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(71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: ALLEN, Jennifer R.; 4404 Via Juanita, Newbury Park, California 91320 (US). BOURBEAU, Matthew P.; 23510 Aetna Street, Woodland Hills, California 91367 (US). CHEN, Ning; 2342 Gillingham Circle, Thousand Oaks, California 91362 (US). LIU, Qingyan; 4631 Paseo Girasol, Camarillo, California 93012 (US). PETTUS, Liping H.; 301 Virgo Court, Thousand Oaks, California 91360 (US). SIEGMUND, Aaron C.; 5665 Pembroke Street, Ventura, California 93003 (US).

(74) Agent: BERGAUER, Markus; AMGEN INC., One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

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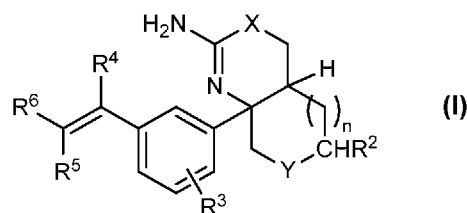
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(54) Title: BICYCLIC THIAZINE AND OXAZINE DERIVATIVES AS BETA-SECRETASE INHIBITORS AND METHODS OF USE



(57) Abstract: The present disclosure provides a new class of compounds useful for the modulation of beta-secretase enzyme (BACE) activity. The compounds have a general Formula (I): (Formula (I)) wherein variables X, Y, R², R³, R⁴, R⁵, R⁶, and n of Formula (I) are defined herein. This disclosure also provides pharmaceutical compositions comprising the compounds, and uses of the compounds and compositions for treatment of disorders and/or conditions related to Aβ plaque formation and deposition, resulting from the biological activity of BACE. Such BACE mediated disorders include, for example, Alzheimer's disease, cognitive deficits, cognitive impairments, and other central nervous system conditions.



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BICYCLIC THIAZINE AND OXAZINE DERIVATIVES AS BETA-SECRETASE INHIBITORS AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application No.
5 62/434,719, filed December 15, 2016 and U.S. Provisional Patent Application No.
62/570,429, filed October 10, 2017, each of which is incorporated by reference herein in its
entirety.

FIELD

The present disclosure relates generally to pharmaceutically active compounds and
10 pharmaceutical compositions thereof for the modulation of beta site amyloid precursor
protein cleaving enzyme (BACE) activity. Provided herein are uses of these compounds and
pharmaceutical compositions thereof for treatment of disorders and/or conditions related to
beta-amyloid plaque formation and deposition, resulting from the biological activity of
BACE. Such BACE mediated disorders include, for example, Alzheimer's disease, cognitive
15 deficits, cognitive impairments, and other central nervous system conditions.

BACKGROUND

Alzheimer's disease (AD) affects greater than 12 million aging people worldwide,
and, importantly, the number affected continues to grow. AD accounts for the majority of
dementias clinically diagnosed after the age of 60. AD is generally characterized by the
20 progressive decline of memory, reasoning, judgement and orientation. As the disease
progresses, motor, sensory, and vocal abilities are affected until there is global impairment of
multiple cognitive functions. The loss of cognitive function occurs gradually. Patients with
severe cognitive impairment and/or diagnosed as end-stage AD are generally bedridden,
incontinent, and dependent on custodial care. The AD patient eventually dies in about nine to
25 ten years, on average, after initial diagnosis. Due to the incapacitating, generally humiliating
and ultimately fatal effects of AD, there is a need to treat AD effectively upon diagnosis.

AD is characterized by two major physiological changes in the brain. The first
change, beta amyloid plaque formation, supports the "amyloid cascade hypothesis" which
conveys the thought that AD is caused by the formation of characteristic beta amyloid (A β)

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peptide deposits in the brain (commonly referred to as A β “plaques” or “plaque deposits”) and in cerebral blood vessels (beta amyloid angiopathy). A wealth of evidence suggests that A β and accompanying amyloid plaque formation is central to the pathophysiology of AD and is likely to play an early role in this intractable neurodegenerative disorder. Yan *et al.*,
5 *Lancet Neurol.* 13(3):319-329 (2014). The second change in AD is the formation of intraneuronal tangles, consisting of an aggregate form of the microtubule-binding protein tau. Besides being found in patients with AD, intraneuronal tangles are also found in other dementia-inducing disorders. Joachim *et al.*, *Alzheimer. Dis. Assoc. Disord.* 6(1):7-34 (1992).

10 Several lines of evidence indicate that progressive cerebral deposition of A β peptide plays a seminal role in the pathogenesis of AD and can precede cognitive symptoms by years or even decades. Selkoe, *Neuron* 6(4):487-498 (1991). Release of A β peptide from neuronal cells grown in culture and the presence of A β peptide in cerebrospinal fluid (CSF) of both normal individuals and AD patients has been demonstrated. Seubert *et al.*, *Nature* 359:325-
15 327 (1992). Autopsies of AD patients have revealed large numbers of lesions comprising A β and tau peptides in areas of the human brain believed to be important for memory and cognition.

Smaller numbers of these lesions in a more restricted anatomical distribution are found in the brains of most aged humans who do not have clinical AD. Amyloid containing
20 plaques and vascular amyloid angiopathy were also found in the brains of individuals with Down’s Syndrome, Hereditary Cerebral Hemorrhage with Amyloidosis of the Dutch-type (HCHWA-D), and other neurodegenerative disorders.

It has been hypothesized that A β peptide formation is a causative precursor or factor in the development of AD. More specifically, deposition of A β peptide in areas of the brain
25 responsible for cognition is believed to be a major factor in the development of AD. A β plaques are primarily composed of A β peptide. A β peptide is derived from the proteolytic cleavage of a large transmembrane amyloid precursor protein (APP), and is a peptide comprised of about 39-42 amino acid residues. A β 1-42 (42 amino acids long) is thought to be the major component of these plaque deposits in the brains of AD patients. Citron, *Trends*
30 *Pharmacol. Sci.* 25(2):92-97 (2004).

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Similar plaques appear in some variants of Lewy body dementia and in inclusion body myositis, a muscle disease. A β peptides also form aggregates coating cerebral blood vessels in cerebral amyloid angiopathy. These plaques are composed of fibrillar A β aggregates that display a characteristic β -sheet structure, a protein fold shared by other peptides such as prions associated with protein misfolding diseases. Research on laboratory rats suggest that the dimeric, soluble form of the peptide is a causative agent in the development of AD and is the smallest synaptotoxic species of soluble amyloid beta oligomer. Shankar *et al.*, *Nat. Med.* 14(8):837-842 (2008).

Several aspartyl proteases, including β -secretase and γ -secretase, are involved in the processing or cleavage of APP, resulting in the formation of A β peptide. β -Secretase (BACE, also commonly referred to as memapsin) is the first to cleave APP to generate two fragments: (1) a first N-terminus fragment (sAPP β) and (2) a second C-99 fragment, which is subsequently cleaved by γ -secretase to generate the A β peptide. APP has also been found to be cleaved by α -secretase to produce sAPP α , a secreted form of APP that does not result in A β plaque formation. This alternate pathway precludes the formation of A β peptide. A description of the proteolytic processing fragments of APP is found, for example, in U.S. Patent Nos. 5,441,870, 5,712,130 and 5,942,400.

BACE is an aspartyl protease enzyme comprising 501 amino acids and responsible for processing APP at the β -secretase specific cleavage site. BACE is present in two forms, BACE 1 and BACE 2, designated as such depending upon the specific cleavage site of APP. β -Secretase is described in Sinha *et al.*, *Nature* 402:537-540 (1999) and International Patent Application Publication No. WO2000/017369. It has been proposed that A β peptide accumulates as a result of APP processing initiated by BACE. Moreover, *in vivo* processing of APP at the β -secretase cleavage site is thought to be a rate-limiting step in A β peptide production. Sabbagh *et al.*, *Alzheimer's Disease Review* 3:1-19 (1997). Thus, inhibition of the BACE enzyme activity is desirable for the treatment of AD.

Studies have shown that the inhibition of BACE may be linked to the treatment of AD. The BACE enzyme is essential for the generation of A β peptide. BACE knockout mice do not produce A β peptide and are free from AD associated pathologies including neuronal loss and certain memory deficits. Cole *et al.*, *Molecular Neurodegeneration* 2:22, pages 1-25 (2007). When crossed with transgenic mice that over express APP, the progeny of BACE

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deficient mice show reduced amounts of A β peptide in brain extracts as compared with control animals. Luo *et al.*, *Nat. Neurosci.* 4(3):231-232 (2001). The fact that BACE initiates the formation of A β peptide, and the observation that BACE levels are elevated in this disease provide direct and compelling reasons to develop therapies directed at BACE inhibition, thus, reducing A β peptide formation and its associated toxicities. To this end, inhibition of β -secretase activity and a corresponding reduction of A β peptide in the brain should provide a therapeutic method for treating AD and other A β peptide or plaque related disorders.

Consequently, the approach of regulating or reducing A β peptide formation and deposition as a potential treatment for AD has received tremendous attention, support and commitment from both researchers and investors alike. A small molecule γ -secretase inhibitor, LY450139 ("Semagacestat"), an A β peptide lowering agent, advanced to phase III clinical trials for the treatment of AD. The pharmacokinetics of semagacestat in plasma, as well as the plasma and cerebral spinal fluid (CSF) A β peptide levels as pharmacodynamic responses to semagacestat administration were evaluated in healthy human subjects in single and multiple doses, and pharmacokinetic and pharmacodynamic changes were also assessed in mild to moderate AD patients in two (2) clinical trials (Henley *et al.*, *Expert Opin. Pharmacother.* 10(10):1657-1664 (2009); Siemers *et al.*, *Clin. Neuropharmacol.* 30(6): 317-325 (2007); and Siemers *et al.*, *Neurology* 66(4):602-604 (2006)). Additional approaches have been taken in attempts to treat AD and plaque-related disorders. See, for example, Yan *et al.*, *Lancet Neurology* 13(3):319-329 (2014).

Furthermore, each of the following exemplary patent application publications describes inhibitors of BACE, useful for treating AD and other β -secretase mediated disorders: WO2014/098831, WO2014/099794, WO2014/099788, WO2014/097038, WO2014/093190, WO2014/066132, WO2014/065434, WO2014/062553, WO2014/062549, WO2014/045162, WO2014/013076, WO2013/182638, WO2013/164730, WO2013/030713, WO2013/028670, WO2013/004676, WO2012/162334, WO2012/162330, WO2012/147762, WO2012/139425, WO2012/138734, US2012/0245157, US2012/0245154, US2012/0238557, WO2011/029803, WO2011/005738, US2011/0152253, WO2010/013794, WO2010/013302, US2010/0160290, US2010/0075957, WO2009/151098, WO2009/134617, US2009/0209755, US2009/0082560, EP2703401 (equivalent of WO2012/146762) and EP1942105.

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The lysosomal aspartic protease Cathepsin D (CatD) is ubiquitously expressed in eukaryotic organisms. CatD activity is essential to accomplish the acid-dependent extensive or partial proteolysis of protein substrates within endosomal and lysosomal compartments therein delivered via endocytosis, phagocytosis or autophagocytosis. CatD may also act at physiological pH on small-size substrates in the cytosol and in the extracellular milieu. Mouse and fruit fly CatD knock-out models have highlighted the multi-pathophysiological roles of CatD in tissue homeostasis and organ development.

Inhibition of protein CatD has been implicated in undesirable side effects. For instance, the inhibition of CatD is believed to be linked to adverse retinal development and retinal atrophy. Particularly, in mice it was found that CatD is essential for the metabolic maintenance of retinal photoreceptor cells and that its deficiency induces apoptosis of the cells, while the loss of inner nuclear layer (INL) neurons is mediated by nitric oxide release from microglial cells. However, in the very same mice, it was also found that no atrophic change was detected in the retina of mice deficient in Cathepsin B or L. Koike *et al.*, *Mol. Cell Neurosci.* 22(2):146-161 (2003). Further, animal models of CatD deficiency are characterized by a progressive and relentless neurodegenerative phenotype similar to that observed in Neuronal Ceroid Lipofuscinoses (NCL), a group of pediatric neurodegenerative diseases known collectively as Batten Disease. It has been shown that the targeted deletion of the pro-apoptotic molecule Bax prevents apoptotic markers, but not neuronal cell death and neurodegeneration induced by CatD deficiency, which suggests that alterations in the macroautophagy-lysosomal degradation pathway can mediate neuronal cell death in NCL/Batten Disease in the absence of apoptosis. Shacka *et al.*, *Autophagy* 3(5):474-476 (2007). Finally, an adverse effect of the inhibition of CatD is evident from the data presented in Folio *et al.*, *PLoS One* 6(7):e21908 (2011). The authors of the PLoS One paper found that knock-down of CatD affects the retinal pigment epithelium, impairs swim-bladder ontogenesis and causes premature death in zebrafish. The main phenotypic alterations produced by CatD knock-down in zebrafish were: 1. abnormal development of the eye and of retinal pigment epithelium; 2. absence of the swim-bladder; 3. skin hyper-pigmentation; 4. reduced growth and premature death. Rescue experiments confirmed the involvement of CatD in the developmental processes leading to these phenotypic alterations.

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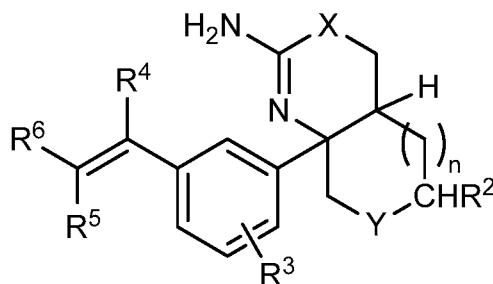
Moreover, such toxicity findings which, in view of the literature, may have played a role in the termination of a human BACE-mediated AD clinical trial. Eli Lilly terminated a phase I clinical trial of LY 2811376 after rat toxicology studies showed that a higher compound dose given for three months damaged the pigment epithelium of the rat's eye. The retinal layer had inclusions and extensive damage. The Phase I dosing trial was terminated and people brought in for eye assessments did not show any abnormalities. (Alzheimer's Research Forum News, 3-31-2011 reporting on Martin Citron's presentation at the AD/PD Conference 3-2011 in Barcelona, Spain).

Hence, it is desirable to provide compounds which modulate the activity of and are selective for BACE, while not suffering from undesirable side effects possibly due to intervention with or the reduction and/or direct or indirect inhibition of the expression and/or function of other proteins or biological pathways.

SUMMARY

The compounds disclosed herein are useful for the modulation of β -secretase activity, and as treatment of AD. Particularly, the compounds provided herein are useful for the regulation or reduction of the formation of A β peptide and, consequently, the regulation and/or reduction of formation of A β plaque both in the brain, as well as in the CNS. To this end, the compounds are useful for the treatment of AD and other β -secretase and/or plaque-related and/or mediated disorders. For example, the compounds are useful for the prophylaxis and/or treatment, acute and/or chronic, of AD and other diseases or conditions involving the deposition or accumulation of A β peptide, and formation of plaque, in the brain.

First, provided herein is a compound of Formula I



I

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or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

X is S or O;

Y is O or NR¹;

5 R¹ is -C(O)C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, or 6-membered nitrogen-containing heteroaryl,

wherein the C₁₋₆alkyl of -C(O)C₁₋₆alkyl and -C(O)OC₁₋₆alkyl is optionally substituted with 1 to 3 fluoro substituents, and

10 wherein the heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy;

R² is H or C₁₋₆alkyl, wherein the C₁₋₆alkyl is optionally substituted with 1 to 3 fluoro substituents;

R³ is halogen;

R⁴ is H or F;

15 one of R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is a 6-membered nitrogen-containing heteroaryl, which heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butynyloxy, 3-buten-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,

20 wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy; and

n is 0 or 1.

Second, provided herein are pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable excipient.

25 Third, provided herein are compounds of Formula I or pharmaceutical compositions thereof for use as a medicament.

Fourth, provided herein are compounds of Formula I or pharmaceutical compositions thereof for use in reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

30 Fifth, provided herein are compounds of Formula I or pharmaceutical compositions thereof for use in treating Alzheimer's disease, cognitive impairment, or a combination thereof in a subject. In addition, provided herein are compounds of Formula I or

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pharmaceutical compositions thereof for use in treating a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject.

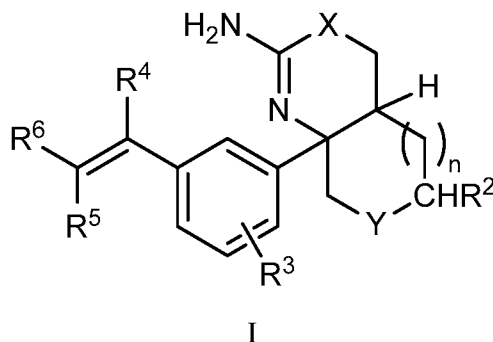
Sixth, provided herein are compounds of Formula I or pharmaceutical compositions thereof for use in reducing formation of plaque in the brain of a subject.

Reference will now be made in detail to embodiments of the present disclosure.

While certain embodiments of the present disclosure will be described, it will be understood that it is not intended to limit the embodiments of the present disclosure to those described embodiments. To the contrary, reference to embodiments of the present disclosure is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the embodiments of the present disclosure as defined by the appended claims.

DETAILED DESCRIPTION

Provided herein as Embodiment 1 is a compound of Formula I



or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

X is S or O;

Y is O or NR¹;

R¹ is -C(O)C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, or 6-membered nitrogen-containing

heteroaryl,

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wherein the C₁₋₆alkyl of -C(O)C₁₋₆alkyl and -C(O)OC₁₋₆alkyl is optionally substituted with 1 to 3 fluoro substituents, and

wherein the heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy;

5 R² is H or C₁₋₆alkyl, wherein the C₁₋₆alkyl is optionally substituted with 1 to 3 fluoro substituents;

 R³ is halogen;

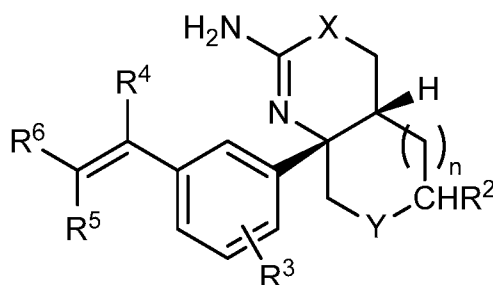
 R⁴ is H or F;

 one of R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is a 6-membered nitrogen-containing heteroaryl, which heteroaryl is optionally substituted with 1 to 3 substituents
10 independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butynyloxy, 3-butyln-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,

 wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy; and

15 n is 0 or 1.

 Provided herein as Embodiment 2 is the compound according to Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound of Formula I is a compound of Formula II

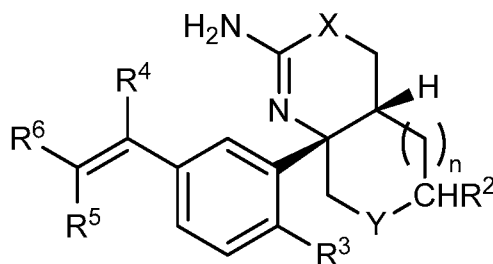


II.

