (m, 2H), 2.13 (br d, *J* = 3.6 Hz, 2H), 1.76 - 1.69 (m, 1H), 1.63 (t, *J* = 6.4 Hz, 2H), 1.11 (s, 6H), MS (LC/MS) *m/z* observed 448.3, expected 448.2 [M+H].

EXAMPLE 6

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-7





To a solution of *tert*-butyl 7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**70**, 558.31 mg, 2.29 mmol, 1.75 eq) and NHC-1 (829.23 mg, 2.10 mmol, 1.6 *eq*) in MTBE (5 mL) was added pyridine (165.96 mg, 2.10 mmol, 169.34 uL, 1.6 eq) in MTBE (1 mL) dropwise over 5 min at 25 °C. After a further stirring of 10 min, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 500 mg, 1.31 mmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (17.98 mg, 19.67 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (20.23 mg, 65.56 μmol, 0.05 eq), quinuclidine (255.15 mg, 2.29 mmol, 1.75 eq), and dtbbpy (26.40 mg, 98.35 μmol, 0.075 eq) in DMA (5 mL) under N_2. The mixture was stirred at 25 °C for 3 hr under blue LED lights. The reaction was monitored by LC/MS (R_t = 0.935 min, [M+H] = 528.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 30 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *tert*-butyl 7-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**71**, 580 mg, 1.10 mmol, 83.8 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 8.26 - 8.17 (m, 1H), 7.02 - 6.96 (m, 1H), 6.90 (s, 1H), 5.82 (br s, 1H), 4.17 - 4.11 (m, 1H), 4.02 (br s, 1H), 3.95 (br t, *J* = 12.3 Hz, 2H), 3.86 - 3.77 (m, 2H), 2.49 - 2.29 (m, 2H), 2.19 - 1.88 (m, 7H), 1.50 (d, *J* = 1.9 Hz, 18H), 1.03 (s, 6H), MS (LC/MS) *m/z* observed 528.4, expected 528.3 [M+H].

A solution of *tert*-butyl 7-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**71**, 580 mg, 1.10 mmol, 1 eq) in HCl/dioxane (10 mL) was stirred at 25 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 0.603 min, [M+H] = 328.3) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue, without further purification. 2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)pyridin-3-amine (**72**, 350 mg, 1.07 mmol, 97.2 % yield) was

obtained as a yellow solid that was used further as is. MS (LC/MS) *m/z* observed 328.3, expected 328.2 [M+H].

To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)pyridin-3-amine (**72**, 350 mg, 1.07 mmol, 1 eq) in DCM (10 mL) was added Boc_2O (233.27 mg, 1.07 mmol, 245.54 uL, 1 eq) and TEA (324.46 mg, 3.21 mmol, 446.30 uL, 3 eq) which was stirred at 25 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 0.776 min, [M+H] = 428.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with DCM (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc gradient at a flow rate of 60 mL/min) to afford *tert*-butyl 7-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**73**, 200 mg, 467.75 μmol, 43.8 % yield) as a yellow solid that was used further as is. MS (LC/MS) *m/z* observed 428.3, expected 428.3 [M+H].

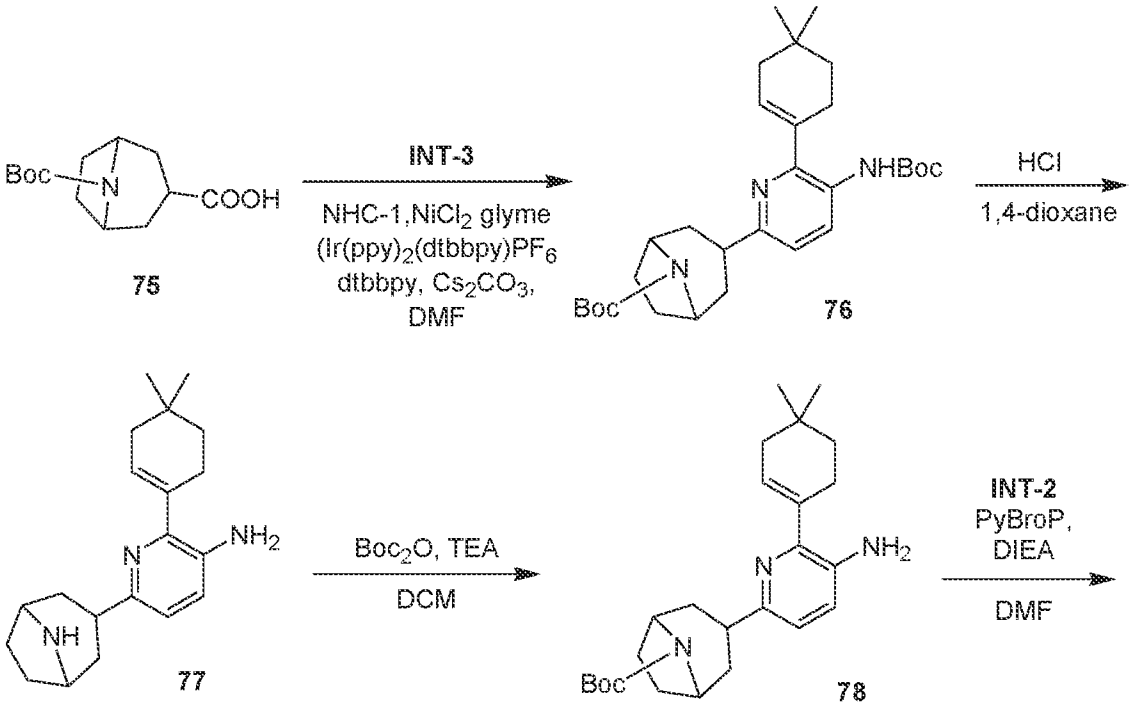
To a solution of *tert*-butyl 7-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**73**, 180 mg, 420.98 μmol, 1 eq) in DMF (3 mL) was added 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylic acid (**INT-2**, 258.02 mg, 841.95 μmol, 2 eq), DIEA (108.82 mg, 841.95 μmol, 146.65 uL, 2 eq) and PyBroP (294.38 mg, 631.46 μmol, 1.5 eq), The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 1.078 min, [M+H] = 667.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, washed with brine(15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 2/1 to 1/1 gradient) to afford *tert*-butyl 7-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**74**, 280 mg, 413.64 μmol, 98.3 % yield) as a yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is. MS (LC/MS) *m/z* observed 677.4, expected 677.4 [M+H].

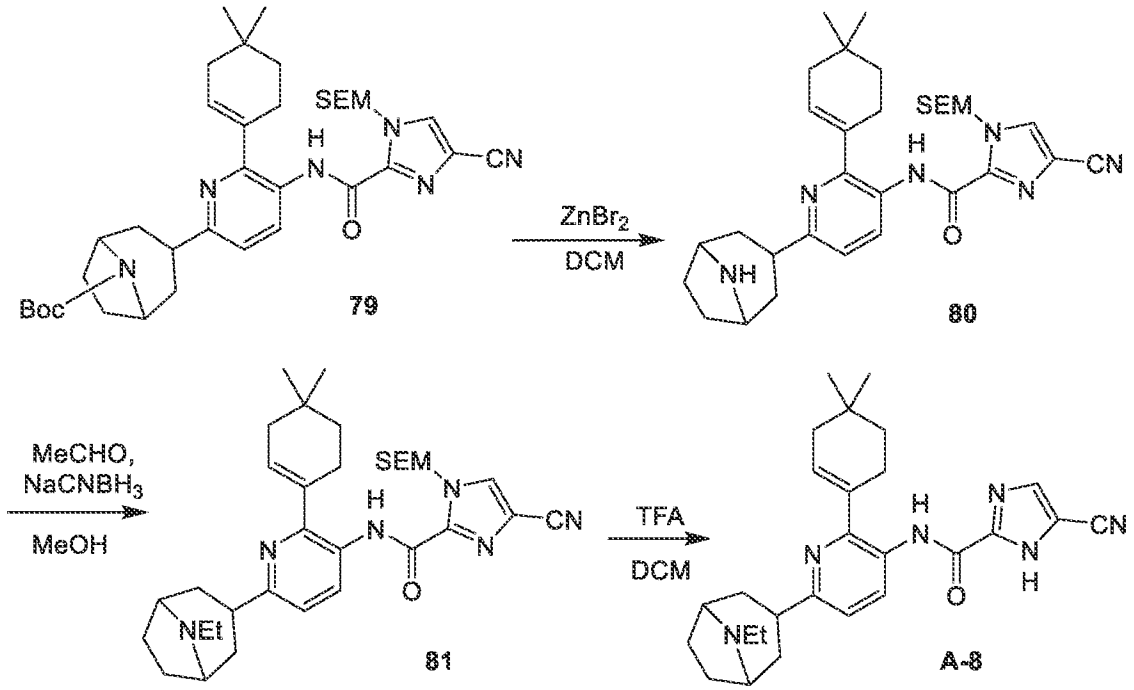
To a solution of *tert*-butyl 7-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (**74**, 120 mg, 177.3 μmol, 1 eq) in DCM (1 mL) was added TFA (687.25 mg, 6.03 mmol, 446.3 μL, 34 eq). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 2.501 min, M+H+ = 447.2) until it showed that the starting material had been

completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, washed with brine (15 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase: [water (TFA) - ACN]; B%: 15 % - 45 % gradient, 8 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-7**, 15.5 mg, 27.65 μmol, 15.6 % yield) as the TFA salt, as a white solid. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.61 (d, *J* = 8.5 Hz, 1H), 8.03 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 5.99 (td, *J* = 1.9, 3.5 Hz, 1H), 4.32 - 4.21 (m, 1H), 4.21 - 4.14 (m, 2H), 4.09 (s, 1H), 4.07 - 4.04 (m, 1H), 3.63 (br s, 2H), 2.52 - 2.47 (m, 2H), 2.46 - 2.39 (m, 2H), 2.37 - 2.28 (m, 2H), 2.10 (br d, *J* = 3.4 Hz, 2H), 1.60 (t, *J* = 6.4 Hz, 2H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 447.2, expected 447.3 [M+H].

EXAMPLE 7

4-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-8





To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 0.5 g, 1.31 mmol, 1 eq) and 8-*tert*-butoxycarbonyl-8-azabicyclo[3.2.1]octane-3-carboxylic acid (**75**, 334.78 mg, 1.31 mmol, 1 eq) in DMF (5 mL) was added dichloronickel;1,2-dimethoxyethane (28.81 mg, 131.13 μmol, 0.1 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (52.79 mg, 196.69 μmol, 0.15 eq), Cs_2CO_3 (854.48 mg, 2.62 mmol, 2 eq) and $(Ir(dF(CH_3)ppy)_2(dtbbpy))PF_6$ (13.30 mg, 13.11 μmol, 0.01 eq). The mixture was stirred at 20 °C for 12 h under 34w blue LED lights. The reaction was monitored by TLC (Pet. Et. : EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc=1/0 to 10/1 gradient) to afford *tert*-butyl 3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**76**, 0.8 g, 1.56 mmol, 39.7 % yield) as yellow oil that was used further as is without further characterization.

To a solution of *tert*-butyl 3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**76**, 1 g, 1.95 mmol, 1 eq) in dioxane (4 mL) was added HCl/dioxane (4 M, 5.00 mL, 10.23 eq). The mixture was stirred at 20 °C for 2 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.436 min, [M+H] = 312.2) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to remove dioxane, without further purification, to afford 6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine hydrochloride

(77, 0.65 g, 1.87 mmol, 95.6 % yield) as yellow oil that was used further as is. MS (LC/MS) *m/z* observed 312.2, expected 312.2 [M+H].

To a solution of 6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine hydrochloride salt (**77**, 0.65 g, 1.87 mmol, 1 eq) in DCM (1 mL) was added Boc_2O (407.74 mg, 1.87 mmol, 429.20 uL, 1 eq) and TEA (207.95 mg, 2.06 mmol, 286.04 uL, 1.1 eq). The mixture was stirred at 20 °C for 1 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. : EtOAc = 10:1) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (10 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc= 1/0 to 10/1) to afford *tert*-butyl 3-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**78**, 0.3 g, 728.90 μmol, 39.0 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is., MS (LC/MS) *m/z* observed 312.1 [M-Boc] expected 412.2 [M+H].

To a solution of *tert*-butyl 3-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**78**, 0.3 g, 728.90 μmol, 1 eq) and 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylic acid (**INT-2**, 446.75 mg, 1.46 mmol, 2 eq) in DMF (3 mL) was added DIEA (282.61 mg, 2.19 mmol, 380.88 uL, 3 eq) and PyBroP (509.70 mg, 1.09 mmol, 1.5 eq). The mixture was stirred at 20 °C for 12 h under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. : EtOAc=10:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (1 mL) and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase : [water (TFA) - ACN]; B%: 65 % - 100 % gradient, 8 min) to afford tert-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**79**, 0.2 g, 302.61 μmol, 41.52% yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is. MS (LC/MS) *m/z* observed 661.5, expected 661.4 [M+H].

To a solution of *tert*-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-8-azabicyclo[3.2.1]octane-8-carboxylate (**79**, 0.2 g, 302.61 μmol, 1 eq) in DCM (5 mL) was added $ZnBr_2$ (545.18 mg, 2.42 mmol, 121.15 uL, 8 eq). The mixture was stirred at 20 °C for 12 h under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.886 min, [M+H] = 561.3) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (3 mL) and extracted with

DCM (5 mL x 3). The organic layers were combined, washed with brine (5 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford *N*-[6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**80**, 0.1 g, 178.32 μmol, 58.9 % yield) as a white solid that was used further as is. MS (LC/MS) *m/z* observed 561.3, expected 561.3 [M+H].

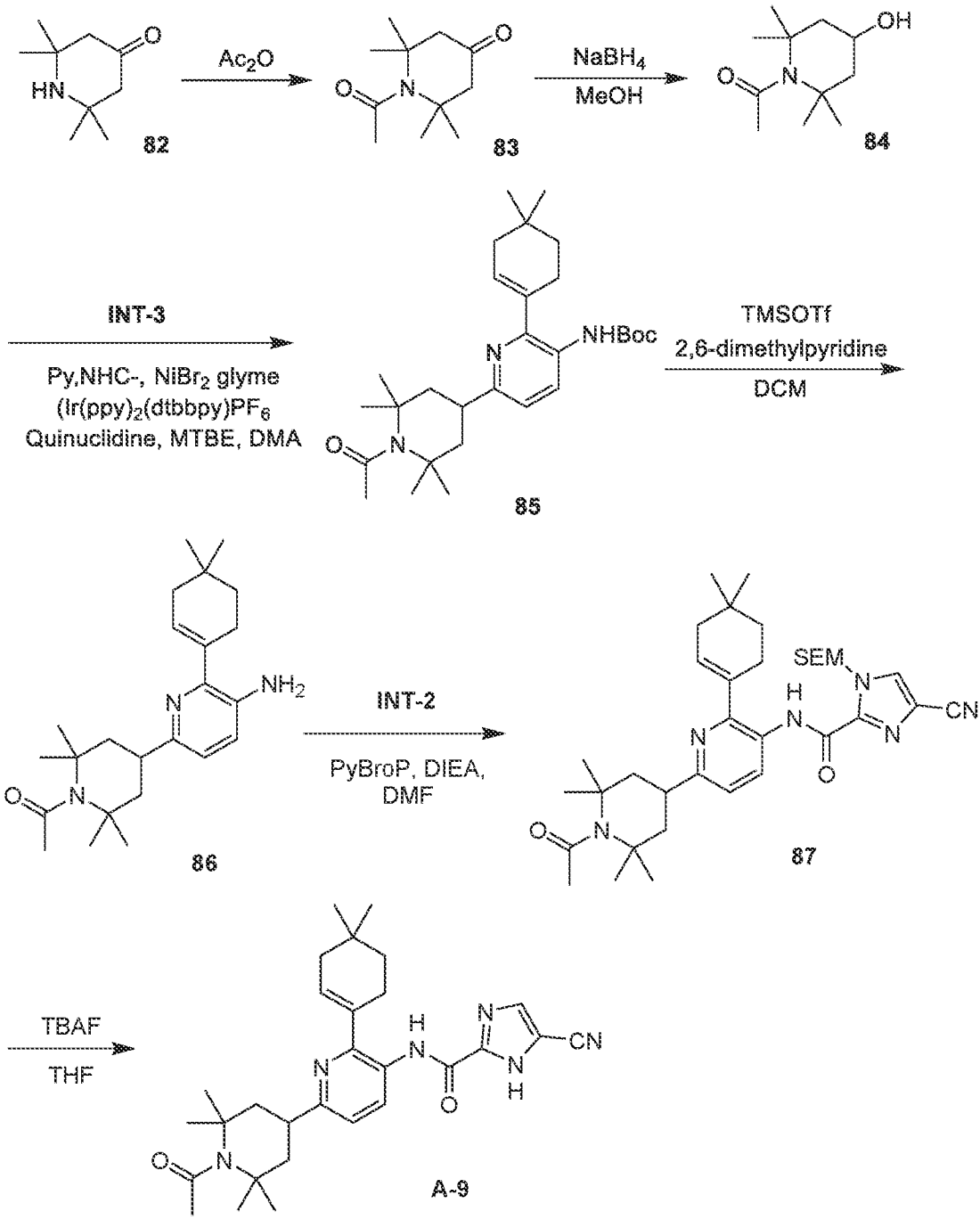
To a solution of *N*-[6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**80**, 0.1 g, 178.32 μmol, 1 eq) in MeOH (2 mL) was added acetaldehyde (98.19 mg, 891.58 μmol, 125.08 μL, 5 eq). The mixture was stirred at 0 °C for 0.5 h under an N_2 atmosphere. $NaBH_3CN$ (28.01 mg, 445.79 μmol, 2.5 eq) was then added. The mixture was stirred at 20 °C for 11.5 h under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.897 min, [M+H] = 589.4) until it showed that the reaction had completed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, washed with brine (5 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**81**, 0.04 g, 67.93 μmol, 38.1 % yield) as a white solid that was used further as is. MS (LC/MS) *m/z* observed 589.4, expected 589.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**81**, 0.04 g, 67.93 μmol, 1 eq) in DCM (1 mL) was added TFA (1.20 g, 10.55 mmol, 780.94 μL, 155.3 eq). The mixture was stirred at 20 °C for 2 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.766 min, [M+H] = 459.3) until it showed that the reaction was complete. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, washed with brine (5 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 20 % - 50 % gradient, 8 min) to afford title compound, 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-8**, 0.017 g, 37.07 μmol, 54.6 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.01 (s, 1H), 8.50 (br d, *J* = 8.1 Hz, 1H), 7.70 (br s, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 5.86 (br s, 1H), 3.88 (br s, 2H), 3.19 (br d, *J* = 5.1 Hz, 1H), 2.87 (br d, *J* = 5.6 Hz, 2H), 2.38 (br s, 2H), 2.18 - 2.05 (m, 4H), 2.04 - 1.93 (m, 4H), 1.86 (br d, *J* =

12.9 Hz, 2H), 1.50 (br t, J = 6.2 Hz, 2H), 1.20 (br t, J = 7.1 Hz, 3H), 1.03 (s, 6H), MS (LC/MS) m/z observed 459.3, expected 459.3 [M+H].

EXAMPLE 8

N-[6-(1-Acetyl-2,2,6,6-tetramethyl-4-piperidyl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1H-imidazole-2-carboxamide A-9



A solution of 2,2,6,6-tetramethylpiperidin-4-one (**82**, 3 g, 19.33 mmol, 1 eq) in Ac_2O (15 mL) was heated and stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. : EtOAc =3:1) until one major new spot with lower polarity had been detected. The reaction mixture was basified to pH = 7 ~ 8 with NaOH (aqueous, 10 %) and extracted with

DCM (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc=10/0 to 1/1) to afford 1-acetyl-2,2,6,6-tetramethyl-piperidin-4-one (**83**, 3.6 g, 18.25 mmol, 94.4 % yield) as yellow oil that was used further as is. 1H NMR to be analyzed.

To a solution of 1-acetyl-2,2,6,6-tetramethyl-piperidin-4-one (**83**, 2.6 g, 13.18 mmol, 1 eq) in MeOH (26 mL) was added $NaBH_4$ (747.88 mg, 19.77 mmol, 1.5 eq) at 0 °C, the mixture was stirred at 20 °C for 2 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (aqueous, 35 mL) and extracted with DCM (25 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 1/1) to afford 1-(4-hydroxy-2,2,6,6-tetramethyl-1-piperidyl)ethanone (**84**, 1.5 g, 7.53 mmol, 57.1 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ = 4.26 - 4.15 (m, 1H), 2.21 - 2.13 (m, 5H), 1.85 (dd, *J* = 5.9, 14.7 Hz, 2H), 1.56 (s, 6H), 1.45 (s, 6H).

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 800 mg, 2.10 mmol, 1 eq) and 1-(4-hydroxy-2,2,6,6-tetramethyl-1-piperidyl)ethanone (**84**, 731.71 mg, 3.67 mmol, 1.75 eq) in MTBE (7 mL), was added bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (28.76 mg, 31.47 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (32.38 mg, 104.90 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (42.23 mg, 157.35 μmol, 0.075 eq), isoindoline-1,3-dione (69.45 mg, 472.06 μmol, 0.225 eq), pyridine (265.53 mg, 3.36 mmol, 270.95 uL, 1.6 eq), NHC-1 (1.33 g, 3.36 mmol, 1.6 eq), quinuclidine (408.24 mg, 3.67 mmol, 1.75 eq) and DMA (7 mL) at 25 °C. The mixture was further stirred at 25 °C for 2 hr under 34W blue LED lights. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (15 mL), extracted with EtOAc (10 mL x 3) and washed with brine (30 mL). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 3/1) to afford *tert*-butyl *N*-[6-(1-acetyl-2,2,6,6-tetramethyl-4-piperidyl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**85**, 900 mg, 1.86 mmol, 88.7 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27 (br d, *J* = 8.0 Hz, 1H), 7.92 - 7.74 (m, 1H), 7.04 (br d, *J* = 8.5 Hz, 1H), 6.93 (s, 1H), 5.83 (br s, 1H), 3.25 (quin, *J* = 7.9 Hz, 1H), 2.42 (br s, 2H), 2.24 (s, 3H), 2.16 (br dd, *J* =

9.3, 14.0 Hz, 2H), 2.08 - 1.97 (m, 4H), 1.55 (d, J = 7.8 Hz, 12H), 1.51 (s, 9H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 484.3, expected 484.4 [M+H].

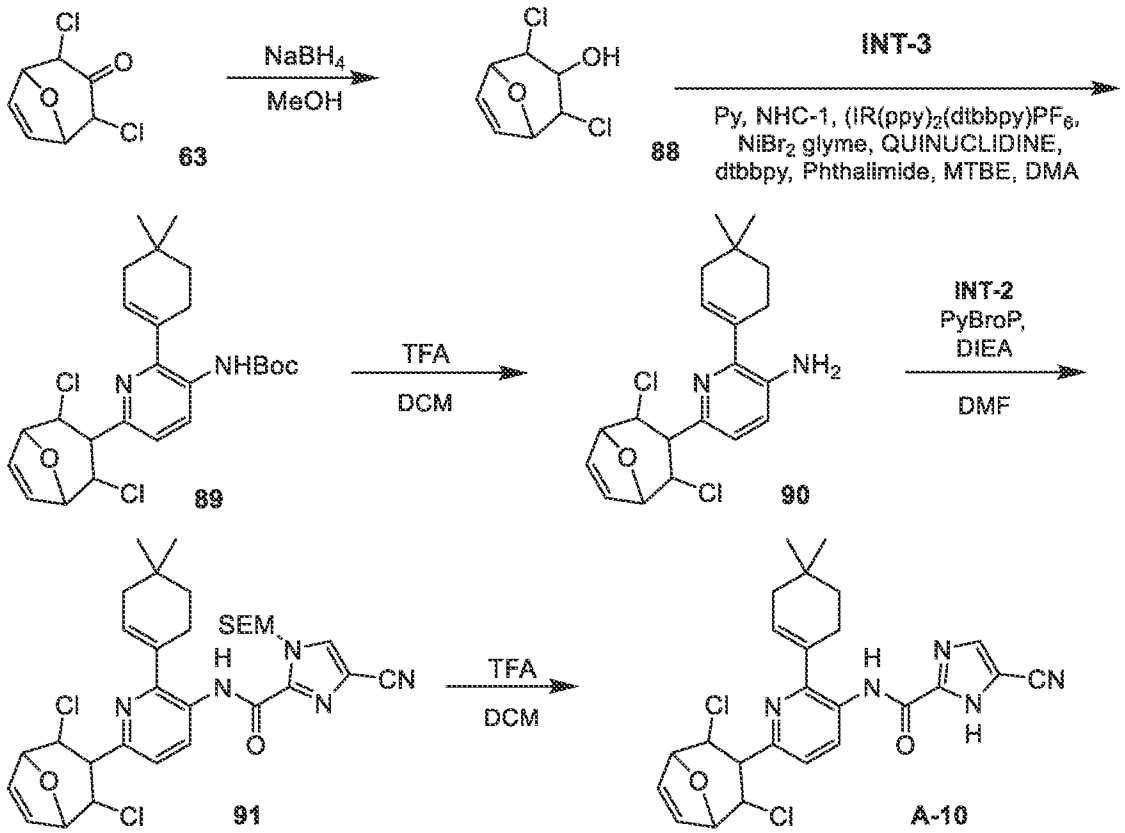
To a solution of *tert*-butyl *N*-[6-(1-acetyl-2,2,6,6-tetramethyl-4-piperidyl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**85**, 350 mg, 723.61 μmol, 1 eq) in DCM (4 mL), was added TMSOTf (643.32 mg, 2.89 mmol, 523.02 μL, 4 eq) and 2,6-dimethylpyridine (465.21 mg, 4.34 mmol, 505.66 μL, 6 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.729 min, [M+H] = 384.4) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction was poured into water (6 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (Pet. Et. / EtOAc = 1/1) to afford 1-[4-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,2,6,6-tetramethyl-1-piperidyl]ethanone (**86**, 190 mg, 495.35 μmol, 68.5 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 7.17 - 6.94 (m, 2H), 5.86 (br s, 1H), 3.26 - 3.15 (m, 1H), 2.43 - 2.36 (m, 2H), 2.25 (s, 3H), 2.07 - 2.01 (m, 4H), 1.57 (s, 8H), 1.54 (s, 6H), 1.29 (br d, J = 3.5 Hz, 2H), 1.05 (s, 6H), MS (LC/MS) *m/z* observed 384.4, expected 384.3 [M+H].

To a solution of 1-[4-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,2,6,6-tetramethyl-1-piperidyl]ethenone (**86**, 190 mg, 495.35 μmol, 1 eq) and 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylate (**INT-2**, 302.60 mg, 990.70 μmol, 2 eq) in DMF (3 mL) was added DIEA (192.06 mg, 1.49 mmol, 258.84 μL, 3 eq), PyBroP (346.38 mg, 743.02 μmol, 1.5 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (7 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Pet. Et. / EtOAc = 1/1) to afford *N*-[6-(1-acetyl-2,2,6,6-tetramethyl-4-piperidyl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**87**, 100 mg, 158.00 μmol, 31.9 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.57 (d, J = 8.6 Hz, 1H), 8.22 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 5.97 - 5.89 (m, 3H), 3.70 - 3.64 (m, 2H), 2.47 (br d, J = 1.8 Hz, 2H), 2.27 - 2.24 (m, 3H), 2.21 (br d, J = 4.6 Hz, 2H), 2.18 (d, J = 4.3 Hz, 1H), 2.11 (br s, 3H), 2.10 - 2.06 (m, 3H), 1.59 (s, 6H), 1.57 (s, 6H), 1.11 (s, 6H), 0.96 - 0.92 (m, 2H), -0.01 - -0.04 (m, 9H), MS (LC/MS) *m/z* observed 633.5, expected 633.4 [M+H].

To a solution of *N*-[6-(1-acetyl-2,2,6,6-tetramethyl-4-piperidyl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**87**, 90 mg, 142.20 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 284.40 μL, 2 eq) at 0 °C. The mixture was allowed to warm and then stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 0/1) until it showed that the starting material had been completely consumed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 35 % - 85 % gradient, 8 min) to afford title compound, *N*-[6-(1-acetyl-2,2,6,6-tetramethyl-4-piperidyl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-9**, 18.3 mg, 36.41 μmol, 25.6 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.02 (s, 1H), 8.30 (s, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 5.89 (br s, 1H), 3.28 (br s, 1H), 2.42 (br s, 2H), 2.13 (s, 3H), 2.10 - 2.03 (m, 2H), 2.01 - 1.95 (m, 2H), 1.92 (br s, 2H), 1.49 (s, 6H), 1.47 (s, 6H), 1.23 (br s, 2H), 0.97 (s, 6H), MS (LC/MS) *m/z* observed 503.5, expected 503.3 [M+H].

EXAMPLE 9

5-Cyano-*N*-[6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-10



To a solution of 2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**63**, 20 g, 103.61 mmol, 1 eq) in MeOH (200 mL) was added $NaBH_4$ (5.88 g, 155.42 mmol, 1.5 eq) at 0 °C. The mixture was allowed to warm and further at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc= 3:1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with NH_4Cl (aqueous, 80 mL) and extracted with EtOAc (70 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % EtOAc/Pet. Et. gradient with a flow rate of 60 mL/min) to afford 2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**88**, 2.7 g, 13.84 mmol, 13.4 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.55 (s, 2H), 4.76 (d, *J* = 3.5 Hz, 2H), 4.35 (dd, *J* = 3.8, 4.6 Hz, 2H), 4.27 - 4.21 (m, 1H), 2.32 (d, *J* = 5.4 Hz, 1H).

To a solution of 2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**88**, 268.54 mg, 1.38 mmol, 1.75 eq) and NHC-1 (497.54 mg, 1.26 mmol, 1.6 eq) in MTBE (5 mL) was added pyridine (99.57 mg, 1.26 mmol, 101.61 μL, 1.6 eq) in MTBE (1 mL) dropwise over 5 mins at 25 °C. After a further 10 min of stirring, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 300 mg, 786.77 μmol, 1 eq), *bis*[2-(2-pyridyl)phenyl]iridium(1+); 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine; hexafluorophosphate (10.79 mg, 11.80 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (12.14 mg, 39.34 μmol, 0.05 eq), quinuclidine (153.09 mg, 1.38 mmol, 1.75 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (15.84 mg, 59.01 μmol, 0.075 eq) and isoindoline-1,3-dione (26.05 mg, 177.02 μmol, 0.225 eq) in DMA (5 mL) under N_2. The mixture was stirred at 25 °C for 3 hr under blue LED lights. The reaction was monitored by LC/MS (R_t = 2.786 min, [M+H] = 479.2) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *tert*-butyl *N*-[6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**89**, 150 mg, 312.87 μmol, 4.4 % yield) as a yellow solid, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 8.32 (br d, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.01 (s, 1H), 6.56 (s, 2H), 5.88 (br s, 1H), 4.91 (d, *J* = 3.9 Hz, 2H), 4.38 (dd, *J* = 3.9, 9.5 Hz, 2H), 3.10 (t, *J* = 9.4 Hz, 1H), 2.45 (br d, *J* = 1.9 Hz, 2H), 2.06 (br d, *J* = 3.1 Hz,

2H), 1.58 (t, J = 6.4 Hz, 2H), 1.51 (s, 9H), 1.05 (s, 6H), MS (LC/MS) m/z observed 479.2, expected 479.2 [M+H].

To a solution of *tert*-butyl *N*-[6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**89**, 150 mg, 312.87 μmol, 1 eq) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 0.523 min, [M+H] = 379.1) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue without further purification, to afford 6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**90**, 110 mg, 289.99 μmol, 92.7 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4, 298 K) δ (ppm) = 7.86 - 7.82 (m, 1H), 7.79 - 7.76 (m, 1H), 6.64 (s, 2H), 6.14 (td, J = 2.0, 3.7 Hz, 1H), 4.98 (d, J = 3.9 Hz, 2H), 4.33 (dd, J = 3.9, 10.1 Hz, 2H), 3.64 (t, J = 10.1 Hz, 1H), 2.37 - 2.30 (m, 2H), 2.15 - 2.08 (m, 2H), 1.63 (t, J = 6.3 Hz, 2H), 1.07 (s, 6H), MS (LC/MS) m/z observed 379.1, expected 379.1 [M+H].

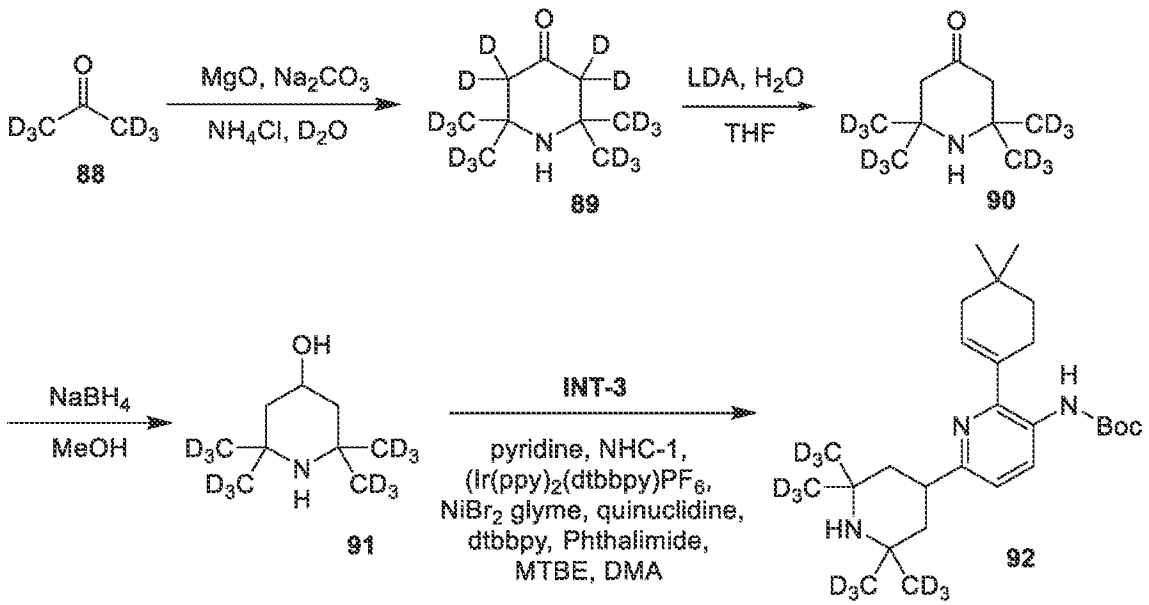
To a solution of 6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**90**, 110 mg, 289.99 μmol, 1 eq) in DMF (5 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 177.15 mg, 579.98 μmol, 2 eq), DIEA (112.44 mg, 869.97 μmol, 151.53 μL, 3 eq) and PyBroP (202.78 mg, 434.99 μmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction was monitored by LC/MS (R_t = 1.216 min, [M+H] = 628.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford 4-cyano-*N*-[6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**91**, 130 mg, 206.79 μmol, 71.3 % yield) as a yellow oil, which was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.02 (s, 1H), 8.68 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H), 7.11 (d, J = 8.3 Hz, 1H), 6.58 (s, 2H), 6.01 (br s, 1H), 5.94 (s, 2H), 4.93 (d, J = 3.8 Hz, 2H), 4.42 (dd, J = 3.9, 9.5 Hz, 2H), 3.72 - 3.60 (m, 2H), 3.16 (t, J = 9.5 Hz, 1H), 2.52 (br d, J = 1.6 Hz, 2H), 2.17 (br d, J = 3.1 Hz, 2H), 1.63 (t, J = 6.4 Hz, 2H), 1.13 (s, 6H), 1.01 - 0.95 (m, 2H), 0.01 (s, 9H), MS (LC/MS) m/z observed 628.3, expected 628.3 [M+H].

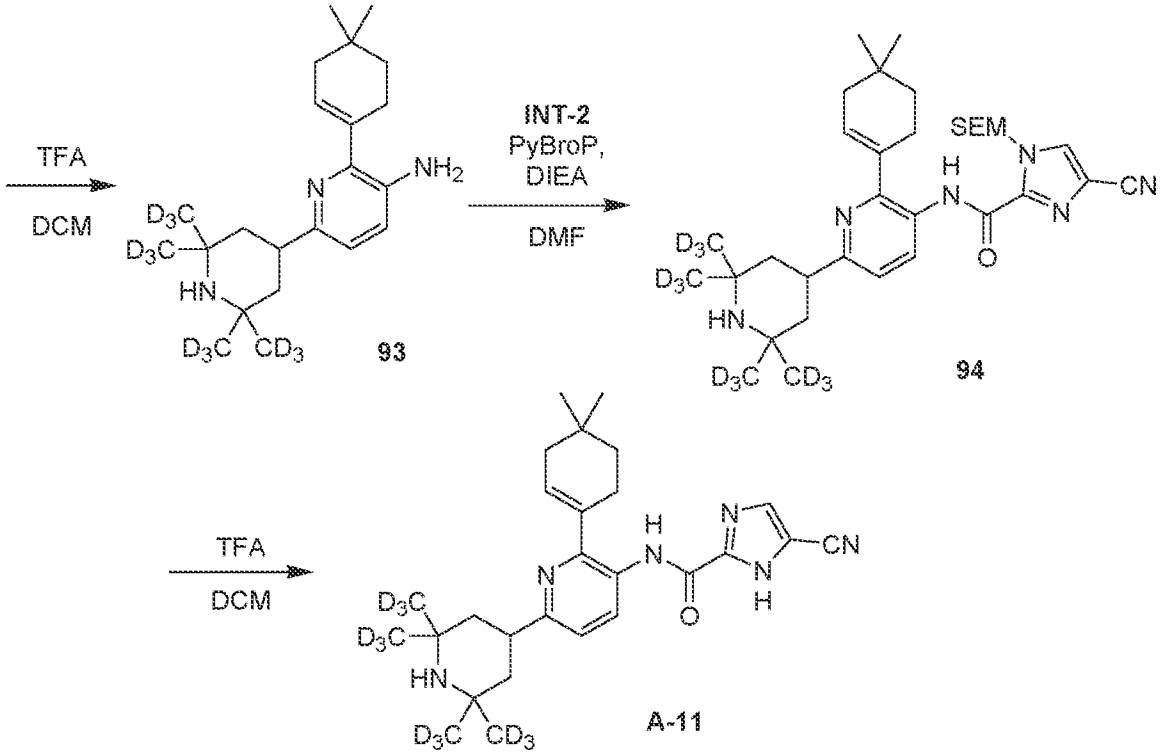
To a solution of 4-cyano-*N*-[6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide

(**91**, 130 mg, 206.79 μmol, 1 eq) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 2.486 min, [M+H] = 498.2) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1% TFA) - ACN]; 60 % - 90 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[6-[2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-10**, 42.8 mg, 85.87 μmol, 41.5 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.29 (br s, 1H), 10.09 (s, 1H), 8.34 (s, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.65 (s, 2H), 5.98 (br s, 1H), 4.98 (d, *J* = 4.0 Hz, 2H), 4.34 (br dd, *J* = 4.0, 9.6 Hz, 4H), 3.13 (t, *J* = 9.6 Hz, 1H), 1.94 (br s, 2H), 1.50 (br t, *J* = 6.4 Hz, 2H), 0.99 (s, 6H), MS (LC/MS) *m/z* observed 498.2, expected 498.2 [M+H].

EXAMPLE 10

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-11





To a solution of MgO (1.57 g, 38.99 mmol, 438.93 μL, 0.5 eq), Na_2CO_3 (1.65 g, 15.60 mmol, 0.2 eq) and NH_4Cl (1.67 g, 31.19 mmol, 0.4 eq) was added 1,1,1,3,3,3-hexadeuteriopropan-2-one (**88**, 5 g, 77.98 mmol, 5.73 mL, 1 eq) at 20 °C. The mixture was heated and further stirred at 50 °C for 12 hr under an N_2 atmosphere. The reaction was monitored by TLC (EtOAc/MeOH = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 0/1) to afford 3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**89**, 500 mg, 2.92 mmol, 3.7 % yield) as a yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is. MS (LC/MS) *m/z* observed 172.3, expected 172.2 [M+H].

To a solution of 3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**89**, 100 mg, 583.65 μmol, 1 eq) in THF (3 mL) was added LDA (2 M, 1.46 mL, 5 *eq*) at -60 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.133 min, [M+H] = 168.2) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (aqueous, 5 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 3/1 to 0/1) to afford 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**90**, 20 mg, 119.54 μmol, 20.48% yield) as a yellow

solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.37 (s, 4H), MS (LC/MS) *m/z* observed 168.2, expected 168.2 [M+H].

To a solution of 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**90**, 1 g, 5.98 mmol, 1 eq) in MeOH (20 mL) was added $NaBH_4$ (339.18 mg, 8.97 mmol, 1.5 eq) at 0 °C, the mixture was allowed to warm and further stirred at 25 °C for 2 hr under an N_2 atmosphere. The reaction was monitored by TLC (EtOAc/MeOH = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (aqueous, 30 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford a residue without further purification to afford 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (**91**, 1 g, 5.91 mmol, 98.8 % yield) as a yellow solid, that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ (ppm) = 4.01 - 3.93 (m, 1H), 1.89 - 1.79 (m, 1H), 1.14 (br dd, *J* = 7.6, 14.0 Hz, 2H), 1.05 (t, *J* = 12.0 Hz, 1H).

To a solution of 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (**91**, 412.99 mg, 2.44 mmol, 1.55 eq) and NHC-1 (995.08 mg, 2.52 mmol, 1.6 eq) in MTBE (10 mL) was added pyridine (199.15 mg, 2.52 mmol, 203.21 µL, 1.6 eq) in MTBE (1 mL) dropwise over 5 min at 25 °C. After 10 min of further stirring, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 600 mg, 1.57 mmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (21.57 mg, 23.60 µmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (24.28 mg, 78.68 µmol, 0.05 eq), quinuclidine (306.17 mg, 2.75 mmol, 1.75 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (31.67 mg, 118.02 µmol, 0.075 eq), and isoindoline-1,3-dione (52.09 mg, 354.05 µmol, 0.225 eq) in DMA (10 mL) under N_2. The mixture was stirred at 25 °C for 12 hr under blue LED lights. The reaction was monitored by LC/MS (R_t = 0.451 min, [M+H] = 454.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 µm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 25 % - 55 % B gradient over 8.0 min) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**92**, 160 mg, 352.64 µmol, 22.4 % yield) as a yellow solid, that was used further as is. MS (LC/MS) *m/z* observed 454.4, expected 454.4 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**92**, 160 mg, 352.6 µmol, 1 eq) in DCM (3 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 hr. The reaction

was monitored by LC/MS (R_t = 0.330 min, [M+H] = 354.3) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue without further purification. 2-(4,4-Dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**93**, 160 mg, 339.36 μmol, 96.2 % yield, 75 % purity) was obtained as a yellow oil and used further as is. ^{1}H NMR (400 MHz, MeOH-d4, 298 K) δ (ppm) = 7.73 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 6.19 (td, *J* = 1.9, 3.7 Hz, 1H), 3.74 - 3.62 (m, 1H), 2.45 - 2.36 (m, 2H), 2.13 (br d, *J* = 3.5 Hz, 2H), 2.09 - 2.03 (m, 1H), 2.02 (s, 1H), 1.64 (t, *J* = 6.3 Hz, 2H), 1.58 - 1.46 (m, 2H), 1.08 (s, 6H), MS (LC/MS) *m/z* observed 354.3, expected 354.4 [M+H].

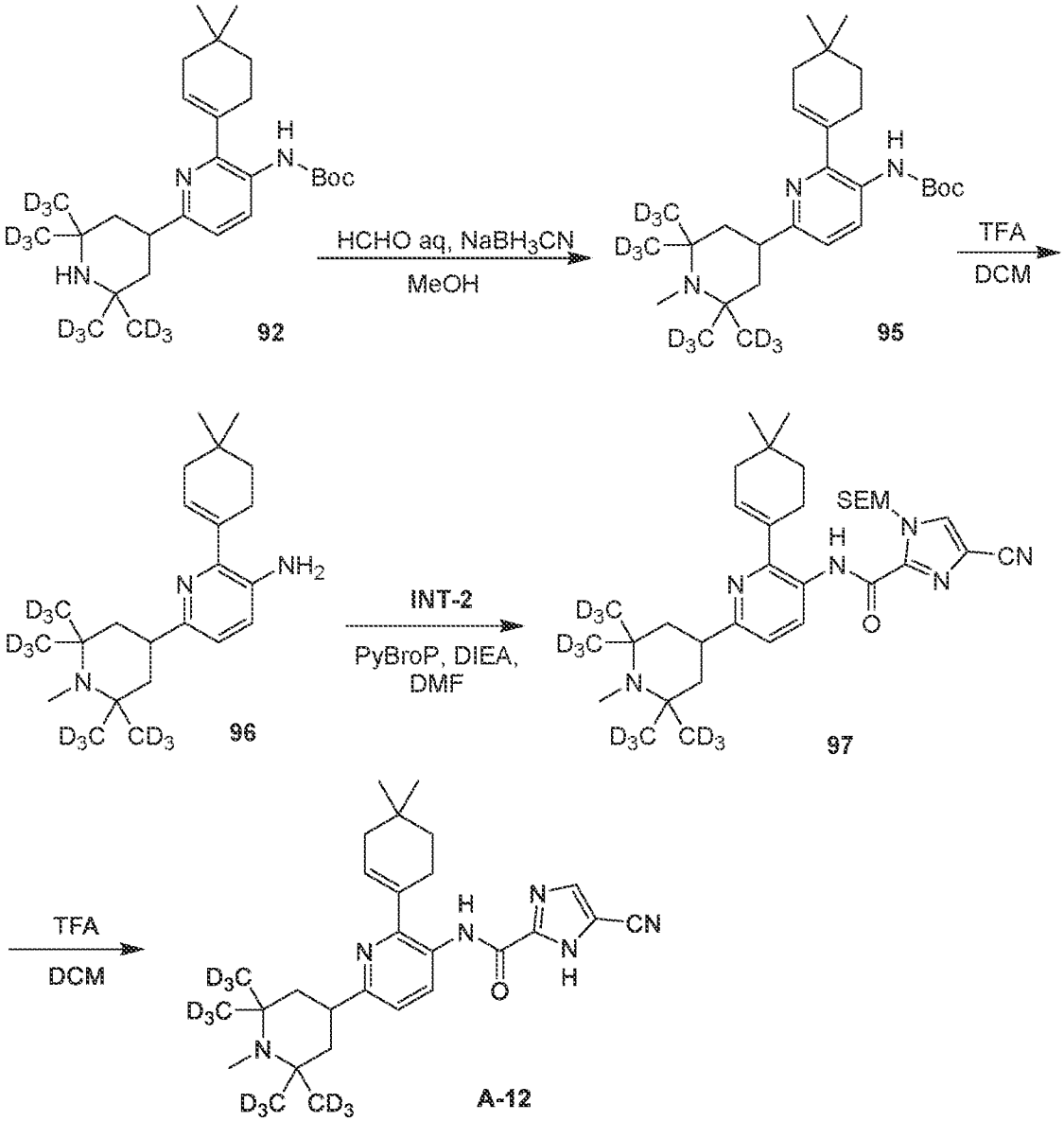
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**93**, 220 mg, 622.16 μmol, 1 eq) in DMF (5 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 380.07 mg, 1.24 mmol, 2 eq), DIEA (241.23 mg, 1.87 mmol, 325.11 μL, 3 eq) and PyBroP (435.06 mg, 933.24 μmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction was monitored by LC/MS (R_t = 2.508 min, [M+H] = 603.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**94**, 200 mg, 331.70 μmol, 53.3 % yield) as a yellow oil and used further as is. ^{1}H NMR (400 MHz, MeOH-d4, 298 K) δ (ppm) = 8.72 (d, *J* = 8.5 Hz, 1H), 8.24 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 6.03 (br s, 1H), 5.91 (s, 2H), 3.70 - 3.64 (m, 2H), 3.52 - 3.44 (m, 1H), 2.47 (br d, *J* = 2.0 Hz, 2H), 2.13 (br d, *J* = 3.4 Hz, 2H), 2.10 - 2.01 (m, 2H), 1.88 (t, *J* = 13.5 Hz, 2H), 1.62 (t, *J* = 6.3 Hz, 2H), 1.58 -1.53 (m, 1H), 1.48 - 1.43 (m, 1H), 1.11 (s, 6H), -0.02 (s, 9H), MS (LC/MS) *m/z* observed 603.5, expected 603.5 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**94**, 200 mg, 331.70 μmol, 1 eq) in DCM (5 mL)was added TFA (2 mL). The mixture was stirred at 25 °C for 1 h. The reaction was monitored by LC/MS (R_t = 1.899 min, [M+H] = 473.4) until it showed reactant had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column:

Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 20 % - 50 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-11**, 52.6 mg, 111.28 μmol, 33.6 % yield) as a yellow oil. ^{1}H NMR (400 MHz, MeOH-d4, 295 K) δ (ppm) = 8.59 (d, *J* = 8.5 Hz, 1H), 8.03 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 5.99 - 5.93 (m, 1H), 3.47 - 3.38 (m, 1H), 2.47 (br d, *J* = 2.0 Hz, 2H), 2.11 (br d, *J* = 3.1 Hz, 2H), 2.06 - 1.82 (m, 3H), 1.61 (t, *J* = 6.3 Hz, 2H), 1.57 - 1.44 (m, 1H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 473.4, expected 473.4 [M+H].

EXAMPLE 11

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-12



To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**92**, 210 mg, 462.84 μmol, 1 eq) and formaldehyde (187.80 mg, 2.31 mmol, 172.29 μL, 5 *eq*) in MeOH (5 mL), was added $NaBH_3CN$ (72.71 mg, 1.16 mmol, 2.5 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.816 min, [M+H] = 468.5) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was diluted with H_2O (10 mL), extracted with DCM (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**95**, 200 mg) as a crude yellow solid which was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 7.88 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 5.81 (td, *J* = 2.0, 3.5 Hz, 1H), 3.28 - 3.21 (m, 1H), 2.55 (br s, 3H), 2.44 - 2.35 (m, 2H), 2.02 (br d, *J* = 3.4 Hz, 2H), 1.87 (br s, 2H), 1.55 (t, *J* = 6.4 Hz, 2H), 1.48 (s, 9H), 1.30 (br d, *J* = 5.9 Hz, 2H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 468.5, expected 468.4 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**95**, 200 mg, 427.58 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.314 min, [M+H] = 368.4) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction was adjusted to pH = 8 ~ 9 with $NaHCO_3$ (aqueous) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification. 2-(4,4-Dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**96**, 120 mg, 326.41 μmol, 76.3 % yield) was obtained as a yellow solid and used further as is. MS (LC/MS) *m/z* observed 368.4, expected 368.4 [M+H].

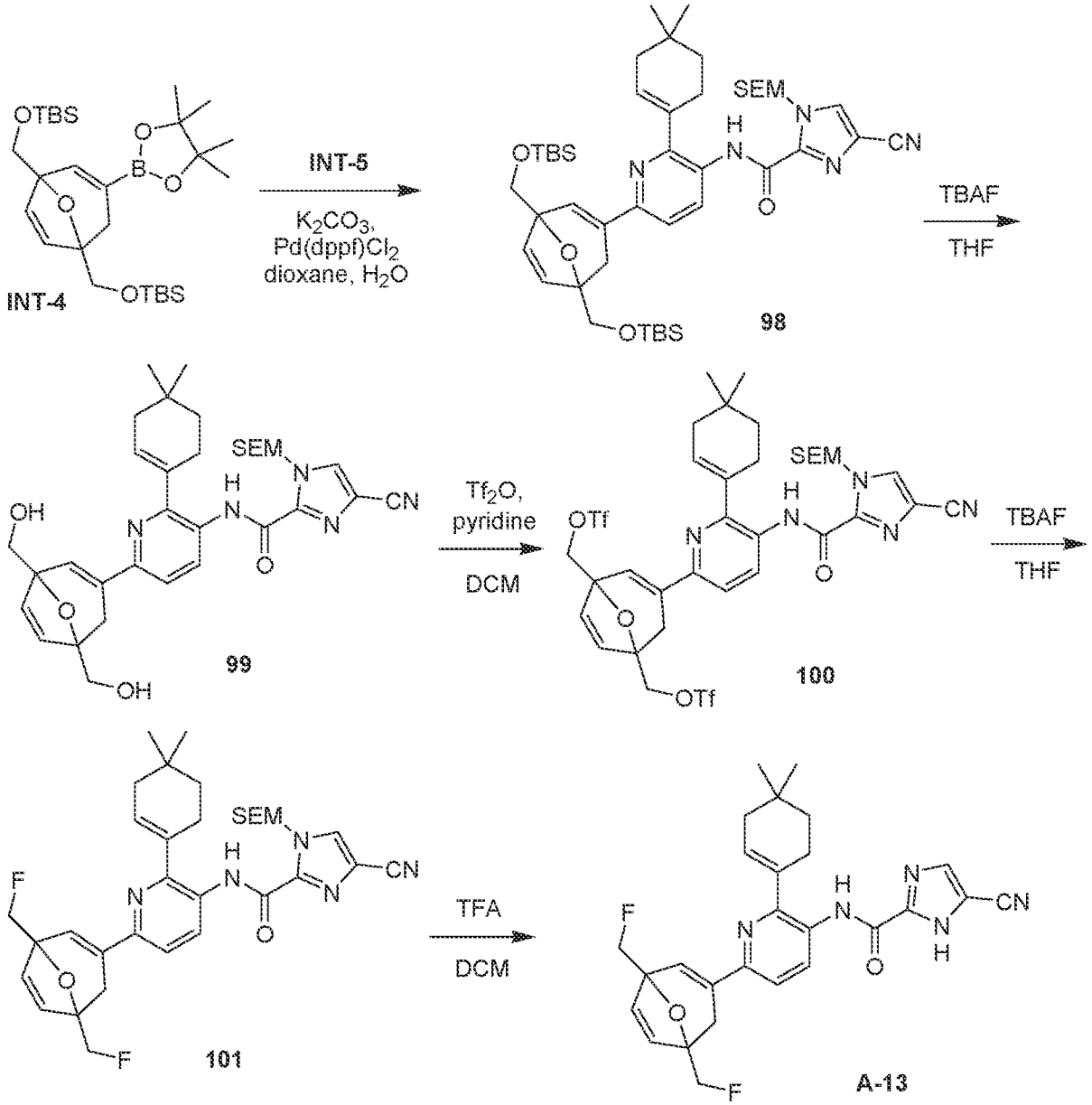
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**96**, 120 mg, 326.41 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 224.93 mg, 736.39 μmol, 2.26 eq) in DMF (2 mL) was added DIEA (126.56 mg, 979.24 μmol, 170.56 μL, 3 eq), PyBroP (228.25 mg, 489.62 μmol, 1.5 eq) at 0 °C. The mixture was allowed to warm and stirred at 20 °C for a further 16 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.927 min, [M+H] = 617.6) until it showed that the starting material had been

completely consumed and the desired product mass was observed. The reaction mixture was diluted with H_2O (7 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 40 % - 70 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**97**, 110 mg, 150.48 μmol, 46.1 % yield) as a TFA salt, as a white solid, that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.77 (d, *J* = 8.5 Hz, 1H), 8.24 (s, 1H), 7.46 (d, *J* = 8.6 Hz, 1H), 6.07 (br s, 1H), 5.91 (s, 2H), 3.70 - 3.64 (m, 2H), 3.52 (qdd, *J* = 4.0, 8.2, 12.2 Hz, 1H), 2.90 (s, 3H), 2.47 (br d, *J* = 1.9 Hz, 2H), 2.18 - 2.12 (m, 4H), 1.62 (t, *J* = 6.3 Hz, 2H), 1.56 - 1.48 (m, 2H), 1.11 (s, 6H), 0.97 - 0.91 (m, 2H), -0.02 (s, 9H), MS (LC/MS) *m/z* observed 617.6, expected 617.5 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**97**, 110 mg, 178.29 μmol, 1 eq) in DCM (1.5 mL), was added TFA (0.5 mL) at 0 °C, allowed to warm and further stirred at 20 °C for 2 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.415 min, [M+H] = 486.5) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1% TFA) - ACN]; 25 % - 55 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-12**, 84.2 mg, 140.16 μmol, 78.6 % yield) as a TFA salt, as a white solid. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.68 - 8.60 (m, 1H), 8.03 (s, 1H), 7.40 - 7.32 (m, 1H), 5.99 (br s, 1H), 3.53 - 3.41 (m, 1H), 2.89 (s, 3H), 2.51 - 2.44 (m, 2H), 2.13 (br d, *J* = 9.0 Hz, 4H), 1.61 (t, *J* = 6.3 Hz, 2H), 1.56 - 1.47 (m, 2H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 486.5, expected 487.4 [M+H].

EXAMPLE 12

N-[6-[1,5-Bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide A-13



To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]-dimethyl-silane (**INT-4**, 3.4 g, 6.51 mmol, 1 eq) in dioxane (40 mL) and H_2O (4 mL) was added *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 3.28 g, 6.18 mmol, 0.95 eq), K_2CO_3 (2.70 g, 19.52 mmol, 3 eq) and Pd(dppf)Cl_2 (475.98 mg, 650.51 μmol, 0.1 eq). The mixture was stirred at 100 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The organic

layers were combined, washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**98**, 4.2 g, 4.96 mmol, 76.3 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.00 (s, 1H), 8.68 (d, *J* = 8.8 Hz, 1H), 7.77 (s, 1H), 7.29 (s, 1H), 7.17 (s, 1H), 6.42 (d, *J* = 5.8 Hz, 1H), 5.97 (br d, *J* = 3.8 Hz, 1H), 5.95 - 5.92 (m, 4H), 3.91 - 3.86 (m, 4H), 3.69 - 3.63 (m, 3H), 2.82 (dd, *J* = 1.9, 18.1 Hz, 1H), 2.52 (br d, *J* = 1.1 Hz, 2H), 2.45 (br dd, *J* = 1.4, 18.1 Hz, 2H), 2.14 (br s, 3H), 1.64 - 1.58 (m, 4H), 1.11 (s, 9H), 0.99 - 0.97 (m, 2H), 0.94 (d, *J* = 2.4 Hz, 18H), 0.01 (s, 12H).

To a solution of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl) imidazole-2-carboxamide (**98**, 4.2 g, 4.96 mmol, 1 eq) in THF (50 mL) was added TBAF·$3H_2O$ (4.70 g, 14.89 mmol, 3 eq). The mixture was stirred at 25 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 2.676 min, [M+H] = 618.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (40 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 180 x 70 mm x 10 μm; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; 50 % - 80 % B gradient over 20.0 min) to afford *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**99**, 1.1 g, 1.78 mmol, 35.9 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.01 (s, 1H), 8.68 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.29 (s, 1H), 6.95 (s, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 5.98 - 5.91 (m, 4H), 4.05 - 3.87 (m, 4H), 3.72 - 3.61 (m, 2H), 2.89 (dd, *J* = 1.6, 18.0 Hz, 1H), 2.49 (br d, *J* = 1.5 Hz, 2H), 2.40 - 2.23 (m, 3H), 2.14 (br d, *J* = 2.5 Hz, 2H), 1.67 - 1.54 (m, 4H), 1.25 (s, 1H), 1.13 (s, 6H), 1.02 - 0.95 (m, 2H), 0.01 (s, 8H), MS (LC/MS) *m/z* observed 618.3, expected 618.3 [M+H].

To a solution of *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**99**, 300 mg, 485.6 μmol, 1 eq) in DCM (10 mL) was added pyridine (192.05 mg, 2.43 mmol, 195.97 μL, 5 eq) and trifluoromethylsulfonyl trifluoromethanesulfonate (411.01

mg, 1.46 mmol, 240.36 μL, 3 eq). The mixture was stirred at 25 °C for 2 hr. The reaction mixture was monitored by TLC (Pet. Et. / EtOAc = 3/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-1-yl]methyltrifluoromethanesulfonate (**100**, 400 mg, 453.55 μmol, 93.4 % yield) was obtained as a yellow solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

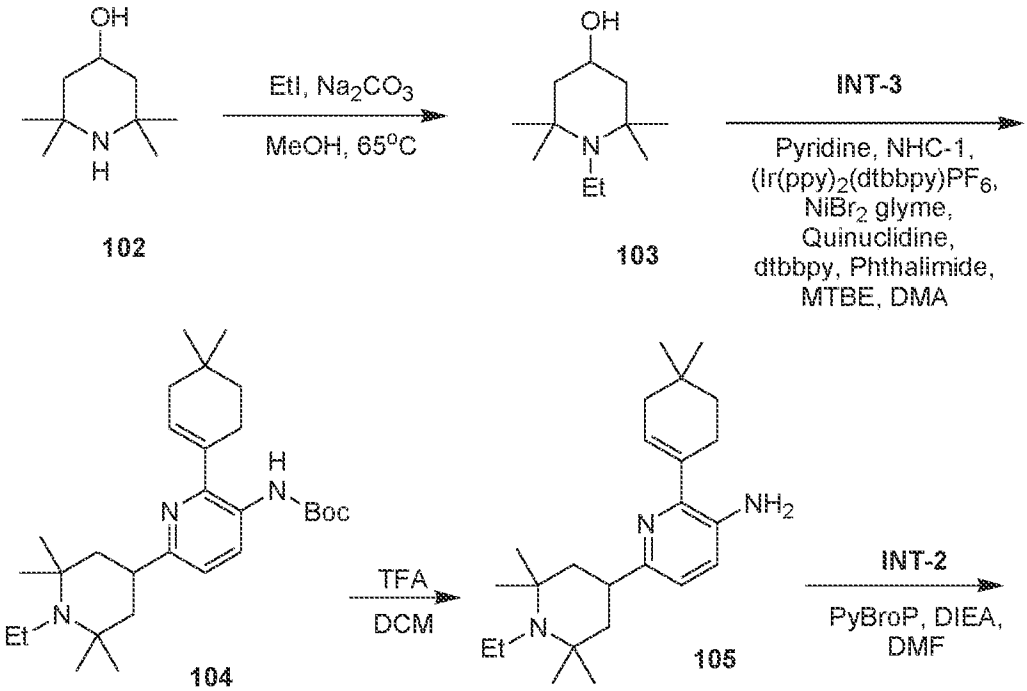
To a solution of [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-1-yl]methyl trifluoromethanesulfonate (**100**, 400 mg, 453.55 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.27 mL, 5 eq). The mixture was stirred at 40 °C for 4 hr. The reaction was monitored by LC/MS (Rt = 0.721 min, [M+H] = 622.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**101**, 210 mg, 337.73 μmol, 74.5 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.02 (s, 1H), 8.69 (d, J = 8.8 Hz, 1H), 7.77 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.02 (s, 1H), 6.46 (d, J = 5.8 Hz, 1H), 6.00 - 5.95 (m, 2H), 5.93 (s, 2H), 4.85 - 4.73 (m, 2H), 4.72 - 4.61 (m, 2H), 3.70 - 3.63 (m, 2H), 2.93 (dd, J = 1.7, 18.0 Hz, 1H), 2.53 - 2.40 (m, 3H), 2.15 (br d, J = 2.9 Hz, 2H), 1.63 (t, J = 6.3 Hz, 2H), 1.13 (s, 6H), 1.04 - 0.94 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 622.4, expected 622.3 [M+H].

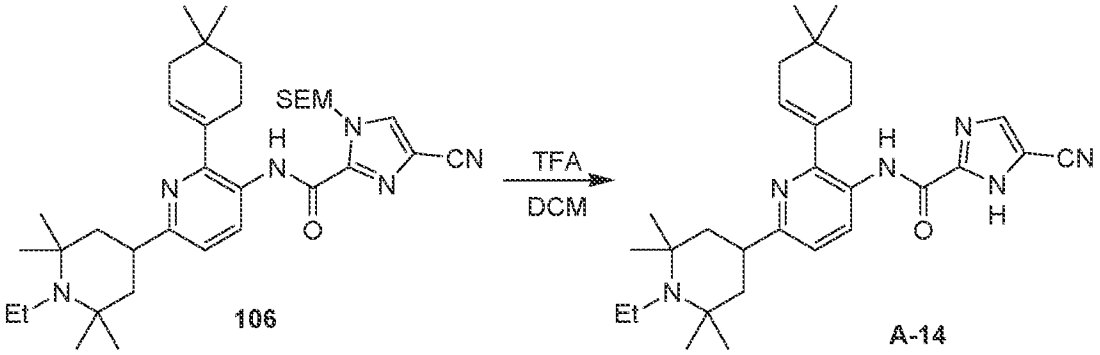
To a solution of *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**101**, 210 mg, 337.7 μmol, 1 eq) in DCM (5 mL) was added TFA (3 mL). The mixture was stirred at 25 °C for 1 hr. The reaction was monitored by LC/MS (R_t = 0.591 min,

[M+H] = 492.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase: [water (TFA) - ACN]; B%: 40 % - 75 % gradient, 8 min) to afford title compound, *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-13**, 105.9 mg, 215.45 μmol, 63.8 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.29 (br s, 1H), 10.01 (s, 1H), 8.34 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.04 (s, 1H), 6.50 (d, *J* = 5.6 Hz, 1H), 6.03 (dd, *J* = 1.2, 5.7 Hz, 1H), 5.90 (br s, 1H), 4.88 - 4.61 (m, 4H), 2.74 (dd, *J* = 1.6, 18.2 Hz, 1H), 2.41 (br s, 2H), 2.31 (br d, *J* = 17.8 Hz, 1H), 1.94 (br s, 2H), 1.49 (t, *J* = 6.4 Hz, 2H), 0.99 (s, 6H), MS (LC/MS) *m/z* observed 492.2, expected 492.2 [M+H].

EXAMPLE 13

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-14





To a solution of 2,2,6,6-tetramethylpiperidin-4-ol (**102**, 2.5 g, 15.90 mmol, 1 eq) in MeOH (25 mL) was added CH_3CH_2I (18.85 g, 120.82 mmol, 9.66 mL, 7.6 eq) and Na_2CO_3 (960.47 mg, 9.06 mmol, 0.57 eq) at 20 °C. The mixture was heated and stirred at 65 °C for 120 hr under an N_2 atmosphere. The reaction was monitored by ^{1}H NMR until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (40 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum, to provide a residue without further purification. 1-Ethyl-2,2,6,6-tetramethyl-piperidin-4-ol (**103**, 2 g, 6.48 mmol, 40.7 % yield, 60 % purity) was obtained as a white solid, that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 3.91 (tt, J = 4.1, 11.6 Hz, 1H), 2.59 (q, J = 6.6 Hz, 2H), 1.76 (dd, J = 4.1, 12.3 Hz, 2H), 1.34 (br t, J = 11.9 Hz, 2H), 1.15 (s, 6H), 1.08 (s, 6H), 1.06 - 1.02 (m, 3H), MS (LC/MS) *m/z* observed 186.2, expected 186.2 [M+H].

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 350 mg, 917.90 μmol, 1 eq) and 1-ethyl-2,2,6,6-tetramethyl-piperidin-4-ol (**103**, 510.27 mg, 2.75 mmol, 3 *eq*) in MTBE (5 mL), was added bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (12.58 mg, 13.77 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (14.16 mg, 45.89 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (18.48 mg, 68.84 μmol, 0.075 eq), NHC-1 (1.16 g, 2.94 mmol, 3.2 eq) pyridine, (232.34 mg, 2.94 mmol, 237.08 μL, 3.2 eq), quinuclidine (178.61 mg, 1.61 mmol, 1.75 eq) isoindoline-1,3-dione (30.39 mg, 206.53 μmol, 0.225 eq) and DMA (3 mL) at 25 °C. The mixture was further stirred at 25 °C for 16 hr under 34W blue LED lights. The reaction was monitored by LC/MS (R_t = 0.487 min, [M+H] = 470.4) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was quenched by NH_4Cl (aqueous, 8 mL) and extracted with DCM (6 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250 x 70 mm, 15 μm);mobile phase: [H_2O (0.1 % TFA) - ACN]; 30 % - 60 % B gradient over 20.0 min) to afford *tert*-butyl *N*-[2-

(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)-3-pyridyl]carbamate (**104**, 250 mg, 342.63 μmol, 187 6 % yield, 80 % purity) as a TFA salt, as a white solid. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.33 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 6.03 (td, *J* = 2.0, 3.6 Hz, 1H), 3.66 (tt, *J* = 3.4, 12.6 Hz, 1H), 3.41 (q, *J* = 7.4 Hz, 2H), 2.43 - 2.37 (m, 2H), 2.25 - 2.18 (m, 2H), 2.12 (br d, *J* = 3.5 Hz, 2H), 2.10 - 2.04 (m, 3H), 1.60 (br s, 1H), 1.55 (d, *J* = 2.6 Hz, 12H), 1.51 (s, 9H), 1.47 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 470.4, expected 470.4 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)-3-pyridyl]carbamate (**104**, 250 mg, 425.80 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 1 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.326 min, [M+H] = 370.4) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction was adjusted to pH=8 ~ 9 with $NaHCO_3$ (aqueous) and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification. 2-(4,4-Dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)pyridin-3-amine (**105**, 150 mg) was obtained as a crude yellow oil and used further as is. MS (LC/MS) *m/z* observed 370.4, expected 370.3 [M+H].

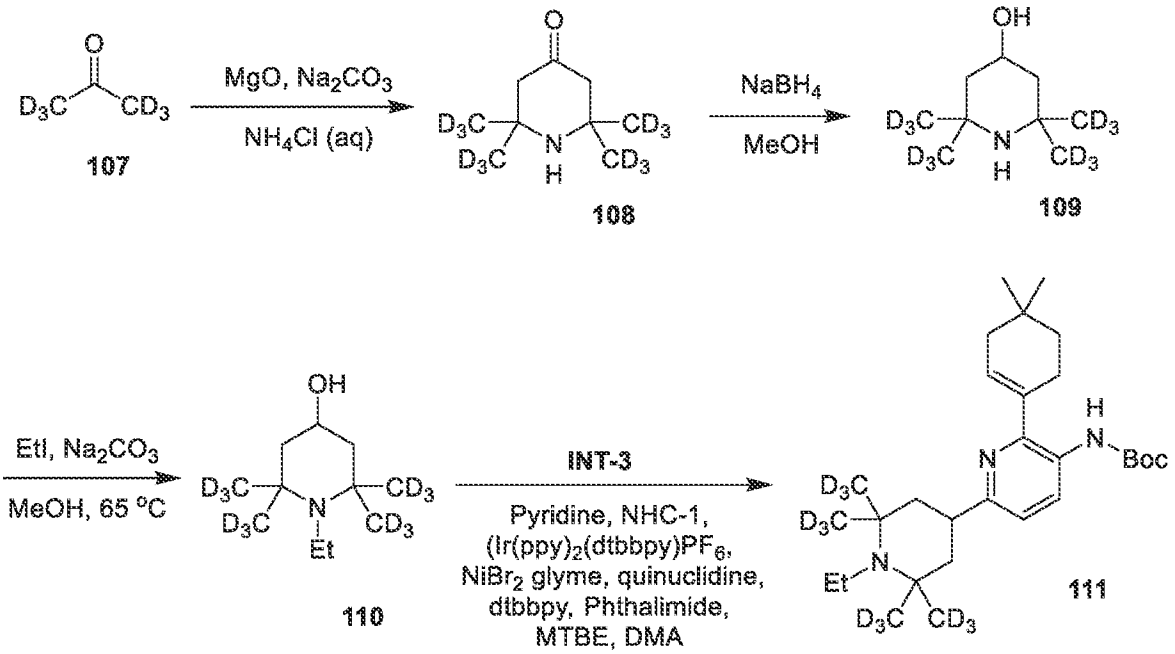
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)pyridin-3-amine (**105**, 150 mg, 324.69 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 198.35 mg, 649.38 μmol, 2 eq) in DMF (2 mL) was added DIEA (125.89 mg, 974.07 μmol, 169.66 μL, 3 eq), and PyBroP (227.04 mg, 487.03 μmol, 1.5 eq) at 20 °C. The mixture was further stirred at 20 °C for 16 hr under an N_2 atmosphere. LC/MS (R_t = 0.941min, [M+H] = 619.5) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**106**, 150 mg, 204.65 μmol, 63.0 % yield,) as a TFA salt, as a white solid, which was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.65 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 5.99 (br s, 1H), 5.92 (s, 2H), 3.67 (t, *J* = 7.9 Hz, 2H), 3.42 (br d, *J* = 7.4 Hz, 2H), 2.47 (br s, 2H), 2.22 - 2.16 (m, 2H), 2.15 - 2.04 (m, 5H), 1.63 - 1.60 (m, 2H), 1.57 (s, 6H), 1.54 (s, 6H), 1.46 (br t, *J* = 7.4 Hz, 3H),

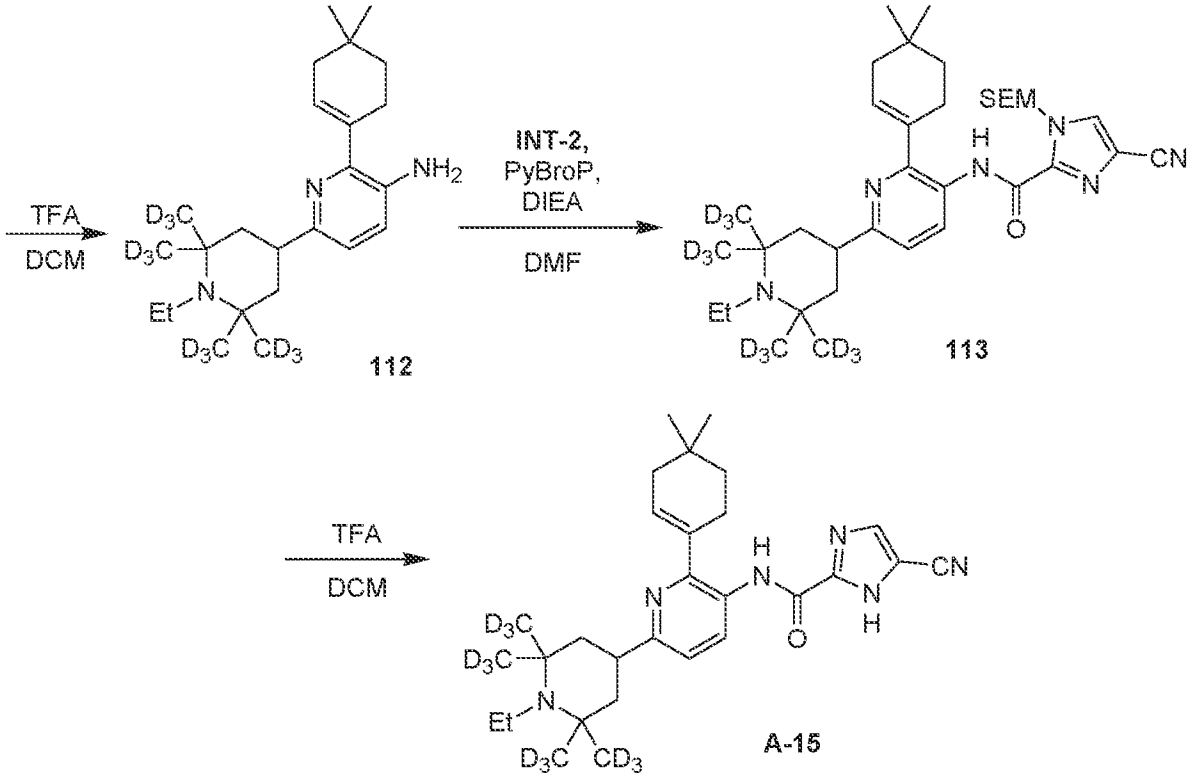
1.11 (s, 6H), 0.94 (t, J = 8.0 Hz, 2H), -0.02 (s, 9H), MS (LC/MS) m/z observed 619.5, expected 619.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**106**, 150 mg, 204.65 μmol, 1 eq) as the TFA salt, in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 1 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.422 min, [M+H] = 489.4) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 3 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(1-ethyl-2,2,6,6-tetramethyl-4-piperidyl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-14**, 81.6 mg, 133.70 μmol, 65.3 % yield, 98.8 % purity) as a TFA salt, as a white solid. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.65 (br d, J = 8.5 Hz, 1H), 8.03 (s, 1H), 7.37 (br d, J = 8.5 Hz, 1H), 6.00 (br s, 1H), 3.51 (br t, J = 12.7 Hz, 1H), 3.42 (q, J = 7.3 Hz, 2H), 2.47 (br d, J = 1.8 Hz, 2H), 2.25 - 2.16 (m, 2H), 2.13 - 2.03 (m, 4H), 1.61 (t, J = 6.4 Hz, 2H), 1.57 (s, 6H), 1.54 (s, 6H), 1.46 (t, J = 7.4 Hz, 3H), 1.10 (s, 6H), MS (LC/MS) m/z observed 489.4, expected 489.3 [M+H].

EXAMPLE 14

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-15





To a solution of MgO (1.57 g, 38.99 mmol, 438.93 μL, 0.5 eq), Na_2CO_3 (1.65 g, 15.60 mmol, 0.2 eq) and NH_4Cl (1.67 g, 31.19 mmol, 0.4 eq) was added 1,1,1,3,3,3-hexadeuteriopropan-2-one (**107**, 5 g, 77.98 mmol, 5.73 mL, 1 eq) at 20 °C. The mixture was warmed and further stirred at 50 °C for 48 hr under an N_2 atmosphere. The reaction was monitored by TLC (EtOAc/MeOH = 5/1) until it showed a single new product spot. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 0/1) to afford 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**108**, 1.5 g, 8.97 mmol, 3.8 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 2.30 (s, 4H).

To a solution of 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**108**, 1.5 g, 8.97 mmol, 1 eq) in MeOH (15 mL) was added $NaBH_4$ (678.32 mg, 17.93 mmol, 2 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by TLC (EtOAc/MeOH = 5/1)until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (aqueous, 20 mL) and extracted with DCM (15 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification to afford 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (**109**, 1.2 g, 7.09 mmol, 79.1 % yield) as a yellow solid, used further as is. ^{1} MS (LC/MS) *m/z* observed 170.2, expected 170.2 [M+H].

To a solution of 2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (**109**, 600 mg, 3.54 mmol, 1 eq) and in MeOH (5 mL) and CH_3CH_2I (3 mL) was added Na_2CO_3 (214.07 mg, 2.02

mmol, 0.57 eq) at 20 °C. The mixture was then heated to 65 °C and stirred a further 120 hr under an N_2 atmosphere. The reaction was monitored by ^{1}H NMR until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum, without further purification, to afford 1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (**110**, 700 mg, 2.48 mmol, 70.1 % yield, 70 % purity) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 3.95 (br s, 1H), 2.72 (br s, 2H), 1.82 (br d, *J* = 11.1 Hz, 2H), 1.40 (br s, 2H), 1.11 (br s, 3H), MS (LC/MS) *m/z* observed 198.3, expected 198.3 [M+H].

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**110**, 350 mg, 917.90 μmol, 1 eq) and 1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (543.52 mg, 2.75 mmol, 3 eq) in MTBE (2 mL), was added bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (12.58 mg, 13.77 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (14.16 mg, 45.89 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (18.48 mg, 68.84 μmol, 0.075 eq), NHC-1 (1.16 g, 2.94 mmol, 3.2 eq), pyridine (232.34 mg, 2.94 mmol, 237.08 μL, 3.2 eq), quinuclidine (178.61 mg, 1.61 mmol, 1.75 eq), isoindoline-1,3-dione (30.39 mg, 206.53 μmol, 0.225 eq) and DMA (1 mL) at 25 °C. The mixture was further stirred at 25 °C for 16 hr under 34W blue LED lights. The reaction was monitored by LC/MS (R_t = 0.809 min, [M+H] = 482.5) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was diluted with H_2O (5 mL), extracted with EtOAc (4 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250 x 70 mm, 15 μm); mobile phase: [H_2O (0.1 %TFA) - ACN]; 30 % - 60 % B gradient over 20.0 min) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**111**, 150 mg, 249.08 μmol, 27.1 % yield, 80 % purity) as a white solid that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.30 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 6.02 (br s, 1H), 3.69 - 3.58 (m, 1H), 3.42 (q, *J* = 7.4 Hz, 2H), 2.42 (br d, *J* = 1.8 Hz, 3H), 2.25 - 2.17 (m, 2H), 2.13 (br d, *J* = 3.5 Hz, 2H), 2.08 (br d, *J* = 3.3 Hz, 3H), 1.52 (s, 9H), 1.48 (t, *J* = 7.4 Hz, 3H), 1.06 (s, 6H), MS (LC/MS) *m/z* observed 482.5, expected 482.5 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**111**, 150 mg, 249.08 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL) at 0 °C, the mixture was allowed to warm and further stirred at 20 °C for 1 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t =

0.313 min, [M+H] = 381.4) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction was adjusted to pH = 8 ~ 9 with $NaHCO_3$ (aqueous) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue without further purification to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**112**, 110 mg, TFA salt) as a crude yellow oil, that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 7.10 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 5.85 (br d, *J* = 1.4 Hz, 1H), 3.28 - 3.23 (m, 1H), 2.41 - 2.32 (m, 3H), 2.03 (br d, *J* = 3.5 Hz, 2H), 1.96 - 1.87 (m, 2H), 1.56 (t, *J* = 6.4 Hz, 3H), 1.40 (br d, *J* = 7.0 Hz, 5H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 381.4, expected 382.4 [M+H].