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 Provided herein as Embodiment 3 is the compound according to Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound of Formula I is a compound of Formula III

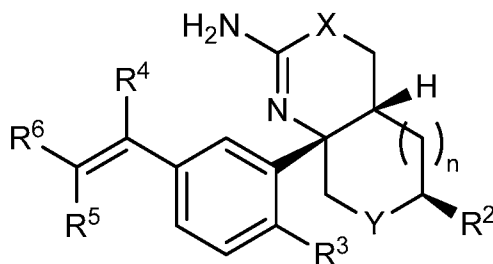
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III.

Provided herein as Embodiment 4 is the compound according to Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer,

5 wherein the compound of Formula I is a compound of Formula III'



III'.

Provided herein as Embodiment 5 is the compound according to any one of Embodiments 1 to 4, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein n is 0.

Provided herein as Embodiment 6 is the compound according to any one of Embodiments 1 to 4, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein n is 1.

Provided herein as Embodiment 7 is the compound according to any one of Embodiments 1 to 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein X is O.

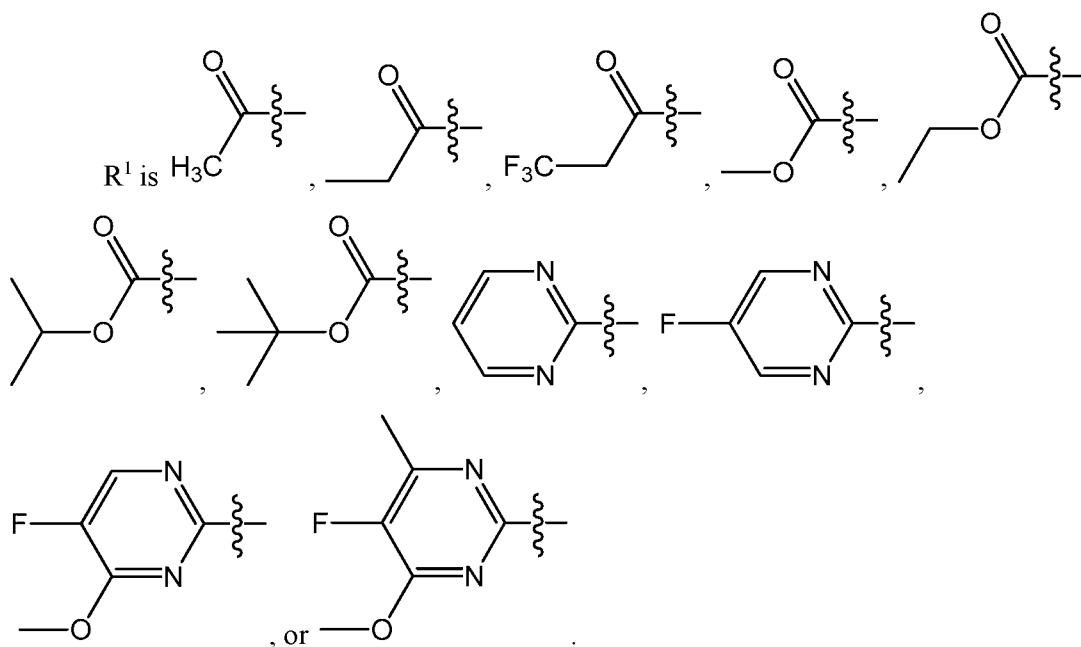
Provided herein as Embodiment 8 is the compound according to any one of Embodiments 1 to 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein X is S.

Provided herein as Embodiment 9 is the compound according to any one of Embodiments 1 to 8, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein Y is O.

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Provided herein as Embodiment 10 is the compound according to any one of Embodiments 1 to 8, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein Y is NR¹.

5 Provided herein as Embodiment 11 is the compound according to any one of Embodiments 1 to 8 and 10, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein



10 Provided herein as Embodiment 12 is the compound according to any one of Embodiments 1 to 8 and 10, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

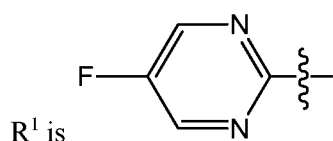
15 R¹ is a 6-membered nitrogen-containing heteroaryl, wherein the heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy.

Provided herein as Embodiment 13 is the compound according to any one of Embodiments 1 to 8, 10, and 12, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

20 R¹ is pyrimidinyl optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy.

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Provided herein as Embodiment 14 is the compound according to any one of Embodiments 1 to 8 and 10 to 13, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein



5 Provided herein as Embodiment 15 is the compound according to any one of Embodiments 1 to 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R² is H, methyl, monofluoromethyl, difluoromethyl, or trifluoromethyl.

10 Provided herein as Embodiment 16 is the compound according to any one of Embodiments 1 to 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R² is trifluoromethyl.

15 Provided herein as Embodiment 17 is the compound according to any one of Embodiments 1 to 17, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein R³ is F.

20 Provided herein as Embodiment 18 is the compound according to any one of Embodiments 1 to 17, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is pyridyl or pyrazinyl, which pyridyl or pyrazinyl is optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butynyloxy, 3-butyln-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,

wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy.

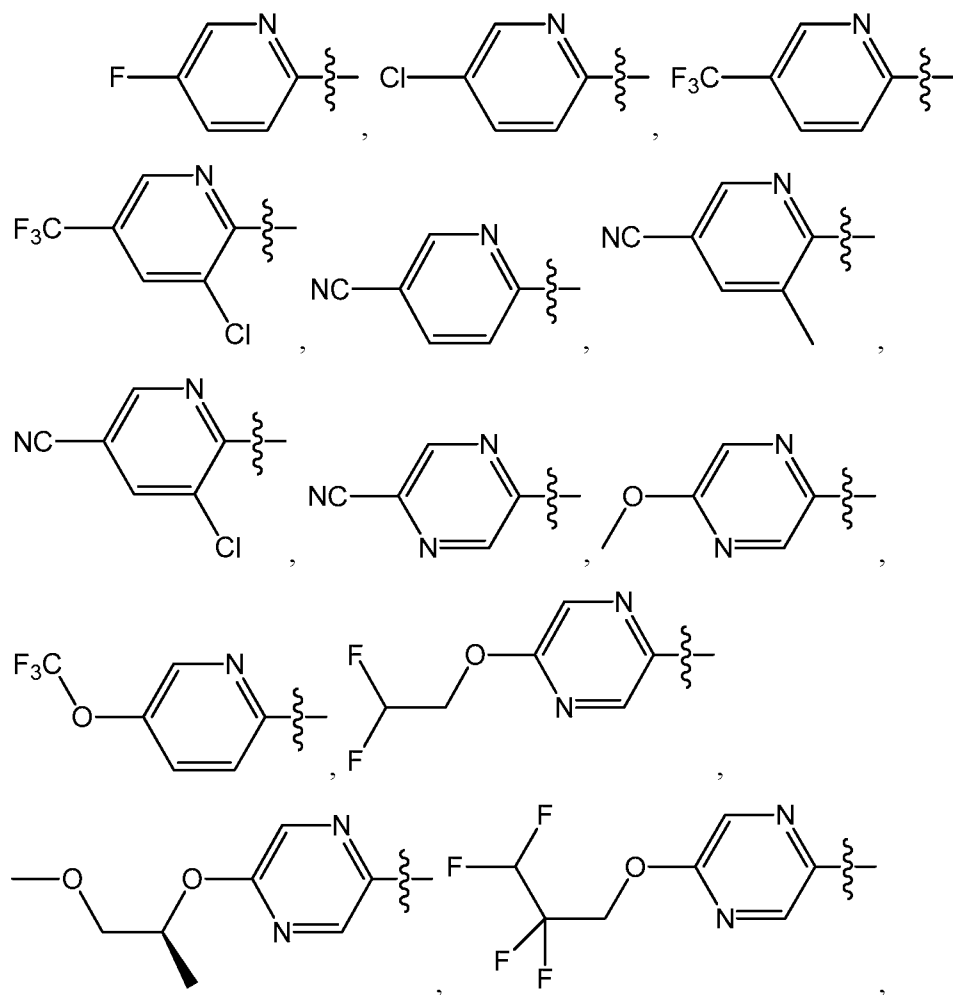
25 Provided herein as Embodiment 19 is the compound according to any one of Embodiments 1 to 17, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is pyridyl or pyrazinyl, which pyridyl or pyrazinyl is optionally substituted with 1 to 3 substituents independently selected from -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butynyloxy, 3-butyln-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,

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wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy.

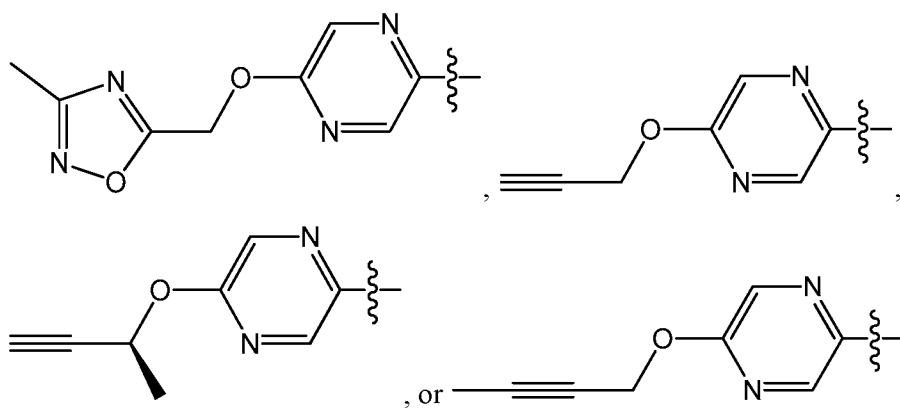
Provided herein as Embodiment 20 is the compound according to any one of Embodiments 1 to 18, or a tautomer thereof, or a pharmaceutically acceptable salt of said

5 compound or tautomer, wherein one of R⁶ and R⁷ is

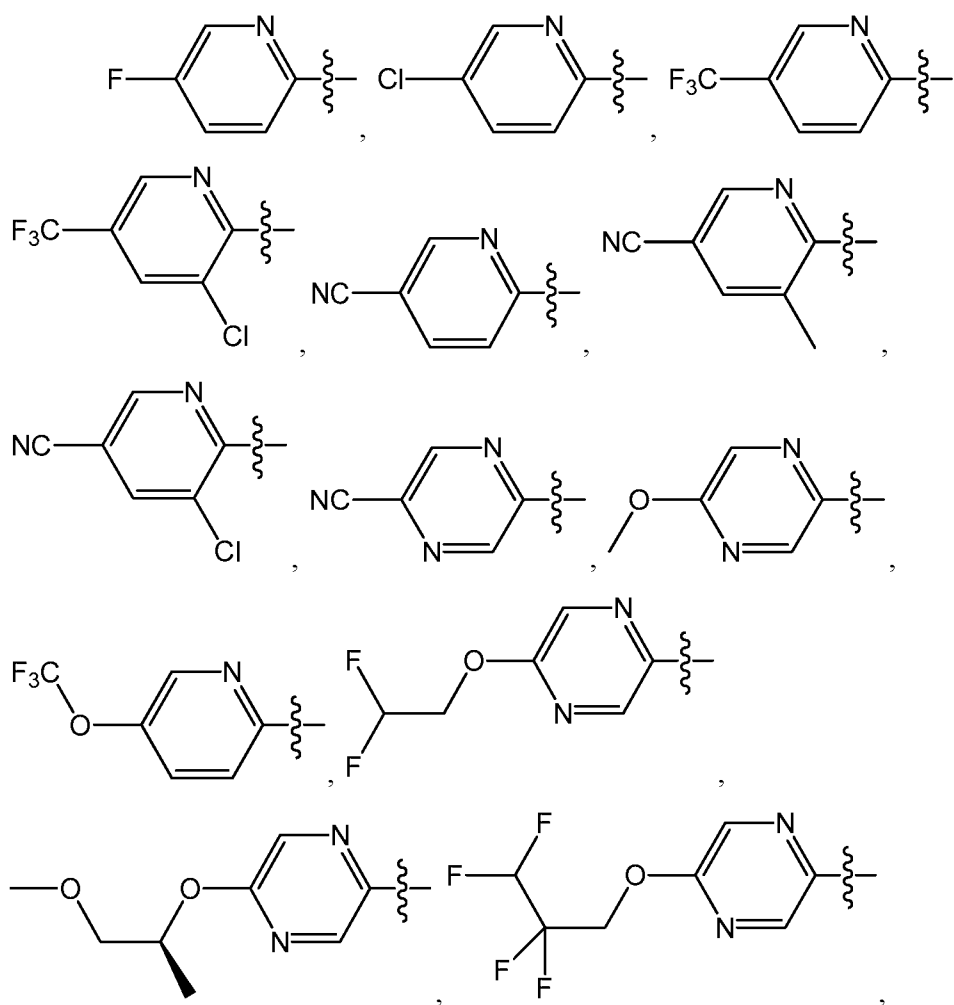


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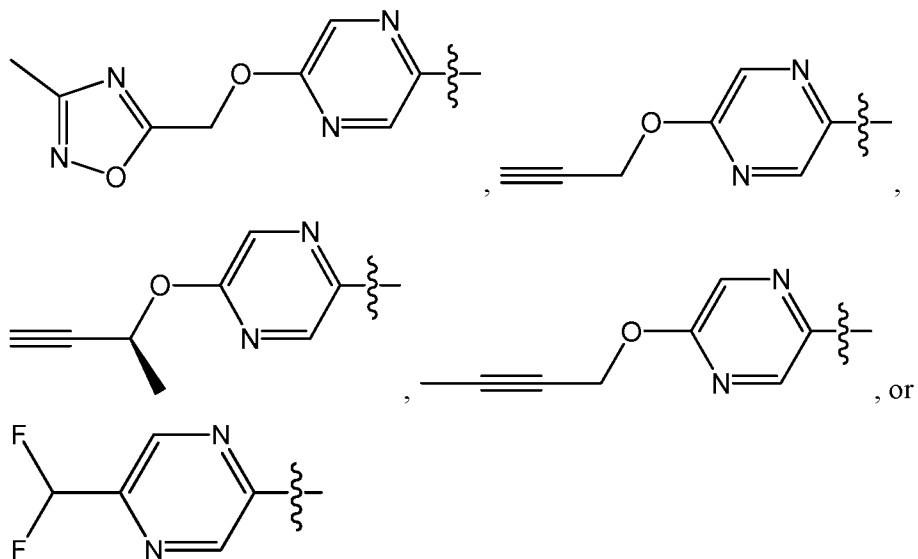
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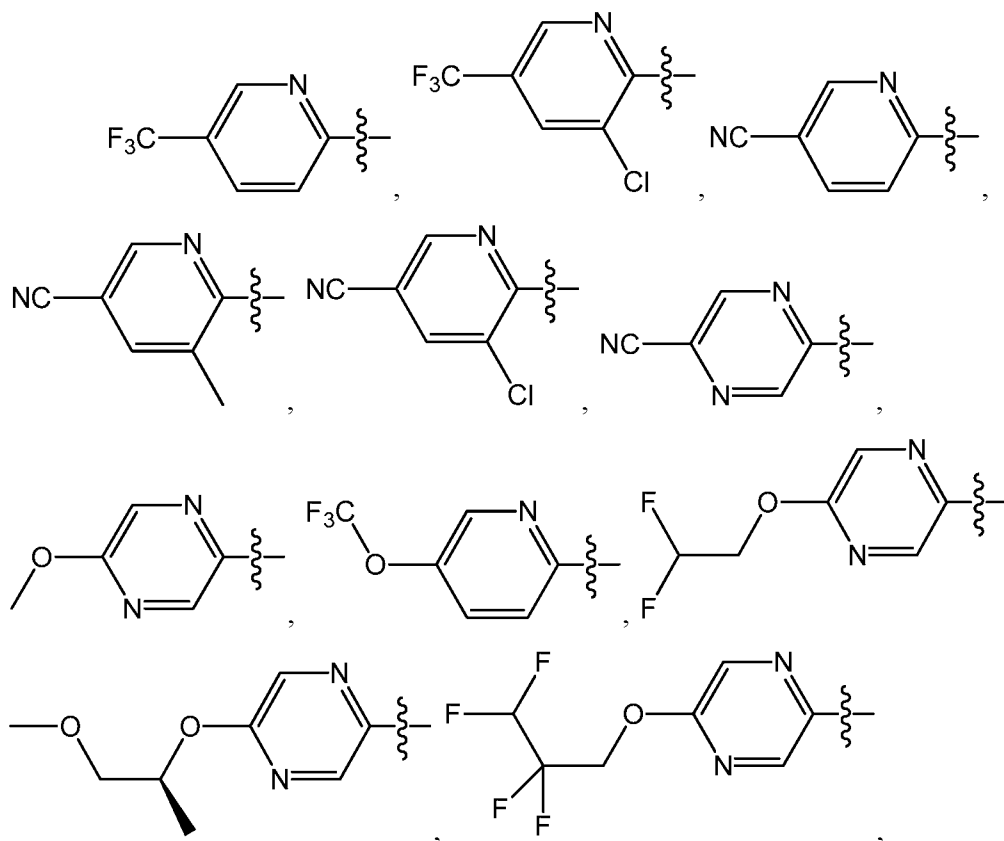
Provided herein as an alternative Embodiment 20 is the compound according to any one of Embodiments 1 to 18, or a tautomer thereof, or a pharmaceutically acceptable salt of
 5 said compound or tautomer, wherein one of R^6 and R^7 is



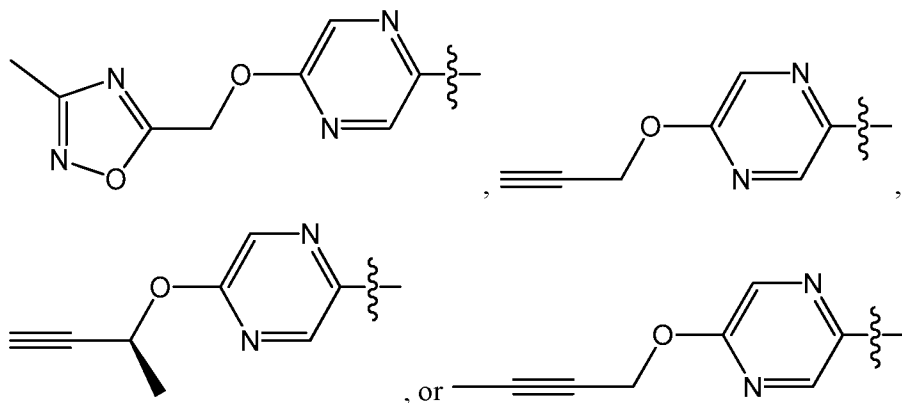
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Provided herein as Embodiment 21 is the compound according to any one of
5 Embodiments 1 to 19, or a tautomer thereof, or a pharmaceutically acceptable salt of said
compound or tautomer, wherein one of R⁶ and R⁷ is



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Provided herein as Embodiment 22 is the compound according to any one of Embodiments 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R^4 is H; and

R^5 is H.

Provided herein as Embodiment 23 is the compound according to any one of Embodiments 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R^4 is H; and

R^6 is H.