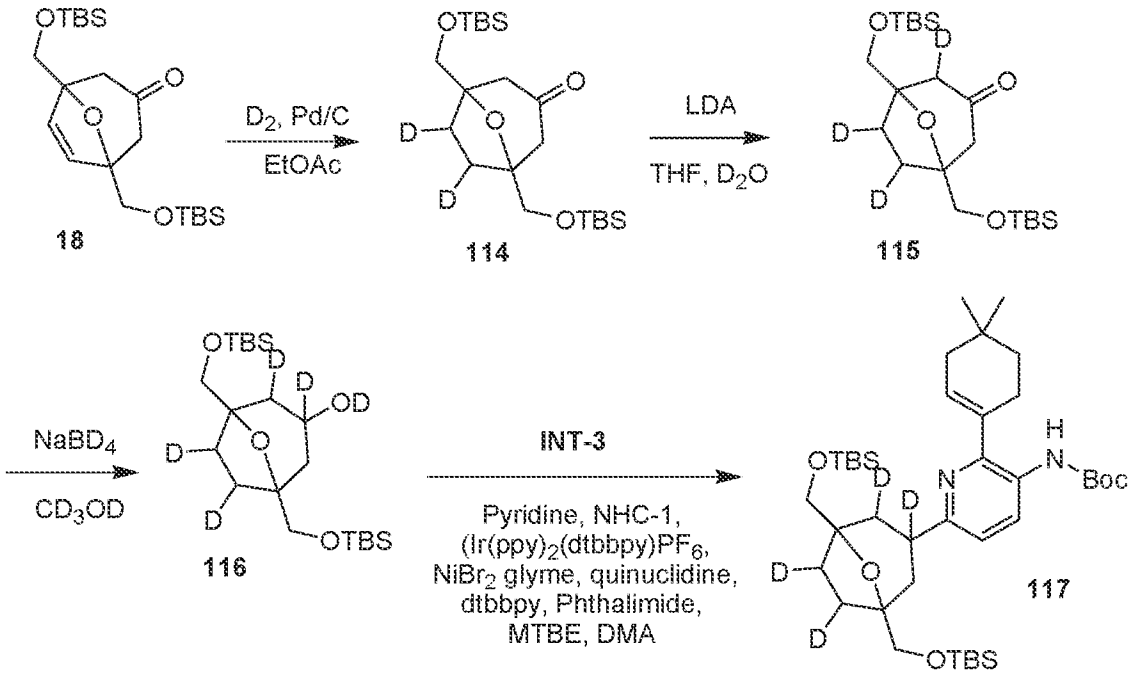
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**112**, 110.00 mg, 230.57 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 140.85 mg, 461.14 μmol, 2 eq) in DMF (2 mL) was added DIEA (89.40 mg, 691.72 μmol, 120.48 μL, 3 eq) and PyBroP (161.23 mg, 345.86 μmol, 1.5 eq) at 0 °C. The mixture was stirred at 20 °C for 16 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.937 min, [M+H] = 631.6) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 3 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**113**, 110 mg, 147.65 μmol, 64.0 % yield, TFA salt) as a white solid that was used further as is. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.65 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 7.35 (br d, *J* = 8.4 Hz, 1H), 5.98 (br s, 1H), 5.91 (s, 2H), 3.67 (t, *J* = 7.9 Hz, 2H), 3.48 (br d, *J* = 3.5 Hz, 1H), 3.41 (q, *J* = 7.4 Hz, 2H), 2.46 (br d, *J* = 1.5 Hz, 2H), 2.23 - 2.14 (m, 2H), 2.14 - 2.02 (m, 4H), 1.61 (t, *J* = 6.3 Hz, 2H), 1.56 - 1.49 (m, 2H), 1.45 (t, *J* = 7.4 Hz, 3H), 1.11 (s, 6H), 0.94 (t, *J* = 8.0 Hz, 2H), -0.02 (s, 9H), MS (LC/MS) *m/z* observed 631.6, expected 631.5 [M+H].

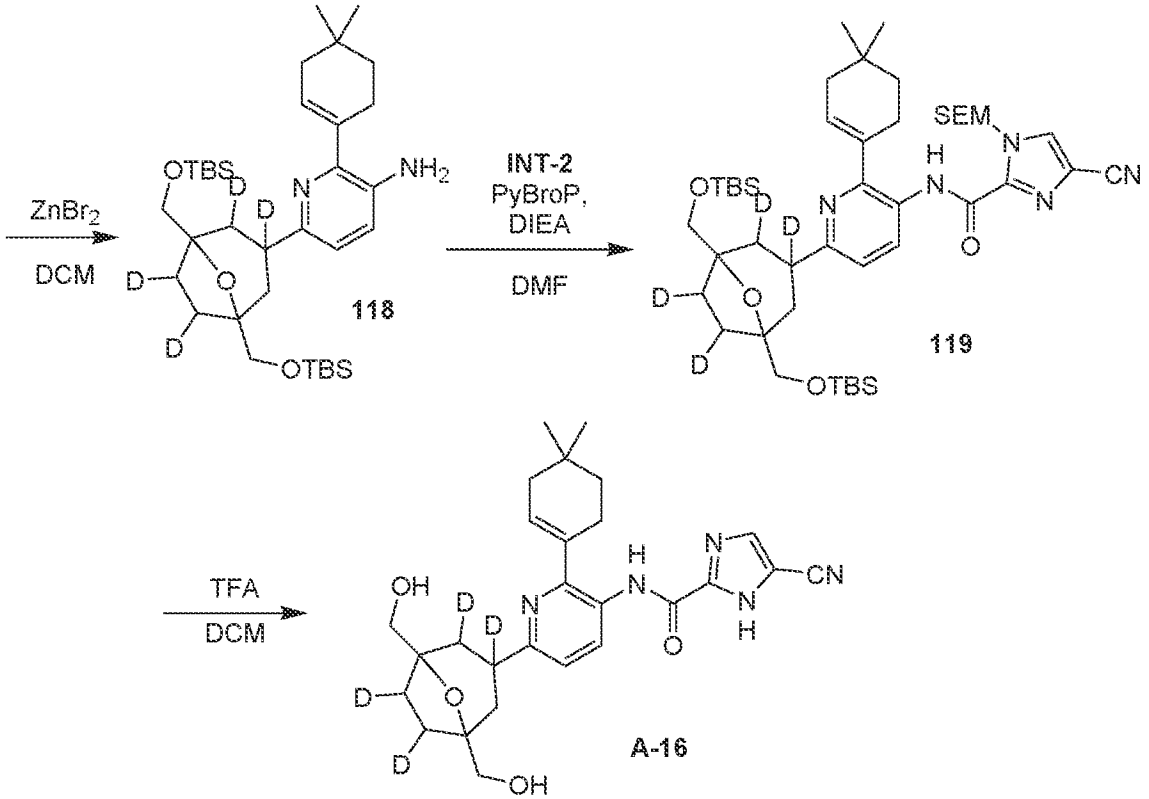
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide TFA salt (**113**, 120 mg, 161.07 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was stirred at 20 °C for 1 hr under an N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.428 min, [M+H] = 501.5) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction was

concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 3 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 30 % - 60 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-ethyl-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-15**, 62.8 mg, 100.0 μmol, 62.1 % yield, 97.9 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.61 (d, *J* = 8.4 Hz, 1H), 8.02 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.00 - 5.95 (m, 1H), 3.53 - 3.44 (m, 1H), 3.41 (q, *J* = 7.5 Hz, 2H), 2.47 (br d, *J* = 1.9 Hz, 2H), 2.23 - 2.14 (m, 2H), 2.13 - 2.02 (m, 4H), 1.60 (t, *J* = 6.4 Hz, 2H), 1.45 (t, *J* = 7.4 Hz, 3H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 501.5, expected 501.4 [M+H].

EXAMPLE 15

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1*H*-pyrrole-2-carboxamide A-16





To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**, 2 g, 4.85 mmol, 1 eq) in EtOAc (30 mL) was added Pd/C (1.03 g, 969.21 μmol, 10 % purity, 0.2 eq) at 25 °C. The mixture was stirred at 25 °C for a further 2 hr under D_2 (15 Psi). The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]octan-3-one (**114**, 1.9 g, 4.56 mmol, 94.1 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 3.75 - 3.60 (m, 4H), 2.62 (d, *J* = 15.6 Hz, 2H), 2.32 (d, *J* = 15.5 Hz, 2H), 1.82 - 1.72 (m, 1H), 1.70 (s, 1H), 0.90 (s, 17H), 0.07 (s, 11H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]octan-3-one (**114**, 1.9 g, 4.56 mmol, 1 eq) in THF (30 mL) was added LDA (2 M, 2.74 mL, 1.2 eq) at -78 °C. After 1 hr, D_2O (4.57 g, 227.96 mmol, 50 eq) was added. The mixture was allowed to warm and further stirred at 25 °C for 1 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by D_2O (2 mL) and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient

at a flow rate of 80 mL/min) to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,6,7-trideuterio-8-oxabicyclo[3.2.1]octan-3-one (**115**, 1.6 g, 3.83 mmol, 84. % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 3.74 - 3.60 (m, 4H), 2.62 (d, *J* = 15.5 Hz, 1H), 2.37 - 2.27 (m, 2H), 1.81 - 1.69 (m, 2H), 0.90 (s, 18H), 0.08 (s, 11H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,6,7-trideuterio-8-oxabicyclo[3.2.1]octan-3-one (**115**, 1.6 g, 3.83 mmol, 1 eq) in THF (15 mL) and CD_3OD (1 mL) was added sodium tetradeuterioboranide (173.88 mg, 4.60 mmol, 1.2 eq) at 0 °C. The mixture was allowed to warm and further stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by H_2O (20 mL) and extracted with EtOAc(20 mL x 2). The organic layers were combined, washed with brine (10 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-3-deuteriooxy-8-oxabicyclo[3.2.1]octan-1-yl]methoxy]-dimethyl-silane (**116**, 1.6 g, 3.79 mmol, 99.0 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 3.60 (q, *J* = 10.3 Hz, 4H), 2.06 - 1.98 (m, 2H), 1.70 - 1.67 (m, 1H), 1.65 (s, 1H), 1.32 (s, 1H), 0.90 (s, 18H), 0.06 (d, *J* = 1.0 Hz, 12H).

To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-3-deuteriooxy-8-oxabicyclo[3.2.1]octan-1-yl]methoxy]-dimethyl-silane (**116**, 707.92 mg, 1.68 mmol, 1.6 eq) and NHC-1 (663.39 mg, 1.68 mmol, 1.6 eq) in MTBE (8 mL) was added pyridine (132.76 mg, 1.68 mmol, 135.47 μL, 1.6 eq) in MTBE (1 mL) dropwise over 5 mins at 25 °C. After a further 10 min, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 400 mg, 1.05 mmol, 1 eq), *bis*[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (14.38 mg, 15.74 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (16.19 mg, 52.45 μmol, 0.05 eq), quinuclidine (204.12 mg, 1.84 mmol, 1.75 *eq*), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (21.12 mg, 78.68 μmol, 0.075 eq) and isoindoline-1,3-dione (34.73 mg, 236.03 μmol, 0.225 eq) in DMA (8 mL) under N_2. The mixture was stirred at 25 °C for 3 hr under blue LED lights. The reaction was monitored by LC/MS (R_t =3.054 min, [M+H] =705.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

prep-HPLC column: column: Welch Xltimate C4 100 x 30 x 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; gradient: 70 % - 100 % B over 10.0 min) to afford *tert*-butyl *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**117**, 300 mg, 425.43 μmol, 20.28% yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 8.24 (br d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.88 (s, 1H), 5.81 (br s, 1H), 3.68 - 3.58 (m, 4H), 2.40 (br d, *J* = 1.9 Hz, 2H), 2.06 - 2.02 (m, 2H), 1.89 - 1.81 (m, 4H), 1.69 (br d, *J* = 13.1 Hz, 1H), 1.58 (br t, *J* = 6.4 Hz, 2H), 1.50 (s, 9H), 1.04 (s, 6H), 0.88 (s, 18H), 0.04 (s, 12H), MS (LC/MS) *m/z* observed 705.5, expected 705.5 [M+H].

To a solution of *tert*-butyl *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**117**, 300 mg, 425.43 μmol, 1 eq) in DCM (15 mL) was added $ZnBr_2$ (958.07 mg, 4.25 mmol, 212.90 μL, 10 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 2.938 min, [M+H] = 605.5) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue without further purification. 6-[1,5-Bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**118**, 250 mg, 413.19 μmol, 97.1 % yield) was obtained as a yellow solid that was used further as is. MS (LC/MS) *m/z* observed 605.5, expected 605.5 [M+H].

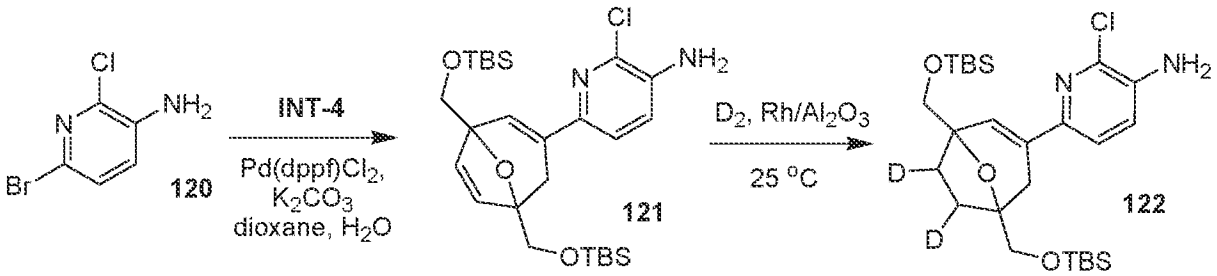
To a solution of 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**118**, 250 mg, 413.19 μmol, 1 eq) in DMF (10 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 252.42 mg, 826.38 μmol, 2 eq) , DIEA (160.21 mg, 1.24 mmol, 215.91 μL, 3 eq) and PyBroP (288.93 mg, 619.79 μmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction was monitored by LC/MS (R_t = 4.359 min, [M+H] =854.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**119**, 240 mg, 280.9 μmol, 68.0 % yield) as a yellow solid that was used further

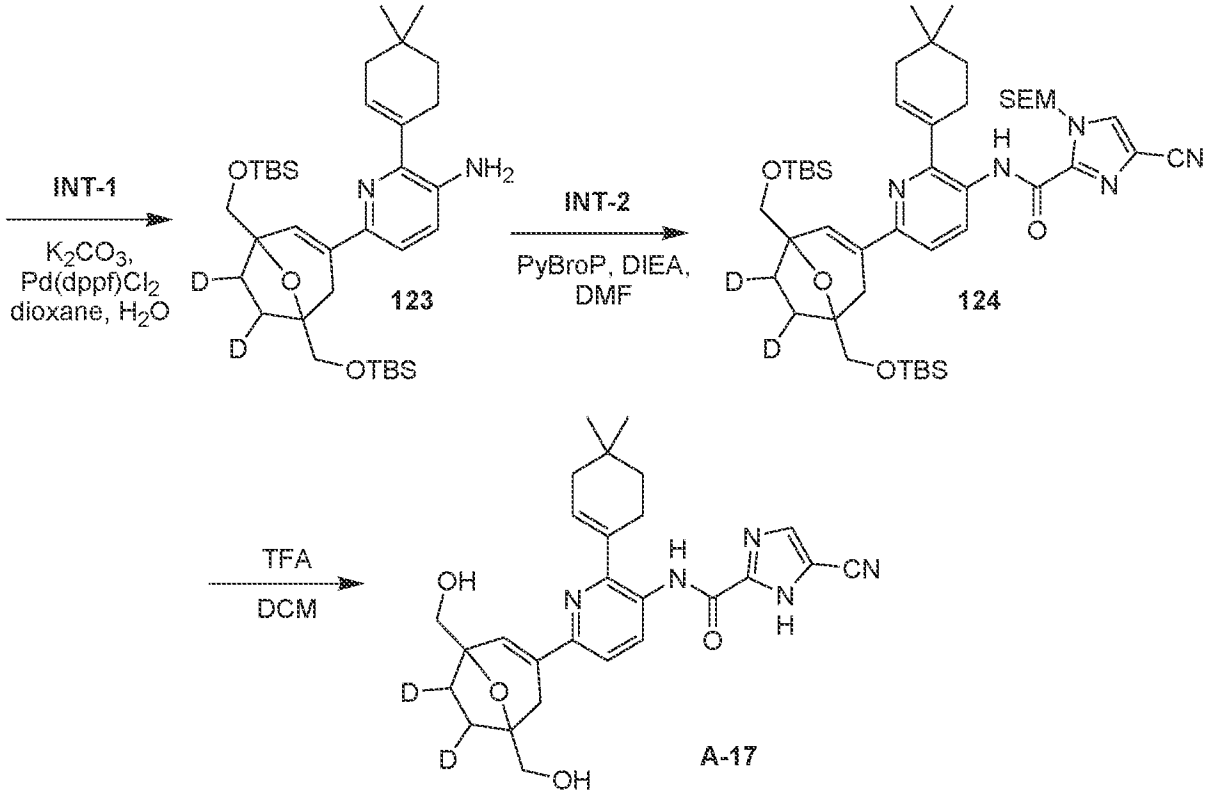
as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.90 (s, 1H), 8.63 (d, *J* = 8.5 Hz, 1H), 7.77 (s, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 5.94 (s, 3H), 3.72 - 3.56 (m, 7H), 2.49 (br d, *J* = 1.6 Hz, 2H), 2.14 (br d, *J* = 3.0 Hz, 2H), 1.91 - 1.85 (m, 4H), 1.79 (br dd, *J* = 6.4, 10.2 Hz, 1H), 1.73 (br d, *J* = 13.0 Hz, 1H), 1.62 (t, *J* = 6.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 1H), 1.12 (s, 6H), 1.00 - 0.96 (m, 2H), 0.89 (s, 18H), 0.05 (s, 12H), 0.03 - -0.01 (m, 9H), MS (LC/MS) *m/z* observed 854.6, expected 854.5 [M+H].

To a solution of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)pyrrole-2-carboxamide (**119**, 140 mg, 164.05 μmol, 1 eq) in DCM (3 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 0.375 min, [M+H] = 496.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 15 % - 50 % B gradient over 7.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1*H*-pyrrole-2-carboxamide (**A-16**, 37.9 mg, 76.62 μmol, 46.7 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.29 (br s, 1H), 10.10 (s, 1H), 8.33 (s, 1H), 8.21 (br d, *J* = 8.4 Hz, 1H), 7.36 (br d, *J* = 8.0 Hz, 1H), 5.92 (br s, 1H), 3.45 - 3.36 (m, 4H), 2.39 (br s, 2H), 1.93 (br s, 2H), 1.83 - 1.75 (m, 2H), 1.68 (d, *J* = 7.6 Hz, 3H), 1.48 (t, *J* = 6.4 Hz, 2H), 0.97 (s, 6H), MS (LC/MS) *m/z* observed 496.4, expected 496.3 [M+H].

EXAMPLE 16

5-Cyano-*N*-[6-[6,7-dideuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-17





To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]-dimethyl-silane (**INT-4**, 5 g, 9.57 mmol, 1 eq) in dioxane (50 mL) and H_2O (5 mL) was added 6-bromo-2-chloro-pyridin-3-amine (**120**, 1.98 g, 9.57 mmol, 1 eq), K_2CO_3 (3.97 g, 28.70 mmol, 3 eq) and Pd(dppf)Cl_2 (699.97 mg, 956.63 μmol, 0.1 eq). The mixture was heated and stirred at 100 °C for 12 hr under N_2. The reaction was monitored by LC/MS (R_t = 3.093 min, [M+H] = 523.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The organic layers were combined, washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 x 50 mm 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 70 % - 98 % B gradient over 8.0 min) to afford 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-chloro-pyridin-3-amine (**121**, 1.6 g, 3.06 mmol, 32.0 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.15 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.91 (s, 1H), 6.40 (d, *J* = 5.8 Hz, 1H), 5.90 (d, *J* = 5.8 Hz, 1H), 4.04 (s, 2H), 3.94 - 3.82 (m, 4H), 2.73 (dd, *J* = 1.6, 18.0 Hz, 1H), 2.34 (d, *J* = 18.0 Hz, 1H), 0.93 (d, *J* = 2.3 Hz, 18H), 0.13 - 0.08 (m, 12H), MS (LC/MS) *m/z* observed 523.3, expected 523.3 [M+H].

To a solution of 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-chloro-pyridin-3-amine (**121**, 500 mg, 955.56 μmol, 1

eq) in CD_3OD (5 mL) was added Rh/Al_2O_3 (98.34 mg, 955.56 μmol, 1 eq) at 25 °C. The mixture was stirred at 25 °C for 2 hr under D_2. The reaction was monitored by LC/MS (R_t = 3.383 min, [M+H] =527.3) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue without further purification, to afford 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-chloropyridin-3-amine (**122**, 400 mg, 758.61 μmol, 79.4 % yield) as a yellow solid, that was used further as is. MS (LC/MS) *m/z* observed 527.3, expected 527.3 [M+H].

To a solution of 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-chloro-pyridin-3-amine (**122**, 400 mg, 758.61 μmol, 1 eq) in dioxane (5 mL) and H_2O (0.5 mL) was added 2-(4,4-dimethylcyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**INT-1**, 358.30 mg, 1.52 mmol, 2 eq), K_2CO_3 (314.53 mg, 2.28 mmol, 3 eq) and $Pd(dppf)Cl_2$ (55.51 mg, 75.86 μmol, 0.1 eq). The mixture was stirred at 100 °C for 12 hr under N_2. The reaction was monitored by LC/MS (R_t =1.082 min, [M+H] = 601.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, Eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**123**, 400 mg, 665.54 μmol, 87.7 % yield) as a yellow solid, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.06 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 6.04 - 5.98 (m, 1H), 3.88 (br s, 2H), 3.81 - 3.73 (m, 4H), 2.77 - 2.65 (m, 2H), 2.53 (br d, *J* = 1.6 Hz, 2H), 2.46 (d, *J* = 17.8 Hz, 1H), 1.73 (d, *J* = 9.1 Hz, 1H), 1.59 - 1.51 (m, 4H), 1.02 (s, 6H), 0.93 (s, 18H), 0.10 (s, 12H), MS (LC/MS) *m/z* observed 601.5, expected 601.4 [M+H].

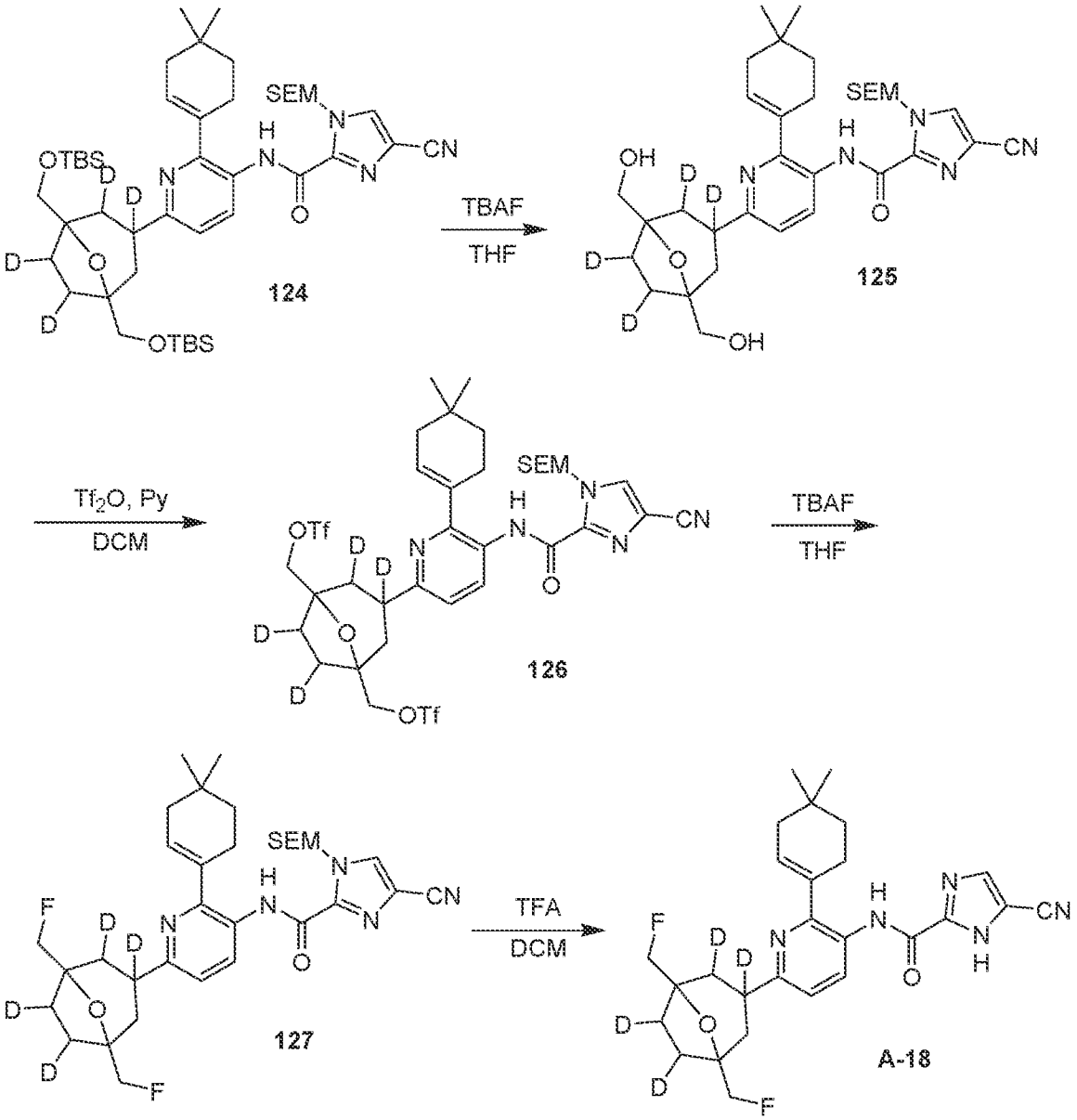
To a solution of 6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**123**, 400 mg, 665.54 μmol, 1 eq) in DMF (10 mL) was added potassium 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylate (**INT-2**, 406.57 mg, 1.33 mmol, 2 eq), DIEA (258.05 mg, 2.00 mmol, 347.77 μL, 3 eq) and PyBroP (465.39 mg, 998.31 μmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h. The reaction was monitored by LC/MS (R_t = 0.802 min, [M+H] = 850.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and

concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®;12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc at a flow rate of 60 mL/min) to afford *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**124**, 260 mg, 305.75 μmol, 45.9 % yield) as a yellow solid, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.02 (s, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.28 (s, 1H), 6.99 (s, 1H), 5.99 (br s, 1H), 5.96 - 5.92 (m, 2H), 3.83 (d, *J* = 10.4 Hz, 2H), 3.78 (s, 2H), 3.70 - 3.64 (m, 2H), 2.82 - 2.74 (m, 1H), 2.54 (br s, 2H), 2.47 (br d, *J* = 17.0 Hz, 1H), 2.15 (br d, *J* = 2.5 Hz, 2H), 2.07 (d, *J* = 9.3 Hz, 1H), 1.74 (d, *J* = 9.3 Hz, 1H), 1.61 (br t, *J* = 6.3 Hz, 2H), 1.12 (s, 6H), 0.99 (br d, *J* = 8.4 Hz, 2H), 0.93 (s, 18H), 0.12 - 0.09 (m, 12H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 850.5, expected 850.5 [M+H].

To a solution of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-6,7-dideuterio-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**124**, 260 mg, 305.75 μmol, 1 eq) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 2.202 min, [M+H] = 429.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 25 % - 60 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[6-[6,7-dideuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-17**, 51.5 mg, 104.76 μmol, 34.3 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.29 (br s, 1H), 10.02 (s, 1H), 8.33 (s, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 7.45 - 7.38 (m, 1H), 6.93 (s, 1H), 5.90 (br s, 1H), 3.65 - 3.48 (m, 4H), 2.70 (br d, *J* = 17.9 Hz, 1H), 2.43 (br s, 2H), 2.34 (br d, *J* = 16.6 Hz, 1H), 1.94 (br s, 2H), 1.88 (d, *J* = 9.4 Hz, 1H), 1.61 (d, *J* = 9.3 Hz, 1H), 1.50 (br t, *J* = 6.2 Hz, 2H), 0.99 (s, 6H), MS (LC/MS) *m/z* observed 491.6, expected 491.6 [M+H].

EXAMPLE 17

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-18



To a solution of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**124**, 400 mg, 468.17 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 1.17 mL, 2.5 eq). The mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 2.615 min, [M+H] = 626.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20mL) and extracted with EtOAc (20mL x 2). The organic layers were combined, washed with brine (20mL), dried over Na_2SO_4,filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column

Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 30 % - 80 % B gradient over 8.0 min) to afford 4-cyano-N-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**125**, 200 mg, 319.56 μmol, 68.3 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.82 (s, 1H), 9.19 (d, *J* = 8.9 Hz, 1H), 7.82 (s, 1H), 7.57 (d, *J* = 8.9 Hz, 1H), 6.18 (br s, 1H), 5.90 (s, 2H), 3.72 - 3.61 (m, 6H), 2.44 (br d, *J* = 1.4 Hz, 2H), 2.17 (br d, *J* = 3.0 Hz, 2H), 1.92 - 1.87 (m, 4H), 1.85 (s, 1H), 1.64 (t, *J* = 6.2 Hz, 2H), 1.13 (s, 6H), 1.04 - 0.95 (m, 2H), 0.05 - -0.02 (m, 9H), **MS (LC/MS)** *m/z* observed 626.4, expected 626.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**125**, 200 mg, 319.56 μmol, 1 eq) in DCM (5 mL) was added pyridine (126.38 mg, 1.60 mmol, 128.96 μL, 5 eq) and Tf_2O (270.48 mg, 958.67 μmol, 158.17 μL, 3 eq). The mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t =1.111 min, [M+H] =890.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 40 mL/min) to afford [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,4,6,7-tetradeuterio-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyltrifluoromethane-sulfonate (**126**, 200 mg, 224.72 μmol, 70.3 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.93 (s, 1H), 8.79 - 8.58 (m, 1H), 7.78 (s, 1H), 7.10 (br d, *J* = 8.6 Hz, 1H), 6.04 - 5.85 (m, 3H), 4.60 - 4.51 (m, 2H), 4.50 - 4.43 (m, 1H), 4.35 - 4.28 (m, 1H), 3.70 - 3.64 (m, 2H), 2.47 (br s, 2H), 2.15 (br s, 2H), 2.04 - 1.95 (m, 2H), 1.94 - 1.87 (m, 1H), 1.86 - 1.80 (m, 2H), 1.64 (br t, *J* = 6.2 Hz, 2H), 1.13 (s, 6H), 1.04 - 0.94 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 890.3, expected 890.3 [M+H].

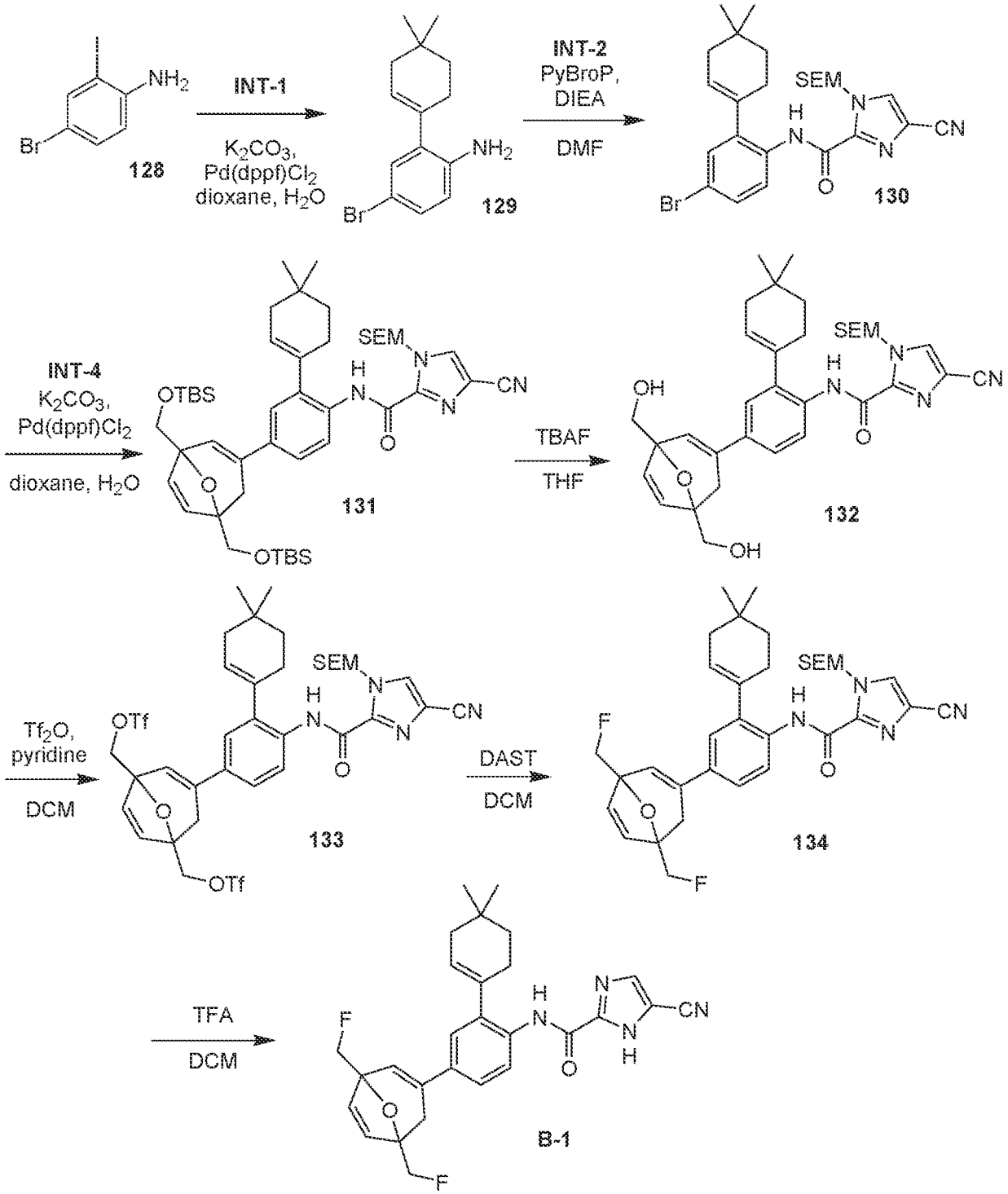
To a solution of [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,4,6,7-tetradeuterio-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyl trifluoromethanesulfonate (**126**, 200 mg, 224.72 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 1.12 mL, 5 eq). The mixture was stirred at 40 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 1.046 min, [M+H] = 630.5) until it showed that the starting material had been

completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 40 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**127**, 100 mg, 158.77 μmol, 70.7 % yield) as a yellow solid that was used further as is. MS (LC/MS) *m/z* observed 630.5, expected 630.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**127**, 100 mg, 158.77 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 0.505 min, [M+H] = 500.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA)- ACN]; 35 % - 60 % B gradient over 8.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2,3,6,7-tetradeuterio-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-18**, 32.5 mg, 65.05 μmol, 41.0 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.28 (br s, 1H), 10.06 (s, 1H), 8.33 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 5.89 (br s, 1H), 4.53 - 4.42 (m, 2H), 4.41 - 4.29 (m, 2H), 2.40 (br s, 2H), 1.91 (br d, *J* = 9.2 Hz, 4H), 1.82 - 1.75 (m, 1H), 1.72 - 1.66 (m, 2H), 1.48 (br t, *J* = 6.4 Hz, 2H), 0.97 (s, 6H), MS (LC/MS) *m/z* observed 500.4, expected 500.3 [M+H].

EXAMPLE 18

***N*-[4-[1,5-Bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide B-1**



To a solution of 4-bromo-2-iodo-aniline (**128**, 20 g, 67.13 mmol, 1 eq) and 2-(4,4-dimethylcyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**INT-1**, 23.78 g, 100.70 mmol, 1.5 eq) in toluene (200 mL) and EtOH (100 mL) was added Na_2CO_3 (2 M, 268.53 mL, 8 eq) and $Pd(PPh_3)_4$ (3.88 g, 3.36 mmol, 0.05 eq). The mixture was heated and stirred at 80 °C for 12 h under N_2. The reaction was monitored by TLC (Pet. Et. : EtOAc = 1:1) until it showed that

the reaction had completed. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Waters Xbridge BEH C18 250 x 70 mm x 10 μm; mobile phase: [water (NH_4HCO_3) - ACN]; B%: 60 % - 90 % gradient, 18 min) to afford to give 4-bromo-2-(4,4-dimethylcyclohexen-1-yl)aniline (**129**, 10 g, 35.69 mmol, 53.2 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of 4-bromo-2-(4,4-dimethylcyclohexen-1-yl)aniline (**129**, 3 g, 10.71 mmol, 1 eq) in DMF (15 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 5.89 g, 19.27 mmol, 1.8 eq), PyBroP (7.49 g, 16.06 mmol, 1.5 eq) and DIEA (4.15 g, 32.12 mmol, 5.59 mL, 3 eq). The mixture was stirred at 25 °C for 12 h. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The organic layers were combined, washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 50 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 3.7 g, 6.99 mmol, 65.3 % yield) as a yellow oil, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.73 (s, 1H), 8.30 (d, J = 8.9 Hz, 1H), 7.77 (s, 1H), 7.40 (dd, J = 2.4, 8.8 Hz, 1H), 7.32 (d, J = 2.3 Hz, 1H), 5.94 (s, 2H), 5.79 (td, J = 1.9, 3.6 Hz, 1H), 3.70 - 3.62 (m, 2H), 2.30 - 2.25 (m, 2H), 2.14 - 2.08 (m, 2H), 1.59 (t, J = 6.3 Hz, 2H), 1.11 (s, 6H), 0.98 (s, 2H), 0.03 - 0.00 (m, 9H).

To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]-dimethyl-silane (**INT-4**, 2.96 g, 5.67 mmol, 1 eq) in dioxane (40 mL) and H_2O (4 mL) was added *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 3 g, 5.67 mmol, 1 eq), K_2CO_3 (2.35 g, 17.00 mmol, 3 eq) and Pd(dppf)Cl_2 (414.53 mg, 566.53 μmol, 0.1 eq). The mixture was heated and stirred at 100 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel

chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**131**, 1.7 g, 2.01 mmol, 35.5 % yield) as a yellow oil that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.77 (s, 1H), 8.33 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 1.0 Hz, 1H), 7.18 (s, 1H), 6.60 (s, 1H), 6.43 (d, *J* = 5.8 Hz, 1H), 5.96 (s, 2H), 5.92 (d, *J* = 5.8 Hz, 1H), 5.76 (br s, 1H), 5.33 - 5.28 (m, 1H), 3.91 - 3.83 (m, 4H), 3.69 - 3.64 (m, 2H), 2.75 (br d, *J* = 17.1 Hz, 1H), 2.28 (br s, 2H), 2.22 - 2.18 (m, 1H), 2.10 (br s, 2H), 1.44 (s, 5H), 1.11 (s, 6H), 0.95 - 0.92 (m, 18H), 0.11 (s, 11H), 0.02 - -0.01 (m, 9H).

To a solution of *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**131**, 1.7 g, 2.01 mmol, 1 eq) in THF (30 mL) was added TBAF·$3H_2O$ (3.17 g, 10.06 mmol, 5 eq). The mixture was stirred at 25 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 1.287 min, [M+H] = 617.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition;) column: Waters Xbridge C18 150 x 50 mm x 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN] 70 % - 98 % B gradient over 8.0 min) to afford *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**132**, 400 mg, 648.49 μmol, 32.3 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.77 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7.29 (dd, *J* = 2.3, 8.8 Hz, 1H), 7.18 (d, *J* = 2.1 Hz, 1H), 6.44 (s, 1H), 6.40 (d, *J* = 5.9 Hz, 1H), 5.95 (s, 2H), 5.94 (d, *J* = 5.9 Hz, 1H), 5.76 (br s, 1H), 4.03 - 3.85 (m, 4H), 3.70 - 3.62 (m, 2H), 2.88 (dd, *J* = 1.8, 17.5 Hz, 1H), 2.28 (br d, *J* = 1.9 Hz, 2H), 2.15 (dd, *J* = 1.4, 17.4 Hz, 1H), 2.10 (br d, *J* = 3.0 Hz, 2H), 1.60 (t, *J* = 6.3 Hz, 2H), 1.12 (s, 6H), 1.01 - 0.94 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 617.3, expected 617.3 [M+H].

To a solution of *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**132**, 200 mg, 324.24 μmol, 1 eq) in DCM (5 mL) was added pyridine (128.24 mg, 1.62 mmol, 130.86 μL, 5 eq) and trifluoromethylsulfonyl trifluoromethanesulfonate (274.45 mg, 972.73 μmol, 160.49 μL, 3 eq). The mixture was stirred at 25 °C for 4 hr. The reaction was

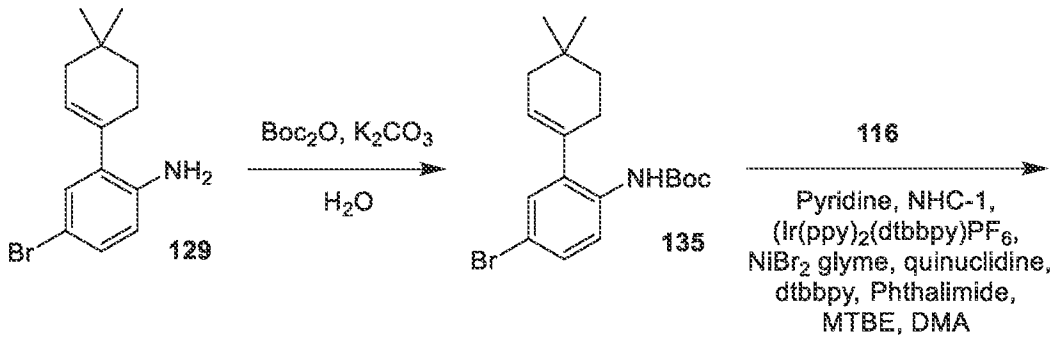
monitored by TLC (Pet. Et. / EtOAc = 3/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford [3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-1-yl]methyltrifluoromethanesulfonate (**133**, 200 mg, 227.03 μmol, 70.0 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.79 (s, 1H), 8.38 (d, J = 8.7 Hz, 1H), 7.77 (s, 1H), 7.25 (dd, J = 2.1, 8.7 Hz, 1H), 7.12 (d, J = 1.9 Hz, 1H), 6.49 (d, J = 5.8 Hz, 1H), 6.39 (s, 1H), 6.00 (d, J = 5.9 Hz, 1H), 5.95 (s, 2H), 5.77 (br s, 1H), 4.84 - 4.78 (m, 1H), 4.77 - 4.71 (m, 3H), 3.71 - 3.63 (m, 2H), 2.90 - 2.81 (m, 1H), 2.32 - 2.21 (m, 3H), 2.11 (br s, 2H), 1.61 (t, J = 6.3 Hz, 2H), 1.13 (s, 6H), 1.03 - 0.94 (m, 2H), 0.01 (s, 9H).

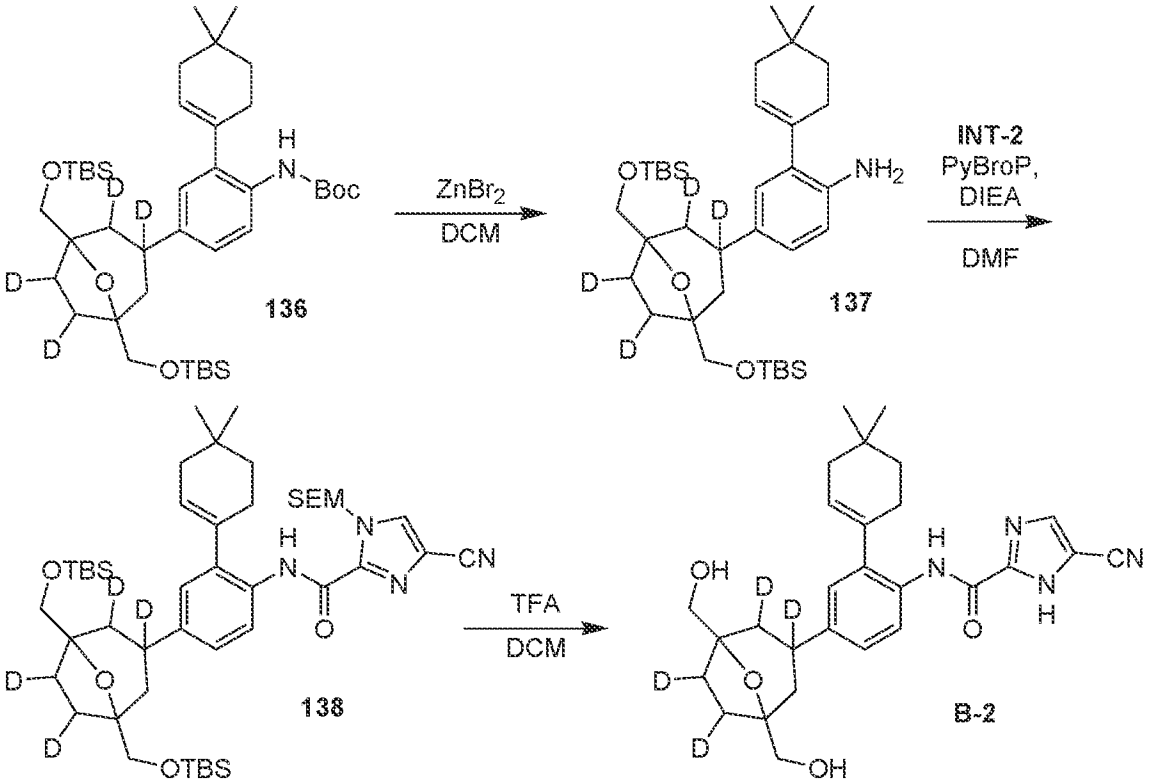
To a solution of [3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octa-3,6-dien-1-yl]methyl trifluoromethanesulfonate (**133**, 200 mg, 227.03 μmol, 1 eq) in THF (8 mL) was added TBAF (1 M, 1.14 mL, 5 eq). The mixture was stirred at 40 °C for 4 hr. The reaction was monitored by LC/MS (R_t = 0.741 min, [M+H] = 621.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 60 mL/min) to afford *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**134**, 100 mg, 161.08 μmol, 71.0 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.78 (s, 1H), 8.35 (d, J = 8.5 Hz, 1H), 7.76 (s, 1H), 7.30 (br d, J = 1.8 Hz, 1H), 7.18 (d, J = 1.9 Hz, 1H), 6.51 (s, 1H), 6.47 (d, J = 5.8 Hz, 1H), 6.00 - 5.94 (m, 3H), 5.76 (br s, 1H), 4.82 - 4.60 (m, 4H), 3.70 - 3.63 (m, 2H), 2.91 (d, J = 17.0 Hz, 1H), 2.28 (br s, 2H), 2.21 (d, J = 17.5 Hz, 1H), 2.11 (br d, J = 2.3 Hz, 2H), 1.60 (t, J = 6.3 Hz, 2H), 1.12 (s, 7H), 1.02 - 0.94 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 621.3, expected 621.3 [M+H].

To a solution of *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**134**, 100 mg, 161.08 μmol, 1 eq) in DCM (5 mL) was added TFA (3 mL). The mixture was stirred at 25 °C for 1 hr. The reaction was monitored by LC/MS (R_t = 0.615 min, [M+H] = 491.3) until it showed reactant had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 μm; mobile phase: [water(TFA) - ACN]; B%: 40 % - 75 % gradient, 8 min) to afford title compound, *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide (**B-1**, 35.2 mg, 71.76 μmol, 44.6 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.29 (br s, 1H), 9.71 (s, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 6.49 (d, *J* = 5.6 Hz, 1H), 6.00 (dd, *J* = 1.2, 5.7 Hz, 1H), 5.69 (br s, 1H), 4.85 - 4.58 (m, 4H), 2.72 (dd, *J* = 1.2, 17.9 Hz, 1H), 2.25 (br s, 2H), 2.18 (d, *J* = 17.6 Hz, 1H), 1.97 (br s, 2H), 1.50 (t, *J* = 6.4 Hz, 2H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 491.3, expected 491.2 [M+H].

EXAMPLE 19

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]phenyl]-1*H*-imidazole-2-carboxamide B-2





To a solution of 4-bromo-2-(4,4-dimethylcyclohexen-1-yl)aniline (**129**, 16 g, 57.10 mmol, 1 eq) in dioxane (160 mL) and H_2O (40 mL) was added Boc_2O (16.20 g, 74.23 mmol, 17.05 mL, 1.3 eq) and K_2CO_3 (15.78 g, 114.20 mmol, 2 eq) at 20 °C under N_2. The resulting mixture was heated and stirred at 60 °C for 12 hours. The reaction was monitored by TLC (Pet. Et. : EtOAc= 10:1) until it showed that the starting material had been completely consumed. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 10/1 gradient) to afford *tert*-butyl *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**135**, 18 g, 47.33 mmol, 82.9 % yield) as white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-3-deuteriooxy-8-oxabicyclo[3.2.1]octan-1-yl]methoxy]-dimethyl-silane (**116**, 582.22 mg, 1.38 mmol, 1.75 eq) and NHC-1 (498.83 mg, 1.26 mmol, 1.6 eq) in MTBE (10 mL) was added pyridine (99.83 mg, 1.26 mmol, 101.87 µL, 1.6 eq) in MTBE (1 mL) dropwise over 5 mins at 25 °C. After 10 min, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**135**, 300 mg, 788.81 µmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (10.81 mg, 11.83 µmol, 0.015 eq), dibromonickel;1,2-

dimethoxyethane (12.17 mg, 39.44 μmol, 0.05 eq), quinuclidine (153.49 mg, 1.38 mmol, 1.75 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (15.88 mg, 59.16 μmol, 0.075 eq) and isoindoline-1,3-dione (26.11 mg, 177.48 μmol, 0.225 eq) in DMA (10 mL) under N_2. The mixture was stirred at 25 °C for 3 hr under blue LED lights. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xltimate C4 100 x 30 x 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 90 % - 100 % B gradient over 10.0 min) to afford *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**136**, 1.3 g, 1.85 mmol, 33.4 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.88 (br d, *J* = 8.8 Hz, 1H), 7.12 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.69 (s, 1H), 5.68 - 5.55 (m, 1H), 3.65 - 3.58 (m, 4H), 2.22 (br d, *J* = 2.0 Hz, 2H), 2.01 - 1.97 (m, 2H), 1.83 - 1.76 (m, 3H), 1.74 - 1.73 (m, 1H), 1.62 (br d, *J* = 13.3 Hz, 1H), 1.55 (br d, *J* = 2.0 Hz, 2H), 1.50 (s, 9H), 1.03 (s, 6H), 0.88 (s, 18H), 0.04 (d, *J* = 1.5 Hz, 12H).

To a solution of *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**136**, 1.3 g, 1.85 mmol, 1 eq) in DCM (15 mL) was added $ZnBr_2$ (4.16 g, 18.46 mmol, 923.89 μL, 10 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 3.860 min, [M+H] = 604.5) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue without further purification to afford 4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**137**, 1.3 g, 1.72 mmol, 93.3 % yield, 80 % purity) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.95 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 6.73 - 6.66 (m, 1H), 5.70 (br s, 1H), 3.65 - 3.58 (m, 4H), 2.33 - 2.22 (m, 2H), 1.98 (br d, *J* = 3.3 Hz, 2H), 1.54 - 1.51 (m, 2H), 1.01 (s, 6H), 0.90 - 0.88 (m, 18H), 0.06 - 0.03 (m, 12H), MS (LC/MS) *m/z* observed 604.5, expected 604.5 [M+H].

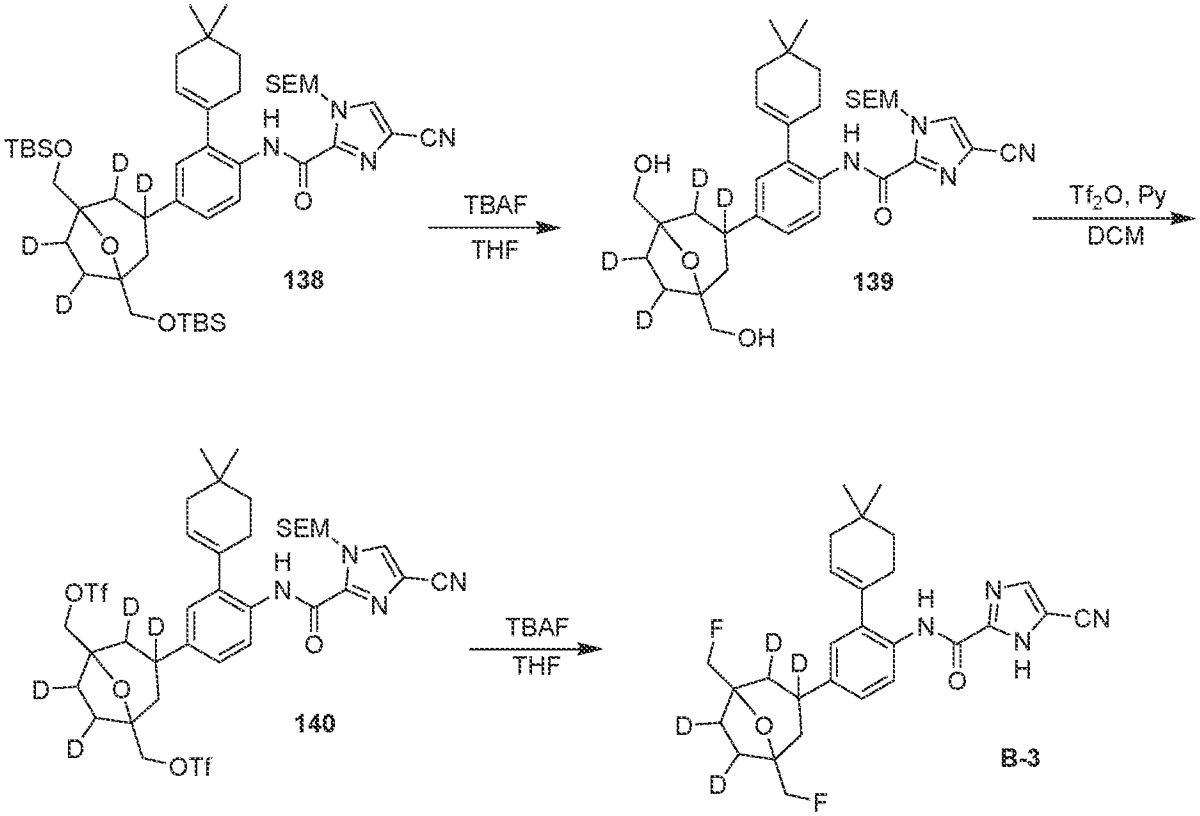
To a solution of 4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**137**, 1.3 g, 2.15 mmol, 1 eq) in DMF (20 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 1.31 g, 4.30 mmol, 2 eq), DIEA (834.42 mg, 6.46 mmol, 1.12 mL, 3 eq) and PyBroP (1.50 g, 3.23 mmol, 1.5 eq). The mixture was stirred at 25 °C for 12 h.

The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with and eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient at a flow rate of 80 mL/min) to afford *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**138**, 1.1 g, 1.29 mmol, 59.9 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.73 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.18 (dd, *J* = 1.9, 8.5 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 5.96 (s, 2H), 5.76 (br s, 1H), 3.69 - 3.61 (m, 6H), 2.30 (br d, *J* = 1.3 Hz, 2H), 2.10 (br s, 2H), 1.82 (s, 2H), 1.77 (s, 2H), 1.65 (br d, *J* = 12.9 Hz, 1H), 1.59 (t, *J* = 6.3 Hz, 2H), 1.11 (s, 6H), 1.00 - 0.95 (m, 2H), 0.89 (s, 18H), 0.05 (d, *J* = 1.1 Hz, 12H), 0.01 (s, 9H).

To a solution of *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**138**, 200 mg, 234.36 μmol, 1 eq) in DCM (3 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 1.959 min, [M+H] = 495.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 15 % - 50 % B gradient over 7.0 min) to afford title compound, 5-cyano-N-[2-(4,4-dimethylcyclohexen-1-yl)-4-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]phenyl]-1*H*-imidazole-2-carboxamide (**B-2**, 35.3 mg, 71.37 μmol, 30.5 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.24 (s, 1H), 9.71 (s, 1H), 8.31 (s, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.19 (dd, *J* = 2.0, 8.3 Hz, 1H), 7.12 (d, *J* = 2.1 Hz, 1H), 5.65 (br s, 1H), 4.59 (t, *J* = 5.8 Hz, 2H), 3.44 - 3.34 (m, 4H), 2.24 (br s, 2H), 1.95 (br s, 2H), 1.81 - 1.71 (m, 2H), 1.69 - 1.60 (m, 2H), 1.53 (br d, *J* = 12.9 Hz, 1H), 1.48 (t, *J* = 6.4 Hz, 2H), 1.00 (s, 6H), MS (LC/MS) *m/z* observed 495.3, expected 495.3 [M+H].

EXAMPLE 20

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[2,3,6,7-tetradeuterio-1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]phenyl]-1*H*-imidazole-2-carboxamide B-3



To a solution of *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,3,6,7-tetradeuterio-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**138**, 900 mg, 1.05 mmol, 1 eq) in THF (15 mL) was added TBAF·$3H_2O$ (998.22 mg, 3.16 mmol, 3 eq). The mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 0.641 min, [M+Na] =647.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10mL) and extracted with EtOAc (10mL x2). The organic layers were combined, washed with brine (20mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 100 % Pet. Et.: EtOAc with a flow rate of 80 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**139**, 440 mg, 704.14 μmol, 66.8 % yield) as a yellow solid, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K) δ (ppm) = 9.72 (s, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.17 (dd, *J* = 2.2, 8.5 Hz, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 5.96 (s, 2H), 5.75 (br s, 1H), 4.13 (q, *J* = 7.1 Hz, 4H), 2.32 - 2.24 (m, 2H), 2.10 (br d, *J* = 2.9 Hz, 2H), 1.85 - 1.80 (m, 2H), 1.80 - 1.75 (m, 2H), 1.69 - 1.64 (m, 3H), 1.59 (t, *J* = 6.3 Hz,

2H), 1.11 (s, 6H), 1.00 - 0.95 (m, 2H), 0.04 - -0.02 (m, 9H), MS (LC/MS) *m/z* observed 647.6, expected 647.4 [M+Na].

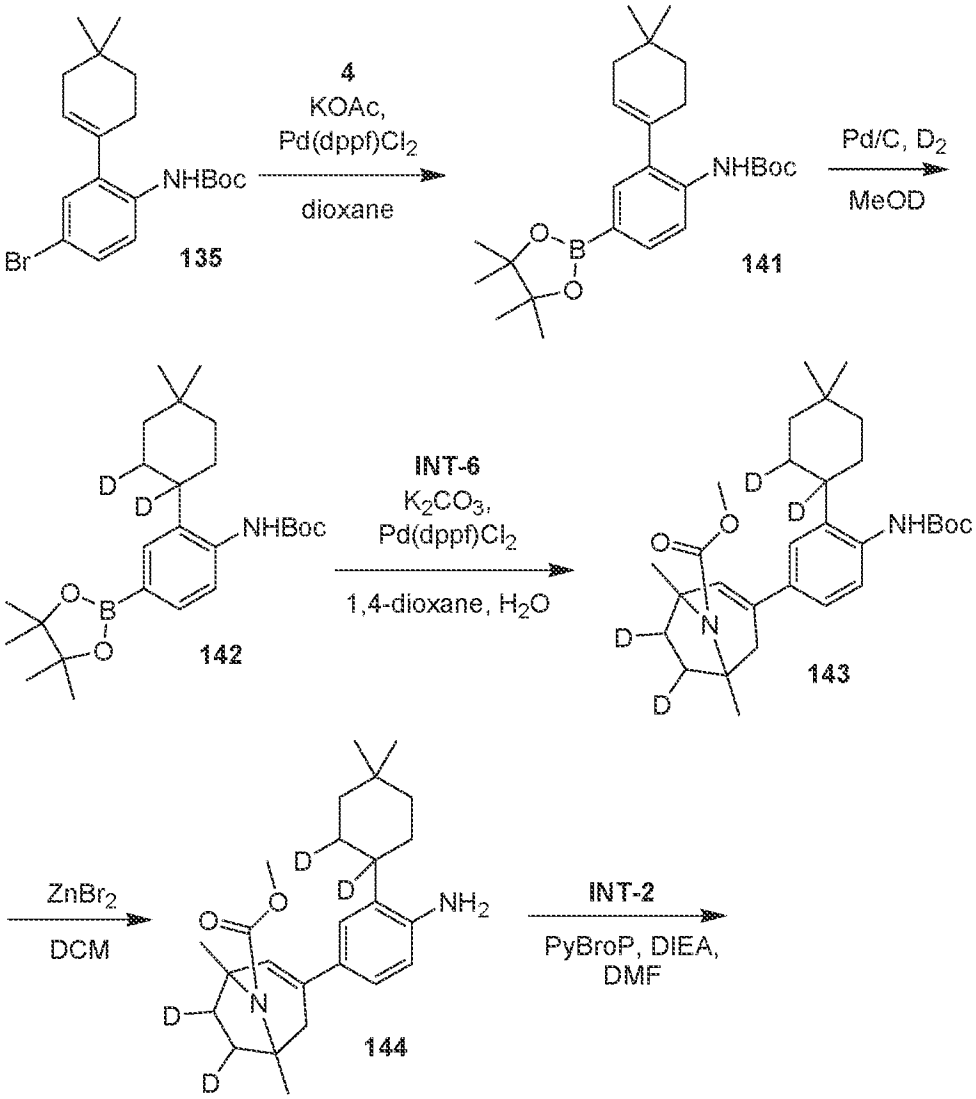
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[2,3,6,7-tetradeuterio-1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**139**, 440 mg, 704.14 μmol, 1 eq) in DCM (15 mL) was added pyridine (556.97 mg, 7.04 mmol, 568.34 μL, 10 eq) and Tf_2O (993.33 mg, 3.52 mmol, 580.89 μL, 5 eq). The mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 0.774 min, [M + Na] =911.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (15 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et.: EtOAc gradient with a flow rate of 40 mL/min) to afford [3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-3,4,6,7-tetradeuterio-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyltrifluoromethanesulfonate (**140**, 380 mg, 427.45 μmol, 60.7 % yield) as a yellow solid that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.74 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 7.77 (s, 1H), 7.15 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 5.96 (s, 2H), 5.77 (br s, 1H), 4.57 - 4.53 (m, 2H), 4.48 - 4.44 (m, 2H), 3.71 - 3.61 (m, 2H), 2.29 (br s, 2H), 2.11 (br d, *J* = 2.5 Hz, 2H), 2.02 (s, 2H), 1.87 - 1.78 (m, 2H), 1.76 (s, 1H), 1.60 (t, *J* = 6.2 Hz, 2H), 1.12 (s, 6H), 1.02 - 0.95 (m, 2H), 0.01 (s, 9H), **MS (LC/MS)** *m/z* observed 911.4, expected 911.3 [M+Na].

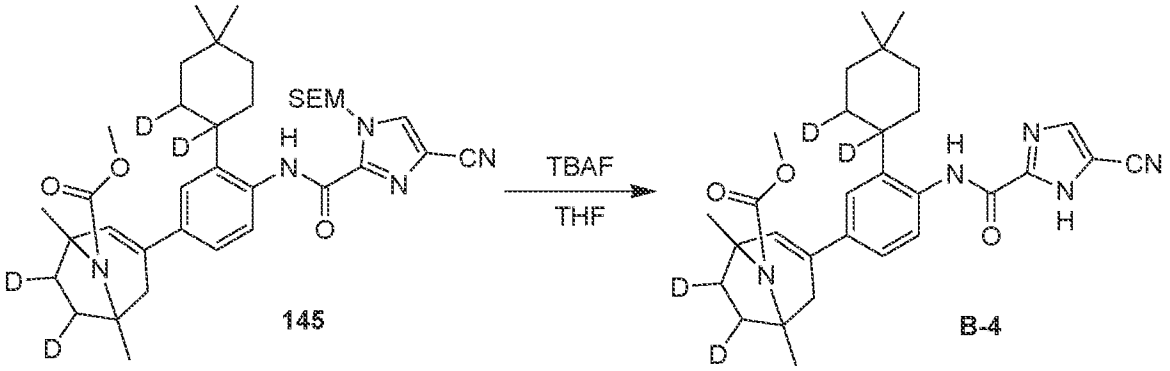
To a solution of [3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-3,4,6,7-tetradeuterio-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyltrifluoromethanesulfonate (**140**, 380 mg, 427.45 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.14 mL, 5 eq). The mixture was heated and stirred at 40 °C for 12 hrs. The reaction was monitored by LC/MS (Rt = 2.462 min, [M+H] = 499.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (15 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 μm; mobile phase: [H_2O (0.1 % TFA) - ACN]; 50 % - 100 % B gradient over 7.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[2,3,6,7-tetradeuterio-1,5-

bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]phenyl]-1*H*-imidazole-2-carboxamide (**B-3**, 75.5 mg, 123.24 μmol, 28.8 % yield) as a TFA salt, as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.25 (s, 1H), 9.72 (s, 1H), 8.32 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 5.66 (br s, 1H), 4.52 - 4.40 (m, 2H), 4.40 - 4.28 (m, 2H), 2.25 (br s, 2H), 1.95 (br d, *J* = 1.6 Hz, 2H), 1.92 - 1.87 (m, 2H), 1.70 - 1.60 (m, 3H), 1.48 (t, *J* = 6.4 Hz, 2H), 1.00 (s, 6H), MS (LC/MS) *m/z* observed 499.3, expected 499.3 [M+H].

EXAMPLE 21

Methyl 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate B-4





To a solution of *tert*-butyl *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**135**, 0.5 g, 1.31 mmol, 1 eq) and Pin_2B_2 (**4**, 400.62 mg, 1.58 mmol, 1.2 eq) in dioxane (10 mL) was added KOAc (322.56 mg, 3.29 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (96.20 mg, 131.47 μmol, 0.1 eq). The mixture was heated and stirred at 90 °C for 12 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc=1/0 to 1/1 gradient) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (**141**, 0.4 g, 935.93 μmol, 71.2 % yield) as a yellow solid, where the ^1H NMR was consistent with the expected structure and the product was used further as is.

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (**141**, 2 g, 4.68 mmol, 1 eq) in MeOD (3 mL) was added Pd/C (400.00 mg, 375.87 μmol, 10 % purity, 0.08 eq). The mixture was stirred at 30 °C for 12 h under D_2 (15 psi) atmosphere. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the reaction had completed. The reaction mixture was filtered and concentrated under reduced pressure to remove EtOAc, to give a residue, without further purification to afford *tert*-butyl *N*-[2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (**142**, 1.8 g, 4.17 mmol, 89.2 % yield) as yellow oil, where the ^1H NMR was consistent with the expected structure and the product was used further as is.

To a solution of methyl 6,7-dideuterio-1,5-dimethyl-3-(trifluoromethylsulfonyloxy)-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**INT-6**, 1.3 g, 3.76 mmol, 1 eq) in H_2O (2 mL) and 1,4-dioxane (20 mL) was added *tert*-butyl *N*-[2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (**142**, 1.79 g, 4.14 mmol, 1.1 eq) K_2CO_3 (1.30 g, 9.41 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (275.45 mg, 376.45 μmol, 0.1 eq) at 20 °C. The mixture was then heated and further stirred at 80 °C for 12 h under an N_2 atmosphere. The

reaction was monitored by TLC (Pet. Et.: EtOAc = 1:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-TLC (SiO_2, Pet. Et.: EtOAc = 1/0 to 0/1) to afford methyl 3-[4-(*tert*-butoxycarbonylamino)-3-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**143**, 1.4 g, 2.80 mmol, 74.3 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

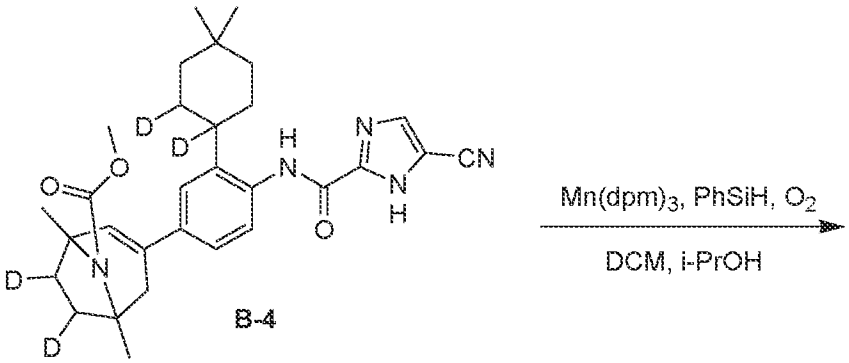
To a solution of methyl 3-[4-(*tert*-butoxycarbonylamino)-3-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**143**, 1.4 g, 2.80 mmol, 1 eq) in DCM (15 mL) was added $ZnBr_2$ (5.04 g, 22.37 mmol, 1.12 mL, 8 eq). The mixture was stirred at 20 °C for 12 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et.: EtOAc = 1:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (15 mL) and extracted with DCM (15 mL x 3). The organic layers were combined, washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification to afford methyl 3-[4-amino-3-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**144**, 1 g, 2.50 mmol, 89.3 % yield) as a white solid, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

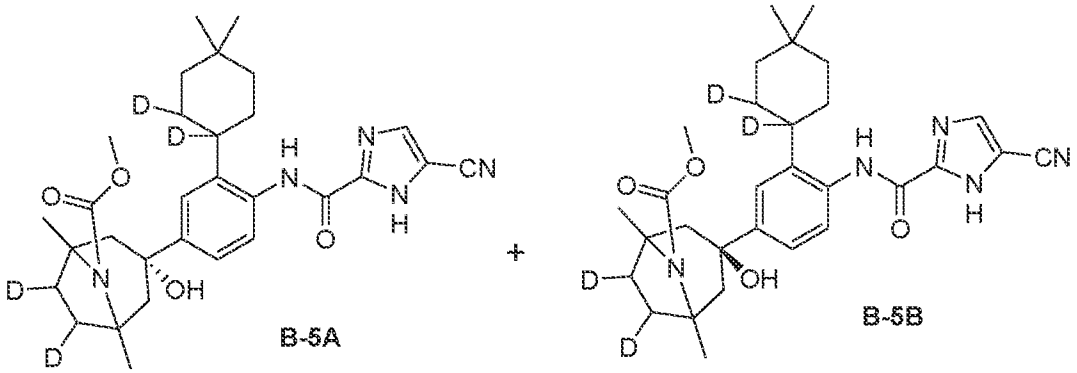
To a solution of methyl 3-[4-amino-3-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**144**, 1 g, 2.50 mmol, 1 eq) and 4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxylic acid (**INT-2**, 1.53 g, 4.99 mmol, 2 eq) in DMF (5 mL) was added PyBroP (1.75 g, 3.74 mmol, 1.5 eq) and DIEA (967.88 mg, 7.49 mmol, 1.30 mL, 3 eq). The mixture was stirred at 20 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et.: EtOAc = 5:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (20 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc=1/0 to 10/1 gradient) to afford methyl 3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**145**, 1.2 g, 1.85 mmol, 74.0 % yield) as yellow oil, where the ^{1}H NMR was consistent with the expected structure and the product was used further as is.

To a solution of methyl 3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)-imidazole-2-carbonyl]amino]-3-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**145**, 1.2 g, 1.85 mmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.77 mL, 1.5 eq). The mixture was stirred at 70 °C for 12 hr under an N_2 atmosphere. The reaction was monitored by TLC (Pet. Et.: EtOAc = 3:1) until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (5 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Waters Xbridge BEH C18 250 x 50 mm x 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 50 % - 80 % B gradient over 10.0 min) to afford title compound, 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**B-4**, 0.58 g, 1.12 mmol, 60.5 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.37 - 13.99 (m, 1H), 10.26 (s, 1H), 8.32 (s, 1H), 7.35 (s, 1H), 7.26 (s, 2H), 6.42 (s, 1H), 3.52 (s, 3H), 2.90 (br d, *J* = 17.0 Hz, 1H), 2.33 (br d, *J* = 17.0 Hz, 1H), 1.93 - 1.76 (m, 3H), 1.63 (s, 6H), 1.60 - 1.50 (m, 3H), 1.47 - 1.15 (m, 3H), 1.00 (s, 3H), 0.91 (s, 3H), MS (LC/MS) *m/z* observed 520.3, expected 520.3 [M+H].

EXAMPLES 22 and 23

Methyl 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-(*s*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate isomer 1 B-5Amethyl 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-(*s*)-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate isomer 2 B-5B (Absolute stereochemistry is indicated to distinguish isomer but has not been determined)



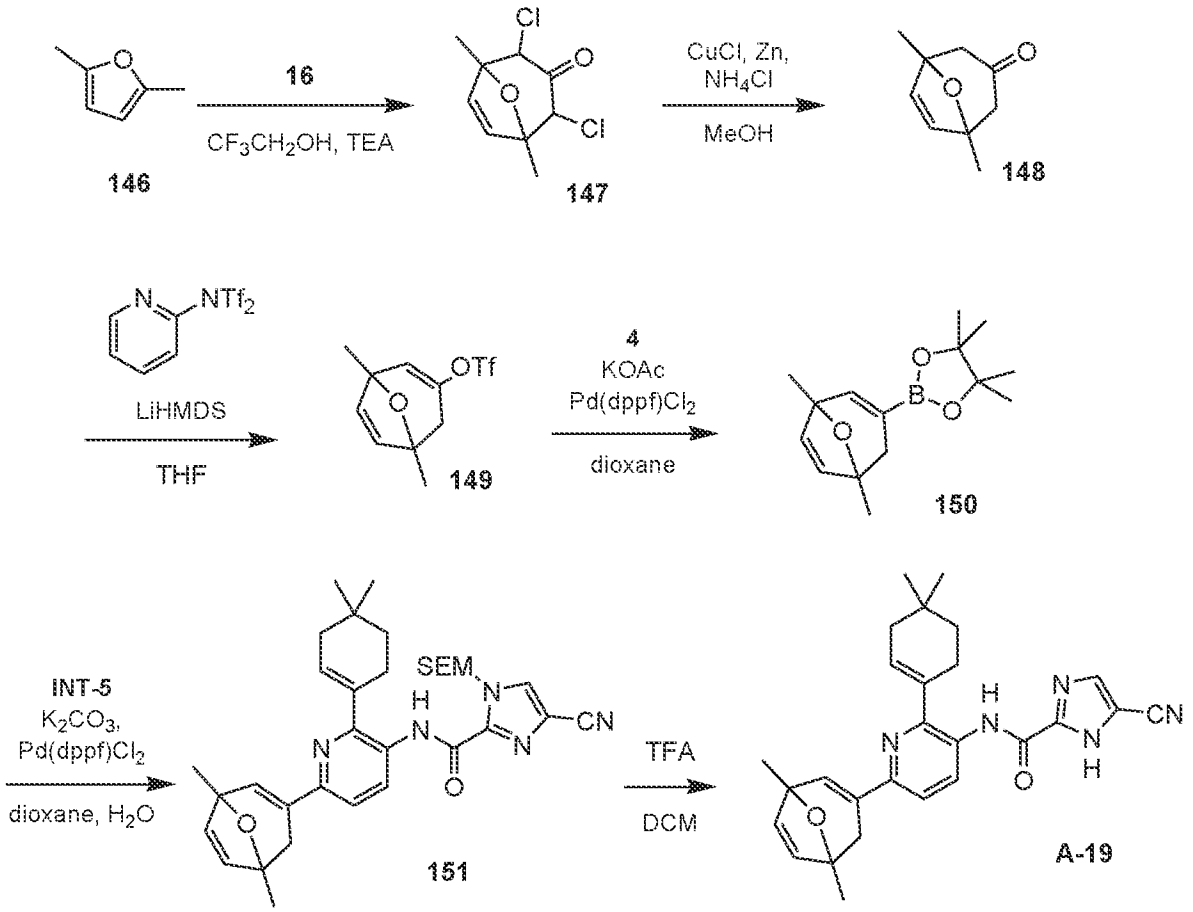


Absolute stereochemistry is indicated to distinguish isomer but has not been determined

To a solution of methyl 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylate (**B-4**, 570 mg, 1.10 mmol, 1 eq) in DCM (4 mL) and *i*-PrOH (40 mL) was added tris[(*Z*)-1-*tert*-butyl-4,4-dimethyl-3-oxo-pent-1-enoxy]manganese (66.33 mg, 109.69 μmol, 0.1 eq) and phenylsilane (237.38 mg, 2.19 mmol, 270.67 μL, 2 eq) at 20 °C. The mixture was stirred at 20 °C for 12 h under an O_2 atmosphere (15 psi). The reaction was monitored by LC/MS until it showed that the reaction had completed. The reaction mixture was quenched by H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by (SiO_2, Pet. Et.: EtOAc = 1/0 to 0/1 gradient) and then further purified by Prep-HPLC (column: Waters Xbridge C18 150 x 50 mm x 10 μm; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 40 % - 70 % B gradient over 8.0 min) to afford title compounds methyl 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (**B-5A**, 58.3 mg, 108.43 μmol, 9.9 % yield) as a white solid ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.15 (br d, *J* = 4.5 Hz, 1H), 10.25 (s, 1H), 8.30 (s, 1H), 7.26 (s, 1H), 7.21 - 7.10 (m, 2H), 5.07 (s, 1H), 3.64 (s, 3H), 2.36 - 2.25 (m, 2H), 2.15 (br d, *J* = 14.4 Hz, 2H), 1.66 (br d, *J* = 14.4 Hz, 2H), 1.61 - 1.50 (m, 3H), 1.43 (s, 8H), 1.31 - 1.13 (m, 2H), 0.98 (s, 3H), 0.90 (s, 3H), MS (LC/MS) *m/z* observed 531.4, expected 538.3 [M+H]. and methyl 3-[4-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-3-(1,2-dideuterio-4,4-dimethylcyclohexyl)phenyl]-6,7-dideuterio-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octane-8-carboxylate (**B-5B**, 10.1 mg, 18.78 μmol, 1.7 % yield) as white solids. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.39 - 13.74 (m, 1H), 10.21 (s, 1H), 8.31 (s, 1H), 7.55 (s, 1H), 7.45 (br d, *J* = 8.8 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 4.91 (s, 1H), 3.59 (s, 3H), 2.42 (br d, *J* = 14.4 Hz, 2H), 2.02 (br d, *J* = 14.4 Hz, 2H), 1.63 - 1.52 (m, 3H), 1.48 (s, 6H), 1.44 - 1.34 (m, 4H), 1.30 - 1.14 (m, 2H), 0.99 (s, 3H), 0.91 (s, 3H), MS (LC/MS) *m/z* observed 531.4, expected 538.3 [M+H].

EXAMPLE 24

5-Cyano-1*H*-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(1,5-dimethyl-8-oxa-bicyclo[3.2.1]octa-2,6-dien-3-yl)-pyridin-3-yl]-amide A-19



To a solution of 2,5-dimethylfuran (**146**, 5 g, 52.01 mmol, 5.52 mL, 1 eq) and 1,1,3-trichloropropan-2-one (**16**, 25.19 g, 156.04 mmol, 3 eq) in 2,2,2-trifluoroethanol (100 mL) was added TEA (21.05 g, 208.06 mmol, 28.96 mL, 4 eq) at 0 °C and the resulting mixture was stirred at 20 °C for 12 hr. The reaction was monitored by TLC (Pet. Et.: EtOAc e= 5:1) until it showed a major desired spot. The reaction mixture was diluted with H_2O (150 mL) and extracted with EtOAc (100 mL × 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2,4-dichloro-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**147**, 16 g) as a crude yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = NMR not integrated or assigned, MS (LC/MS) *m/z* observed Mass not immediately observable in supplied spectrum, expected 221.1 [M+H].

To a solution of 2,4-dichloro-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**147**, 16 g, 72.37 mmol, 1 eq) in MeOH (250 mL) was added CuCl (3.58 g, 36.19 mmol, 865.31 μL, 0.5 eq) and NH_4Cl (27.10 g, 506.60 mmol, 7 eq) at 0 °C, followed by Zn (28.39 g, 434.23 mmol, 6 eq)

in several portions. The resulting mixture was allowed to warm and further stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered through a CELITE™ pad. The filtrate was diluted with water (200 mL) and extracted with EtOAc (150 mL × 3). The organic layers were combined, washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 20/1) to afford 1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**148**, 7.5 g, 49.28 mmol, 68.1 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 5.96 (s, 2H), 2.49 - 2.44 (m, 2H), 2.39 - 2.33 (m, 2H), 1.50 (s, 6H).

To a solution of 1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**148**, 3 g, 19.71 mmol, 1 eq) in THF (10 mL) was added to LiHMDS (1 M, 23.65 mL, 1.2 eq) in THF (10 mL) at -70 °C, the mixture was allowed to warm to 20 °C and stirred for a further 0.5 h. The mixture was again cooled to -78 °C and 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (8.47 g, 23.65 mmol, 1.2 eq) in THF (12 mL) was added dropwise. The resulting mixture was allowed to warm to 25 °C and stirred for a further 2 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (50 mL, aqueous) and extracted with EtOAc (50 mL × 3). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 20/1) to afford [1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**149**, 5.6 g, 19.70 mmol, 99.9 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 6.25 (d, J = 5.6 Hz, 1H), 6.11 (s, 1H), 5.77 (d, J = 5.6 Hz, 1H), 2.63 (dd, J = 1.6, 17.5 Hz, 1H), 2.12 (d, J = 17.5 Hz, 1H), 1.52 (s, 6H), MS (LC/MS) *m/z* observed 283.2, expected 283.0 [M-H].

To a solution of [1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoro-methanesulfonate (**149**, 5.6 g, 19.70 mmol, 1 eq) and Pin_2B_2 (**4**, 6.00 g, 23.64 mmol, 1.2 eq) in 1,4-dioxane (60 mL) was added KOAc (4.83 g, 49.25 mmol, 2.5 eq), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (6.00 g, 23.64 mmol, 1.2 eq) and $Pd(dppf)Cl_2$ (720.76 mg, 985.04 μmol, 0.05 eq). The resulting mixture was stirred at 100 °C for 12 hr, under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (50 mL, aqueous) and extracted with EtOAc (50 mL × 3). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under

reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 30/1) to afford 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**150**, 4.5 g, 17.17 mmol, 87.1 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.82 (t, J = 1.9 Hz, 1H), 6.16 (d, *J* = 5.6 Hz, 1H), 5.67 (d, *J* = 5.6 Hz, 1H), 2.41 (dd, *J* = 2.3, 18.6 Hz, 1H), 1.90 (dd, *J* = 2.0, 18.5 Hz, 1H), 1.43 (s, 6H), 1.25 (s, 12H).