Provided herein as Embodiment 24 is the compound according to any one of Embodiments 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R^4 is F; and

R^5 is H.

Provided herein as Embodiment 25 is the compound according to any one of Embodiments 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R^4 is F; and

R^6 is H.

Provided herein as Embodiment 26 is the compound according to any one of Embodiments 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

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R⁴ is H; and

R⁵ is F.

Provided herein as Embodiment 27 is the compound according to any one of Embodiments 1 to 21 or a tautomer thereof, or a pharmaceutically acceptable salt of said

5 compound or tautomer, wherein

R⁴ is H; and

R⁶ is F.

Provided herein as Embodiment 28 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

10 (4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

15 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,7aR)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aR,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

20 (4aS,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

25 6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-

30 d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

5 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

10 (4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

15 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

20 (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

25 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-trifluoropropan-1-one;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one;

(4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-ynyloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

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(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

5 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

10 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

(4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile;

15 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile;

20 6-((Z)-2-(3-((4aR,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; or

6-((Z)-2-(3-((4aS,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.

25 Provided herein as an alternative Embodiment 28 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

(4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

30 (4aR,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

- 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- 6-((Z)-2-(3-((4aS,7aR)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- 5 (4aR,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;
- (4aS,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;
- 6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- 10 6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 15 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 20 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;
- (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 25 (4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

5 (4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

10 (4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone;

15 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-trifluoropropan-1-one;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

20 (4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

25 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one;

(4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

30 (4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

5 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-ynloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

10 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-

15 fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

20 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-

25 hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

(4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

30 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile;

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(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile;

6-((Z)-2-(3-((4aR,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,5R,7aR)-2-Amino-5-(difluoromethyl)-4a,5-dihydro-4H-furo[3,4-d][1,3]thiazin-7a(7H)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; or

(4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.

Provided herein as yet another alternative Embodiment 28 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

(4aS,5R,7aS)-7a-(5-((Z)-2-(5-(difluoromethyl)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine; or

(4aR,5S,7aR)-7a-(5-((Z)-2-(5-(difluoromethyl)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.

Provided herein as Embodiment 29 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,7aR)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

5 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

10 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

20 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

25 (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

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1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-

5 trifluoropropan-1-one;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one;

(4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

20 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

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6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

5 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
10 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-
15 5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

(4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile;
20 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile;

25 6-((Z)-2-(3-((4aR,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; or

6-((Z)-2-(3-((4aS,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.

30 Provided herein as an alternative Embodiment 29 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

- 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- 6-((Z)-2-(3-((4aS,7aR)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- 5 6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- 6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
- (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 10 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 15 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;
- 20 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- (4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- 25 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
- (4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;
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(4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-trifluoropropan-1-one;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one;

(4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

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(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-ynyloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

5 5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

10 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

15 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

20 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

25 (4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile;

30 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

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6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile;

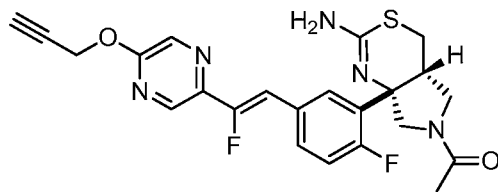
6-((Z)-2-(3-((4aR,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

5 6-((Z)-2-(3-((4aS,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; or

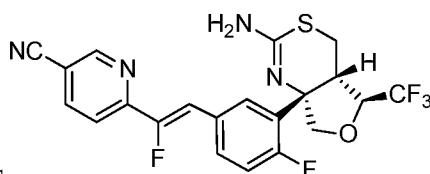
10 6-((Z)-2-(3-((4aR,5R,7aR)-2-Amino-5-(difluoromethyl)-4a,5-dihydro-4H-furo[3,4-d][1,3]thiazin-7a(7H)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.

Provided herein as Embodiment 30 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the



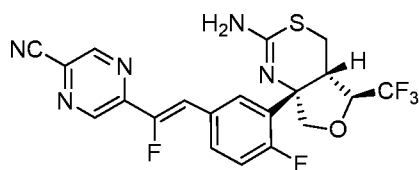
compound is

15 Provided herein as Embodiment 31 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the



compound is

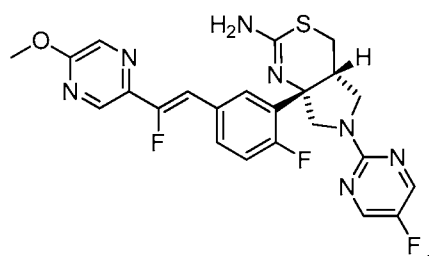
Provided herein as Embodiment 32 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is



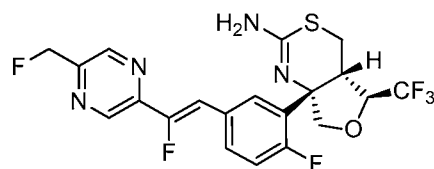
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Provided herein as Embodiment 33 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is



5 Provided herein as Embodiment 34 is the compound of Embodiment 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is



10 Provided herein as Embodiment 35 is a pharmaceutical composition comprising the compound according to any one of Embodiments 1 to 34 and a pharmaceutically acceptable excipient.

 Provided herein as Embodiment 36 is a compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 for
15 use as a medicament.

 Provided herein as Embodiment 37 is a compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 for use in reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

20 Provided herein as Embodiment 38 is a compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 for use in treating Alzheimer's disease, cognitive impairment, or a combination thereof in a subject.

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Provided herein as Embodiment 39 is a compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 for use in treating a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject.

Provided herein as Embodiment 40 is a compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 for use in reducing formation of plaque on the brain of a subject.

Provided herein as Embodiment 41 is a use of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 in the preparation of a medicament for reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

Provided herein as Embodiment 42 is a use of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 in the preparation of a medicament for treating Alzheimer's disease, cognitive impairment, or a combination thereof in a subject.

Provided herein as Embodiment 43 is a use of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 in the preparation of a medicament for the treatment of a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject.

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Provided herein as Embodiment 44 is a use of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Embodiment 35 in the preparation of a medicament for the reduction of formation of plaque on the brain of a subject.

Provided herein as Embodiment 45 is a method of reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

Provided herein as Embodiment 46 is a method of treating Alzheimer's disease, cognitive impairment or a combination thereof in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

Provided herein as Embodiment 47 is a method of treating a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

Provided herein as Embodiment 48 is a method of reducing the formation of plaque on the brain of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Embodiments 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

If one or more alternative embodiments to a certain embodiment are provided, a reference to the certain embodiment is also considered to be a reference to any alternative

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embodiment provided. For example, the reference in Embodiment 35 to, *inter alia*, Embodiment 29 is meant to also include a reference to the alternative Embodiment 29 provided herein above.

The foregoing merely summarizes certain aspects of this disclosure and is not intended, nor should it be construed, as limiting the disclosure in any way.

DEFINITIONS

The following definitions are provided to assist in understanding the scope of this disclosure.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the standard deviation found in their respective testing measurements.

As used herein, if any variable occurs more than one time in a chemical formula, its definition on each occurrence is independent of its definition at every other occurrence. If the chemical structure and chemical name conflict, the chemical structure is determinative of the identity of the compound.

Stereoisomers

The compounds of the present disclosure may contain, for example, double bonds, one or more asymmetric carbon atoms, and bonds with a hindered rotation, and therefore, may exist as stereoisomers, such as double-bond isomers (*i.e.*, geometric isomers (E/Z)), enantiomers, diastereomers, or atropoisomers. Accordingly, the scope of the instant disclosure is to be understood to encompass all possible stereoisomers of the illustrated compounds including the stereoisomerically pure form (for example, geometrically pure, enantiomerically pure, diastereomerically pure, and atropoisomerically pure) and stereoisomeric mixtures (for example, mixtures of geometric isomers, enantiomers, diastereomers, and atropoisomers) of any chemical structures disclosed herein (in whole or in part). This disclosure also encompasses the pharmaceutical compositions comprising stereoisomerically pure forms and the use of stereoisomerically pure forms of any

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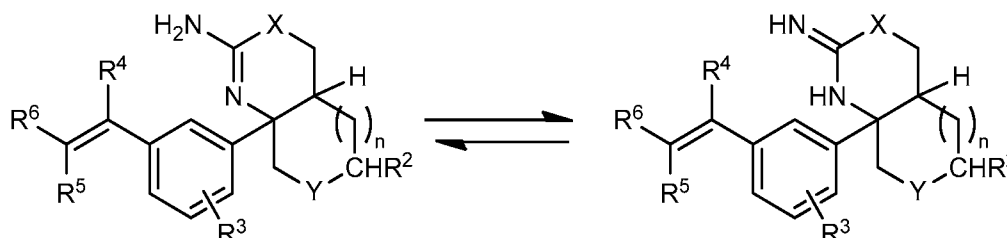
compounds disclosed herein. Further, this disclosure also encompasses pharmaceutical compositions comprising mixtures of stereoisomers of any compounds disclosed herein and the use of said pharmaceutical compositions or mixtures of stereoisomers. These stereoisomers or mixtures thereof may be synthesized in accordance with methods well known in the art and methods disclosed herein. Mixtures of stereoisomers may be resolved using standard techniques, such as chiral columns or chiral resolving agents. *See*, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725; Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions*, page 268 (Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

The term “stereoisomer” or “stereoisomerically pure” compound as used herein refers to one stereoisomer (for example, geometric isomer, enantiomer, diastereomer and atropoisomer) of a compound that is substantially free of other stereoisomers of that compound. For example, a stereoisomerically pure compound having one chiral center will be substantially free of the mirror image enantiomer of the compound and a stereoisomerically pure compound having two chiral centers will be substantially free of other enantiomers or diastereomers of the compound. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. A bond drawn with a wavy line indicates that both stereoisomers are encompassed. This is not to be confused with a wavy line drawn perpendicular to a bond which indicates the point of attachment of a group to the rest of the molecule.

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Tautomers

As known by those skilled in the art, certain compounds disclosed herein may exist in one or more tautomeric forms. Because one chemical structure may only be used to represent one tautomeric form, it will be understood that for convenience, referral to a compound of a given structural formula includes other tautomers of said structural formula. For example, the following is illustrative of tautomers of the compounds of Formula I:



Accordingly, the scope of the instant disclosure is to be understood to encompass all tautomeric forms of the compounds disclosed herein.

Isotopically-Labelled Compounds

Further, the scope of present disclosure includes all pharmaceutically acceptable isotopically-labelled compounds of the compounds disclosed herein, such as the compounds of Formula I, wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds disclosed herein include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S . Certain isotopically-labelled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^3H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with isotopes such as deuterium (^2H) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be advantageous in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission

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Topography (PET) studies, for example, for examining target occupancy. Isotopically-labelled compounds of the compounds disclosed herein can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying General Synthetic Schemes and Examples using an appropriate isotopically-labelled reagents in place of the non-labelled reagent previously employed.

Solvates

As discussed above, the compounds disclosed herein and the stereoisomers, tautomers and isotopically-labelled forms thereof or a pharmaceutically acceptable salt of any of the foregoing may exist in solvated or unsolvated forms.

The term “solvate” as used herein refers to a molecular complex comprising a compound or a pharmaceutically acceptable salt thereof as described herein and a stoichiometric or non-stoichiometric amount of one or more pharmaceutically acceptable solvent molecules. If the solvent is water, the solvate is referred to as a “hydrate.”

Accordingly, the scope of the instant disclosure is to be understood to encompass all solvents of the compounds disclosed herein and the stereoisomers, tautomers and isotopically-labelled forms thereof or a pharmaceutically acceptable salt of any of the foregoing.

Amorphous and Crystalline Forms

In certain embodiments, the compounds described herein and the stereoisomers, tautomers, isotopically-labelled forms thereof or pharmaceutically acceptable salts of any of the foregoing or solvates of any of the foregoing may exist in different forms, such as amorphous forms and crystalline forms (polymorphs). Accordingly, the scope of the instant disclosure is to be understood to encompass all such forms.

Miscellaneous Definitions

This section will define additional terms used to describe the scope of the compounds, compositions and uses disclosed herein.

The term “C₁₋₆alkyl” as used herein means a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of C₁₋₆alkyl include, but are

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not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl.

The term "C₁₋₆alkoxy" as used herein refers to a radical -OR where R represents a C₁₋₆alkyl group as defined herein. Representative examples of C₁₋₆alkoxy include, but are not
5 limited to, methoxy, ethoxy, propoxy, and butoxy.

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

The term "6-membered nitrogen-containing heteroaryl" as used herein refers to a heteroaryl ring having 6 ring atoms in which at least one of the ring atoms is a nitrogen, with the remaining ring atoms being independently selected from the group consisting of carbon
10 and nitrogen. Examples of 6-membered nitrogen-containing heteroaryls include, but are not limited to, pyridyl, pyrazinyl, pyrimidinyl, and pyridazinyl.

The term "pharmaceutically acceptable" as used herein refers to generally recognized for use in subjects, particularly in humans.

The term "pharmaceutically acceptable salt" as used herein refers to a salt of a
15 compound that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid,
20 malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, for example, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as
25 ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, dicyclohexylamine, and the like. Additional examples of such salts can be found in Berge *et al.*, *J. Pharm. Sci.* 66(1):1-19 (1977). *See also* Stahl *et al.*, *Pharmaceutical Salts: Properties, Selection, and Use*, 2nd Revised Edition (2011).

The term "pharmaceutically acceptable excipient" as used herein refers to a broad
30 range of ingredients that may be combined with a compound or salt disclosed herein to prepare a pharmaceutical composition or formulation. Typically, excipients include, but are

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not limited to, diluents, colorants, vehicles, anti-adherants, glidants, disintegrants, flavoring agents, coatings, binders, sweeteners, lubricants, sorbents, preservatives, and the like.

The term "subject" as used herein refers to humans and mammals, including, but not limited to, primates, cows, sheep, goats, horses, dogs, cats, rabbits, rats, and mice. In one
5 embodiment the subject is a human.

The term "treating" as used herein refers not only to treating a subject to relieve the subject of one or more signs and symptoms of a disease or condition or to eliminate one or more such signs and symptoms, but also to prophylactically treating an asymptomatic subject to prevent the onset of the disease or condition or preventing, slowing or reversing the
10 progression of the disease or condition.

The term "therapeutically effective amount" as used herein refers to that amount of a compound disclosed herein that will elicit the biological or medical response of a tissue, a system, or subject that is being sought by a researcher, veterinarian, medical doctor or other clinician. The term also encompasses the amount of compound disclosed herein that will
15 prevent or reduce the risk of occurrence of the biological or medical event that is sought to be prevented in a tissue, a system, or subject by a researcher, veterinarian, medical doctor or other clinician.

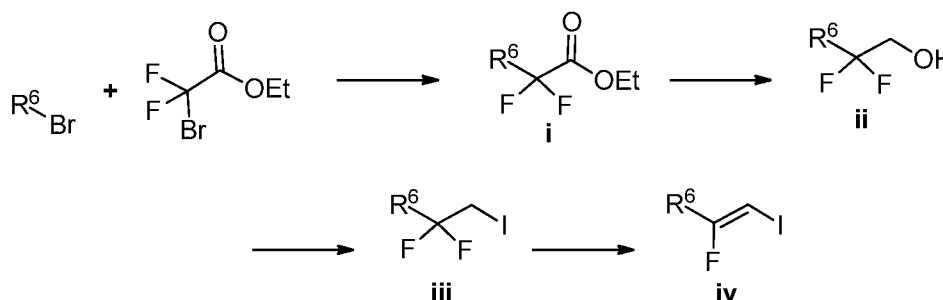
GENERAL SYNTHETIC PROCEDURES

The compounds provided herein can be synthesized according to the procedures
20 described in this and the following sections. The synthetic methods described herein are merely exemplary, and the compounds disclosed herein may also be synthesized by alternate routes utilizing alternative synthetic strategies, as appreciated by persons of ordinary skill in the art. It should be appreciated that the general synthetic procedures and specific examples provided herein are illustrative only and should not be construed as limiting the scope of the
25 present disclosure in any manner.

Generally, the compounds of Formula I can be synthesized according to the following schemes. Any variables used in the following schemes are the variables as defined for Formula I, unless otherwise noted. All starting materials are either commercially available, for example, from Sigma-Aldrich Chemical Company, Inc., St. Louis, MO, USA,
30 or known in the art and may be synthesized by employing known procedures using ordinary skill. Starting material may also be synthesized via the procedures disclosed herein.

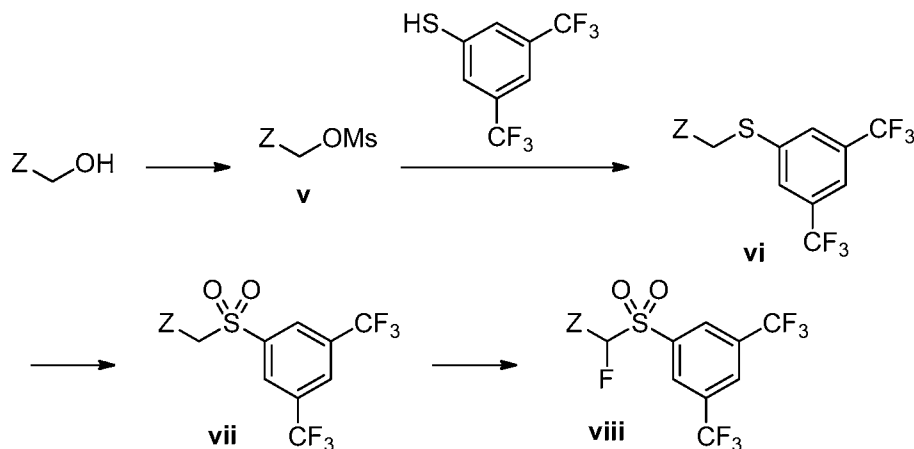
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Scheme 1



The alkene **iv** may be synthesized as shown in Scheme 1. The starting material $\text{R}^6\text{-Br}$ is reacted with ethyl 2-bromo-2,2-difluoroacetate to give ester **i**. Ester **i** is then reduced, for example, with sodium borohydride, to give alcohol **ii**. The OH group of alcohol **ii** is then transformed into an iodo group yielding compound **iii** by transforming the OH group in a leaving group followed by a nucleophilic substitution, for example, by reacting alcohol **ii** with triflic anhydride in presence of a base, such as pyridine, followed by reaction with I⁻, sourced from, for example, sodium iodide. Alkene **iv** is then obtained by reacting compound **iii** with a base, such as potassium tert-butoxide.