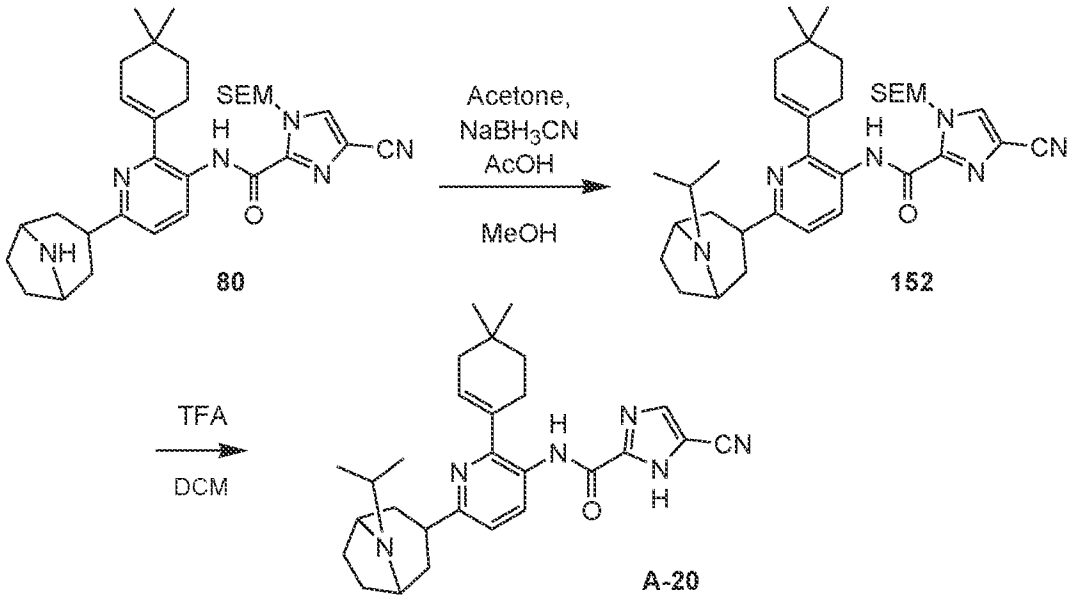
To a solution of 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**150**, 148.24 mg, 565.47 μmol, 1.5 eq) and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 0.2 g, 376.98 μmol, 1 eq) in 1,4-dioxane (10 mL) and H_2O (1 mL) was added K_2CO_3 (156.30 mg, 1.13 mmol, 3 eq) and cyclopentyl(diphenyl)phosphane; dichloropalladium; iron (27.58 mg, 37.70 μmol, 0.1 eq). The resulting mixture was stirred at 100 ° C for 12 hr, under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (20 mL, aqueous) and extracted with EtOAc (20 mL × 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 10/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)-imidazole-2-carboxamide (**151**, 0.18 g, 307.27 μmol, 81.5 % yield) as crude yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.99 (s, 1H), 8.64 (d, *J* = 8.8 Hz, 1H), 7.76 (s, 1H), 7.26 (s, 2H), 6.94 (s, 1H), 6.22 (d, *J* = 5.5 Hz, 1H), 5.96 - 5.93 (m, 1H), 5.93 (s, 2H), 5.75 (d, *J* = 5.6 Hz, 1H), 3.68 - 3.62 (m, 2H), 2.69 (dd, *J* = 1.8, 18.1 Hz, 1H), 2.49 (br d, *J* = 1.5 Hz, 2H), 2.39 (dd, *J* = 1.4, 18.1 Hz, 1H), 2.13 (br d, J = 3.1 Hz, 2H), 1.56 (s, 6H), 1.12 (s, 6H), 1.00 - 0.95 (m, 2H), 0.01 - -0.01 (m, 9H), MS (LC/MS) *m/z* observed 586.4, expected 586.3 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**151**, 0.18 g, 307.27 μmol, 1 eq) in DCM (3 mL) was added TFA (35.04 mg, 307.27 μmol, 22.82 μL, 1 eq). The resulting mixture was stirred at 20 °C for 5 hr. The reaction was monitored by LCMS (R_t = 0.593 min, M+H = 456.2) until it showed that the starting material had been completely consumed and a major desired product had been detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 %-85 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-

yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-19**, 0.0485 g, 106.46 μmol, 34.7 % yield) as yellow solid. ^{1}H NMR (400 MHz, MeOH-d4) δ = 8.78 (d, *J* = 8.9 Hz, 1H), 8.03 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 6.97 (s, 1H), 6.30 (d, *J* = 5.6 Hz, 1H), 6.08 (br s, 1H), 5.85 (d, *J* = 5.5 Hz, 1H), 2.69 (dd, *J* = 1.6, 18.1 Hz, 1H), 2.47 (br s, 2H), 2.41 (br d, *J* = 18.0 Hz, 1H), 2.14 (br s, 2H), 1.64 (t, *J* = 6.4 Hz, 2H), 1.53 (s, 6H), 1.11 (s, 6H), MS (LC/MS) *m/z* observed 456.3, expected 456.2 [M+H].

EXAMPLE 25

5-Cyano-1*H*-imidazole-2-carboxylic acid [2-(4,4-dimethyl-cyclohex-1-enyl)-6-(8-isopropyl-8-aza-bicyclo[3.2.1]oct-3-yl)-pyridin-3-yl]-amide A-20



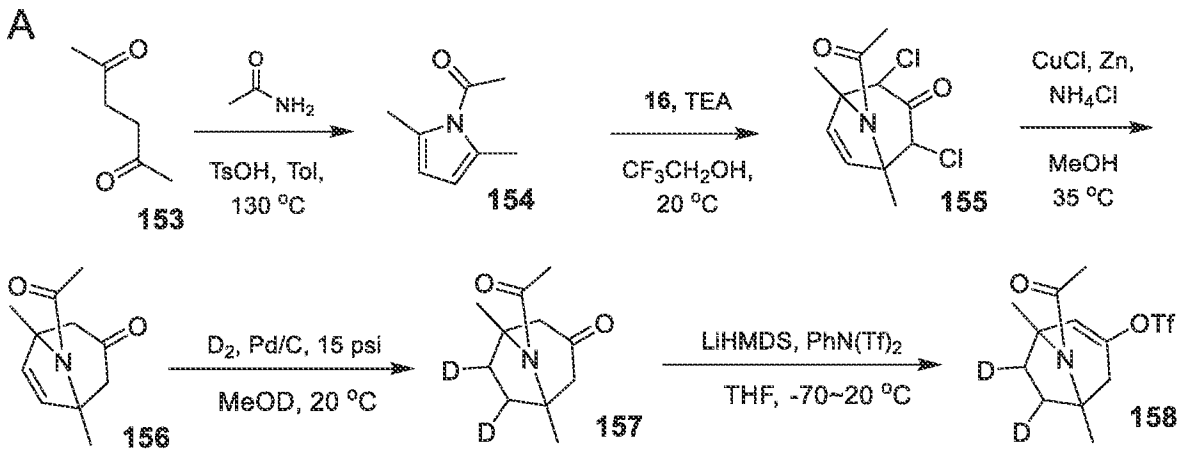
To a solution of *N*-[6-(8-azabicyclo[3.2.1]octan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**80**, 0.5 g, 891.58 μmol, 1 eq) in MeOH (5 mL) was added acetone (1.04 g, 17.83 mmol, 1.31 mL, 20 eq) and $NaBH_3CN$ (196.10 mg, 3.12 mmol, 3.5 eq) at 20 °C for 20 min. The mixture was adjusted pH=7 with acetic acid and stirring. The mixture was further stirred at 20 °C for 12 hr under N_2 atmosphere and monitored by LC/MS (R_t = 0.543 min, [M+H] = 603.3) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (5mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250 x 70 mm x15 um); mobile phase: [H_2O (0.1 % TFA) - ACN]; 45 % - 75 % B gradient over 20.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1-(2-

trimethylsilylethoxymethyl)imidazole-2-carboxamide, hydrochloride salt (**152**, 0.25 g, 414.67 μmol, 46.5 % yield) as a crude yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.80 (s, 1H), 9.14 (d, *J* = 8.8 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.81 (s, 2H), 6.12 (br s, 1H), 5.91 (s, 2H), 4.22 (br s, 3H), 3.67 (s, 2H), 3.03 (br d, *J* = 7.3 Hz, 1H), 2.77 (br s, 2H), 2.42 (br s, 4H), 2.20 (br s, 3H), 2.22 - 2.19 (m, 1H), 1.65 (s, 2H), 1.54 - 1.52 (m, 6H), 1.13 (s, 6H), 0.99 (s, 2H), 0.02 (s, 9H), MS (LC/MS) *m/z* observed 603.3, expected 603.3 [M+H].

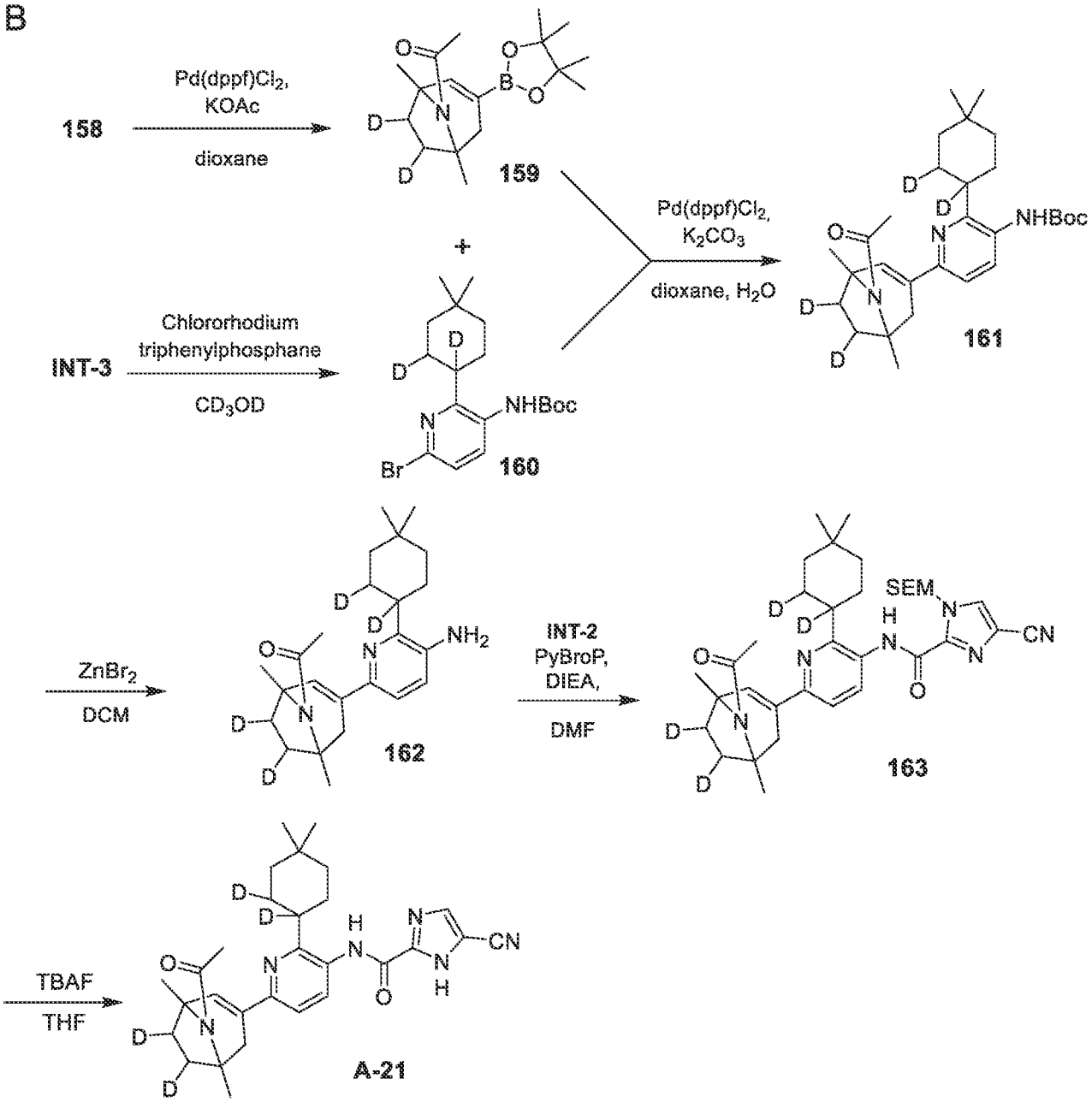
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**152**, 0.25 g, 391.03 μmol, 1 eq, HCl salt) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 20 °C for 2 hr under N_2 atmosphere and monitored by LC/MS (R_t = 0.407 min, [M+H] = 473.4) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge C18 150 x 50 mm x 10um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 30 % - 70 % B gradient over 6.0 min) to afford title compound, 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(8-isopropyl-8-azabicyclo[3.2.1]octan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-20**, 83.28 mg, 176.21 μmol, 45.1 % yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.55 (d, *J* = 8.4 Hz, 1H), 7.69 (s, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 5.91 (br s, 1H), 4.17 (br s, 2H), 3.44 - 3.32 (m, 2H), 2.42 (br d, *J* = 1.9 Hz, 2H), 2.30 - 2.19 (m, 4H), 2.16 - 2.06 (m, 4H), 1.96 (br d, *J* = 13.5 Hz, 2H), 1.59 (t, *J* = 6.3 Hz, 2H), 1.37 (d, *J* = 6.4 Hz, 6H), 1.08 (s, 6H), MS (LC/MS) *m/z* observed 473.4, expected 473.3 [M+H].

EXAMPLE 26

***N*-[6-[8-Acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide A-21**



B



To a solution of acetamide (5 g, 84.65 mmol, 1 eq) and hexane-2,5-dione (**153**, 12.56 g, 110.04 mmol, 12.91 mL, 1.3 eq) in toluene (150 mL) was added TsOH (728.84 mg, 4.23 mmol, 0.05 eq) at 20 °C. The mixture was stirred at 140 °C for 12 hr under N_2 atmosphere with Dean-Stark trap. The reaction was monitored by TLC (Pet. Et. : EtOAc = 10:1, Rf = 0.7) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford 1-(2,5-dimethylpyrrol-1-yl)ethanone (**154**, 3.2 g, 23.33 mmol, 27.6 % yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.84 (s, 2H), 2.54 (s, 3H), 2.42 (s, 6H).

To a solution of 1-(2,5-dimethylpyrrol-1-yl)ethanone (**154**, 3.2 g, 23.33 mmol, 1 eq) and 1,1,3-trichloropropan-2-one (**16**, 11.30 g, 69.98 mmol, 3 eq) in CF_3CH_2OH (30 mL) was added TEA (7.08 g, 69.98 mmol, 9.74 mL, 3 eq) at 20 °C. The mixture was stirred at 20 °C for 12 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.435 min, [M+H] = 262.1) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 8-acetyl-2,4-dichloro-1,5-dimethyl-8-azabicyclo[3.2.1]oct-6-en-3-one (**155**, 6 g, 11.44 mmol, 49.1 % yield, 50 % purity) as a crude brown solid, used as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.83 (s, 2H), 4.59 - 4.53 (m, 1H), 3.99 - 3.92 (m, 1H), 2.54 (s, 3H), 2.41 (s, 5H), 2.42 - 2.39 (m, 1H), MS (LC/MS) *m/z* observed 262.1, expected 262.0 [M+H].

To a solution of 8-acetyl-2,4-dichloro-1,5-dimethyl-8-azabicyclo[3.2.1]oct-6-en-3-one (**155**, 6 g, 22.89 mmol, 1 eq) in MeOH (60 mL) was added CuCl (1.13 g, 11.44 mmol, 273.67 μL, 0.5 eq), NH_4Cl (8.57 g, 160.22 mmol, 7 eq), and Zn (7.48 g, 114.45 mmol, 5 eq). The mixture was stirred at 20 °C for 12 hr under N_2 and monitored by TLC (Pet. Et. : EtOAc = 1:1, Rf = 0.5) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1), to afford 8-acetyl-1,5-dimethyl-8-azabicyclo[3.2.1]oct-6-en-3-one (**156**, 1.7 g, 8.80 mmol, 38.4 % yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.78 (s, 2H), 2.78 (br d, *J* = 16.8 Hz, 2H), 2.36 (d, *J* = 17.1 Hz, 2H), 2.17 (s, 3H), 1.74 (s, 6H), MS (LC/MS) *m/z* observed 194.2, expected 194.1 [M+H].

To a solution of 8-acetyl-1,5-dimethyl-8-azabicyclo[3.2.1]oct-6-en-3-one (**156**, 1.7 g, 8.80 mmol, 1 eq) in CD_3OD (20 mL) was added Pd/C (468.10 mg, 439.86 μmol, 10 % purity, 0.05 eq). The mixture was stirred at 200 °C for 12 hr under D_2 (15 psi) and monitored by LC/MS (R_t = 0. 34 min, [M+H] = 198.2) until it showed that the reaction had completed. The suspension was filtered through a pad of CELITE™ or silica gel and the pad or filter cake was washed with CD_3OD (5 mL x 3). The filtrates were combined, concentrated to dryness and without further purification, afforded 8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]-octan-3-one (**157**, 1.5 g, 7.60 mmol, 86.4 % yield) as a brown solid, used as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.75 (br d, *J* = 15.6 Hz, 2H), 2.30 (br d, *J* = 15.8 Hz, 2H), 2.22 (br s, 3H), 1.69 (br s, 2H), 1.65 (s, 6H), MS (LC/MS) *m/z* observed 198.2, expected 198.2 [M+H].

To a solution of LiHMDS (1 M, 7.60 mL, 1 eq) in THF (3 mL) was added dropwise a solution of 8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-one (**157**, 1.5 g, 7.60 mmol, 1 eq) in THF (15 mL) at -70 °C. The mixture was allowed to warm and further stirred at 20 °C for 0.5 h. Then a solution of 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethyl-sulfonyl)methanesulfonamide (3.00 g, 8.36 mmol, 1.1 eq) in THF (3 mL) was added at -70 °C. The reaction was allowed to warm and further stirred at 20 °C for 2.5 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. : EtOAc = 1:1, Rf = 0.7) until it showed that the reaction had completed. The reaction mixture was quenched with NH_4Cl (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford [8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**158**, 0.96 g, 2.91 mmol, 38.34% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.00 - 5.93 (m, 1H), 3.12 (dd, *J* = 1.6, 17.0 Hz, 1H), 2.17 - 2.11 (m, 4H), 2.02 - 1.96 (m, 1H), 1.90 - 1.86 (m, 1H), 1.73 (s, 3H), 1.70 (s, 3H), MS (LC/MS) *m/z* observed 330.1, expected 330.1 [M+H].

To a solution of [8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**158**, 960.00 mg, 2.91 mmol, 1 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (888.27 mg, 3.50 mmol, 1.2 eq) in dioxane (10 mL) was added KOAc (715.21 mg, 7.29 mmol, 2.5 eq) and Pd(dppf)Cl_2 (213.29 mg, 291.50 μmol, 0.1 eq). The mixture was stirred at 90 °C for 12 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. : EtOAc = 10:1, Rf = 0.7) until it showed that the reaction had completed. The reaction mixture was quenched with NH_4Cl (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford 1-[6,7-dideuterio-1,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl]ethanone (**159**, 0.79 g, 2.57 mmol, 88.2 % yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.60 (t, *J* = 2.0 Hz, 1H), 2.82 (dd, *J* = 1.8, 17.8 Hz, 1H), 2.11 (s, 3H), 1.98 (dd, *J* = 1.7, 17.6 Hz, 1H), 1.88 - 1.75 (m, 2H), 1.64 (d, *J* = 1.9 Hz, 6H), 1.25 (d, *J* = 0.8 Hz, 12H), MS (LC/MS) *m/z* observed 308.3, expected 308.2 [M+H].

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 0.5 g, 1.31 mmol, 1 eq) in CD_3OD (10 mL) was added chlororhodium; triphenylphosphane (606.61 mg, 655.64 μmol, 0.5 eq). The mixture was stirred at 50 °C for 12 hr under D_2 (50 psi). The reaction was monitored by TLC (Pet. Et. : EtOAc =

10:1) until it showed that the reaction had completed. The suspension was filtered through a pad of CELITE™ or silica gel and the pad or filter cake was washed with CD_3OD (10 mL x 3). The filtrates were combined and concentrated to dryness. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford *tert*-butyl *N*-[6-bromo-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]carbamate (**160**, 1.85 g, 2.40 mmol, 36.6 % yield, 50 % purity) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (br d, *J* = 8.5 Hz, 1H), 7.92 (br d, *J* = 6.5 Hz, 1H), 6.81 (br s, 1H), 2.34 - 2.27 (m, 2H), 1.95 (br d, *J* = 3.3 Hz, 2H), 1.81 (br s, 1H), 1.46 (s, 9H), 1.30 - 1.26 (m, 2H), 0.95 (s, 6H), MS (LC/MS) *m/z* observed 385.1, expected 385.2 [M+H].

To a solution of 1-[6,7-dideuterio-1,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-azabicyclo[3.2.1]oct-2-en-8-yl]ethanone (**159**, 0.59 g, 1.92 mmol, 1 eq) and *tert*-butyl *N*-[6-bromo-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]carbamate (**160**, 887.98 mg, 2.30 mmol, 1.2 eq) in dioxane (5 mL) and H_2O (1 mL) was added K_2CO_3 (796.22 mg, 5.76 mmol, 3 eq) and $Pd(dppf)Cl_2$ (140.51 mg, 192.04 μmol, 0.1 eq). The mixture was stirred at 90 °C for 12 h under N_2 atmosphere and monitored by LC/MS (R_t = 0.664 min, [M+H] = 486.4) until it showed that the reaction had completed. The reaction mixture was quenched by NH_4Cl (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 (250 x 70 mm x 15 um); mobile phase: [H_2O (0.1 % TFA) - ACN]; 68 % - 88 % B gradient over 20.0 min) to afford *tert*-butyl *N*-[6-[8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]carbamate (**161**, 0.43 g, 885.33 μmol, 46.1 % yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 - 8.03 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.78 (s, 1H), 6.38 (br s, 1H), 3.17 (br d, *J* = 17.1 Hz, 1H), 2.45 (d, *J* = 17.4 Hz, 1H), 2.16 (s, 3H), 2.00 - 1.86 (m, 4H), 1.78 (d, *J* = 11.6 Hz, 6H), 1.64 - 1.52 (m, 12 H), 1.42 - 1.31 (m, 2H), 1.01 (d, J = 14.3 Hz, 6H), MS (LC/MS) *m/z* observed 486.3, expected 486.4 [M+H].

To a solution of *tert*-butyl *N*-[6-[8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]carbamate (**161**, 0.33 g, 679.44 μmol, 1 eq) in DCM (5 mL) was added $ZnBr_2$ (1.53 g, 6.79 mmol, 340.02 μL, 10 eq) at 20 °C. The mixture was stirred at 20 °C for 12 hr under N_2 atmosphere and monitored by LC/MS (R_t = 0.434 min, [M+H] = 386.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification,

to afford 1-[3-[5-amino-6-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-2-pyridyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-8-yl]ethanone (**162**, 0.25 g, 648.38 μmol, 95.4 % yield) as a yellow solid, used further as is. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.21 - 7.06 (m, 1H), 6.59 (s, 1H), 3.11 (br d, *J* = 17.1 Hz, 1H), 2.48 (d, *J* = 17.1 Hz, 1H), 2.15 (s, 3H), 1.96 - 1.83 (m, 4H), 1.75 (d, *J* = 6.8 Hz, 6H), 1.66 - 1.53 (m, 2H), 1.51 - 1.34 (m , 4H) , 1.04 - 0.97 (m, 6H)), MS (LC/MS) *m/z* observed 386.3, expected 386.4 [M+H].

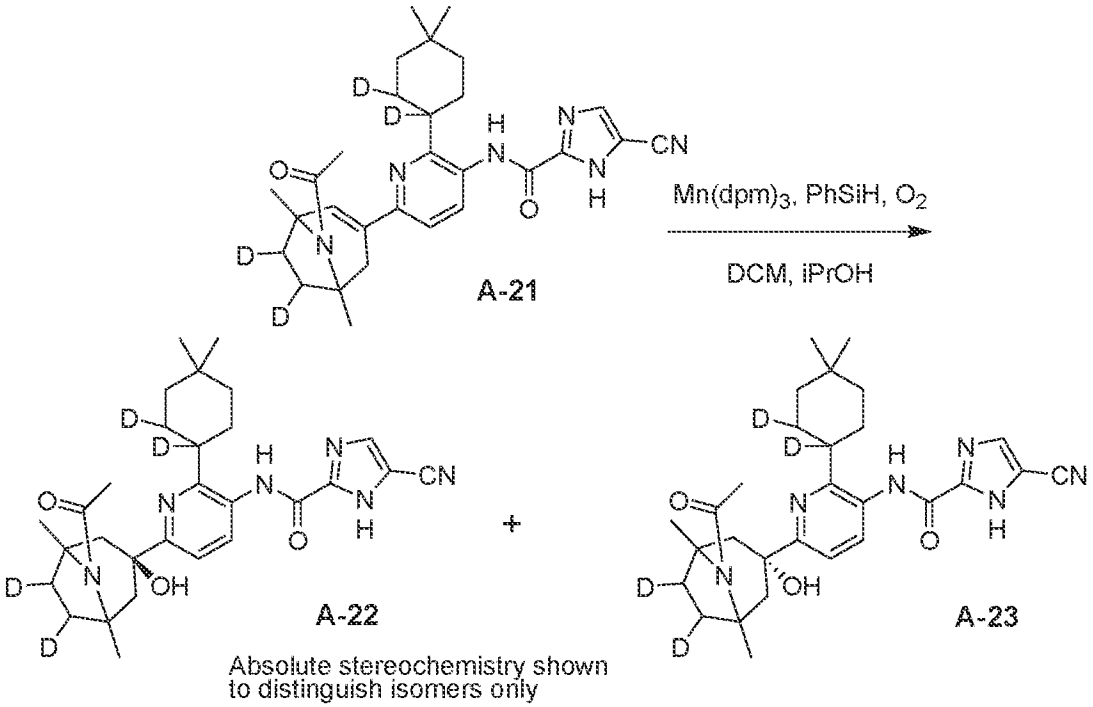
To a solution of 1-[3-[5-amino-6-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-2-pyridyl]-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-8-yl]ethanone (**162**, 0.25 g, 648.38 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 237.65 mg, 778.05 μmol, 1.2 eq) in DMF (5 mL) was added PyBroP (453.39 mg, 972.57 μmol, 1.5 eq) and DIEA (251.39 mg, 1.95 mmol, 338.81 μL, 3 eq). The mixture was stirred at 20 °C for 2 hr under N_2 atmosphere and monitored by LC/MS (R_t = 0.768 min, [M+H] = 635.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford *N*-[6-[8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**163**, 0.25 g, 393.75 μmol, 60.7 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.19 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 6.86 (s, 1H), 5.95 (s, 2H), 3.70 -3.64 (m, 2H), 3.18 (br d, *J* = 17.5 Hz, 1H), 2.47 (d, *J* = 17.4 Hz, 1H), 2.15 (s, 3H), 1.98 - 1.94 (m, 2H), 1.79 (d, *J* = 11.4 Hz, 4H), 1.56 (s, 6H), 1.47 - 1.42 (m, 2H), 1.03 (d, *J* = 12.0 Hz, 6H), 0.98 (d, *J* = 8.3 Hz, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 635.4, expected 635.4 [M+H].

To a solution of *N*-[6-[8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**163**, 0.22 g, 346.50 μmol, 1 eq) in THF (2 mL) was added TBAF (1 M, 693.00 μL, 2 eq). The mixture was stirred at 20 °C for 12 hr under N_2 atmosphere, and the reaction was monitored by LC/MS (R_t = 0.613 min, [M+H] = 505.3) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 50 %-80 % B gradient over 6.0 min) to afford title compound *N*-[6-[8-acetyl-6,7-dideuterio-1,5-dimethyl-8-

azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-21**, 0.13 g, 257.60 μmol, 74.3 % yield) as a white solid. 1H NMR (400 MHz, CD_3OD) δ = 8.01 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 3.17 (br d, *J* = 17.2 Hz, 1H), 2.57 (d, *J* = 17.6 Hz, 1H), 2.16 (s, 3H), 2.03 - 1.97 (m, 1H), 1.95 - 1.87 (m, 3H), 1.78 (d, *J* = 4.6 Hz, 6H), 1.67 - 1.59 (m, 1H), 1.54 - 1.47 (m, 2H), 1.41 - 1.34 (m, 2H), 1.03 (s, 3H), 0.96 (s, 3H), MS (LC/MS) *m/z* observed 505.3, expected 505.3 [M+H].

EXAMPLES 27 and 28

_N_-[6-[8-Acetyl-6,7-dideuterio-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1_H_-imidazole-2-carboxamide A-22 and _N_-[6-[8-acetyl-6,7-dideuterio-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1_H_-imidazole-2-carboxamide A-23 (stereochemistry is indicated to distinguish isomers but has not been determined)

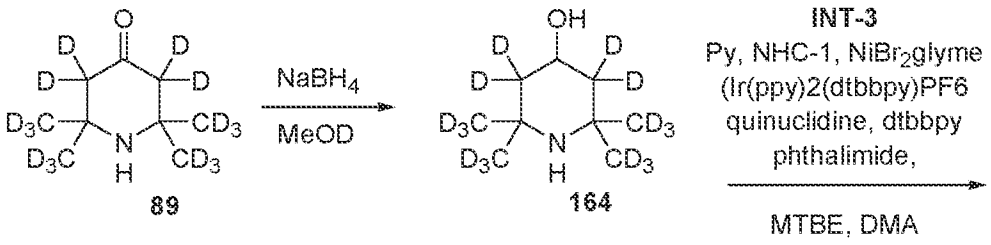


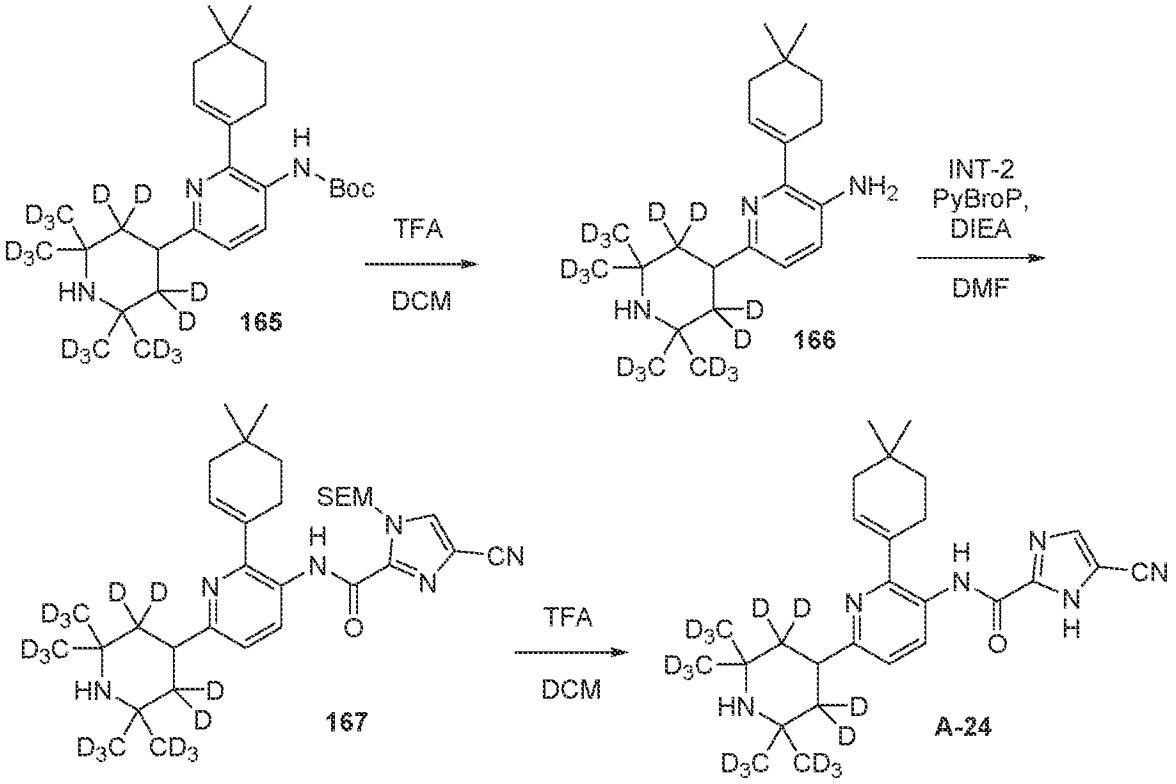
To a solution of *N*-[6-[8-acetyl-6,7-dideuterio-1,5-dimethyl-8-azabicyclo[3.2.1]oct-2-en-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-21**, 0.1 g, 198.15 μmol, 1 eq) in DCM (0.5 mL) and *i*-PrOH (5 mL) was added phenylsilane (85.77 mg, 792.62 μmol, 97.80 μL, 4 eq) and tris[(Z)-1-*tert*-butyl-4,4-dimethyl-3-oxo-pent-1-enoxy]manganese (35.95 mg, 59.45 μmol, 0.3 eq). The mixture was stirred at 25 °C for 12 hr under O_2 (15 psi) atmosphere and monitored by LC/MS (R_t = 0.528 min, [M+H] =

523.4) and LC/MS (R_t = 0.572 min, [M+H] = 523.4) until it showed that the reactions had completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 45 % - 70 % B gradient over 8.0 min) to afford title compounds *N*-[6-[8-acetyl-6,7-dideuterio-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide isomer 1 (**A-22**, 4.6 mg, 8.80 μmol, 4.4 % yield; Example 27) and *N*-[6-[8-acetyl-6,7-dideuterio-3-hydroxy-1,5-dimethyl-8-azabicyclo[3.2.1]octan-3-yl]-2-(1,2-dideuterio-4,4-dimethyl-cyclohexyl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide isomer 2 (**A-23**, 2.3 mg, 4.40 μmol, 2.2 % yield; Example 28) as white solids. **A-22**: ^{1}H NMR (400 MHz, CD_3OD) δ = 8.05 (t, *J* = 4.2 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 3.63 (d, *J* = 15.3 Hz, 2H), 2.32 (d, *J* = 15.3 Hz, 2H), 1.98 (s, 2H), 1.94 (br d, *J* = 3.1 Hz, 1H), 1.89 (s, 3H), 1.71 - 1.65 (m, 1H), 1.64 - 1.59 (m, 1H), 1.55 (s, 6H), 1.51 (br s, 2H), 1.47 - 1.37 (m, 2H), 1.03 (s, 3H), 1.00 - 0.96 (m, 3H), MS (LC/MS) *m/z* observed 523.4, expected 523.4 [M+H], and **A-23**: ^{1}H NMR (400 MHz, CD_3OD) δ = 8.03 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 2.71 (d, *J* = 14.4 Hz, 2H), 2.41 - 2.37 (m, 2H), 2.22 (s, 3H), 1.95 - 1.84 (m, 2H), 1.64 (br d, *J* = 14.4 Hz, 3H), 1.59 (s, 6H), 1.53 - 1.46 (m, 2H), 1.40 - 1.31 (m, 2H), 1.06 - 0.95 (m, 6H), MS (LC/MS) *m/z* observed 523.4, expected 523.4 [M+H].

EXAMPLE 29

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-24





To a solution of 3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-one (**89**, 1 g, 5.84 mmol, 1 eq) in CD3OD (10 mL) was added NaBH4 (287.03 mg, 7.59 mmol, 1.3 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hr and monitored by TLC (EtOAc : MeOH= 3:1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with D_2O (2 mL) and concentrated under reduced pressure to give a residue, without purification, to afford 3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-piperidin-4-ol (**164**, 1 g, 5.77 mmol, 98.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, CD3OD, 301 K) δ (ppm) = 3.96 (s, 1H).

To a solution of 3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)piperidin-4-ol (**164**, 477.36 mg, 2.75 mmol, 1.75 eq) and NHC-1 (995.08 mg, 2.52 mmol, 1.6 eq) in MTBE (15 mL) was added pyridine (199.15 mg, 2.52 mmol, 203.21 μL, 1.6 eq) in MTBE (1 mL) dropwise in 5 mins at 25 °C, after 10 min, the mixture was filtrate and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 0.6 g, 1.57 mmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine;hexafluorophosphate (21.57 mg, 23.60 μmol, 0.015 eq), dibromonickel;1,2-dimethoxyethane (24.28 mg, 78.68 μmol, 0.05 eq), quinuclidine (306.18 mg, 2.75 mmol, 1.75 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (31.68 mg, 118.02 μmol, 0.075 eq) and isoindoline-1,3-dione (52.09 mg, 354.05 μmol, 0.225 eq) in DMA (15 mL) under N_2. The mixture was stirred at 25 °C for 3 hr under blue LEDs and monitored by LC/MS (R_t = 0.447 min, [M+H] = 458.5) until it showed that the starting material had been completely consumed.

The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 50 % - 90 % B gradient over 8.0 min) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-carbamate (**165**, 150 mg, 327.69 μmol, 10.4 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD3OD, 298 K) δ (ppm) = 8.11 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 5.93 (br t, *J* = 3.7 Hz, 1H), 3.48 - 3.43 (m, 1H), 2.44 - 2.34 (m, 2H), 2.05 (br d, *J* = 3.4 Hz, 2H), 1.57 (t, *J* = 6.3 Hz, 2H), 1.50 (s, 9H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 458.4, expected 458.5 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]carbamate (**165**, 150 mg, 327.69 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 2 hr and monitored by LC/MS (R_t = 0.323 min, [M+H] = 358.4) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue, without further purification, to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**166**, 150 mg, 318.03 μmol, 97.05% yield, TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, CD3OD, 298 K) δ (ppm) = 7.71 (d, *J* = 8.8 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 1H), 6.18 (td, *J* = 2.0, 3.6 Hz, 1H), 3.62 (s, 1H), 2.44 - 2.32 (m, 2H), 2.12 (br d, *J* = 3.4 Hz, 2H), 1.63 (t, *J* = 6.3 Hz, 2H), 1.07 (s, 6H), MS (LC/MS) *m/z* observed 358.4, expected 358.4 [M+H].

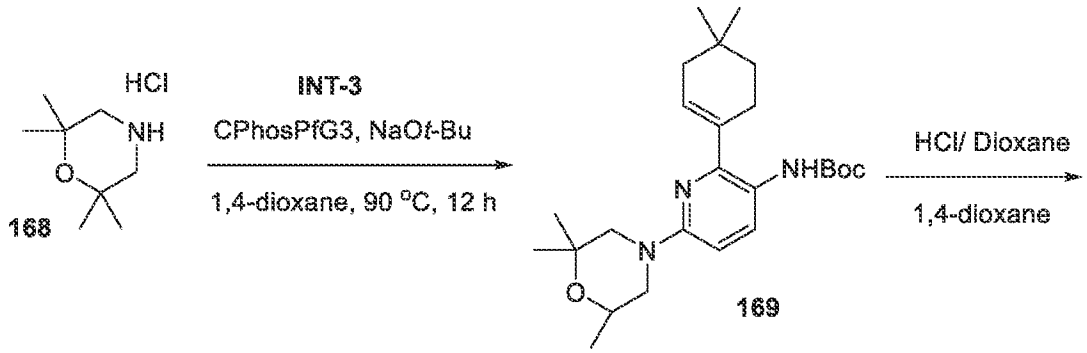
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]pyridin-3-amine (**166**, 150 mg, 419.43 μmol, 1 eq) in DMF (5 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]-oxypotassium (**INT-2**, 256.22 mg, 838.85 μmol, 2 eq), DIEA (162.62 mg, 1.26 mmol, 219.16 μL, 3 eq) and PyBroP (293.29 mg, 629.14 μmol, 1.5 eq). The mixture was stirred at 25 °C for 2 hr and monitored by LC/MS (R_t = 0.553 min, [M+H]=607.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 40 % - 75 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**167**, 100 mg, 164.75 μmol, 39.3 % yield) as a yellow solid. ^{1}H NMR (400 MHz,

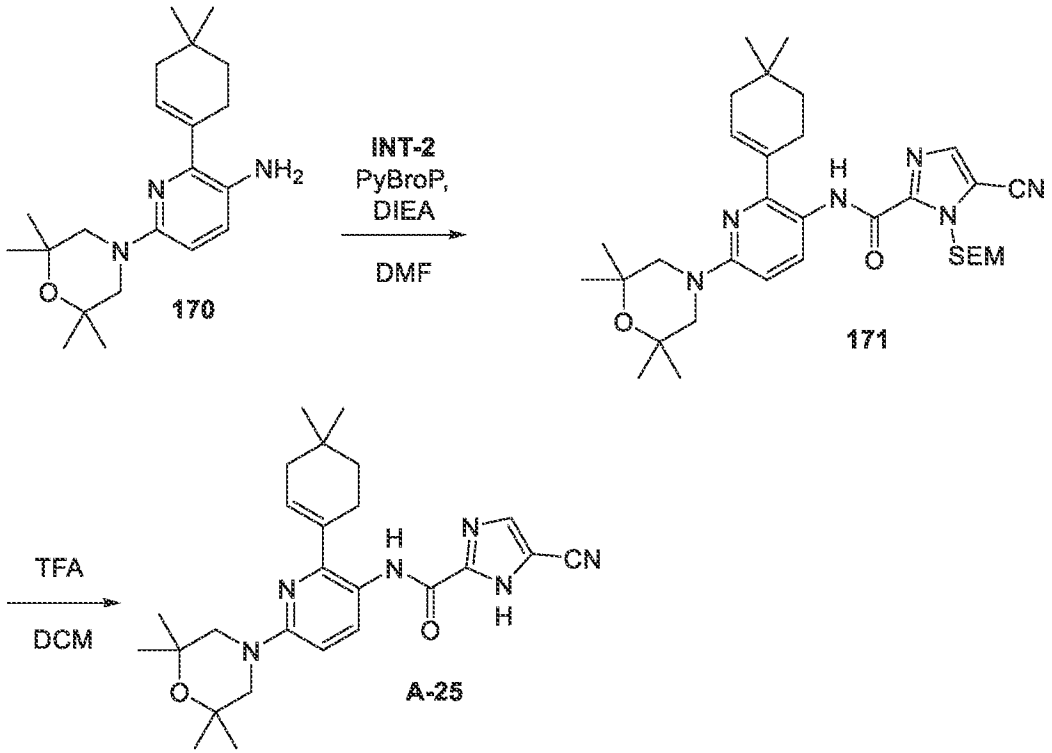
CD3OD, 298 K) δ (ppm) = 8.62 (d, *J* = 8.4 Hz, 1H), 8.23 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 5.96 (br s, 1H), 5.91 (s, 2H), 3.71 - 3.64 (m, 2H), 3.40 (s, 1H), 2.46 (br d, *J* = 2.0 Hz, 2H), 2.12 (br d, *J* = 3.1 Hz, 2H), 1.61 (t, *J* = 6.3 Hz, 2H), 1.11 (s, 6H), 0.96 - 0.93 (m, 2H), -0.01 - -0.03 (m, 9H), MS (LC/MS) *m/z* observed 607.5, expected 607.5 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)-imidazole-2-carboxamide (**167**, 0.1 g, 164.75 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL) at 25 °C. The mixture was stirred at 25 °C for 2 h and monitored by LC/MS (R_t = 0.400 min, [M+H] = 477.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 25 % - 50 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[3,3,5,5-tetradeuterio-2,2,6,6-tetrakis(trideuteriomethyl)-4-piperidyl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-24**, 69.9 mg, 118.33 μmol, 71.8 % yield, TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, CD3OD, 295 K) δ (ppm) = 8.61 (d, *J* = 8.4 Hz, 1H), 8.03 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 5.97 (br s, 1H), 3.41 (s, 1H), 2.46 (br d, *J* = 1.8 Hz, 2H), 2.11 (br d, *J* = 3.0 Hz, 2H), 1.61 (t, *J* = 6.3 Hz, 2H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 477.3, expected 477.3 [M+H].

EXAMPLE 30

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-25





To a solution of 2,2,6,6-tetramethylmorpholine (**168**, 282.74 mg, 1.57 mmol, 1.2 eq, HCl salt) and *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 0.5 g, 1.31 mmol, 1 eq) in dioxane (10 mL) and THF (3 mL) was added *t*-BuONa (378.06 mg, 3.93 mmol, 3 eq) and [2-(2-aminophenyl)phenyl]palladium(1+); 2-(2-dicyclohexyl-phosphanylphenyl)-*N1,N1,N3,N3*-tetramethyl-benzene-1,3-diamine; methanesulfonate (105.73 mg, 131.13 μmol, 0.1 eq) at 20 °C under N_2. The mixture was stirred at 90 °C for 12 hr under microwave irradiation and monitored by LC/MS (R_t = 0.58 min, [M+H] = 444.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, EtOAc : MeOH =1/0 to 0/1) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)-3-pyridyl]carbamate (**169**, 0.2 g, 450.84 μmol, 34.4 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 - 7.88 (m, 1H), 6.58 - 6.43 (m, 2H), 5.83 (br s, 1H), 3.39 (br s, 4H), 2.40 (dt, *J* = 2.1, 6.3 Hz, 2H), 2.03 (br s, 2H), 1.57 (br s, 2H), 1.49 (s, 9H), 1.27 (s, 12H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 444.4, expected 444.4 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)-3-pyridyl]carbamate (**169**, 0.175 g, 394.48 μmol, 1 eq) in HCl/dioxane (1 mL) and dioxane (3 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.428 min, [M+H] = 344.4) until it showed that the reaction had been completed. The reaction mixture was

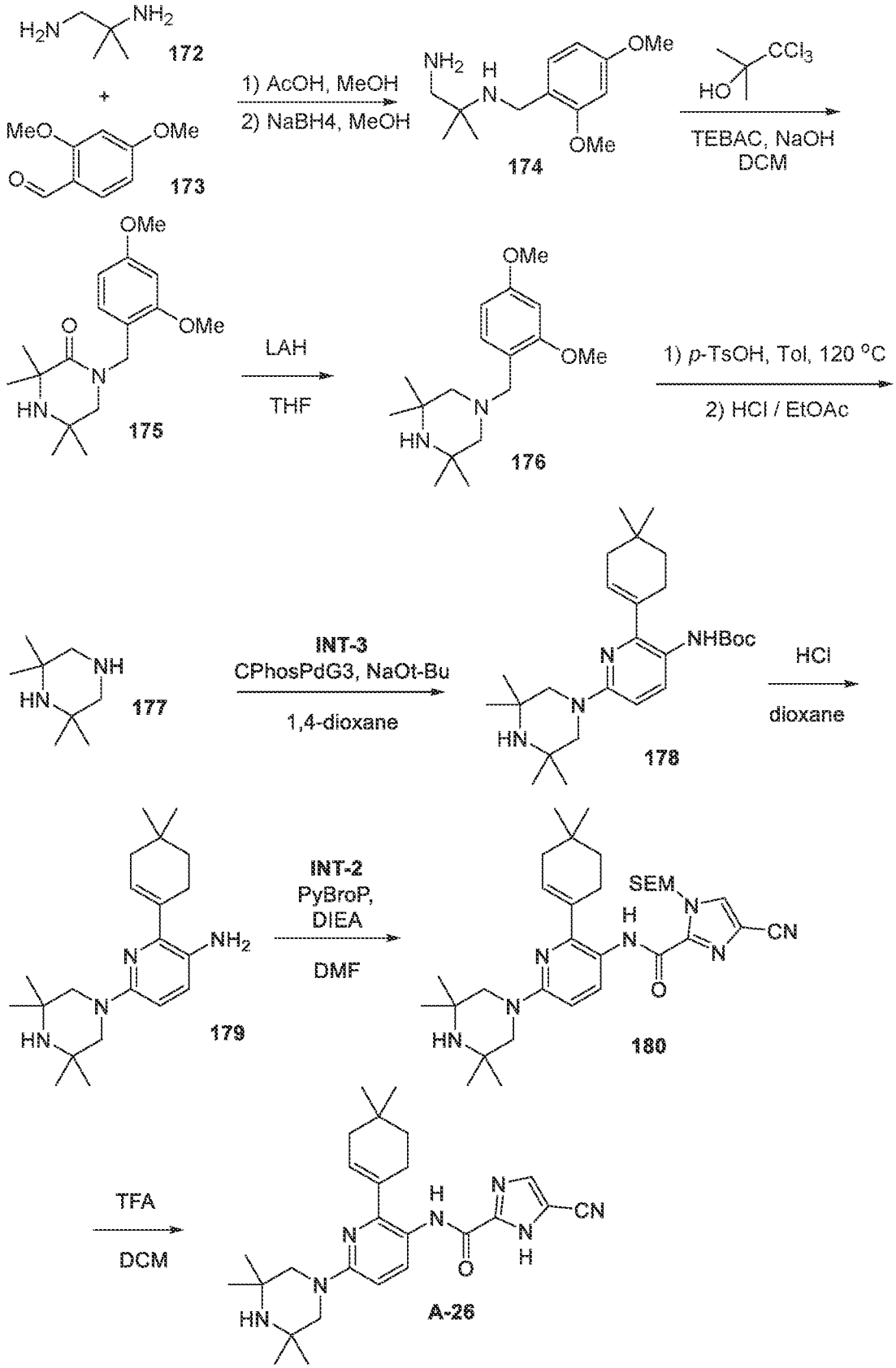
concentrated under reduced pressure to give a residue, without further purification, to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)pyridin-3-amine (**170**, 0.13 g, 378.45 μmol, 95.9 % yield) as a crude yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.76 (d, *J* = 9.5 Hz, 1H), 7.12 (d, *J* = 9.5 Hz, 1H), 6.11 - 6.03 (m, 1H), 3.58 (s, 4H), 2.43 - 2.38 (m, 2H), 2.12 - 2.09 (m, 2H), 1.61 (t, *J* = 6.4 Hz, 2H), 1.28 (s, 12H), 1.06 (s, 6H), MS (LC/MS) *m/z* observed 344.4, expected 344.4 [M+H].

To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)pyridin-3-amine (**170**, 0.13 g, 378.45 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxy-methyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 231.19 mg, 756.90 μmol, 2 eq) in DMF (5 mL) was added PyBroP (264.64 mg, 567.68 μmol, 1.5 eq) and DIEA (146.74 mg, 1.14 mmol, 197.76 μL, 3 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2 and monitored by TLC (EtOAc : MeOH = 5:1, Rf = 0.3) until it showed that the reaction had been completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, EtOAc : MeOH =1/0 to 0/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**171**, 0.15 g, 253.02 μmol, 66.9 % yield) as a crude white oil, without further characterization.

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**171**, 0.15 g, 253.02 μmol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 53.21 eq) dropwise at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 6 hr, monitored by LC/MS (R_t = 0.580 min, [M+H] = 463.4) until it showed major desired product peaks were detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by Prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 50 % - 75 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(2,2,6,6-tetramethylmorpholin-4-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-25**, 0.1044 g, 180.93 μmol, 71.5 % yield, 99.93 % purity, TFA salt) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.22 (d, *J* = 9.4 Hz, 1H), 8.00 (s, 1H), 6.99 (d, *J* = 9.4 Hz, 1H), 6.02 (br t, *J* = 3.7 Hz, 1H), 3.57 (s, 4H), 2.49 - 2.35 (m, 2H), 2.04 (br d, *J* = 3.4 Hz, 2H), 1.56 (t, *J* = 6.4 Hz, 2H), 1.29 (s, 12H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 463.4, expected 463.4 [M+H].

EXAMPLE 31

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-26



To a solution of 2-methylpropane-1,2-diamine (**172**, 2.65 g, 30.09 mmol, 3.12 mL, 1 eq) and 2,4-dimethoxybenzaldehyde (**173**, 5 g, 30.09 mmol, 1 eq) in MeOH (100 mL) was added AcOH (1.45 g, 24.07 mmol, 1.38 mL, 0.8 eq). The reaction mixture was stirred at 20 °C for 1 hr. The reaction mixture was then diluted with MeOH (100 mL), then $NaBH_4$ (2.28 g, 60.18 mmol, 2 eq) was added portion wise. The mixture was stirred at 20 °C for 1 hr under N_2 and the reaction was monitored by LC/MS (R_t = 0.33 min, [M+H] = 239.2) until it showed that the reaction had been completed. The reaction mixture was quenched with NH_4Cl (30 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford *N1*-[(3,4-dimethylphenyl)methyl]-2-methyl-propane-1,2-diamine (**174**, 5.6 g, 27.14 mmol, 90.2 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 (d, *J* = 7.9 Hz, 1H), 6.47 - 6.42 (m, 2H), 3.89 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.66 (s, 2H), 1.35 (s, 6H), MS (LC/MS) *m/z* observed 239.2, expected 239.2 [M+H].

To a solution of *N1*-[(3,4-dimethoxyphenyl)methyl]-2-methyl-propane-1,2-diamine (**174**, 4.6 g, 19.30 mmol, 1 eq), 1,1,1-trichloro-2-methyl-propan-2-ol (8.56 g, 48.25 mmol, 2.5 eq) and TEBAC (439.63 mg, 1.93 mmol, 0.1 eq) in DCM (100 mL) was added NaOH (7.72 g, 96.51 mmol, 50 % purity, 5 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 20 hr under N2, monitored by LC/MS (R_t = 0.326 min, [M+H] = 307.2) until it showed that the reaction had been completed. The reaction mixture was quenched with H_2O (30 mL) and extracted with DCM (50 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250 x 70 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 20 % - 50 % B gradient over 20.0 min) to afford 1-[(2,4-dimethoxyphenyl)methyl]-3,3,5,5-tetramethyl-piperazin-2-one (**175**, 2.14 g, 6.98 mmol, 36.2 % yield) as a white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 (d, *J* = 7.9 Hz, 1H), 6.47 - 6.43 (m, 2H), 4.58 (s, 2H), 3.79 (d, *J* = 3.9 Hz, 6H), 3.09 (s, 2H), 1.39 (s, 6H), 1.09 (s, 6H), MS (LC/MS) *m/z* observed 307.2, expected 307.2 [M+H].

To a solution of 1-[(2,4-dimethoxyphenyl)methyl]-3,3,5,5-tetramethyl-piperazin-2-one (**175**, 2.14 g, 6.98 mmol, 1 eq) in THF (30 mL) was added $LiAlH_4$ (2.5 M, 5.59 mL, 2 eq) at 0 °C. The mixture was allowed to warm and further stirred at 25 °C for 2 hr under N_2, monitored by LC/MS (R_t = 0.321 min, [M+H] = 293.3) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with H_2O (3.6 mL) and to the resulting mixture was added dropwise, NaOH (7.2 mL, 1 M). The mixture was washed with THF, filtered and concentrated under reduced pressure to give a residue, without further

purification, to afford 1-[(2,4-dimethoxyphenyl)methyl]-3,3,5,5-tetramethyl-piperazine (**176**, 1.9 g, 6.50 mmol, 93.0 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CDCl3, 298 K) δ (ppm) = 7.38 (d, *J* = 8.3 Hz, 1H), 6.49 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.46 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.43 (s, 2H), 2.12 (s, 4H), 1.17 (s, 12H), MS (LC/MS) *m/z* observed 293.3, expected 293.3 [M+H].

To a solution of 1-[(2,4-dimethoxyphenyl)methyl]-3,3,5,5-tetramethyl-piperazine (**176**, 1.3 g, 4.45 mmol, 1 eq) in toluene (10 mL) was added TsOH (1.68 g, 9.78 mmol, 2.2 eq) at 25 °C. The mixture was heated and further stirred at 120 °C for 12 hr under N_2. The reaction was monitored by ^{1}H NMR until it showed that the reaction had been completed. The reaction mixture was concentrated under reduced pressure to give a residue. The mixture was stirred with HCl/EtOAc to form a suspension that was filtered through a pad of CELITE™ or silica gel and the pad or filter cake was washed with EtOAc (5 mL x 3). The filter cake, which was the desired product, was collected and without further purification afforded 2,2,6,6-tetramethylpiperazine (**177**, 0.75 g, 4.20 mmol, 94.4 % yield, HCl salt) as a crude brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 3.46 (s, 4H), 2.38 (s, 1H), 1.63 (s, 12H).

To a solution of 2,2,6,6-tetramethylpiperazine (**177**, 731.11 mg, 4.09 mmol, 1.2 eq, HCl salt) and *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 1.3 g, 3.41 mmol, 1 eq) in 1,4-dioxane (9 mL) and THF (3 mL) was added CPHOS Pd G3 (274.91 mg, 340.93 μmol, 0.1 eq) and NaO*t*Bu (982.95 mg, 10.23 mmol, 3 eq) at 20 °C under N_2. The mixture was warmed and further stirred at 90 °C for 12 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.498 min, [M+H] = 443.4) until it showed that the reaction had been completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)-3-pyridyl]carbamate (**178**, 0.57 g, 1.29 mmol, 37.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ = 6.98 (d, *J* = 8.6 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 6.02 - 5.94 (m, 1H), 3.76 - 3.61 (m, 2H), 3.26 (br s, 4H), 2.50 - 2.45 (m, 2H), 2.02 (br d, *J* = 3.3 Hz, 2H), 1.56 - 1.54 (m, 2H), 1.39 - 1.29 (m, 12H) , 1.02 (s, 6H)), MS (LC/MS) *m/z* observed 443.4, expected 443.4 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)-3-pyridyl]carbamate (**178**, 0.57 g, 1.29 mmol, 1 eq) in HCl/dioxane (1 mL) and dioxane (2 mL) at 0 °C. The mixture was stirred at 20 °C for 2 hr under N_2 and monitored by LC/MS (R_t = 0.340 min, [M+H] = 343.4) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to give a residue,

without further purification, to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridin-3-amine (**179**, 0.4 g, 1.06 mmol, 82.0 % yield, HCl salt) as a crude yellow oil, that was used further as is. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.01 (br d, J = 8.4 Hz, 1H), 6.67 - 6.52 (m, 1H), 5.95 (br s, 1H), 2.47 (br s, 2H), 2.09 - 2.05 (m, 2H), 1.73 - 1.66 (m, 2H), 1.50 (s, 12H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 343.4, expected 343.4 [M+H].

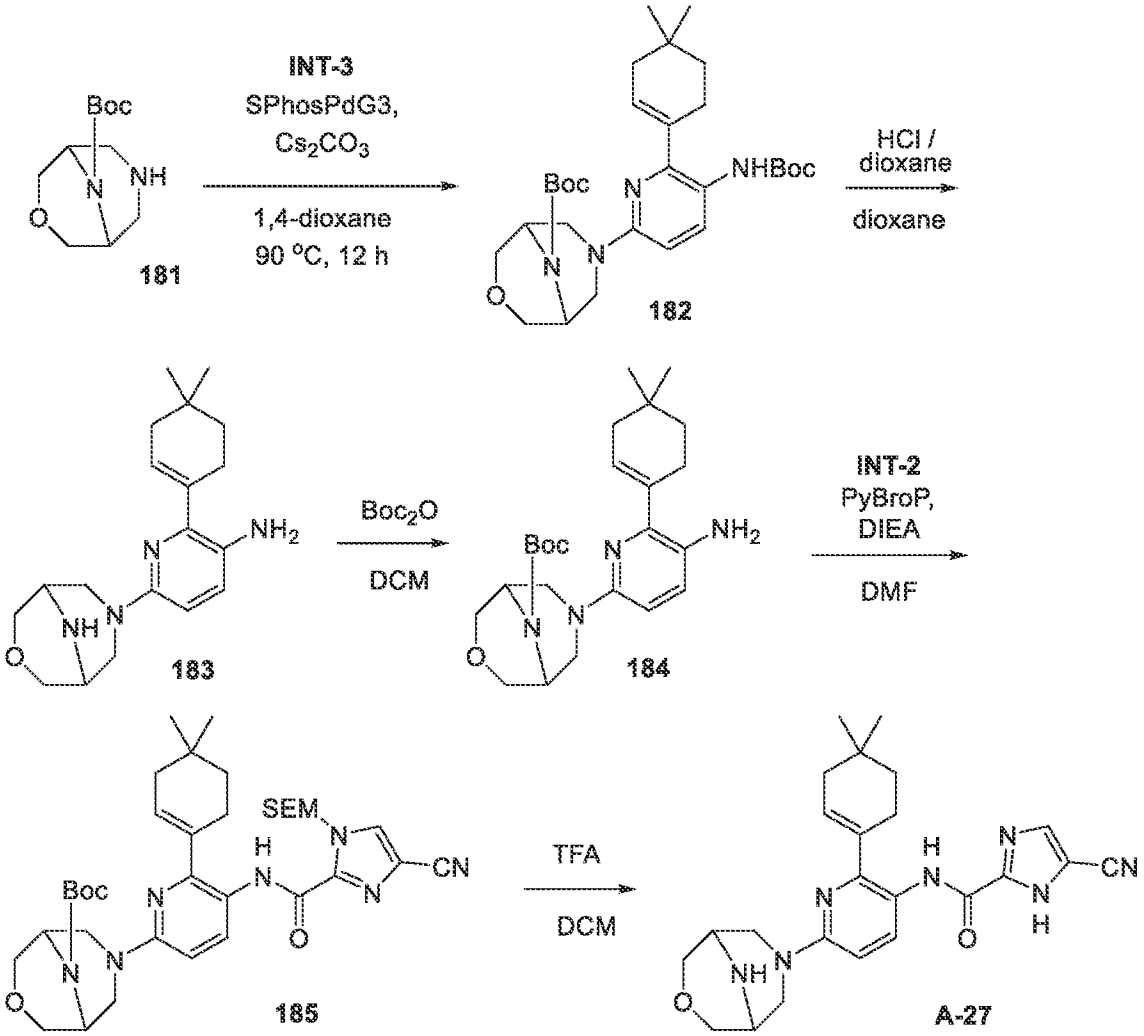
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)pyridin-3-amine (**179**, 0.25 g, 729.88 μmol, 1 eq, HCl salt) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 445.88 mg, 1.46 mmol, 2 eq) in DMF (5 mL) was added PyBroP (510.39 mg, 1.09 mmol, 1.5 eq) and DIEA (283.00 mg, 2.19 mmol, 381.40 μL, 3 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2 and the reaction was monitored by LC/MS (R_t = 0.548 min, [M+H] = 592.5) until it showed that the reaction had been completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with DCM (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**180**, 0.25 g, 422.40 μmol, 57.9 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.64 (s, 1H), 8.41 (d, *J* = 9.0 Hz, 1H), 7.75 (s, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 6.02 - 5.93 (m, 3H), 3.64 (br d, *J* = 8.3 Hz, 2H), 3.42 (br s, 4H), 2.45 - 2.42 (m, 2H), 2.10 (br d, *J* = 3.1 Hz, 2H), 1.82 (s , 12H), 1.60 - 1.57 (m, 2H), 1.08 (s, 6H), 0.98 - 0.95 (m, 2H), 0.00 (s, 9H), MS (LC/MS) *m/z* observed 592.5, expected 592.5 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**180**, 0.25 g, 422.40 μmol, 1 eq) in TFA (1 mL) and DCM (3 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.407 min, [M+H] = 462.4) until it showed that the reaction had been completed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 35 % - 75 % B gradient over 6.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3,3,5,5-tetramethylpiperazin-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-26**, 0.0506 g, 109.62 μmol, 26.0 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.44 (br s, 1H), 8.20 (br d, *J* = 8.9 Hz, 1H), 7.56 (s, 1H), 6.50 (d, *J* = 9.1 Hz, 1H), 5.96 (br s, 1H), 3.41 (s, 4H), 2.44 (br s, 2H), 2.08 (br s, 2H), 1.57 (t, *J* =

6.4 Hz, 2H), 1.28 (s, 12H), 1.06 (s, 6H), MS (LC/MS) *m/z* observed 462.4, expected 462.4 [M+H].

EXAMPLE 32

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-27



To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 500 mg, 1.31 mmol, 1 eq) and *tert*-butyl 3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylate (**181**, 299.35 mg, 1.31 mmol, 1 eq) in dioxane (5 mL), was added Cs_2CO_3 (854.48 mg, 2.62 mmol, 2 eq) and SPhos Pd G3 (102.31 mg, 131.13 μmol, 0.1 eq) at 20 °C, the mixture was warmed and further stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.553 min, [M+H] = 529.4) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a

residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 3/1) to afford *tert*-butyl 7-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**182**, 280 mg, 529.62 μmol, 40.4 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 - 7.96 (m, 1H), 6.49 (br d, *J* = 9.3 Hz, 1H), 5.82 (br s, 1H), 4.26 - 4.17 (m, 2H), 4.16 - 4.04 (m, 2H), 4.00 - 3.92 (m, 2H), 3.86 - 3.78 (m, 2H), 3.28 - 3.14 (m, 2H), 2.41 (br s, 2H), 2.02 (br d, *J* = 2.4 Hz, 2H), 1.56 - 1.53 (m, 2H), 1.49 (s, 18H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 529.4, expected 529.4 [M+H].

To a solution of *tert*-butyl 7-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**182**, 280 mg, 529.62 μmol, 1 eq) in dioxane (2 mL) was added HCl/dioxane (2 mL) at 0 °C, the mixture was allowed to warm and further stirred at 25 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.274 min, [M+H] = 329.1) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction was concentrated under reduced pressure to give a residue, without further purification, to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)pyridin-3-amine (**183**, 170 mg, 465.87 μmol, 88.0 % yield, HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.62 (d, *J* = 9.0 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 5.94 - 5.90 (m, 1H), 4.75 (br d, *J* = 14.4 Hz, 2H), 4.14 - 4.03 (m, 5H), 3.65 - 3.58 (m, 3H), 2.49 (dt, *J* = 2.1, 6.2 Hz, 2H), 2.07 (br d, *J* = 3.5 Hz, 2H), 1.58 (t, *J* = 6.4 Hz, 2H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 329.1, expected 329.1 [M+H].

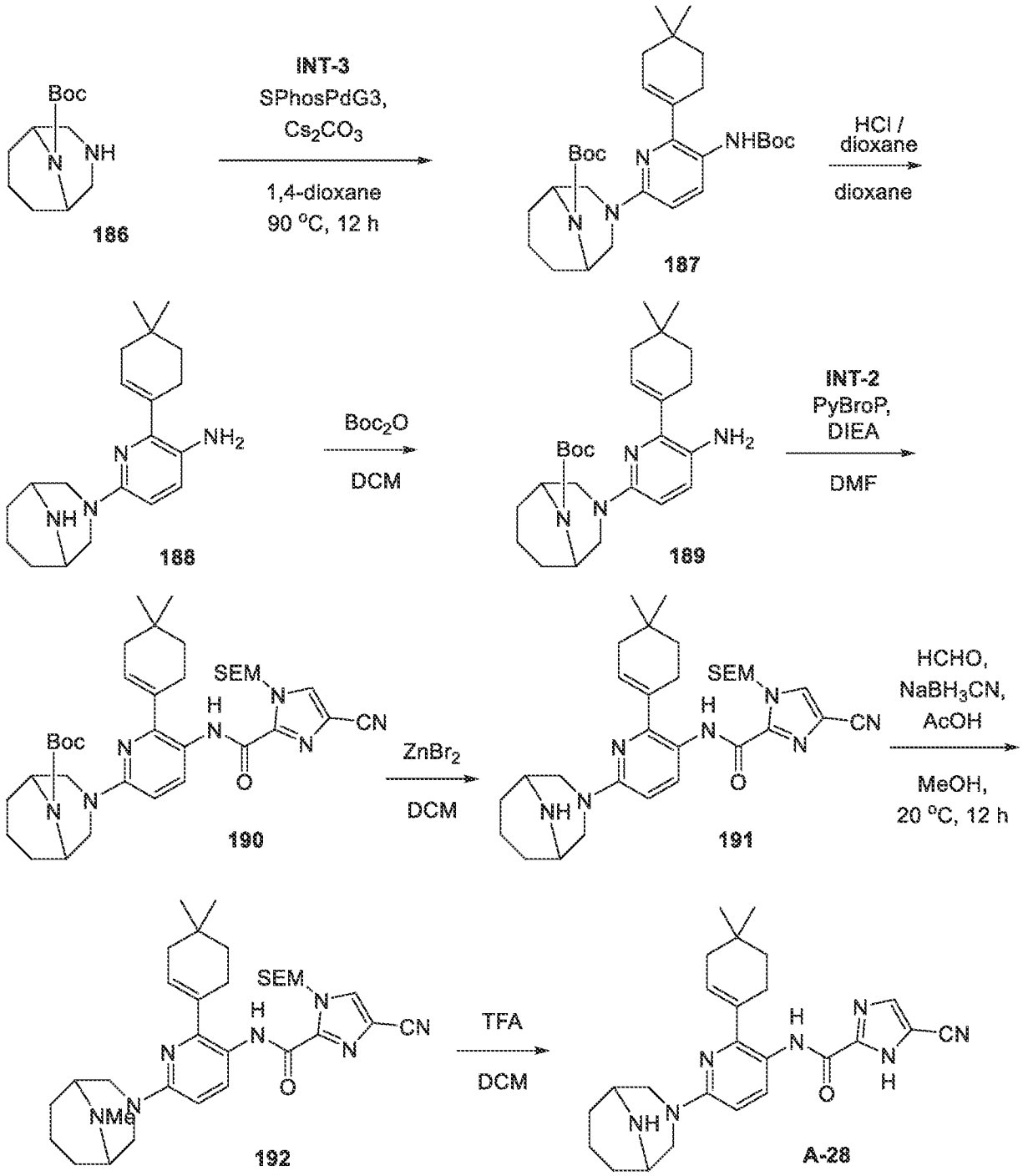
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]-nonan-7-yl)pyridin-3-amine (**183**, 170 mg, 465.87 μmol, 1 eq, HCl salt) in DCM (3 mL) was added TEA (141.42 mg, 1.40 mmol, 194.53 μL, 3 eq) and Boc_2O (111.84 mg, 512.45 μmol, 117.73 μL, 1.1 eq) at 25 °C, the mixture was further stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.436 min, [M+H] = 429.4) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (5 mL) and extracted with DCM (6 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 3/1 to 1/1) to afford *tert*-butyl 7-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**184**, 130 mg, 303.34 μmol, 65.1 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.11 (d, *J* = 8.8 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 1H), 5.89 (br s, 1H), 4.17 - 4.07 (m, 4H), 3.94 (br t, *J* = 11.2 Hz, 2H), 3.77 (br d, *J* = 11.3 Hz, 2H), 3.07 (br d, *J* = 11.8 Hz, 2H), 2.48 - 2.39 (m, 2H), 2.02 (br d, *J* = 3.1 Hz, 2H), 1.54 (br t, *J* = 6.4 Hz, 2H), 1.49 (s, 9H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 429.4, expected 429.4 [M+H].

To a solution of *tert*-butyl 7-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-7,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**184**, 130 mg, 303.34 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 185.31 mg, 606.67 μmol, 2 eq) in DMF (2 mL) was added DIEA (117.61 mg, 910.01 μmol, 158.50 μL, 3 eq), PyBroP (212.11 mg, 455.01 μmol, 1.5 eq) at 25 °C. The mixture was further stirred at 25 °C for 16 hr under N_2 atmosphere and the reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 1/1) to afford *tert*-butyl 7-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-7,9-diazabicyclo[3.3.1]-nonane-9-carboxylate (**185**, 180 mg, 265.52 μmol, 87.5 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 9.1 Hz, 1H), 7.75 (s, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 5.94 (s, 2H), 5.93 (br s, 1H), 4.34 (br d, *J* = 12.8 Hz, 1H), 4.23 - 4.18 (m, 2H), 4.08 (br s, 1H), 4.01 - 3.93 (m, 2H), 3.87 - 3.79 (m, 2H), 3.68 - 3.63 (m, 2H), 3.33 - 3.21 (m, 2H), 2.46 (br s, 2H), 2.11 (br d, *J* = 3.0 Hz, 2H), 1.60 - 1.56 (m, 4H), 1.50 (s, 9H), 1.09 (s, 6H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 678.4, expected 678.4 [M+H].

To a solution of *tert*-butyl 7-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3-oxa-7,9-diaza-bicyclo[3.3.1]nonane-9-carboxylate (**185**, 180 mg, 159.31 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.375 min, [M+H] = 448.4) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 15 % - 45 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(3-oxa-7,9-diazabicyclo[3.3.1]nonan-7-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-27**, 76.7 mg, 136.46 μmol, 85.7 % yield, 99.9 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.19 (d, *J* = 9.0 Hz, 1H), 7.99 (s, 1H), 6.79 (d, *J* = 9.1 Hz, 1H), 5.93 (br s, 1H), 4.70 (d, *J* = 14.3 Hz, 2H), 4.16 - 4.04 (m, 4H), 3.66 (br s, 2H), 3.50 (br d, *J* = 14.3 Hz, 2H), 2.47 (br d, *J* = 1.8 Hz, 2H), 2.02 (br d, *J* = 3.0 Hz, 2H), 1.55 (t, *J* = 6.4 Hz, 2H), 1.03 (s, 6H), MS (LC/MS) *m/z* observed 448.3, expected 448.4 [M+H].

EXAMPLE 33

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(9-methyl-3,9-diazabicyclo[3.3.1]nonan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-28



To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 1 g, 2.62 mmol, 1 eq) and *tert*-butyl 3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**186**, 593.52 mg, 2.62 mmol, 1 eq) in dioxane (10 mL) was added Cs_2CO_3 (1.71 g, 5.25 mmol, 2 eq) and SPhos Pd G3 (204.63 mg, 262.26 μmol, 0.1 eq) at 20 °C, the mixture was warmed and further stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction was

monitored by LC/MS (R_t = 0.622 min, [M+H] = 527.4) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (12 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 3/1) to afford *tert*-butyl 3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,9-diazabicyclo[3.3.1]-nonane-9-carboxylate (**187**, 800 mg, 1.52 mmol, 57.9 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 - 7.90 (m, 1H), 6.54 (br s, 1H), 6.48 (br d, *J* = 9.0 Hz, 1H), 5.84 (br s, 1H), 4.36 (br s, 1H), 4.24 (br s, 1H), 4.13 - 4.02 (m, 2H), 3.07 (br t, *J* = 12.8 Hz, 2H), 2.42 (br d, *J* = 1.3 Hz, 2H), 2.31 - 2.16 (m, 1H), 2.03 (br d, *J* = 2.4 Hz, 2H), 1.89 - 1.73 (m, 4H), 1.60 (s, 1H), 1.54 (br t, *J* = 6.4 Hz, 2H), 1.49 (d, *J* = 2.1 Hz, 18H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 527.4, expected 527.4 [M+H].

To a solution of *tert*-butyl 3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**187**, 800 mg, 1.52 mmol, 1 eq) in dioxane (5 mL) was added HCl/dioxane (5 mL) at 0 °C, the mixture was allowed to warm and further stirred at 25 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.295 min, [M+H] = 327.1) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction mixture was concentrated under reduced pressure to give a residue, without further purification, to afford 6-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**188**, 500 mg, crude, HCl salt) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.66 (d, *J* = 9.0 Hz, 1H), 6.93 (d, *J* = 9.1 Hz, 1H), 5.93 (br s, 1H), 4.53 (d, *J* = 13.9 Hz, 2H), 3.79 (br s, 2H), 3.50 - 3.41 (m, 2H), 2.52 - 2.45 (m, 2H), 2.19 - 2.05 (m, 8H), 1.58 (t, *J* = 6.4 Hz, 2H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 327.1, expected 327.1 [M+H].

To a solution of 6-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**188**, 500 mg, 1.38 mmol, 1 eq, HCl) in DCM (8 mL) was added TEA (418.21 mg, 4.13 mmol, 575.26 μL, 3 eq) and Boc_2O (330.74 mg, 1.52 mmol, 348.14 μL, 1.1 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.468 min, [M+H] = 427.3) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (10 mL) and extracted with DCM (8 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 3/1) to afford *tert*-butyl 3-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**189**, 300 mg, 703.25 μmol, 51.1 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 7.11 (d, *J* =

8.8 Hz, 1H), 6.53 (d, J = 8.8 Hz, 1H), 5.89 (td, J = 1.9, 3.5 Hz, 1H), 4.24 (br s, 2H), 4.04 (br d, J = 12.3 Hz, 2H), 2.93 (br dd, J = 2.5, 12.0 Hz, 2H), 2.44 - 2.41 (m, 2H), 2.02 (br d, J = 4.4 Hz, 2H), 1.86 - 1.79 (m, 4H), 1.57 - 1.50 (m, 4H), 1.49 (s, 9H), 1.03 (s, 6H), MS (LC/MS) *m/z* observed 427.3, expected 427.3 [M+H].

To a solution of *tert*-butyl 3-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**189**, 300 mg, 703.25 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 429.61 mg, 1.41 mmol, 2 eq) in DMF (3 mL) was added DIEA (272.66 mg, 2.11 mmol, 367.47 μL, 3 eq), PyBroP (491.76 mg, 1.05 mmol, 1.5 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford *tert*-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**190**, 300 mg, 443.83 μmol, 63.1 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.20 - 8.17 (m, 2H), 6.70 (d, J = 9.0 Hz, 1H), 5.91 (s, 2H), 5.80 (s, 1H), 4.29 (br s, 4H), 3.64 (d, J = 8.1 Hz, 2H), 3.05 (br d, J = 10.6 Hz, 2H), 2.50 - 2.43 (m, 2H), 2.04 (br d, J = 3.3 Hz, 2H), 1.87 - 1.80 (m, 4H), 1.59 - 1.47 (m, 13H), 1.05 (s, 6H), 0.93 (t, J = 8.0 Hz, 2H), -0.02 (s, 9H), MS (LC/MS) *m/z* observed 676.5, expected 676.4 [M+H].

To a solution of *tert*-butyl 3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-3,9-diazabicyclo[3.3.1]nonane-9-carboxylate (**190**, 300 mg, 443.83 μmol, 1 eq) in DCM (5 mL) was added $ZnBr_2$ (999.51 mg, 4.44 mmol, 222.11 μL, 10 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere and monitored by LC/MS (R_t = 0.542 min, [M+H] = 576.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (6 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 4-cyano-*N*-[6-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**191**, 250 mg, crude) as a yellow solid, and used further as is. MS (LC/MS) *m/z* observed 576.4, expected 576.4 [M+H]

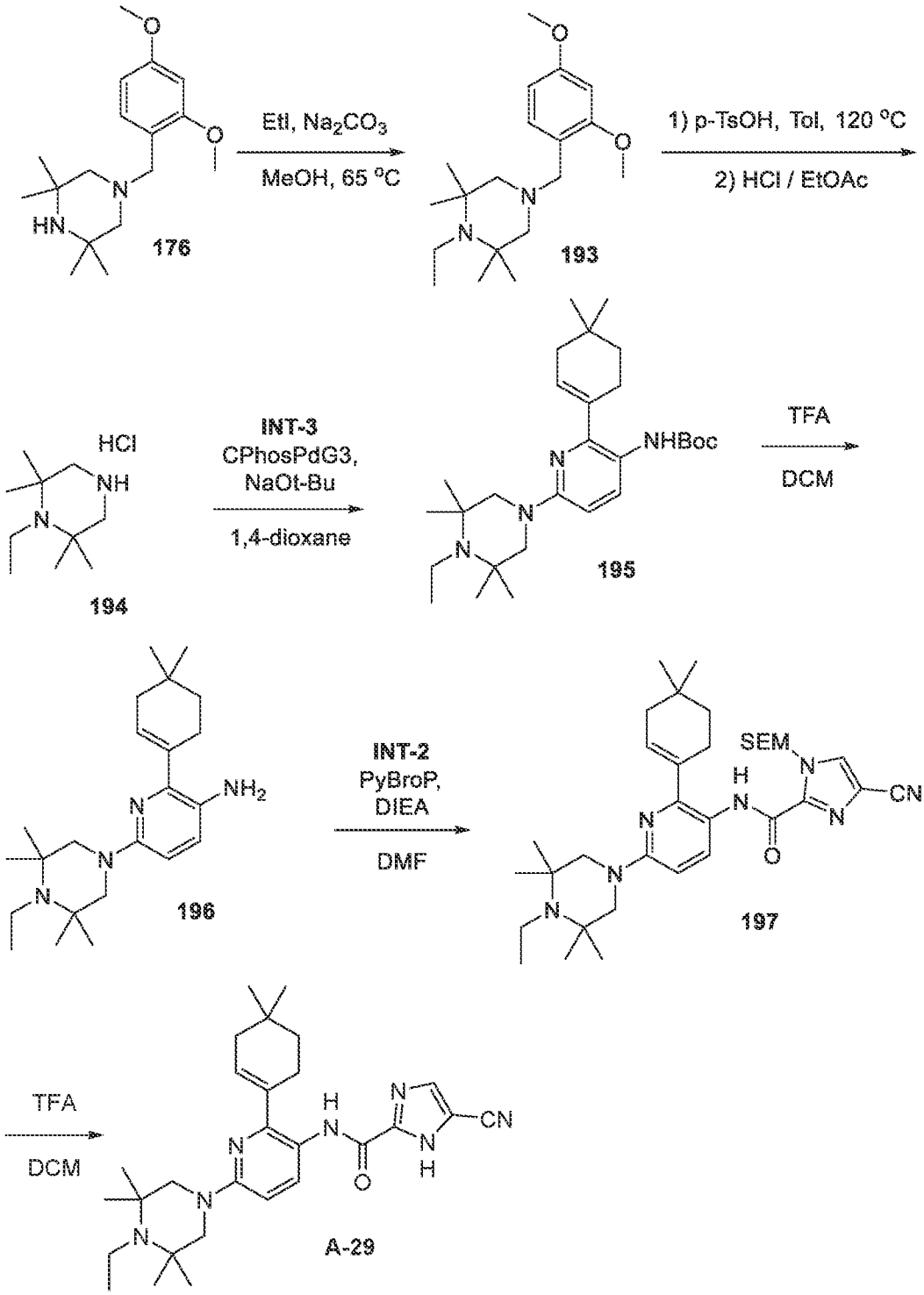
To a solution of 4-cyano-*N*-[6-(3,9-diazabicyclo[3.3.1]nonan-3-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide

(**191**, 250 mg, 434.16 μmol, 1 eq) and formaldehyde (176.16 mg, 2.17 mmol, 161.62 μL, 5 eq) in MeOH (5 mL) was added $NaBH_3CN$ (68.21 mg, 1.09 mmol, 2.5 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.509 min, [M+H] = 590.5) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction mixture was diluted with H_2O (6 mL) and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 40 % - 70 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(9-methyl-3,9-diaza-bicyclo[3.3.1]nonan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**192**, 200 mg, 284.14 μmol, 65.5 % yield, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.28 (d, *J* = 9.0 Hz, 1H), 8.19 (s, 1H), 6.81 (br d, *J* = 8.5 Hz, 1H), 5.94 (br s, 1H), 5.90 (s, 2H), 3.65 (br t, *J* = 7.9 Hz, 6H), 3.15 - 3.06 (m, 4H), 2.48 (br s, 2H), 2.21 (br s, 3H), 2.04 (br d, *J* = 3.1 Hz, 2H), 1.65 - 1.53 (m, 4H), 1.49 (s, 2H), 1.05 (s, 6H), 0.94 (d, *J* = 8.0 Hz, 2H), -0.02 (s, 9H), MS (LC/MS) *m/z* observed 590.5, expected 590.5 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(9-methyl-3,9-diazabicyclo[3.3.1]nonan-3-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**192**, 200 mg, 284.14 μmol, 1 eq, TFA) in DCM (1.5 mL) was added TFA (0.5 mL) at 0 °C, The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.414 min, [M+H] = 460.3) until it showed that the starting material had been completely consumed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 18 % - 48 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(9-methyl-3,9-diazabicyclo[3.3.1]nonan-3-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-28**, 93.5 mg, 200.58 μmol, 70.6 % yield, 98.6 % purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.22 (d, *J* = 8.9 Hz, 1H), 7.99 (s, 1H), 6.81 (br d, *J* = 8.9 Hz, 1H), 5.96 - 5.91 (m, 1H), 4.62 (br d, *J* = 13.8 Hz, 1H), 4.38 (br d, *J* = 14.4 Hz, 1H), 3.66 (br s, 2H), 3.64 - 3.40 (m, 2H), 3.08 (br s, 3H), 2.48 (br d, *J* = 1.6 Hz, 2H), 2.41 - 2.28 (m, 1H), 2.21 (br s, 3H), 2.02 (br d, *J* = 3.4 Hz, 2H), 1.96 (br d, *J* = 14.5 Hz, 1H), 1.61 (br s, 1H), 1.55 (t, *J* = 6.4 Hz, 2H), 1.03 (s, 6H), MS (LC/MS) *m/z* observed 460.4, expected 460.3 [M+H].