Scheme 2

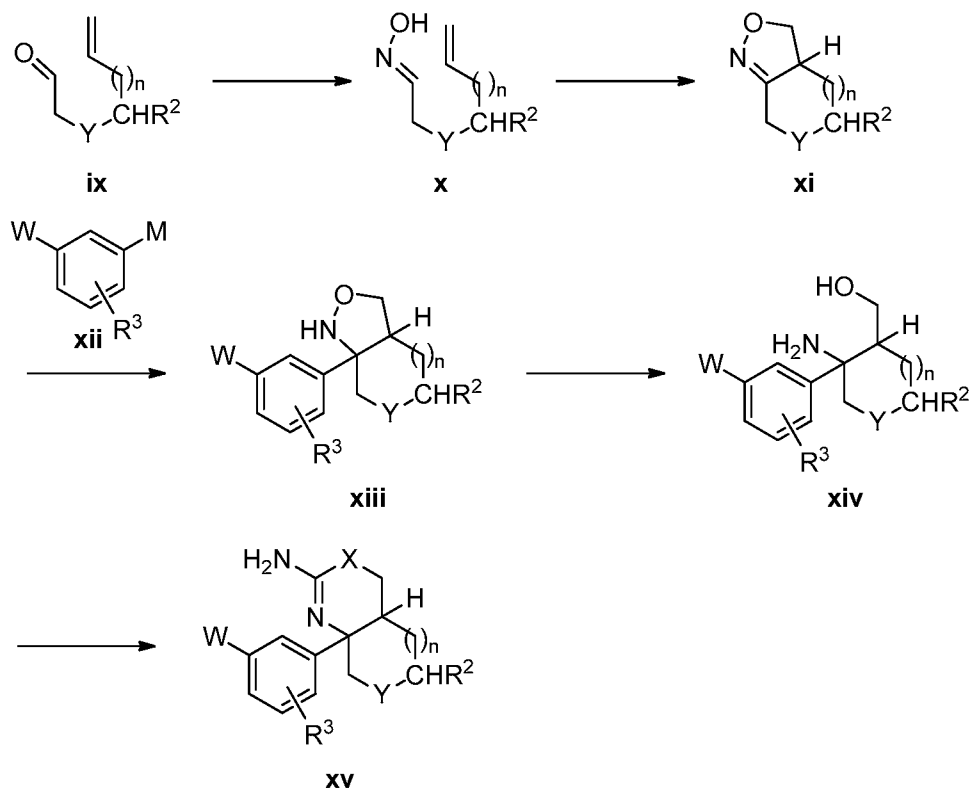


Sulfone **viii**, wherein Z is R^5 or R^6 , may be synthesized as shown in Scheme 2. First, the OH group of ZCH_2OH is transformed into a leaving group, for example by reacting ZCH_2OH with methane sulfonyl chloride in presence of a base, such as trimethylamine, to give compound **v**. Then, compound **v** is reacted with 3,5-bis(trifluoromethyl)benzenethiol in presence of a base, such as sodium hydroxide, to give compound **vi**. Alternatively, ZCH_2X , wherein X is Cl, Br, or I, may be directly reacted with 3,5-bis(trifluoromethyl)benzenethiol in

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presence of a base, such as potassium carbonate, to give compound **vi**. The sulfone **vii** is obtained by reacting compound **vi** under oxidizing conditions using, for example, hydrogen peroxide. Sulfone **viii** was obtained reacting sulfone **vii** with an electrophilic fluorination agent, such as N-fluorodibenzenesulfonimide, in presence of a base, such as lithium diisopropylamide.

Scheme 3

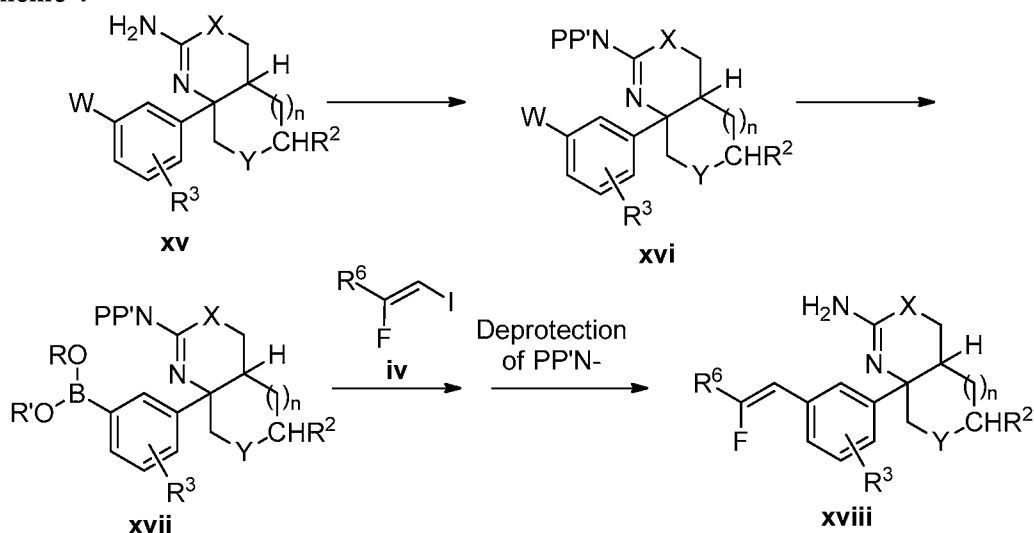


Compound **xv**, wherein W is Cl, Br, or I, may be synthesized as shown in Scheme 3. The aldehyde **ix** is reacted with hydroxylamine in form of, for example, hydroxylamine hydrochloride, in presence of a base, such as sodium acetate trihydrate, to give aldoxime **x**. The bicyclic compound **xi** is formed by reacting the aldoxime **x** with, for example, an aqueous solution of sodium hypochlorite. Compound **xiii** is then obtained by reacting the bicyclic compound **xi** with the organometallic reagent **xii**, wherein M is, for example, Li or MgCl. Compound **xiii** is then reacted with, for example, powdered zinc in, for example, acetic acid, to give the hydroxyl compound **xiv**. The hydroxyl compound **xiv** is then reacted with, for example, BzNCS, followed by treatment with, for example, Tf_2O in presence of a

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base, such as pyridine, to give compound **xv**, wherein X is S, or followed by treatment with, for example, N,N'-carbonyldiimidazole and subsequently with acetic acid and trifluoroacetic acid, to give compound **xv**, wherein X is O.

Scheme 4



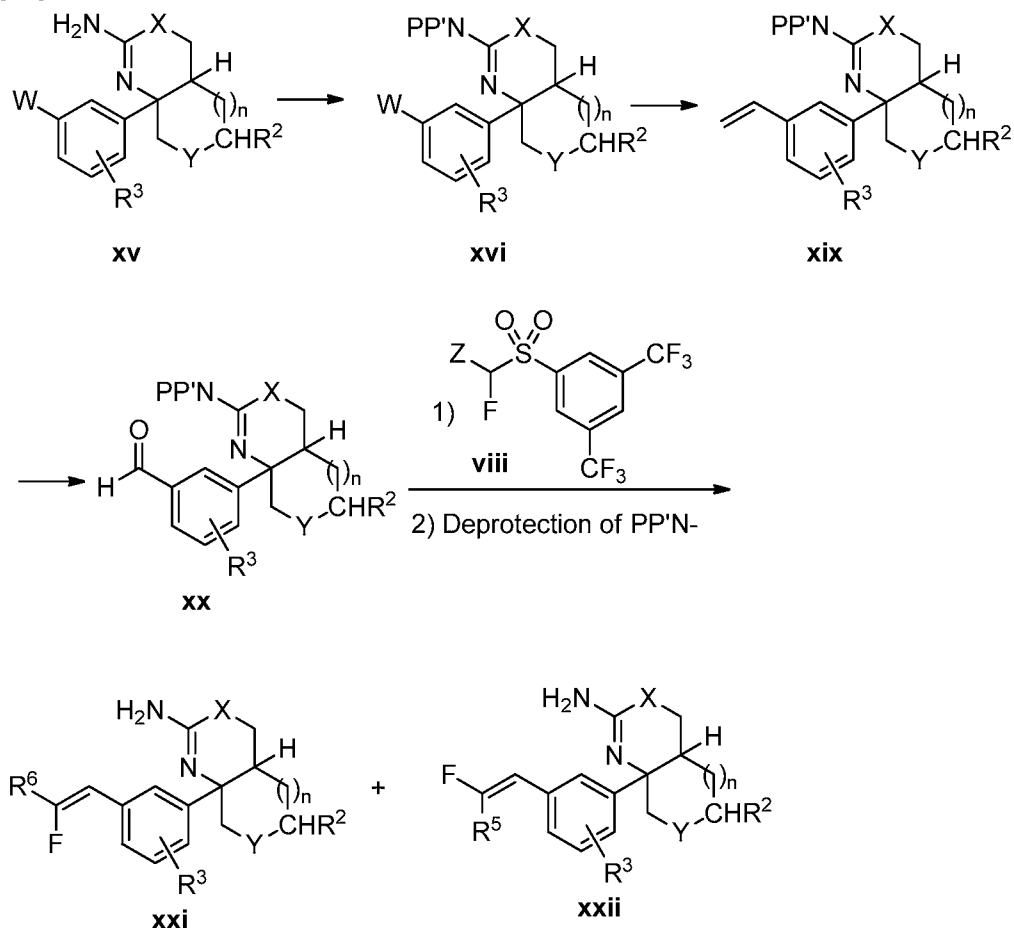
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The final compound **xviii** may be synthesized as shown in Scheme 4. First, the free amino group of compound **xv**, wherein W is Cl, Br, or I, is suitably protected, for example by reaction with di-tert-butyl dicarbonate in presence of a base, such as N,N-diisopropylethylamine (Hünig's base). The suitably protected compound **xvi** is then transformed into boronic acid **xvii**, for example by reacting bis(pinacolato)diboron in presence of a base, such as potassium acetate, and a suitable palladium catalyst, such [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II). The final compound **xviii** is obtained by reacting boronic acid **xvii** with compound **iv** under Suzuki conditions, in presence of, for example, bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II) and a base, such as potassium phosphate, followed by a deprotection of the amino group by reacting the Suzuki product with, for example, trifluoroacetic acid, if a di-BOC protecting strategy was employed.

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Scheme 5

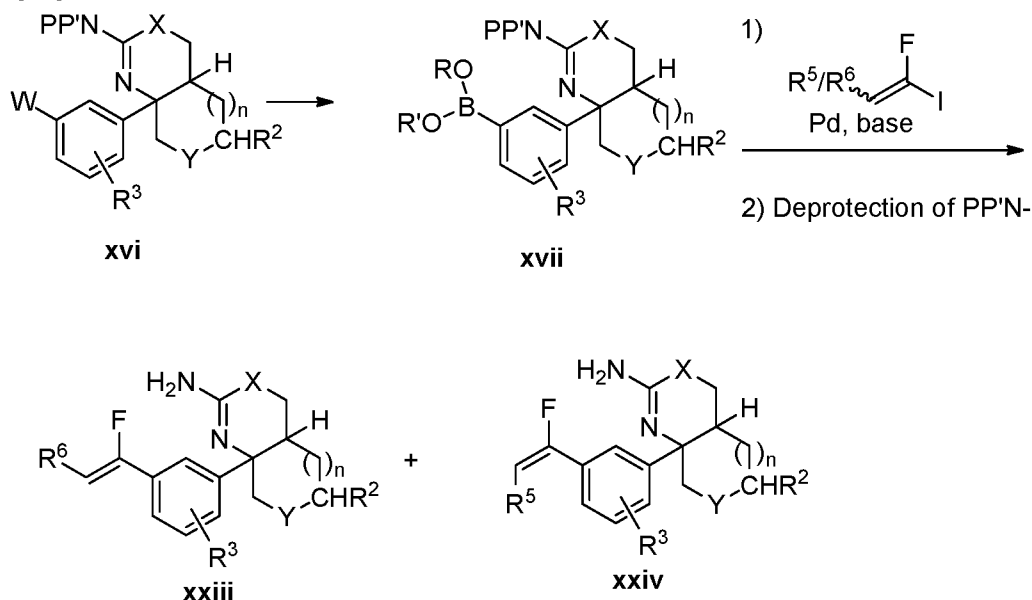


The final compounds **xxi** and **xxii** may be synthesized as shown in Scheme 5. First, the free amino group of compound **xv** is suitably protected, for example by reaction with benzoic anhydride in presence of a base, such as trimethylamine. The suitably protected compound **xvi** is then transformed into alkene **xix** by reacting compound **xvi** with, for example, potassium vinyltrifluoroborate in presence of a base, such as potassium acetate, and a suitable palladium catalyst, such as bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II). Aldehyde **xx** is obtained by subjecting alkene **xix** to oxidizing conditions using, for example osmium tetroxide, 4-methylmorpholine-N-oxide, and potassium periodate. Aldehyde **xx** is then reacted with compound **viii**, wherein Z is R^5 or R^6 , in presence of a base, such as lithium bis(trimethylsilyl)amide, followed by conditions removing the protecting group(s) from the amino group using, for example, 1,8-

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diazabicyclo[5.4.0]undec-7-ene (DBU), if a benzoyl protecting strategy was employed, to give final compound(s) **xxi** and/or **xxii**.

Scheme 6



- 5 The final compounds **xxiii** and **xxiv** may be synthesized as shown in Scheme 6. The suitably protected compound **xvi** is transformed into boronic ester **xvii** by reacting compound **xvi** with, for example, bispinacolatodioron in presence of a base, such as potassium acetate, and a suitable palladium catalyst, such as bis(di-tert-butyl(4-
- 10 to a suitable vinyl iodide, for example, in presence of a base, such as potassium acetate, and a suitable palladium catalyst, such as bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II). Boronic ester **xvii** is then coupled to a suitable vinyl iodide, for example, in presence of a base, such as potassium acetate, and a suitable palladium catalyst, such as bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)-dichloropalladium(II). The vinyl iodide may be synthesized by methods known in the art. Applying conditions removing the protecting group(s) from the amino group using, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), if a benzoyl protecting strategy was
- 15 employed, gives final compound(s) **xxiii** and/or **xxiv**.

As can be appreciated by the skilled artisan, the above synthetic schemes and representative examples are not intended to comprise a comprehensive list of all means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art. Additionally, the various

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synthetic steps described above may be performed in an alternate sequence or order to give the desired compounds.

For example, in these procedures, the steps may be preceded, or followed, by additional protection/deprotection steps as necessary. Particularly, if one or more functional groups, for example carboxy, hydroxy, amino, or mercapto groups, are or need to be protected in preparing the compounds disclosed herein, because they are not intended to take part in a specific reaction or chemical transformation, various known conventional protecting groups may be used. For example, protecting groups typically utilized in the synthesis of natural and synthetic compounds, including peptides, nucleic acids, derivatives thereof and sugars, having multiple reactive centers, chiral centers and other sites potentially susceptible to the reaction reagents and/or conditions, may be used.

Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); A. Katritzky and A. Pozharski, *Handbook of Heterocyclic Chemistry*, 2nd edition (2001); M. Bodanszky, A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, Berlin Heidelberg (1984); J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd edition, Wiley-VCH, (1997); and L. Paquette, editor, *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995).

All synthetic procedures described herein can be carried out under known reaction conditions, advantageously under those described herein, either in the absence or in the presence (usually) of solvents. As appreciated by those of ordinary skill in the art, the solvents should be inert with respect to, and should be able to dissolve, the starting materials and other reagents used. Solvents should be able to partially or wholly solubilize the reactants in the absence or presence of catalysts, condensing agents or neutralizing agents, for example ion exchangers, typically cation exchangers for example in the H⁺ form. The ability of the solvent to allow and/or influence the progress or rate of the reaction is generally dependent on the type and properties of the solvent(s), the reaction conditions including

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temperature, pressure, atmospheric conditions such as in an inert atmosphere under argon or nitrogen, and concentration, and of the reactants themselves.

Suitable solvents for conducting reactions to synthesize the compounds provided herein include, but are not limited to, water; esters, including lower alkyl-lower alkanoates, for example, EtOAc; ethers including aliphatic ethers, for example, Et₂O and ethylene glycol dimethylether or cyclic ethers, for example, THF; liquid aromatic hydrocarbons, for example, benzene, toluene and xylene; alcohols, for example, MeOH, EtOH, 1-propanol, iPrOH, n- and t-butanol; nitriles, for example, CH₃CN; halogenated hydrocarbons, for example, CH₂Cl₂, CHCl₃ and CCl₄; acid amides, for example, DMF; sulfoxides, for example, DMSO; bases, including heterocyclic nitrogen bases, for example, pyridine; carboxylic acids, for example, lower alkanecarboxylic acids, for example, AcOH; inorganic acids, for example, HCl, HBr, HF, and H₂SO₄; carboxylic acid anhydrides, for example, lower alkane acid anhydrides, for example, acetic anhydride; cyclic, linear, or branched hydrocarbons, for example, cyclohexane, hexane, pentane, and isopentane; and mixtures of any of these solvents, such as purely organic solvent combinations, or water-containing solvent combinations, for example, aqueous solutions. These solvents and solvent mixtures may also be used in “working-up” the reaction as well as in processing the reaction and/or isolating the reaction product(s), such as in chromatography.

Purification methods are known in the art and include, for example, crystallization, chromatography (for example, liquid and gas phase), extraction, distillation, trituration, and reverse phase HPLC. Reactions conditions such as temperature, duration, pressure, and atmosphere (inert gas, ambient) are known in the art and may be adjusted as appropriate for the reaction.

The disclosure further encompasses “intermediate” compounds, including structures produced from the synthetic procedures described, whether isolated or generated in-situ and not isolated, prior to obtaining the finally desired compound. Structures resulting from carrying out steps from a transient starting material, structures resulting from divergence from the described method(s) at any stage, and structures forming starting materials under the reaction conditions are all “intermediates” included in the scope of this disclosure.

Further, processes for making and further reacting these intermediates are also understood to be encompassed in the scope of this disclosure.

Also provided herein are new starting materials and/or intermediates, as well as processes for the preparation thereof. In select embodiments, such starting materials are used and reaction conditions so selected as to obtain the desired compound(s). Starting materials are either known, commercially available, or can be synthesized in analogy to or according to methods that are known in the art. Many starting materials may be prepared according to known processes and, in particular, can be prepared using processes described in the examples. In synthesizing starting materials, functional groups may be protected with suitable protecting groups when necessary. Protecting groups, their introduction and removal are described above.

EXAMPLES

This section provides specific examples of compounds of Formula I and methods of making the same.

List of Abbreviations

Table 1

ACN	acetonitrile
Ac ₂ O	acetic anhydride
Boc	tert-butylcarboxy
Boc ₂ O	di-tert-butylidicarbonate
(BPin) ₂	bis(pinacolato)diboron
Bz	phenylcarbonyl
CDI	carbonyldiimidazole
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	diisopropylethylamine
DMA	dimethylacetamide
DMSO	dimethylsulfoxide
MsCl	methanesulfonylchloride
MTBE	methyl tert-butyl ether
NMP	N-methylpyrrolidinone

Pd(Amphos)Cl ₂	bis(di-tert-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II)
Pd ₂ (ddba) ₃	tris(dibenzylideneacetone)dipalladium
Pd(dppf)Cl ₂	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PdCl ₂ (dtbpf)	1,1'-bis(di-tert-butylphosphino)ferrocene palladium
Pyr	pyridine
SFC	Supercritical fluid chromatography
s-Phos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
Tf ₂ O	trifluoromethanesulfonic anhydride
T3P	1-propanephosphonic anhydride

General Analytical and Purification Methods

Provided in this section are descriptions of the general analytical and purification methods used to prepare the specific compounds provided herein.