EXAMPLE 34

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-29



To a solution of 1-[(2,4-dimethoxyphenyl)methyl]-3,3,5,5-tetramethyl-piperazine (**176**, 2 g, 6.84 mmol, 1 eq) in MeOH (30 mL) was added Na_2CO_3 (2.17 g, 20.52 mmol, 3 eq) and EtI (10.67 g, 68.40 mmol, 5.47 mL, 10 eq). The mixture was stirred at 65 °C for 72 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.357 min, [M+H] = 321.3) until it

showed that the reaction had been completed. The reaction mixture was quenched by H_2O (20 mL) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 250 x 70 mm x 10 um; mobile phase: [H_2O (10mM NH4HCO3) - ACN]; 40 % - 80 % B gradient over 20.0 min) to afford 4-[(2,4-dimethoxyphenyl)methyl]-1-ethyl-2,2,6,6-tetramethyl-piperazine (**193**, 1.2 g, 3.74 mmol, 54.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.3 Hz, 1H), 6.50 - 6.46 (m, 1H), 6.45 (d, *J* = 2.3 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.41 (s, 2H), 2.47 (q, *J* = 7.0 Hz, 2H), 2.17 (br s, 4H), 1.05 (s, 12H), 1.01 (t, *J* = 3.1 Hz, (3H), MS (LC/MS) *m/z* observed 321.3, expected 321.3 [M+H].

To a solution of 4-[(2,4-dimethoxyphenyl)methyl]-1-ethyl-2,2,6,6-tetramethyl-piperazine (**193**, 1.2 g, 3.74 mmol, 1 eq) in toluene (10 mL) was added TsOH (1.42 g, 8.24 mmol, 2.2 eq) at 25 °C. The mixture was heated and further stirred at 120 °C for 12 hr under N_2. The reaction was monitored by ^{1}H NMR until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to give a residue. The mixture was stirred with HCl / EtOAc and the resulting suspension was filtered through a pad of CELITE™ or silica gel and the pad or filter cake was washed with EtOAc (5 mL x 3). The filter cake was the desired product, was without further purification afforded 1-ethyl-2,2,6,6-tetramethyl-piperazine (**194**, 0.7 g, 3.39 mmol, 90.4 % yield, HCl salt) as a crude brown solid, and was used further as is. ^{1}H NMR (400 MHz, CD_3OD) δ = 3.83 - 3.57 (m, 4H), 3.52 (q, *J* = 7.5 Hz, 2H), 1.66 (br d, *J* = 17.0 Hz, 12H), 1.55 (t, *J* = 7.4 Hz, 3H).

To a solution of 1-ethyl-2,2,6,6-tetramethyl-piperazine (**194**, 650.67 mg, 3.15 mmol, 1.2 eq, HCl salt) and *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 1 g, 2.62 mmol, 1 eq) in 1,4-dioxane (9 mL) and THF (3 mL) was added NaOtBu (756.11 mg, 7.87 mmol, 3 eq) and CPHOS Pd G3 (211.47 mg, 262.26 μmol, 0.1 eq) at 20 °C under N_2. The mixture was warmed and further stirred at 90 °C for 12 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.496 min, [M+H] = 471.5) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)-3-pyridyl]carbamate (**195**, 0.5 g, 1.06 mmol, 40.5 % yield) as a crude yellow oil. MS (LC/MS) *m/z* observed 471.5, expected 471.5 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)-3-pyridyl]carbamate (**195**, 0.5 g, 1.06 mmol, 1 eq) in TFA (2 mL) and DCM (6 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.343 min, [M+H] = 371.4) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to give a residue, without further purification, to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)pyridin-3-amine (**196**, 0.3 g, 809.56 μmol, 76.21% yield) as a crude yellow oil, used further as is. MS (LC/MS) *m/z* observed 371.4, expected 371.4 [M+H].

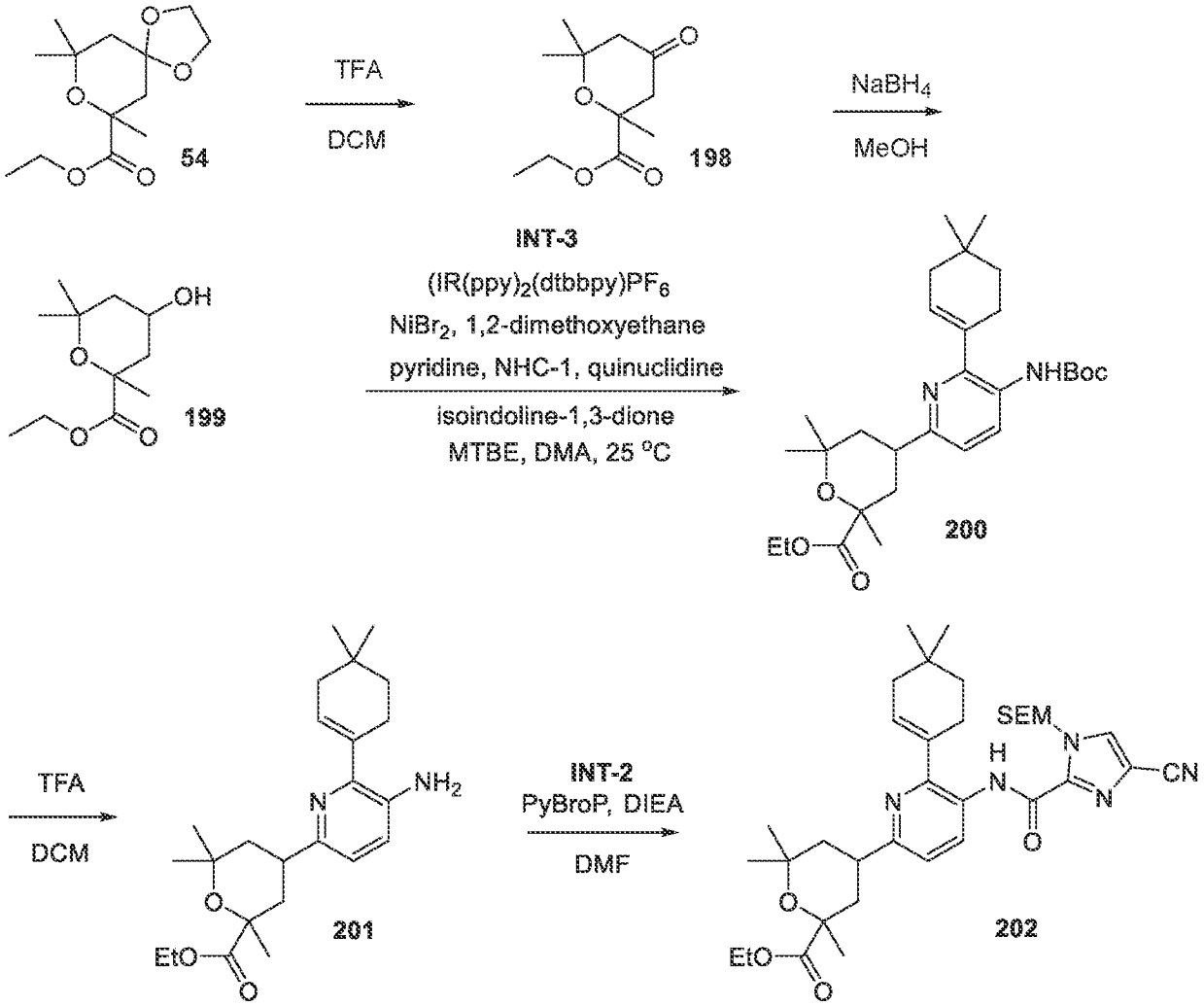
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)pyridin-3-amine (**196**, 0.3 g, 809.56 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 494.55 mg, 1.62 mmol, 2 eq) in DMF (5 mL) was added PyBroP (566.10 mg, 1.21 mmol, 1.5 eq) and DIEA (313.89 mg, 2.43 mmol, 423.03 μL, 3 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.555 min, [M+H] = 620.5) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1% TFA) - ACN]; 40 % - 70 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**197**, 0.19 g, 306.49 μmol, 37.9 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.25 (d, *J* = 9.0 Hz, 1H), 8.20 (s, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 5.94 - 5.87 (m, 3H), 4.51 (d, *J* = 13.9 Hz, 2H), 3.68 - 3.63 (m, 2H), 3.40 (q, *J* = 7.5 Hz, 2H), 3.10 (br d, *J* = 14.0 Hz, 2H), 2.45 (br d, *J* = 1.9 Hz, 2H),2.04 (br d, *J* = 3.3 Hz, 2H), 1.58 - 1.55 (m, 2H), 1.53 (s, 6H), 1.49 - 1.46 (m, 9H), 1.05 (s, 6H), 0.93 (t, *J* = 8.0 Hz, 2H), -0.02 (s, 8H), MS (LC/MS) *m/z* observed 620.5, expected 620.5 [M+H].

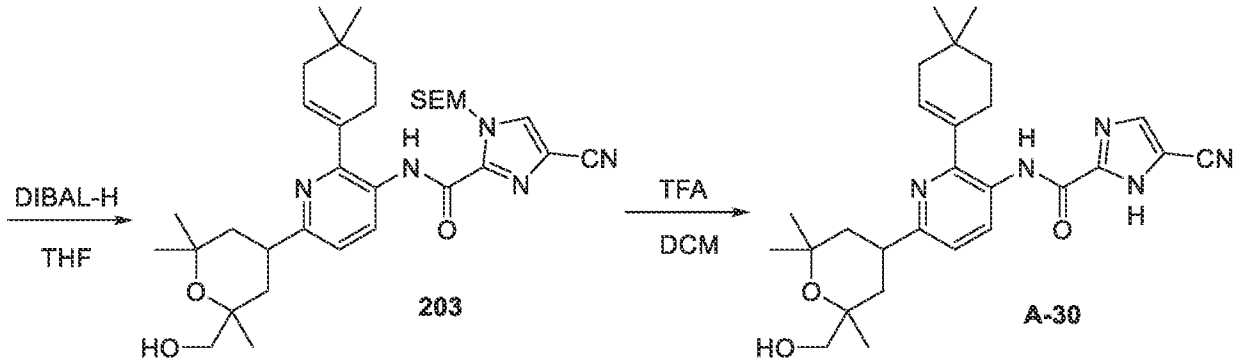
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**197**, 0.19 g, 306.49 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.434 min, [M+H] = 490.4) until it showed that the reaction had completed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 30 % - 60 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-

(4,4-dimethylcyclohexen-1-yl)-6-(4-ethyl-3,3,5,5-tetramethyl-piperazin-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-29**, 59.7 mg, 121.92 μmol, 39.8 % yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.19 (d, *J* = 8.9 Hz, 1H), 7.99 (s, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 5.93 (td, *J* = 2.0, 3.6 Hz, 1H), 4.51 (d, *J* = 14.0 Hz, 2H), 3.40 (q, *J* = 7.4 Hz, 2H), 3.11 (br d, *J* = 14.0 Hz, 2H), 2.50 - 2.40 (m, 2H), 2.01 (br d, *J* = 3.5 Hz, 2H), 1.57 - 1.54 (m, 2H), 1.53 (s, 6H), 1.50 - 1.45 (m, 9H), 1.03 (s, 6H), MS (LC/MS) *m/z* observed 490.4, expected 490.4 [M+H].

EXAMPLE 35

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(hydroxymethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-30





To a solution of ethyl 7,9,9-trimethyl-1,4,8-trioxaspiro[4.5]decane-7-carboxylate (**54**, 3.2 g, 12.39 mmol, 1 eq) in DCM (30 mL) was added TFA (10 mL) at 0 °C. The mixture was allowed to warm and further stirred at 25 °C for 2 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction was adjusted to pH = 8~9 with $NaHCO_3$ (aqueous) and extracted with DCM (30 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford ethyl 2,6,6-trimethyl-4-oxo-tetrahydropyran-2-carboxylate (**198**, 2.4 g, crude) as a yellow oil, used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.20 (q, *J* = 7.0 Hz, 2H), 3.11 (d, *J* = 16.9 Hz, 1H), 2.47 - 2.34 (m, 3H), 1.51 (s, 3H), 1.33 - 1.28 (m, 9H).

To a solution of ethyl 2,6,6-trimethyl-4-oxo-tetrahydropyran-2-carboxylate (**198**, 2.4 g, 11.20 mmol, 1 eq) in MeOH (25 mL) was added $NaBH_4$ (508.50 mg, 13.44 mmol, 1.2 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.2) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with NH_4Cl (30 mL, aqueous) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford ethyl 4-hydroxy-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**199**, 1.9 g, 8.79 mmol, 78.4 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.26 - 4.16 (m, 3H), 2.34 (ddd, *J* = 0.9, 4.2, 14.5 Hz, 1H), 1.79 (dd, *J* = 4.7, 14.6 Hz, 1H), 1.69 - 1.63 (m, 2H), 1.42 - 1.41 (m, 3H), 1.33 - 1.29 (m, 6H), 1.24 (s, 3H).

To a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**199**, 1.71 g, 4.49 mmol, 1 eq) and ethyl 4-hydroxy-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (1.7 g, 7.86 mmol, 1.75 eq) in MTBE (10 mL) was added bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl) pyridine; hexafluorophosphate (61.58 mg, 67.38 μmol, 0.015 eq), dibromonickel; 1,2-dimethoxyethane

(69.31 mg, 224.58 μmol, 0.05 eq), 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine (90.42 mg, 336.88 μmol, 0.075 eq), NHC-1 (2.84 g, 7.19 mmol, 1.6 eq), pyridine (568.47 mg, 7.19 mmol, 580.07 μL, 1.6 eq), quinuclidine (874.00 mg, 7.86 mmol, 1.75 eq), isoindoline-1,3-dione (148.69 mg, 1.01 mmol, 0.225 eq) and DMA (10 mL) at 25 °C, The mixture was stirred at 25 °C for 16 hr under 34W blue LED light. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (15 mL x 3) and washed with brine (30 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 3/1) to afford ethyl 4-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyltetrahydropyran-2-carboxylate (**200**, 1.1 g, 2.20 mmol, 48.9 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25 (br d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.92 (s, 1H), 5.82 (br s, 1H), 4.25 - 4.12 (m, 2H), 3.27 - 3.15 (m, 1H), 2.53 (br dd, *J* = 1.4, 13.2 Hz, 1H), 2.42 (br d, *J* = 1.6 Hz, 2H), 2.05 (br s, 2H), 1.77 - 1.70 (m, 1H), 1.66 (br t, *J* = 6.3 Hz, 2H), 1.58 (br t, *J* = 6.3 Hz, 2H), 1.51 (s, 9H), 1.43 (s, 3H), 1.34 - 1.31 (m, 6H), 1.21 (s, 3H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 501.5, expected 501.3 [M+H].

To a solution of ethyl 4-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyltetrahydropyran-2-carboxylate (**200**, 1.16 g, 2.32 mmol, 1 eq) in DCM (9 mL) was added TFA (3 mL) at 0 °C. The mixture was stirred at 25 °C for 2 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.1) until it showed that the starting material had been completely consumed. The reaction was adjusted to pH = 8~9 with $NaHCO_3$ (aqueous) and extracted with DCM (15 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford ethyl 4-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**201**, 900 mg, crude) as a yellow oil, that was used further as is, without further characterization.

To a solution of ethyl 4-[5-amino-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**201**, 900 mg, 2.25 mmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 1.37 g, 4.49 mmol, 2 eq) in DMF (10 mL) was added DIEA (871.17 mg, 6.74 mmol, 1.17 mL, 3 eq), PyBroP (1.57 g, 3.37 mmol, 1.5 eq) at 25 °C, The mixture was stirred at 25 °C for 3 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, dried over

Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 1/1) to afford ethyl 4-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**202**, 1.1 g, 1.69 mmol, 75.3 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.92 (s, 1H), 8.65 (br d, *J* = 8.3 Hz, 1H), 7.77 (s, 1H), 7.10 (br d, *J* = 8.4 Hz, 1H), 5.95 (br s, 1H), 5.93 (s, 2H), 4.24 - 4.16 (m, 2H), 3.69 - 3.63 (m, 2H), 3.27 (br s, 1H), 2.48 (br s, 2H), 2.15 (br d, *J* = 2.6 Hz, 2H), 2.08 (br s, 1H), 1.88 (br dd, *J* = 3.2, 13.2 Hz, 1H), 1.75 - 1.61 (m, 4H), 1.58 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H), 1.28 - 1.26 (m, 3H), 1.13 (s, 6H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

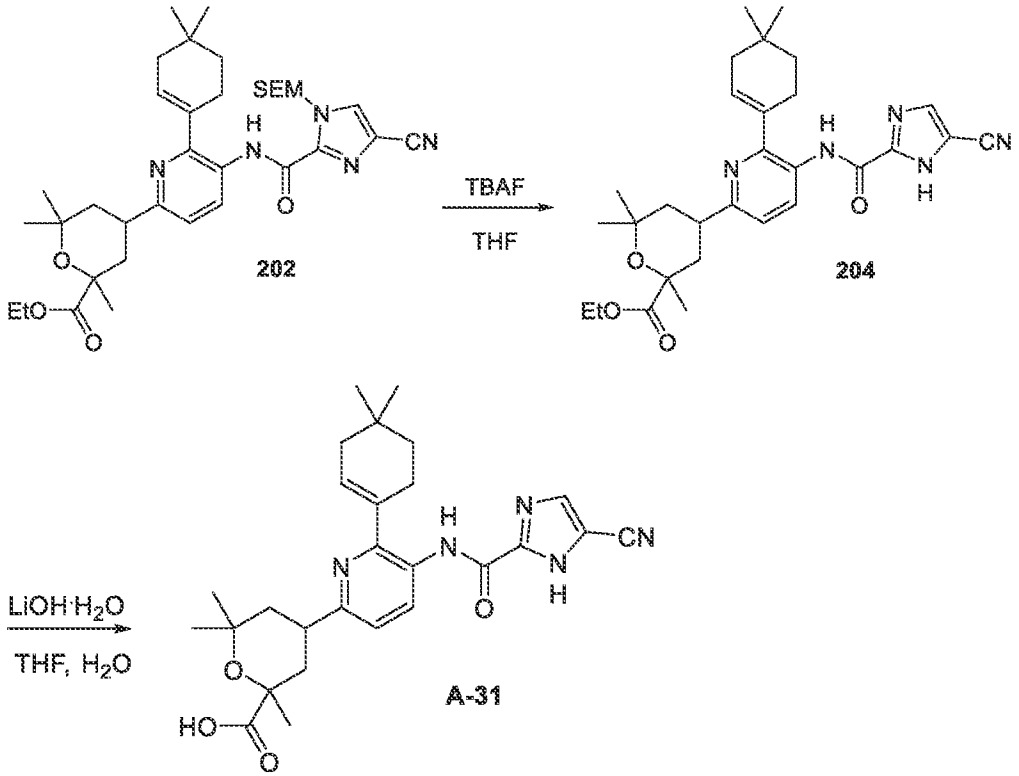
To a solution of ethyl 4-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**202**, 200 mg, 307.74 μmol, 1 eq) in THF (3 mL) was added DIBAL-H (1 M, 1.85 mL, 6 eq) dropwise at 0 °C, the mixture was allowed to warm and further stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.630 min, [M+H] = 608.4) until it showed ~40% starting material remained and ~40% of the desired product mass was observed. The reaction mixture was quenched by the addition of Na_2SO_4 (5 g, decahydrate). The resulting solid was collected by filtration, washed with EtOAc (10 mL x 3) and dried to obtain a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 % - 85 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(hydroxymethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**203**, 90 mg, 124.67 μmol, 40.5 % yield, TFA salt) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.86 (d, *J* = 8.8 Hz, 1H), 8.25 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 6.15 - 6.10 (m, 1H), 5.91 (s, 2H), 3.70 - 3.65 (m, 2H), 3.52 (tt, *J* = 3.7, 12.1 Hz, 1H), 2.46 (br d, *J* = 2.0 Hz, 2H), 2.16 (br d, *J* = 3.3 Hz, 2H), 1.91 - 1.84 (m, 1H), 1.80 - 1.73 (m, 2H), 1.67 - 1.63 (m, 3H), 1.41 (s, 3H), 1.40 (s, 2H), 1.34 (s, 3H), 1.28 (s, 3H), 1.13 (s, 6H), 0.96 - 0.92 (m, 2H), -0.02 (s, 9H), MS (LC/MS) *m/z* observed 608.4, expected 608.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(hydroxymethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**203**, 90 mg, 148.06 μmol, 1 eq) in DCM (0.9 mL) was added TFA (0.3 mL). The mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.459 min, [M+H] = 478.4) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN];

25 % - 60 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[2-(hydroxymethyl)-2,6,6-trimethyl-tetrahydropyran-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-30**, 52.3 mg, 86.60 μmol, 58.5 % yield, 97.96 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.93 (d, *J* = 8.6 Hz, 1H), 8.05 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 6.21 - 6.15 (m, 1H), 3.58 (tt, *J* = 3.7, 12.2 Hz, 1H), 3.42 - 3.36 (m, 1H), 3.30 - 3.27 (m, 1H), 2.46 (br d, *J* = 2.0 Hz, 2H), 2.16 (br d, *J* = 3.4 Hz, 2H), 1.89 (td, *J* = 1.5, 12.7 Hz, 1H), 1.84 - 1.68 (m, 3H), 1.67 - 1.64 (m, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.12 (s, 6H), MS (LC/MS) *m/z* observed 478.4, expected 478.4 [M+H].

EXAMPLE 36

4-[5-[(5-Cyano-1*H*-imidazole-2-carbonyl)amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylic acid A-31



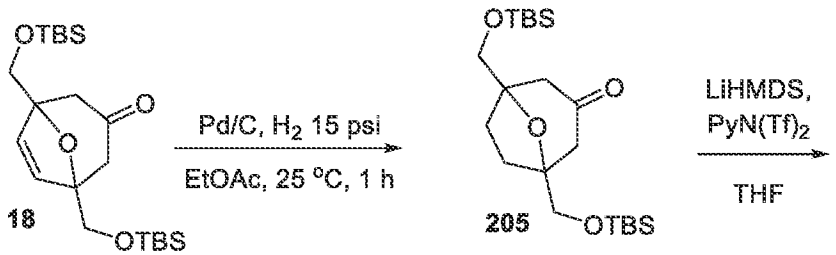
To a solution of ethyl 4-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**202**, 0.2 g, 307.74 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 615.49 μL, 2 eq) at 20 °C, the mixture was stirred at 65 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.2) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc (5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

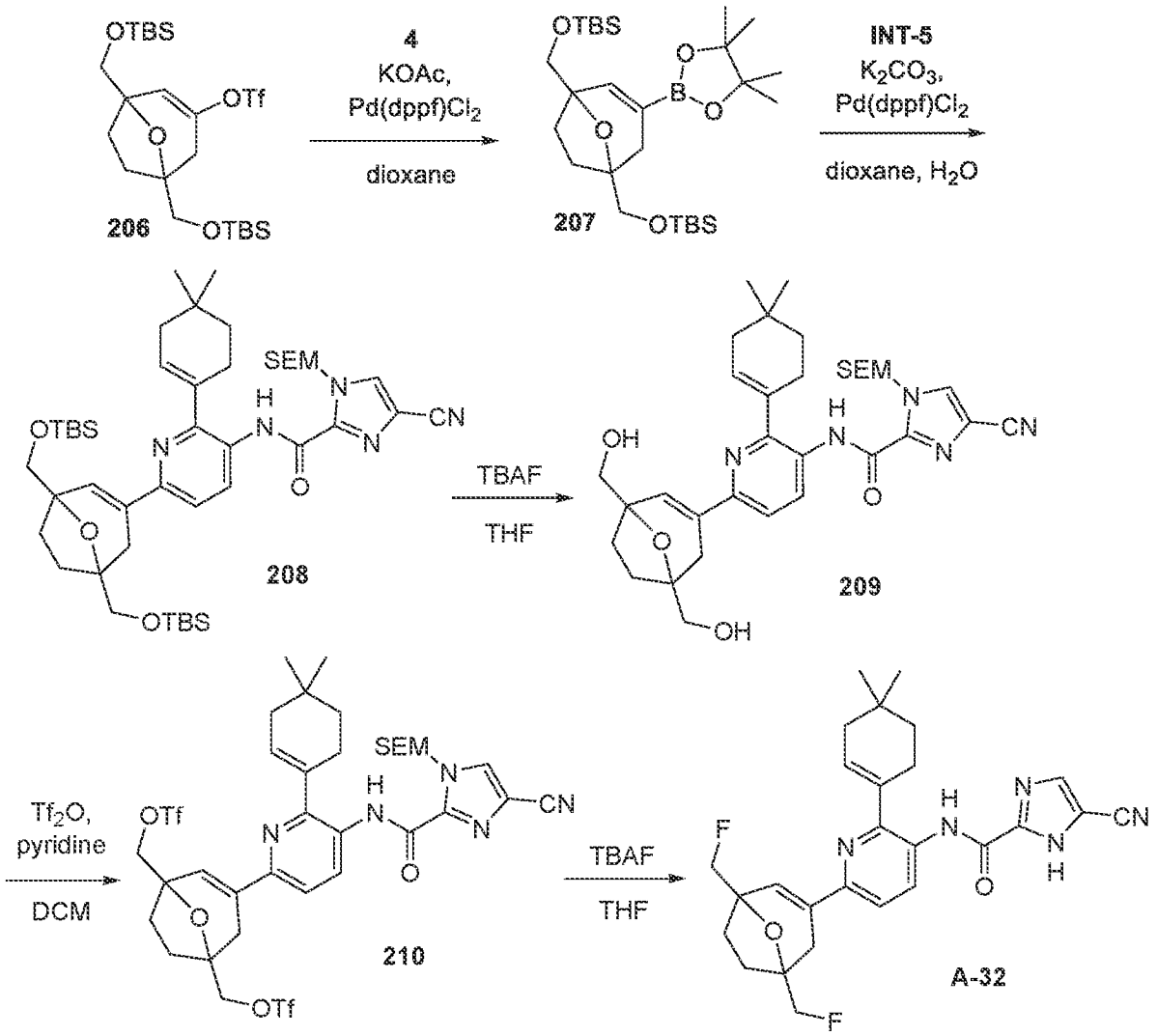
column (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford ethyl 4-[5-[(4-cyano-1H-imidazole-2-carbonyl)amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**204**, 150 mg, crude) as a yellow oil, that was used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.77 (s, 1H), 8.68 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 5.96 (br s, 1H), 4.24 - 4.16 (m, 2H), 3.27 (br s, 1H), 2.47 (br s, 2H), 2.13 (br d, *J* = 2.3 Hz, 2H), 1.68 - 1.61 (m, 6H), 1.59 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.28 - 1.26 (m, 3H), 1.11 (s, 6H), MS (LC/MS) *m/z* observed 520.4, expected 520.3 [M+H].

To a solution of ethyl 4-[5-[(4-cyano-1*H*-imidazole-2-carbonyl)amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylate (**204**, 150 mg, 288.66 μmol, 1 eq) in THF (2 mL) was added LiOH·H_2O (60.56 mg, 1.44 mmol, 5 eq) in H_2O (1 mL) dropwise at 25 °C. The mixture was stirred at 25 °C for 2 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was adjusted to pH 4~6 with 2 N HCl and extracted with EtOAc (8 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 30 % - 60 % B gradient over 8.0 min) to afford title compound 4-[5-[(5-cyano-1*H*-imidazole-2-carbonyl)amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-2,6,6-trimethyl-tetrahydropyran-2-carboxylic acid (**A-31**, 47.3 mg, 94.00 μmol, 32.6 % yield, 97.7 % purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.68 (d, *J* = 8.6 Hz, 1H), 8.02 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 6.02 (br s, 1H), 3.43 (tt, *J* = 3.7, 12.3 Hz, 1H), 2.46 (br d, *J* = 1.8 Hz, 2H), 2.15 - 2.06 (m, 3H), 2.03 - 1.94 (m, 1H), 1.89 (br dd, *J* = 1.8, 13.1 Hz, 1H), 1.76 - 1.68 (m, 1H), 1.66 - 1.59 (m, 5H), 1.42 (s, 3H), 1.35 (s, 3H), 1.11 (s, 6H), MS (LC/MS) *m/z* observed 492.4, expected 492.3 [M+H].

EXAMPLE 37

***N*-[6-[1,5-Bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide A-32**





To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**, 5 g, 12.12 mmol, 1 eq) in EtOAc (60 mL) was added Pd/C (1.29 g, 1.21 mmol, 10 % purity, 0.1 eq) at 25 °C. The mixture was stirred at 25 °C for 1 hr under H_2 (1 5psi). The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-one (**205**, 5 g, crude) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.66 - 3.60 (m, 2H), 3.59 - 3.53 (m, 2H), 2.55 (d, *J* = 15.5 Hz, 2H), 2.24 (d, *J* = 15.8 Hz, 2H), 1.76 - 1.69 (m, 2H), 1.68 - 1.63 (m, 2H), 0.82 (s, 18H), 0.00 (d, *J* = 1.4 Hz, 12H).

To a solution of LiHMDS (1 M, 4.34 mL, 1.2 eq) in THF (10 mL) was added 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-one (**205**, 1.5 g, 3.62 mmol, 1 eq) in THF (5 mL) dropwise at -78 °C under N_2. The mixture was allowed to warm and further stirred at 20 °C for 1 h. The mixture was cooled and 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-

(trifluoromethylsulfonyl)methanesulfonamide (1.55 g, 4.34 mmol, 1.2 eq) in THF (5 mL) was then added dropwise at -78 °C under N_2, the mixture was again allowed to warm and further stirred at 20 °C for 3 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.9) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (20 mL, aqueous) and extracted with EtOAc (15 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford [1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**206**, 1.6 g, 2.93 mmol, 80.9 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.07 (s, 1H), 3.79 - 3.70 (m, 2H), 3.68 (s, 2H), 2.80 (br d, *J* = 16.4 Hz, 1H), 2.18 - 2.08 (m, 2H), 2.02 - 1.92 (m, 1H), 1.87 - 1.74 (m, 2H), 0.90 (d, *J* = 2.0 Hz, 18H), 0.09 - 0.06 (m, 12H).

To a solution of [1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**206**, 1.6 g, 2.93 mmol, 1 eq) in dioxane (20 mL) was added Pin_2B_2 (**4**, 891.69 mg, 3.51 mmol, 1.2 eq) and KOAc (861.53 mg, 8.78 mmol, 3 eq) and Pd(dppf)Cl_2 (214.11 mg, 292.62 μmol, 0.1 eq) at 20 °C. The mixture was warmed and further stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.7) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2,Pet. Et. / EtOAc = 10/1 to 3/1) to afford *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-1-yl]methoxy]-dimethyl-silane (**207**, 1.4 g, 2.67 mmol, 91.2 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.73 (s, 1H), 3.74 (s, 2H), 3.69 - 3.57 (m, 2H), 2.44 (br d, *J* = 17.4 Hz, 1H), 2.06 - 1.98 (m, 1H), 1.98 - 1.91 (m, 2H), 1.86 - 1.76 (m, 1H), 1.69 - 1.63 (m, 1H), 1.26 (s, 12H), 0.90 (s, 18H), 0.06 (s, 12H).

To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-1-yl]methoxy]-dimethyl-silane (**207**, 400 mg, 762.36 μmol, 1 eq)and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 404.46 mg, 762.36 μmol, 1 eq) in dioxane (6 mL) and H_2O (1.2 mL) was added K_2CO_3 (263.41 mg, 1.91 mmol, 2.5 eq) and Pd(dppf)Cl_2 (55.78 mg, 76.24 μmol, 0.1 eq) at 20 °C. The mixture was warmed and further stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.3) until it showed that the starting material

had been completely consumed. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc (7 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2,Pet. Et. / EtOAc = 10/1 to 3/1) to afford *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**208**, 380 mg, 447.93 μmol, 58.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.01 (s, 1H), 8.68 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.28 - 7.27 (m, 1H), 6.98 (s, 1H), 5.99 (br s, 1H), 5.94 (s, 2H), 3.83 (q, *J* = 10.1 Hz, 2H), 3.78 (s, 2H), 3.69 - 3.64 (m, 2H), 2.79 (br d, *J* = 17.0 Hz, 1H), 2.53 (br s, 2H), 2.47 (br d, *J* = 17.0 Hz, 1H), 2.15 (br d, *J* = 2.5 Hz, 2H), 2.08 (br d, *J* = 9.9 Hz, 1H), 2.00 (br t, *J* = 11.3 Hz, 1H), 1.90 - 1.83 (m, 1H), 1.82 - 1.75 (m, 1H), 1.12 (s, 6H), 1.00 - 0.96 (m, 2H), 0.93 (s, 18H), 0.12 - 0.08 (m, 12H), 0.04 - 0.02 (m, 9H).

To a solution of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**208**, 380 mg, 447.93 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 895.86 μL, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.2) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc(5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**209**, 200 mg, crude) as a yellow oil, and used further as is. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.59 (d, *J* = 8.8 Hz, 1H), 8.21 (s, 1H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.82 (s, 1H), 5.93 (td, *J* = 2.0, 3.5 Hz, 1H), 5.91 (s, 2H), 3.87 - 3.78 (m, 2H), 3.77 - 3.72 (m, 2H), 3.69 - 3.66 (m, 2H), 2.79 (br d, *J* = 17.0 Hz, 1H), 2.52 - 2.43 (m, 3H), 2.11 (br d, *J* = 3.1 Hz, 2H), 1.99 (br dd, *J* = 2.3, 8.6 Hz, 2H), 1.69 - 1.66 (m, 2H), 1.11 (s, 6H), 1.05 (s, 2H), -0.03 (s, 9H), MS (LC/MS) *m/z* observed 620.4, expected 620.3 [M+H].

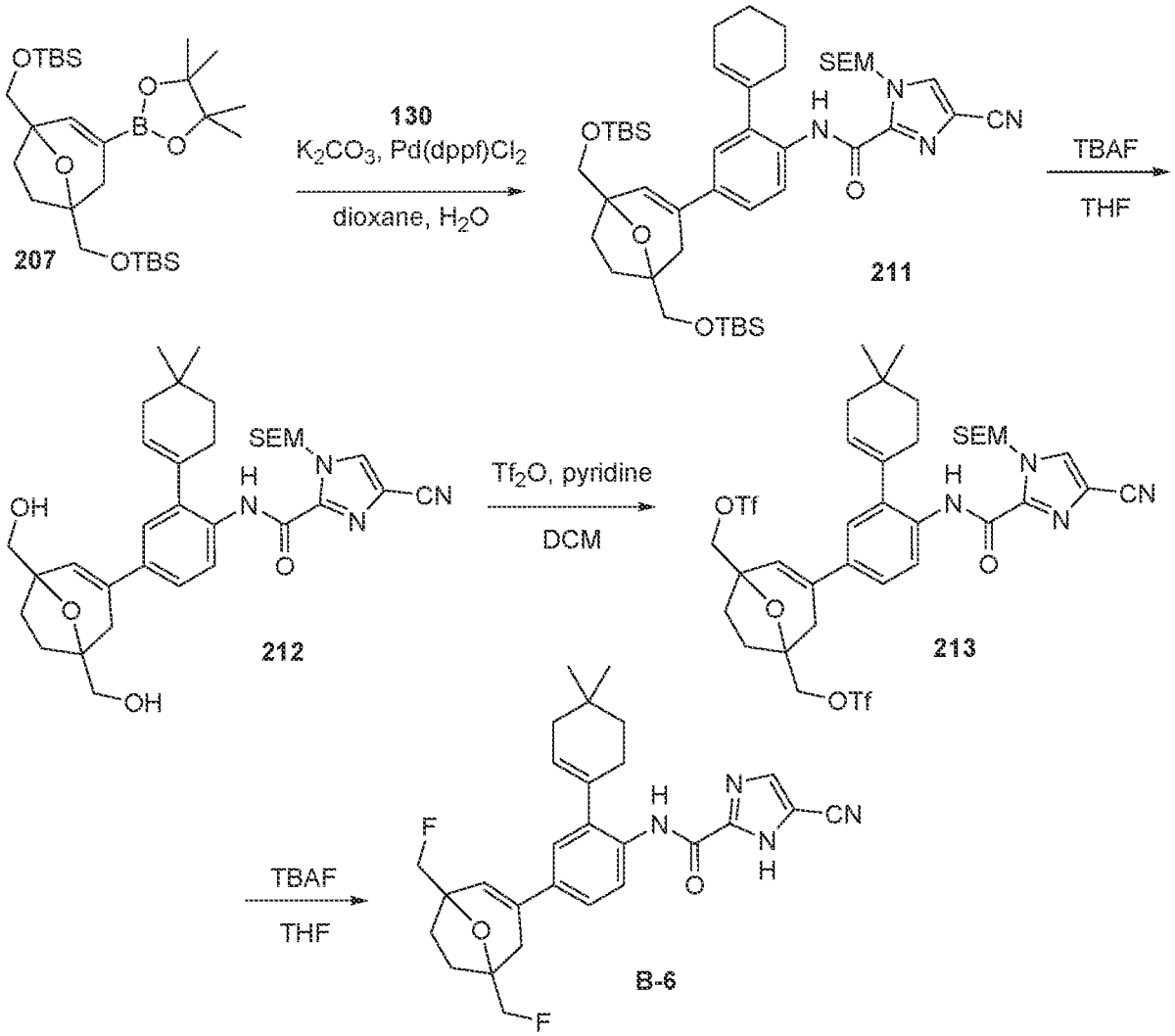
To a solution of *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**209**, 200 mg, 322.67 μmol, 1 eq) in DCM (3 mL) was added pyridine (127.62 mg, 1.61 mmol, 130.22 μL, 5 eq) and Tf_2O (273.12 mg, 968.02 μmol, 159.72 μL, 3 eq) at 25 °C. The mixture was stirred at 25 °C for 0.5 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (6 mL) and extracted with

EtOAc (5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-3-en-1-yl]methyl trifluoromethanesulfonate (**210**, 150 mg, crude) as a yellow oil and used further as is. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.61 (br d, *J* = 2.6 Hz, 1H), 8.21 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.94 - 6.76 (m, 1H), 5.95 (br d, *J* = 3.5 Hz, 1H), 5.91 (s, 2H), 3.67 (t, *J* = 8.0 Hz, 2H), 3.26 - 3.21 (m, 4H), 2.92 - 2.76 (m, 1H), 2.54 - 2.43 (m, 3H), 2.11 (br s, 4H), 1.62 - 1.59 (m, 2H), 1.10 (s, 6H), 1.05 (s, 2H), -0.02 (s, 9H).

To a solution of [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-3-en-1-yl]methyl trifluoromethanesulfonate (**210**, 150 mg, 169.69 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 848.47 μL, 5 eq) at 25 °C. The mixture was warmed and further stirred at 40 °C for 1 h and then warmed again and further stirred at 60 °C for a further 15 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc (5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 3/1 to 0/1) and then by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 45 % - 75 % B gradient over 8.0 min) to afford title compound *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-32**, 31.4 mg, 51.60 μmol, 30.4 % yield, 99.8 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.70 (d, *J* = 8.6 Hz, 1H), 8.02 (s, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 6.86 (s, 1H), 6.02 (td, *J* = 1.9, 3.6 Hz, 1H), 4.76 - 4.64 (m, 1H), 4.64 - 4.60 (m, 1H), 4.59 - 4.52 (m, 1H), 4.52 - 4.43 (m, 1H), 2.93 (br d, *J* = 16.4 Hz, 1H), 2.54 - 2.45 (m, 3H), 2.13 (br d, *J* = 3.5 Hz, 3H), 2.03 (br d, *J* = 12.1 Hz, 1H), 1.99 - 1.88 (m, 2H), 1.63 (t, *J* = 6.3 Hz, 2H), 1.11 (s, 6H), MS (LC/MS) *m/z* observed 494.3, expected 494.2 [M+H].

EXAMPLE 38

***N*-[4-[1,5-Bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide B-6**



To a solution of tert-*butyl*-[[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-1-yl]methoxy]-dimethyl-silane (**207**, 500 mg, 952.95 μmol, 1 eq) and *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 504.63 mg, 952.95 μmol, 1 eq) in dioxane (6 mL) and H_2O (1.2 mL) was added K_2CO_3 (329.27 mg, 2.38 mmol, 2.5 eq) and Pd(dppf)Cl_2 (69.73 mg, 95.29 μmol, 0.1 eq) at 20 °C. The mixture was warmed and further stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.55) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by

column chromatography (SiO_2,Pet. Et. / EtOAc = 10/1 to 3/1) to afford *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**211**, 320 mg, 377.64 μmol, 39.6 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.32 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.21 (d, *J* = 2.1 Hz, 1H), 6.42 (s, 1H), 5.96 (s, 2H), 5.78 (br s, 1H), 3.82 (d, *J* = 2.6 Hz, 2H), 3.76 (d, *J* = 1.4 Hz, 2H), 3.69 - 3.64 (m, 2H), 2.76 (br d, *J* = 16.5 Hz, 1H), 2.34 - 2.25 (m, 3H), 2.11 (br d, *J* = 2.9 Hz, 2H), 2.05 - 1.97 (m, 2H), 1.89 - 1.80 (m, 1H), 1.79 - 1.71 (m, 1H), 1.61 - 1.57 (m, 2H), 1.12 (s, 6H), 1.00 - 0.96 (m, 2H), 0.93 (s, 18H), 0.13 - 0.08 (m, 12H), 0.01 (s, 9H).

To a solution of *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**211**, 320 mg, 377.64 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 755.29 μL, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.2) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc(5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**212**, 180 mg, crude) as a yellow oil, used further as is. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.23 (d, *J* = 8.5 Hz, 1H), 8.18 (s, 1H), 7.36 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 6.38 (s, 1H), 5.92 (s, 2H), 5.74 (br d, *J* = 1.8 Hz, 1H), 3.83 - 3.75 (m, 2H), 3.73 - 3.68 (m, 2H), 3.68 - 3.64 (m, 2H), 2.77 (br d, *J* = 16.6 Hz, 1H), 2.34 - 2.28 (m, 3H), 2.08 (br s, 2H), 1.99 - 1.94 (m, 2H), 1.85 - 1.78 (m, 1H), 1.71 - 1.67 (m, 1H), 1.61 - 1.58 (m, 2H), 1.10 (s, 6H), 0.99 - 0.95 (m, 2H), -0.03 (s, 9H), MS (LC/MS) *m/z* observed 619.4, expected 619.3 [M+H].

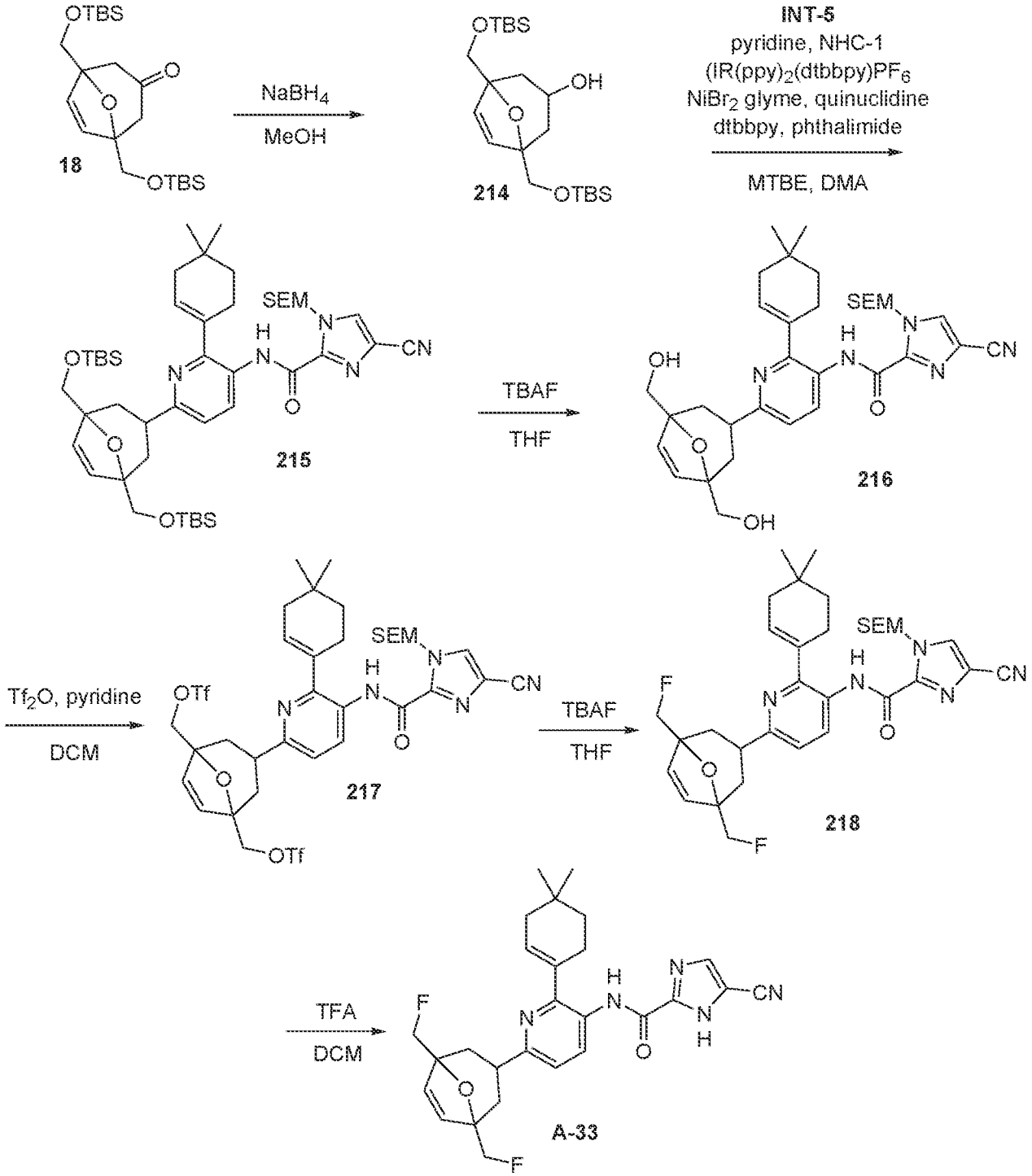
To a solution of *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**212**, 180 mg, 290.87 μmol, 1 eq) in DCM (5 mL) was added pyridine (115.04 mg, 1.45 mmol, 117.39 μL, 5 eq) and Tf_2O (246.20 mg, 872.61 μmol, 143.97 μL, 3 eq) at 25 °C. The mixture was stirred at 25 °C for 0.5 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (6 mL) and extracted with EtOAc (5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford [3-

[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-3-en-1-yl]methyl trifluoromethanesulfonate (**213**, 180 mg, 203.86 μmol, 70.1 % yield) as a yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.57 (br d, *J* = 4.5 Hz, 2H), 7.51 (dd, *J* = 5.9, 7.4 Hz, 2H), 6.37 (s, 1H), 5.92 (s, 2H), 5.75 (br s, 1H), 3.67 (br t, *J* = 7.9 Hz, 2H), 3.25 (br d, *J* = 8.5 Hz, 4H), 2.84 (br d, *J* = 16.5 Hz, 1H), 2.31 (br s, 3H), 2.19 - 2.11 (m, 2H), 2.06 - 1.96 (m, 2H), 1.64 - 1.58 (m, 4H), 1.10 (s, 6H), 0.93 (br s, 2H), -0.03 (s, 9H).

To a solution of [3-[4-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-3-en-1-yl]methyl trifluoromethanesulfonate (**213**, 180 mg, 203.86 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 1.02 mL, 5 eq) at 25 °C. The mixture was warmed and further stirred at 40 °C for 1h and then warmed again and further stirred at 60 °C for 15 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with water (8 mL) and extracted with EtOAc(5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 3/1 to 0/1) and then by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 50 % - 80 % B gradient over 8.0 min) to afford title compound *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide (**B-6**, 44.2 mg, 70.72 μmol, 34.7 % yield, 97.1 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.23 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.38 (dd, *J* = 2.2, 8.6 Hz, 1H), 7.26 (d, *J* = 2.1 Hz, 1H), 6.39 (s, 1H), 5.76 (td, *J* = 1.9, 3.4 Hz, 1H), 4.74 - 4.61 (m, 1H), 4.59 (d, *J* = 8.9 Hz, 1H), 4.57 - 4.49 (m, 1H), 4.49 - 4.41 (m, 1H), 2.87 (br d, *J* = 16.8 Hz, 1H), 2.32 (br s, 3H), 2.12 - 2.05 (m, 3H), 2.04 - 1.98 (m, 1H), 1.97 - 1.85 (m, 2H), 1.60 (t, *J* = 6.3 Hz, 2H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 493.4, expected 493.2 [M+H].

EXAMPLE 39

***N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide A-33**



To a mixture of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**, 2 g, 4.85 mmol, 1 eq) in MeOH (20 mL) was added $NaBH_4$ (201.67 mg, 5.33 mmol, 1.1 eq) at 0 °C. The mixture was warmed and further stirred at 25 ° C for 2 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10:1, Rf = 0.5) until it showed that the

reaction had completed. The reaction mixture was concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**214**, 2 g, 4.82 mmol, 99.5 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.98 (s, 2H), 3.88 - 3.78 (m, 1H), 3.69 (s, 4H), 2.09 (dd, *J* = 6.4, 12.9 Hz, 2H), 1.35 (dd, *J* = 9.8, 12.8 Hz, 2H), 0.90 (s, 18H), 0.06 (s, 12H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**214**, 492.48 mg, 1.19 mmol, 1.75 eq), NHC-1 (429.11 mg, 1.09 mmol, 1.6 eq) and pyridine (85.88 mg, 1.09 mmol, 87.63 μL, 1.6 eq) in MTBE (9 mL) was added *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 0.36 g, 678.56 μmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (9.30 mg, 10.18 μmol, 0.015 eq), dibromonickel; 1,2-dimethoxyethane (10.47 mg, 33.93 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (13.66 mg, 50.89 μmol, 0.075 eq), quinuclidine (132.03 mg, 1.19 mmol, 1.75 eq) and isoindoline-1,3-dione (22.46 mg, 152.68 μmol, 0.225 eq) in DMA (6 mL) at 20 °C under N_2 atmosphere. The mixture was stirred at 20 °C for 12 hr under Blue 34W LED light. The reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1, Rf = 0.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 0/1) to afford *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**215**, 1.8 g, 2.12 mmol, 78.2 % yield) as a crude yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.89 (s, 1H), 8.65 (s, 1H), 7.77 (s, 1H), 7.21 (br s, 1H), 6.11 (s, 2H), 5.98 (s, 3H), 3.73 (s, 4H), 3.68 (br s, 2H), 3.17 - 3.05 (m, 1H), 2.47 (br d, *J* = 7.1 Hz, 2H), 2.14 (br s, 2H), 2.09 (dd, *J* = 6.4, 12.9 Hz, 4H), 1.73 - 1.67 (m, 2H), 1.17 (s, 6H), 0.98 (s, 2H), 0.90 (s, 18H), 0.06 (s, 12H), 0.01 (s, 9H).

To a mixture of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**215**, 1.8 g, 2.12 mmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 4.24 mL, 2 eq). The mixture was stirred at 25 °C for 1 hr. The reaction was monitored by LC/MS (R_t = 0.530 min, [M+H] = 620.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (10mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The

residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 3/1) to afford *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**216**, 0.4 g, 645.34 μmol, 30.4 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.90 (s, 1H), 8.70 - 8.61 (m, 1H), 7.77 (s, 1H), 7.15 - 7.08 (m, 1H), 6.14 (s, 2H), 5.93 (s, 3H), 3.80 (s, 4H), 3.66 (s, 2H), 3.31 - 3.16 (m, 1H), 2.47 (br s, 2H), 2.14 (br d, *J* = 2.3 Hz, 2H), 1.86 (s, 2H), 1.74 - 1.69 (m, 2H), 1.61 (br s, 4H), 1.12 (s, 6H), 0.98 (s, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 620.4, expected 620.4 [M+H].

To a solution of *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**216**, 0.4 g, 645.34 μmol, 1 eq) in DCM (5 mL) was added Tf_2O (546.23 mg, 1.94 mmol, 319.43 μL, 3 eq) and pyridine, (255.23 mg, 3.23 mmol, 260.44 μL, 5 eq) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 0.5 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.741 min, [M+H] = 884.3) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 5/1) to afford [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl trifluoromethanesulfonate (**217**, 0.3 g, 339.39 μmol, 52.6 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.92 (s, 1H), 9.03 (br s, 1H), 7.79 - 7.77 (m, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.22 (s, 1H), 5.93 (s, 1H), 5.31 (s, 4H), 4.71 - 4.54 (m, 4H), 3.68 - 3.64 (m, 2H), 3.26 (tt, *J* = 5.6, 11.2 Hz, 1H), 2.46 (br d, *J* = 1.5 Hz, 2H), 2.15 (br s, 2H), 1.98 - 1.91 (m, 2H), 1.79 (dd, *J* = 5.8, 13.1 Hz, 2H), 1.13 (s, 6H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 884.3, expected 884.3 [M+H].

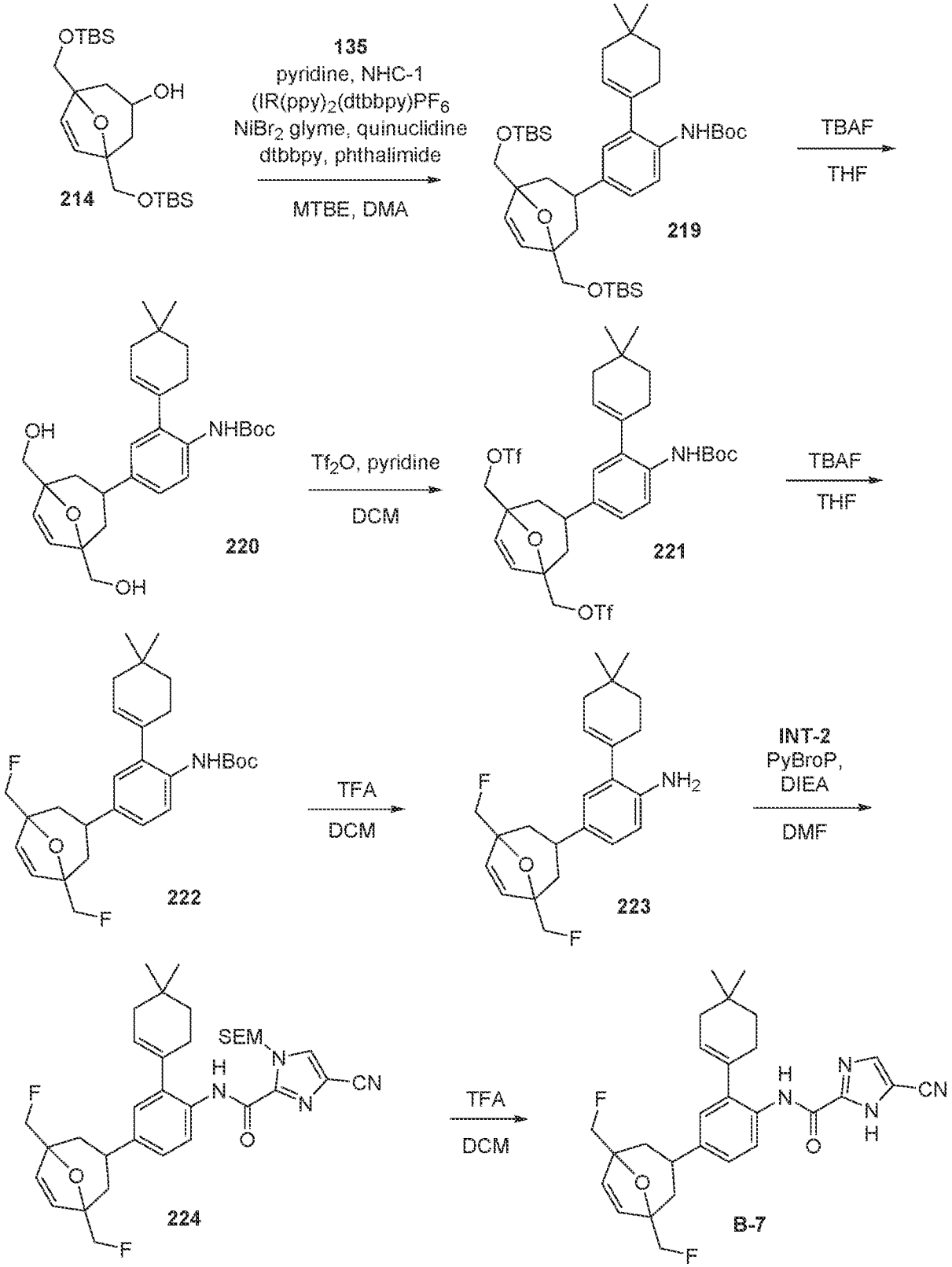
To a solution of [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl trifluoromethanesulfonate (**217**, 0.3 g, 339.39 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 1.36 mL, 4 eq) at 20 °C. The mixture was stirred at 40 °C for 0.5 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.647min, [M+H] = 624.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 5/1) to afford *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**218**, 0.1 g, 160.31 μmol, 47.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 8.73 - 8.56 (m, 1H), 7.77 (s, 1H), 7.16 - 7.08 (m, 1H), 6.17 (s, 2H), 5.93 (s, 3H), 4.62 (d, *J* = 2.5 Hz, 2H), 4.50 (d, J = 2.5 Hz, 2H), 3.69 - 3.64 (m, 2H), 3.28 - 3.15 (m, 1H), 2.47 (br s, 2H), 2.14 (br d, *J* = 2.6 Hz, 2H), 1.95 - 1.89 (m, 2H), 1.82 - 1.76 (m, 2H), 1.62 (br t, *J* = 6.4 Hz, 2H), 1.12 (s, 6H), 1.01 - 0.97 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 624.4, expected 624.4 [M+H].

To a solution of *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**218**, 0.1 g, 160.31 μmol, 1 eq) in DCM (3 mL) and TFA (1 mL) at 0 °C. The mixture was allowed to warm and further stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.505 min, [M+H] = 494.3) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (100 mL) and extracted with EtOAc (150 mL x 3). The organic layers were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 40 % - 65 % B gradient over 8.0 min) to afford title compound *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-33**, 44.5 mg, 90.16 μmol, 56.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.83 (dd, *J* = 3.4, 8.6 Hz, 1H), 8.04 (s, 1H), 7.60 (dd, *J* = 4.1, 8.6 Hz, 1H), 6.24 (s, 2H), 6.10 (br d, *J* = 1.3 Hz, 1H), 4.65 - 4.56 (m, 2H), 4.53 - 4.45 (m, 2H), 3.40 (tt, *J* = 5.8, 11.6 Hz, 1H), 2.48 - 2.42 (m, 2H), 2.14 (br d, *J* = 3.4 Hz, 2H), 1.95 - 1.87 (m, 2H), 1.81 - 1.75 (m, 2H), 1.63 (t, *J* = 6.3 Hz, 2H), 1.11 (s, 6H), MS (LC/MS) *m/z* observed 494.3, expected 494.3 [M+H].

EXAMPLE 40

N-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1H-imidazole-2-carboxamide B-7



To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**214**, 190.83 mg, 460.14 μmol, 1.75 eq) , NHC-1 (166.28 mg, 420.70 μmol, 1.6 eq) and pyridine (33.28 mg, 420.70 μmol, 33.96 μL, 1.6 eq) in MTBE (9 mL) was added *tert*-butyl *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**135**, 0.1 g, 262.94 μmol, 1 eq), bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (3.60 mg, 3.94 μmol, 0.015 eq), dibromonickel; 1,2-dimethoxyethane (4.06 mg, 13.15 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (5.29 mg, 19.72 μmol, 0.075 eq), quinuclidine (51.16 mg, 460.14 μmol, 1.75 eq) and isoindoline-1,3-dione (8.70 mg, 59.16 μmol, 0.225 eq) in DMA (6 mL) at 20 °C under N_2 atmosphere. The mixture was stirred at 20 °C for 12 hr under Blue 34W LED light. The reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1, Rf = 0.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 4/1) to afford *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**219**, 1.4 g, 2.01 mmol, 76.3 % yield) as a crude yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.88 (m, 1H), 7.16-7.12 (m, 1H), 6.92-6.88 (m, 1H), 6.09 (s, 1H), 5.68-5.64 (m, 2H), 3.72-3.64 (m, 4H), 2.91-2.76 (m, 1H), 2.24-2.16 (m, 2H), 2.00-1.96 (m, 2H), 1.68-1.52 (m, 4H), 1.51 (s, 9H), 1.46-1.42 (m, 2H), 1.17 (s, 6H), 0.92-0.88 (m, 18H), 0.08-0.06 (m, 12H).

To a mixture of *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**219**, 0.8 g, 1.15 mmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.29 mL, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 0.570 min, [M+H] = 492.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 1/1) to afford *tert*-butyl *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**220**, 0.18 g, 383.30 μmol, 33.5 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.86 (m, 1H), 7.08 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz 1H), 6.92 (d, J = 2.0 Hz, 1H), 6.69 (s, 1H), 6.11 (s, 2H), 5.64-5.60 (m, 1H), 3.77 (s, 4H), 3.03-2.92 (m, 1H), 2.22-2.17 (m, 2H), 2.00-1.96 (m, 2H), 1.76-1.66

(m, 2H), 1.62-1.52 (m, 4H), 1.51 (s, 9H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 492.4, expected 492.4 [M+H].

To a mixture of *tert*-butyl *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**220**, 0.18 g, 383.30 μmol, 1 eq) in DCM (5 mL) was added Tf_2O (324.43 mg, 1.15 mmol, 189.72 μL, 3 eq) and pyridine (151.59 mg, 1.92 mmol, 154.69 μL, 5 eq). The mixture was stirred at 25 °C for 0.5 hr. The reaction was monitored by LC/MS (R_t = 0.749 min, [M+H] = 634.3) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (10mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 1/1) to afford [3-[4-(*tert*-butoxycarbonylamino)-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl trifluoromethanesulfonate (**221**, 0.2 g, 272.58 μmol, 71.1 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.90 (m, 1H), 7.08-7.04 (m, 1H), 6.90-6.88 (m, 1H), 6.19 (s, 2H), 5.63 (br s, 1H), 4.65-4.55 (m, 4H), 3.02-2.90 (m, 1H), 2.24-2.18 (m, 2H), 2.00-1.98 (m, 2H), 1.76-1.62 (m, 4H), 1.56-1.51 (m, 2H), 1.50 (s, 9H), 1.03 (s, 6H), MS (LC/MS) *m/z* observed 634.3, expected 634.3 [M+H].

To a solution of [3-[4-(*tert*-butoxycarbonylamino)-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]oct-6-en-1-yl]methyl trifluoromethanesulfonate (**221**, 0.2 g, 272.58 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 1.09 mL, 4 eq) at 20 °C. The mixture was warmed and stirred at 40 °C for 0.5 hr under N_2. The reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1, Rf = 0.6) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. : EtOAc =1/0 to 5/1) to afford *tert*-butyl *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**222**, 0.07 g, 147.81 μmol, 54.2 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 1H), 6.87-6.83 (m, 1H), 6.62 (br s, 1H), 6.07 (s, 1H), 5.88 (s, 1H), 5.56-5.52 (m, 1H), 4.54-4.48 (m, 2H), 4.42-4.35 (m, 2H), 2.94-2.82 (m, 1H), 2.14-2.08 (m, 2H), 1.94-1.90 (m, 2H), 1.48-1.44 (m, 2H), 1.42 (s, 9H), 1.32 (s, 2H), 1.25 (s, 2H), 0.95 (s, 6H).

To a solution of *tert*-butyl *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**222**, 0.07 g, 147.81 μmol, 1 eq) in DCM

(5 mL) and TFA (1 mL) at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.464 min, [M+H] = 374.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**223**, 0.04 g, 107.10 μmol, 72.5 % yield) as a yellow oil. MS (LC/MS) *m/z* observed 374.4, expected 374.4 [M+H].

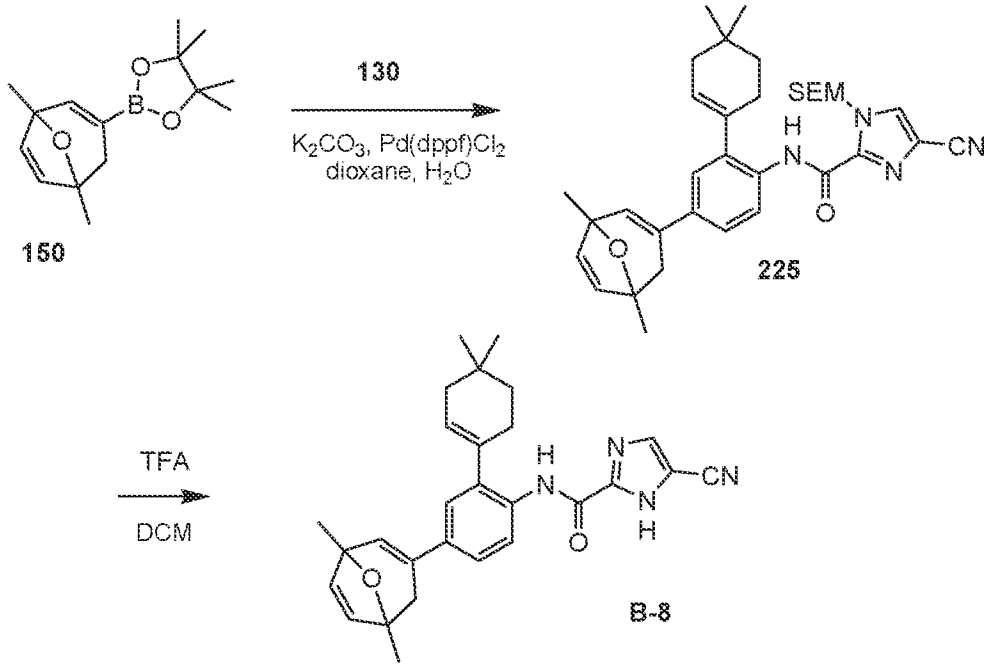
To a solution of 4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**223**, 0.04 g, 107.10 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 65.43 mg, 214.20 μmol, 2 eq) in DMF (5 mL) was added DIEA (69.21 mg, 535.51 μmol, 93.27 μL, 5 eq) and PyBroP (74.89 mg, 160.65 μmol, 1.5 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2. The reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1, Rf = 0.6) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by TLC (SiO_2, Pet. Et. : EtOAc = 5:1) to afford *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**224**, 0.03 g, 48.17 μmol, 45.0 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.16 (dd, J_1 = 2.0 Hz, J_1 = 8.4 Hz, 1H), 7.08-7.06 (m, 1H), 6.17 (s, 2H), 5.96 (s, 2H), 5.78-5.72 (m, 1H), 4.64-4.57 (m, 2H), 4.52-4.45 (m, 2H), 3.69-3.63 (m, 2H), 3.06-2.96 (m, 1H), 2.32-2.24 (m, 2H), 2.12-2.08 (m, 2H), 1.84-1.76 (m, 2H), 1.73-1.66 (m, 2H), 1.62-1.58 (m, 2H), 1.11 (s, 6H), 1.00 - 0.95 (m, 2H), 0.01 (s, 9H).

To a solution of *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**224**, 0.03 g, 48.17 μmol, 1 eq) in DCM (3 mL) and TFA (1 mL) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.590 min, [M+H] = 493.4) until it showed that the reaction had completed. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 % - 85 % B gradient over 8.0 min) to afford title compound *N*-[4-[1,5-

bis(fluoromethyl)-8-oxabicyclo[3.2.1]oct-6-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide (**B-7**, 0.003 g, 6.09 μmol, 12.6 % yield) as a white solid. ^{1}H NMR (400 MHz, CD3OD) δ = 8.12 (d, *J* = 8.4 Hz, 1H), 7.99 (s, 1H), 7.18 (dd, *J* = 1.9, 8.4 Hz, 1H), 7.08 (d, *J* = 1.8 Hz, 1H), 6.18 (s, 2H), 5.73 (br s, 1H), 4.62 - 4.55 (m, 2H), 4.50 - 4.43 (m, 2H), 3.11 - 2.98 (m, 1H), 2.30 (br d, *J* = 1.5 Hz, 2H), 2.07 (br s, 2H), 1.75 - 1.63 (m, 4H), 1.59 (t, *J* = 6.3 Hz, 2H), 1.08 (s, 6H), MS (LC/MS) *m/z* observed 493.4, expected 493.4 [M+H].

EXAMPLE 41

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1*H*-imidazole-2-carboxamide B-8



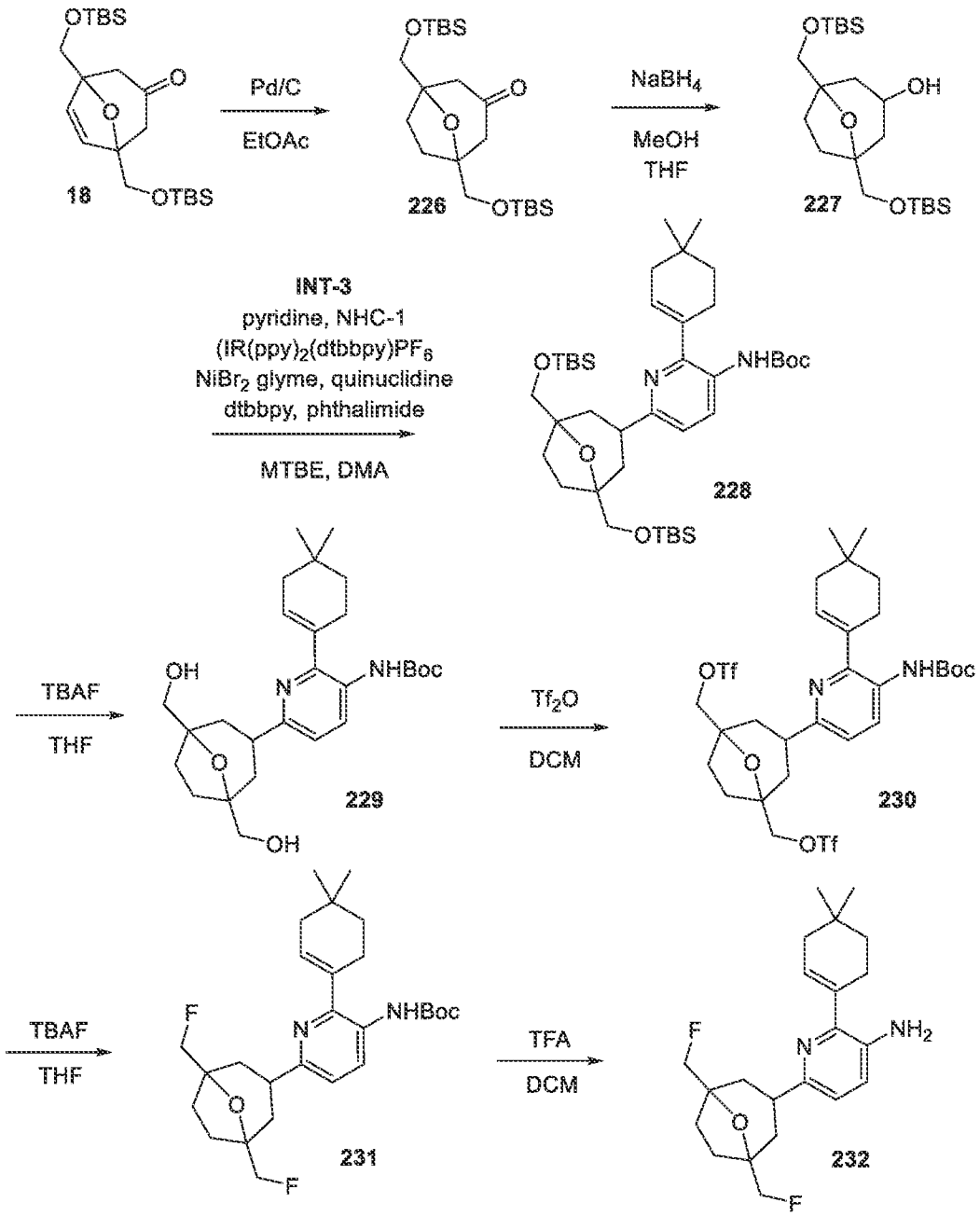
To a solution of 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**150**, 222.77 mg, 849.79 μmol, 1.5 eq) and N-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 0.3 g, 566.53 μmol, 1 eq) in 1,4-dioxane (10 mL) and H_2O (2 mL) was added K_2CO_3 (195.75 mg, 1.42 mmol, 2.5 eq) and cyclopentyl(diphenyl)phosphane; dichloropalladium; iron (41.45 mg, 56.65 μmol, 0.1 eq). The resulting mixture was warmed and stirred at 100 °C for 12 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.843 min) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (50 mL, aqueous) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 75 % -

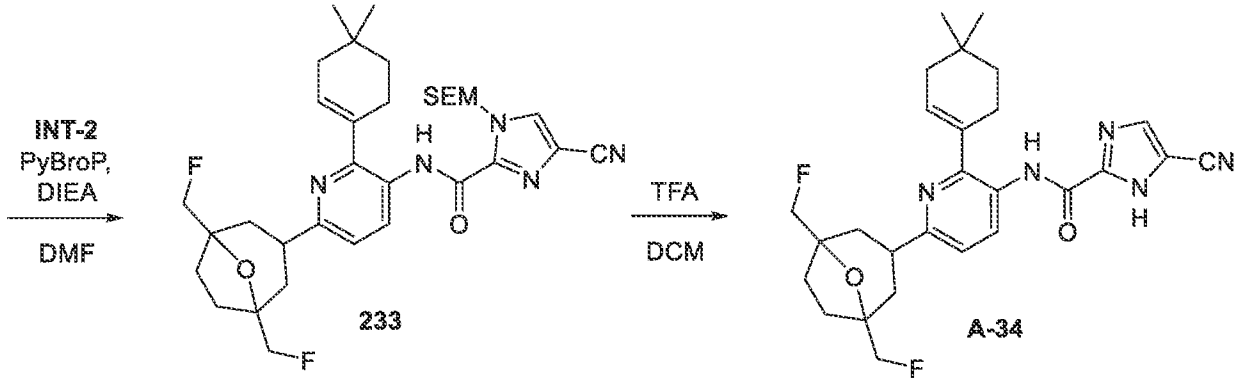
98 % B gradient over 8.0 min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**225**, 0.12 g, 205.19 μmol, 36.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 6.42 (s, 1H), 6.23 (d, *J* = 5.6 Hz, 1H), 5.95 (s, 2H), 5.76 - 5.72 (m, 2H), 3.68 - 3.62 (m, 2H), 2.68-2.60 (m, 1H), 2.32-2.26 (m, 2H), 2.24-2.12 (m, 1H), 2.10-2.08 (m, 2H), 1.55 (s, 3H), 1.54 (s, 3H), 1.11 (s, 6H), 1.02- 0.92 (m, 2H), 0.00 (s, 9H), MS (LC/MS) *m/z* observed 585.5, expected 585.3 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**225**, 0.12 g, 205.19 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 410.38 μL, 2 eq). The resulting mixture was warmed and stirred at 60 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 0.638, [M+H] = 455.4) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (20 mL, aqueous) and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 60 % - 95 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1*H*-imidazole-2-carboxamide (**B-8**, 0.0596 g, 104.82 μmol, 51.1 % yield, TFA salt) as white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.18 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.32 (br d, *J* = 8.3 Hz, 1H), 7.20 (s, 1H), 6.47 (s, 1H), 6.28 (d, *J* = 5.8 Hz, 1H), 5.79 (d, *J* = 5.6 Hz, 1H), 5.74 (br s, 1H), 2.59 (br d, *J* = 17.8 Hz, 1H), 2.36 - 2.20 (m, 3H), 2.09 (br s, 2H), 1.60 (br t, *J* = 6.1 Hz, 2H), 1.50 (d, *J* = 5.8 Hz, 6H), 1.09 (s, 6H), MS (LC/MS) *m/z* observed 455.4, expected 455.4 [M+H].

EXAMPLE 42

N-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1H-imidazole-2-carboxamide A-34





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To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**18**, 5 g, 12.12 mmol, 1 eq)in EtOAc (60 mL) was added Pd/C (1.29 g, 1.21 mmol, 10 % purity, 0.1 eq) at 25 °C. The mixture was stirred at 25 °C for 1 hr under H_2 (15 psi). The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-one (**226**, 5 g, crude) as a yellow oil and used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.66 - 3.60 (m, 2H), 3.59 - 3.53 (m, 2H), 2.55 (d, *J* = 15.5 Hz, 2H), 2.24 (d, *J* = 15.8 Hz, 2H), 1.76 - 1.69 (m, 2H), 1.68 - 1.63 (m, 2H), 0.82 (s, 18H), 0.00 (d, *J* = 1.4 Hz, 12H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-one (**226**, 5 g, 12.06 mmol, 1 eq) in THF (40 mL) and MeOH (5 mL) was added $NaBH_4$ (592.95 mg, 15.67 mmol, 1.3 eq) at 0 °C. The mixture was warmed and stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (30 mL, aqueous) and extracted with EtOAc(20 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-ol (**227**, 5 g, 12.00 mmol, 99.5 % yield) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3, 298 K) δ (ppm) = 4.18 - 4.02 (m, 1H), 3.66 - 3.52 (m, 4H), 2.07 - 2.00 (m, 2H), 1.75 - 1.64 (m, 4H), 1.41 (t, *J* = 11.6 Hz, 2H), 0.90 (s, 18H), 0.06 (s, 12H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-ol (**227**, 2 g, 4.80 mmol, 1.75 eq) and *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 1.05 g, 2.74 mmol, 1 eq) in MTBE (15 mL) was added bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine;

hexafluorophosphate (37.60 mg, 41.14 μmol, 0.015 eq), dibromonickel; 1,2-dimethoxyethane (42.32 mg, 137.12 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (55.20 mg, 205.68 μmol, 0.075 eq), NHC-1 (1.73 g, 4.39 mmol, 1.6 eq), pyridine (347.07 mg, 4.39 mmol, 354.16 μL, 1.6 eq), quinuclidine (533.62 mg, 4.80 mmol, 1.75 eq), isoindoline-1,3-dione (90.78 mg, 617.03 μmol, 0.225 eq) and DMA (15 mL) at 25 °C. The mixture was stirred at 25 °C for 16 hr under 34W blue LED light. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (15 mL x 3) and washed with brine (30 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford *tert*-butyl *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**228**, 1.7 g, 1.21 mmol, 44.2 % yield, 50 % purity) as a yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ = 8.25 (br d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 6.88 (s, 1H), 5.81 (br s, 1H), 3.67 - 3.63 (m, 2H), 3.63 - 3.59 (m, 2H), 3.24 - 3.14 (m, 1H), 2.41 (br d, *J* = 1.4 Hz, 2H), 2.05 (br s, 2H), 1.90 - 1.84 (m, 4H), 1.78 (br d, *J* = 7.3 Hz, 2H), 1.72 (br d, *J* = 12.8 Hz, 2H), 1.58 (br t, *J* = 6.3 Hz, 2H), 1.51 (s, 9H), 1.04 (s, 6H), 0.88 (s, 18H), 0.05 (s, 12H), MS (LC/MS) *m/z* observed 701.3, expected 701.5 [M+H].

To a solution of *tert*-butyl *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**228**, 1.9 g, 2.71 mmol, 1 eq) in THF (20 mL) was added TBAF (1 M, 5.42 mL, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (20 mL) and extracted with EtOAc (15 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 5/1 to 1/1) to afford *tert*-butyl *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**229**, 650 mg, 1.38 mmol, 50.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.26 (br d, *J* = 7.6 Hz, 1H), 7.06 (br d, *J* = 8.6 Hz, 1H), 6.88 (s, 1H), 5.81 (br s, 1H), 3.71 (br dd, *J* = 4.3, 11.8 Hz, 2H), 3.58 (br dd, *J* = 6.9, 11.7 Hz, 2H), 3.38 - 3.26 (m, 1H), 2.42 - 2.38 (m, 2H), 2.05 - 2.02 (m, 2H), 1.98 (br d, *J* = 7.0 Hz, 2H), 1.91 - 1.80 (m, 4H), 1.73 (br dd, *J* = 5.1, 13.0 Hz, 2H), 1.58 (br t, *J* = 6.3 Hz, 2H), 1.50 (s, 9H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 473.4, expected 473.3 [M+H].

To a solution of *tert*-butyl *N*-[6-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**229**, 650 mg, 1.38 mmol, 1 eq) in DCM

(8 mL) was added pyridine (543.94 mg, 6.88 mmol, 555.04 μL, 5 eq) and Tf_2O (1.16 g, 4.13 mmol, 680.76 μL, 3 eq) at 25 °C. The mixture was stirred at 25 °C for 0.5 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.95) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (6 mL) and extracted with EtOAc (5 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford [3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyl trifluoromethanesulfonate (**230**, 400 mg, crude) as a yellow oil, used further as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.41 - 8.27 (m, 1H), 7.05 (dd, *J* = 8.5, 17.8 Hz, 1H), 6.90 (br d, *J* = 12.0 Hz, 1H), 5.85 (br dd, *J* = 1.6, 4.0 Hz, 1H), 4.67 - 4.52 (m, 2H), 4.49 - 4.36 (m, 2H), 3.45 - 3.33 (m, 1H), 2.39 (br d, *J* = 1.9 Hz, 2H), 2.05 (br s, 2H), 2.01 - 1.80 (m, 6H), 1.79 - 1.66 (m, 2H), 1.62 - 1.56 (m, 2H), 1.51 (d, J = 2.6 Hz, 9H), 1.04 (d, *J* = 4.8 Hz, 6H).

To a solution of [3-[5-(*tert*-butoxycarbonylamino)-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyl trifluoromethanesulfonate (**230**, 0.4 g, 542.93 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.71 mL, 5 eq) at 25 °C. The mixture was warmed and stirred at 40 °C for 1 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.55) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (15 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford *tert*-butyl *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**231**, 160 mg, 335.71 μmol, 61.8 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.28 (br d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.89 (s, 1H), 5.81 (td, *J* = 2.0, 3.7 Hz, 1H), 4.53 - 4.44 (m, 2H), 4.41 - 4.32 (m, 2H), 3.35 - 3.24 (m, 1H), 2.39 (dt, *J* = 2.1, 6.3 Hz, 2H), 2.05 - 2.02 (m, 2H), 1.97 - 1.86 (m, 6H), 1.83 - 1.77 (m, 2H), 1.58 (t, J = 6.4 Hz, 2H), 1.51 (s, 9H), 1.04 (s, 6H), MS (LC/MS) *m/z* observed 477.3, expected 477.3 [M+H].

To a solution of *tert*-butyl *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**231**, 160 mg, 335.71 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL)at 25 °C. The mixture was stirred at 25 °C for 2 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.1) until it showed that the starting material had been completely consumed. The reaction was adjusted to

pH = 8~9 with $NaHCO_3$ (aqueous) and extracted with DCM (6 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**232**, 120 mg, crude) as a yellow oil, used further as is. MS (LC/MS) *m/z* observed 377.3, expected 377.2 [M+H].

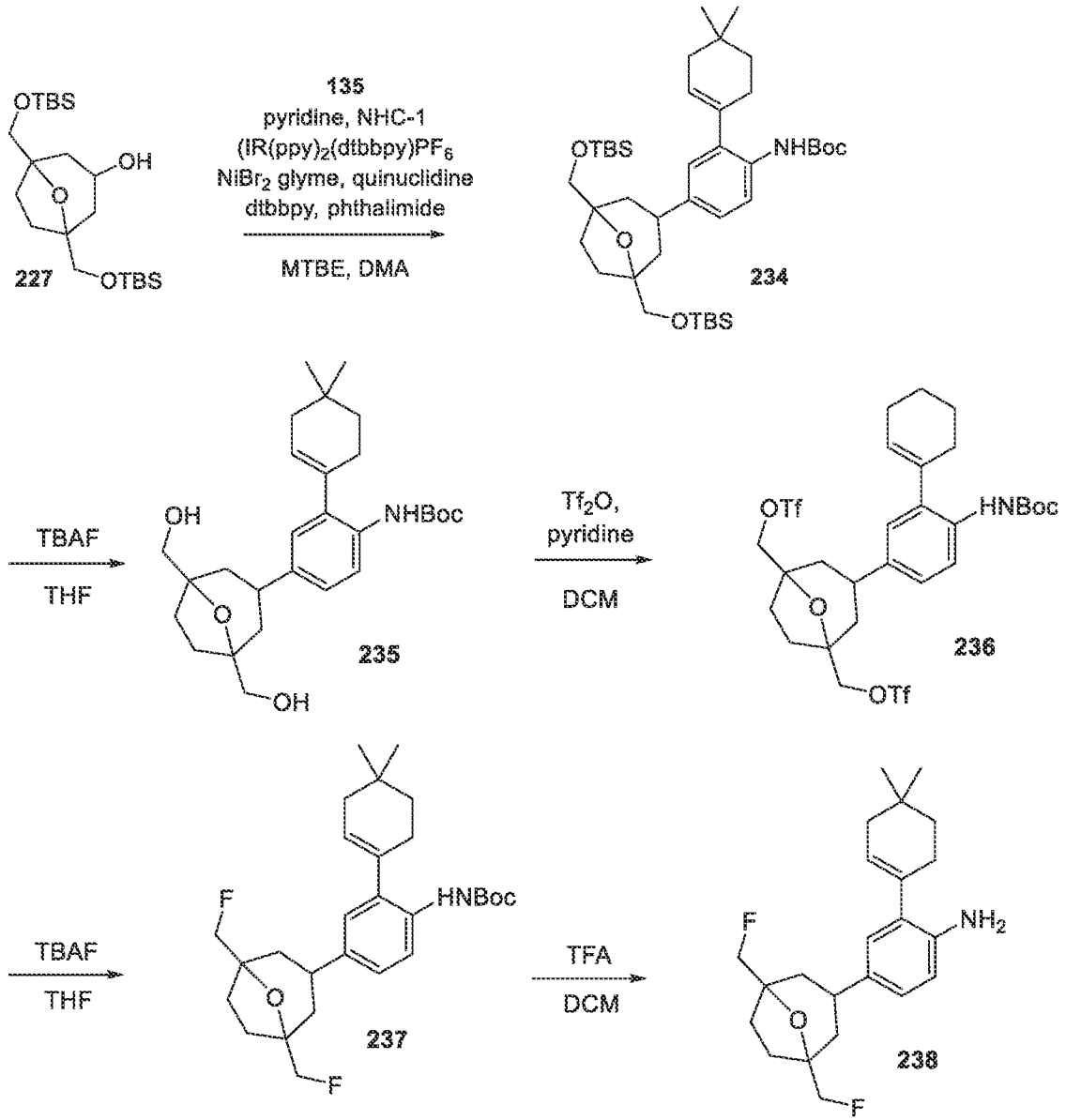
To a solution of 6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)pyridin-3-amine (**232**, 120 mg, 318.74 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 194.72 mg, 637.48 μmol, 2 eq) in DMF (2 mL) was added DIEA (123.58 mg, 956.22 μmol, 166.55 μL, 3 eq), PyBroP (222.89 mg, 478.11 μmol, 1.5 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.654 min, [M+H] = 626.4) until it showed that the starting material had been completely consumed and the desired product mass was observed. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 1/1) to afford *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**233**, 150 mg, 167.78 μmol, 52.6 % yield, 70 % purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 8.67 (br d, *J* = 7.5 Hz, 1H), 7.78 (s, 1H), 7.13 (br d, *J* = 7.6 Hz, 1H), 5.95 (br s, 1H), 5.93 (s, 2H), 4.54 - 4.46 (m, 2H), 4.41 - 4.34 (m, 2H), 3.69 - 3.63 (m, 2H), 3.42 - 3.29 (m, 1H), 2.47 (br s, 2H), 2.15 (br d, *J* = 2.3 Hz, 2H), 1.98 - 1.89 (m, 6H), 1.65 - 1.59 (m, 4H), 1.13 (s, 6H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 626.4, expected 626.4 [M+H].

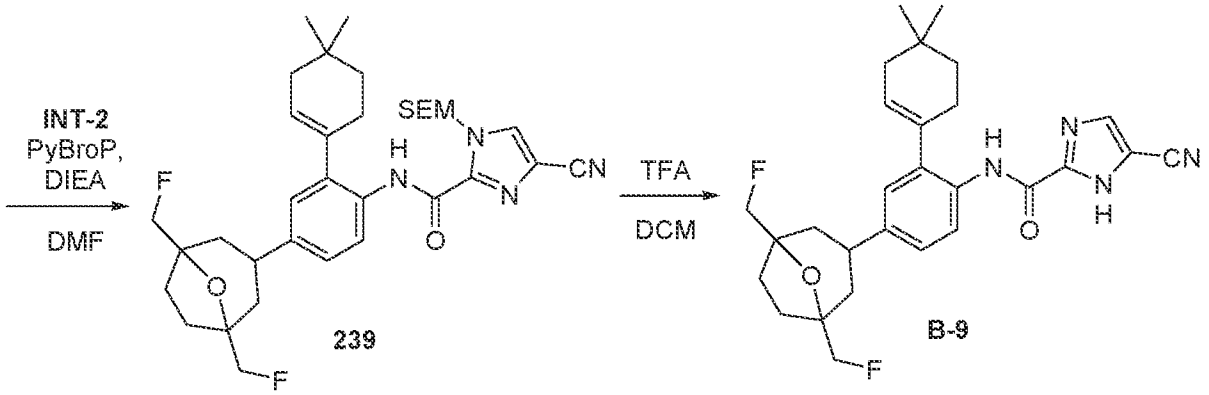
To a solution of *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**233**, 150 mg, 239.68 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.512 min, [M+H] = 496.4) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75 x 30 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford title compound *N*-[6-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-34**, 93.5 mg, 151.74 μmol, 63.3 % yield, 98.9 % purity,

TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.71 (d, *J* = 8.6 Hz, 1H), 8.03 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 6.04 (td, *J* = 1.9, 3.5 Hz, 1H), 4.47 (q, *J* = 10.1 Hz, 2H), 4.35 (q, *J* = 10.1 Hz, 2H), 3.59 - 3.47 (m, 1H), 2.49 - 2.42 (m, 2H), 2.12 (br d, *J* = 3.4 Hz, 2H), 2.04 - 1.93 (m, 4H), 1.91 - 1.80 (m, 4H), 1.63 (t, J = 6.3 Hz, 2H), 1.10 (s, 6H), MS (LC/MS) *m/z* observed 496.4, expected 496.4 [M+H].

EXAMPLE 43

***N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide B-9**





To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-ol (**227**, 400 mg, 959.83 μmol, 1.75 eq) and *tert*-butyl *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**135**, 208.59 mg, 548.47 μmol, 1 eq) in MTBE (3 mL) was added bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (7.52 mg, 8.23 μmol, 0.015 eq), dibromonickel; 1,2-dimethoxyethane (8.46 mg, 27.42 μmol, 0.05 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (11.04 mg, 41.14 μmol, 0.075 eq), NHC-1 (346.85 mg, 877.56 μmol, 1.6 eq), pyridine (69.41 mg, 877.56 μmol, 70.83 μL, 1.6 eq), quinuclidine (106.72 mg, 959.83 μmol, 1.75 eq), isoindoline-1,3-dione (18.16 mg, 123.41 μmol, 0.225 eq) and DMA (3 mL) at 25 °C. The mixture was stirred at 25 °C for 16 hr under 34W blue LED light. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf =0.9) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (15 mL x 3) and washed with brine (40 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 5/1) to afford *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**234**, 1.7 g, 1.21 mmol, 44.3 % yield, 50 % purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (br d, *J* = 8.1 Hz, 1H), 7.12 (br dd, *J* = 2.1, 8.4 Hz, 1H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.70 (s, 1H), 5.67 - 5.61 (m, 1H), 3.66 - 3.58 (m, 4H), 3.03 - 2.92 (m, 1H), 2.22 (br d, *J* = 2.0 Hz, 2H), 2.00 (br d, *J* = 3.3 Hz, 2H), 1.83 - 1.73 (m, 6H), 1.65 (br d, *J* = 12.5 Hz, 4H), 1.50 (s, 9H), 1.03 (s, 6H), 0.89 (s, 18H), 0.05 (d, *J* = 1.3 Hz, 12H).

To a solution of *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**234**, 1.80 g, 2.57 mmol, 1 eq) in THF (20 mL) was added TBAF (1 M, 5.13 mL, 2 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (20 mL) and extracted with EtOAc (15 mL x 2).

The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 5/1 to 1/1) to afford *tert*-butyl *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**235**, 500 mg, 1.06 mmol, 41.3 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (br d, *J* = 8.3 Hz, 1H), 7.09 (s, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.69 (s, 1H), 5.62 (td, *J* = 1.9, 3.6 Hz, 1H), 3.70 (d, *J* = 11.9 Hz, 2H), 3.57 (d, *J* = 11.9 Hz, 2H), 3.17 - 3.06 (m, 1H), 2.24 - 2.19 (m, 2H), 2.03 - 1.96 (m, 4H), 1.83 (br d, *J* = 7.0 Hz, 2H), 1.80 - 1.72 (m, 2H), 1.67 - 1.60 (m, 2H), 1.52 (br d, *J* = 6.6 Hz, 2H), 1.50 (s, 9H), 1.02 (s, 6H).

To a solution of *tert*-butyl *N*-[4-[1,5-bis(hydroxymethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**235**, 500 mg, 1.06 mmol, 1 eq) in DCM (8 mL) was added pyridine (419.29 mg, 5.30 mmol, 427.85 μL, 5 eq) and Tf_2O (897.34 mg, 3.18 mmol, 524.76 μL, 3 eq) at 25 °C. The mixture was stirred at 25 °C for 0.5 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.95) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (10 mL) and extracted with DCM (6 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford [3-[4-(*tert*-butoxycarbonylamino)-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyl trifluoromethanesulfonate (**236**, 300 mg, crude) as a yellow oil, used further as is. ^{1}H NMR (400 MHz, CDCl3) δ = 7.72 (br d, *J* = 8.5 Hz, 1H), 7.08 (dd, *J* = 2.1, 8.5 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 6.70 (s, 1H), 5.62 (br d, *J* = 1.8 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 2H), 4.39 (d, *J* = 11.4 Hz, 2H), 3.18 - 3.14 (m, 1H), 2.33 - 2.28 (m, 2H), 2.10 (br d, *J* = 5.0 Hz, 4H), 1.93 - 1.87 (m, 4H), 1.76 (br d, *J* = 6.1 Hz, 2H), 1.55 (br d, *J* = 2.6 Hz, 2H), 1.48 (s, 9H), 1.01 (s, 6H).

To a solution of [3-[4-(*tert*-butoxycarbonylamino)-3-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-(trifluoromethylsulfonyloxymethyl)-8-oxabicyclo[3.2.1]octan-1-yl]methyl trifluoromethanesulfonate (**236**, 300 mg, 407.75 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.04 mL, 5 eq) at 25 °C. The mixture was warmed and stirred at 40 °C for 1 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.4) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by water (15 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford *tert*-butyl *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-

dimethylcyclohexen-1-yl)phenyl]carbamate (**237**, 70 mg, 147.18 μmol, 36.1 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (br d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.70 (s, 1H), 5.63 (br s, 1H), 4.52 - 4.44 (m, 2H), 4.40 - 4.32 (m, 2H), 3.15 - 3.04 (m, 1H), 2.21 (br d, *J* = 1.9 Hz, 2H), 2.00 (br d, *J* = 3.0 Hz, 2H), 1.91 (s, 4H), 1.86 - 1.80 (m, 2H), 1.74 - 1.69 (m, 2H), 1.55 - 1.52 (m, 2H), 1.50 (s, 9H), 1.03 (s, 6H).

To a solution of *tert*-butyl *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**237**, 70 mg, 147.18 μmol, 1 eq) in DCM (0.9 mL) was added TFA (0.3 mL) at 25 °C. The mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.05) until it showed that the starting material had been completely consumed. The reaction was adjusted to pH = 8~9 with $NaHCO_3$ (aqueous) and extracted with DCM (6 mL x 2). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**238**, 50 mg, crude) as a yellow oil, used further as is. MS (LC/MS) *m/z* observed 376.3, expected 376.2 [M+H].

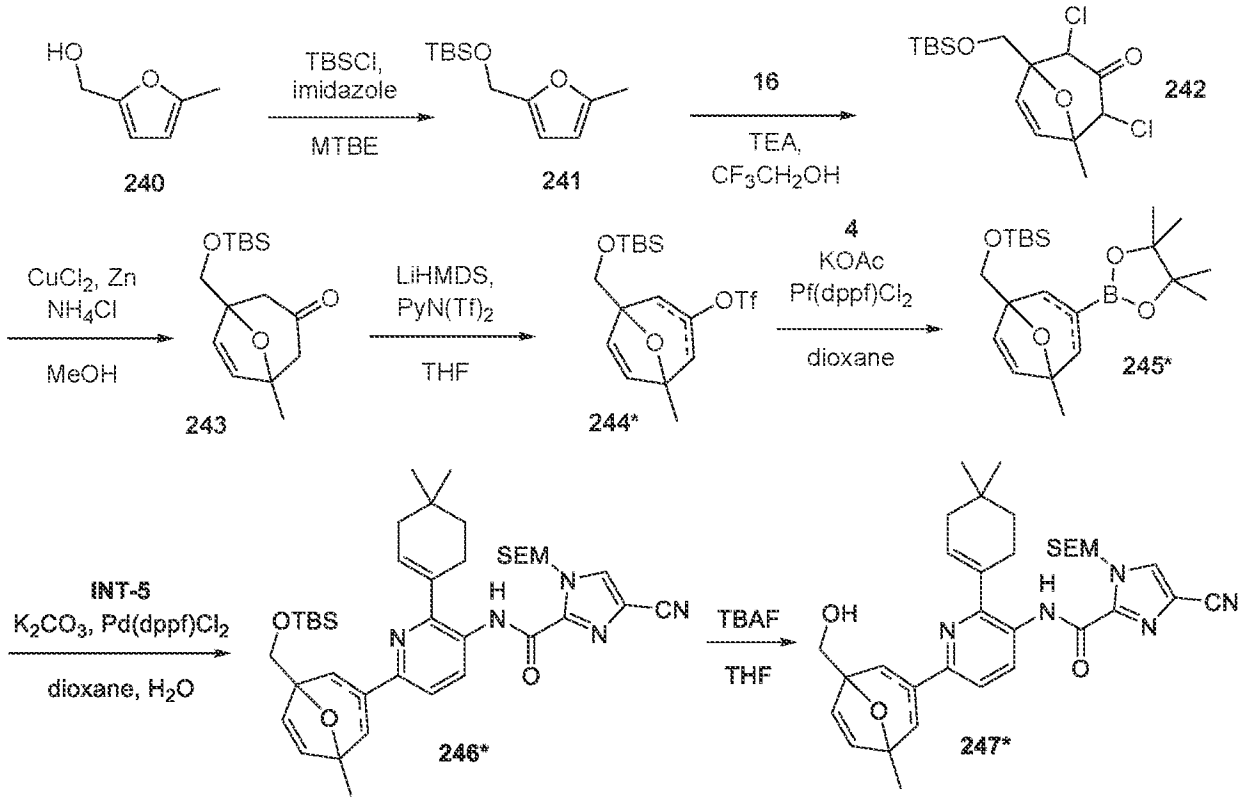
To a solution of 4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**238**, 50 mg, 133.16 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 81.35 mg, 266.32 μmol, 2 eq) in DMF (2 mL) was added DIEA (51.63 mg, 399.47 μmol, 69.58 μL, 3 eq), PyBroP (93.11 mg, 199.74 μmol, 1.5 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (Rt (product) = 0.748 min, [M+H] = 625.5) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2, Pet. Et. / EtOAc = 3/1) to afford *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**239**, 60 mg, 67.22 μmol, 50.5 % yield, 70 % purity) as a yellow oil, used further as is. MS (LC/MS) *m/z* observed 625.4, expected 625.5 [M+H].

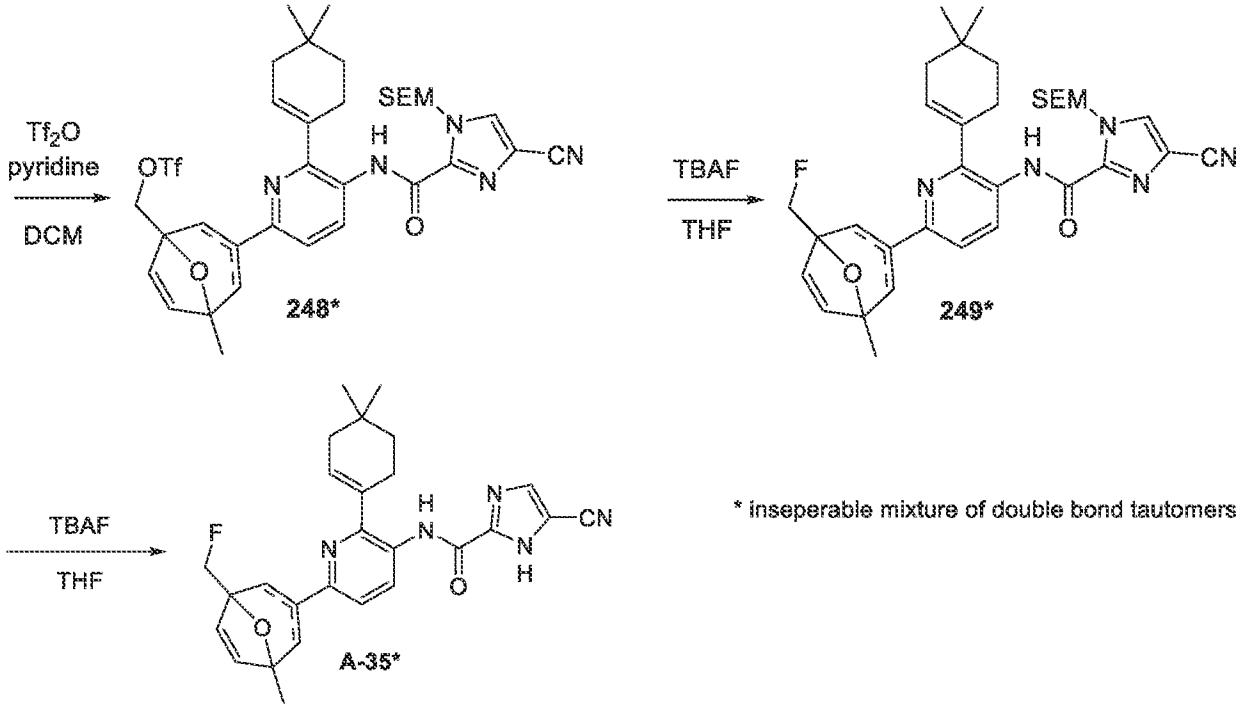
To a solution of *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**239**, 60 mg, 96.03 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 0.5 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.595 min, [M+H] = 495.4) until it showed that the starting material

had been completely consumed and the desired product mass had been observed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 3 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 45 % - 75 % B gradient over 8.0 min) to afford title compound *N*-[4-[1,5-bis(fluoromethyl)-8-oxabicyclo[3.2.1]octan-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide (**B-9**, 3 mg, 4.83 μmol, 5.0 % yield, 98.0 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.23 (br s, 1H), 9.71 (s, 1H), 8.31 (s, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.21 (dd, *J* = 1.8, 8.4 Hz, 1H), 7.15 (d, *J* = 1.9 Hz, 1H), 5.66 (br s, 1H), 4.52 - 4.28 (m, 4H), 3.26 - 3.22 (m, 1H), 2.25 (br s, 2H), 1.99 - 1.89 (m, 4H), 1.77 - 1.61 (m, 6H), 1.48 (br t, *J* = 6.3 Hz, 2H), 1.00 (s, 6H), MS (LC/MS) *m/z* observed 495.4, expected 495.4 [M+H].

EXAMPLE 44

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(fluoromethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-5-(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-35* (* Inseparable mixture of double bond tautomers)





To a solution of (5-methyl-2-furyl)methanol (**240**, 6 g, 53.51 mmol, 1 eq) in MTBE (50 mL) was added imidazole (4.37 g, 64.21 mmol, 1.2 eq) and TBSCl (8.87 g, 58.86 mmol, 7.24 mL, 1.1 eq). The resulting mixture was stirred at 20 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 20/1, Rf = 0.85) until it showed that the starting material had been completely consumed. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 20/1) to afford *tert*-butyl-dimethyl-[(5-methyl-2-furyl)methoxy]silane (**241**, 11.2 g, 49.47 mmol, 92.5 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.11 (d, J = 3.2 Hz, 1H), 5.90 (d, J = 2.0 Hz, 1H), 4.59 (s, 2H), 2.29 (s, 3H), 0.92 (s, 9H), 0.10 (s, 6H).

To a solution of *tert*-butyl-dimethyl-[(5-methyl-2-furyl)methoxy]silane (**241**, 11.2 g, 49.47 mmol, 1 eq) and 1,1,3-trichloropropan-2-one (**16**, 23.96 g, 148.42 mmol, 3 eq) in 2,2,2-trifluoroethanol (100 mL) was added TEA (20.02 g, 197.89 mmol, 27.54 mL, 4 eq) at 0 °C. The resulting mixture was allowed to warm and further stirred at 20 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. : EtOAc = 5:1, Rf = 0.56) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (150 mL) and extracted with EtOAc (100 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,4-dichloro-5-methyl-8-

oxabicyclo[3.2.1]oct-6-en-3-one (**242**, 26 g, crude) as yellow oil, without further characterization, further used as is.

To a solution of 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-2,4-dichloro-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**242**, 26 g, 74.00 mmol, 1 eq) in MeOH (300 mL) was added NH_4Cl (27.71 g, 518.02 mmol, 7 eq) and CuCl (3.66 g, 37.00 mmol, 884.80 μL, 0.5 eq) at 0 °C. Zn (29.03 g, 444.01 mmol, 6 eq) was then added in several portions and the resulting mixture was allowed to warm and further stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.43) until it showed that the starting material had been completely consumed. The reaction mixture was filtered through CELITE™ pad. The filtrate was diluted with water (200 mL) and extracted with EtOAc (200 mL x 3). The organic layers were combined, washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 20/1) to afford 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**243**, 7.3 g, 25.85 mmol, 34.9 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.07-6.04 (m, 1H), 6.01-5.98 (m, 1H), 3.80 (s, 2H), 2.57 - 2.32 (m, 4H), 1.49 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H).

To a solution of LiHMDS (1 M, 29.31 mL, 1.15 eq) in THF (20 mL) was added 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**243**, 7.2 g, 25.49 mmol, 1 eq) in THF (10 mL) at -70 °C. The mixture was allowed to warm and further stirred at 20 °C for 0.5 h, then cooled to -78 °C. 1,1,1-Trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (10.96 g, 30.59 mmol, 1.2 eq) in THF (20 mL) was then added dropwise. The resulting mixture was again allowed to warm and further stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.43) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (30 mL, aqueous) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 20/1) to afford the mixture of [1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate and [5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] (**244***, 7.1 g, 17.13 mmol, 67.2 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40-6.38 (m, 0.4H), 6.32 - 6.24 (m, 1H), 6.09 (s, 0.6H), 5.92-5.88 (m, 0.6H), 5.82-5.76 (m, 0.4H), 3.80 (s, 2H), 2.82 - 2.62 (m, 1H), 2.19 - 2.08 (m, 1H), 1.58 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H).

To a solution of the mixture of [1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate and [5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] (**244***, 7.1 g, 17.13 mmol, 1 eq) in 1,4-dioxane (70 mL) was added KOAc (4.20 g, 42.82 mmol, 2.5 eq), Pin_2B_2 (**4**, 5.22 g, 20.55 mmol, 1.2 eq) and cyclopentyl(diphenyl)phosphane; dichloropalladium;iron (626.65 mg, 856.43 μmol, 0.05 eq). The resulting mixture was warmed and further stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.57) until it showed that the starting material had been completely consumed. The reaction mixture was poured into NH_4Cl (50 mL, aqueous) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 50/1 to 30/1) to afford the mixture of *tert*-butyl-dimethyl-[[5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]silane and *tert*-butyl-dimethyl-[[1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-5-yl]methoxy]silane (**245***, 4.2 g, 10.70 mmol, 62.49% yield) as crude yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98-6.94 (m, 0.5H), 6.84-6.80 (m, 0.5H), 6.30 (d, *J* = 6.0 Hz, 0.5H), 6.17 (d, *J* = 5.6 Hz, 0.5H), 5.82 (d, *J* = 5.6 Hz, 0.5H), 5.68 (d, *J* = 5.6 Hz, 0.5H), 3.96-3.78 (m, 1H), 3.68-3.58 (m, 1H), 2.22-2.02 (m, 1H), 1.84-1.74 (m, 1H), 1.56 (s, 3H), 1.28-1.22 (m, 12H), 0.92-0.88 (m, 6H), 0.09-0.04 (m, 9H).

To a solution of the mixture of *tert*-butyl-dimethyl-[[5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methoxy]silane and *tert*-butyl-dimethyl-[[1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-5-yl]methoxy]silane (**245***, 2.22 g, 5.65 mmol, 2 eq) and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-3**, 1.5 g, 2.83 mmol, 1 eq) in 1,4-dioxane (10 mL) and H_2O (2 mL) was added K_2CO_3 (976.89 mg, 7.07 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (103.44 mg, 141.37 μmol, 0.05 eq). The resulting mixture was warmed and further stirred at 100 °C for 12 hr under N_2. The reaction was monitored by LC/MS (R_t = 0.793 min) until it showed that some desired product had been detected. The reaction mixture was poured into NH_4Cl (50 mL, aqueous) and extracted with EtOAc (50 mL x 3). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 80/1 to 50/1) to afford the mixture of *N*-[6-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-

trimethylsilylethoxymethyl)imidazole-2-carboxamide and *N*-[6-[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**246***, 1.1 g, 1.54 mmol, 54.33% yield) as crude yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.66-8.62 (m, 1H), 7.76 (s, 1H), 7.25 (s, 1H), 6.38 (d, *J* = 5.6 Hz, 0.5H), 6.25 (d, *J* = 5.6 Hz, 0.5H), 5.96-5.90 (m, 3.5H), 5.84-5.76 (m, 0.5H), 3.92-3.82 (m, 2H), 3.68-3.62 (m, 2H), 2.78-2.72 (m, 1H), 2.54-2.44 (m, 3H), 2.13 (br s, 2H), 1.64-1.54 (m, 5H), 1.27-1.23 (m, 2H), 1.11 (s, 6H), 0.98-0.92 (m, 9H), 0.14-0.08 (m, 6H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 716.6, expected 716.4 [M+H].

To a solution of *N*-[6-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and *N*-[6-[5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**246***, 1.1 g, 1.54 mmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 1.54 mL, 1 eq) dropwise. The resulting mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 0.661 min) until it showed that the starting material had been completely consumed and the major desired product mass had been detected. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford the mixture of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(hydroxymethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[5-(hydroxymethyl)-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**247***, 0.7 g, 1.16 mmol, 75.7 % yield) as a yellow solid. MS (LC/MS) *m/z* observed 602.5, expected 602.3 [M+H].

To a solution of the mixture of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(hydroxymethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[5-(hydroxymethyl)-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**247***, 0.7 g, 1.16 mmol, 1 eq) in DCM (3 mL) was added pyridine (460.03 mg, 5.82 mmol, 469.42 μL, 5 eq) and Tf_2O (984.52 mg, 3.49 mmol, 575.74 μL, 3 eq). The resulting mixture was stirred at 25 °C for 2 hrs. The reaction was monitored by LC/MS (R_t = 0.77 min) until it showed that some desired

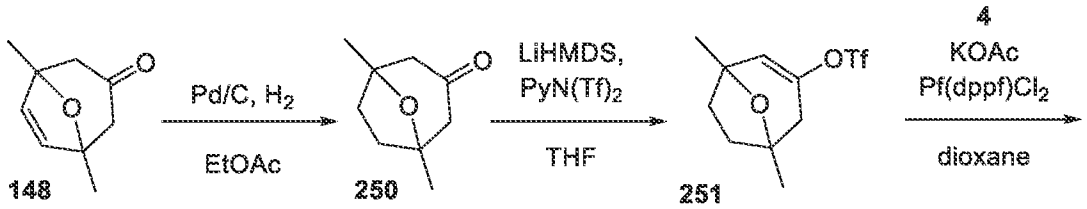
product mass had been detected. The reaction mixture was poured into NH_4Cl (50 mL, aqueous) and extracted with DCM (50 mL x 3). The organic layers were combined, washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 80/1 to 50/1) to afford the mixture of [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methyl trifluoromethanesulfonate and [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-5-yl]methyl trifluoromethanesulfonate (**248***, 0.6 g, 817.58 μmol, 70.3 % yield) as crude yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02-10.00 (m, 1H), 8.74-8.66 (m, 1H), 7.77 (s, 1H), 7.32-7.25 (m, 1H), 6.96-6.88 (m, 1H), 6.42-6.24 (m, 1H), 6.02-5.80 (m, 4H), 4.84-4.70 (m, 2H), 3.69-3.62 (m, 2H), 2.82-2.74 (m, 1H), 2.52-2.42 (m, 3H), 2.16-2.12 (m, 2H), 1.68-1.58 (m, 5H), 1.32-1.24 (m, 6H), 1.13 (s, 6 H), 0.99-0.94 (m, 2H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 734.3, expected 734.3 [M+H].

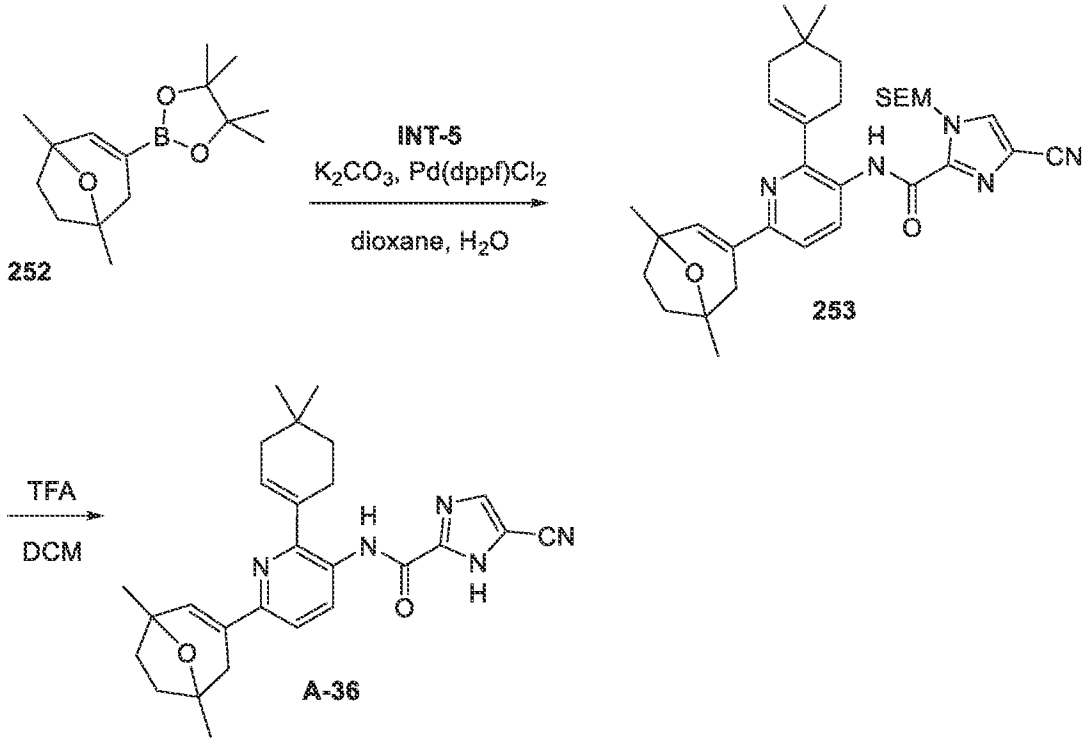
To a solution of the mixture of [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]methyl trifluoromethanesulfonate and [3-[5-[[4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]amino]-6-(4,4-dimethylcyclohexen-1-yl)-2-pyridyl]-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-5-yl]methyl trifluoromethanesulfonate (**248***, 0.6 g, 817.58 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 2.04 mL, 2.5 eq) dropwise. The resulting mixture was warmed and stirred at 40 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 0.729 min) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford the mixture of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(fluoromethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[5-(fluoromethyl)-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**249***, 0.3 g, 496.85 μmol, 60.8 % yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.00 (s, 1H), 8.69-8.67 (m, 1H), 7.77 (s, 1H), 7.29-7.27 (m, 1H), 7.03 - 6.94 (m, 1H), 6.37-6.30 (m, 1H), 5.96 - 5.84 (m, 4H), 4.78 - 4.59 (m, 2H), 3.67 - 3.63 (m, 2H), 2.86 - 2.81 (m, 1H), 2.49-2.37 (m, 2H), 2.37 - 2.33 (m, 1H), 2.14-2.13 (m, 2H), 1.63-1.61 (m, 5H), 1.12 (s, 6H), 0.98 - 0.95 (m, 2H), 0.00 (s, 9H), MS (LC/MS) *m/z* observed 604.4, expected 604.3 [M+H].

To a solution of the mixture of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(fluoromethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[5-(fluoromethyl)-1-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**249***, 0.3 g, 496.85 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 993.71 μL, 2 eq) dropwise. The resulting mixture was warmed and stirred at 60 °C for 3 hr. The reaction was monitored by LC/MS (R_t = 0.569 min, [M+H] =474.5) until it showed that the major desired product mass had been detected. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL x 3). The organic layers were combined, washed with brine (20 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 50 % - 85 % B gradient over 8.0 min) to afford the mixture of title compounds 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(fluoromethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-5-(fluoromethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-35***, 0.12 g, 253.41 μmol, 51. % yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.02 (s, 1H), 8.34 (s, 1H), 8.22 (dd, *J* = 3.8, 8.4 Hz, 1H), 7.45 (dd, *J* = 8.6, 12.3 Hz, 1H), 7.09 - 6.95 (m, 1H), 6.48 - 6.33 (m, 1H), 5.97 - 5.87 (m, 2H), 4.85 - 4.56 (m, 2H), 2.63 (br dd, *J* = 12.0, 18.3 Hz, 1H), 2.44 - 2.19 (m, 3H), 1.93 (br s, 2H), 1.48 (br d, *J* = 4.8 Hz, 5H), 0.98 (s, 6H), MS (LC/MS) *m/z* observed 474.4, expected 474.5 [M+H].

EXAMPLE 45

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-36





To a solution of 1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**148**, 2 g, 13.14 mmol, 1 eq)in EtOAc (30 mL) was added Pd/C (699.26 mg, 657.07 μmol, 10 % purity, 0.05 eq) at 25 °C. The mixture was stirred at 25 °C for 16 hr under H_2 (30 psi). The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (**250**, 2 g, crude) as a yellow oil, used further, as is. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.49 - 2.40 (m, 2H), 2.37 - 2.28 (m, 2H), 1.88 - 1.75 (m, 4H), 1.45 (s, 6H).

To a solution of LiHMDS (1 M, 15.56 mL, 1.2 eq) was added 1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (**250**, 2 g, 12.97 mmol, 1 eq) in THF (10 mL) dropwise at -65 °C under N_2. The mixture was allowed to warm and stirred at 25 °C for 0.5 h. 1,1,1-Trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (5.58 g, 15.56 mmol, 1.2 eq) in THF (10 mL) was then added dropwise at -65 °C under N_2. The mixture was allowed to warm and stirred at 25 °C for 2 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (25 mL, aqueous) and extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford [1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**251**, 2.3 g, 8.03 mmol, 62.0 % yield) as a yellow oil. ^{1}H NMR (400

MHz, $CDCl_3$) δ = 5.87 (s, 1H), 2.64 (br d, *J* = 16.6 Hz, 1H), 2.18 (d, *J* = 16.6 Hz, 1H), 2.12 (dd, *J* = 1.4, 10.6 Hz, 1H), 2.00 - 1.91 (m, 1H), 1.88 - 1.79 (m, 2H), 1.46 (d, *J* = 1.4 Hz, 6H).

To a solution of [1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**251**, 2.3 g, 8.03 mmol, 1 eq) in dioxane (30 mL) was added Pin_2B_2 (**4**, 2.65 g, 10.44 mmol, 1.3 eq) and KOAc (1.97 g, 20.09 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (293.94 mg, 401.72 μmol, 0.05 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (35 mL), extracted with EtOAc (25 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**252**, 2 g, 6.06 mmol, 75.4 % yield, 80 % purity) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.59 (t, *J* = 1.9 Hz, 1H), 2.40 (br d, *J* = 17.4 Hz, 1H), 2.04 - 1.97 (m, 2H), 1.87 - 1.79 (m, 1H), 1.76 - 1.69 (m, 2H), 1.39 (d, *J* = 5.0 Hz, 6H), 1.26 (s, 12H).

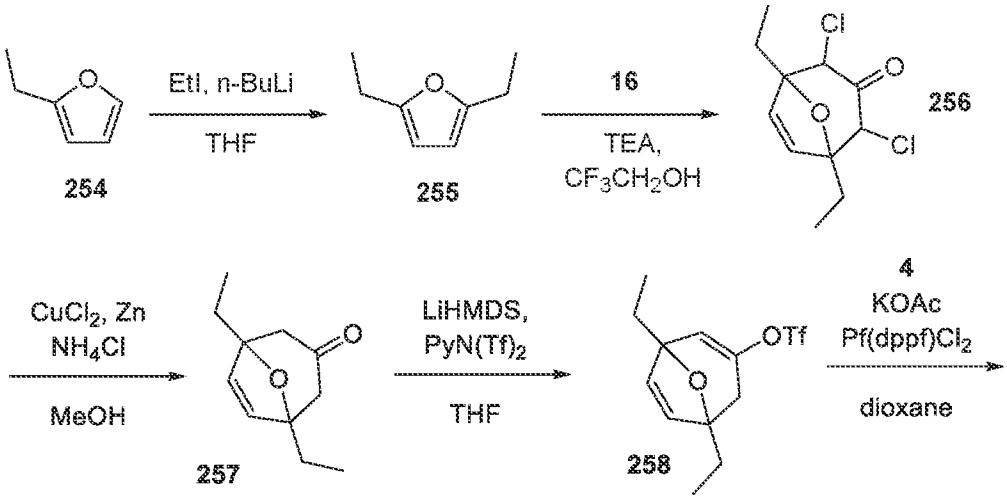
To a solution of 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**252**, 300 mg, 1.14 mmol, 2 eq) and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 301.25 mg, 567.82 μmol, 1 eq) in dioxane (5 mL) and H_2O (1 mL) was added K_2CO_3 (196.20 mg, 1.42 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (41.55 mg, 56.78 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**253**, 210 mg, 285.80 μmol, 50.3 % yield, 80 % purity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ = 10.04 (s, 1H), 8.70 (d, *J* = 8.6 Hz, 1H), 7.80 (s, 1H), 7.30 (s, 1H), 6.80 (s, 1H), 6.00 (br s, 1H), 5.97 (s, 2H), 3.72 - 3.66 (m, 2H), 2.72 (br d, *J* = 16.8 Hz, 1H), 2.57 - 2.49 (m, 3H), 2.18 (br d, *J* = 2.8 Hz, 2H), 2.16 - 2.09 (m, 1H), 1.98 - 1.89 (m, 1H), 1.84 (br d, *J* = 8.1 Hz, 1H), 1.68 - 1.65 (m, 2H), 1.56 (d, *J* = 2.1 Hz, 6H), 1.29 (s, 1H), 1.16 (s, 6H), 1.03 - 0.99 (m, 2H), 0.04 (s, 9H).

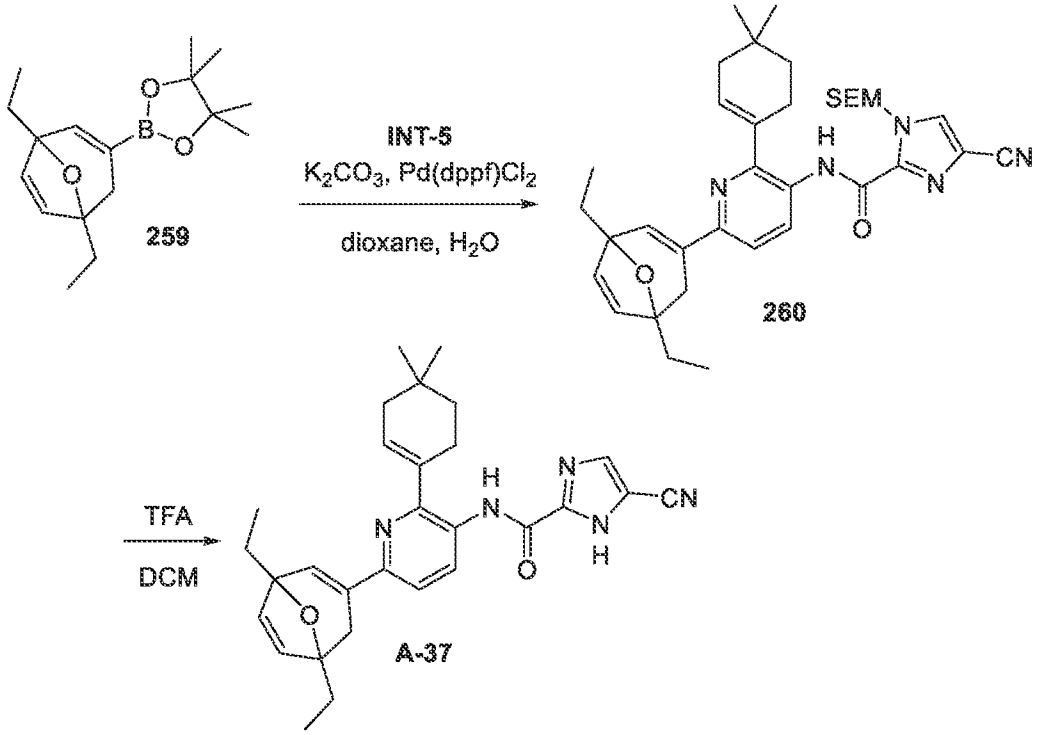
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-

carboxamide (**253**, 210 mg, 357.25 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.592min, [M+H] = 458.4) until it showed that the starting material had been consumed and the desired product mass had been observed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 % - 70 % B gradient over 10.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-36**, 116.7 mg, 201.74 μmol, 56.5 % yield, 98.8 % purity, TFA salt) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.78 (d, *J* = 8.8 Hz, 1H), 8.03 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 6.76 (s, 1H), 6.07 (br s, 1H), 2.73 - 2.64 (m, 1H), 2.56 - 2.43 (m, 3H), 2.20 - 2.11 (m, 3H), 2.02 - 1.94 (m, 1H), 1.91 - 1.80 (m, 2H), 1.64 (t, *J* = 6.3 Hz, 2H), 1.50 (s, 6H), 1.12 (s, 6H), MS (LC/MS) *m/z* observed 458.3, expected 458.4 [M+H].

EXAMPLE 46

5-Cyano-*N*-[6-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-37





To a solution of 2-ethylfuran (**254**, 4 g, 41.61 mmol, 1 eq) in THF (50 mL) was added *n*-BuLi (2.5 M, 16.64 mL, 1 eq) at 0 °C. The mixture was stirred for 0.5 h. A solution of iodoethane (9.73 g, 62.42 mmol, 4.99 mL, 1.5 eq) in THF (20 mL) was then added dropwise at 0 °C. The mixture was allowed to warm and stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et. /EtOAc = 1/0, Rf = 0.9) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (50 mL, saturated, aqueous) and extracted with EtOAc(50 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2,5-diethylfuran (**255**, 4 g, 32.21 mmol, 77.4 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 5.86 (s, 2H), 2.61 (q, J = 7.6 Hz, 4H), 1.22 (t, J = 7.6 Hz, 6H).

To a solution of 2,5-diethylfuran (**255**, 4 g, 32.21 mmol, 1 eq) in CF_3CH_2OH (40 mL) was added 1,1,3-trichloropropan-2-one (**16**, 15.60 g, 96.63 mmol, 3 eq) and *N,N*-diethylethanamine (13.04 g, 128.85 mmol, 17.93 mL, 4 eq) at 0 °C. The mixture was allowed to warm and further stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf =0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (80 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford (1*S*,5*R*)-2,4-dichloro-1,5-diethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**256**, 8 g, 32.11 mmol, 99.7 % yield) as a yellow oil, without further characterization.

To a mixture of 2,4-dichloro-1,5-diethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**256**, 8 g, 32.11 mmol, 1 eq) in MeOH (100 mL) was added CuCl (1.59 g, 16.06 mmol, 383.94 μL, 0.5 eq), NH_4Cl (12.02 g, 224.78 mmol, 7 eq) and zinc (10.50 g, 160.56 mmol, 5 eq) at 0 °C. The mixture was allowed to warm and stirred at 25 °C for 16 hours. The reaction was monitored by TLC (Pet. Et. /EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was diluted with water (100 mL) and extracted with EtOAc (80 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent gradient of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 50 mL/min) to afford 1,5-diethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**257**, 2 g, 11.10 mmol, 34.6 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 5.96 (s, 2H), 2.50 - 2.41 (m, 2H), 2.40 - 2.28 (m, 2H), 1.87 - 1.71 (m, 4H), 0.98 (t, *J* = 7.5 Hz, 6H).

To a solution of 1,5-diethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**257**, 2 g, 11.10 mmol, 1 eq) in THF (20 mL) was added to LiHMDS (1 M, 13.32 mL, 1.2 eq) at -65 °C. The mixture was warmed to 25 °C and stirred for 0.5 h, then cooled to -65 ° C. A solution of 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (4.77 g, 13.32 mmol, 1.2 eq) in THF (10 mL) was then added dropwise at -65 °C. The mixture was stirred at 25 °C for 2.5 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (50 mL, saturated, aqueous) and extracted with EtOAc(30 mL x 2). The organic layers were combined, washed with brine (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent gradient of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford [1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**258**, 2 g, 6.40 mmol, 57.7 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 6.24 (d, *J* = 5.8 Hz, 1H), 6.10 (s, 1H), 5.80 (d, *J* = 5.8 Hz, 1H), 2.62 (d, *J* = 17.5 Hz, 1H), 2.10 (d, J = 17.4 Hz, 1H), 1.88 - 1.78 (m, 4H), 0.99 (t, *J* = 7.5 Hz, 6H).

To a solution of [1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**258**, 2 g, 6.40 mmol, 1 eq) in dioxane (25 mL) was added Pin_2B_2 (**4**, 2.11 g, 8.33 mmol, 1.3 eq) and KOAc (1.57 g, 16.01 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (234.29 mg, 320.20 μmol, 0.05 eq) at 20 °C. The mixture was allowed to warm and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6)

until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (25 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 2-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**259**, 1 g, 3.45 mmol, 53.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.84 (t, *J* = 2.0 Hz, 1H), 6.15 (d, *J* = 5.8 Hz, 1H), 5.70 (d, *J* = 5.8 Hz, 1H), 2.40 (dd, *J* = 2.3, 18.5 Hz, 1H), 1.88 (dd, *J* = 2.1, 18.5 Hz, 1H), 1.78 - 1.70 (m, 4H), 1.24 (s, 12H), 0.98 (dt, *J* = 1.3, 7.5 Hz, 6H).

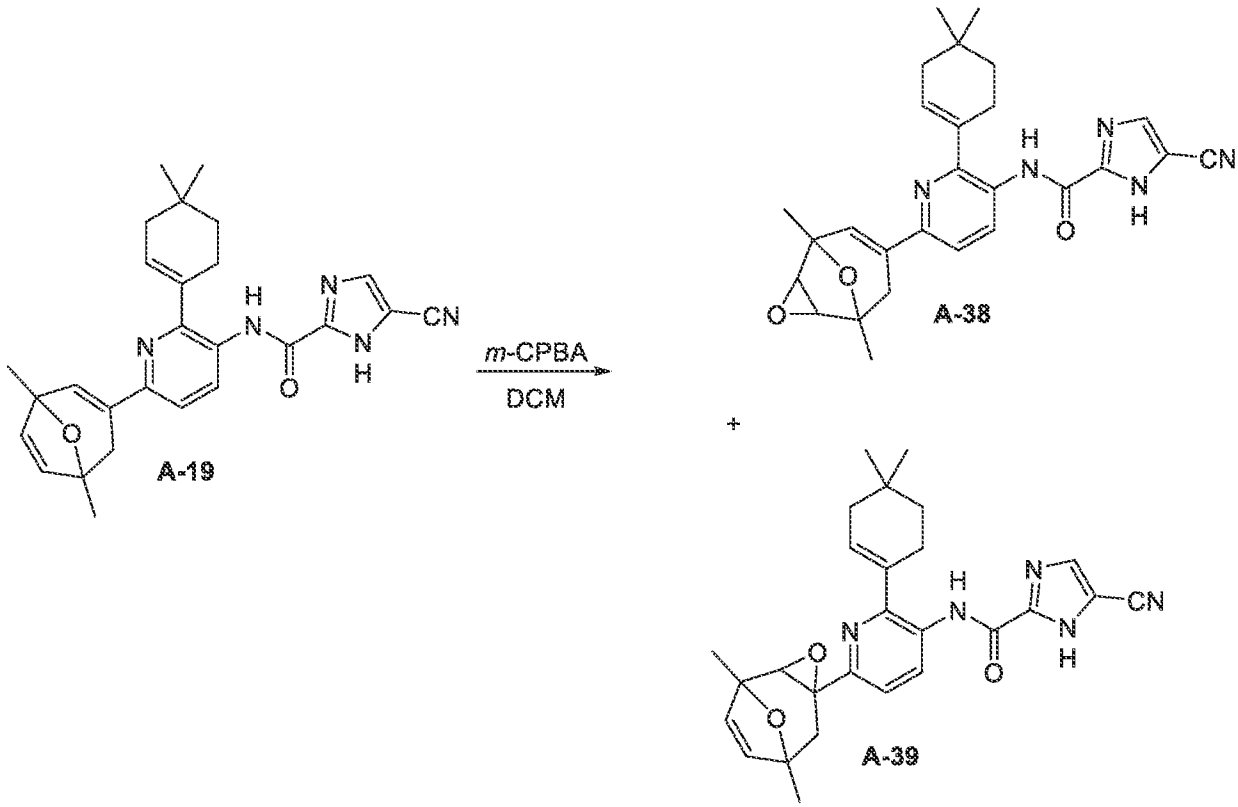
To a solution of 2-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**259**, 200 mg, 689.17 μmol, 1.3 eq) and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (281.25 mg, 530.13 μmol, 1 eq) in dioxane (5 mL) and H_2O (1 mL) was added K_2CO_3 (183.17 mg, 1.33 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (38.79 mg, 53.01 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.1) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 4-cyano-*N*-[6-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**260**, 200 mg, 325.81 μmol, 61.5 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.00 (s, 1H), 8.66 (d, *J* = 8.8 Hz, 1H), 7.77 (s, 1H), 7.28 (s, 1H), 6.97 (s, 1H), 6.22 (d, *J* = 5.6 Hz, 1H), 5.96 (br s, 1H), 5.93 (s, 2H), 5.79 (d, *J* = 5.6 Hz, 1H), 3.69 - 3.63 (m, 2H), 2.68 (dd, *J* = 1.8, 18.0 Hz, 1H), 2.50 (br d, *J* = 1.6 Hz, 2H), 2.38 (dd, *J* = 1.4, 17.9 Hz, 1H), 2.15 (br d, *J* = 2.9 Hz, 2H), 1.94 - 1.83 (m, 4H), 1.63 (t, *J* = 6.4 Hz, 2H), 1.13 (s, 6H), 1.05 (dt, *J* = 1.4, 7.4 Hz, 6H), 1.01 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[6-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**260**, 200 mg, 325.81 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.653 min, [M+H] = 484.4) until it showed that the starting material had been consumed and the desired product mass had been observed. The reaction was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC

(column: Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 % - 85 % B gradient over 8.0 min followed by column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 60 % - 90 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[6-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-37**, 53.3 mg, 109.54 μmol, 33.6 % yield, 99.4 % purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 9.99 (s, 1H), 8.27 (br s, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.95 (s, 1H), 6.29 (d, *J* = 5.6 Hz, 1H), 5.89 (br s, 1H), 5.84 (d, *J* = 5.6 Hz, 1H), 2.56 (br d, *J* = 1.6 Hz, 1H), 2.40 (br s, 2H), 2.30 - 2.23 (m, 1H), 1.94 (br s, 2H), 1.85 - 1.76 (m, 3H), 1.76 - 1.68 (m, 1H), 1.49 (br t, *J* = 6.3 Hz, 2H), 0.99 (s, 6H), 0.94 (dt, *J* = 4.9, 7.3 Hz, 6H), MS (LC/MS) *m/z* observed 484.3, expected 484.4 [M+H].

EXAMPLES 47 AND 48

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]non-6-en-7-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-38 and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-3,9-dioxatricyclo[4.2.1.0^{2,4}]non-7-en-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-39

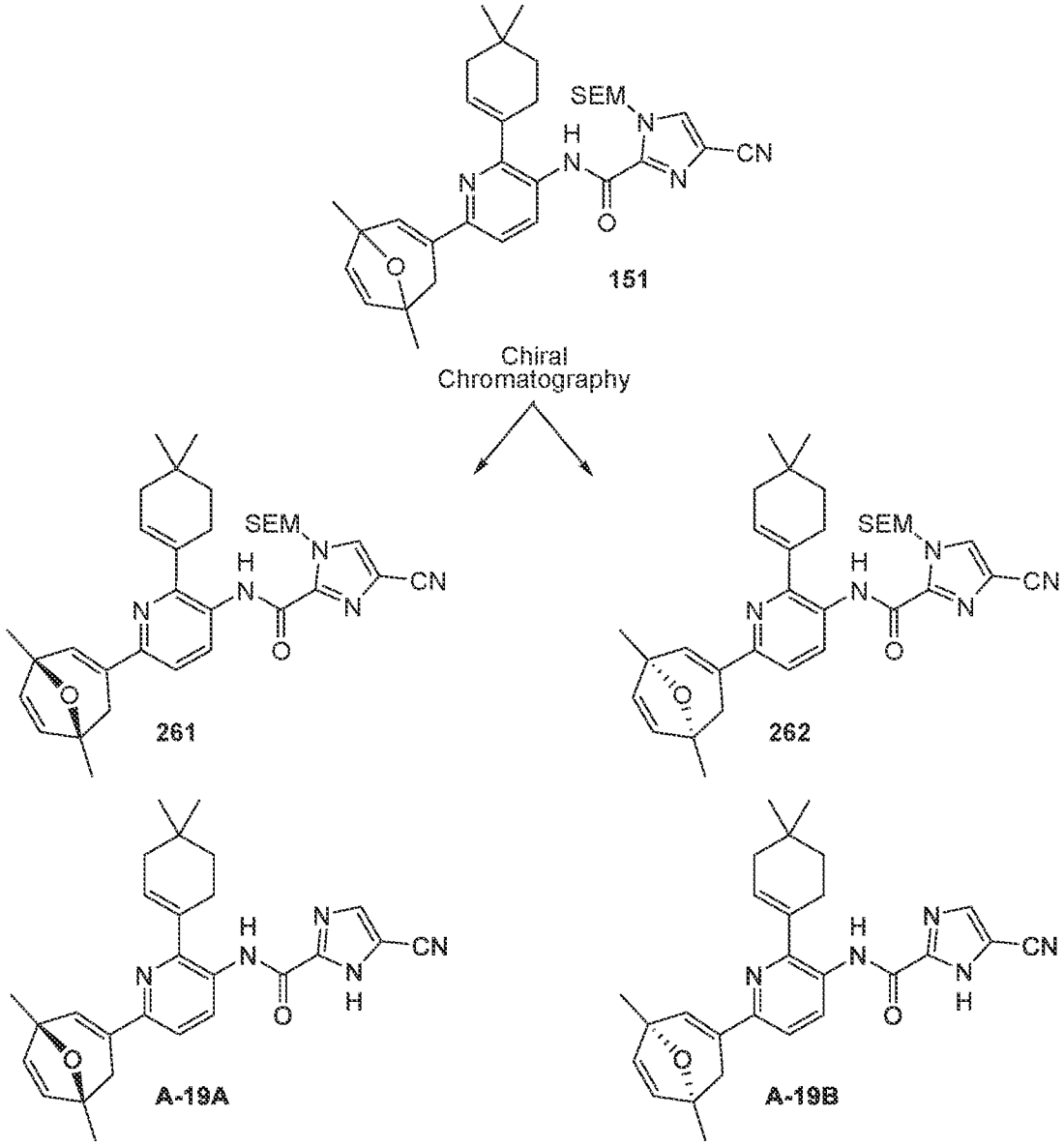


To a solution of 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-19**, 200 mg, 439.03 μmol, 1 eq) in DCM (10 mL)was added *m*-CPBA (89.13 mg, 439.03 μmol, 85 % purity,

1 eq). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 0.577 min (or 0.568 min), [M+H] =472.5) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with Na_2SO_3 (20 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC: column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 35 % - 65 % B gradient over 8.0 min to afford title compounds 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-3,9-dioxatricyclo[4.2.1.$0^{2,4}$]non-7-en-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-39**, 30.6 mg, 61.65 μmol, 14.0 % yield, 95 % purity; ; Example 48) and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-3,9-dioxatricyclo[3.3.1.02,4]non-6-en-7-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (22 mg, 40.77 μmol, 9.3 % yield, 87.5 % purity; Example 47) as a yellow solids. **A-38**: ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 10.03 (s, 1H), 8.31 - 8.24 (m, 2H), 7.48 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 5.94 - 5.87 (m, 1H), 3.64 (d, *J* = 3.1 Hz, 1H), 3.47 (d, *J* = 3.3 Hz, 1H), 2.59 - 2.52 (m, 1H), 2.47 - 2.38 (m, 3H), 1.95 (br s, 2H), 1.50 (br t, *J* = 6.3 Hz, 2H), 1.37 (d, *J* = 1.8 Hz, 6H), 1.00 (s, 6H), MS (LC/MS) *m/z* observed 472.4, expected 472.5 [M+H]. **A-39**: ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 10.07 (s, 1H), 8.30 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.22 (d, *J* = 5.6 Hz, 1H), 6.06 (d, *J* = 5.8 Hz, 1H), 5.90 (br s, 1H), 3.25 (s, 1H), 2.75 (d, *J* = 15.0 Hz, 1H), 2.39 (br dd, *J* = 3.0, 5.8 Hz, 2H), 1.92 (br s, 2H), 1.85 (d, *J* = 15.0 Hz, 1H), 1.48 (br t, *J* = 6.4 Hz, 2H), 1.41 (s, 3H), 1.34 (s, 3H), 0.97 (s, 6H), MS (LC/MS) *m/z* observed 472.4, expected 472.5 [M+H].

EXAMPLES 49 AND 50

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*R*,5*R*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-19A and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*S*,5*S*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-19B (Absolute stereochemistry of each isomer is unknown and depicted only to distinguish the isomers)



Absolute stereochemistry not known: depicted only to distinguish isomers

151 was purified by SFC Separation column: DAICEL CHIRALPAK AD-H (250 mm x 30 mm, 5 um); mobile phase: [Heptane – IPA (0.1 % NH_4OH)]; B %: 5 %, with isocratic elution to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*R*,5*R*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**261**, 80 mg, 136.56 μmol, 22.9 % yield) and 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*S*,5*S*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**262**, 40 mg, 68.28 μmol, 11.4 % yield) were obtained as white solids. The absolute stereochemistry of isomer is unknown and depicted only to distinguish the isomers. **261**: ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 10.00 (s, 1H), 8.69 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.29 - 7.27 (m, 1H), 6.99 (s, 1H), 6.24 (d, *J* = 5.6 Hz, 1H), 5.97 (br s, 1H), 5.93 (s, 2H), 5.76 (d, *J* = 5.5 Hz, 1H), 3.70 - 3.63 (m, 2H), 2.70

(dd, J = 1.8, 18.0 Hz, 1H), 2.51 (br s, 2H), 2.41 (dd, J = 1.3, 18.0 Hz, 1H), 2.15 (br d, J = 3.0 Hz, 2H), 1.64 (t, J = 6.3 Hz, 2H), 1.58 (s, 6H), 1.13 (s, 6H), 1.03 - 0.94 (m, 2H), 0.04 - -0.02 (m, 9H), MS (LC/MS) m/z observed 586.4, expected 586. [M+H]. **262**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.00 (s, 1H), 8.70 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.30 (s, 1H), 7.01 (s, 1H), 6.24 (d, J = 5.6 Hz, 1H), 5.98 (br s, 1H), 5.93 (s, 2H), 5.77 (d, J = 5.6 Hz, 1H), 3.70 - 3.62 (m, 2H), 2.70 (dd, J = 1.9, 17.9 Hz, 1H), 2.51 (br s, 2H), 2.42 (dd, J = 1.4, 18.0 Hz, 1H), 2.15 (br d, J = 3.4 Hz, 2H), 1.64 (br t, J = 6.4 Hz, 2H), 1.58 (s, 6H), 1.13 (s, 6H), 1.01 - 0.96 (m, 2H), 0.03 - -0.01 (m, 9H), MS (LC/MS) m/z observed 586.4, expected 586.3 [M+H].

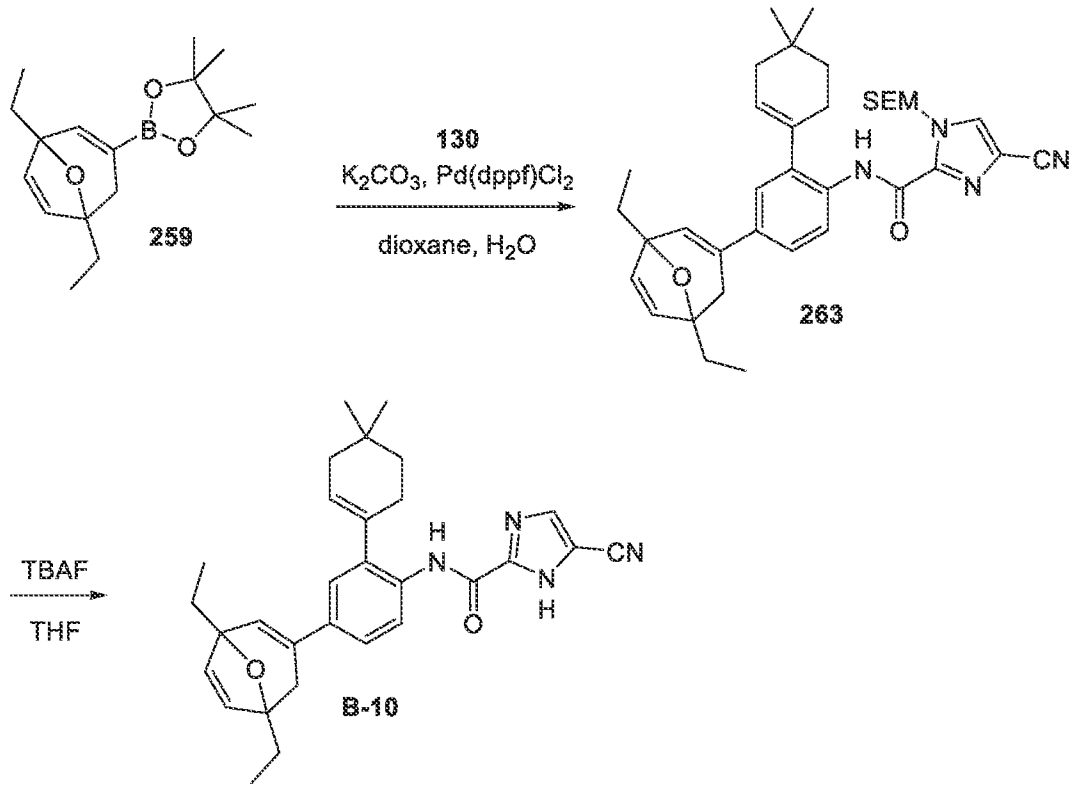
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*R*,5*R*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**261**, 80 mg, 136.56 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 0.590 min, [M+H] = 456.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH4HCO3) - ACN]; 40 % - 80 % B gradient over 8.0 min) to afford the first title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*R*,5*R*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-19A**, 26.7 mg, 58.61 μmol, 42.9 % yield; Example 49) as a white solid. The absolute stereochemistry of isomer is unknown and depicted only to distinguish the isomers. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.46 - 14.11 (m, 1H), 10.00 (s, 1H), 8.31 (s, 1H), 8.21 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 6.95 (s, 1H), 6.29 (d, J = 5.6 Hz, 1H), 5.89 (br s, 1H), 5.80 (d, J = 5.5 Hz, 1H), 2.55 (br d, J = 1.6 Hz, 1H), 2.41 (br s, 2H), 2.34 - 2.27 (m, 1H), 1.94 (br s, 2H), 1.49 (br t, J = 6.4 Hz, 2H), 1.44 (d, J = 3.0 Hz, 6H), 0.99 (s, 6H), MS (LC/MS) m/z observed 456.1, expected 456.2 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*S*,5*S*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**262**, 40.00 mg, 68.28 μmol, 1 eq) in DCM (1 mL) was added TFA (3 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 1.402 min, [M+H] = 456.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3)

- ACN]; 50 % - 80 % B gradient over 8.0 min to afford the second title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[(1*S*,5*S*)-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-19B**, 16.7 mg, 36.66 μmol, 53.7 % yield; Example 50) as a pink solid. The absolute stereochemistry of isomer is unknown and depicted only to distinguish the isomers.^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.39 - 14.23 (m, 1H), 10.00 (s, 1H), 8.33 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 1H), 6.95 (s, 1H), 6.29 (d, *J* = 5.5 Hz, 1H), 5.89 (br s, 1H), 5.80 (d, *J* = 5.5 Hz, 1H), 2.55 (br d, *J* = 1.5 Hz, 1H), 2.41 (br s, 2H), 2.34 - 2.27 (m, 1H), 1.94 (br s, 2H), 1.49 (br t, *J* = 6.3 Hz, 2H), 1.44 (d, *J* = 3.0 Hz, 6H), 0.99 (s, 6H), MS (LC/MS) *m/z* observed 456.3, expected 456.2 [M+H].

EXAMPLE 51

5-Cyano-N-[4-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1H-imidazole-2-carboxamide B-10



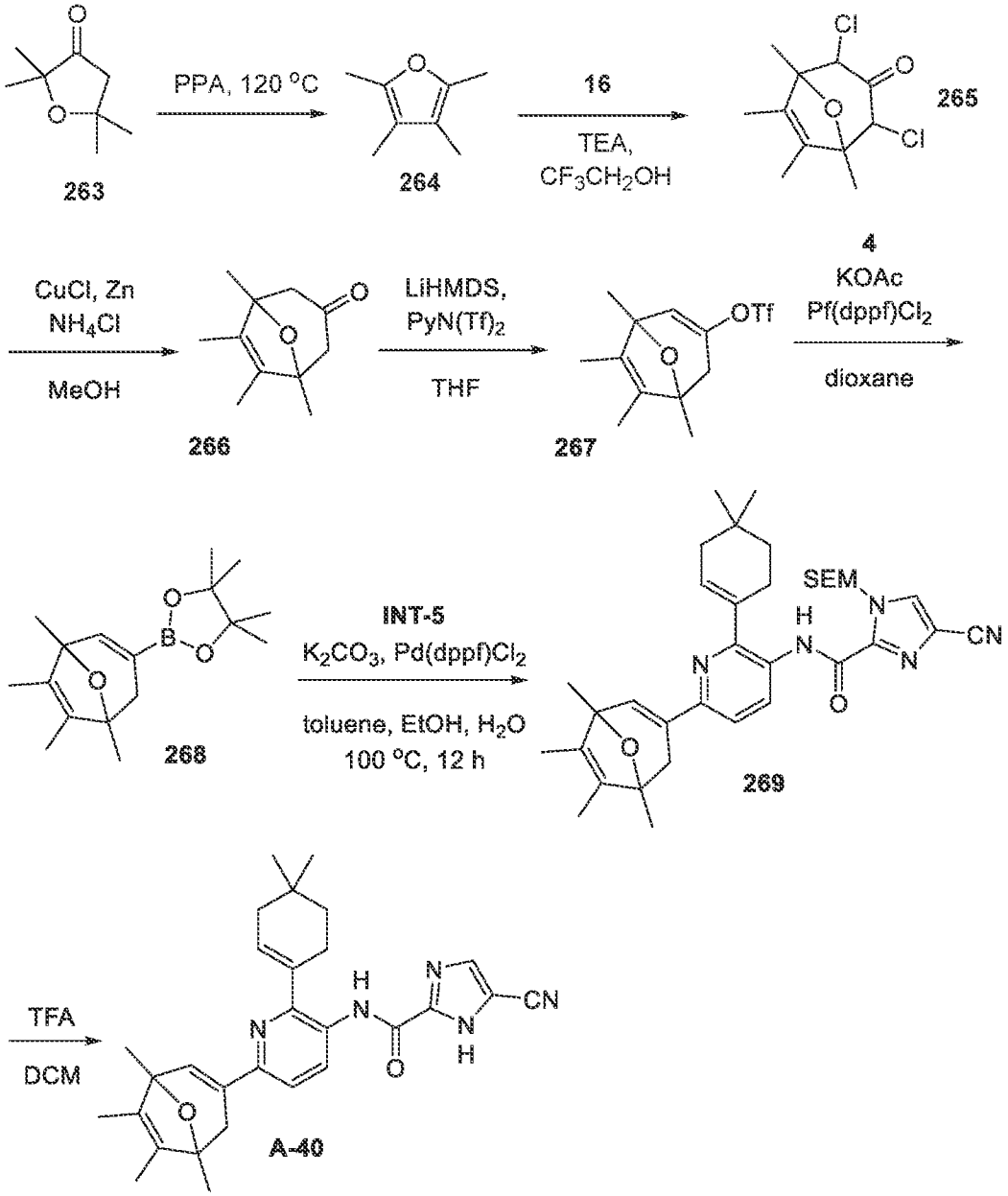
To a solution of 2-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**259**, 142.49 mg, 490.99 μmol, 1.3 eq) and *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 200 mg, 377.68 μmol, 1 eq) in dioxane (5 mL)and H_2O (1 mL) was added K_2CO_3 (130.50 mg, 944.21 μmol, 2.5 eq) and Pd(dppf)Cl2 (27.64 mg, 37.77 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.55) until it showed that the starting

material had been completely consumed. The reaction mixture was diluted with H_2O (6 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 5-cyano-N-[4-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**263**, 170 mg, 277.38 μmol, 73.4 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7.29 (br d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.43 (s, 1H), 6.23 (d, *J* = 5.8 Hz, 1H), 5.95 (s, 2H), 5.79 - 5.74 (m, 2H), 3.70 - 3.62 (m, 2H), 2.63 (dd, *J* = 1.6, 17.5 Hz, 1H), 2.29 (br d, *J* = 1.6 Hz, 2H), 2.16 (dd, *J* = 1.1, 17.5 Hz, 1H), 2.11 (br d, *J* = 2.9 Hz, 2H), 1.92 - 1.82 (m, 4H), 1.62 - 1.58 (m, 2H), 1.12 (s, 6H), 1.04 (dt, *J* = 2.4, 7.4 Hz, 6H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[4-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**263**, 150.00 mg, 244.75 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 734.24 μL, 3 eq) at 25 °C. The mixture was warmed and stirred at 60 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.755 min, [M+H] = 483.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (8 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 60 % - 90 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[4-[1,5-diethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1*H*-imidazole-2-carboxamide (**B-10**, 61.4 mg, 127.22 μmol, 52.0 % yield, 100 % purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.56 - 14.06 (m, 1H), 9.69 (s, 1H), 8.31 (s, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.35 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 6.54 (s, 1H), 6.28 (d, *J* = 5.8 Hz, 1H), 5.81 (d, *J* = 5.6 Hz, 1H), 5.67 (br s, 1H), 2.54 (br s, 1H), 2.25 (br s, 2H), 2.13 (br d, *J* = 17.8 Hz, 1H), 1.97 (br s, 2H), 1.82 - 1.67 (m, 4H), 1.49 (br t, *J* = 6.1 Hz, 2H), 1.02 (s, 6H), 0.94 (q, *J* = 7.2 Hz, 6H), MS (LC/MS) *m/z* observed 483.3, expected 483.4 [M+H].

EXAMPLE 52

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-40



A solution of 2,2,5,5-tetramethyltetrahydrofuran-3-one (263, 5 g, 35.16 mmol, 1 eq) in polyphosphoric acid (15 mL) was stirred at 120 °C for 6 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/0, Rf = 0.7) until it showed that the starting material has been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (30 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with Eluent of 0 ~ 5 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford

2,3,4,5-tetramethylfuran (**264**, 1.3 g, 10.47 mmol, 29.8 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 2.16 (s, 6H), 1.83 (s, 6H).

To a solution of 2,3,4,5-tetramethylfuran (**264**, 1.3 g, 10.47 mmol, 1 eq) in CF_3CH_2OH (20 mL) was added 1,1,3-trichloropropan-2-one (**16**, 5.07 g, 31.41 mmol, 3 eq) and TEA (4.24 g, 41.87 mmol, 5.83 mL, 4 eq) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2,4-dichloro-1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**265**, 3 g, 9.63 mmol, 92.0 % yield, 80 % purity) as a yellow oil, used further as is, without further characterization.

To a mixture of 2,4-dichloro-1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**265**, 3 g, 12.04 mmol, 1 eq) in MeOH (50 mL) was added CuCl (596.07 mg, 6.02 mmol, 143.98 μL, 0.5 eq), NH_4Cl (4.51 g, 84.29 mmol, 7 eq) and zinc (4.72 g, 72.25 mmol, 6 eq) at 0 °C. The mixture was allowed to warm and further stirred at 25 °C for 16 hours. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was diluted with water (30 mL) and extracted with EtOAc(20 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford 1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**266**, 0.5 g, 2.77 mmol, 23.0 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 2.39 - 2.24 (m, 4H), 1.57 (s, 6H), 1.40 (s, 6H).

To a solution of 1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**266**, 0.5 g, 2.77 mmol, 1 eq) in THF (3 mL) was added to LiHMDS (1 M, 3.33 mL, 1.2 eq) at -65 °C. The mixture was warmed to 25 °C and stirred for 0.5 h, then cooled to -65 ° C. 1,1,1-Trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (1.09 g, 3.05 mmol, 1.1 eq) in THF (3 mL) was then added dropwise at -65 °C. The mixture was allowed to warm and stirred at 25 °C for 2.5 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (20 mL, saturated, aqueous) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under

reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford [1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**267**, 0.35 g, 1.12 mmol, 40.4 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 6.14 (s, 1H), 2.45 (dd, *J* = 1.4, 17.3 Hz, 1H), 2.10 (d, *J* = 17.3 Hz, 1H), 1.64 (s, 3H), 1.60 (s, 3H), 1.46 (s, 3H), 1.43 (s, 3H).

To a solution of [1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**267**, 0.2 g, 640.40 μmol, 1 eq) in dioxane (5 mL) was added Pin_2B_2 (**4**, 211.41 mg, 832.52 μmol, 1.3 eq), KOAc (188.55 mg, 1.92 mmol, 3 eq) and $Pd(dppf)Cl_2$ (46.86 mg, 64.04 μmol, 0.1 eq). The mixture was warmed and stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf =0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 10 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford 4,4,5,5-tetramethyl-2-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-1,3,2-dioxaborolane (**268**, 150 mg, 516.88 μmol, 80.7 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 6.87 (s, 1H), 2.20 (dd, *J* = 2.0, 18.3 Hz, 1H), 1.91 (dd, *J* = 1.9, 18.3 Hz, 1H), 1.63 (s, 3H), 1.58 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.25 (s, 12H).