Chromatography:

- 5 Unless otherwise indicated, crude product-containing residues were purified by passing the crude material or concentrate through either a Biotage or Isco brand silica gel column (pre-packed or individually packed with SiO₂) and eluting the product off the column with a solvent gradient as indicated. For example a description of (330 g SiO₂, 0-40% EtOAc/hexane) means the product was obtained by elution from the column packed with 330
- 10 grams of silica, with a solvent gradient of 0% to 40% EtOAc in hexanes.

Preparative HPLC Method:

- Where so indicated, the compounds described herein were purified via reverse phase HPLC using one of the following instruments: Shimadzu, Varian, Gilson; utilizing one of the following two HPLC columns: (a) a Phenomenex Luna or (b) a Gemini column (5 micron or
- 15 10 micron, C18, 150x50 mm)

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A typical run through the instrument included: eluting at 45 mL/min with a linear gradient of 10% (v/v) to 100% MeCN (0.1% v/v TFA) in water (0.1% TFA) over 10 minutes; conditions can be varied to achieve optimal separations.

Proton NMR Spectra:

- 5 Unless otherwise indicated, all ¹H NMR spectra were collected on a Bruker NMR Instrument at 300 MHz or 400 MHz. Where so characterized, all observed protons are reported as parts-per-million (ppm) downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated.

¹⁹F NMR Spectra:

- 10 Unless otherwise indicated, all ¹⁹F NMR spectra were run on a Bruker NMR Instrument at 376 MHz. All observed protons are reported as parts-per-million (ppm) downfield.

Mass Spectra (MS)

- 15 Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an (M+H⁺) molecular ion. The molecular ion reported was obtained by electrospray detection method (commonly referred to as an ESI MS) utilizing a PE SCIEX API 150EX MS instrument or an Agilent 1100 series LC/MSD system. Compounds having an isotopic atom, such as bromine and the like, are generally reported according to the detected isotopic pattern, as appreciated
20 by those skilled in the art.

Compound Names

- The compounds disclosed and described herein have been named using either (1) the naming convention provided with Chem-Draw Ultra 12.0.3. software, available in Chem Office, or (2) by the ISIS database software (Advanced Chemistry Design Labs or ACD
25 software).

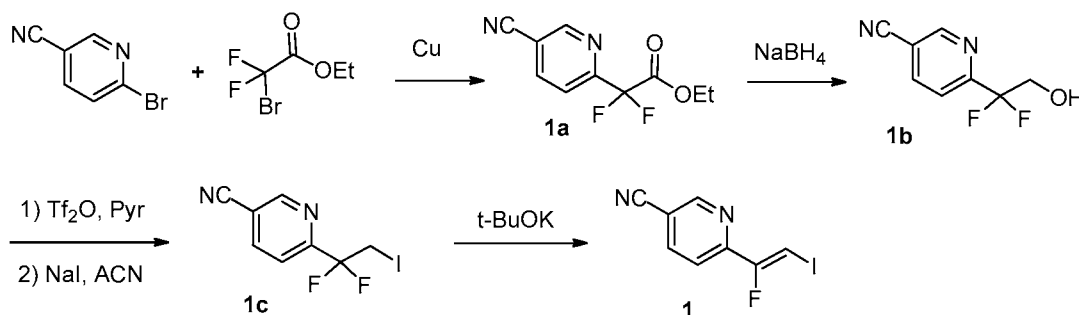
Specific Examples

Provided in this section are the procedures to synthesize specific examples of the compounds provided herein. All starting materials are either commercially available from

Sigma-Aldrich Chemical Company, Inc., St. Louis, MO, USA, unless otherwise noted, or known in the art and may be synthesized by employing known procedures using ordinary skill.

Intermediates

5 Intermediate 1: (Z)-6-(1-fluoro-2-iodovinyl)nicotinonitrile.



Preparation of ethyl 2-(5-cyanopyridin-2-yl)-2,2-difluoroacetate (**1a**).

To a suspension of copper(0) powder (Spectrochem PVT. LTD., Mumbai, India) (413 g, 6557 mmol) in dimethyl sulfoxide (6 L) was added ethyl 2-bromo-2,2-difluoroacetate (Matrix Scientific, Columbia, SC, USA) (665 g, 3279 mmol) dropwise under nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature for 1 hour and 2-bromo-5-cyanopyridine (Sigma-Aldrich, St. Louis, MO, USA) (300 g, 1639 mmol) was added portion-wise. The reaction mixture was stirred at room temperature for 12 hours. It was filtered through a pad of celite and the filtrate was partitioned between EtOAc (3 L) and sat'd aqueous ammonium chloride (2.5 mL) solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 2 L). The combined organic solution was washed with water (2 x 2 L), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (0 - 10% EtOAc in hexanes) to give **1a** (320 g, 86% yield) as a colourless oil. MS (ESI +ve ion) m/z: [M+1] = 227.1. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.93 (d, *J* = 2.0 Hz, 1H), 8.18 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.90 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

Preparation of 6-(1,1-difluoro-2-hydroxyethyl)nicotinonitrile (1b).

To a solution of **1a** (105 g, 464 mmol) in THF (1.5 L) at -20 °C was added sodium borohydride (10.5 g, 279 mmol) in a portion-wise manner. The reaction mixture was stirred at -20 °C for 30 minutes and methanol (525 mL) was added dropwise. The reaction mixture
5 was stirred at -20 °C for 1 hour then quenched with water (500 mL). The mixture was concentrated under reduced pressure. The residue was diluted with water (0.5 L) and extracted with EtOAc (2 x 1 L). The combined organic solution was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (0 - 25% EtOAc in hexanes) to provide **1b** (43.0 g, 50% yield) as a light-yellow solid. MS (ESI +ve ion) m/z:
10 [M+1] = 185.1. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.97 – 8.90 (m, 1H), 8.18 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.89 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.29 (t, *J* = 12.4 Hz, 2H). Note: OH proton was not observed.

Preparation of 6-(1,1-difluoro-2-iodoethyl)nicotinonitrile (1c).

To a solution of **1b** (87 g, 472 mmol) in acetonitrile (1.3 L) was added pyridine (74.7 g, 945 mmol) followed by dropwise addition of trifluoromethanesulfonic anhydride (Sigma-Aldrich, St. Louis, MO, USA) (240 g, 850 mmol) at -10 °C under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 hours then cooled to 0 °C. Sodium iodide (354 g, 2362 mmol) was added in a portion-wise manner. The reaction mixture was
15 heated at 60 °C for 2 hours then cooled to room temperature, diluted with water (2 L) and extracted with EtOAc (3 x 3 L). The combined organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified on a silica gel column (0 - 10% EtOAc in hexanes) to afford **1c** (107 g, 77 % yield) as a light-yellow solid. MS (ESI +ve ion) m/z: [M+1] = 295.0. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.95 (s, 1H), 8.17 – 8.14 (m, 1H), 7.87 – 7.85 (d, *J* = 8.0 Hz, 1H), 3.97 (t, *J* = 14.4 Hz, 2H).
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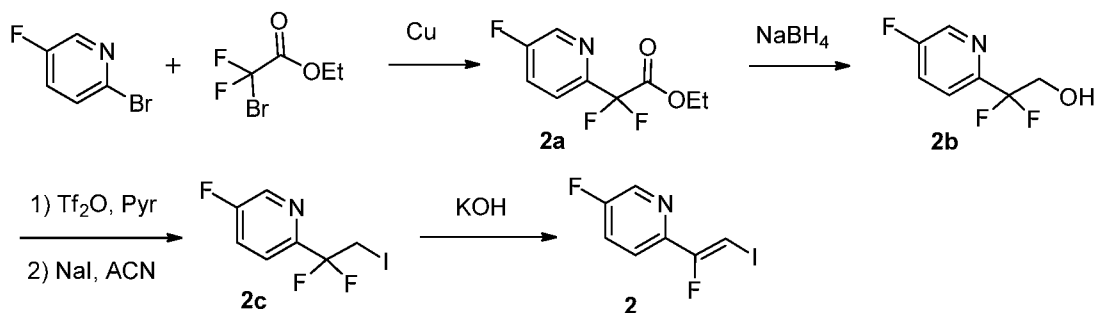
Preparation of 6-(1,1-difluoro-2-iodoethyl)nicotinonitrile (1).

To a solution of **1c** (58 g, 197 mmol) in THF (580 mL) was added potassium *tert*-butoxide (26.6 g, 237 mmol) portion-wise at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours then quenched with sat'd aqueous NH₄Cl (100 mL) and diluted with water (100 mL). The mixture was extracted with EtOAc (3 x 700 mL). The combined organic extracts
25 were dried over Na₂SO₄ and concentrated. Purification of the residue by silica gel
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chromatography (1 to 5% EtOAc in hexanes) gave 6-(1,1-difluoro-2-iodoethyl)nicotinonitrile (**1**) (33 g, 61% yield) as a light yellow solid. MS (ESI +ve ion) m/z : $[M+1] = 274.9$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.04 (dd, $J = 2.1, 1.0$ Hz, 1H), 8.45 (dd, $J = 8.3, 2.1$ Hz, 1H), 7.81 (dt, $J = 8.3, 1.1$ Hz, 1H), 7.42 (d, $J = 36.4$ Hz, 1H).

5 **Intermediate 2: (Z)-5-fluoro-2-(1-fluoro-2-iodovinyl)pyridine.**



Preparation of ethyl 2,2-difluoro-2-(5-fluoropyridin-2-yl)acetate (2a).

Ethyl 2,2-difluoro-2-(5-fluoropyridin-2-yl)acetate (**2a**, 44.8 g, 80% yield) as a viscous colourless liquid was prepared in a fashion similar to that described for **1a**, here starting from ethyl 2-bromo-2,2-difluoroacetate (104 g, 511 mmol) and 2-bromo-5-fluoropyridine (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China) (45 g, 256 mmol). MS (ESI +ve ion) m/z : $[M+1] = 220.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.73 (d, $J = 2.5$ Hz, 1H), 8.05 – 7.95 (m, 2H), 4.34 (dd, $J = 7.2, 5.2$ Hz, 2H), 1.23 (t, $J = 7.2$ Hz, 3H).

Preparation of 2,2-difluoro-2-(5-fluoropyridin-2-yl)ethanol (2b).

2,2-Difluoro-2-(5-fluoropyridin-2-yl)ethanol (**2b**) (25 g, 69% yield) as a colourless liquid was prepared in a fashion similar to that described for **1b**, here starting from **2a** (45 g, 205 mmol). MS (ESI +ve ion) m/z : $[M+1] = 178.2$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.69 (d, $J = 2.8$ Hz, 1H), 7.90 (td, $J = 8.7, 2.8$ Hz, 1H), 7.78 (dd, $J = 8.7, 4.3$ Hz, 1H), 5.56 (td, $J = 6.4, 1.3$ Hz, 1H), 4.03 – 3.96 (m, 2H).

20 **Preparation of 2-(1,1-difluoro-2-iodoethyl)-5-fluoropyridine (2c).**

2-(1,1-Difluoro-2-iodoethyl)-5-fluoropyridine (**2c**, 25 g, 62% yield) as a yellow solid was prepared in a fashion similar to that described for **1c**, here starting from **2b** (25 g, 141

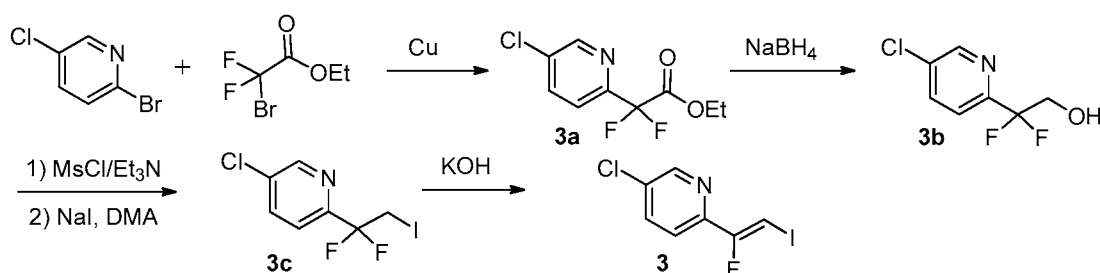
- 54 -

mmol). MS (ESI +ve ion) m/z : $[M+1] = 288.0$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.73 (d, $J = 2.7$ Hz, 1H), 7.96 (td, $J = 8.7, 2.8$ Hz, 1H), 7.88 – 7.82 (m, 1H), 4.08 – 3.98 (m, 2H).

Preparation of (Z)-5-fluoro-2-(1-fluoro-2-iodovinyl)pyridine (2).

To a solution of 2-(1,1-difluoro-2-iodoethyl)-5-fluoropyridine (**2c**, 25 g, 87 mmol) in DMSO (200 mL) was added 5.0 M aqueous NaOH solution (30 mL, 150 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 hours then quenched with water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic solution was washed with brine (200 mL), dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel chromatography (0 - 5% EtOAc in hexanes) provided (Z)-5-fluoro-2-(1-fluoro-2-iodovinyl)pyridine (**2**) (18 g, 77% yield) as a clear oil. MS (ESI +ve ion) m/z : $[M+1] = 268.0$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.64 (d, $J = 2.9$ Hz, 1H), 7.86 (m, 1H), 7.72 (ddt, $J = 8.4, 3.8, 1.9$ Hz, 1H), 7.02 (dd, $J = 36.7, 1.9$ Hz, 1H).

Intermediate 3: (Z)-5-chloro-2-(1-fluoro-2-iodovinyl)pyridine.



Preparation of ethyl 2-(5-chloropyridin-2-yl)-2,2-difluoroacetate (3a).

Ethyl 2-bromo-2,2-difluoroacetate (105 g, 520 mmol) was added slowly to a suspension of copper(0) powder (66.0 g, 1039 mmol) in DMSO (1.2 L) under nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature for 1 hour and 2-bromo-5-chloropyridine (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China) (50.0 g, 260 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 12 hours then filtered through a pad of celite. The filter cake was rinsed with 400 mL of EtOAc. The filtrate was partitioned between EtOAc (1 L) and sat'd aqueous ammonium chloride (100 mL) and water (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic solution was washed with water (2 x 100 mL), dried over Na_2SO_4 and concentrated.

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Purification of the residue by silica gel chromatography (0 - 10 % EtOAc in hexanes) gave **3a** (60 g, 64% yield) as a clear liquid. MS (ESI +ve ion) m/z : $[M+1] = 236.0$. ^1H NMR (400 MHz, Chloroform- d) δ 8.63 – 8.59 (m, 1H), 7.85 (dt, $J = 8.4, 1.6$ Hz, 1H), 7.70 (dt, $J = 8.4, 0.9$ Hz, 1H), 4.11 (q, $J = 7.1, 1.0$ Hz, 2H), 1.26 (t, $J = 7.1, 1.0$ Hz, 3H).

5 **Preparation of 2-(5-chloropyridin-2-yl)-2,2-difluoroethan-1-ol (3b).**

To a solution of **3a** (47.0 g, 199 mmol) in ethanol (600 mL) at 0 °C was added sodium borohydride (7.5 g, 199 mmol) portion-wise. The reaction mixture was stirred at room temperature for 1 hour then quenched with water (500 mL) and concentrated under reduced pressure. The crude material was diluted with water (500 mL) and extracted with EtOAc (2 x 500 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by silica gel chromatography (0 - 10 % EtOAc in hexanes) gave **3b** (35 g, 91% yield) as a light yellow solid. MS (ESI +ve ion) m/z : $[M+1] = 194.2$. ^1H NMR (400 MHz, Chloroform- d) δ 8.64 – 8.58 (m, 1H), 7.86 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.70 (dt, $J = 8.5, 1.5$ Hz, 1H), 4.24 (t, $J = 12.4$ Hz, 2H). Note: OH proton not observed.

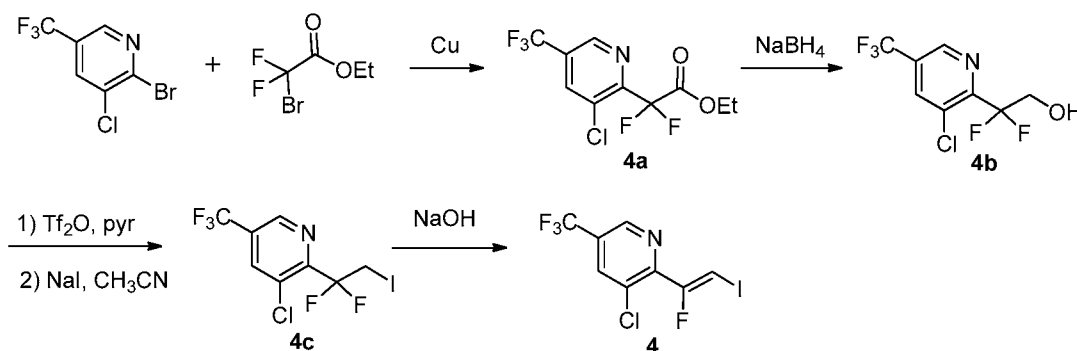
15 **Preparation of 5-chloro-2-(1,1-difluoro-2-iodoethyl)pyridine (3c).**

To a solution of **3b** (31 g, 160 mmol) in DCM (500 mL) at 0 °C was added triethylamine (49.1 mL, 352 mmol) followed by dropwise addition of methanesulfonyl chloride (23.7 mL, 304 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water (500 mL) and extracted with DCM (2 x 500 mL). The combined organic extracts were washed with brine (250 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in N,N -dimethyl acetamide (600 mL) and treated with sodium iodide (96 g, 641 mol) portion-wise. The reaction mixture was heated at 110 °C for 36 hours then cooled to room temperature, diluted with water (500 mL), and extracted with EtOAc (2 x 500 mL). The combined organic solution was washed with brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 10% EtOAc in hexanes) to give **3c** (30 g, 60% yield) as a brown solid. MS (ESI +ve ion) m/z : $[M+1] = 303.9$. ^1H NMR (400 MHz, Chloroform- d) δ 8.59 (s, 1H), 7.87 – 7.84 (m, 1H), 7.27 (d, $J = 2.0$ Hz, 1H), 4.27 (t, $J = 12.4$ Hz, 2H).

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Preparation of (Z)-5-chloro-2-(1-fluoro-2-iodovinyl)pyridine (3).

To a solution of **3c** (30 g, 99 mmol) in DMSO (50 mL, 1.66 mL/g) was added a solution of KOH (19.4 g, 346 mmol) in water (50 mL) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 10 hours then diluted with water (150 mL) and stirred for 15 minutes. The precipitated solids were collected by filtration, washed with water (2 x 100 mL), collected and dried to afford (Z)-5-chloro-2-(1-fluoro-2-iodovinyl)pyridine (**3**) (24.7 g, 87% yield) as a white crystalline solid. MS (ESI +ve ion) m/z: [M+1] = 284.0. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.51 (m, 1H), 7.74 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.50 (ddd, *J* = 8.5, 1.8, 0.8 Hz, 1H), 6.94 (d, *J* = 34.3 Hz, 1H).

Intermediate 4: (Z)-3-chloro-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethyl)pyridine.