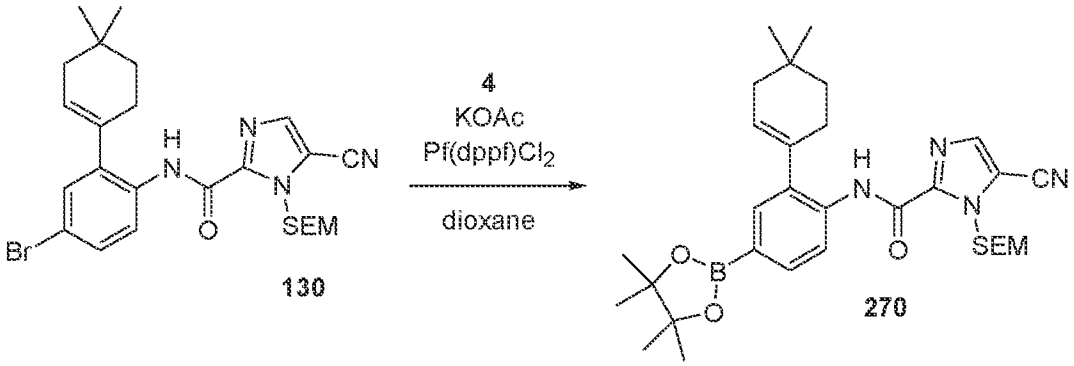
To a solution of 4,4,5,5-tetramethyl-2-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-1,3,2-dioxaborolane (**268**, 142.22 mg, 490.07 μmol, 1.3 eq) in toluene (4 mL), H_2O (1 mL) and EtOH (2 mL) was added *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 200.00 mg, 376.98 μmol, 1 eq), K_2CO_3 (156.31 mg, 1.13 mmol, 3 eq) and $Pd(dppf)Cl_2$ (27.58 mg, 37.70 μmol, 0.1 eq). The mixture was stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**269**, 170 mg, 276.93 μmol, 73.5 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.00 (s, 1H),

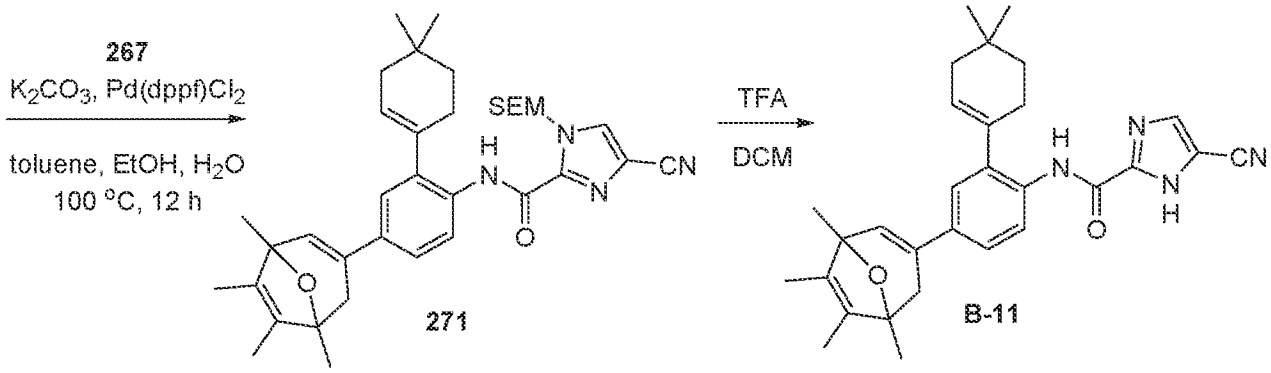
8.65 (d, J = 8.8 Hz, 1H), 7.77 (s, 1H), 7.24 (s, 1H), 7.02 (s, 1H), 5.96 (br s, 1H), 5.94 (s, 2H), 3.70 - 3.61 (m, 2H), 2.55 - 2.36 (m, 4H), 2.15 (br s, 2H), 1.66 (s, 3H), 1.65 - 1.63 (m, 2H), 1.62 (s, 3H), 1.50 (d, J = 12.8 Hz, 6H), 1.13 (s, 6H), 1.01 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**269**, 170.00 mg, 276.93 μmol, 1 eq) in DCM (3 mL)was added TFA (1 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 0.611 min, [M+H] = 484.3) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (20 mL) and extracted with DCM (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 45 % - 75 % B gradient over 8.0 min to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-40**, 54.2 mg, 112.08 μmol, 40.5 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ (ppm) = 11.68 (br s, 1H), 9.82 (s, 1H), 8.62 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 2.3 Hz, 1H), 7.30 (s, 1H), 7.03 (s, 1H), 5.97 (br s, 1H), 2.56 - 2.46 (m, 3H), 2.45 - 2.37 (m, 1H), 2.15 (br d, J = 2.9 Hz, 2H), 1.68 - 1.63 (m, 8H), 1.52 (s, 3H), 1.49 (s, 3H), 1.12 (s, 6H), MS (LC/MS) *m/z* observed 484.3, expected 484.3 [M+H].

EXAMPLE 53

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1*H*-imidazole-2-carboxamide B-11





To a solution of *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 800 mg, 1.51 mmol, 1 eq) in dioxane (10 mL) was added Pin_2B_2 (**4**, 498.73 mg, 1.96 mmol, 1.3 eq) and KOAc (370.66 mg, 3.78 mmol, 2.5 eq) and Pd(dppf)Cl2 (55.27 mg, 75.54 μmol, 0.05 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (12 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**270**, 820 mg, 1.42 mmol, 94.1 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.89 (s, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 7.77 (s, 1H), 7.74 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.62 (d, *J* = 1.0 Hz, 1H), 5.96 (s, 2H), 5.76 (br s, 1H), 3.70 - 3.64 (m, 2H), 2.31 (br d, *J* = 1.8 Hz, 2H), 2.10 (br d, *J* = 3.0 Hz, 2H), 1.60 - 1.58 (m, 2H), 1.36 (s, 12H), 1.12 (s, 6H), 1.01 - 0.96 (m, 2H), 0.01 (s, 9H).

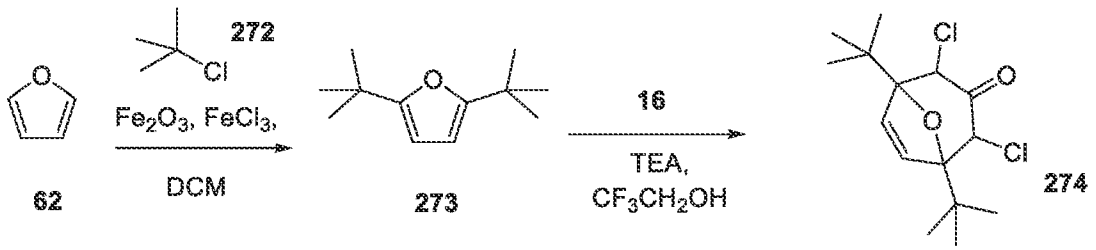
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**270**, 290.79 mg, 504.32 μmol, 1.05 eq) and [1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**267**, 150 mg, 480.30 μmol, 1 eq) in toluene (4 mL), EtOH (2 mL)and H2O (1 mL) was added K_2CO_3 (165.96 mg, 1.20 mmol, 2.5 eq) and Pd(dppf)Cl_2 (35.14 mg, 48.03 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc =

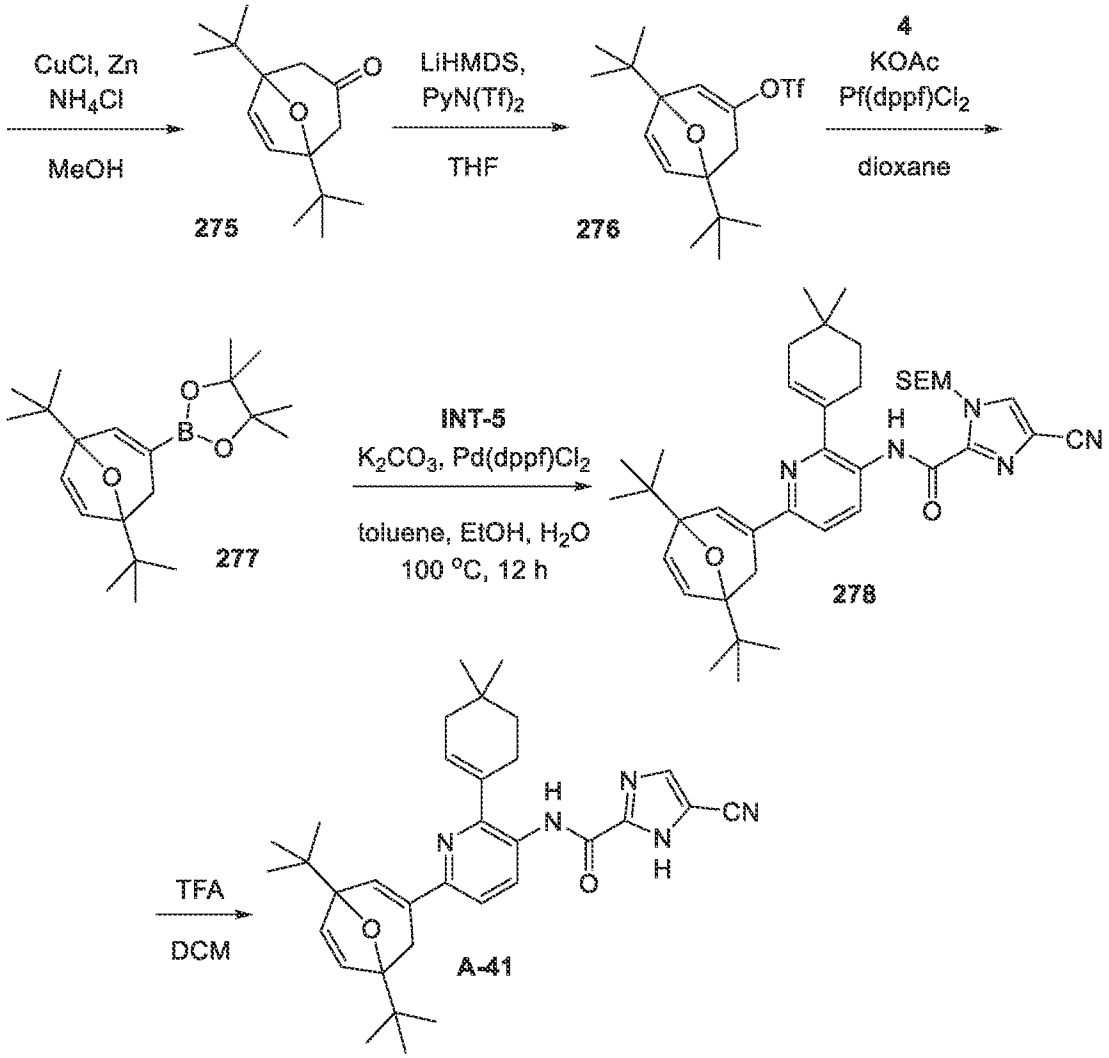
100/1 to 5/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**271**, 180 mg, 293.70 μmol, 61.2 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 7.76 (s, 1H), 7.29 (br d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 6.52 (s, 1H), 5.96 (s, 2H), 5.76 (br s, 1H), 3.71 - 3.62 (m, 2H), 2.44 (d, *J* = 17.4 Hz, 1H), 2.29 (br d, *J* = 1.6 Hz, 2H), 2.21 (d, *J* = 17.4 Hz, 1H), 2.11 (br d, *J* = 2.6 Hz, 2H), 1.64 (d, *J* = 16.8 Hz, 6H), 1.60 (s, 2H), 1.48 (d, *J* = 17.9 Hz, 6H), 1.12 (s, 6H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**271**, 150 mg, 244.75 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 734.24 μL, 3 eq) at 25 °C. The mixture was warmed and stirred at 60 °C for 2 hr under N2 atmosphere. The reaction was monitored by LC/MS (R_t = 2.307 min, [M+H] = 483.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH4HCO3) - ACN]; 60 % - 90 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5,6,7-tetramethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1*H*-imidazole-2-carboxamide (**B-11**, 97.6 mg, 202.23 μmol, 82.6 % yield, 100 % purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.06 (br s, 1H), 9.64 (s, 1H), 8.30 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.33 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.55 (s, 1H), 5.78 (br s, 1H), 2.50 - 2.42 (m, 1H), 2.30 (br d, *J* = 1.6 Hz, 2H), 2.22 (d, *J* = 17.3 Hz, 1H), 2.12 (br d, J = 2.6 Hz, 2H), 1.67 (s, 3H), 1.63 (s, 3H), 1.62 - 1.59 (m, 2H), 1.51 (s, 3H), 1.47 (s, 3H), 1.12 (s, 6H), MS (LC/MS) *m/z* observed 483.2, expected 483.3 [M+H].

EXAMPLE 54

5-Cyano-*N*-[6-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide A-41





DCM (150 mL) , oxo(oxoferriooxy)iron (23.46 g, 146.90 mmol, 1 eq) and $FeCl_3$ (595.68 mg, 3.67 mmol, 212.74 μL, 0.025 eq) were charged to a reaction vessel and the stirred mixture was heated to 40 °C. A mixture of furan (**62**, 10 g, 146.90 mmol, 10.68 mL, 1 eq) and 2-chloro-2-methyl-propane (**272**, 34.00 g, 367.25 mmol, 40.47 mL, 2.5 eq) was then slowly added into the solvent/catalyst mixture, and the mixture further stirred at 40 °C, for 2 hours. The reaction was monitored by TLC (Pet. Et. / EtOAc = 100/1 Rf = 0.95) until it showed that the starting material had been completely consumed. The reaction mixture was then filtered to remove the catalyst, which was washed with dichloromethane (2 x 100 mL) and the filtrate concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1to 10/1) to afford 2,5-di-*tert*-butylfuran (**273**, 7 g, 38.83 mmol, 26.4 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 (s, 2H), 1.28 (s, 18H).

To a solution of 2,5-di-*tert*-butylfuran (**273**, 3 g, 16.64 mmol, 1 eq) and 1,1,3-trichloropropan-2-one (**16**, 8.06 g, 49.92 mmol, 3 eq) in CF_3CH_2OH (30 mL) was added TEA (6.74 g, 66.56 mmol, 9.26 mL, 4 eq) at 0 °C, The mixture was allowed to warm and stirred at 20

°C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 100/1, Rf = 0.95) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-di-*tert*-butyl-2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**274**, 5 g, 16.38 mmol, 98.4 % yield) as a yellow oil, without further characterization.

To a solution of 1,5-di-*tert*-butyl-2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**274**, 5 g, 16.38 mmol, 1 eq) in MeOH (50 mL) was added CuCl (810.84 mg, 8.19 mmol, 195.86 µL, 0.5 eq), NH_4Cl (6.13 g, 114.66 mmol, 7 eq) and Zn (5.36 g, 81.90 mmol, 5 eq) at 0 °C. The mixture was allowed to warm and stirred at 25 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was filtered through CELITE™ pad. The filtrate was diluted with water (40 mL) and extracted with EtOAc (30 mL x 3). The organic layers were combined, washed with brine (400 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 1,5-di *tert*-butyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**275**, 100 mg, 423.10 µmol, 2.6 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.04 (s, 2H), 2.54 - 2.48 (m, 2H), 2.36 - 2.30 (m, 2H), 0.99 (s, 18H).

To a solution of LiHMDS (1 M, 507.72 µL, 1.2 eq) was added 1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**275**, 100 mg, 423.10 µmol, 1 eq) in THF (1.5 mL) dropwise at -65 °C under N_2. The mixture was allowed to cool and stirred at 25 °C for 0.5 h. 1,1,1-Trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (181.89 mg, 507.72 µmol, 1.2 eq) in THF (1.5 mL) was then added dropwise at -65 °C under N_2. The mixture was allowed to warm and further stirred at 25 °C for 2 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (5 mL, aqueous) and extracted with EtOAc (4 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford [1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**276**, 50 mg, 135.72 µmol, 32.1 % yield) as a yellow oil, without further characterization.

To a solution of [1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**276**, 250 mg, 678.59 µmol, 1 eq) in dioxane (5 mL) was added Pin_2B_2 (**4**, 224.02 mg, 882.17 µmol, 1.3 eq) and KOAc (166.49 mg, 1.70 mmol, 2.5 eq) and

$Pd(dppf)Cl_2$ (24.83 mg, 33.93 μmol, 0.05 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.7) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (6 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc= 100/1 to 5/1) to afford 2-[1,5-di *tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**277**, 200 mg, 577.52 μmol, 85.1 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12 (t, *J* = 2.1 Hz, 1H), 6.19 (d, *J* = 5.9 Hz, 1H), 5.74 (d, *J* = 5.9 Hz, 1H), 2.61 (dd, *J* = 2.3, 18.6 Hz, 1H), 1.71 (dd, *J* = 2.1, 18.6 Hz, 1H), 1.25 (d, *J* = 3.3 Hz, 12H), 0.99 (d, *J* = 6.8 Hz, 18H).

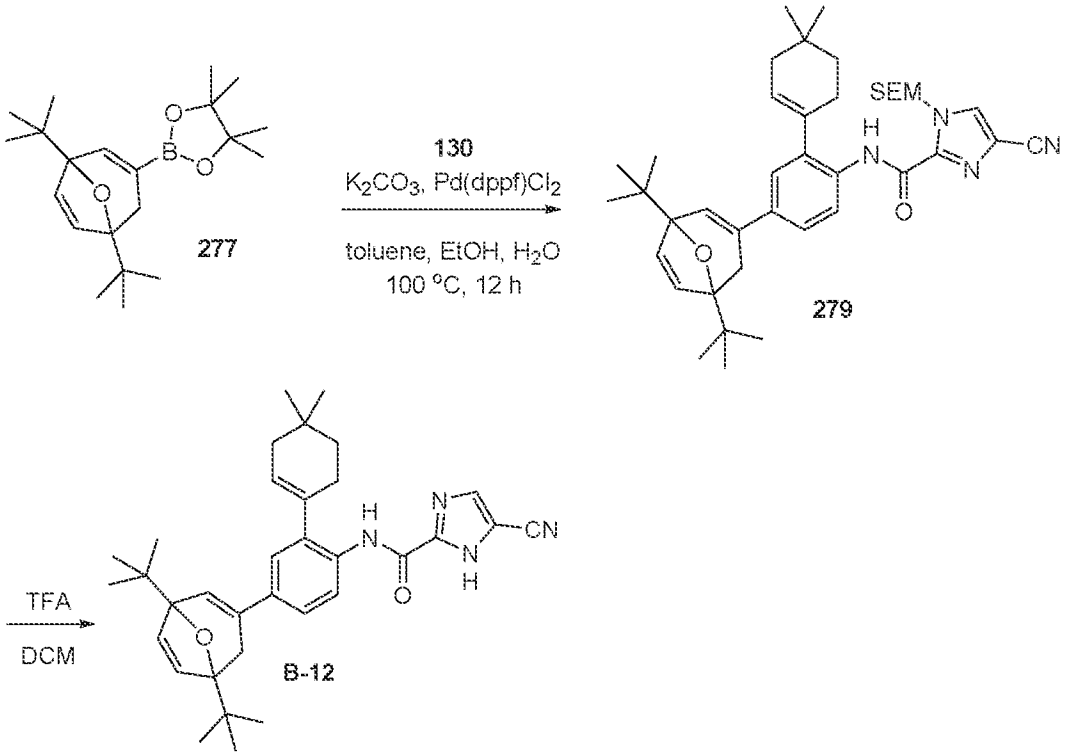
To a solution of 2-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**277**, 100 mg, 288.76 μmol, 1.1 eq) and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 139.27 mg, 262.51 μmol, 1 eq) in dioxane (2.5 mL) and H_2O (0.5 mL) was added K_2CO_3 (90.70 mg, 656.27 μmol, 2.5 eq) and Pd(dppf)Cl2 (19.21 mg, 26.25 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 4-cyano-*N*-[6-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**278**, 110 mg, 164.19 μmol, 62.6 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.00 (s, 1H), 8.65 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.29 (s, 1H), 7.23 (s, 1H), 6.26 (d, *J* = 5.8 Hz, 1H), 5.95 (br s, 1H), 5.94 (s, 2H), 5.84 (d, *J* = 5.9 Hz, 1H), 3.70 - 3.63 (m, 2H), 2.88 (dd, *J* = 1.7, 17.9 Hz, 1H), 2.50 (br s, 2H), 2.19 (dd, *J* = 1.4, 18.1 Hz, 1H), 2.15 (br d, *J* = 2.9 Hz, 2H), 1.63 (t, *J* = 6.3 Hz, 2H), 1.13 (s, 6H), 1.06 (d, *J* = 3.6 Hz, 18H), 1.01 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[6-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**278**, 110.00 mg, 164.19 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 2.985 min, [M+H] = 540.3) until it showed that the starting material had been completely consumed and the desired product mass had been observed. The reaction

mixture was adjusted to pH = 8 ~ 9 with $NaHCO_3$ (aqueous) and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 5/1 to 3/1) and triturated with MeOH (2 mL) for 30 min, and filtered to afford title compound 5-cyano-*N*-[6-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-41**, 37.5 mg, 69.48 μmol, 42.3 % yield, 100 % purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.83 (br s, 1H), 9.84 (s, 1H), 8.63 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.25 (br s, 1H), 6.26 (d, *J* = 5.8 Hz, 1H), 5.97 (br s, 1H), 5.85 (d, *J* = 5.9 Hz, 1H), 2.89 (br d, *J* = 18.0 Hz, 1H), 2.51 (br s, 2H), 2.19 (br d, *J* = 18.1 Hz, 1H), 2.15 (br s, 2H), 1.64 - 1.61 (m, 2H), 1.12 (s, 6H), 1.07 (d, *J* = 3.1 Hz, 18H), MS (LC/MS) *m/z* observed 540.3, expected 540.3 [M+H].

EXAMPLE 55

5-Cyano-*N*-[4-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1*H*-imidazole-2-carboxamide B-12



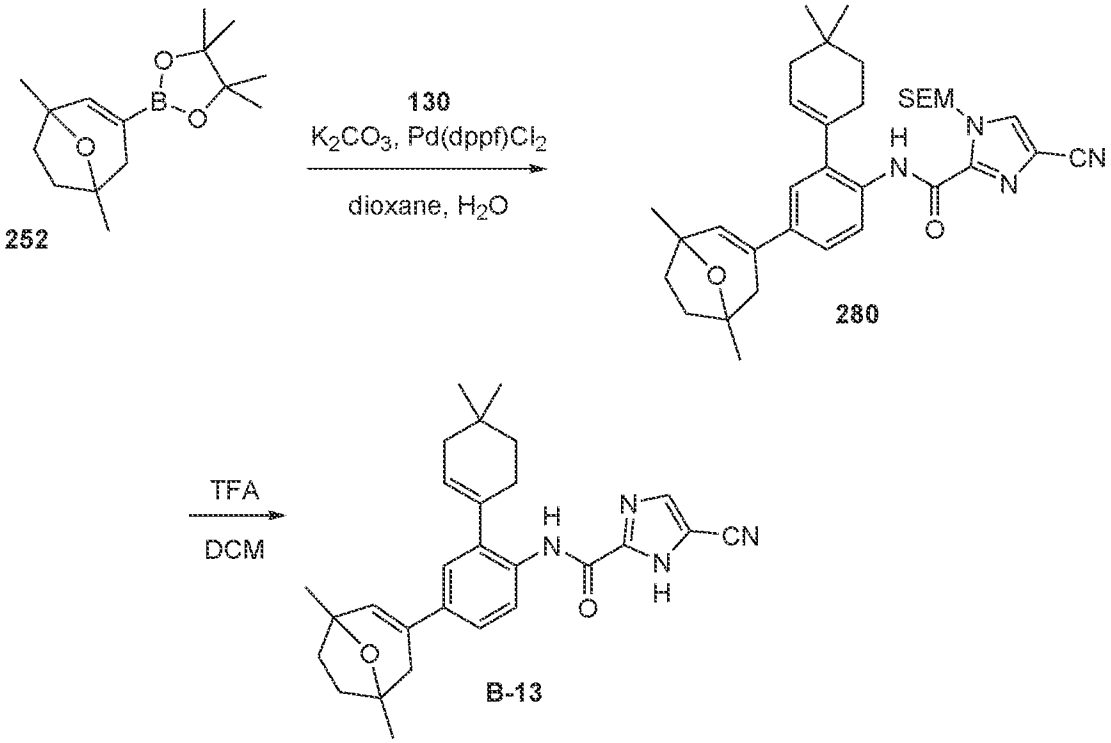
To a solution of 2-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**277**, 100 mg, 288.76 μmol, 1.1 eq) and *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (130, 139.01 mg, 262.51 μmol, 1 eq) in dioxane (2.5 mL) and H_2O (0.5 mL) was added K_2CO_3 (90.70 mg, 656.27 μmol, 2.5 eq) and $Pd(dppf)Cl_2$ (19.21 mg, 26.25 μmol, 0.1 eq)

at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 4-cyano-*N*-[4-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**279**, 110 mg, 164.43 μmol, 62.6 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7.29 (s, 1H), 7.14 (d, *J* = 1.8 Hz, 1H), 6.66 (s, 1H), 6.27 (d, *J* = 5.9 Hz, 1H), 5.96 (s, 2H), 5.83 (d, *J* = 5.8 Hz, 1H), 5.76 (br s, 1H), 3.69 - 3.64 (m, 2H), 2.80 (br d, *J* = 17.1 Hz, 1H), 2.29 (br s, 2H), 2.12 (br d, *J* = 2.1 Hz, 2H), 1.98 (d, *J* = 17.5 Hz, 1H), 1.62 - 1.59 (m, 2H), 1.13 (s, 6H), 1.05 (d, *J* = 1.6 Hz, 18H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[4-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**279**, 110 mg, 164.43 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 493.29 μL, 3 eq) at 25 °C. The mixture was warmed and stirred at 60 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.848 min, [M+H] = 539.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (8 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 70 % - 100 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[4-[1,5-di-*tert*-butyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-1*H*-imidazole-2-carboxamide (**B-12**, 49.1 mg, 90.02 μmol, 54.8 % yield, 98.8 % purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.28 (br s, 1H), 9.67 (s, 1H), 8.31 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.34 (dd, *J* = 1.9, 8.6 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 6.70 (s, 1H), 6.28 (d, *J* = 5.9 Hz, 1H), 5.84 (d, *J* = 5.8 Hz, 1H), 5.79 (br s, 1H), 2.81 (br d, *J* = 17.6 Hz, 1H), 2.30 (br s, 2H), 2.13 (br d, *J* = 2.3 Hz, 2H), 2.00 (d, *J* = 17.4 Hz, 1H), 1.62 (br t, *J* = 6.3 Hz, 2H), 1.13 (s, 6H), 1.06 (d, *J* = 2.1 Hz, 18H), MS (LC/MS) *m/z* observed 539.4, expected 539.4 [M+H].

EXAMPLE 56

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]phenyl]-1*H*-imidazole-2-carboxamide B-13



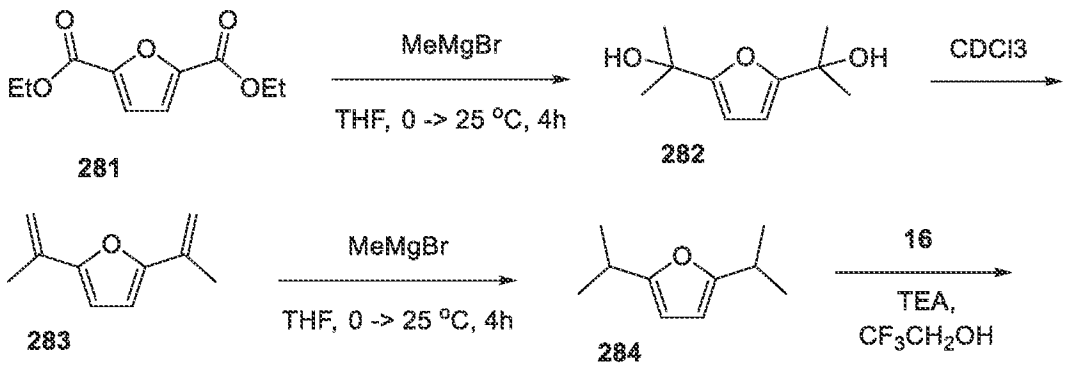
To a solution of 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**252**, 199.54 mg, 755.37 μmol, 2 eq) and *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**130**, 200 mg, 377.68 μmol, 1 eq) in dioxane (5 mL) and H_2O (1 mL) was added K_2CO_3 (130.50 mg, 944.21 μmol, 2.5 eq) and Pd(dppf)Cl_2 (27.64 mg, 37.77 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.55) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (8 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**280**, 100 mg, 170.40 μmol, 45.1 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.77 (s, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7.31 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.19 (d, *J* = 2.1 Hz, 1H), 6.24 (s, 1H), 5.96 (s, 2H), 5.77 (br s, 1H), 3.69 - 3.65 (m, 2H), 2.69 (br d, *J* = 16.6 Hz, 1H), 2.31 (br s, 2H), 2.11 (br d, *J* =

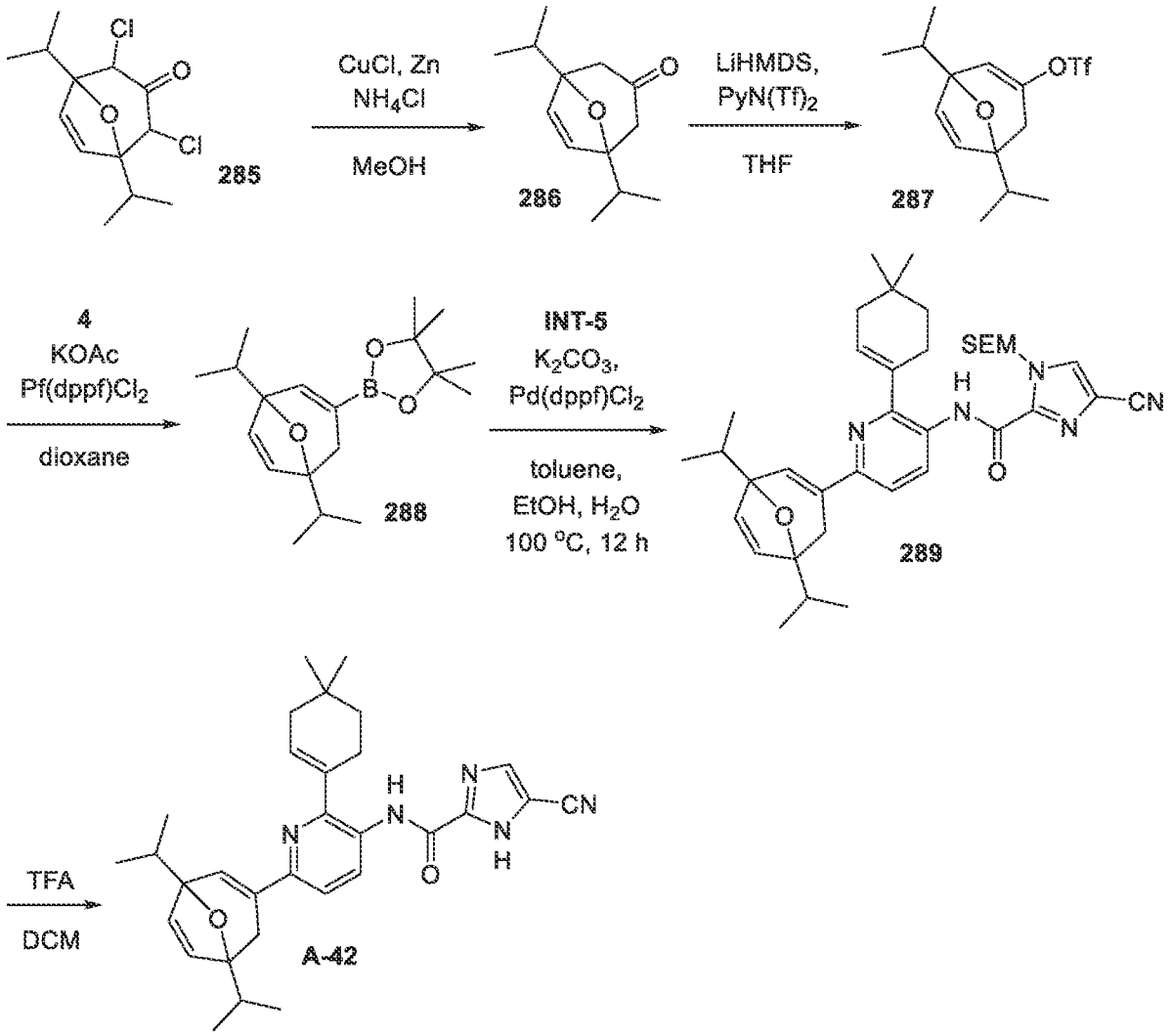
3.4 Hz, 2H), 2.08 (s, 1H), 1.63 - 1.59 (m, 2H), 1.51 (d, J = 5.5 Hz, 6H), 1.36 (s, 2H), 1.27 (s, 2H), 1.13 (s, 6H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**280**, 100 mg, 170.40 μmol, 1 eq) in DCM (1.5 mL) was added TFA (0.5 mL) at 25 °C. The mixture was stirred at 25 °C for 1 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 2.196 min, [M+H] = 457.3) until it showed that the starting material had been consumed and the desired product mass had been observed. The reaction mixture was adjusted to pH = 8 ~ 9 with aq.$NaHCO_3$ and extracted with DCM (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 10/1 to 3/1), followed by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 60 % - 90 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]phenyl]-1*H*-imidazole-2-carboxamide (**B-13**, 39.6 mg, 86.48 μmol, 50.8 % yield, 99.7 % purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.27 (br s, 1H), 9.68 (s, 1H), 8.32 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 2.5 Hz, 1H), 7.35 (dd, J = 2.1, 8.6 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 6.27 (s, 1H), 5.80 (br s, 1H), 2.71 (br d, J = 16.6 Hz, 1H), 2.35 - 2.27 (m, 3H), 2.14 - 2.06 (m, 3H), 1.96 - 1.80 (m, 3H), 1.61 (t, J = 6.2 Hz, 2H), 1.52 (d, J = 5.5 Hz, 6H), 1.13 (s, 6H), MS (LC/MS) *m/z* observed 457.3, expected 457.3 [M+H].

EXAMPLE 57

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-42





To a solution of diethyl furan-2,5-dicarboxylate (**281**, 10 g, 47.13 mmol, 1 eq) in THF (100 mL) was added to MeMgBr (3 M, 70.69 mL, 4.5 eq) in THF (350 mL) at 0 °C. The mixture was allowed to warm and stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf =0.3) until it showed that the starting material had been completely consumed. The reaction mixture was quenched with H_2O (200 mL) and extracted with EtOAc(100 mL x 2). The organic layers were combined, washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford 2-[5-(1-hydroxy-1-methyl-ethyl)-2-furyl]propan-2-ol (**282**, 8 g, 43.42 mmol, 92.1 % yield) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d6, 297 K) δ (ppm) = 6.04 (s, 2H), 1.41 (s, 12H).

A solution of 2-[5-(1-hydroxy-1-methyl-ethyl)-2-furyl]propan-2-ol (**282**, 1 g, 5.43 mmol, 1 eq) in $CDCl_3$ (30 mL) was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/0 Rf = 0.7) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30

mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2,5-di-isopropenylfuran (**283**, 0.8 g, 5.40 mmol, 99.5 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.28 (s, 2H), 5.55 (s, 2H), 4.96 (s, 2H), 2.03 (s, 6H).

To a solution of 2,5-di-isopropenylfuran (**283**, 0.8 g, 5.40 mmol, 1 eq) in DCM (10 mL) was added Pd/C (574.46 mg, 539.81 μmol, 10 % purity, 0.1 eq). The mixture was stirred at 25 °C for 2 hr under H_2 (15 psi). The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/0 Rf =0.8) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2,5-di-isopropylfuran (**284**, 0.8 g, 5.26 mmol, 97.4 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 297 K) δ (ppm) = 5.84 (s, 2H), 2.98 - 2.81 (m, 2H), 1.24 (s, 5H), 1.22 (s, 6H).

To a solution of 2,5-di-isopropylfuran (**284**, 1.3 g, 8.54 mmol, 1 eq) in CF_3CH_2OH (20 mL) was added 1,1,3-trichloropropan-2-one (**16**, 4.14 g, 25.62 mmol, 3 eq) and TEA (3.46 g, 34.16 mmol, 4.75 mL, 4 eq) at 0 °C. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2,4-dichloro-1,5-di-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**285**, 4 g, crude) was obtained as a yellow oil, and used further as is, without further characterization.

To a mixture of 2,4-dichloro-1,5-di-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**285**, 4 g, 14.43 mmol, 1 eq) in MeOH (50 mL) was added CuCl (714.32 mg, 7.22 mmol, 172.54 μL, 0.5 eq), NH_4Cl (5.40 g, 101.02 mmol, 7 eq) and zinc (5.66 g, 86.58 mmol, 6 eq) at 0 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was diluted with water (50 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford 1,5-di-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**286**, 0.35 g, 1.68 mmol, 11.6 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$,

297 K) δ (ppm) = 6.00 (s, 2H), 2.47 - 2.35 (m, 4H), 1.97 (td, J = 6.9, 13.8 Hz, 2H), 1.00 (s, 6H), 0.98 (s, 6H).

To a solution of 1,5-di-isopropyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**286**, 0.35 g, 1.68 mmol, 1 eq) in THF (5 mL) was added to LiHMDS (1 M, 2.02 mL, 1.2 eq) at -65 °C. The mixture was warmed to 25 °C and stirred for 0.5 h, then cooled to -65 ° C. 1,1,1-Trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (662.14 mg, 1.85 mmol, 1.1 eq) in THF (5 mL) was then added dropwise at -65 °C. The mixture was further stirred at 25 °C for 2.5 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (15 mL, saturated, aqueous) and extracted with EtOAc(10 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford [1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**287**, 0.4 g, 1.18 mmol, 69.9 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 6.26 (d, J = 5.8 Hz, 1H), 6.17 (s, 1H), 5.82 (d, J = 5.8 Hz, 1H), 2.62 (dd, J = 1.8, 17.3 Hz, 1H), 2.10 (dd, J = 1.1, 17.3 Hz, 1H), 2.06 - 1.93 (m, 2H), 1.04 - 0.96 (m, 12H).

To a solution of [1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**287**, 250 mg, 734.52 μmol, 1 eq) in dioxane (5 mL) was added Pin_2B_2 (**4**, 242.48 mg, 954.88 μmol, 1.3 eq), KOAc (216.26 mg, 2.20 mmol, 3 eq) and $Pd(dppf)Cl_2$ (53.74 mg, 73.45 μmol, 0.1 eq). The mixture was warmed and stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 10 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford 4,4,5,5-tetramethyl-2-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-1,3,2-dioxaborolane (**288**, 0.2 g, 628.42 μmol, 85.6 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.96 (s, 1H), 6.17 (d, J = 5.9 Hz, 1H), 5.72 (d, J = 5.9 Hz, 1H), 2.42 (dd, J = 2.2, 18.4 Hz, 1H), 1.95 - 1.87 (m, 3H), 1.25 (s, 12H), 1.02 - 0.97 (m, 12H).

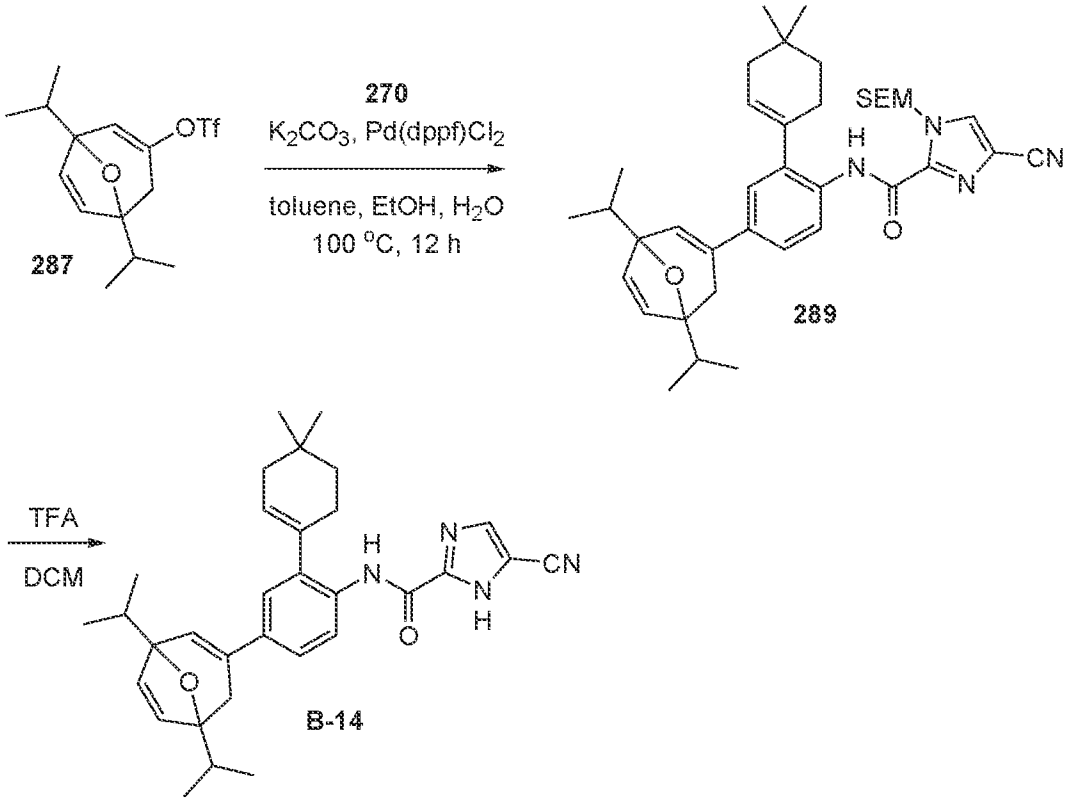
To a solution of 4,4,5,5-tetramethyl-2-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-1,3,2-dioxaborolane (**288**, 194.96 mg, 612.59 μmol, 1.3 eq) in toluene (6 mL), H_2O

(1.5 mL) and EtOH (3 mL) was added *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 250 mg, 471.23 μmol, 1 eq), K_2CO_3 (195.38 mg, 1.41 mmol, 3 eq) and $Pd(dppf)Cl_2$ (34.48 mg, 47.12 μmol, 0.1 eq). The mixture was warmed and stirred at 100 °C for 12 hr under N_2. The reaction was monitored by TLC (Pet. Et / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**289**, 0.25 g, 389.46 μmol, 82.7 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.00 (s, 1H), 8.67 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.29 (s, 1H), 7.09 (br s, 1H), 6.24 (d, *J* = 5.8 Hz, 1H), 5.96 (br s, 1H), 5.94 (s, 2H), 5.81 (d, *J* = 5.9 Hz, 1H), 3.71 - 3.61 (m, 2H), 2.69 (dd, *J* = 1.6, 17.8 Hz, 1H), 2.51 (br d, *J* = 1.4 Hz, 2H), 2.40 (br d, *J* = 17.9 Hz, 1H), 2.15 (br d, *J* = 2.8 Hz, 2H), 2.12 - 2.07 (m, 1H), 2.05 - 2.00 (m, 1H), 1.64 (br t, *J* = 6.3 Hz, 2H), 1.13 (s, 6H), 1.07 (ddd, *J* = 6.9, 11.3, 16.4 Hz, 12H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**289**, 250 mg, 389.46 μmol, 1 eq) in DCM (3 mL)was added TFA (1 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 1.752 min, [M+H] = 512.4) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (20 mL) and extracted with DCM (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 70 % - 100 % B gradient over 8.0 min to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-diisopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-42**, 63.2 mg, 123.52 μmol, 31.7 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6, 297 K) δ (ppm) = 14.28 (br s, 1H), 10.01 (s, 1H), 8.33 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.05 (s, 1H), 6.33 (d, *J* = 5.8 Hz, 1H), 5.89 (d, *J* = 5.9 Hz, 2H), 2.57 (dd, *J* = 1.3, 18.0 Hz, 1H), 2.42 (br s, 2H), 2.28 (d, *J* = 18.0 Hz, 1H), 2.03 (quin, *J* = 6.8 Hz, 1H), 1.97 - 1.90 (m, 3H), 1.49 (t, *J* = 6.3 Hz, 2H), 1.04 (d, *J* = 6.9 Hz, 3H), 1.01 - 0.92 (m, 15H), MS (LC/MS) *m/z* observed 512.4, expected 512.4 [M+H].

EXAMPLE 58

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1*H*-imidazole-2-carboxamide B-14



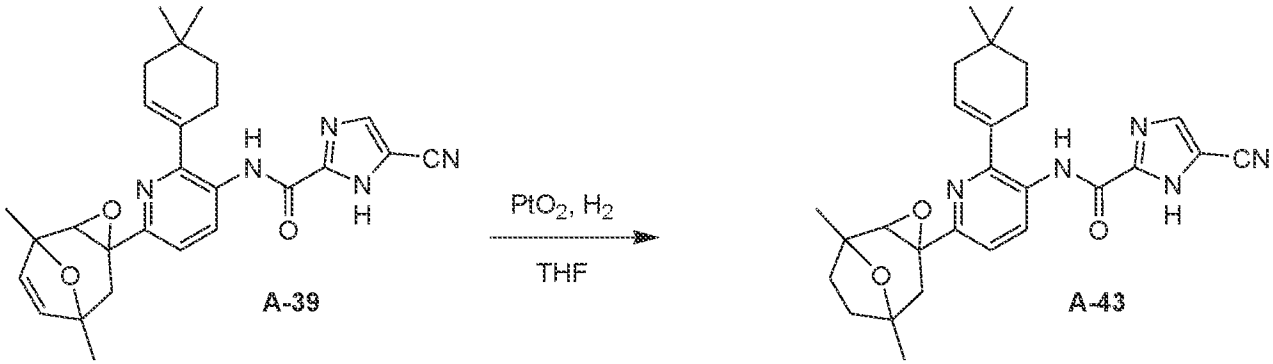
To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**270**, 266.82 mg, 462.75 μmol, 1.05 eq) and [1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**287**, 150 mg, 440.71 μmol, 1 eq) in toluene (4 mL), EtOH (2 mL) and H_2O (1 mL) was added K_2CO_3 (152.28 mg, 1.10 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (32.25 mg, 44.07 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Pet. Et. / EtOAc = 100/1 to 5/1) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**289**, 200 mg, 312.05 μmol, 70.8 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 8.32 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7.30 - 7.27 (m, 1H), 7.15 (d, *J* = 2.1 Hz, 1H), 6.51 (s, 1H), 6.25 (d, *J* = 5.9 Hz, 1H), 5.96 (s, 2H), 5.79 (d, *J* = 5.8 Hz, 1H), 5.76 (br t, *J* = 3.6 Hz, 1H), 3.69 - 3.64 (m, 2H), 2.63 (dd, *J* = 1.8, 17.5 Hz, 1H), 2.29 (br d, *J* = 1.9

Hz, 2H), 2.18 (dd, J = 1.4, 17.4 Hz, 1H), 2.11 (br d, J = 3.1 Hz, 2H), 2.05 - 1.97 (m, 2H), 1.63 - 1.58 (m, 2H), 1.12 (s, 6H), 1.06 (ddd, J = 6.9, 10.3, 14.1 Hz, 12H), 1.00 - 0.95 (m, 2H), 0.02 - 0.00 (m, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-di-isopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**289**, 200 mg, 312.05 μmol, 1 eq) in THF (5 mL) was added TBAF (1 M, 936.14 μL, 3 eq) at 25 °C. The mixture was warmed and stirred at 70 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 0.852 min, [M+H] = 511.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 70 % - 100 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-4-[1,5-diisopropyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]phenyl]-1*H*-imidazole-2-carboxamide (**B-14**, 60.9 mg, 119.18 μmol, 38.2 % yield, 99.9 % purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.27 (br s, 1H), 9.70 (s, 1H), 8.32 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.37 (dd, J = 2.1, 8.6 Hz, 1H), 7.25 (d, J = 2.1 Hz, 1H), 6.61 (s, 1H), 6.31 (d, J = 5.8 Hz, 1H), 5.85 (d, J = 5.8 Hz, 1H), 5.67 (br s, 1H), 2.61 - 2.52 (m, 1H), 2.26 (br s, 2H), 2.13 (d, J = 17.3 Hz, 1H), 2.04 - 1.88 (m, 4H), 1.50 (t, J = 6.3 Hz, 2H), 1.06 - 0.99 (m, 9H), 0.99 - 0.93 (m, 9H), MS (LC/MS) *m/z* observed 511.4, expected 511.4 [M+H].

EXAMPLE 59

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-3,9-dioxatricyclo[4.2.1.0^{2,4}]nonan-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-43

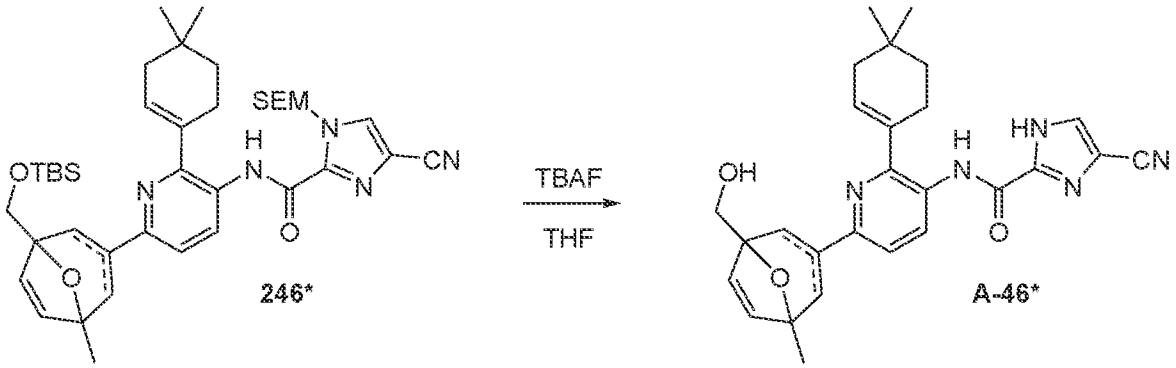


To a solution of 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-3,9-dioxatricyclo[4.2.1.0^{2,4}]non-7-en-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-39**, 50 mg, 106.03 μmol, 1 eq) in EtOAc (5 mL) was added PtO_2 (24.08 mg, 10.60 μmol, 10 % purity, 0.1

eq). The mixture was stirred at 25 °C for 2 hr under H_2 (15 psi). The reaction was monitored by LC/MS (R_t = 0.619 min, [M+H] =474.3) until it showed that the reactant had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 40 % - 70 % B gradient over 8.0 min to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-3,9-dioxatricyclo[4.2.1.$0^{2,4}$]nonan-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-43**, 10 mg, 21.12 μmol, 19.9 % yield)was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d6, 299 K) δ (ppm) = 14.44 - 14.06 (m, 1H), 10.11 (s, 1H), 8.28 (s, 1H), 8.20 (d, *J* = 8.4 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 5.94 (br s, 1H), 3.02 (s, 1H), 2.80 (d, *J* = 14.6 Hz, 1H), 2.47 - 2.40 (m, 2H), 2.03 - 1.87 (m, 4H), 1.82 (br d, *J* = 14.5 Hz, 1H), 1.73 (br t, *J* = 12.1 Hz, 1H), 1.58 (dt, *J* = 6.8, 11.5 Hz, 1H), 1.49 (br t, J = 6.3 Hz, 2H), 1.34 (s, 3H), 1.27 (s, 3H), 0.98 (s, 6H), MS (LC/MS) *m/z* observed 474.3, expected 474.3 [M+H].

EXAMPLE 60

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(hydroxymethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-5-(hydroxymethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-46* (* Inseparable mixture of double bond tautomers)



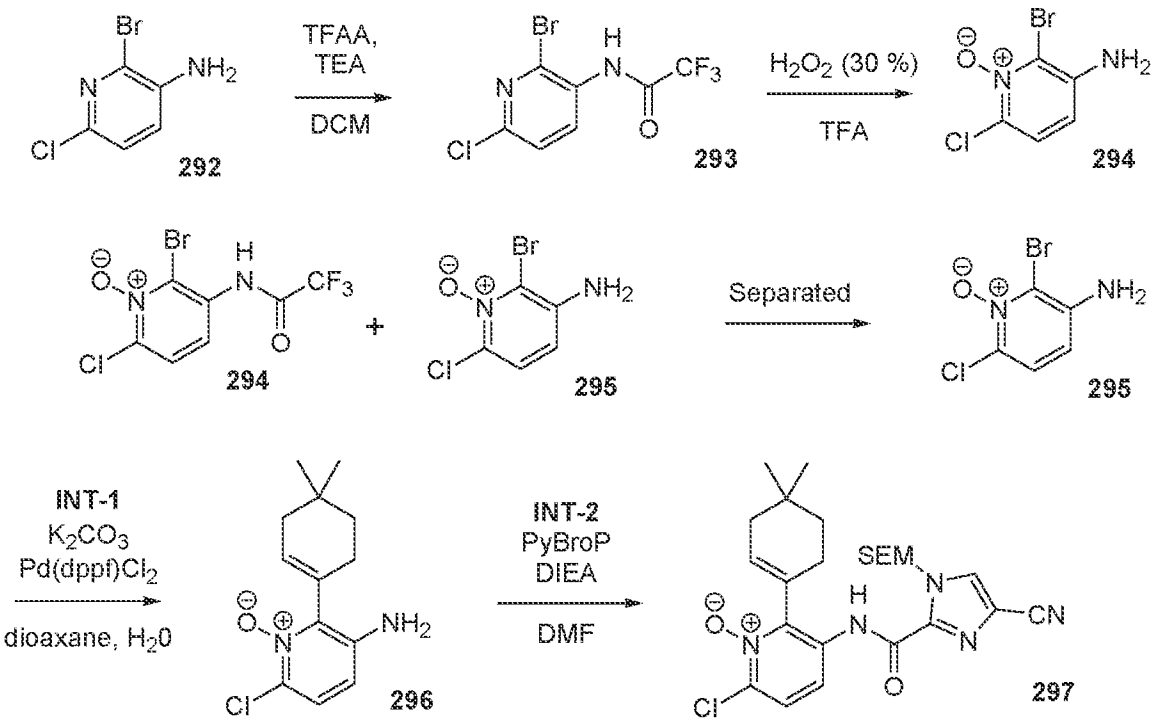
* inseperable mixture of double bond tautomers

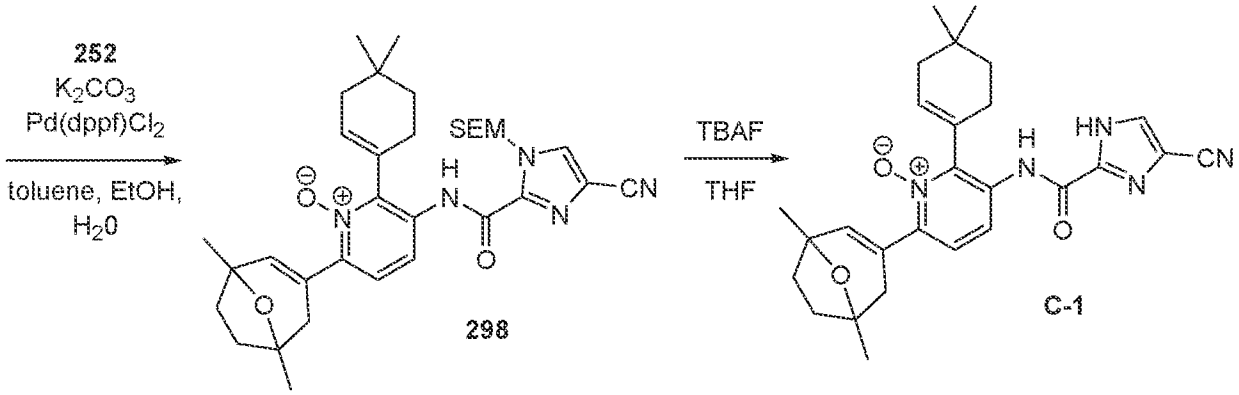
To a solution of the mixture of *N*-[6-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and *N*-[6-[1-methyl-5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**246***, 100 mg, 139.65 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 558.60 μL, 4 eq) at 25 °C. The mixture was warmed and stirred at 70 °C for 16 hr under N_2 atmosphere.

The reaction was monitored by LC/MS (R_t = 0.852 min, [M+H] = 472.2) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (6 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 35 % - 65 % B gradient over 8.0 min) to afford the mixture of title compounds 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(hydroxymethyl)-5-methyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-5-(hydroxymethyl)-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-46***, 22.1 mg, 45.58 μmol, 32.6 % yield, 97.3 % purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.57 (d, *J* = 8.6 Hz, 1H), 8.01 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.06 - 6.91 (m, 1H), 6.37 (dd, *J* = 1.9, 5.8 Hz, 1H), 5.96 (br s, 1H), 5.91 (dd, *J* = 5.8, 10.9 Hz, 1H), 3.89 - 3.76 (m, 2H), 2.83 - 2.69 (m, 1H), 2.49 (br s, 2H), 2.47 - 2.29 (m, 1H), 2.12 (br d, *J* = 2.9 Hz, 2H), 1.63 (t, J = 6.1 Hz, 2H), 1.56 (d, *J* = 3.3 Hz, 3H), 1.12 (s, 6H), MS (LC/MS) *m/z* observed 472.3, expected 472.2 [M+H].

EXAMPLE 61

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-1-oxido-pyridin-1-ium-3-yl]-1*H*-imidazole-2-carboxamide C-1





To a solution of 2-bromo-6-chloro-pyridin-3-amine (**292**, 2 g, 9.64 mmol, 1 eq) in DCM (25 mL) was added TEA (1.95 g, 19.28 mmol, 2.68 mL, 2 eq) and TFAA (2.43 g, 11.57 mmol, 1.61 mL, 1.2 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.7) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (15 mL) and extracted with DCM (20 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 5 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford *N*-(2-bromo-6-chloro-3-pyridyl)-2,2,2-trifluoro-acetamide (**293**, 2.2 g, 7.25 mmol, 75.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63 (d, *J* = 8.5 Hz, 1H), 8.43 (br s, 1H), 7.40 (d, *J* = 8.6 Hz, 1H).

To a solution of *N*-(2-bromo-6-chloro-3-pyridyl)-2,2,2-trifluoro-acetamide (**293**, 2.2 g, 7.25 mmol, 1 eq) in TFA (22 mL) was added H_2O_2 (2.47 g, 21.75 mmol, 2.09 mL, 30 % purity, 3 eq) at 20 °C. The mixture was stirred at 70 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.1) until it showed some starting material remaining, while showing new spots. The reaction mixture was adjusted to pH = 7 ~ 9 with $NaHCO_3$ (aqueous) and extracted with EtOAc (40 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 10 ~ 70 % EtOAc /Pet. Et. gradient at a flow rate of 80 mL/min) to afford *N*-(2-bromo-6-chloro-1-oxido-pyridin-1-ium-3-yl)-2,2,2-trifluoro-acetamide (**294**, 100 mg, 313.03 μmol, 4.3 % yield) as a yellow solid and the desired product, 2-bromo-6-chloro-1-oxido-pyridin-1-ium-3-amine (**295**, 400 mg, 1.79 mmol, 24.7 % yield) as a yellow solid. **295**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (d, J = 8.9 Hz, 1H), 6.66 (d, *J* = 8.9 Hz, 1H).

To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**INT-1**, 232.51 mg, 984.54 μmol, 1.1 eq) and 2-bromo-6-chloro-1-oxido-pyridin-

1-ium-3-amine (**295**, 200 mg, 895.04 μmol, 1 eq) in dioxane (5 mL), H_2O (1 mL) was added K_2CO_3 (371.11 mg, 2.69 mmol, 3 eq) and Pd(dppf)Cl_2 (65.49 mg, 89.50 μmol, 0.1 eq) at 20 °C. The mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 0/1, Rf = 0.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 15 ~ 40 % EtOAc /Pet. Et. gradient at a flow rate of 50 mL/min) to afford 6-chloro-2-(4,4-dimethylcyclohexen-1-yl)-1-oxido-pyridin-1-ium-3-amine (**296**, 120 mg, 474.80 μmol, 53.1 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 8.8 Hz, 1H), 6.63 (br d, *J* = 8.6 Hz, 1H), 5.87 (br s, 1H), 3.03 - 2.71 (m, 1H), 2.04 (br d, *J* = 10.4 Hz, 2H), 1.97 - 1.80 (m, 1H), 1.72 - 1.45 (m, 2H), 1.12 - 0.98 (m, 6H).

To a solution of 6-chloro-2-(4,4-dimethylcyclohexen-1-yl)-1-oxido-pyridin-1-ium-3-amine (**296**, 120 mg, 474.80 μmol, 1 eq) and [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 159.53 mg, 522.28 μmol, 1.1 eq) in DMF (2 mL) was added DIEA (184.09 mg, 1.42 mmol, 248.10 μL, 3 eq), PyBroP (332.01 mg, 712.20 μmol, 1.5 eq) at 20 °C. The mixture was stirred at 20 °C for 2 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf = 0.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (4 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 15 ~ 30 % EtOAc /Pet. Et. gradient at a flow rate of 40 mL/min) to afford *N*-[6-chloro-2-(4,4-dimethylcyclohexen-1-yl)-1-oxido-pyridin-1-ium-3-yl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**297**, 150 mg, 298.76 μmol, 62.9 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.79 (s, 1H), 8.40 (d, *J* = 9.1 Hz, 1H), 7.79 (s, 1H), 7.43 (d, *J* = 9.1 Hz, 1H), 6.01 (br s, 1H), 5.90 (s, 2H), 3.69 - 3.62 (m, 2H), 2.19 (br s, 2H), 1.79 - 1.53 (m, 4H), 1.15 (br d, *J* = 17.8 Hz, 6H), 1.00 - 0.96 (m, 2H), 0.02 - 0.00 (m, 9H).

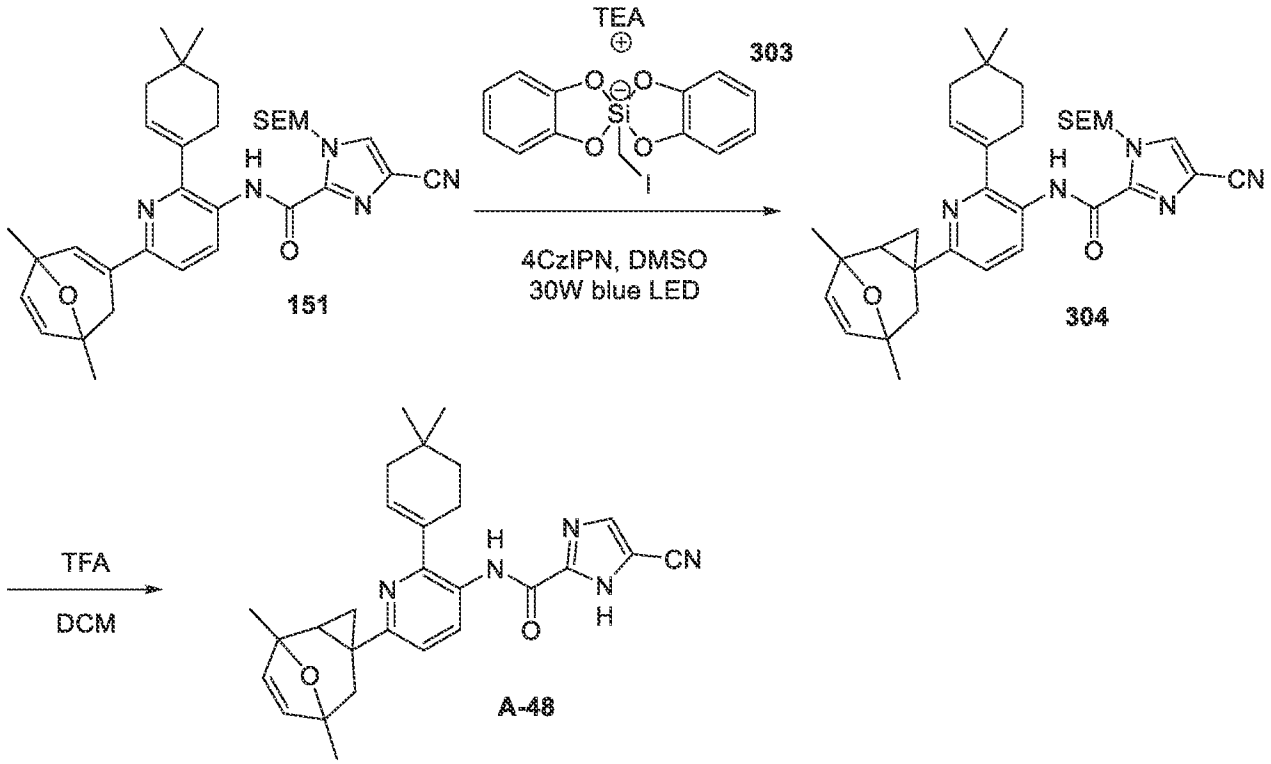
To a solution of 2-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**252**, 86.81 mg, 328.63 μmol, 1.1 eq) and *N*-[6-chloro-2-(4,4-dimethylcyclohexen-1-yl)-1-oxido-pyridin-1-ium-3-yl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**297**, 150 mg, 298.76 μmol, 1 eq) in toluene (4 mL), EtOH (2 mL) and H_2O (1 mL) was added K_2CO_3 (103.23 mg, 746.89 μmol, 2.5

eq) and Pd(dppf)Cl_2 (21.86 mg, 29.88 μmol, 0.1 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 1/1, Rf =0.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (8 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 15 ~ 25 % EtOAc / Pet. Et. gradient at a flow rate of 50 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-1-oxido-pyridin-1-ium-3-yl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**298**, 120 mg, 198.73 μmol, 66.5 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (br s, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 7.78 (s, 1H), 7.18 (d, *J* = 8.9 Hz, 1H), 6.52 (br s, 1H), 5.97 (br s, 1H), 5.91 (s, 2H), 3.70 - 3.63 (m, 2H), 2.75 - 2.41 (m, 2H), 2.20 (br s, 4H), 2.04 - 1.88 (m, 2H), 1.78 - 1.69 (m, 2H), 1.64 - 1.53 (m, 2H), 1.49 - 1.44 (m, 6H), 1.20 (br s, 3H), 1.10 (br s, 3H), 1.00 - 0.96 (m, 2H), 0.01 (s, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-1-oxido-pyridin-1-ium-3-yl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**298**, 120 mg, 198.73 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 596.20 μL, 3 eq) at 25 °C. The mixture was warmed and stirred at 70 °C for 16 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 1.127 min, [M+H] = 474.2) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (6 mL) and extracted with EtOAc (5 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 30 % - 65 % B gradient over 8.0 min) to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-1-oxido-pyridin-1-ium-3-yl]-1*H*-imidazole-2-carboxamide (43.3 mg, 89.40 μmol, 45.0 % yield, 97.8 % purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.37 (br s, 1H), 9.81 (s, 1H), 8.35 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 6.63 (s, 1H), 5.81 (br s, 1H), 2.58 - 2.50 (m, 2H), 2.49 - 2.41 (m, 2H), 2.09 - 1.92 (m, 4H), 1.75 - 1.63 (m, 2H), 1.46 (br t, *J* = 5.9 Hz, 2H), 1.35 (d, *J* = 5.4 Hz, 6H), 1.00 (s, 6H), MS (LC/MS) *m/z* observed 474.3, expected 474.2 [M+H].

EXAMPLE 62

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-9-oxatricyclo[4.2.1.0^{2,4}]non-7-en-4-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-48

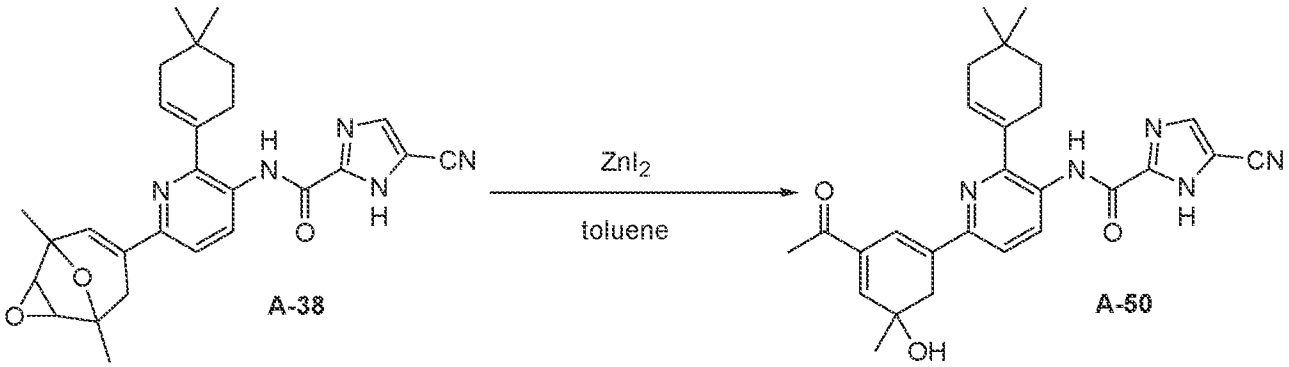


To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**151**, 160 mg, 273.13 μmol, 1 eq) and 8-(iodomethyl)-8,8'-spirobi[7,9-dioxa-8-silanuidabicyclo[4.3.0]nona-1(6),2,4-triene] triethylammonium (**303**, 199.68 mg, 409.69 μmol, 1.5 eq) in DMSO (3 mL) was added 2,4,5,6-tetra(carbazol-9-yl)benzene-1,3-dicarbonitrile (4CzIPN, 10.77 mg, 13.66 μmol, 0.05 eq) at 25 °C. The mixture was stirred at 25 °C for 2 hr under blue LED light (30 W). The reaction was monitored by LC/MS (R_t = 2.667min, [M+H] = 600.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 70 % - 90 % B gradient over 8.0 min to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-9-oxatricyclo[4.2.1.0^{2,4}]non-7-en-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**304**, 50 mg, 83.36 μmol, 30.5 % yield) as a yellow solid. MS (LC/MS) *m/z* observed 600.3, expected 600.2 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-9-oxatricyclo[4.2.1.$0^{2,4}$]non-7-en-4-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**304**, 50 mg, 83.36 μmol, 1 eq) in DCM (0.5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t =2.136 min, [M+H] = 470.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % NH_4HCO_3) - ACN]; 70 % - 85 % B gradient over 8.0 min to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,6-dimethyl-9-oxatricyclo[4.2.1.$0^{2,4}$]non-7-en-4-3-pyridyl]-1*H*-imidazole-2-carboxamide (11.8 mg, 25.13 μmol, 30.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 296 K) δ (ppm) = 14.39 - 14.06 (m, 1H), 10.03 (s, 1H), 8.32 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.23 (d, *J* = 5.6 Hz, 1H), 5.86 (br s, 1H), 5.80 (d, *J* = 5.6 Hz, 1H), 2.36 (br s, 2H), 2.31 (br d, *J* = 14.0 Hz, 1H), 1.88 (br s, 2H), 1.84 (d, *J* = 14.0 Hz, 1H), 1.66 (dd, *J* = 6.0, 8.3 Hz, 1H), 1.45 (t, *J* = 6.4 Hz, 2H), 1.35 (s, 3H), 1.30 (s, 3H), 1.16 - 1.07 (m, 2H), 0.94 (s, 6H), MS (LC/MS) *m/z* observed 470.2, expected 470.2 [M+H].

EXAMPLE 63

***N*-[6-(3-Acetyl-5-hydroxy-5-methyl-cyclohexa-1,3-dien-1-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide A-50**

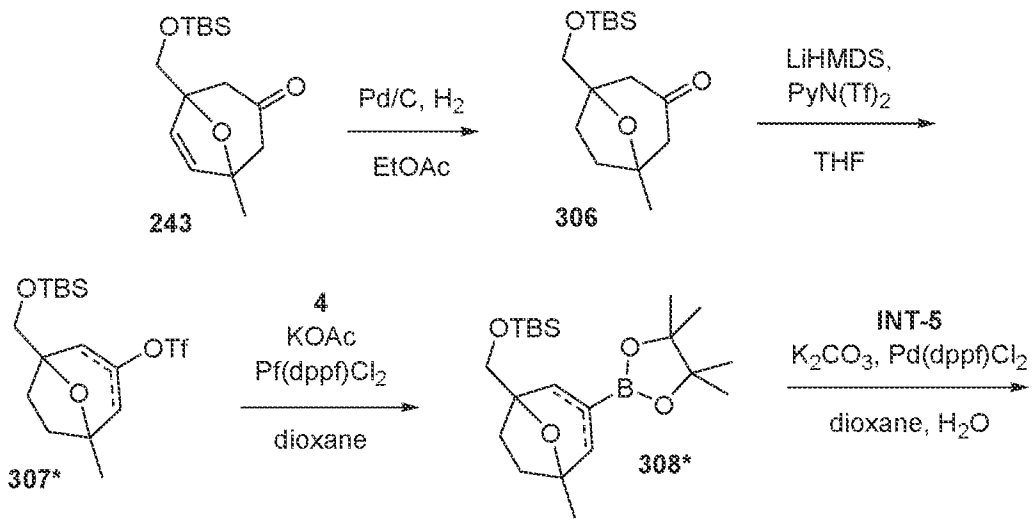


To a solution of 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-3,9-dioxatricyclo[3.3.1.$0^{2,4}$]non-6-en-7-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-38**, 40 mg, 84.83 μmol, 1 eq) in toluene (4 mL) was added ZnI_2 (54.15 mg, 169.65 μmol, 2 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 1.227 min, [M+H] = 472.2) until it showed that the reactant had been completely consumed. The reaction mixture

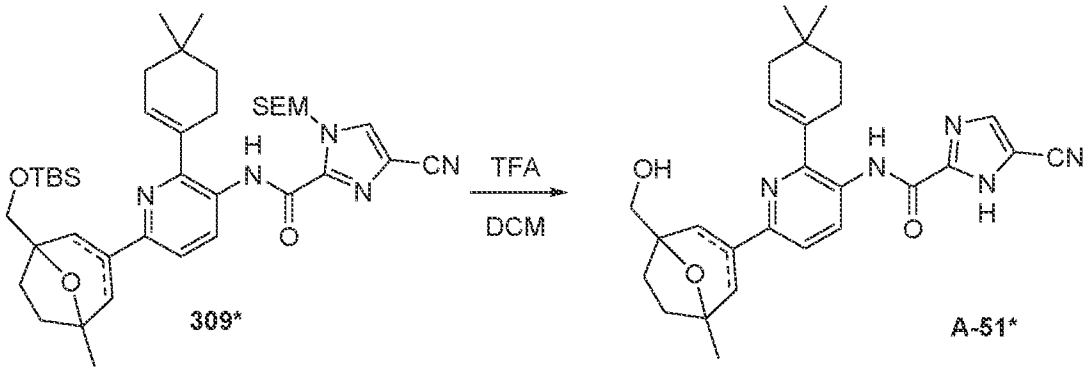
was diluted with $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 45 % - 80 % B gradient over 8.0 min to afford title compound *N*-[6-(3-acetyl-5-hydroxy-5-methyl-cyclohexa-1,3-dien-1-yl)-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-50**, 5 mg, 10.60 μmol, 12.5 % yield, and other products) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.31 (br s, 1H), 10.05 (s, 1H), 8.34 - 8.26 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.24 (s, 1H), 6.84 (s, 1H), 5.94 (s, 1H), 5.18 (s, 1H), 2.86 (s, 2H), 2.47-2.42 (m, 2H), 2.38 (s, 3H), 1.97 (s, 2H), 1.56 - 1.50 (m, 2H), 1.29 (s, 3H), 1.01 (s, 6H), MS (LC/MS) *m/z* observed 472.2, expected 472.2 [M+H].

EXAMPLE 64

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(hydroxymethyl)-5-methyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-5-(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-51* (* Inseparable mixture of double bond tautomers)



* inseperable mixture of double bond tautomers



* inseperable mixture of double bond tautomers

To a solution of 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**243**, 2 g, 7.08 mmol, 1 eq) in EtOAc (30 mL) was added Pd/C (376.78 mg, 354.05 μmol, 10 % purity, 0.05 eq) at 25 °C. The mixture was stirred at 25 °C for 3 hr under H_2 (15 psi). The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octan-3-one (**306**, 2 g, 7.03 mmol, 99.3 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.75 - 3.71 (m, 1H), 3.67 - 3.63 (m, 1H), 2.63 - 2.55 (m, 1H), 2.51 - 2.42 (m, 1H), 2.37 - 2.27 (m, 2H), 1.89 - 1.80 (m, 2H), 1.78 - 1.68 (m, 2H), 1.44 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H).

To a solution of LiHMDS (1 M, 8.44 mL, 1.2 eq) was added 1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]octan-3-one (**306**, 2 g, 7.03 mmol, 1 eq) in THF (15 mL) dropwise at -65 °C under N_2. The mixture was allowed to warm and stirred at 25 °C for 0.5 h. 1,1,1-Trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (3.02 g, 8.44 mmol, 1.2 eq) in THF (10 mL) was then added dropwise at -65 °C under N2. The mixture was allowed to warm and further stirred at 25 °C for 2.5 h under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH4Cl (30 mL, aqueous) and extracted with EtOAc (20 mL x 3). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 10 % EtOAc /Pet. Et. gradient at a flow rate of 60 mL/min) to afford the mixture [1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate and [1-methyl-5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**307***, 1.9 g, 4.56 mmol, 64.9 %

yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.07 (d, *J* = 0.6 Hz, 1H), 5.86 (s, 1H), 3.80 - 3.68 (m, 2H), 2.78 - 2.64 (m, 1H), 2.25 - 2.08 (m, 2H), 2.06 - 1.94 (m, 1H), 1.88 - 1.80 (m, 1H), 1.79 (s, 1H), 1.46 - 1.43 (m, 3H), 0.93 - 0.89 (m, 9H), 0.08 (s, 6H).

To a solution of the mixture of [1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate and [1-methyl-5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl] trifluoromethanesulfonate (**307***, 1.9 g, 4.56 mmol, 1 eq) in dioxane (20 mL) was added Pin_2B_2 (**4**, 1.51 g, 5.93 mmol, 1.3 eq) and KOAc (1.12 g, 11.40 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (166.88 mg, 228.08 μmol, 0.05 eq) at 20 °C. The mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.7) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (15 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 10 % EtOAc / Pet. Et. gradient at a flow rate of 80 mL/min) to afford the mixture *tert*-butyl-dimethyl-[[5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-1-yl]methoxy]silane and *tert*-butyl-dimethyl-[[1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-5-yl]methoxy]silan (**308***, 1.6 g, 4.06 mmol, 88.9 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.76 - 6.57 (m, 1H), 3.76 - 3.58 (m, 2H), 2.49 - 2.33 (m, 1H), 2.09 - 1.94 (m, 2H), 1.94 - 1.79 (m, 1H), 1.74 - 1.59 (m, 2H), 1.39 - 1.36 (m, 3H), 1.26 (s, 12H), 0.91 (s, 9H), 0.09 - 0.05 (m, 6H).

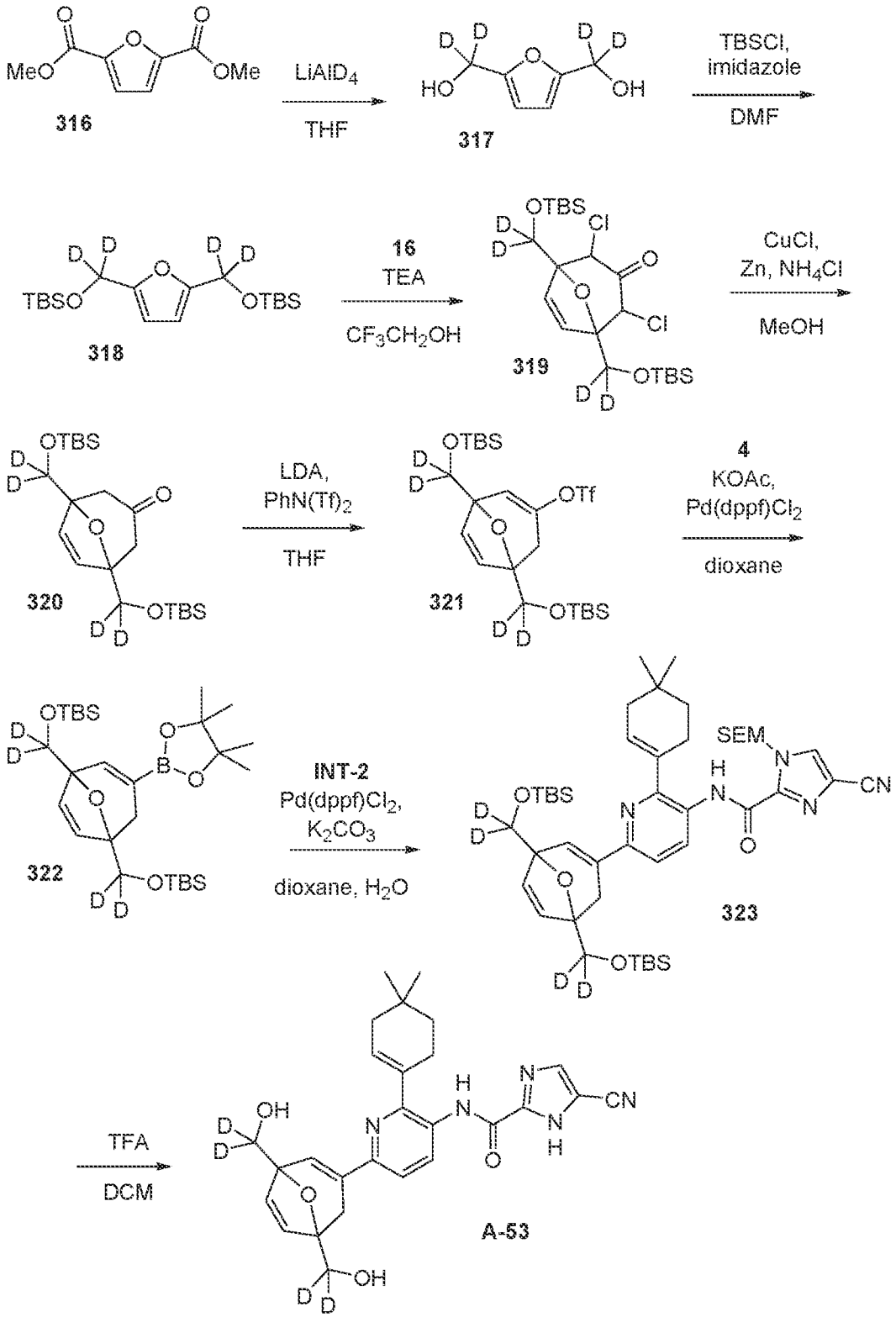
To a solution of the mixture *tert*-butyl-dimethyl-[[5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-1-yl]methoxy]silane and *tert*-butyl-dimethyl-[[1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]oct-2-en-5-yl]methoxy]silan (**308***, 600 mg, 1.52 mmol, 1.2 eq) and *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**INT-5**, 672.53 mg, 1.27 mmol, 1 eq) in dioxane (10 mL) and H_2O (2 mL) was added K_2CO_3 (438.01 mg, 3.17 mmol, 2.5 eq) and $Pd(dppf)Cl_2$ (92.75 mg, 126.77 μmol, 0.1 eq) at 20 °C, the mixture was warmed and stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (15 mL) and extracted with EtOAc (10 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 15 % EtOAc / Pet. Et. gradient at a flow rate of 60 mL/min)

to afford the mixture *N*-[6-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and *N*-[6-[1-methyl-5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamid (**309***, 700 mg, 896.83 μmol, 70.8 % yield, 92 % purity) as a white solid. 1H NMR (400 MHz, $CDCl_3$) δ = 10.02 (s, 1H), 8.71 - 8.66 (m, 1H), 7.78 (s, 1H), 7.27 - 7.24 (m, 1H), 7.01 - 6.77 (m, 1H), 5.99 (br s, 1H), 5.94 (s, 2H), 3.90 - 3.77 (m, 2H), 3.70 - 3.63 (m, 2H), 2.78 - 2.69 (m, 1H), 2.53 (br d, *J* = 1.6 Hz, 2H), 2.45 (d, *J* = 17.3 Hz, 1H), 2.15 (br d, *J* = 2.5 Hz, 2H), 2.13 - 2.07 (m, 1H), 2.04 - 1.92 (m, 1H), 1.83 - 1.69 (m, 2H), 1.63 (br t, *J* = 6.3 Hz, 2H), 1.53 - 1.50 (m, 3H), 1.13 (s, 6H), 1.01 - 0.96 (m, 2H), 0.94 (s, 9H), 0.13 - 0.10 (m, 6H), 0.02 - 0.00 (m, 9H). MS (LC/MS) *m/z* observed 718.4, expected 718.4 [M+H].