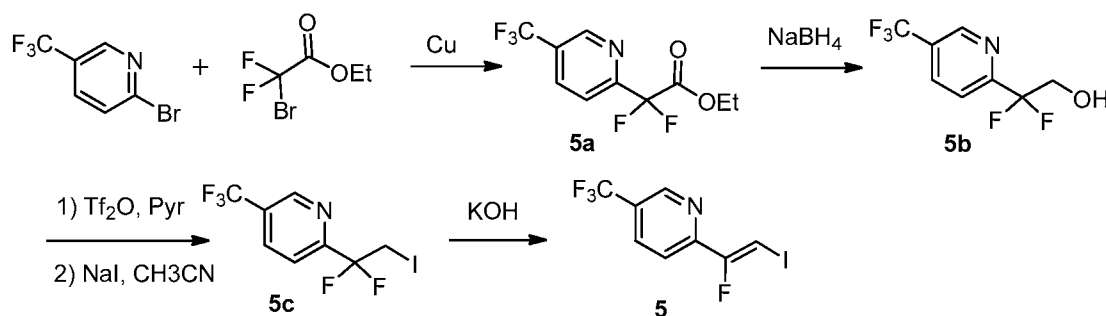
Ethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2,2-difluoroacetate (**4a**, 90 g, 86% yield) as a colorless oil was synthesized using a protocol similar to described for **5a**, here starting from 2-bromo-3-chloro-5-(trifluoromethyl)pyridine (ChemPure Chemicals, Plymouth, MI, USA) (90 g, 346 mmol) and ethyl bromodifluoroacetate (140 g, 691 mmol). MS (ESI +ve ion) m/z: [M+1] = 304.1. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 4.47 – 4.41 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H).

Compounds **4b**, **4c**, and **4** were synthesized in a fashion similar to that described for **5b**, **5c**, and **5**, respectively. 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2,2-difluoroethanol (**4b**): MS (ESI +ve ion) m/z: [M+1] = 262.3. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.77 (d, *J* = 2.0 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 4.34 (m, 2H), 2.97 (t, *J* = 7.7 Hz, 1H). 3-Chloro-2-(1,1-difluoro-2-iodoethyl)-5-(trifluoromethyl)pyridine (**4c**): MS (ESI +ve ion) m/z: [M+1] = 372.0. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.80 (d, *J* = 6.1 Hz, 1H), 8.10 (s, 1H), 4.05 (tdd, *J* = 15.1, 4.2, 2.6 Hz, 2H). (Z)-3-chloro-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethyl)pyridine

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(4): MS (ESI +ve ion) m/z: [M+1] = 352.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (d, *J* = 2.0 Hz, 1H), 8.62 (d, *J* = 2.1 Hz, 1H), 7.22 – 7.05 (m, 1H).

Intermediate 5: (Z)-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethyl)pyridine.



5

Preparation of ethyl 2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)acetate (5a).

To a suspension of copper(0) powder (229 g, 1128 mmol) in DMSO (1.7 L) was added ethyl 2-bromo-2,2-difluoroacetate (47.9 g, 752 mmol) at room temperature. The reaction mixture was stirred for 1 hour and 2-bromo-5-(trifluoromethyl)pyridine (Arborchem, Mechanicsburg, PA, USA) (85 g, 376 mmol) was added portion-wise. The reaction mixture was stirred at room temperature for 12 hours, then quenched with sat'd ammonia chloride (250 mL). The reaction mixture was filtered through a Celite pad and the filtrate was extracted with EtOAc (3 x 350 mL). The combined organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 - 2% EtOAc in hexanes) to provide **5a** (65 g, 64% yield). MS (ESI, positive ion) m/z: 270.1 (M+1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.94 (d, *J* = 1.7 Hz, 1H), 8.14 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 4.46 – 4.33 (m, 2H), 1.45 – 1.26 (m, 3H).

Preparation of 2,2-difluoro-2-(5-(trifluoromethyl)pyridin-2-yl)ethanol (5b).

To a solution of **5a** (62 g, 230 mmol) in ethanol (620 mL) at 0 °C was added sodium borohydride (8.7 g, 230 mmol) portion-wise. The reaction mixture was stirred for 30 minutes at 0 °C, then quenched with water (100 mL) and extracted with EtOAc (3 x 250 mL). The combined organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2 - 10% EtOAc in hexanes) to

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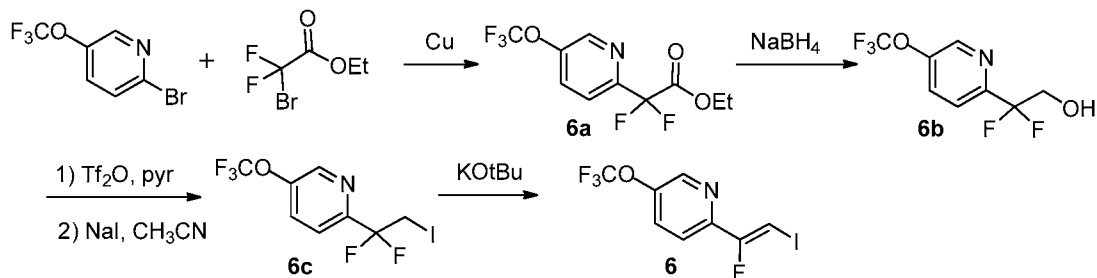
provide **5b** (45 g, 86% yield) as a colourless liquid. MS (ESI, positive ion) m/z : 228.1 (M+1). ^1H NMR (400 MHz, Chloroform- d) δ 9.01 – 8.88 (m, 1H), 8.15 (dd, J = 8.3, 2.2 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 4.30 (td, J = 12.4, 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 1H).

Preparation of 2-(1,1-difluoro-2-iodoethyl)-5-(trifluoromethyl)pyridine (5c).

5 To a solution of **5b** (45 g, 198 mmol) in acetonitrile (450 mL) at 0 °C was added pyridine (32.0 mL, 396 mmol) followed by drop-wise addition of trifluoromethane sulfonic anhydride (50.2 mL, 297 mmol). The reaction mixture was stirred at 0 °C for 30 minutes. Sodium iodide (89 g, 594 mmol) was added portion-wise to the reaction mixture at room temperature. The reaction mixture was stirred at 70 °C for 2 hours. After the completion of
10 the reaction (monitored by TLC), the reaction mixture was quenched with saturated sodium thiosulfate solution (250 mL) and extracted with EtOAc (3 x 250 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0 - 2% EtOAc in hexanes) to afford **5c** (45 g, 67% yield). MS (ESI, positive ion) m/z : 338.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 9.15 (s, 1H), 8.60 – 8.39 (m, 1H), 8.00 (d, J = 8.2 Hz, 1H), 4.07 (t, J = 16.2 Hz, 2H).
15

Preparation of (Z)-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethyl)pyridine (5).

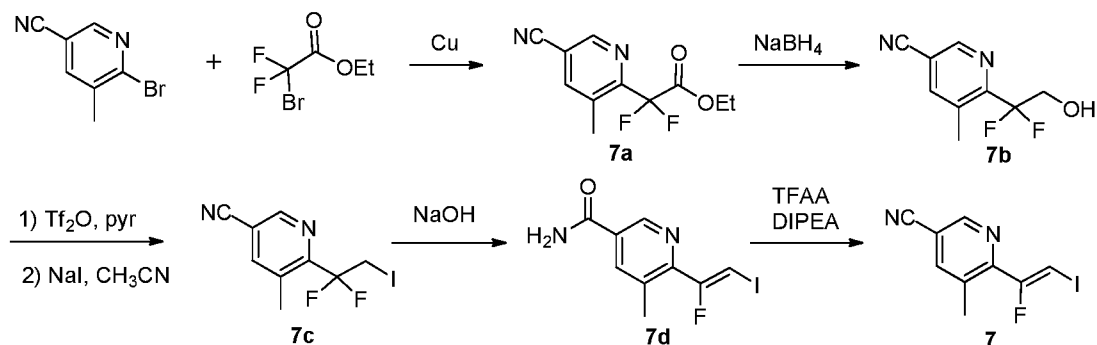
To a solution of **5c** (50 g, 148 mmol) in DMSO (500 mL) was added dropwise a solution of sodium hydroxide (44.5 mL of 5 N solution, 223 mmol) at 0 °C. The reaction
20 mixture was stirred at 0 °C for 5 hours, then quenched with water (100 mL) and extracted with EtOAc (3 x 250 mL). The combined organic solution was washed with brine (150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2 - 10% EtOAc in hexanes) to afford Intermediate **5** (40 g, 85% yield) as an off-white solid. MS (ESI, positive ion) m/z : 318.1 (M+1). ^1H NMR (400
25 MHz, DMSO- d_6) δ 9.07 – 8.91 (m, 1H), 8.34 (dd, J = 8.5, 2.3 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 36.5 Hz, 1H).

Intermediate 6: (Z)-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethyl)pyridine.

Ethyl 2,2-difluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)acetate (**6a**, 2.61 g, 9.15 mmol, 87% yield) as a colorless oil was synthesized using a protocol similar to that described for **1a**, here starting from 2-bromo-5-(trifluoromethoxy)pyridine (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China) (2.54 mL, 10.50 mmol) and ethyl bromodifluoroacetate (1.48 mL, 11.55 mmol). MS (ESI +ve ion) m/z : $[M+1] = 286.2$.

Compounds **6b**, **6c**, and **6** were synthesized in a fashion similar to that described for **1b**, **1c**, and **1**, respectively. 2,2-Difluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)ethanol (**6b**):

MS (ESI +ve ion) m/z : $[M+1] = 244.1$. 2-(1,1-Difluoro-2-iodoethyl)-5-(trifluoromethoxy)pyridine (**6c**): MS (ESI +ve ion) m/z : $[M+1] = 353.9$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.82 (d, $J = 2.15$ Hz, 1H), 8.13 (m, 1H), 7.92 (d, $J = 8.80$ Hz, 1H), 4.04 (t, $J = 16.14$ Hz, 2H). (Z)-2-(1-Fluoro-2-iodovinyl)-5-(trifluoromethoxy)pyridine (**6**): MS (ESI +ve ion) m/z : $[M+1] = 334.0$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.71 (s, 1H), 8.02 (m, 1H), 7.78 (d, $J = 8.61$ Hz, 1H), 7.16 (d, $J = 37.44$ Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -57.16 (s, 3F), -99.23 (s, 1F).

Intermediate 7: (Z)-6-(1-fluoro-2-iodovinyl)-5-methylnicotinonitrile.

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Ethyl 2-(5-cyano-3-methylpyridin-2-yl)-2,2-difluoroacetate (**7a**, 58 g, 59% yield) as a transparent oil was synthesized using a protocol similar to that described for **5a**, starting from 6-bromo-5-methylnicotinonitrile (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China) (80 g, 406 mmol) and ethyl bromodifluoroacetate (165 g, 812 mmol). MS (ESI +ve ion) m/z : $[M+1] = 241.0$. ^1H NMR (400 MHz, Chloroform- d) δ 8.68 (d, $J = 4.1$ Hz, 1H), 7.93 (d, $J = 2.1$ Hz, 1H), 4.46 (q, $J = 7.1$ Hz, 2H), 2.63 (q, $J = 2.5$ Hz, 3H), 1.41 – 1.34 (m, 3H).

Compounds **7b** and **7c** were synthesized in a fashion similar to that described for **5b** and **5c**, respectively. 6-(1,1-Difluoro-2-hydroxyethyl)-5-methylnicotinonitrile (**7b**): MS (ESI +ve ion) m/z : $[M+1] = 199.1$. ^1H NMR (400 MHz, Chloroform- d) δ 8.68 (dd, $J = 2.1, 1.0$ Hz, 1H), 7.95 (dd, $J = 1.8, 0.9$ Hz, 1H), 4.31 (td, $J = 12.4, 7.5$ Hz, 2H), 3.24 (t, $J = 7.6$ Hz, 1H), 2.64 (t, $J = 2.6$ Hz, 3H). -OH proton was not observed. 6-(1,1-Difluoro-2-iodoethyl)-5-methylnicotinonitrile (**7c**): MS (ESI +ve ion) m/z : $[M+1] = 309.2$. ^1H NMR (400 MHz, Chloroform- d) δ 8.70 (dd, $J = 1.8, 1.0$ Hz, 1H), 7.90 (dd, $J = 1.9, 0.9$ Hz, 1H), 4.06 (t, $J = 15.3$ Hz, 2H), 2.62 (t, $J = 3.2$ Hz, 3H).

Preparation of (Z)-6-(1-fluoro-2-iodovinyl)-5-methylnicotinamide (**7d**).

To a solution of **7c** (25 g, 81 mmol) in DMSO (250 mL) at 0 °C was added NaOH (32.5 mL of 5 N solution, 162 mmol). The reaction mixture was stirred at 0 °C for 10 hours, then quenched with water (250 mL) and extracted with EtOAc (2 x 500 mL). The combined organic solution was washed with brine (500 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (20 - 50% EtOAc in hexanes) to afford **7d** (12 g, 48% yield) as an off-white solid. MS (ESI +ve ion) m/z : $[M+1] = 307.2$. ^1H NMR (300 MHz, DMSO- d_6) δ 8.85 (d, $J = 2.2$ Hz, 1H), 8.22 – 8.13 (m, 2H), 7.67 (s, 1H), 6.87 (dd, $J = 36.4, 2.5$ Hz, 1H), 2.43 (t, $J = 3.9$ Hz, 3H).

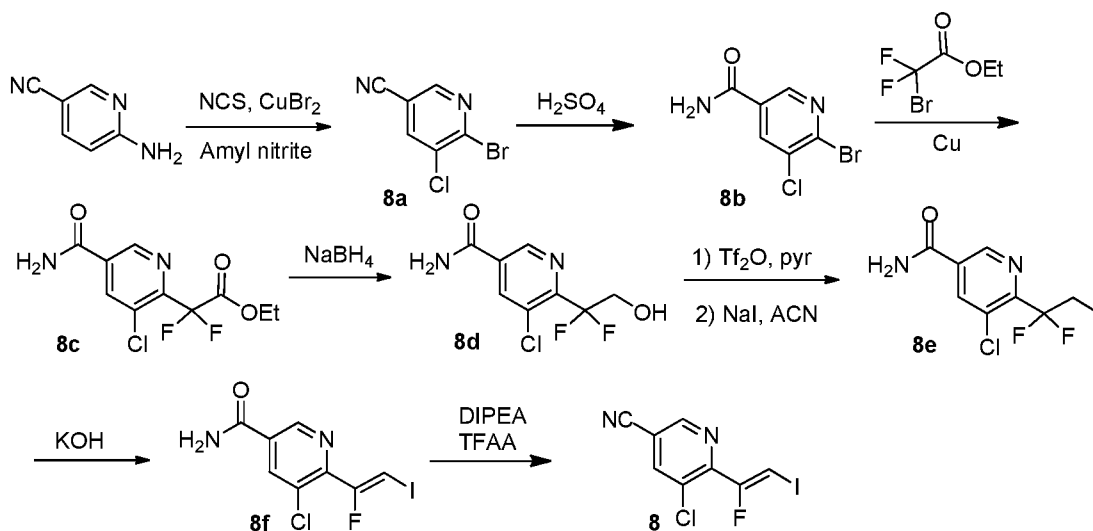
Preparation of (Z)-6-(1-fluoro-2-iodovinyl)-5-methylnicotinonitrile (**7**).

To a solution of (Z)-6-(1-fluoro-2-iodovinyl)-5-methylnicotinonitrile (**7**) (12.0 g, 39.2 mmol) in THF (120 mL) at 0 °C was added DIPEA (34.2 mL, 196 mmol) followed by TFAA (27.7 mL, 196 mmol). The reaction mixture was stirred at 0 °C for 2 hours, then quenched with water (500 mL) and extracted with EtOAc (2 x 500 mL). The combined organic solution was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under

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reduced pressure. The crude residue was purified by silica gel chromatography (10% EtOAc in hexanes) to afford Intermediate 7 (10.5 g, 93% yield) as an off-white solid. MS (ESI +ve ion) m/z : $[M+1]$ = No ionization. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.87 (d, J = 2.0 Hz, 1H), 8.31 (d, J = 2.2 Hz, 1H), 7.13 – 6.93 (m, 1H), 2.42 (d, J = 5.2 Hz, 3H).

5 **Intermediate 8: (Z)-5-chloro-6-(1-fluoro-2-iodovinyl)nicotinonitrile.**



Preparation of 6-bromo-5-chloronicotinonitrile (8a).

A round bottom flask was charged with 6-aminonicotinonitrile (Arborechem, Mechanicsburg, PA, USA) (100 g, 839 mmol), *N*-chlorosuccinimide (Sigma-Aldrich, St. Louis, MO, USA) (123 g, 923 mmol), and acetonitrile (2 L). The reaction mixture was heated at 60 °C for 2 hours. After cooling to room temperature, copper (II) bromide (Sigma-Aldrich, St. Louis, MO, USA) (375 g, 1678 mmol) and isoamyl nitrite (Arborechem, Mechanicsburg, PA, USA) (230 mL, 1678 mmol) were added and the mixture was heated to 65 °C for 2 hours. After cooling to room temperature, the mixture was quenched with sat'd aqueous ammonium chloride solution (200 mL) and extracted with DCM (3 x 500 mL). The combined organic solution was dried over MgSO_4 and concentrated. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to provide 8a (63 g, 34% yield). MS (ESI, positive ion) m/z : no ionization. ^1H NMR (400 MHz, Chloroform- d) δ 8.68 – 8.49 (m, 1H), 8.19 – 7.84 (m, 1H).

Preparation of 6-bromo-5-chloronicotinamide (8b).

A solution of **8a** (63 g, 290 mmol) in sulfuric acid (154 mL) was stirred for 12 hours at 20 °C. The reaction mixture was cooled to 0 °C and quenched by the addition of ice water (500 mL). The mixture was stirred for 10 minutes and the solid thus obtained was filtered and
5 dried under reduced pressure to **8b** (60 g, 88% yield). MS (ESI, positive ion) m/z: 235.2 (M+1).

Preparation of ethyl 2-(5-carbamoyl-3-chloropyridin-2-yl)-2,2-difluoroacetate (8c).

To a solution of copper (0) powder (27.0 g, 425 mmol) in DMSO (250 mL) at 20 °C was added ethyl 2-bromo-2,2-difluoroacetate (64.7 g, 319 mmol). The reaction mixture was
10 stirred at 20 °C for 1 hour and treated with **8b** (25 g, 106 mmol) was added portion-wise. The reaction mixture was stirred at 20 °C for 12 hours, and quenched with sat'd ammonia chloride (100 mL). The reaction mixture was filtered through a pad of celite. The filtrate was extracted with EtOAc (2 x 350 mL). The organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica gel
15 chromatography (10 - 50% EtOAc in hexanes) to afford **8c** (21 g, 71% yield). MS (ESI, positive ion) m/z: 279.4 (M+1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.89 (d, *J* = 1.9 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 6.39 (d, *J* = 72.1 Hz, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

Preparation of 5-chloro-6-(1,1-difluoro-2-hydroxyethyl) nicotinamide (8d).