To a solution of the mixture *N*-[6-[1-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-5-methyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide and *N*-[6-[1-methyl-5-[[*tert*-butyl(dimethyl)silyl]oxymethyl]-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamid (**309***, 200 mg, 278.52 μmol, 1 eq) in THF (3 mL) was added TBAF (1 M, 557.04 μL, 2 eq) at 20 °C. The mixture was warmed and stirred at 60 °C for 2 hr under N_2 atmosphere. The reaction was monitored by LC/MS (R_t = 1.257 min, [M+H] = 474.2) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (8 mL) and extracted with EtOAc (6 mL x 3). The organic layers were combined, dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 30 % - 75 % B gradient over 8.0 min) to afford the mixture of title compounds 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-(hydroxymethyl)-5-methyl-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide and 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1-methyl-5-(hydroxymethyl)-8-oxabicyclo[3.2.1]oct-2-en-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-51***, 74.6 mg, 157.15 μmol, 56.4 % yield, 99.8 % purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ = 14.50 - 14.06 (m, 1H), 10.02 (s, 1H), 8.30 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.46 - 7.38 (m, 1H), 6.94 - 6.76 (m, 1H), 5.90 (br s, 1H), 4.87 (br s, 1H), 3.66 - 3.46 (m, 2H), 3.32 - 3.12 (m, 1H), 2.71 - 2.54 (m, 1H), 2.42 (br s, 2H), 2.31 (br d, *J* = 17.1 Hz, 1H), 2.08 - 1.83 (m, 4H), 1.62 (br t, *J* = 7.8 Hz, 1H), 1.49 (br t, *J* = 6.2 Hz, 2H), 1.45 - 1.37 (m, 3H), 0.99 (s, 6H), MS (LC/MS) *m/z* observed 474.3, expected 474.2 [M+H].

EXAMPLE 65

***N*-[6-{1,5-Bis[dideuterio(hydroxy)methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl}-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*- imidazole-2-carboxamide A-53**



To a solution of dimethyl furan-2,5-dicarboxylate (**316**, 10 g, 54.30 mmol, 1 eq) in THF (150 mL) was added lithium tetradeuterioalumanuide (6.18 g, 162.91 mmol, 8.40 mL, 3 eq) at 0 °C. The mixture was allowed to warm and stirred at 25 °C for 4 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 3/1, Rf = 0.1) until it showed that the starting material had been completely consumed. The reaction mixture was added to water (6.2 mL) and NaOH (15 %, 6.2 mL) and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue, without further purification, to afford dideuterio-[5-[dideuterio(hydroxy)methyl]-2-furyl]methanol (**317**, 3 g, 22.70 mmol, 41.8 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.26 (s, 2H).

To a solution of dideuterio-[5-[dideuterio(hydroxy)methyl]-2-furyl]methanol (**317**, 3 g, 22.70 mmol, 1 eq) in DMF (80 mL) was added TBSCl (8.55 g, 56.75 mmol, 6.98 mL, 2.5 eq) and imidazole (4.64 g, 68.10 mmol, 3 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-2-furyl]-dideuterio-methoxy]-dimethyl-silane (**318**, 10 g, 22.18 mmol, 97.7 % yield, 80 % purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.16 (s, 2H), 0.91 (s, 18H), 0.09 (s, 12H).

To a solution of *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-2-furyl]-dideuterio-methoxy]-dimethyl-silane (**318**, 10 g, 27.73 mmol, 1 eq) in CF_3CH_2OH (100 mL) was added *N*,*N*-diethylethanamine (11.22 g, 110.90 mmol, 15.44 mL, 4 eq), and 1,1,3-trichloropropan-2-one (13.43 g, 83.18 mmol, 3 eq) at 25 °C under N_2. The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**319**, 15 g, crude) as a yellow oil, without further characterization.

To a mixture of CuCl (1.53 g, 15.44 mmol, 369.31 μL, 0.5 eq), NH_4Cl (11.57 g, 216.22 mmol, 7 eq) and zinc (10.10 g, 154.44 mmol, 5 eq) in MeOH (200 mL) was added a solution of

1,5-bis[[*tert*-butyl(dimethyl)silyl]oxydideuterio-methyl]-2,4-dichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**319**, 15 g, 30.89 mmol, 1 eq) in MeOH (20 mL) dropwise at 25 °C. The mixture was stirred at 25 °C for 16 hours. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf =0.5) until it showed that the starting material had been completely consumed. The reaction mixture was filtered through a CELITE™ pad. The filtrate was diluted with water (100 mL) and extracted with EtOAc (100 mL x 2). Precipitate was dissolved by addition of HCl (2 N). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to obtain a residue that was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 50 mL/min) to afford 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**320**, 4.4 g, 10.56 mmol, 34.2 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.10 (s, 2H), 2.63 - 2.56 (m, 2H), 2.45 - 2.38 (m, 2H), 0.92 - 0.89 (m, 18H), 0.10 - 0.06 (m, 12H).

To a solution of 1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]oct-6-en-3-one (**320**, 4.4 g, 10.56 mmol, 1 eq) in THF (50 mL) was added dropwise LDA (2 M, 10.56 mL, 2 eq) at -78 °C. After 0.5 h, a solution of 1,1,1-trifluoro-*N*-(2-pyridyl)-*N*-(trifluoromethylsulfonyl)methanesulfonamide (5.67 g, 15.84 mmol, 1.5 eq) in THF (10 mL) was added dropwise at -78 °C. The mixture was allowed to warm and stirred at 25 °C for 2.5 hr. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.8) until it showed that the starting material had been completely consumed. The reaction mixture was quenched by NH_4Cl (50 mL, saturated, aqueous) and extracted with EtOAc (50 mL x 2). The organic layers were combined, washed with brine (100 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford [1,5-bis[[tert-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**321**, 3.2 g, 5.83 mmol, 55.2 % yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 296 K) δ (ppm) = 6.42 (d, *J* = 5.8 Hz, 1H), 5.92 (d, *J* = 5.8 Hz, 1H), 5.31 (s, 1H), 2.81 (dd, *J* = 1.9, 17.6 Hz, 1H), 2.13 (dd, *J* = 1.3, 17.6 Hz, 1H), 0.91 (s, 18H), 0.09 (s, 12H).

To a solution of [1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl] trifluoromethanesulfonate (**321**, 3.2 g, 5.83 mmol, 1 eq) in dioxane (40 mL) was added $Pd(dppf)Cl_2$ (426.66 mg, 583.09 μmol, 0.1 eq), KOAc (1.72 g, 17.49 mmol, 3 eq) and 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**4**, 2.22 g, 8.75 mmol, 1.5 eq). The mixture was stirred at 90 °C for 3 hr under N_2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 10/1, Rf = 0.6) until it

showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford tert-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]-dideuterio-methoxy]-dimethyl-silane (**322**, 2.6 g, 4.94 mmol, 84.7 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 6.97 (t, *J* = 2.0 Hz, 1H), 6.34 (d, *J* = 5.8 Hz, 1H), 5.84 (d, *J* = 5.8 Hz, 1H), 2.47 (dd, *J* = 2.3, 18.6 Hz, 1H), 1.92 (dd, *J* = 2.1, 18.6 Hz, 1H), 1.24 (s, 12H), 0.90 (s, 12H), 0.09 (s, 17H).

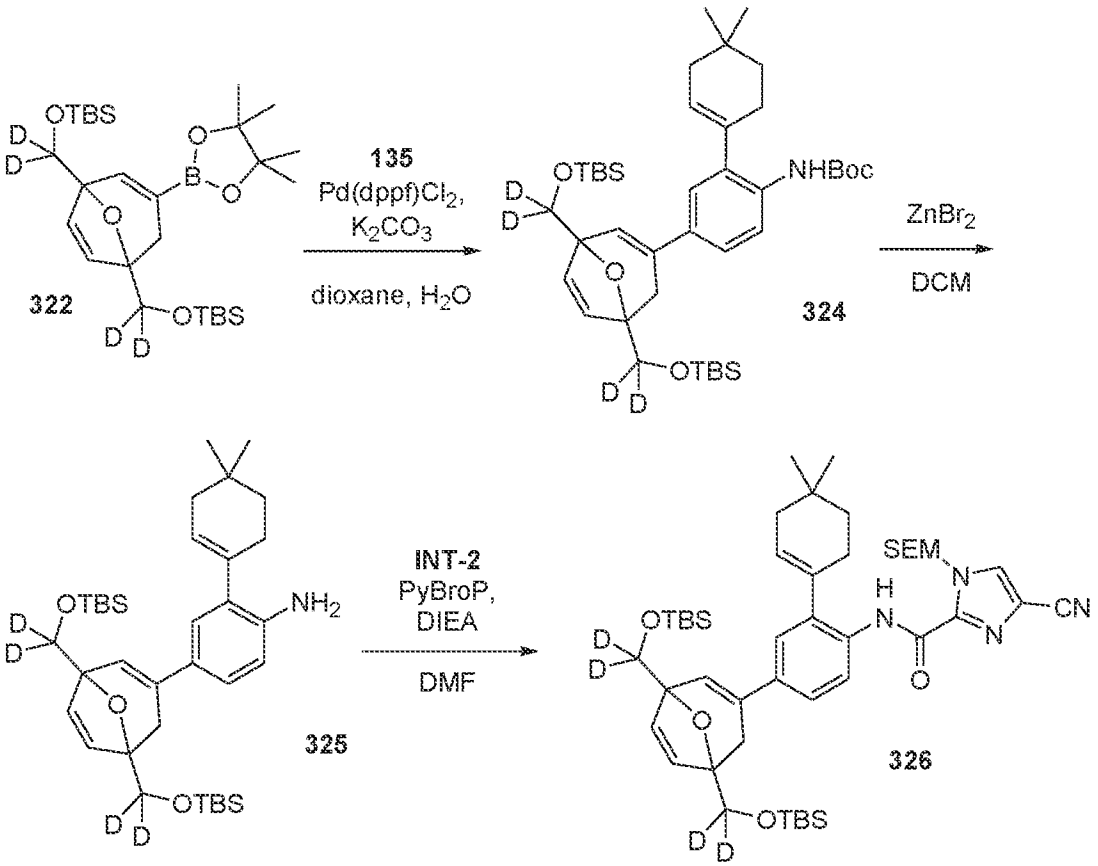
To a solution of *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**322**, 200 mg, 376.98 μmol, 1 eq) in dioxane (10 mL) and H_2O (1 mL) was added *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]-dideuterio-methoxy]-dimethyl-silane (**INT-5**, 297.83 mg, 565.47 μmol, 1.5 eq) , $Pd(dppf)Cl_2$ (27.58 mg, 37.70 μmol, 0.1 eq) and K_2CO_3 (156.31 mg, 1.13 mmol, 3 eq). The mixture was stirred at 90 °C for 12 hr under N2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.6) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**323**, 180 mg, 211.68 μmol, 56.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 10.00 (s, 1H), 8.66 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 6.42 (d, *J* = 5.6 Hz, 1H), 5.98 - 5.95 (m, 1H), 5.95 - 5.92 (m, 3H), 3.69 - 3.64 (m, 2H), 2.81 (dd, *J* = 1.7, 18.1 Hz, 1H), 2.52 (br s, 2H), 2.44 (br d, *J* = 17.8 Hz, 1H), 2.14 (br s, 2H), 1.61 (br t, *J* = 6.4 Hz, 2H), 1.58 - 1.54 (m, 2H), 1.11 (s, 6H), 0.96 - 0.93 (m, 18H), 0.14 - 0.10 (m, 12H), 0.01 (s, 9H).

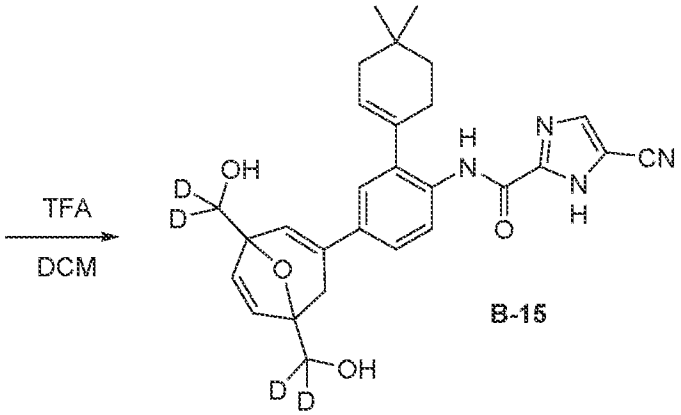
To a solution of *N*-[6-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**323**, 180 mg, 211.68 μmol, 1 eq) in DCM

(2 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 0.432 min, [M+H] = 492.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 % - 85 % B gradient over 8.0 min to afford title compound *N*-[6-[1,5-bis[dideuterio(hydroxy)methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]-5-cyano-1*H*-imidazole-2-carboxamide (**A-53**, 35.4 mg, 58.45 μmol, 27.6 % yield, TFA salt) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.29 (br s, 1H), 10.00 (s, 1H), 8.33 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.10 (s, 1H), 6.39 (d, *J* = 5.8 Hz, 1H), 5.92 (d, *J* = 5.8 Hz, 1H), 5.89 (br s, 1H), 2.71 (dd, *J* = 1.6, 18.2 Hz, 1H), 2.41 (br s, 2H), 2.22 (br d, *J* = 19.3 Hz, 1H), 1.94 (br s, 2H), 1.49 (br t, *J* = 6.3 Hz, 2H), 0.99 (s, 6H), MS (LC/MS) *m/z* observed 492.5, expected 492.5 [M+H].

EXAMPLE 66

***N*-[4-[1,5-Bis[dideuterio(hydroxy)methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide B-15**





To a solution of *tert*-butyl *N*-[4-bromo-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**135**, 300 mg, 788.81 μmol, 1 eq) in dioxane (10 mL) and H_2O (1 mL) was added *tert*-butyl-[[5-[[*tert*-butyl(dimethyl)silyl]oxy-dideuteriomethyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-8-oxabicyclo[3.2.1]octa-2,6-dien-1-yl]-dideuterio-methoxy]-dimethyl-silane (**322**, 415.46 mg, 788.81 μmol, 1 eq), Pd(dppf)Cl_2 (57.72 mg, 78.88 μmol, 0.1 eq) and K_2CO_3 (327.05 mg, 2.37 mmol, 3 eq). The mixture was stirred at 90 °C for 12 hr under N2. The reaction was monitored by TLC (Pet. Et. / EtOAc = 5/1, Rf = 0.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**324**, 400 mg, 571.31 μmol, 72.4 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 7.93 (br d, *J* = 8.5 Hz, 1H), 7.22 (dd, *J* = 2.1, 8.6 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 6.74 (s, 1H), 6.52 (s, 1H), 6.42 (d, *J* = 5.8 Hz, 1H), 5.90 (d, *J* = 5.9 Hz, 1H), 5.64 (br s, 1H), 2.72 (dd, *J* = 1.7, 17.7 Hz, 1H), 2.22 (br d, *J* = 1.4 Hz, 2H), 2.17 (br d, *J* = 1.3 Hz, 1H), 2.00 (br d, *J* = 3.1 Hz, 2H), 1.51 (s, 9H), 1.28 (br s, 2H), 1.03 (s, 6H), 0.93 (d, *J* = 1.6 Hz, 18H), 0.11 - 0.10 (m, 12H).

To a solution of *tert*-butyl *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]carbamate (**324**, 400 mg, 571.31 μmol, 1 eq) in DCM (15 mL) was added $ZnBr_2$ (1.29 g, 5.71 mmol, 285.91 μL, 10 eq). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 0.627 min, [M+H] = 600.2) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with H_2O (20 mL) and

extracted with DCM (20 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**325**, 350 mg, 466.65 μmol, 81.7 % yield, 80 % purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 7.16 - 7.09 (m, 2H), 7.07 - 7.03 (m, 1H), 6.67 - 6.60 (m, 1H), 6.47 - 6.39 (m, 1H), 5.94 - 5.87 (m, 1H), 5.72 - 5.69 (m, 1H), 2.82 - 2.63 (m, 1H), 2.23 - 2.14 (m, 2H), 2.02 - 1.94 (m, 4H), 1.56 - 1.48 (m, 6H), 0.93 (d, J = 1.8 Hz, 18H), 0.11 (d, J = 2.9 Hz, 12H).

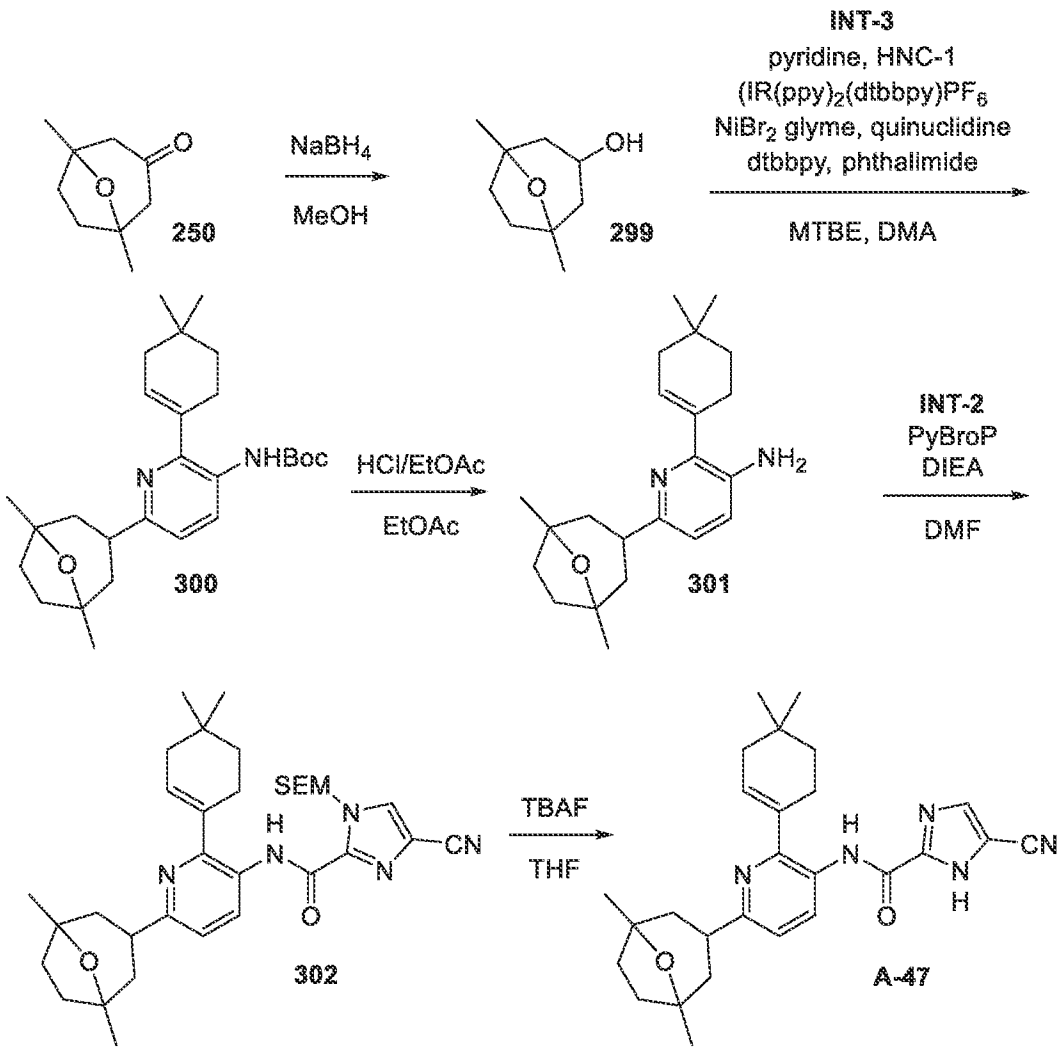
To a solution of 4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)aniline (**325**, 350 mg, 583.31 μmol, 1 eq) in DMF (10 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 356.34 mg, 1.17 mmol, 2 eq), DIEA (226.16 mg, 1.75 mmol, 304.80 μL, 3 eq) and PyBroP (407.89 mg, 874.96 μmol, 1.5 eq). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 0.454 min, [M+H] = 849.5) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL x 2). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**326**, 280 mg, 329.66 μmol, 56.5 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77-9.74 (m, 1H), 8.33-8.29 (m, 1H), 7.77-7.74 (m, 1H), 7.42-7.37 (m, 1H), 7.32 - 7.28 (m, 1H), 7.17-7.15 (m, 1H), 6.61-6.58 (m, 1H), 6.42 (d, J = 5.6 Hz, 1H), 5.95-5.92 (m, 1H), 5.80 - 5.73 (m, 2H), 3.67-3.64 (m, 2H), 2.77-2.72 (m, 1H), 2.28 - 2.26 (m, 2H), 2.24 - 2.17 (m, 1H), 2.12-2.09 (m, 2H), 1.60 - 1.56 (m, 4H), 1.12-1.09 (m, 6H), 0.93 (s, 18H), 0.09 (s, 12H), 0.00 (s, 9H).

To a solution of *N*-[4-[1,5-bis[[*tert*-butyl(dimethyl)silyl]oxy-dideuterio-methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**326**, 280 mg, 329.66 μmol, 1 eq) in THF (10 mL) was added TBAF (1 M, 659.32 μL, 2 eq). The mixture was stirred at 75 °C for 12 h. The reaction was monitored by LC/MS (R_t = 0.463 min, [M+H] = 491.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed

with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Phenomenex Luna C18 100 x 40 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 55 % - 85 % B gradient over 8.0 min to afford title compound *N*-[4-[1,5-bis[dideuterio(hydroxy)methyl]-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-2-(4,4-dimethylcyclohexen-1-yl)phenyl]-5-cyano-1*H*-imidazole-2-carboxamide (**B-15**, 35.9 mg, 73.18 μmol, 22.2 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.27 (br s, 1H), 9.69 (s, 1H), 8.33 (d, *J* = 2.4 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.34 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.67 (s, 1H), 6.38 (d, *J* = 5.8 Hz, 1H), 5.90 (d, *J* = 5.8 Hz, 1H), 5.69 (br s, 1H), 2.67 (dd, *J* = 1.6, 17.8 Hz, 1H), 2.25 (br s, 2H), 2.09 (dd, *J* = 1.1, 17.8 Hz, 1H), 1.97 (br s, 2H), 1.50 (br t, *J* = 6.3 Hz, 2H), 1.02 (s, 6H), MS (LC/MS) *m/z* observed 491.4, expected 491.4 [M+H].

EXAMPLE 67

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-47



To a solution of 1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-one (**250**, 1 g, 6.48 mmol, 1 eq) in THF (20 mL) was added NaBH4 (367.98 mg, 9.73 mmol, 1.5 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by TLC (Pet. Et. : EtOAc= 3:1, Rf = 0.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with NH_4Cl (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®;12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % EtOAc / Pet. Et. gradient at a flow rate of 60 mL/min) to afford 1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-ol (**299**, 700 mg, 4.48 mmol, 69.1 % yield) was obtained as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 2.32 - 2.27 (m, 1H), 1.94 (dd, *J* = 5.8, 12.6 Hz, 1H), 1.85 - 1.72 (m, 4H), 1.69 - 1.62 (m, 4H), 1.31 (s, 6H).

To a solution of 1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-ol (**299**, 294.98 mg, 1.89 mmol, 1.8 eq) and NHC-1 (663.39 mg, 1.68 mmol, 1.6 eq) in MTBE (10 mL) was added pyridine (132.76 mg, 1.68 mmol, 135.47 μL, 1.6 eq) in MTBE (1 mL) dropwise in 5 mins at 25 °C. After 10 min, the mixture was filtered and the filtrate was added to a solution of *tert*-butyl *N*-[6-bromo-2-(4,4-dimethylcyclohexen-1-yl)-3-pyridyl]carbamate (**INT-3**, 400 mg, 1.05 mmol, 1 eq) bis[2-(2-pyridyl)phenyl]iridium(1+); 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine; hexafluorophosphate (14.38 mg, 15.74 μmol, 0.015 eq), dibromonickel; 1,2-dimethoxyethane (16.19 mg, 52.45 μmol, 0.05 eq), quinuclidine (204.10 mg, 1.84 mmol, 1.75 eq), 4-*tert*-butyl-2-(4-*tert*-butyl-2-pyridyl)pyridine (21.12 mg, 78.68 μmol, 0.075 eq) and isoindoline-1,3-dione (34.73 mg, 236.03 μmol, 0.225 eq) in DMA (10 mL) under N_2. The mixture was stirred at 25 °C for 12 hr under blue LED light. The reaction was monitored by LC/MS (R_t =2.590 min, [M+H] = 441.3) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 60 mL/min) to afford *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]carbamate (**300**, 700 mg, 953.21 μmol, 45.4 % yield, 60 % purity) was obtained as a yellow solid. MS (LC/MS) *m/z* observed 441.3, expected 441.3 [M+H].

To a solution of *tert*-butyl *N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]carbamate (**300**, 700 mg, 953.21 μmol, 1 eq) in EtOAc

(5 mL) was added HCl/EtOAc (5 mL). The mixture was stirred at 25 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 0.381 min, [M+H] = 341.3) until it showed that the starting material had been completely consumed. The reaction mixture was filtered and concentrated under reduced pressure to give a residue, without further purification, to afford 2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]pyridin-3-amine (**301**, 300 mg, 795.84 μmol, 83.5 % yield, HCl salt) was obtained as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD, 298 K) δ (ppm) = 7.70 (d, *J* = 8.9 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 6.18 - 6.08 (m, 1H), 3.57 - 3.45 (m, 1H), 2.41 - 2.33 (m, 2H), 2.17 - 2.10 (m, 3H), 2.06 - 1.98 (m, 2H), 1.86 - 1.75 (m, 4H), 1.69 - 1.57 (m, 5H), 1.35 (s, 6H), 1.07 (s, 6H).

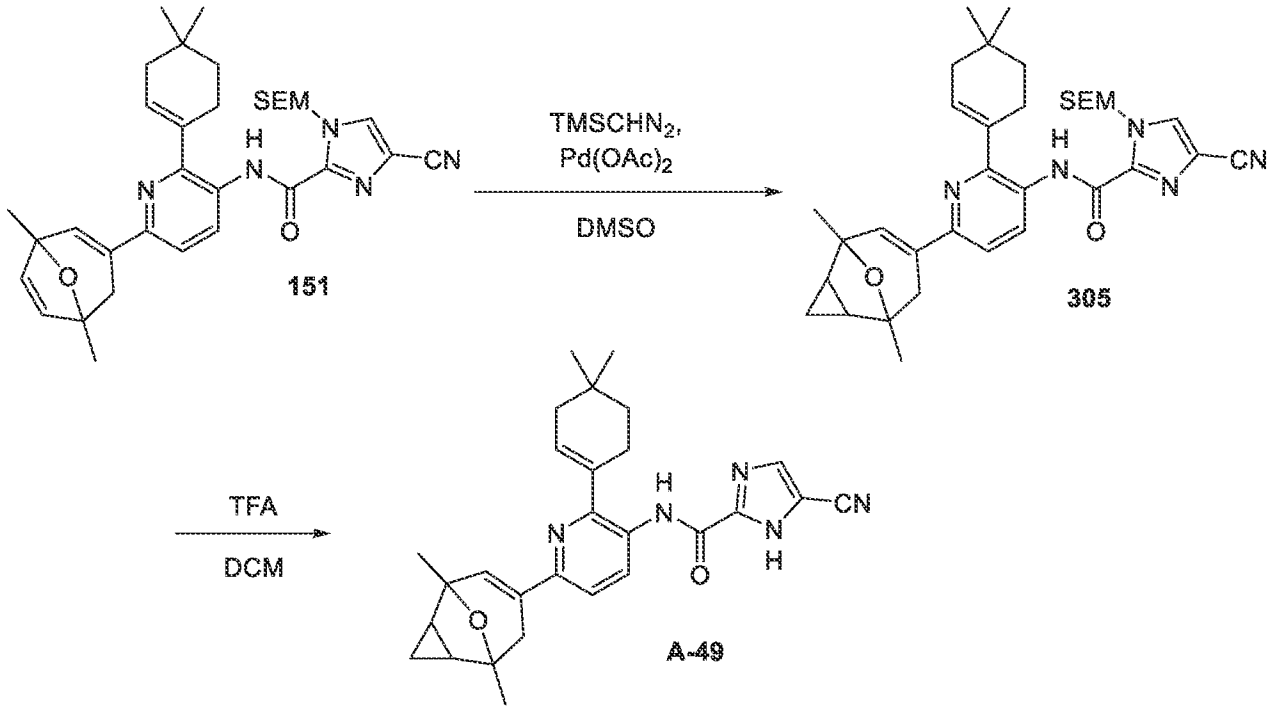
To a solution of 2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]pyridin-3-amine (**301**, 300 mg, 881.05 μmol, 1 eq) in DMF (5 mL) was added [4-cyano-1-(2-trimethylsilylethoxymethyl)imidazole-2-carbonyl]oxypotassium (**INT-2**, 269.11 mg, 881.05 μmol, 1 eq), DIEA (569.34 mg, 4.41 mmol, 767.30 μL, 5 eq) and PyBroP (616.10 mg, 1.32 mmol, 1.5 eq). The mixture was stirred at 25 °C for 2 h. The reaction was monitored by LC/MS (R_t = 0.700 min, [M+H] = 590.4) until it showed that the starting material had been completely consumed. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SEPAFLASH® Silica Flash Column, with an eluent of 0 ~ 20 % Pet. Et. : EtOAc at a flow rate of 80 mL/min) to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**302**, 300 mg, 508.61 μmol, 57.7 % yield) was obtained as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ (ppm) = 9.89 (s, 1H), 8.62 (br d, *J* = 8.4 Hz, 1H), 7.76 (s, 1H), 7.09 (br d, *J* = 8.5 Hz, 1H), 5.93 (s, 3H), 3.69 - 3.62 (m, 2H), 3.26 - 3.13 (m, 1H), 2.47 (br s, 2H), 2.13 (br s, 2H), 1.97 (br d, *J* = 6.8 Hz, 2H), 1.83 - 1.76 (m, 2H), 1.75 - 1.65 (m, 4H), 1.62 (br t, *J* = 6.3 Hz, 2H), 1.37 (s, 6H), 1.11 (s, 6H), 0.99 - 0.94 (m, 2H), 0.00 (s, 9H).

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**302**, 300 mg, 508.61 μmol, 1 eq) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t = 1.418 min, [M+H] = 460.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (50 mL) and extracted with DCM (40 mL x 2). The organic layers were combined, washed with brine (60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column:

Welch Xtimate C18 180 x 70 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 48 % - 78 % B gradient over 17.0 min to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octan-3-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-47**, 53.2 mg, 115.76 μmol, 22.7 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.26 (br s, 1H), 10.00 (s, 1H), 8.31 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 5.86 (br s, 1H), 3.24 - 3.11 (m, 1H), 2.40 (br s, 2H), 1.99 - 1.88 (m, 4H), 1.73 - 1.54 (m, 6H), 1.48 (t, *J* = 6.3 Hz, 2H), 1.25 (s, 6H), 0.97 (s, 6H).

EXAMPLE 68

5-Cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-9-oxatricyclo[3.3.1.0^{2,4}]non-6-en-7-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide A-49



To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**151**, 300 mg, 512.11 μmol, 1 eq) and $Pd(OAc)_2$ (11.50 mg, 51.21 μmol, 0.1 eq) in THF (5 mL) was added diazomethyl(trimethyl)silane (2 M, 2.56 mL, 10 eq). The mixture was warmed and stirred at 65 °C for 12 hr. The reaction was monitored by LC/MS (R_t = 2.065 min, [M+H] = 600.4) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column:

Phenomenex Luna C18 100 x 30 mm x 5 um; mobile phase: [H_2O (0.1 % TFA) - ACN]; 85 % - 98 % B gradient over 8.0 min to afford 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-9-oxatricyclo[3.3.1.$0^{2,4}$]non-6-en-7-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**305**, 15 mg, 25.01 μmol, 4.9 % yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 299 K) δ (ppm) = 10.08 - 9.92 (m, 1H), 8.75 (br d, *J* = 8.8 Hz, 1H), 7.85 - 7.74 (m, 1H), 7.31 (br d, *J* = 8.8 Hz, 1H), 7.04 - 6.86 (m, 1H), 6.15 - 5.84 (m, 3H), 3.77 - 3.60 (m, 2H), 2.75 - 2.55 (m, 4H), 2.23 - 2.09 (m, 2H), 1.73 - 1.61 (m, 3H), 1.43 (br d, *J* = 3.8 Hz, 6H), 1.32 - 1.25 (m, 1H), 1.14 (s, 6H), 1.04 - 0.95 (m, 2H), 0.67 - 0.60 (m, 1H), 0.37 - 0.27 (m, 1H), 0.01 (s, 9H), MS (LC/MS) *m/z* observed 600.5, expected 600.4 [M+H].

To a solution of 4-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-9-oxatricyclo[3.3.1.02,4]non-6-en-7-yl]-3-pyridyl]-1-(2-trimethylsilylethoxymethyl)imidazole-2-carboxamide (**305**, 65.00 mg, 108.36 μmol, 1 eq) in DCM (5 mL) was added TFA (2 mL). The mixture was stirred at 25 °C for 2 hr. The reaction was monitored by LC/MS (R_t =2.445 min, [M+H] = 470.2) until it showed that the reactant had been completely consumed. The reaction mixture was diluted with $NaHCO_3$ (10 mL) and extracted with DCM (10 mL x 2). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 x 40 mm x 10 um; mobile phase: [H_2O (10 mM NH_4HCO_3) - ACN]; 50 % - 100 % B gradient over 8.0 min to afford title compound 5-cyano-*N*-[2-(4,4-dimethylcyclohexen-1-yl)-6-[1,5-dimethyl-9-oxatricyclo[3.3.1.$0^{2,4}$]non-6-en-7-yl]-3-pyridyl]-1*H*-imidazole-2-carboxamide (**A-49**, 10.2 mg, 21.72 μmol, 20.1 % yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6, 298 K) δ (ppm) = 14.37 - 14.18 (m, 1H), 10.02 (s, 1H), 8.26 (br d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.94 (s, 1H), 5.90 (br s, 1H), 2.60 - 2.53 (m, 2H), 2.43 (br d, *J* = 6.9 Hz, 2H), 1.95 (br s, 2H), 1.65 (dt, *J* = 3.9, 6.6 Hz, 1H), 1.50 (br t, *J* = 6.3 Hz, 2H), 1.30 (d, *J* = 4.8 Hz, 7H), 1.00 (s, 6H), 0.44 (q, *J* = 3.8 Hz, 1H), 0.28 - 0.19 (m, 1H), MS (LC/MS) *m/z* observed 470.3, expected 470.2 [M+H].

EXAMPLE 69 **CSF1R Cell-based assay (BPS Bioscience)**

The capability of compounds to inhibit CSF1R activation in cells was determined using the following assay. Cell culture and treatment were carried out in a humidified 37° C., 5% CO2 incubator. CSF1R / SRE – Reporter HEK293 Recombinant Cell Line (BPS Bioscience #79380) was maintained in Growth Media (Growth Medium 1M (BPS Bioscience, #79723): MEM medium supplemented with 10% FBS, 1% non-essential amino acids, 1 mM Na pyruvate, 1% Penicillin/Streptomycin, 400 μg/ml of Geneticin and 0.5 μg/ml Puromycin Dihydrochloride) and

seeded into 96 well plates at 30,000 cells per well in Thaw Media (Thaw Medium 1 (BPS Bioscience, #79723): MEM medium supplemented with 10% FBS, 1% non-essential amino acids, 1 mM Na pyruvate, 1% Penicillin/Streptomycin) for 24 hours. Thaw media was then replaced with low serum Assay Media (Assay Medium 1B (BPS Bioscience, #79617): MEM medium supplemented with 0.5% FBS, 1% non-essential amino acids, 1 mM Na pyruvate, 1% Penicillin/Streptomycin) for 24 hours prior to treatment with compounds for 1 hour. The concentration of compounds was varied over a 10-point, 3-fold dilution series with 3162.28 nM typically being the highest dose. CSF1R signaling was then activated in the treated cells by treatment with 30 ng/mL recombinant human M-CSF for 6 hours. Cells were lysed, and the lysate was analyzed by ONE-Step™ Luciferase Assay System (BPS BIoscience #60690), which detects CSF1R signaling levels by measuring firefly luciferase activity. The luciferase assay working solution is prepared by diluting Luciferase Reagent Substrate (Component B) into Luciferase Reagent Buffer (Component A) at a 1:100 ratio, which is then added to the cells. Cells are rocked for 15 minutes at room temperature. Luciferase activity is measured using a luminometer plate reader. A standard curve was made using a dose-response of purified human recombinant M-CSF. The percent luminescence of SRE luciferase reporter expression = background - subtracted luminescence of stimulated well / average background-subtracted luminescence of unstimulated control wells x 100%. A standard 4-parameter logistic model was fit to the inhibitor dose response curves to identify the IC50, being defined as the concentration of inhibitor that induces half maximal inhibitory concentration.

EXAMPLE 70 **ADP-Glo™ Kinase Assay (Promega) (CSF1R Enzyme Assay)**

The capability of compounds to inhibit CSF1R in vitro was determined using the following assay. CSF1R enzymatic activity was measured using the ADP-Glo™ Kinase Assay from Promega (#V6930). Kinase reactions were done using 1X kinase buffer (Promega #V913A: 40mM Tris (pH 7.5), 20mM $MgCl_2$, 0.1mg/ml BSA) at room temperature with 50ng CSF1R, 25uM ATP, and Kinase Detection Substrate in a total volume of 5 µL. The concentration of compounds was varied over 6-point, 3-fold dilution series with 3.2 uM typically being the highest dose. Incubations were carried out in white 96 well plate at room temperature for 40 minutes, after which 5 µL of a quench solution was added containing ADP-Glo™ Reagent to stop the kinase reaction and deplete the unconsumed ATP. This was incubated for an additional 40 minutes at room temperature. 10 µl of Kinase Detection Reagent was then added to convert the remaining ADP to ATP and introduce luciferase and luciferin to detect ATP, and incubated at room temperature for 30 minutes. Kinase activity was read on a luminometer plate reader to detect luciferase levels. A standard curve was made using a dose-

response Ultra Pure ATP and ADP (Promega, V915A and V916A). The percent luminescence of kinase activity = background - subtracted luminescence of stimulated well / average background-subtracted luminescence of unstimulated control wells x 100%. A standard 4-parameter logistic model was fit to the inhibitor dose response curves to identify the IC50, being defined as the concentration of inhibitor that induces half maximal inhibitory concentration.

EXAMPLE 71 **Metabolic Stability**

Test compounds were incubated at 1 uM with mouse liver microsomes (CD-1; male and female pooled; or human liver microsomes in 50 mM potassium phosphate, pH 7.4, and 1mM NADPH at 37 °C. Aliquots were removed at 0, 5, 15, 30, 45, and 60 min, and amounts of test compounds remaining were determined by LC-MS/MS. Disappearance of the test compound was assessed based on peak area ratios of analyte/internal standard (cold acetonitrile containing internal standard). Half lives (t1/2) were calculated as t1/2 = -0.693/k, where k is the slope of the linear regression of the natural logarithms of percentages of test compounds remaining vs time. Microsome clearance was calculated using 0.693/half-life/mg microsome protein per mL wt: 40g/kg, 30 g/kg, 32 g/kg, 20 g/kg and 88 g/kg for rat, monkey, dog, human and mouse. $CL_{int(mic)}$ to calculate the whole liver clearance: microsomal protein / g liver weight: 45 mg/g for 5 species$_{int(liver)}$ = $CL_{int(mic)}$ * mg microsomal protein/g liver weight * g liver weight/kg body weight.

Test compounds were incubated at 1 uM with Hepatocytes (rat, monkey, dog, human and mouse) at 37°C for different time periods. Samples are removed at each indicated time point during incubation, and the reaction is terminated with a stop solution. The samples are then centrifuged, and supernatants are collected for LC-MS/MS analysis. The clearance of the test article is monitored over a time period of 60 minutes (or longer).

Drug clearance rate and half life (t1/2) were then calculated using the obtained data.

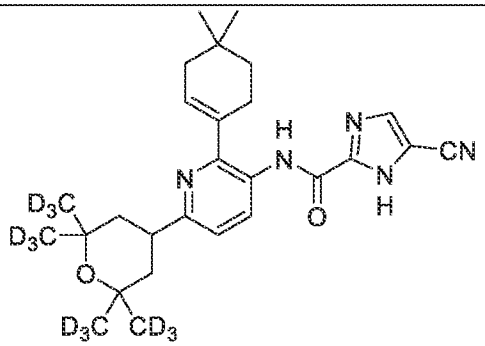
EXAMPLE 72 **Assay of in vivo Pharmacokinetics**

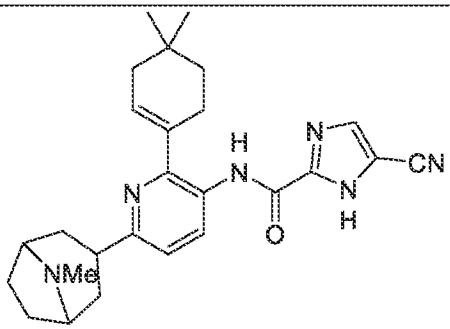
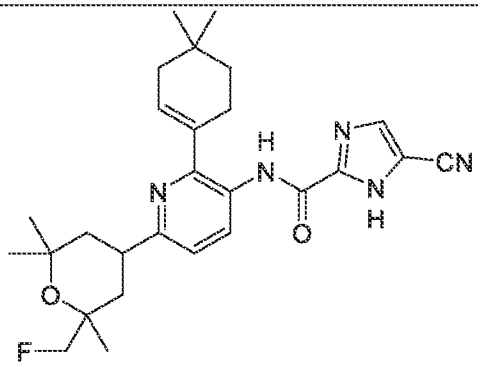
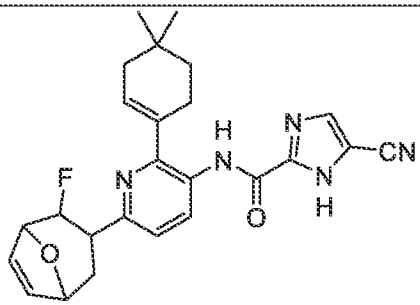
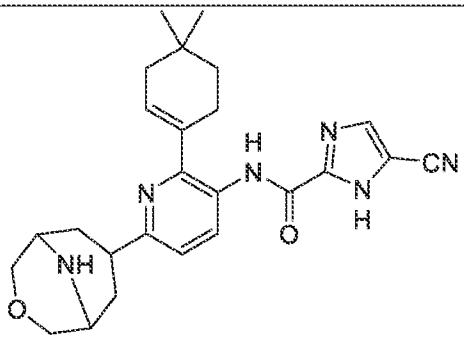
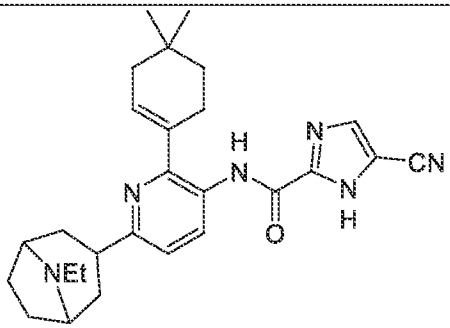
Test compounds (2.5 mg/kg; 0.1 ml of 0.625 mg/ml solution in 5% dimethylacetamide and 4% Cremophor EL in 10 mM sodium phosphate, pH 7.4) were administered to mice (CD-1; 0.024-0.26 kg, n= 3) by intravenous injection into a tail vein at t = 0 h. Blood samples were collected by tail-vein bleed (CB 300 K2E tubes; Sarstedt) at t = 0.02, 0.05, 1, 3, 5, and 8 h, and plasma concentrations of test compounds were determined by LC-MS/MS.

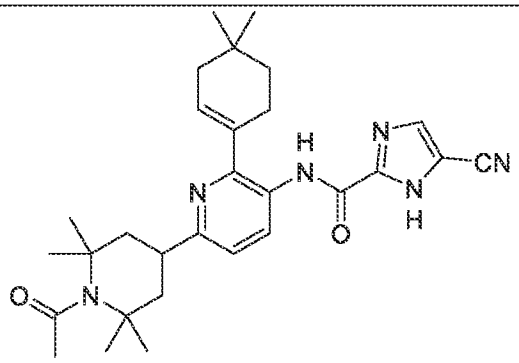
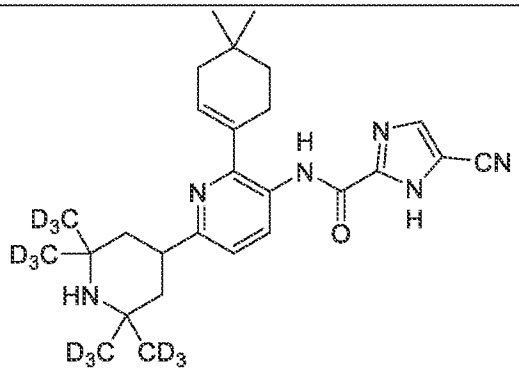
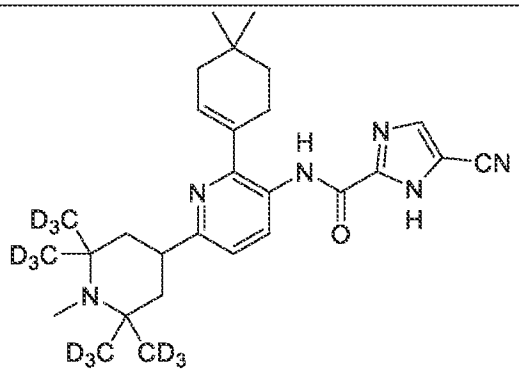
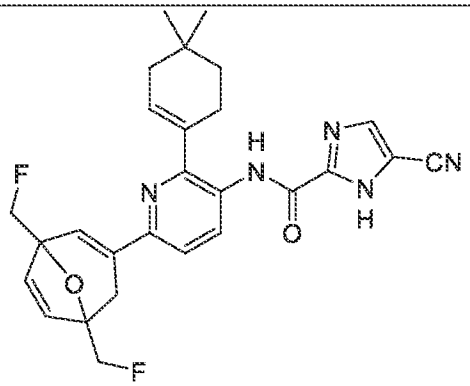
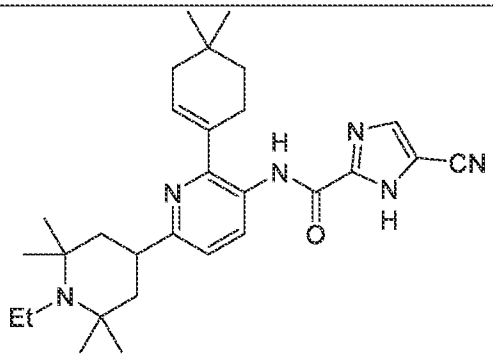
EXAMPLE 73 CSE1R Luciferase Assay.say of in vivo Pharmacokinetics

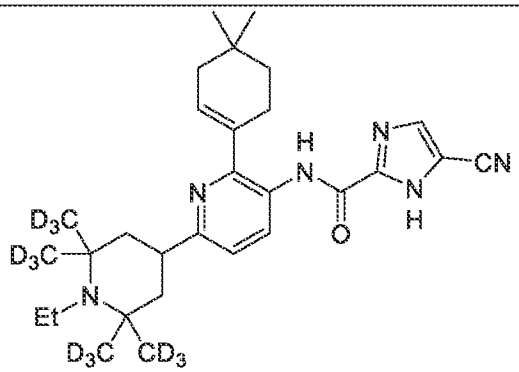
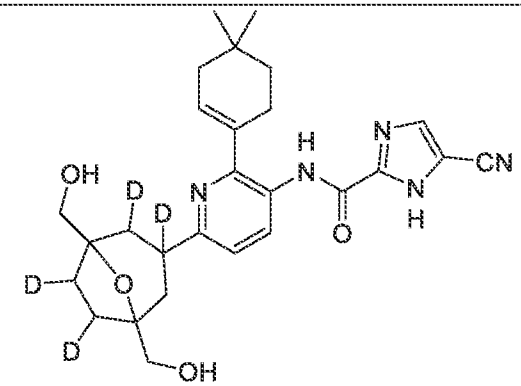
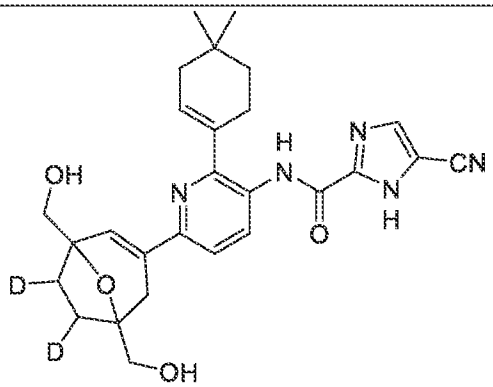
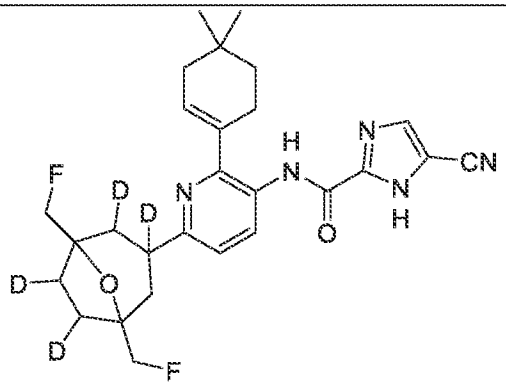
Compounds were analyzed for their capacity to inhibit CSF1R activity utilizing a CSF1R/SRE luciferase reporter cell line (BPS Bioscience). Here, the reporter cell line was maintained at 37 degrees Celsius and 5% CO_2 in HEK maintenance media (MEM, 5% FBS, and P/S) with the addition of selection antibiotics (0.5 µg/ml Puromycin Dihydrochloride and 400 µg/ml G-418). When confluent, cells were split via trypsin treatment and seeded into 0.1% gelatin-coated white 96 well plates at a density of $3x10^4$ cells/well using HEK maintenance media. The next day, maintenance media was replaced with assay media containing low quantities of FBS (0.5%) to minimize cellular signaling processes. 24 hours later, the reporter cells were pretreated with the compounds of interest at various concentrations for 1 hour and then stimulated with CSF1 at a final concentration of 30 ng/ml. Each plate assayed contained control wells lacking CSF1 stimulation and wells treated with CSF1 stimulation but lacking CSF1R inhibition. Following 6 hours of treatment, One-Step Luciferase Assay System was added to each well and then incubated at room temperature for 15 minutes. Luciferase measurements were collected using a BioTek Synergy HT plate readeLr. All assays were performed in triplicate. Graphpad prism was used to generate dose response curves via nonlinear regression, calculate IC_{50} values, and visualize data. Data for representative compounds is provided in the following Table 2. The Compounds of Examples 2, 9, and 58 showed no significant CSF1R inhibition when tested under the specific conditions used in this assay. The compounds of Examples 30, 32, 59, 61, and 67 were not tested.

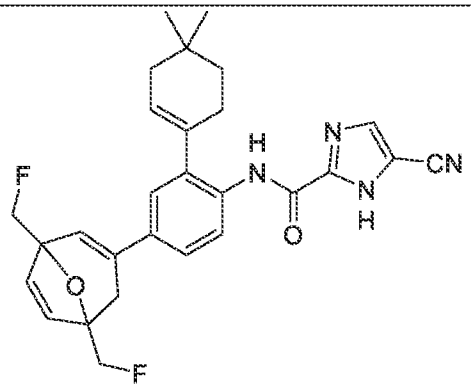
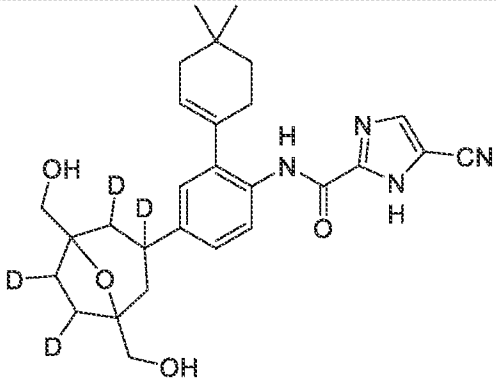
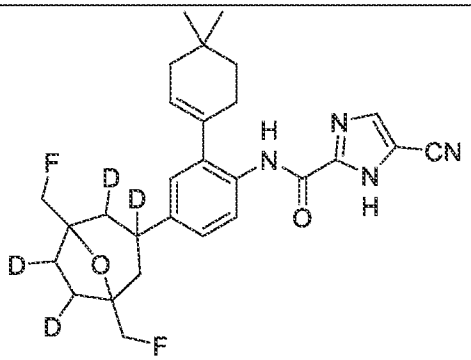
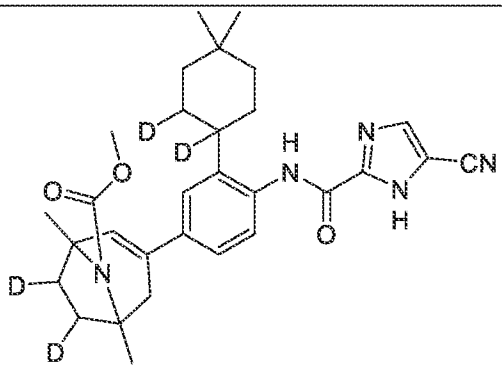
Table 2

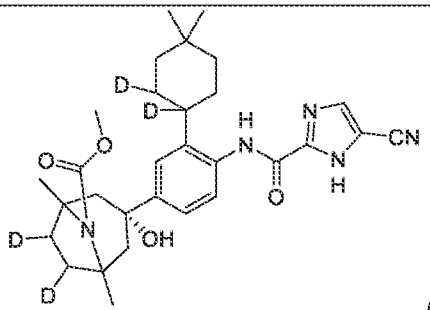
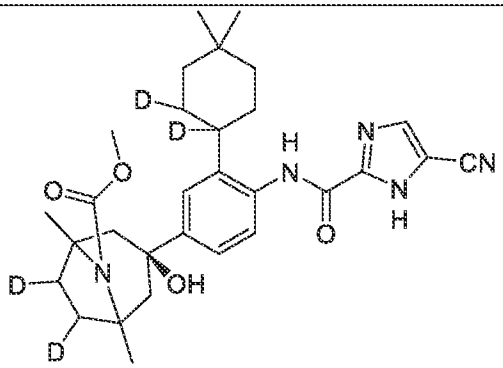
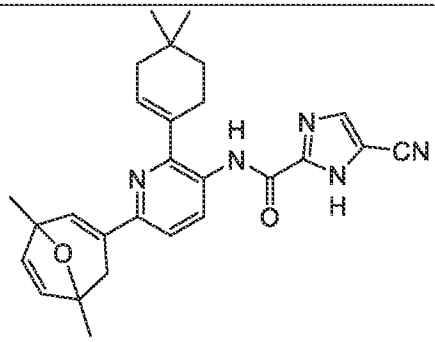
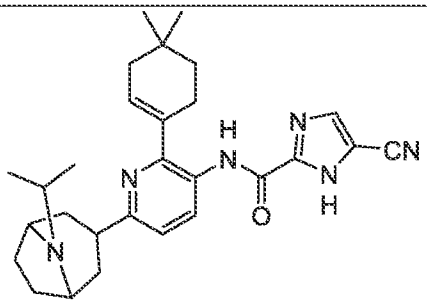
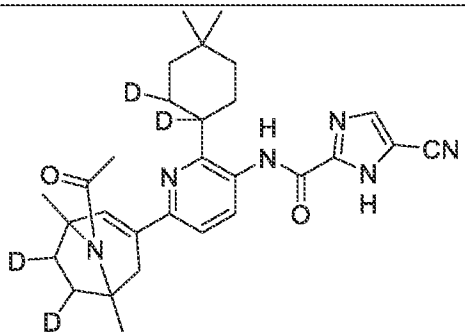
Example	Compound	IC_{50} (nM)
1		19.78

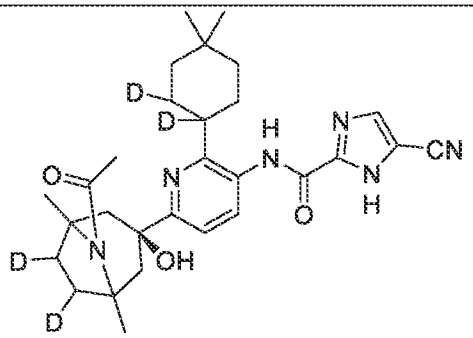
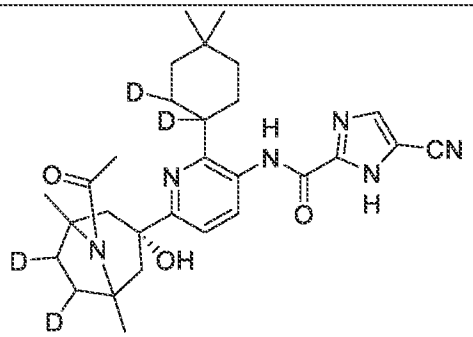
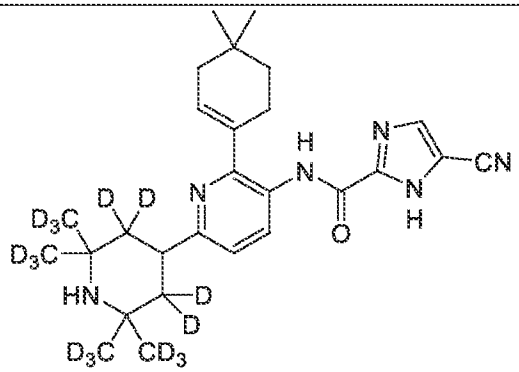
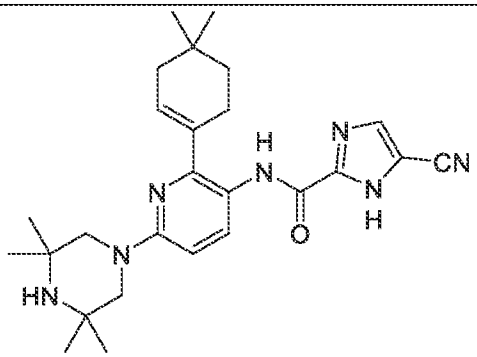
3		44.87
4		22.99
5		7.63
6		59.21
7		27.83

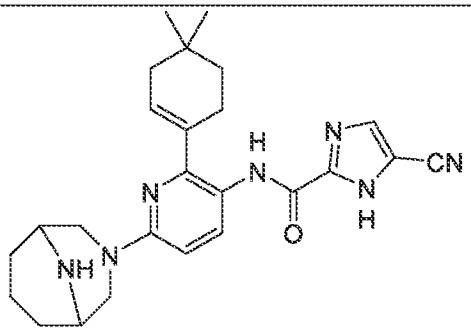
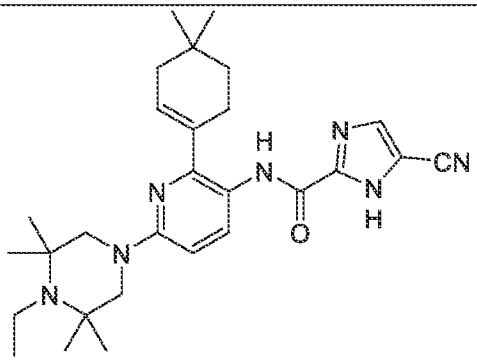
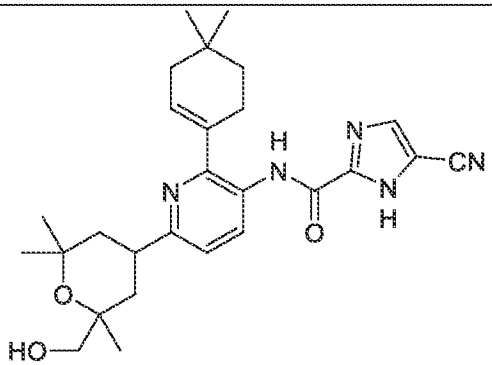
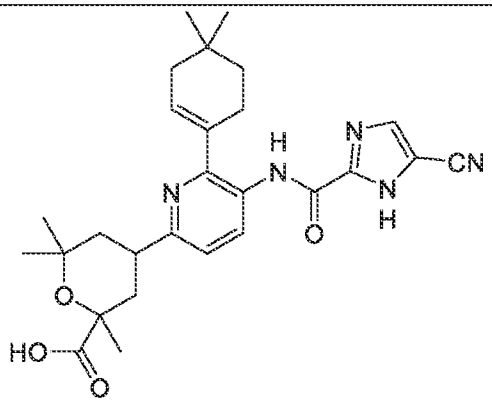
8		21.67
10		3.50
11		14.98
12		13.44
13		8.16

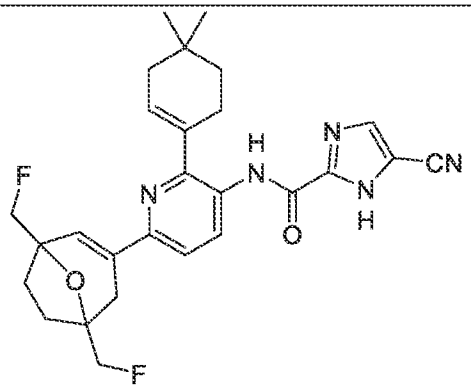
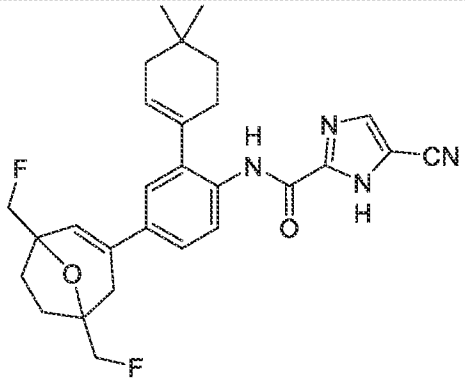
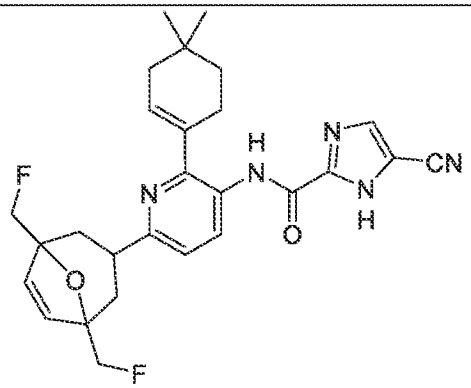
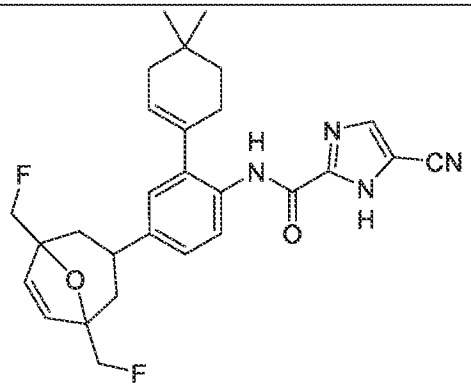
14		5.49
15		8.40
16		6.98
17		11.38

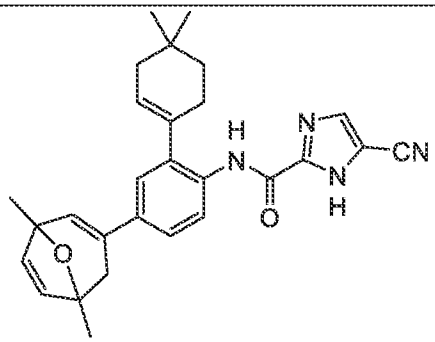
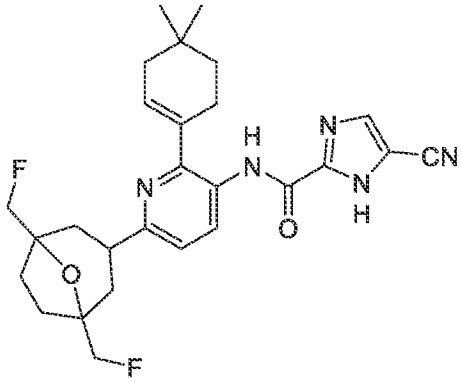
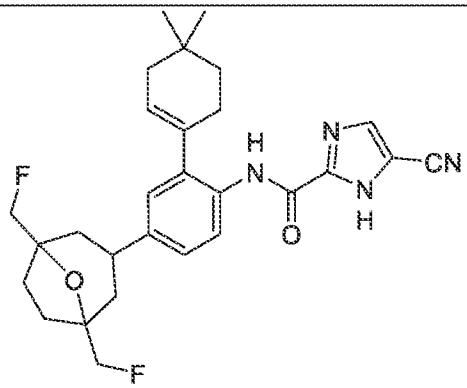
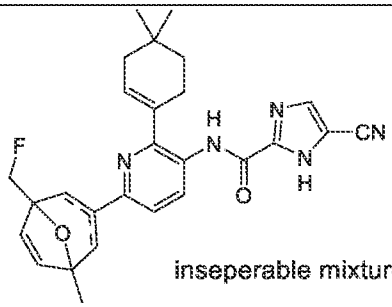
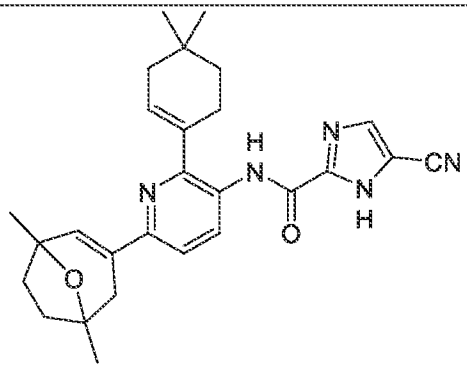
18		13.31
19		5.73
20		37.04
21		1270

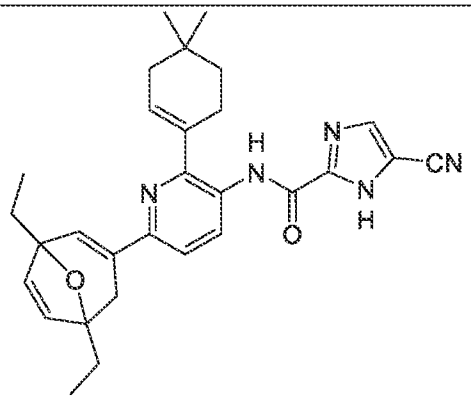
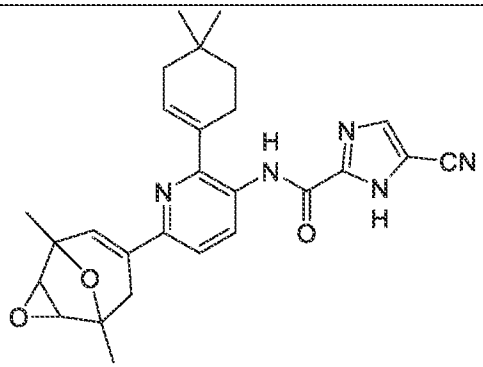
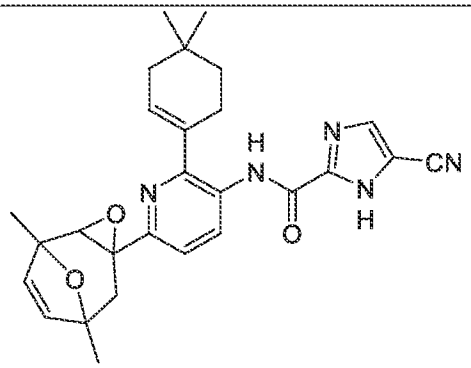
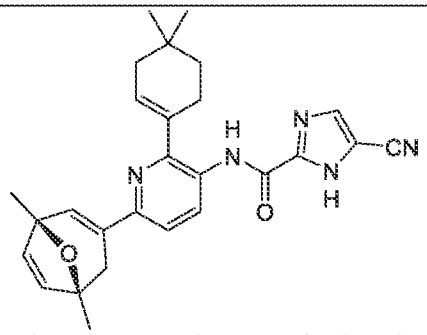
22	 Absolute Stereochemistry not determined (single enantiomer)	359.40
23	 Absolute Stereochemistry not determined (single enantiomer)	261.70
24		14.79
25		34.59
26		102.10

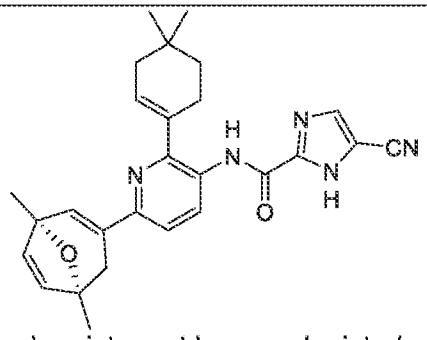
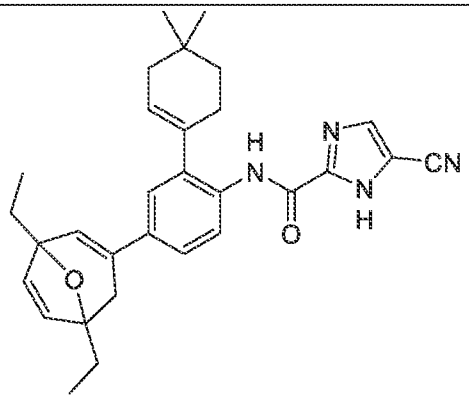
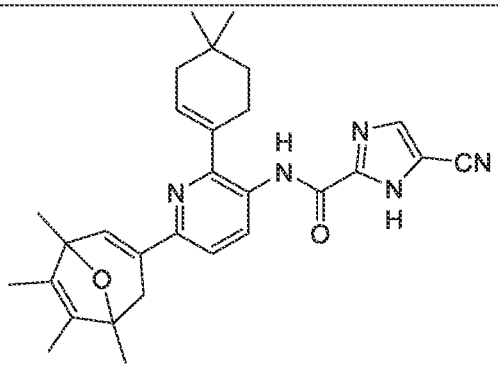
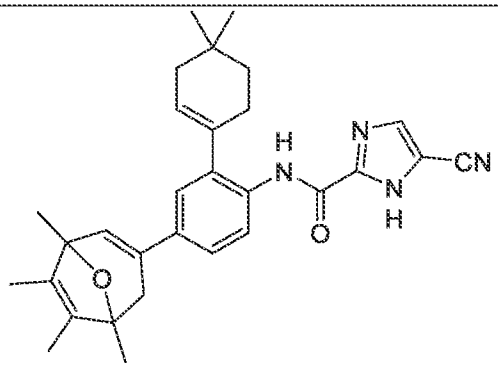
27	 Absolute Stereochemistry not determined (single enantiomer)	1712
28	 Absolute Stereochemistry not determined (single enantiomer)	296.20
29		22.13
31		15.03

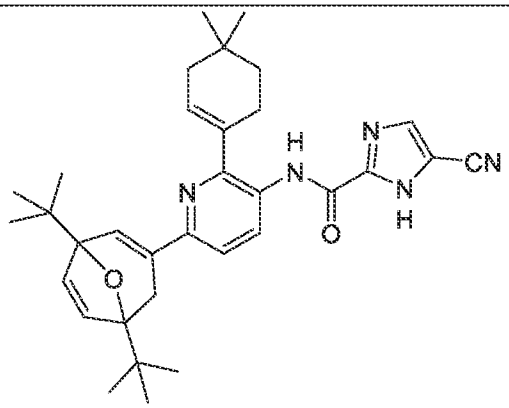
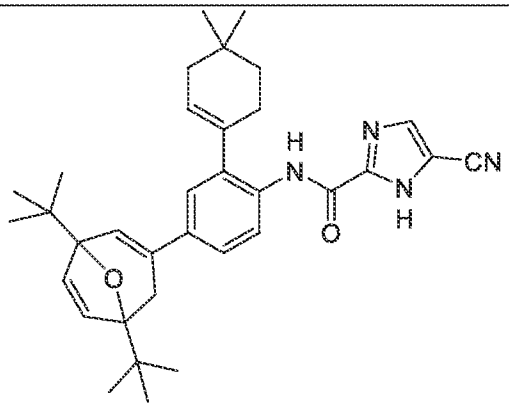
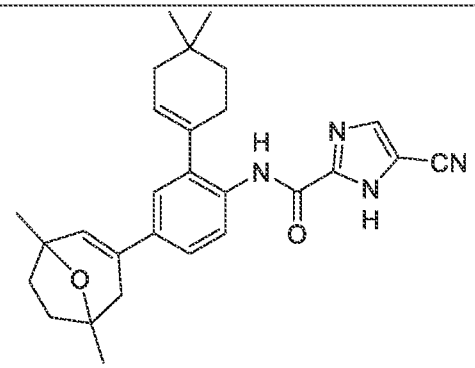
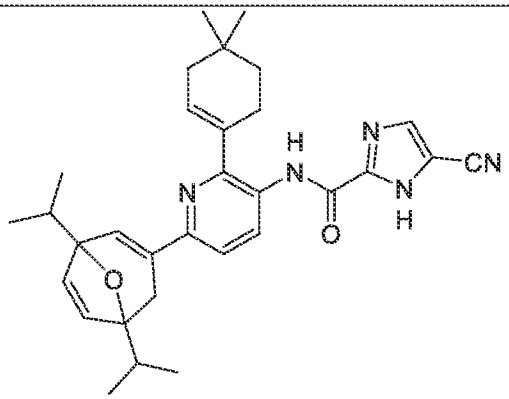
33		7.53
34		36.32
35		5.47
36		6.28

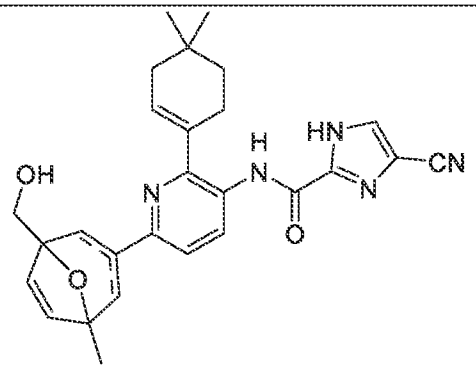
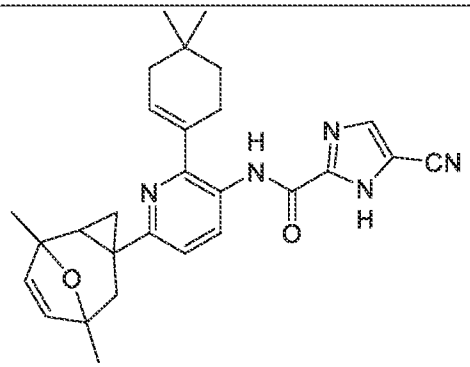
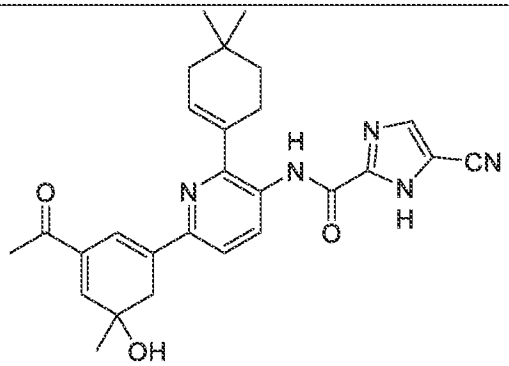
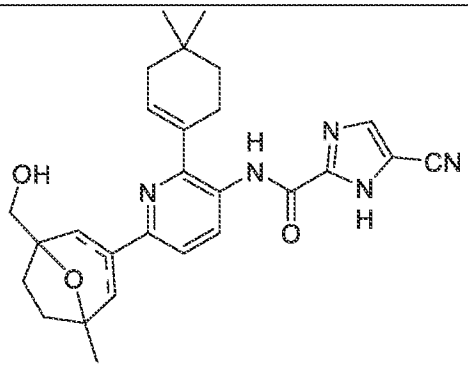
37		8.57
38		9.79
39		10.61
40		8.99

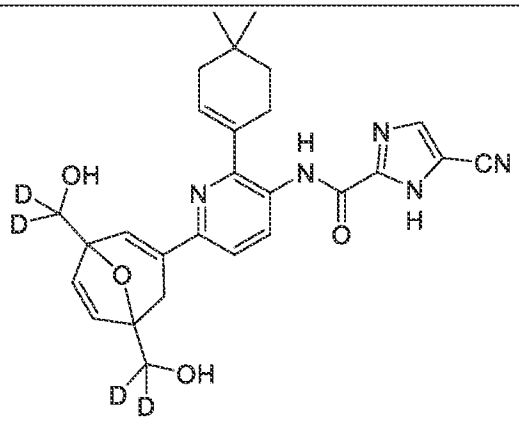
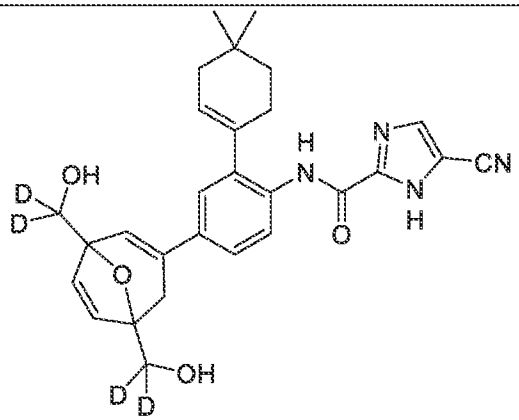
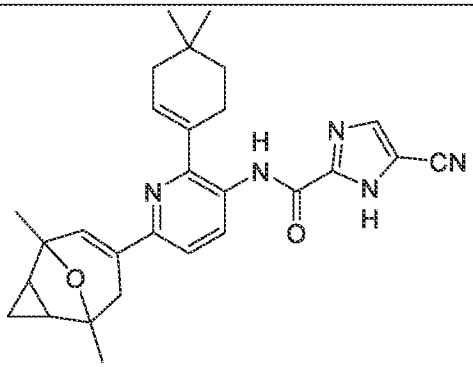
41		17.79
42		17.02
43		12.84
44	 inseperable mixture of double bond tautomers	12.66
45		17.24

46		166.50
47		5.73
48		7.76
49	 Absolute stereochemistry not known: depicted only to distinguish isomers (Single Enantiomer)	10.25

50	 Absolute stereochemistry not known: depicted only to distinguish isomers (Single Enantiomer)	12.22
51		438.10
52		23.45
53		37.95

54		164.90
55		162.60
56		23.68
57		326.5

60	 inseperable mixture of double bond tautomers	2.20
62		25.39
63		10.35
64	 inseperable mixture of double bond tautomers	3.47

65		13.19
66		7.45
68		19.12

EXAMPLE 72 **Pharmaceutical Dosage Forms**

The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

(i) Tablet 1	mg/tablet
Compound X	100.0
Lactose	77.5
Povidone	15.0
Croscarmellose sodium	12.0
Microcrystalline cellulose	92.5
Magnesium stearate	3.0
	300.0

(ii) Tablet 2	mg/tablet
Compound X	20.0
Microcrystalline cellulose	410.0
Starch	50.0
Sodium starch glycolate	15.0
Magnesium stearate	5.0
	500.0

(iii) Capsule	mg/capsule
Compound X	10.0
Colloidal silicon dioxide	1.5
Lactose	465.5
Pregelatinized starch	120.0
Magnesium stearate	3.0
	600.0

(iv) Injection 1 (1 mg/ml)	mg/ml
Compound X (free acid form)	1.0
Dibasic sodium phosphate	12.0
Monobasic sodium phosphate	0.7
Sodium chloride	4.5
1.0 N Sodium hydroxide solution	
(pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

(v) Injection 2 (10 mg/ml)	mg/ml
Compound X (free acid form)	10.0
Monobasic sodium phosphate	0.3
Dibasic sodium phosphate	1.1
Polyethylene glycol 400	200.0
1.0 N Sodium hydroxide solution	
(pH adjustment to 7.0-7.5)	q.s.
Water for injection	q.s. ad 1 mL

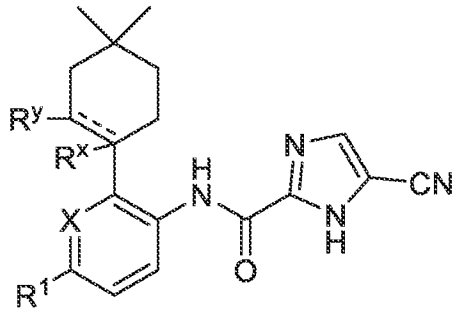
(vi) Aerosol	mg/can
Compound X	20.0
Oleic acid	10.0
Trichloromonofluoromethane	5,000.0
Dichlorodifluoromethane	10,000.0
Dichlorotetrafluoroethane	5,000.0

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

CLAIMS

What is claimed is:

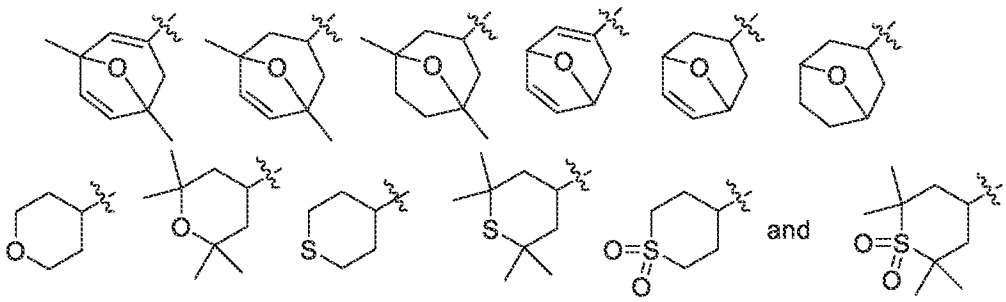
1. A compound of formula (I):



or a prodrug or a salt thereof, wherein:

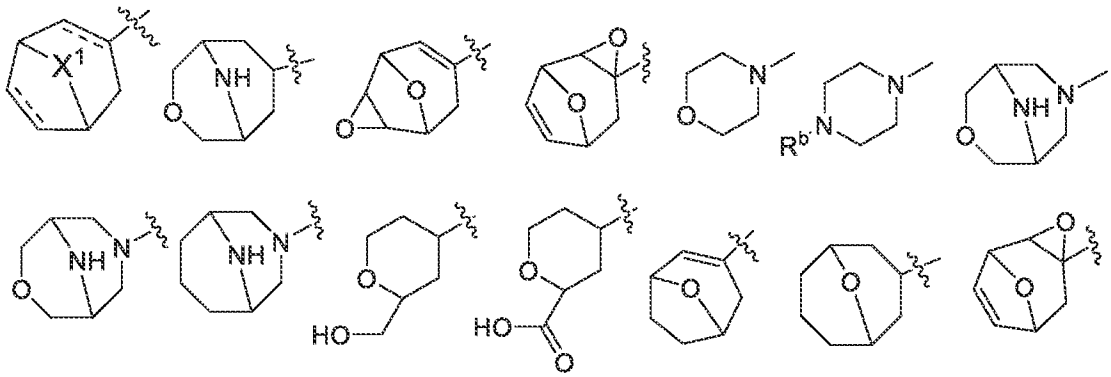
X is N, NR^e, or CH;

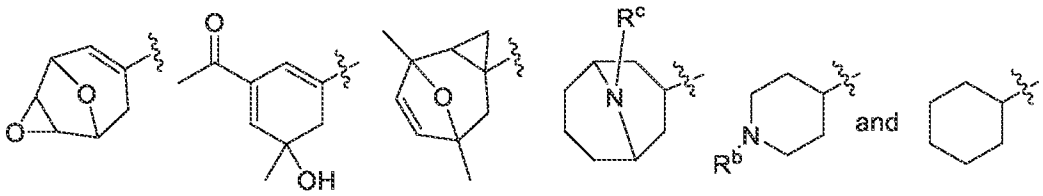
R^1 is selected from the group consisting of:



wherein R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro; or R^1 is R^2 or R^3;

R^2 is:





and is optionally substituted with one or more groups independently selected from D, Cl, F, OH, and (C_1-C_8)alkyl, where (C_1-C_8)alkyl is optionally substituted with one or more groups independently selected from D, Cl, F, OH;

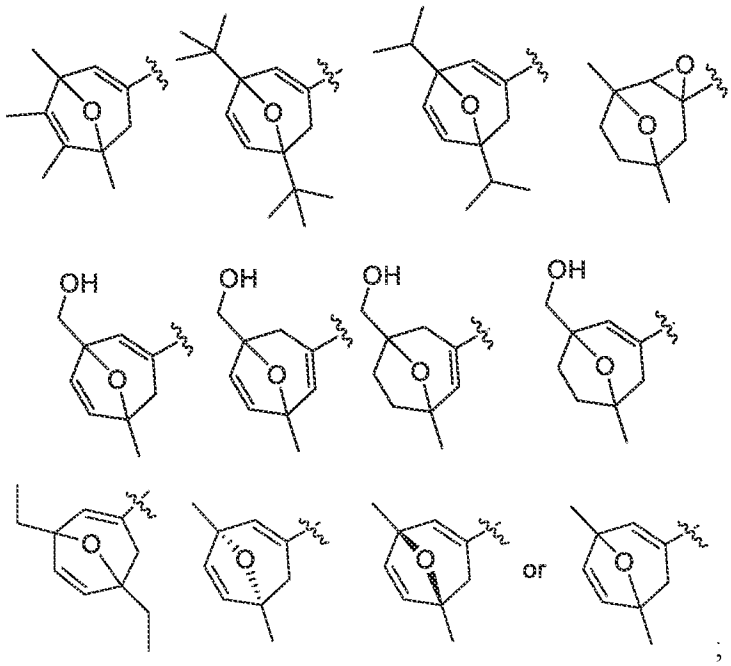
X^1 is NR^a or S;

R^a is selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, and C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^3 is:



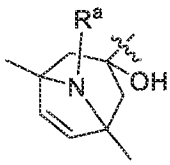
;

R^x and R^y are independently selected from H and D; or R^x and R^y taken together form a double bond;

R^e forms an ammonium oxide with the nitrogen to which it is attached; and

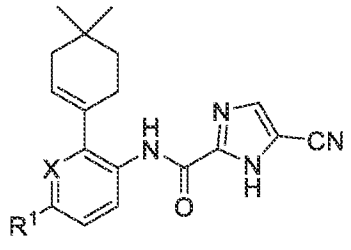
each ------- is independently a single or double bond;

provided that R^2 is not:



wherein R^a is C_1-C_6)alkoxycarbonyl.