To a solution of **8c** (21.00 g, 75 mmol) in THF (210 mL) at 0 °C was added sodium borohydride (2.85 g, 75 mmol) portion-wise followed by methanol (15.25 mL) dropwise. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (100 mL) and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by silica
25 gel chromatography (50% EtOAc in hexanes) to afford **8d** (16 g, 90% yield). MS (ESI, positive ion) m/z: 237.0 (M+1). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.99 (d, *J* = 2.0 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 8.35 (s, 1H), 7.89 (s, 1H), 5.62 (s, 1H), 4.12 (t, *J* = 14.6 Hz, 2H).

Preparation of 5-chloro-6-(1, 1-difluoro-2-iodoethyl) nicotinamide (8e).

To a solution of **8d** (16.0 g, 67.6 mmol) in acetonitrile (160 mL) at -10 °C was added pyridine (10.9 mL, 135 mmol) followed by dropwise addition of trifluoromethane sulphonic anhydride (28.6 g, 101 mmol). The reaction mixture was stirred at 0 °C for 30 minutes then
5 warmed to room temperature and treated with sodium iodide (30.4 g, 203 mmol) portion-
wise. The reaction mixture was stirred at 70 °C for 2 hours. After cooling to room
temperature, it was quenched with sat'd sodium thiosulfate solution (300 mL) and extracted
with EtOAc (2 x 350 mL). The combined organic solution was washed with brine (250 mL),
dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified
10 by silica gel chromatography (20 - 50% EtOAc in hexanes) to afford **8e** (12.0 g, 51% yield).
MS (ESI, positive ion) m/z: 347.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.00 (d, *J* = 1.8
Hz, 1H), 8.47 (d, *J* = 1.8 Hz, 1H), 8.37 (s, 1H), 7.91 (s, 1H), 4.14 (t, *J* = 16.4 Hz, 2H).

Preparation of (Z)-5-chloro-6-(1-fluoro-2-iodovinyl) nicotinamide (8f).

To the solution of **8e** (12 g, 34.6 mmol) in DMSO (120 mL) at 0 °C was added
15 potassium hydroxide (10.39 mL of 5 M solution, 51.9 mmol). The reaction mixture was
stirred at 0 °C for 5 hours. The reaction mixture was quenched with water and extracted with
EtOAc (3 x 250 mL). The combined organic solution was washed with brine (250 mL), dried
over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by
silica gel chromatography (50% EtOAc in hexanes) to afford **8f** (8.0 g, 71% yield). MS (ESI,
20 positive ion) m/z: 327.2 (M+1). ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97 (s, 1H), 8.41 (s, 1H),
8.32 (s, 1H), 7.85 (s, 1H), 7.05 (d, *J* = 36.0 Hz, 1H).

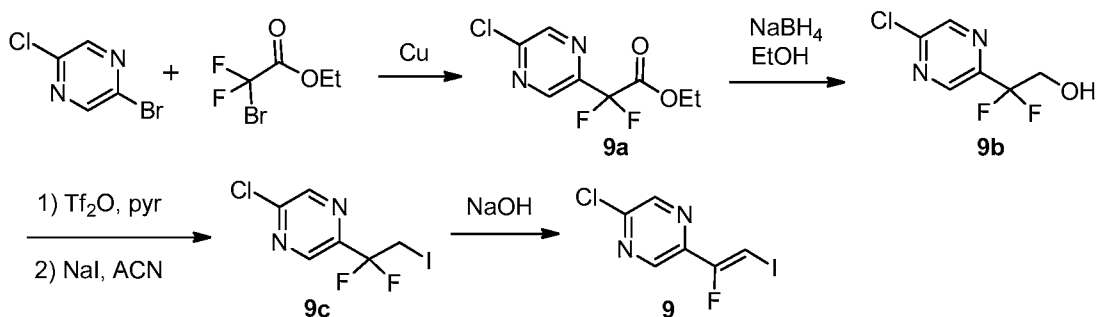
Preparation of (Z)-5-chloro-6-(1-fluoro-2-iodovinyl) nicotinonitrile (8).

To a solution of **8f** (8.0 g, 24.5 mmol) in THF (80 mL) at 0 °C was added drop N,N-
diisopropylethylamine (15.8 g, 123 mmol) followed by trifluoroacetic anhydride (17.3 mL,
25 123 mmol). The reaction mixture was stirred at 0 °C for 2 hours, then quenched with water
(250 mL) and extracted with EtOAc (3 x 250 mL). The combined organic solution was
washed with brine (250 mL), dried over Na₂SO₄ and concentrated under reduced pressure.
The crude residue was purified by silica gel chromatography (2 - 10% EtOAc in hexanes) to
afford Intermediate **8** (6.0 g, 79% yield) as an off-white solid. MS (ESI, positive ion) m/z: no

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ionization. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.84 – 8.67 (m, 1H), 8.15 – 8.00 (m, 1H), 7.21 – 6.99 (m, 1H).

Intermediate 9: (Z)-2-chloro-5-(1-fluoro-2-iodovinyl)pyrazine.



5 Preparation of ethyl 2-(5-chloropyrazin-2-yl)-2,2-difluoroacetate (9a).

To a suspension of copper(0) powder (244 g, 3877 mmol) in DMSO (5 L) was added ethyl 2-bromo-2,2-difluoroacetate (394 g, 1939 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour and 2-bromo-5-chloropyrazine (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China) (250 g, 1292 mmol) was added in portion-wise. The reaction mixture was stirred at room temperature for 3 hours, and quenched with sat'd solution of ammonia chloride (2.0 L). The mixture was filtered through a celite pad and the filtrate was extracted with EtOAc (2 x 2 L). The combined solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 2% EtOAc in hexanes) to afford **9a** (215 g, 70% yield) as a viscous colorless liquid. ^1H NMR (400 MHz, DMSO-*d*₆) δ 9.05 (d, J = 1.4 Hz, 1H), 8.98 (dd, J = 1.4, 0.7 Hz, 1H), 4.39 – 4.34 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

Preparation of 2-(5-chloropyrazin-2-yl)-2,2-difluoroethanol (9b).

To a solution of **9a** (215 g, 909 mmol) in ethanol (400 mL) was added sodium borohydride (34.4 g, 909 mmol) portion-wise at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (200 mL) and concentrated under reduced pressure to give the crude residue. The crude material was diluted with water (750 mL) and extracted with EtOAc (2 x 1.0 L). The combined organic solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 10% EtOAc in

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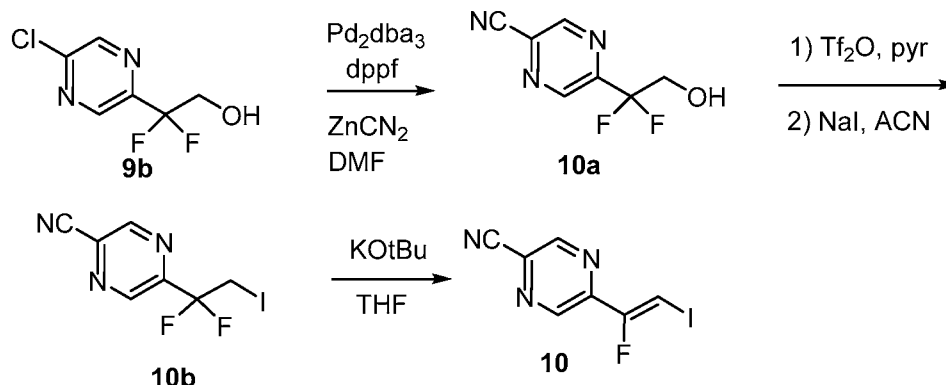
hexanes) to afford **9b** (130 g, 73% yield) as a colorless liquid. MS (ESI +ve ion) m/z: [M+1] = 195.0. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.97 (dt, *J* = 1.4, 0.7 Hz, 1H), 8.82 (d, *J* = 1.4 Hz, 1H), 5.70 (t, *J* = 6.4 Hz, 1H), 4.01 (td, *J* = 13.8, 6.4 Hz, 2H).

Preparation of 2-chloro-5-(1,1-difluoro-2-iodoethyl)pyrazine (9c).

5 To a solution of **9b** (130 g, 668 mmol) in acetonitrile (1.3 L) at 0 °C was added pyridine (54.0 mL, 668 mmol) followed by the dropwise addition of triflic anhydride (147 mL, 869 mmol). The reaction mixture was stirred at 0 °C for 30 minutes then room temperature for 10 minutes. Sodium iodide (300 g, 2004 mmol) was then added in a portion-wise manner. The reaction mixture was stirred at 70 °C for 2 hours then cooled to room
10 temperature and quenched with sat'd aqueous sodium thiosulfate solution (2.0 L). The mixture was extracted with EtOAc (2 x 2.0 L). The combined organic solution was washed with brine (2.0 L), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 2% EtOAc in hexanes) to afford **9c** (150.0 g, 71% yield) as a yellow solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.96 (s, 1H), 8.89 (s, 1H),
15 4.07 (t, *J* = 16.4 Hz, 2H).

Preparation of (Z)-2-chloro-5-(1-fluoro-2-iodovinyl)pyrazine (9).

 To a solution of **9c** (150 g, 493 mmol) in DMSO (900 mL) was added 5.0 M aqueous NaOH solution (148 mL, 740 mmol). The reaction mixture was stirred at 0 °C for 2 hours, and quenched with water (100 mL). It was extracted with EtOAc (2 x 200 mL). The
20 combined organic solution was washed with brine (300 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 5% EtOAc in hexanes) to afford Intermediate **9** (78 g, 54% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.59 (q, *J* = 1.4 Hz, 1H), 8.54 (q, *J* = 1.4 Hz, 1H), 7.05 (dd, *J* = 34.1, 1.3 Hz, 1H).

Intermediate 10: (Z)-5-(1-fluoro-2-iodovinyl)pyrazine-2-carbonitrile.**Preparation of 5-(1,1-difluoro-2-hydroxyethyl)pyrazine-2-carbonitrile (10a).**

A solution of 2-(5-chloropyrazin-2-yl)-2,2-difluoroethanol (**9b**, 30.0 g, 154 mmol) in DMF (300 mL) was degassed with nitrogen for 10 minutes. To the solution was sequentially added dppf (Strem Chemicals, Inc., Newburyport, MA, USA) (4.2 g, 7.7 mmol), $\text{Pd}_2(\text{dba})_3$ (Strem Chemicals, Inc., Newburyport, MA, USA) (7.1 g, 7.7 mmol), and $\text{Zn}(\text{CN})_2$ (36.2 g, 308 mmol). The reaction mixture was heated at 80 °C for 5 hours. It was cooled to room temperature and partitioned between water (200 mL) and EtOAc (200 mL). The reaction mixture was filtered through a pad of celite. The filtrate was transferred to a separatory funnel. The solution was separated. The aqueous layer was extracted with EtOAc (2 x 500 mL). The combined organic solution was washed with brine (300 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 - 20 % EtOAc in hexanes) to provide **10a** (18 g, 62% yield) as a clear oil. MS (ESI +ve ion) m/z : $[\text{M}+1]$ = no ionisation. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.39 (d, J = 1.5 Hz, 1H), 9.16 (d, J = 1.5 Hz, 1H), 5.77 (t, J = 6.4 Hz, 1H), 4.04 (td, J = 13.8, 6.4 Hz, 2H).

Preparation of 5-(1,1-difluoro-2-iodoethyl)pyrazine-2-carbonitrile (10b).

To a solution of 5-(1,1-difluoro-2-hydroxyethyl)pyrazine-2-carbonitrile (**10a**, 18 g, 97 mmol) in acetonitrile (180 mL) at 0 °C was added pyridine (15.7 mL, 194 mmol) followed by dropwise addition of triflic anhydride (65.7 mL, 389 mmol). The reaction mixture was stirred at 0 °C for 30 min then treated with sodium iodide (72.9 g, 486 mmol) in a portion-wise manner. The mixture was stirred at 70 °C for 3 hours then cooled to room temperature and quenched with sat'd aqueous sodium thiosulfate solution (100 mL). The mixture was

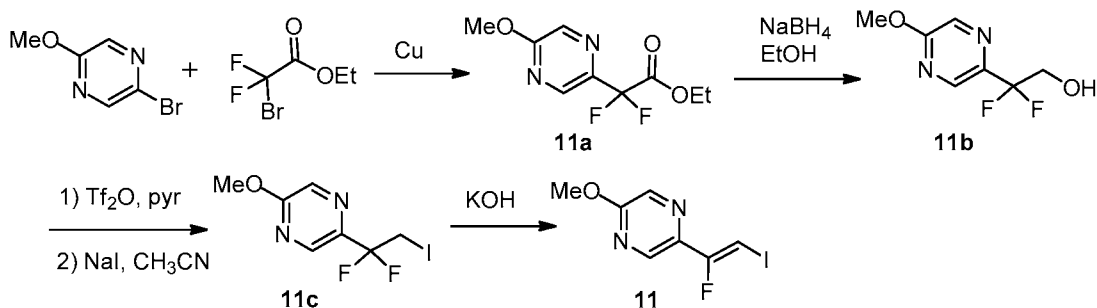
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extracted with EtOAc (2 x 200 mL). The combined organic solution was washed with brine (200 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (0 - 2% EtOAc in hexanes) afforded **10b** (10.0 g, 35% yield) as a yellow solid. MS (ESI +ve ion) m/z: [M+1] = no ionisation. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.10 (t, *J* = 1.2 Hz, 1H), 8.98 (dd, *J* = 1.6, 0.8 Hz, 1H), 3.91 (td, *J* = 14.3, 1.0 Hz, 2H).

Preparation of (Z)-5-(1-fluoro-2-iodovinyl)pyrazine-2-carbonitrile (**10**).

To a solution of **10b** (1.00 g, 3.39 mmol) in THF (10 mL) was added potassium *tert*-butoxide (0.76 g, 6.78 mmol) at -75 °C. The reaction mixture was stirred at -75 °C for 30 minutes. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by silica gel chromatography (0 - 5% EtOAc in hexanes) afforded Intermediate **10** (0.34 g, 36% yield) as an off-white solid. MS (ESI +ve ion) m/z: no ionisation. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.92 (t, *J* = 1.4 Hz, 1H), 8.84 (t, *J* = 1.2 Hz, 1H), 7.38 (d, *J* = 33.5 Hz, 1H).

Intermediate 11: (Z)-2-(1-fluoro-2-iodovinyl)-5-methoxypyrazine.

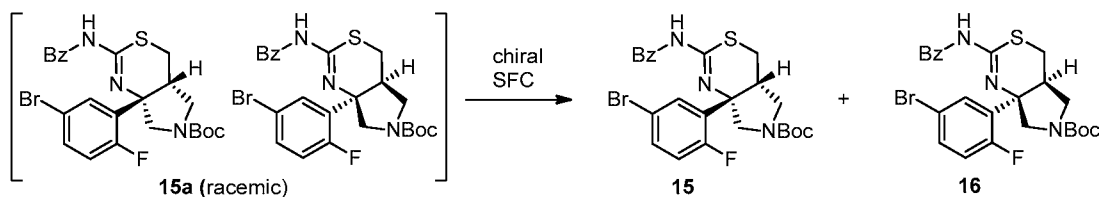


Ethyl 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2,2-difluoroacetate (**11a**, 80 g, 65% yield) as a yellow liquid was synthesized using a protocol similar to that described for **9a**, here starting from 2-bromo-5-methoxypyrazine (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China) (100 g, 529 mmol) and ethyl bromodifluoroacetate (215 g, 1058 mmol). MS (ESI +ve ion) m/z: [M+1] = 233.0. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 8.22 (s, 1H), 4.43 – 4.35 (m, 2H), 4.03 (m, 3H), 1.40 – 1.32 (m, 3H).

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Compounds **11b**, **11c**, and **11** were synthesized in a fashion similar to that described for **9b**, **9c**, and **9**, respectively. 2,2-Difluoro-2-(5-methoxypyrazin-2-yl)ethanol (**11b**): MS (ESI +ve ion) m/z : $[M+1] = 191.0$. ^1H NMR (400 MHz, Chloroform- d) δ 8.51 (d, $J = 2.0$ Hz, 1H), 8.21 (d, $J = 2.0$ Hz, 1H), 4.27 – 4.17 (m, 2H), 4.07 – 4.00 (m, 3H). 2-(1,1-Difluoro-2-iodoethyl)-5-methoxypyrazine (**11c**): MS (ESI +ve ion) m/z : $[M+1] = 301.0$. ^1H NMR (400 MHz, Chloroform- d) δ 8.46 (s, 1H), 8.22 (s, 1H), 4.03 (s, 3H), 3.93 – 3.86 (m, 2H). (Z)-2-(1-Fluoro-2-iodovinyl)-5-methoxypyrazine (**11**): MS (ESI +ve ion) m/z : $[M+1] = 281.0$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.43 (t, $J = 1.3$ Hz, 1H), 8.34 (t, $J = 1.2$ Hz, 1H), 6.86 (d, $J = 37.2$ Hz, 1H), 4.01 (s, 3H).

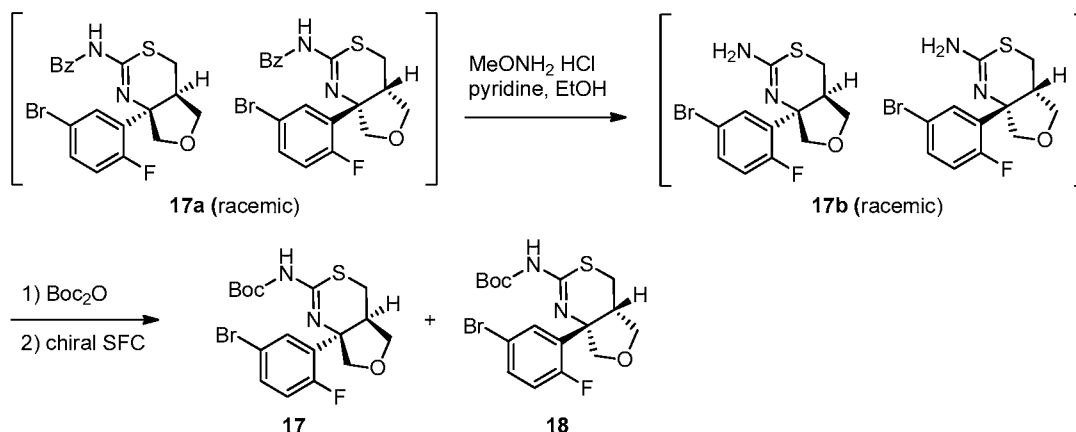
- 10 **Intermediate 15: (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate; and Intermediate 16: (4aS,7aR)-tert-butyl 2-benzamido-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate.**



- 15 **Racemic 15a** (prepared according to the procedures reported in WO 2014143579) (41.0 g) was subjected to chiral SFC to provide two compounds: the 1st eluent was **Intermediate 15** (16.0 g) and the 2nd eluent was **Intermediate 16** (17.0 g). ^1H NMR δ 8.11 (br. s., 2H), 7.61-7.40 (m, 5H), 7.12-6.93 (m, 1H), 4.21-3.99 (m, 1H), 3.84-3.61 (m, 3H), 3.33 (br. s., 1H), 3.07 (d, $J = 11.9$ Hz, 1H), 2.99- 2.82 (m, 1H), 1.48 (s, 9H). NH peak was not observed. The absolute stereochemistry was arbitrarily assigned. Preparative SFC conditions: Chiralpak AD, 300×50 mm I.D., 10 μm ; Mobile phase: A for CO_2 and B for methanol; Gradient: $\text{B}\% = 40\%$; Flow rate: 200 mL/min; Wavelength: 220 nm; Column temperature: 38 $^\circ\text{C}$; System back pressure: 100 bar; Cycle time: 4.3 min; Injection amount: compound was dissolved in ~500 mL of methanol, 7 mL per injection.
- 25 **Intermediate 17: tert-butyl ((4aR,7aR)-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)carbamate; and Intermediate 18: tert-butyl**

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((4aS,7aS)-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)carbamate.