2. The compound of claim 1, which is a compound of formula (III):

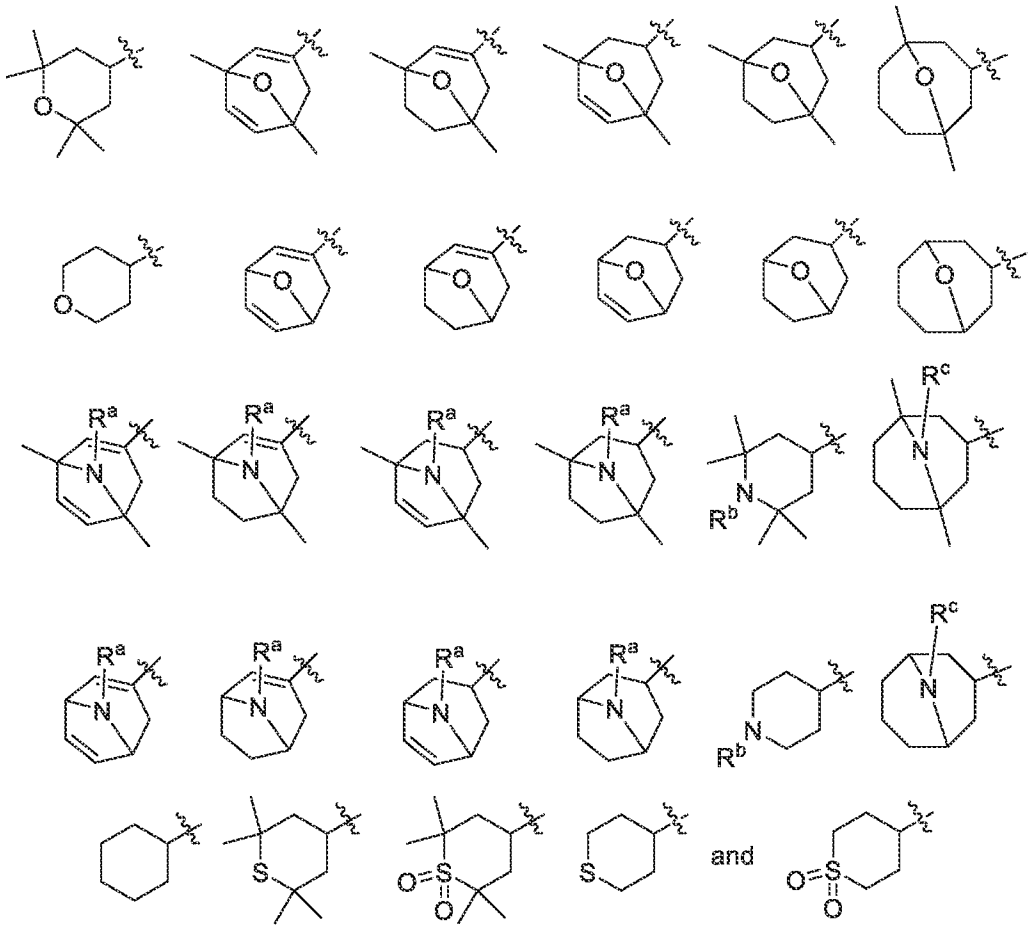


(III)

or a prodrug or a salt thereof, wherein:

X is N or CH;

R^1 is selected from the group consisting of:



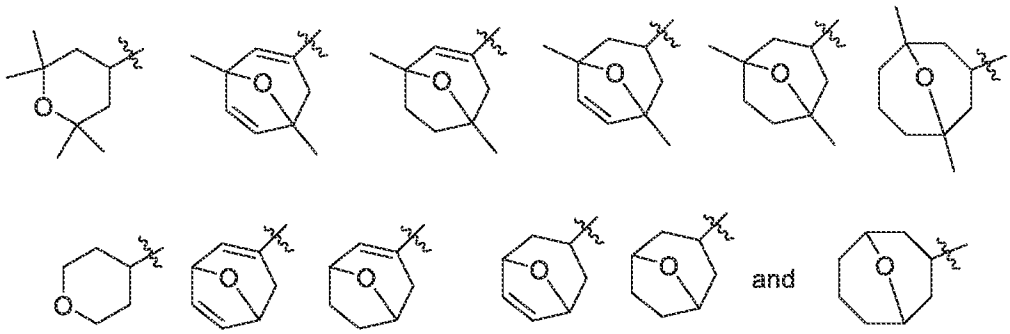
wherein R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro;

R^a is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl;

R^b is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl; and

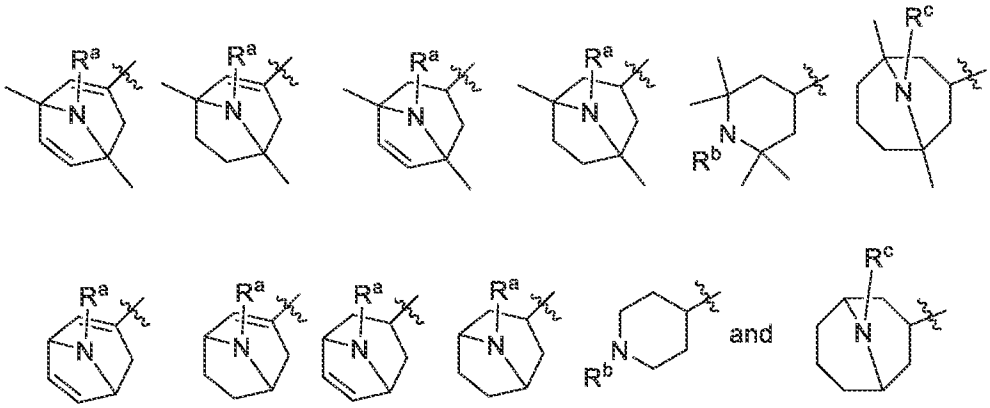
R^c is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl.

3. The compound, prodrug, or salt of claim 2, wherein R^1 is:



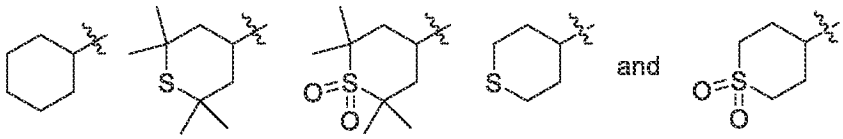
wherein R^1 is optionally substituted with one or more OH and wherein R^1 is substituted with one or more one groups independently selected from deuterium, chloro, and fluoro.

4. The compound, prodrug, or salt of claim 2, wherein R^1 is:



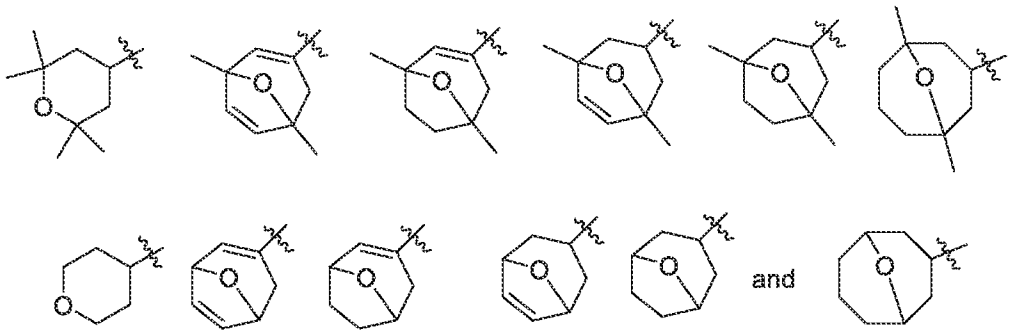
wherein R^1 is optionally substituted with one or more OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro.

5. The compound, prodrug, or salt of claim 2, wherein R^1 is:



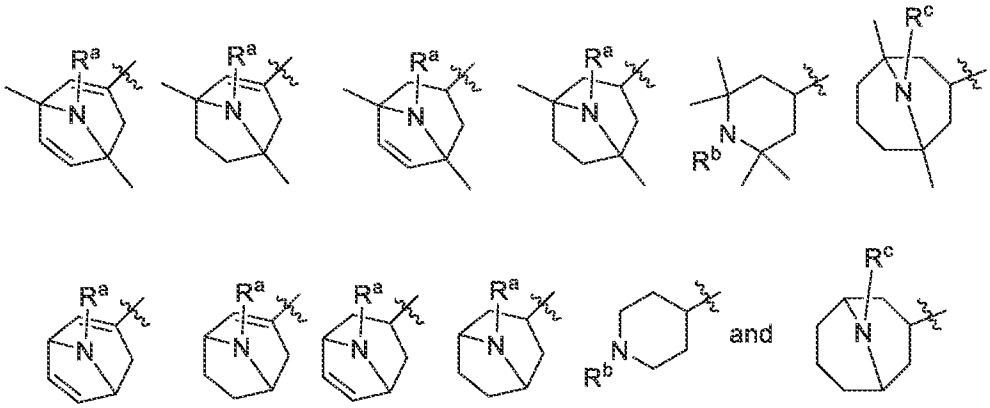
wherein R^1 is optionally substituted with one or more OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro.

6. The compound, prodrug, or salt of claim 2, wherein R^1 is:



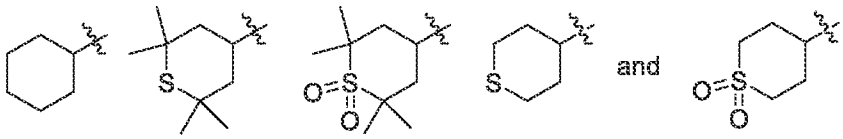
wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro.

7. The compound, prodrug, or salt of claim 2, wherein R^1 is:



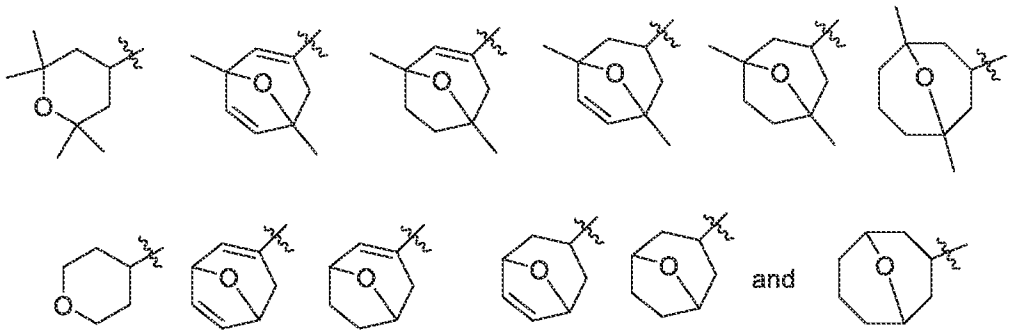
wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro.

8. The compound, prodrug, or salt of claim 2, wherein R^1 is:



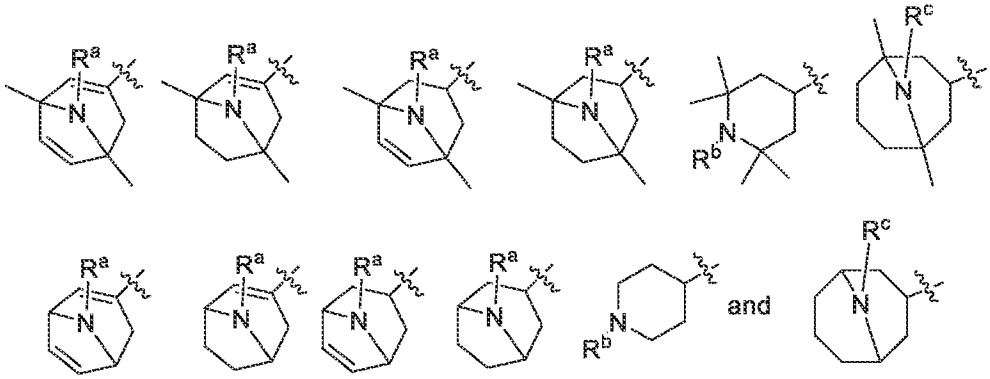
wherein R^1 is substituted with one or more one or more groups independently selected from deuterium, chloro, and fluoro.

9. The compound, prodrug, or salt of claim 2, wherein R^1 is:



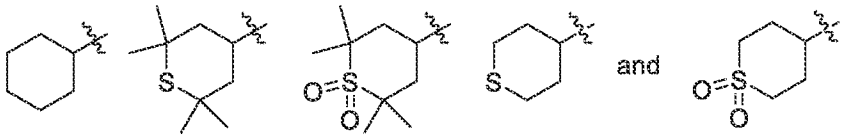
wherein R^1 is substituted with one or more deuterium.

10. The compound, prodrug, or salt of claim 2, wherein R^1 is:



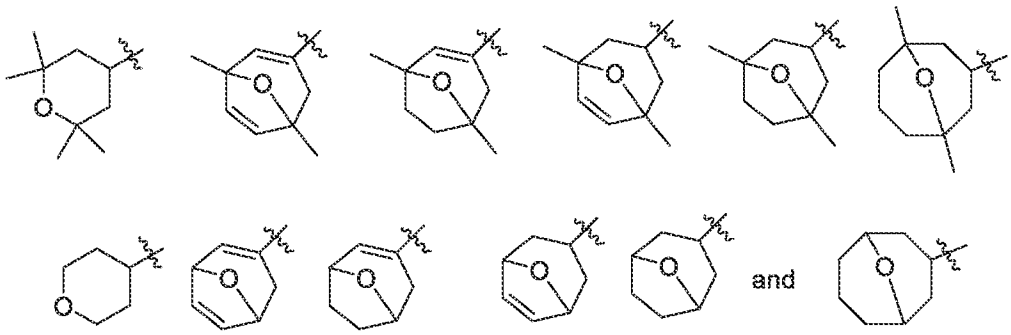
wherein R^1 is substituted with one or more deuterium.

11. The compound, prodrug, or salt of claim 2, wherein R^1 is:



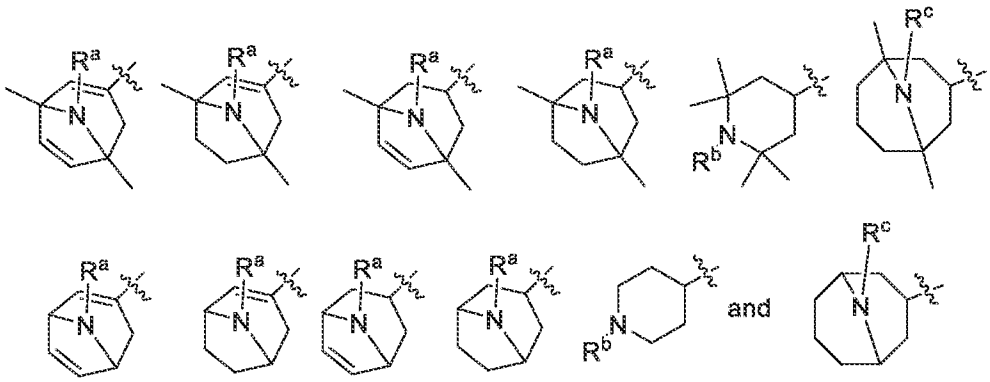
wherein R^1 is substituted with one or more deuterium.

12. The compound, prodrug, or salt of claim 2, wherein R^1 is:



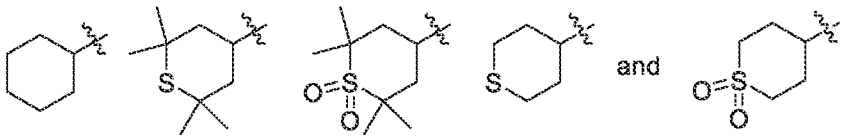
wherein R^1 is substituted with one or more groups independently selected from chloro and fluoro.

13. The compound, prodrug, or salt of claim 2, wherein R^1 is:



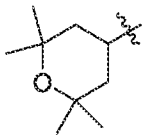
wherein R^1 is substituted with one or more groups independently selected from chloro and fluoro.

14. The compound, prodrug, or salt of claim 2, wherein R^1 is:



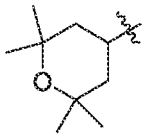
wherein R^1 is substituted with one or more groups independently selected from chloro and fluoro.

15. The compound, prodrug, or salt of claim 2, wherein R^1 is:



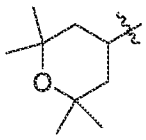
wherein R^1 is substituted with two or more deuterium.

16. The compound, prodrug, or salt of claim 2, wherein R^1 is:



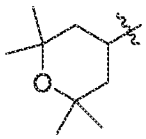
wherein R^1 is substituted with three or more deuterium.

17. The compound, prodrug, or salt of claim 2, wherein R^1 is:



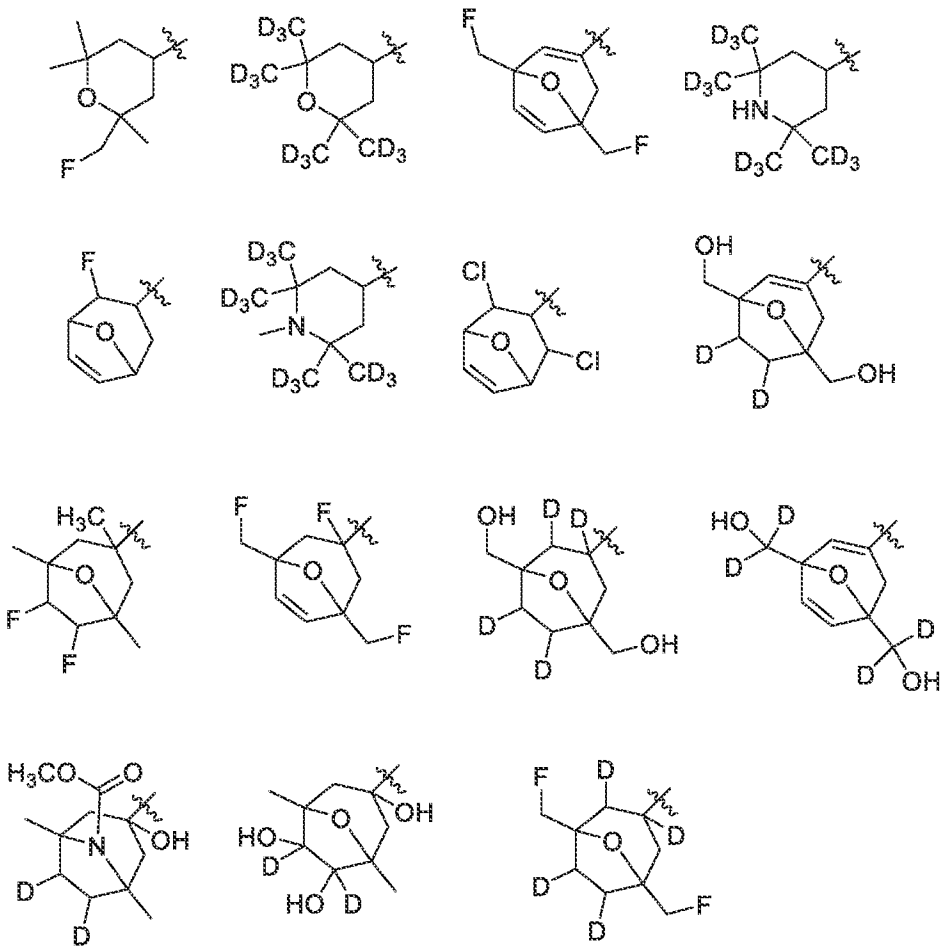
wherein R^1 is substituted with six or more deuterium.

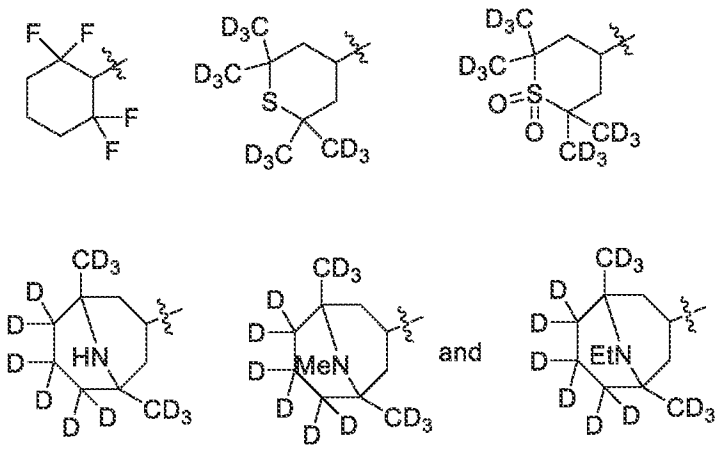
18. The compound, prodrug, or salt of claim 2, wherein R^1 is:



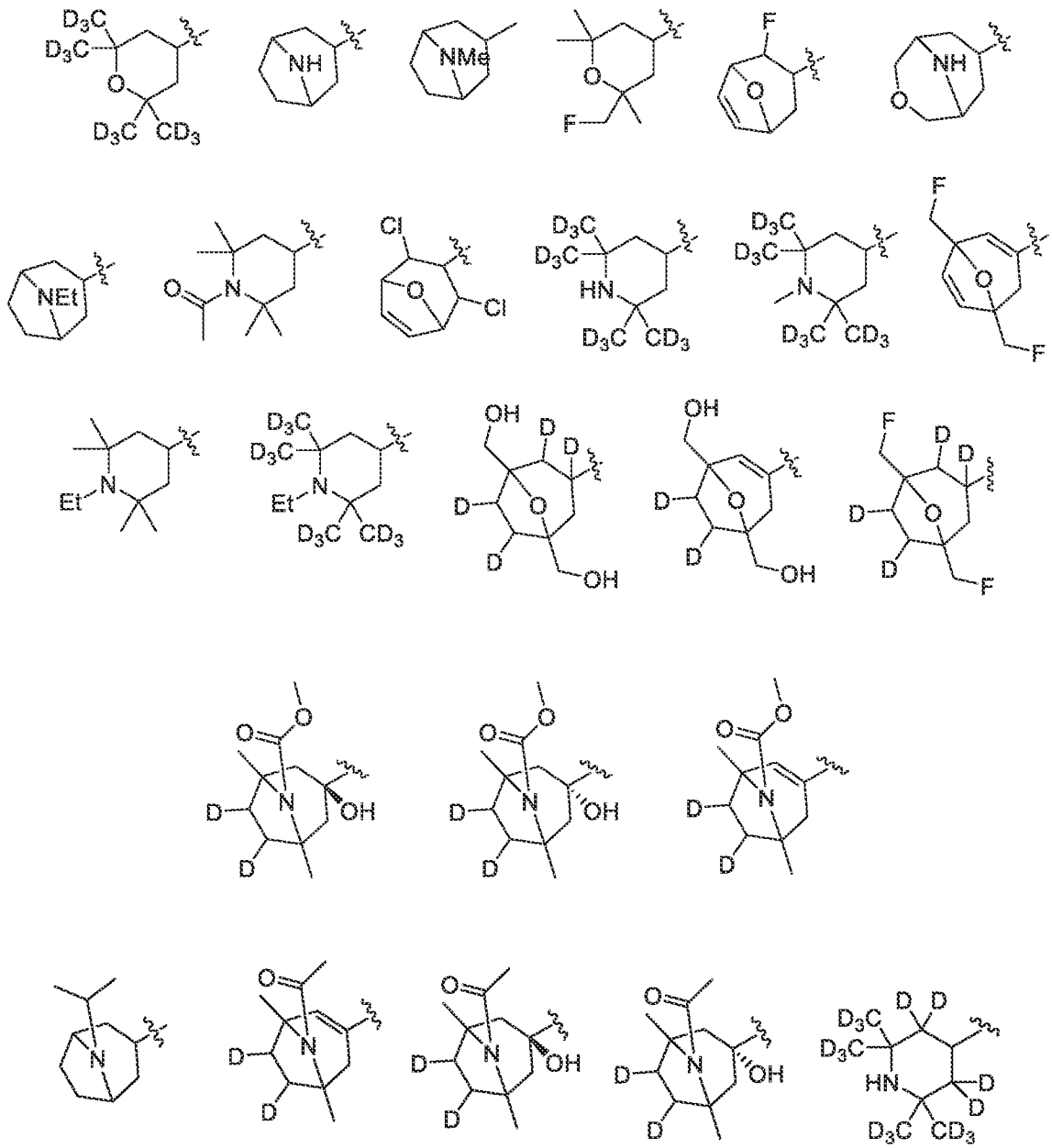
wherein R^1 is substituted with twelve or more deuterium.

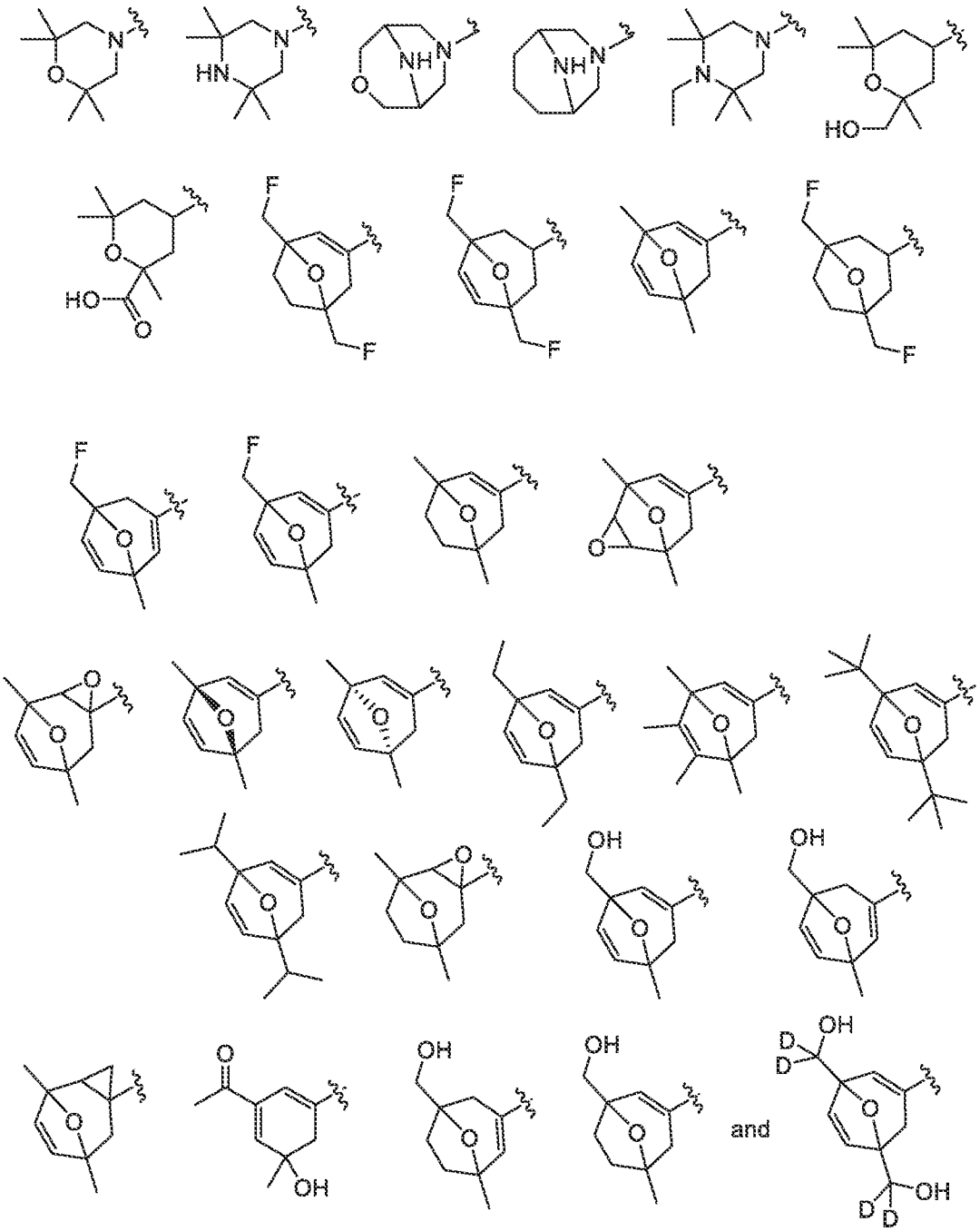
19. The compound, prodrug, or salt of claim 2, wherein R^1 is selected from the group consisting of:





20. The compound, prodrug, or salt of claim 1, wherein R^1 is selected from the group consisting of:

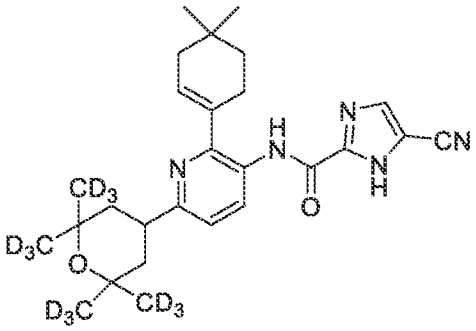




21. The compound, prodrug, or salt of any one of claims 1-20, wherein X is N.

22. The compound, prodrug, or salt of any one of claims 1-20, wherein X is CH.

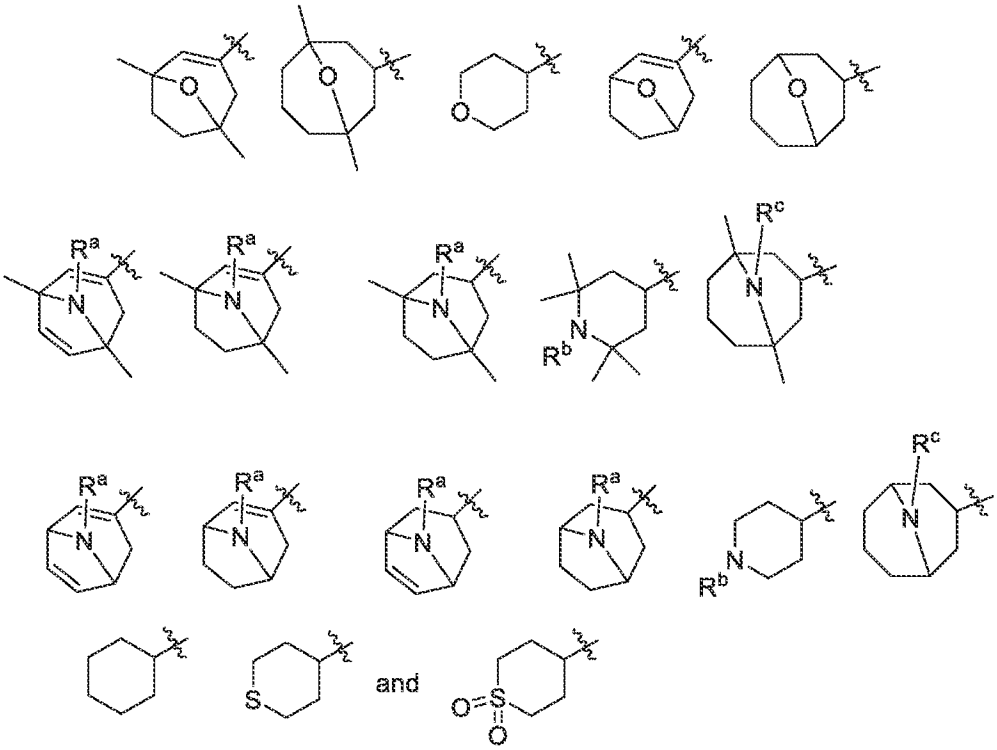
23. The compound, prodrug, or salt of claim 2, which is,



or a prodrug or a salt thereof.

24. The compound of claim 1 or a prodrug or a salt thereof, wherein:

R^1 is selected from the group consisting of:



wherein R^1 is optionally substituted with one or more groups independently selected from OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro;

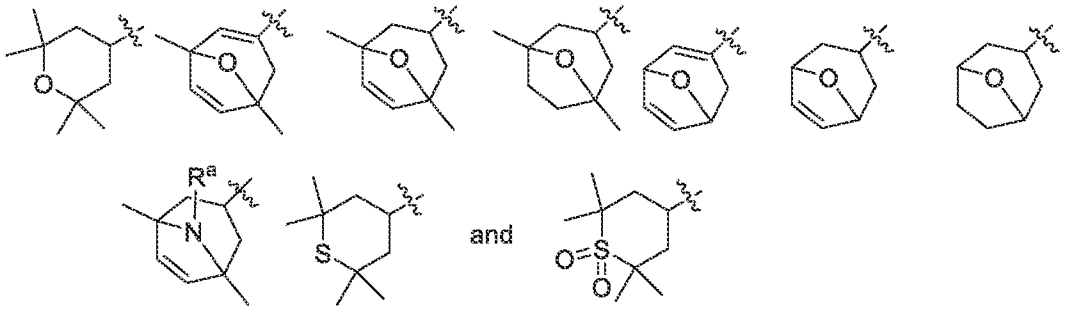
R^a is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, or $(C_1\text{-}C_6)$alkoxycarbonyl;

R^b is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, or $(C_1\text{-}C_6)$alkoxycarbonyl; and

R^c is H, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkanoyl, or $(C_1\text{-}C_6)$alkoxycarbonyl.

25. The compound of claim 1 or a prodrug or a salt thereof, wherein:

R^1 is selected from the group consisting of:

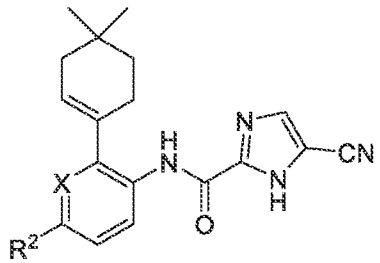


wherein:

R^1 is optionally substituted with one or more groups independently selected from (C_1-C_6)alkyl and OH and wherein R^1 is substituted with one or more groups independently selected from deuterium, chloro, and fluoro; and

R^a is H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, or (C_1-C_6)alkoxycarbonyl.

26. The compound of claim 1, which is a compound of formula (II):

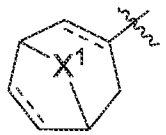


(II)

or a prodrug or a salt thereof, wherein:

X is N or CH;

R^2 is:



;

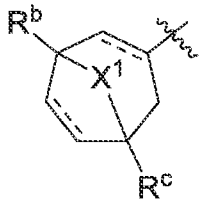
X^1 is NR^a or S;

R^a is selected from H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, and (C_1-C_6)alkoxycarbonyl;

------ is a single or double bond; and

R^2 is optionally substituted with one or more groups independently selected from D, Cl, F, OH, and (C_1-C_6)alkyl, where (C_1-C_6)alkyl is optionally substituted with one or more groups independently selected from D, Cl, F, OH.

27. The compound, prodrug, or salt of claim 26, wherein R^2 is:

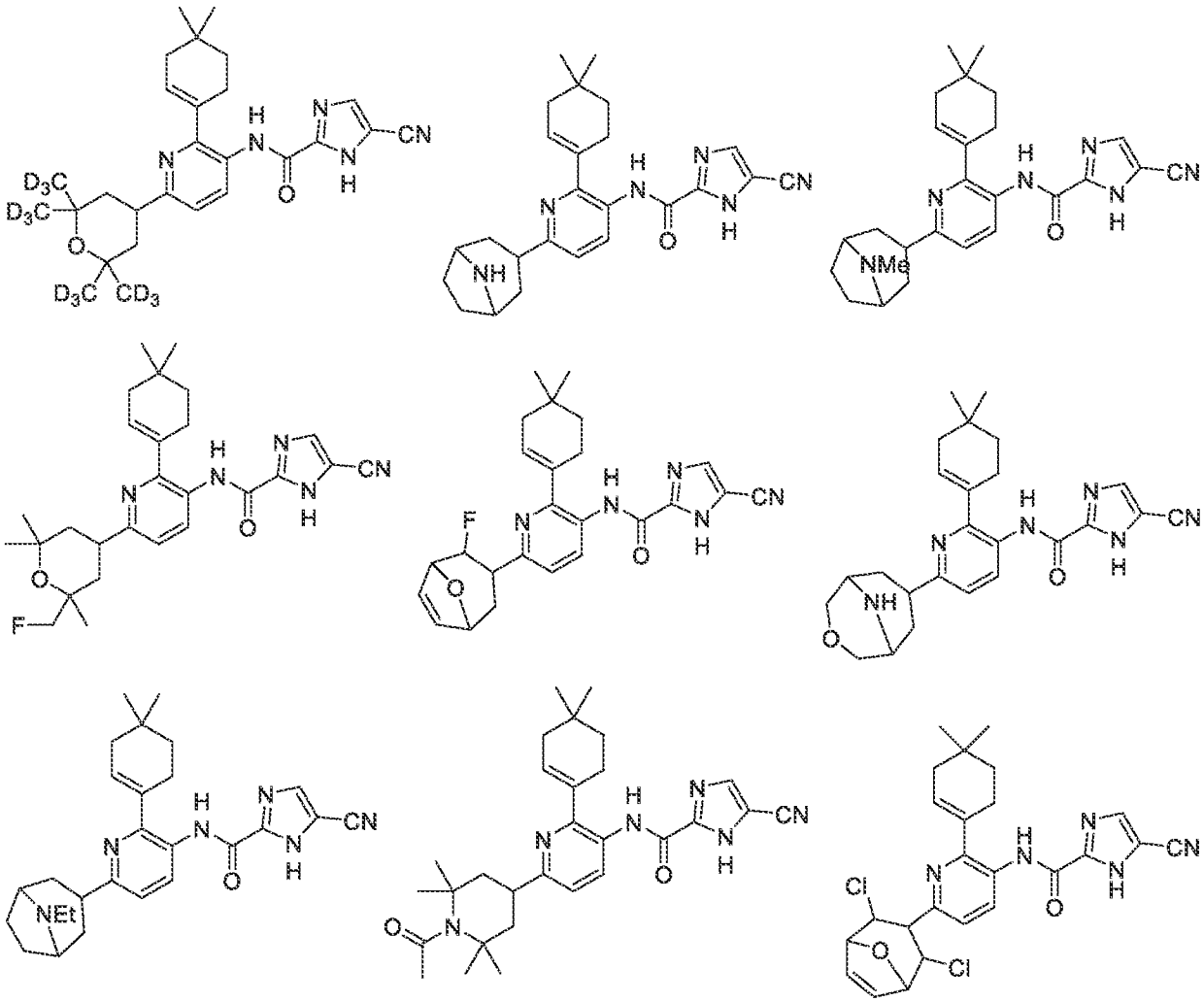


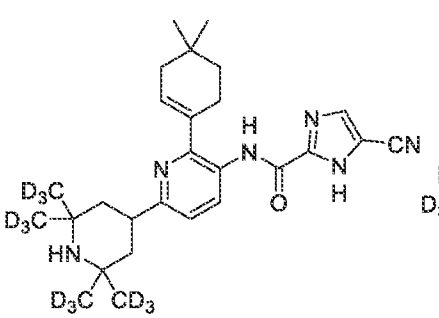
;

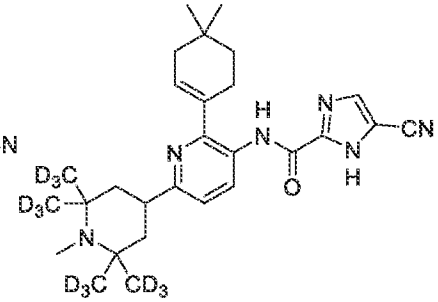
where R^b and R^c are independently selected from D, Cl, F, OH, and $(C_1\text{-}C_6)$alkyl, where $(C_1\text{-}C_6)$alkyl is optionally substituted with one or more groups independently selected from D, Cl, F, OH.

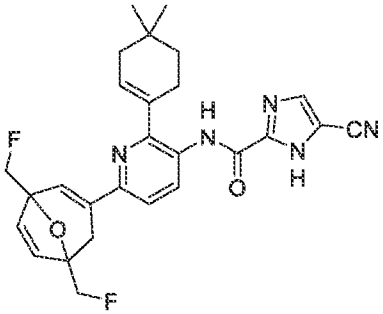
28. The compound, prodrug, or salt of claim 27, wherein R^b and R^c are independently selected from CH_3, CH_2F, and CH_2OH.

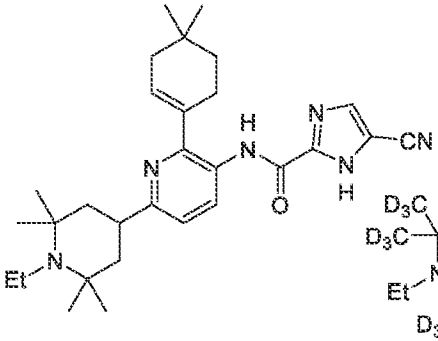
29. The compound, prodrug, or salt of claim 1 selected from the group consisting of:

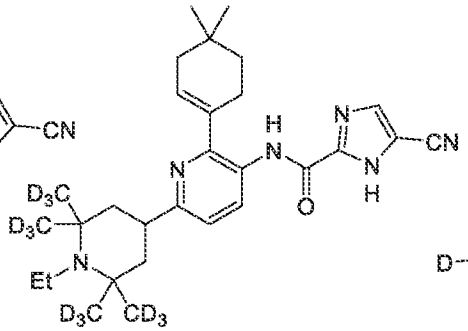


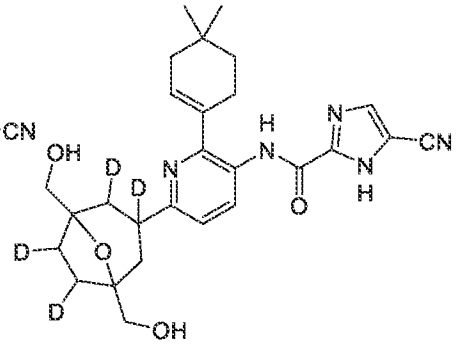


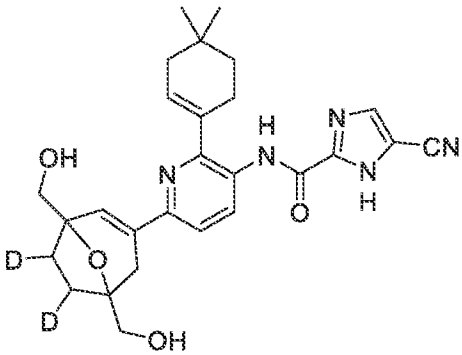


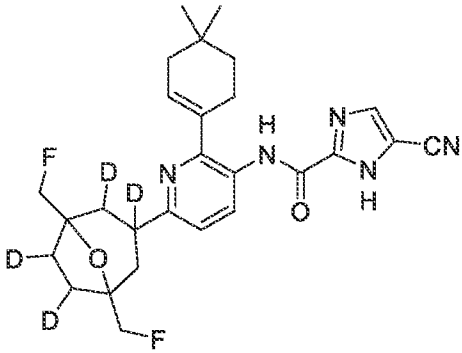


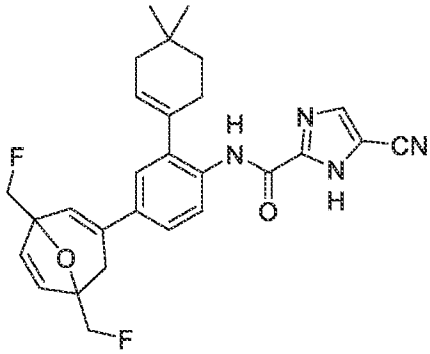


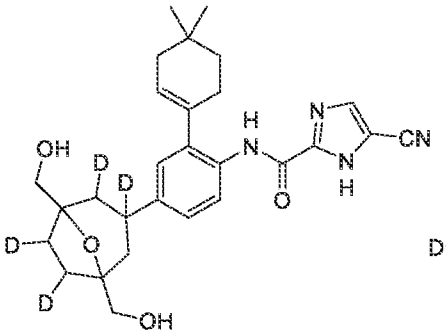


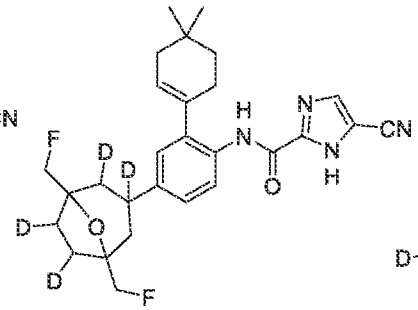


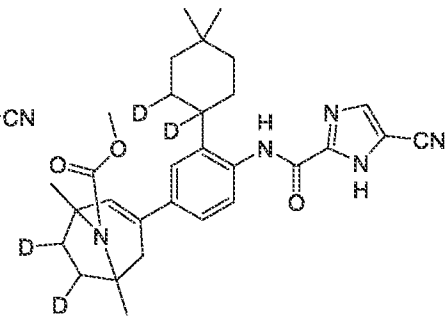


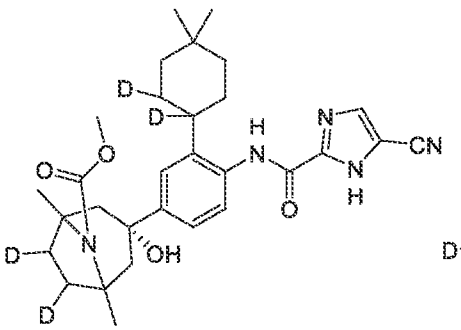


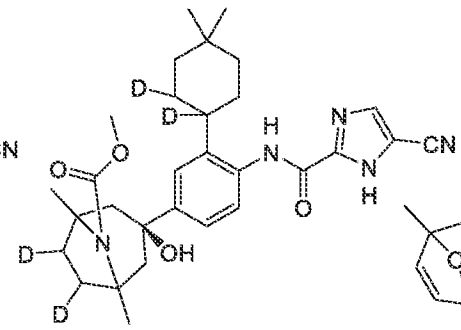


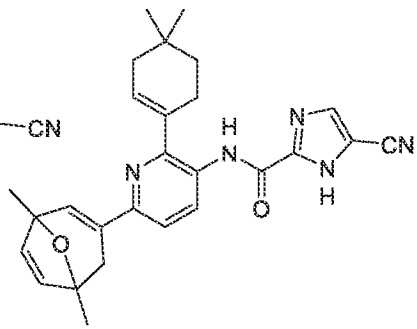


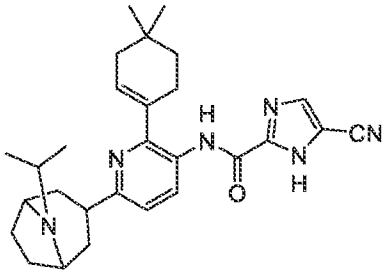


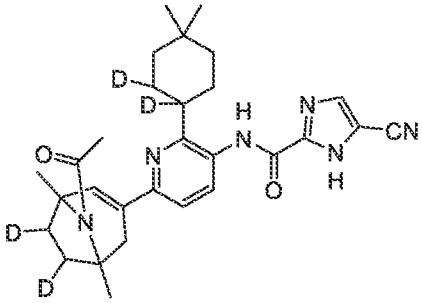


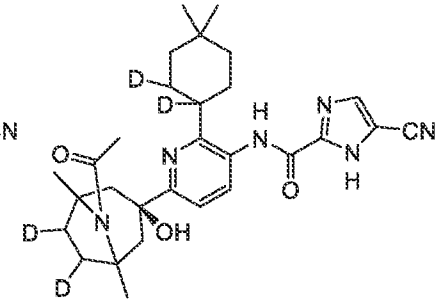


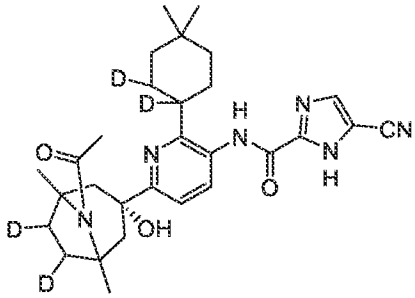


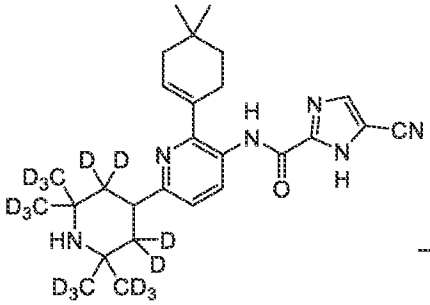


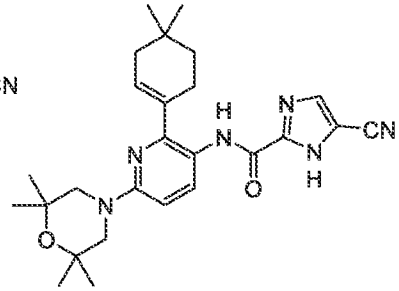


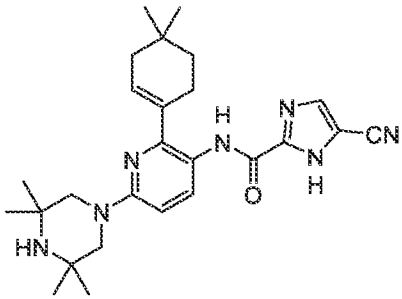


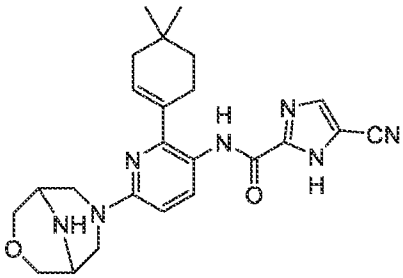


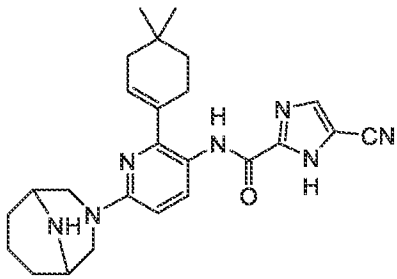


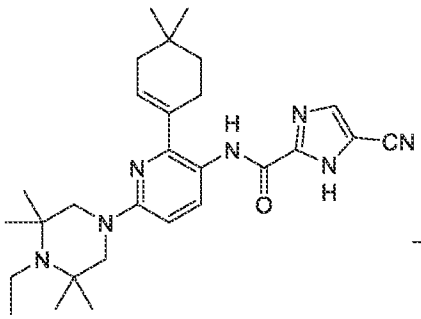


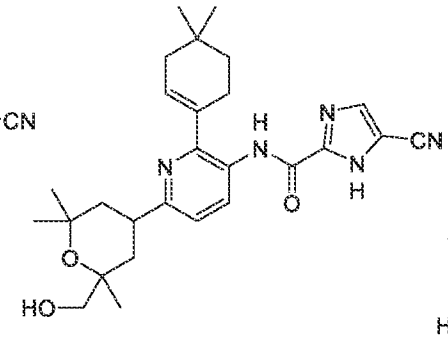


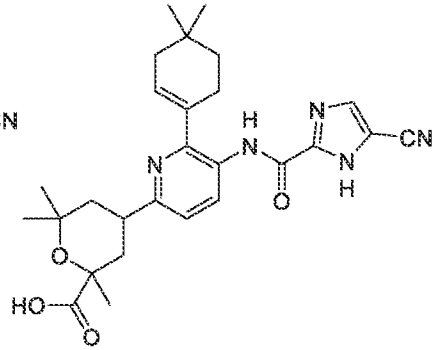


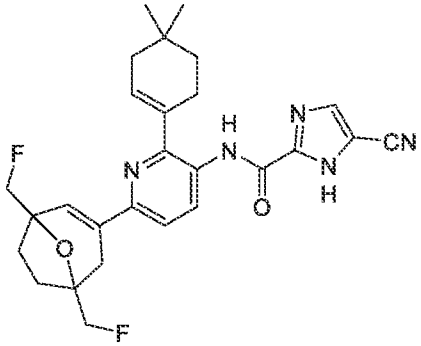


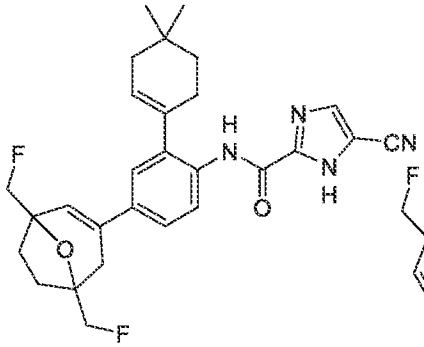


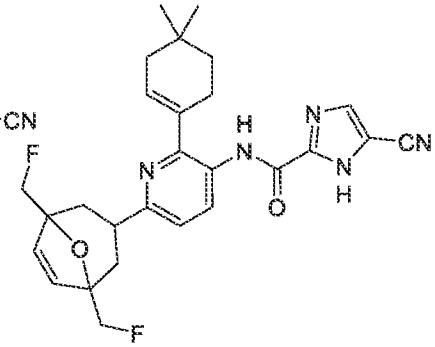


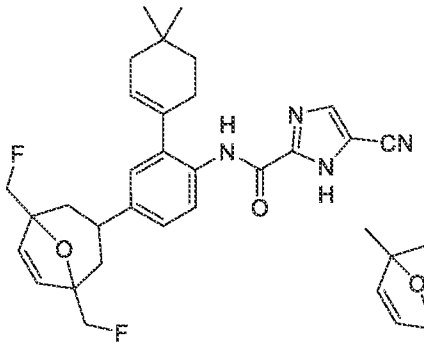


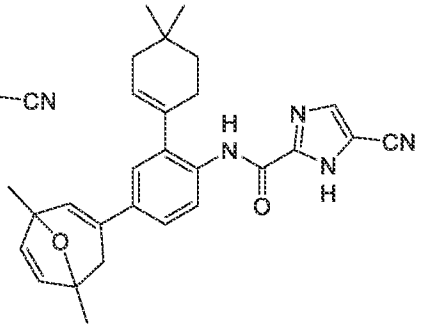


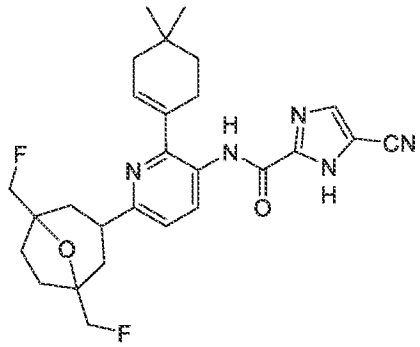


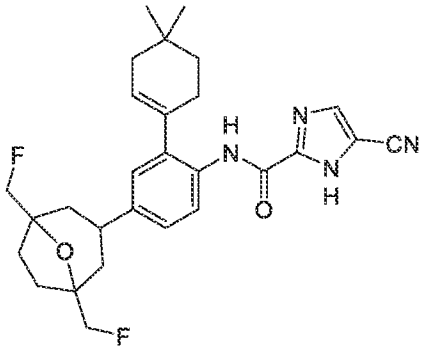


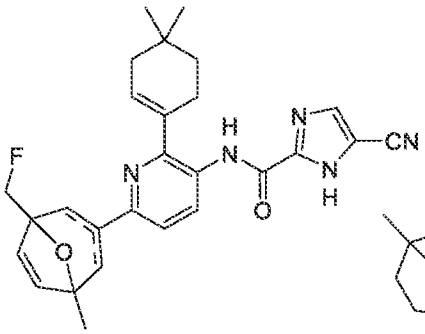


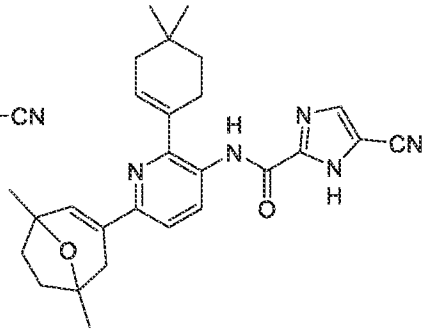


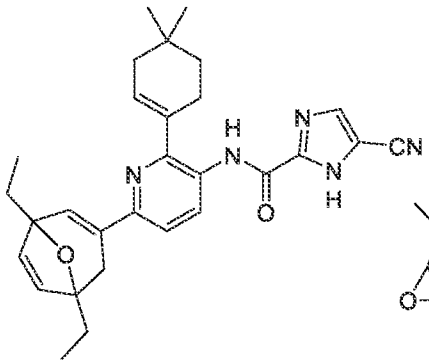


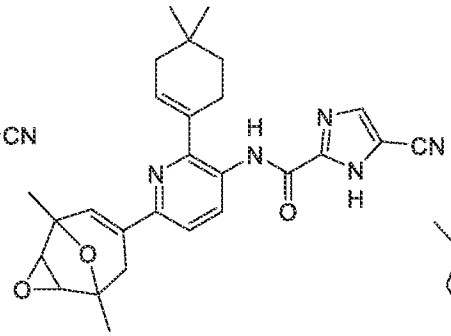


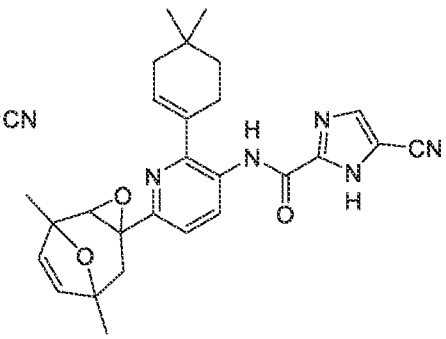


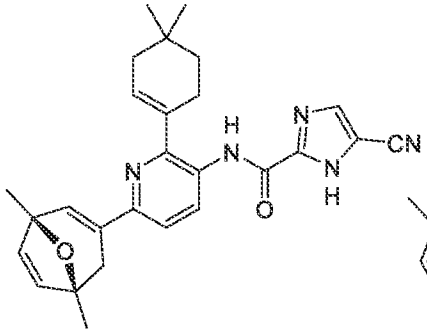


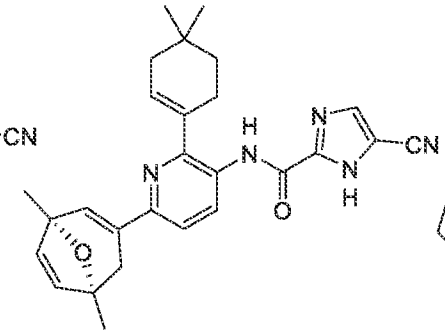


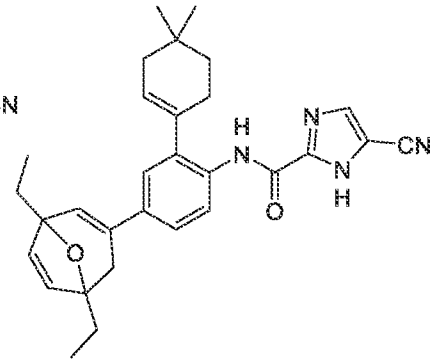


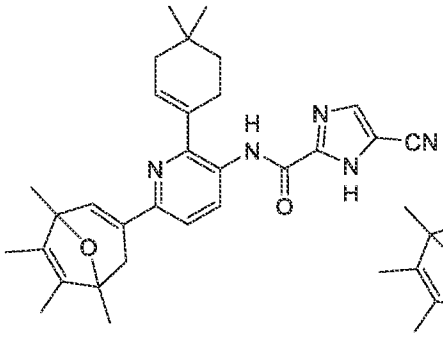


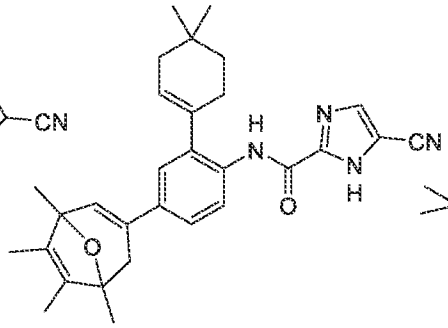


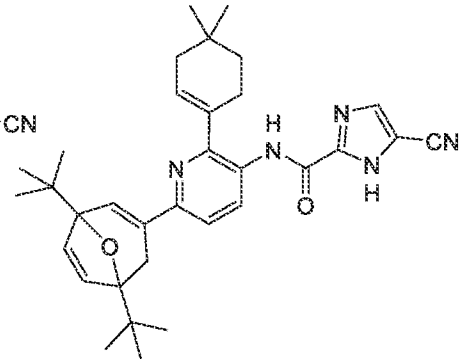


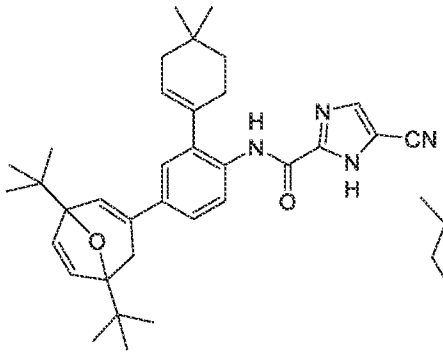


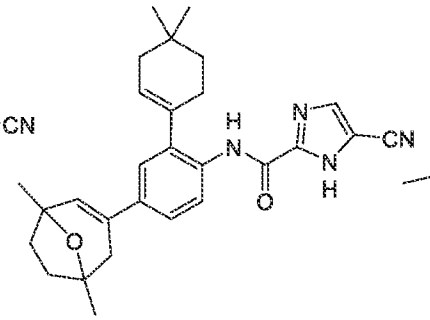


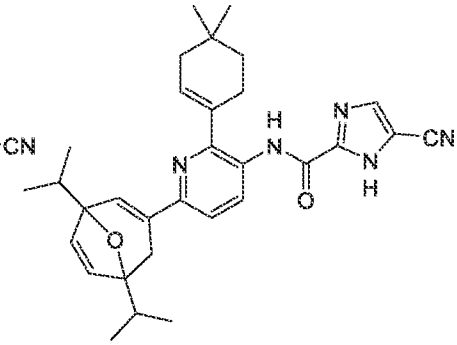


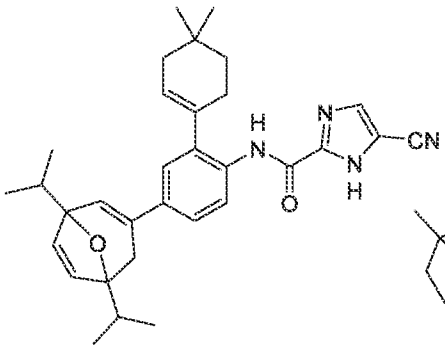


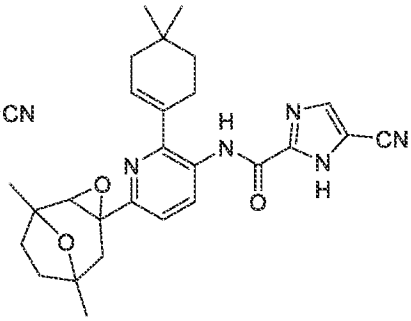


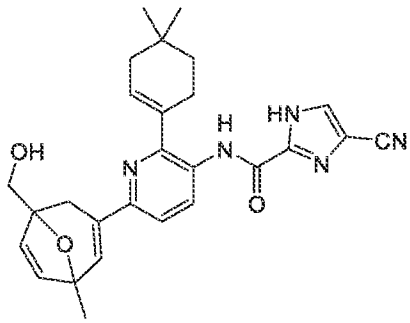


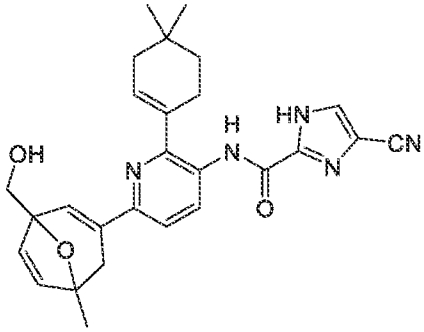


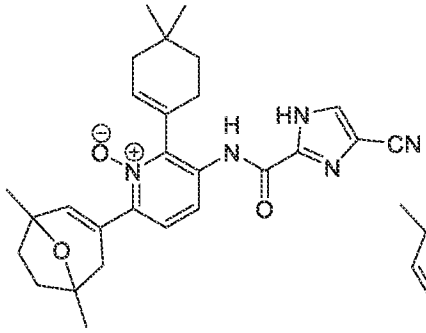


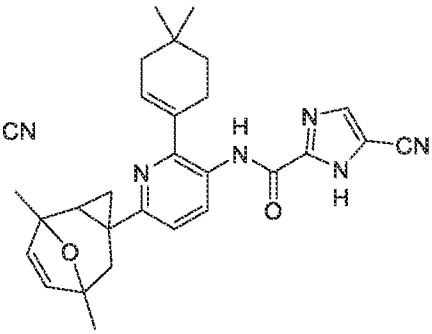


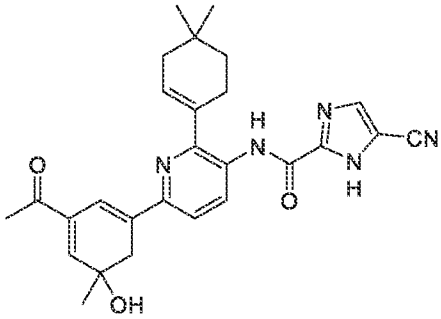


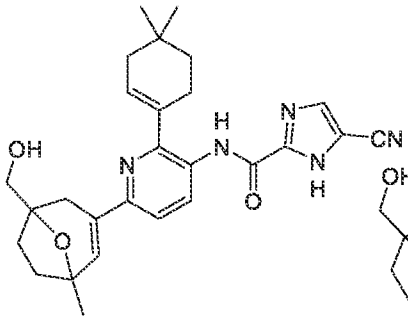


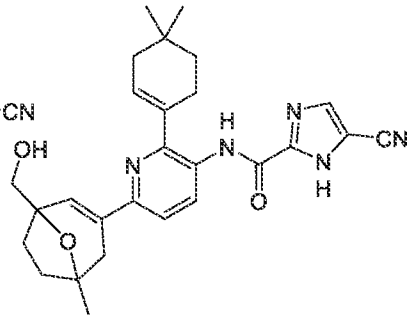


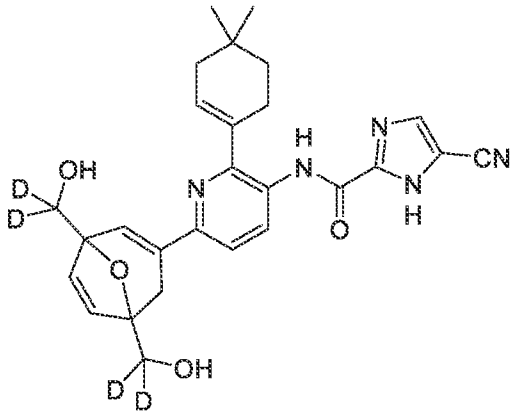


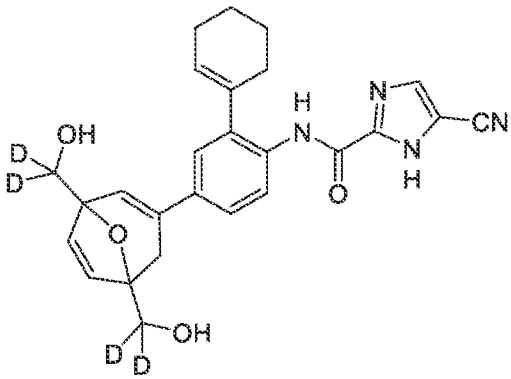


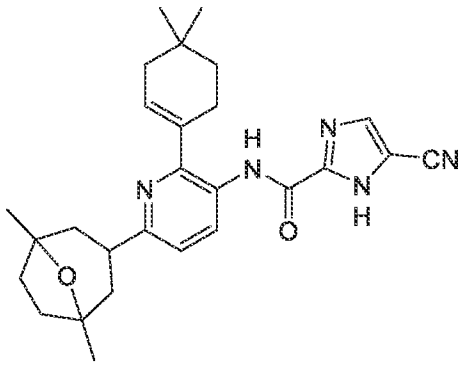












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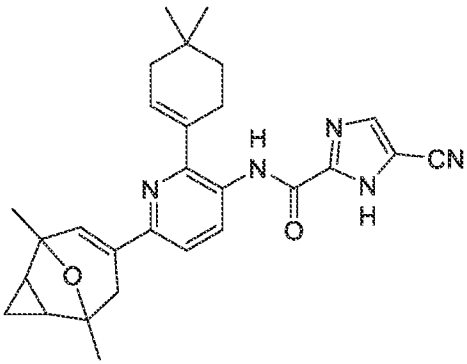

and prodrugs and salts thereof.

30. A pharmaceutical composition comprising a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

31. A method of treating a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, Giant Tenosynovial Carcinoma, brain cancer and tumor metastasis to brain or bone in an animal, comprising administering to the animal a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof.

32. A method of treating a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (*SARS-CoV-2)*, Hepatitis, neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy, Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System disorders, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, tauopathies, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar dementia, epilepsy, any disorder caused by C9ORF72 mutation, age-related loss of motor units, muscular dystrophy and any other form of dementia, radiation induced cognitive impairment, and Crohn's disease in an animal, comprising administering to the animal a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof.

33. A method of treating pain in an animal, comprising administering to the animal a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof.

34. The method of claim 33, wherein the pain is skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, or neurogenic pain.

35. A method of treating cancer in an animal, comprising administering to the animal a

compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof.

36. A method of treating or preventing cancer metastasis in an animal, comprising administering to the animal a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof.

37. The method of claim 35 or 36, wherein the cancer is selected from the group consisting of ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, bladder cancer, pancreatic cancer, glioblastoma, melanoma, lymphoma, leukemia, and hairy cell leukemia.

38. A method of treating an autoimmune disease in an animal, comprising administering to the animal a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof.

39. The method of claim 38, wherein the autoimmune disease is selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, and uveitis.

40. A method for inhibiting the activity of c-fms kinase, comprising contacting the c-fms kinase with a compound or prodrug as described in any one of claims 1-29 or with a salt thereof.

41. The method of claim 40, wherein the c-fms kinase is contacted with the compound or prodrug or the salt *in vitro*.

42. The method of claim 40, wherein the c-fms kinase is contacted with the compound or prodrug as described in any one of claims 1-29 or with a pharmaceutically acceptable salt thereof *in vivo*.

43. A method of treating athlerosclerosis in an animal, comprising administering to the animal a compound of formula (I) as described in any one of claims 1-29 or a prodrug or a pharmaceutically acceptable salt thereof.

44. A method of treating a disease selected from the group consisting of ALS, FTD, C9 related disease, Alzheimers, Parkinsons, MS, Huntington's Disease, Giant Tenosynovial Carcinoma, and Epilepsy in an animal, comprising administering to the animal a compound of formula (I) as described in any one of claims 1-29 or a prodrug or a pharmaceutically acceptable salt thereof.

45. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for use in medical therapy.

46. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, Giant Tenosynovial Carcinoma, brain cancer and tumor metastasis to brain or bone in an animal, any advanced solid tumors and cancer tumor metastasis (especially to the brain, CNS, bone, or lymph nodes).

47. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (*SARS-CoV-2)*, Hepatitis, neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy, Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System disorders, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, tauopathies, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar dementia, epilepsy, any disorder caused by C9ORF72 mutation, age-related loss of motor units, muscular dystrophy and any other form of dementia, radiation induced cognitive impairment, and Crohn's disease.

48. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment of pain.

49. The compound, prodrug, or pharmaceutically acceptable salt of claim 48, wherein the pain is skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, or neurogenic pain.

50. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment cancer.

51. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for treating or preventing cancer metastasis.

52. The compound prodrug, or pharmaceutically acceptable salt of claim 50 or 51, wherein the cancer is selected from the group consisting of ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, bladder cancer, pancreatic cancer, glioblastoma, melanoma, lymphoma, leukemia, and hairy cell leukemia.

53. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for treating athlerosclerosis.

54. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for treating a disease selected from the group consisting of ALS, FTD, C9 related disease, Alzheimers, Parkinsons, MS, Huntington's Disease, Giant Tenosynovial Carcinoma, and Epilepsy.

55. A compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof for the prophylactic or therapeutic treatment an autoimmune disease.

56. The compound, prodrug, or pharmaceutically acceptable salt of claim 55, wherein the autoimmune disease is selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, and uveitis.

57. A compound or prodrug as described in any one of claims 1-29 or a salt thereof for inhibiting the activity of c-fms kinase.

58. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of osteoporosis, Paget's disease, rheumatoid arthritis and other forms of inflammatory arthritis, osteoarthritis, prosthesis failure, osteolytic sarcoma, myeloma, Giant Tenosynovial Carcinoma, brain cancer and tumor metastasis to brain or bone in an animal, any advanced solid tumors and cancer tumor metastasis (especially to the brain, CNS, bone, or lymph nodes) in an animal.

59. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of glomerulonephritis, inflammatory bowel disease, prosthesis failure, sarcoidosis, congestive obstructive pulmonary disease, idiopathic pulmonary fibrosis, asthma, pancreatitis, HIV infection, COVID-19 (*SARS-CoV-2)*, Hepatitis, neurocognitive disorders, chemo brain cognitive impairment or cognitive dysfunction, psoriasis, diabetes, tumor related angiogenesis, age-related macular degeneration, diabetic retinopathy, restenosis, schizophrenia, Parkinson's disease, Alzheimer's disease, Chronic Traumatic Encephalopathy, Huntington Disease, Progressive Bulbar Palsy, Progressive Supranuclear Palsy, Lewy Body Disease, Myotonic Dystrophy, Ataxia Telangiectasia, Bovine Spongiform Encephalopathy, Kuru, Scrapie Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Myasthenia Gravis, Progressive Multifocal Leukoencephalopathy, Central Nervous System disorders, Lupus Vasculitis / Neuropsychiatric Systemic Lupus Erythematosus, Bacterial and Viral Meningitis, corticobasal degeneration, primary age-related tauopathy, tauopathies, argyrophilic grain disease, stroke, traumatic brain injury, ALSP, Sarcopenia, amyotrophic lateral sclerosis, frontotemporal dementia, frontotemporal lobar dementia, epilepsy, any disorder caused by C9ORF72 mutation, age-related loss of motor units, muscular dystrophy and any other form of dementia, radiation induced cognitive impairment, and Crohn's disease in an animal.

60. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating pain in an animal.

61. The use of claim 60, wherein the pain is skeletal pain caused by tumor metastasis or osteoarthritis, or visceral, inflammatory, or neurogenic pain.

62. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating cancer in an animal.

63. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating or preventing cancer metastasis in an animal.

64. The use of claim 62 or 63, wherein the cancer ovarian cancer, uterine cancer, breast cancer, prostate cancer, lung cancer, colon cancer, stomach cancer, bladder cancer, pancreatic cancer, glioblastoma, melanoma, lymphoma, leukemia, or hairy cell leukemia.

65. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating an autoimmune disease in an animal.

66. The use of claim 65, wherein the autoimmune disease selected from the group consisting of systemic lupus erythematosus, rheumatoid arthritis and other forms of inflammatory arthritis, psoriasis, Sjogren's syndrome, multiple sclerosis, and uveitis.

67. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for inhibiting the activity of a c-fms kinase in an animal.

68. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating athlerosclerosis in an animal.

69. The use of a compound or prodrug as described in any one of claims 1-29 or a pharmaceutically acceptable salt thereof to prepare a medicament that is useful for treating a disease selected from the group consisting of ALS, FTD, C9 related disease, Alzheimers, Parkinsons, MS, Huntington's Disease, Giant Tenosynovial Carcinoma, and Epilepsy in an animal.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/032992

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D403/14 C07D405/14 C07D493/08 A61K31/4155 A61K31/4439
C07D498/18 A61P25/28 A61P29/00 A61P35/00

ADD.

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)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/052237 A1 (JANSSEN PHARMACEUTICA NV [BE]; ILLIG CARL R [US] ET AL.) 23 April 2009 (2009-04-23) cited in the application page 3, line 3 - line 4; claims 1,8,12, -----	1,21,22, 26-28, 30-69
X	WO 2006/047277 A2 (JANSSEN PHARMACEUTICA NV [BE]; ILLIG CARL [US] ET AL.) 4 May 2006 (2006-05-04) claims 23-31; example 54 -----	1,21, 30-69
X	WO 2014/151258 A1 (JANSSEN PHARMACEUTICA NV [BE]; CHEN JIE [US] ET AL.) 25 September 2014 (2014-09-25) the whole document -----	1-69

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

☒ See patent family annex.

* Special categories of cited documents :

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"E" earlier application or patent but published on or after the international filing date

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"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
13 August 2024	27/08/2024

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