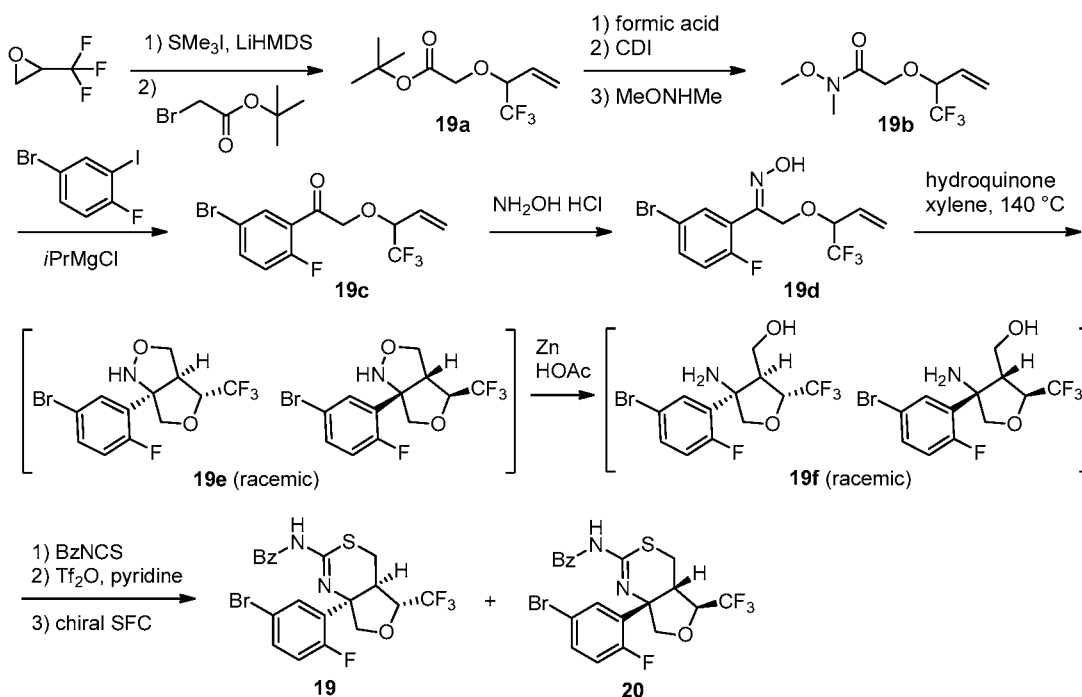
To a solution of compound 17a (prepared according to the procedures reported in WO2011005738) (50 g, 114 mmol) and O-methylhydroxylamine HCl salt (82 g, 987 mmol) in EtOH (500 mL) at 25 °C was added pyridine (78 g, 987 mmol). The mixture was stirred at 80 °C for 2 hours then concentrated *in vacuo*. Water (500 mL) and MTBE (500 mL) were added to the residue. The pH was adjusted to 7 by the dropwise addition of sat'd aqueous Na₂CO₃. The mixture was filtered and the white solid was collected to give compound 17b (25 g, 75 mmol, 65% yield). MS (ESI +ve ion) m/z: [M+1] = 331.0/333.0.

To a solution of compound 17b (39 g, 117 mmol) in DCM (390 mL) and H₂O (39 mL) was added NaHCO₃ (19.8 g, 235 mmol) and (Boc)₂O (38 g, 176 mmol). After the mixture was stirred at 25 °C for 2 hours, it was treated with water (100 mL) and extracted with DCM (2 x 100 mL). The combined organic solution was concentrated and the residue was purified by chromatography on silica gel (petroleum ether : EtOAc = 50:1 to 5:1) to give a racemic mixture of *tert*-butyl ((4aR,7aR)-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)carbamate and *tert*-butyl ((4aS,7aS)-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)carbamate (30 g, 69 mmol, 59% yield) as a white solid. MS (ESI +ve ion) m/z: 431.0/433.0. ¹H NMR (400 MHz, CDCl₃) δ 7.58 - 7.49 (m, 1 H), 7.47 - 7.39 (m, 1 H), 7.06 - 6.92 (m, 1 H), 4.43 - 4.34 (m, 1 H), 4.23 - 4.12 (m, 2 H), 3.89 - 3.75 (m, 1 H), 3.29 - 3.15 (m, 1 H), 3.09 - 2.97 (m, 1 H), 2.84 - 2.72 (m, 1 H), 1.53 (s, 9 H). NH peak was not observed.

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The racemic mixture was subjected to chiral SFC to provide two compounds: the 1st eluent was **17** (11 g, yield 37%) and the 2nd eluent was **18** (11 g, yield 37%). The absolute stereochemistry was arbitrarily assigned. Preparative SFC conditions: Column was Chiralpak (AS-H 250*30mm i.d. 5 μ m); Mobile phase: A for CO₂ and B for 2-propanol (0.1% NH₃H₂O); Gradient: B% = 25%; Flow rate: 60 g/min; Wavelength: 220 nm; Column temperature: 40 °C; System back pressure: 100 bar; Cycle time: 4 min; Injection amount: 70 mg per injection.

Intermediate 19: N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide; and **Intermediate 20:** N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.



Preparation of *tert*-butyl 2-((1,1,1-trifluorobut-3-en-2-yl)oxy)acetate (**19a**).

To a solution of trimethyl sulphoxonium iodide (Avra Synthesis Pvt. Ltd., Habsiguda, Hyderabad, India) (410.0 g, 2.0 mol) in THF (3.0 L) at -78 °C was slowly added LHMDS (1.6 M in THF, 1.7 L, 2.7 mol). The reaction mixture was stirred for 2 hours at -30 °C then treated with 2-trifluoromethyl oxirane (Manchester Chemicals, Alderley Edge, UK) (150.0 g,

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1.3 mol). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. *t*-Butyl-bromoacetate (Spectrochem Pvt. Ltd., Kalbadevi Road, Mumbai, India) (522.0 g, 2.6 mol) in NMP (750 mL) was added and the reaction mixture was stirred for 12 hours at room temperature then quenched with saturated ammonium chloride solution (3.0 L) and
5 extracted with EtOAc (3 x 5.0 L). The combined organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was passed through a short column of silica gel (eluted with 5% EtOAc in hexanes) to provide *tert*-butyl 2-((1,1,1-trifluorobut-3-en-2-yl)oxy)acetate (**19a**, 200.0 g, 62% yield). MS *m/z*: no ionization.

Preparation of N-methoxy-N-methyl-2-((1,1,1-trifluorobut-3-en-2-yl)oxy)acetamide
10 **(19b).**

A solution of **19a** (200.0 g, 830 mmol) in formic acid (400 mL) was heated to 55 °C for 3 hours then concentrated under reduced pressure. The residue was dissolved in DCM (2.0 L), cooled to at 0 °C, and treated with CDI (162.0 g, 990 mmol). The reaction mixture was stirred at 0 °C for one hour and then *N,O*-dimethyl hydroxylamine hydrochloride (97.0
15 g, 990 mmol) was added. The reaction mixture was stirred at room temperature for 12 hours then quenched with water (2.0 L) and extracted by DCM (3 x 5.0 L). The combined organic solution was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (20% EtOAc in hexanes) to afford **19b** (90.0 g, 48% yield) as an oil. MS *m/z* = 228.2 [*M*+*H*]⁺. ¹H NMR (400 MHz, Chloroform-*d*)
20 δ 5.82 (ddd, *J* = 17.4, 7.8, 2.2 Hz, 1H), 5.67 – 5.57 (m, 2H), 4.49 – 4.35 (m, 3H), 3.71 (d, *J* = 1.7 Hz, 3H), 3.21 (d, *J* = 1.7 Hz, 3H).

Preparation of 1-(5-bromo-2-fluorophenyl)-2-((1,1,1-trifluorobut-3-en-2-yl)oxy)ethanone (19c).

A solution of 4-bromo-1-fluoro-2-iodobenzene (177.0 g, 580 mmol) in THF (400
25 mL) at 0 °C was treated with isopropyl magnesium chloride (2.0 M in THF, 290 mL, 580 mmol) and stirred for 30 minutes at 0 °C. The mixture was treated with a solution of **19b** (112.5 g, 490 mmol) in THF (400 mL) and stirred for 2 hours at room temperature. The reaction was quenched with sat'd aqueous NH₄Cl and extracted with EtOAc (3 x 1.0 L). The combined organic solution was dried over sodium sulfate and concentrated under reduced
30 pressure. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to

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give **19c** (125.0 g, 74%). MS m/z = 339.2 $[M-H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 8.07 (dd, J = 6.1, 2.7 Hz, 1H), 7.68 (ddd, J = 8.8, 4.6, 2.6 Hz, 1H), 7.16 – 6.99 (m, 1H), 5.85 (ddd, J = 17.4, 10.3, 7.2 Hz, 1H), 5.69 – 5.52 (m, 2H), 4.87 – 4.72 (m, 2H), 4.42 – 4.30 (m, 1H).

5 **Preparation of (E)-1-(5-bromo-2-fluorophenyl)-2-((1,1,1-trifluorobut-3-en-2-yl)oxy)ethanone oxime (19d).**

To a solution of **19c** (250.0 g, 730 mmol) in methanol (5.0 L) at 0 °C was added sodium acetate (120.2 g, 1460 mmol) and hydroxylamine hydrochloride (76.0 g, 1090 mmol). The resulting mixture was heated to 55 °C for 3 hours. The reaction was quenched
10 with water (1.0 L) and the mixture was concentrated under reduced pressure to remove most of the MeOH. The remaining mixture was extracted with EtOAc (3 x 3.0 L). The combined organic solution was dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (15% EtOAc in hexanes) to provide **19d** (250.0 g, 96% yield) as an off-white solid. MS m/z : 356.1 $[M+H]^+$. 1H NMR
15 (300 MHz, DMSO- d_6) δ 12.02 (s, 1H), 7.69 – 7.59 (m, 2H), 7.25 (ddd, J = 10.1, 8.8, 3.9 Hz, 1H), 5.74 – 5.60 (m, 1H), 5.51 (ddt, J = 16.8, 11.1, 1.7 Hz, 2H), 4.73 (s, 2H), 4.54 (dd, J = 8.9, 5.0 Hz, 1H).

Preparation of (3aS,4R,6aR)-6a-(5-bromo-2-fluorophenyl)-4-(trifluoromethyl)hexahydrofuro[3,4-c]isoxazole and (3aR,4S,6aS)-6a-(5-bromo-2-fluorophenyl)-4-(trifluoromethyl)hexahydrofuro[3,4-c]isoxazole (racemic) (19e).

To a solution of **19d** (125.0 g, 351 mmol) in xylene (1.5 L) was added hydroquinone (9.7 g, 88 mmol) at room temperature. The resulting mixture was heated at 140 °C for 18 hours. The reaction mixture was cooled to room temperature then treated with water (3.0 L) and extracted with EtOAc (3 x 3.0 L). The combined organic solution was dried over Na₂SO₄
25 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5% EtOAc in hexanes) to give **19e** (87.5 g, 70% yield) as an off-white solid. MS m/z = 356.0 $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 7.84 (dd, J = 6.9, 2.6 Hz, 1H), 7.60 (ddt, J = 8.9, 4.5, 2.4 Hz, 1H), 7.25 (ddd, J = 11.2, 8.7, 2.2 Hz, 1H), 6.72 (s, 1H), 4.66 (qd, J = 7.9, 4.4 Hz, 1H), 4.16 (q, J = 9.9 Hz, 3H), 3.99 (t, J = 5.6 Hz, 1H), 3.83 (dt, J =
30 6.9, 4.1 Hz, 1H).

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Preparation of ((2R,3S,4R)-4-amino-4-(5-bromo-2-fluorophenyl)-2-(trifluoromethyl)tetrahydrofuran-3-yl)methanol and ((2S,3R,4S)-4-amino-4-(5-bromo-2-fluorophenyl)-2-(trifluoromethyl)tetrahydrofuran-3-yl)methanol (racemic) (19f).

Zinc(0) powder (88 g, 1.34 mol) was treated with acetic acid (400 mL) slowly while
5 maintaining the internal temperature below 10 °C. After 30 minutes of stirring, a solution of
19e (160 g, 0.449 mol) in THF (1.5 L) was added. The reaction mixture was stirred for 16
hours at room temperature then filtered through a pad of celite. The filter cake was washed
with THF (2 x 200 mL). The filtrate was concentrated under reduced pressure. The residue
was dissolved in EtOAc (3.0 L) and washed with sat'd aqueous sodium bicarbonate solution
10 (3.0 L). The organic layer was concentrated under reduced pressure and the residue was
purified by silica gel chromatography (40% EtOAc in hexanes) to give 19f (75.0 g, 47%
yield). MS (ESI +ve ion) $m/z = 358.0$ [M+1]. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (dt, J
= 7.3, 2.1 Hz, 1H), 7.52 (ddt, J = 8.5, 4.0, 2.1 Hz, 1H), 7.16 (ddd, J = 12.0, 8.6, 1.5 Hz, 1H),
4.38 (p, J = 7.7 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.90 (d, J = 1.6 Hz, 1H), 3.81 – 3.75 (m, 1H),
15 3.71 – 3.65 (m, 1H), 3.55 (dd, J = 11.5, 5.4 Hz, 1H), 3.01 (td, J = 7.9, 5.3 Hz, 1H). NH₂
proton not observed.

**Preparation of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(trifluoromethyl)-
4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (Intermediate 19) and
N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-
20 4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (Intermediate 20).**

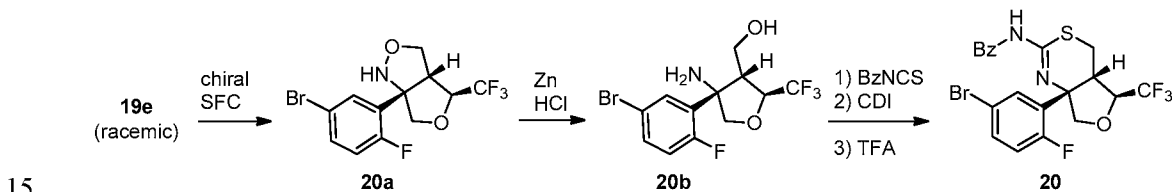
A solution of racemic 19f (20.0 g, 55.8 mmol) in THF (300 mL) at 0 °C was treated
with benzoyl isothiocyanate (Shanghai Fchemicals Technology Co., Ltd., Shanghai, China)
(10.9 g, 67.0 mmol). The resulting mixture was stirred for 12 hours at room temperature then
concentrated under reduced pressure. The residue was dissolved in DCM (300 mL), cooled
25 to -20 °C, and then treated with pyridine (13.2 g, 168.0 mmol) followed by triflic anhydride
(31.5 g, 112.2 mmol) dropwise. The reaction mixture was stirred for 2 hours at -20 °C then
diluted with DCM (500 mL) and washed with sodium bicarbonate (3 x 500 mL). The
organic layer was concentrated under reduced pressure. The residue was purified by silica gel
chromatography (20% EtOAc in hexane) to give the racemic product (6.5 g, 23%) with MS
30 (ESI +ve ion) $m/z = 503.1$ [M+1]. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.99 (d, J = 7.6 Hz,
2H), 7.60 (dd, J = 8.6, 6.3 Hz, 1H), 7.50 (td, J = 9.1, 8.1, 6.0 Hz, 4H), 7.10 – 6.98 (m, 1H),

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4.80 (p, $J = 7.0$ Hz, 1H), 4.60 (d, $J = 8.7$ Hz, 1H), 3.95 (dd, $J = 8.0, 5.1$ Hz, 1H), 3.57 – 3.48 (m, 1H), 3.15 (dd, $J = 14.1, 3.1$ Hz, 1H), 2.83 (dd, $J = 14.0, 3.9$ Hz, 1H). NH proton not observed.

Two more batches were performed on same scale and the combined racemic product (20 g) was purified by chiral SFC to give 2 compounds: the 1st eluent was Intermediate **19** (5.5 g, 99% *ee*) and the 2nd eluent was Intermediate **20** (6.5 g, 99% *ee*). The absolute stereochemistry of Intermediate **19** and **20** was arbitrarily assigned. Preparative SFC conditions: column = Lux-C3 (250 × 30mm, 5 μ m); mobile phase = 55:45 (liquid CO₂ : methanol); flow rate = 150 mL/min; wave length = 240 nm; cycle time = 5 min; run time = 7 min; pressure = 100 bar; sample load = 100 mg/injection; sample was dissolved in methanol 1 g/mL.

Alternative procedure for the preparation of N-((4a*S*,5*S*,7a*S*)-7a-(5-bromo-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide (20**).**



Preparation of (3a*R*,4*S*,6a*S*)-6a-(5-bromo-2-fluorophenyl)-4-(trifluoromethyl)hexahydrofuro[3,4-*c*]isoxazole (20a**).**

Racemic **19e** (87.5 g) was subjected to chiral SFC to give 2 compounds: the 1st eluent was (3a*R*,4*S*,6a*S*)-6a-(5-bromo-2-fluorophenyl)-4-(trifluoromethyl)hexahydrofuro[3,4-*c*]isoxazole (**20a**, 34.2 g, 99% *ee*) and the 2nd eluent was (3a*S*,4*R*,6a*R*)-6a-(5-bromo-2-fluorophenyl)-4-(trifluoromethyl)hexahydrofuro[3,4-*c*]isoxazole (32.3 g, 99% *ee*). MS $m/z = 356.0$ [M+H]⁺. Preparative SFC conditions: column = Chiralpak ADH (250 × 30mm, 5 μ m); mobile phase = 85:15 (liquid CO₂ : 20 mM NH₃ in methanol); flow rate = 100 mL/min; wave length = 230 nm; cycle time = 2 min; run time = 5 min; pressure = 100 bar; sample load = 100 mg/injection; sample was dissolved in methanol 1 g/mL.

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Preparation of ((2S,3R,4S)-4-amino-4-(5-bromo-2-fluorophenyl)-2-(trifluoromethyl)tetrahydrofuran-3-yl)methanol (20b).

Zinc(0) powder (13.8 g, 211.0 mmol) was added in a portion-wise manner to a solution of **20a** (25 g, 70.2 mmol) in ethanol (375 mL) at room temperature. The mixture
5 was cooled with an ice bath and treated with HCl (84.0 mL of 5.0 N aqueous solution, 421.0 mmol) dropwise over a period of 30 minutes. The reaction mixture was stirred for 45 minutes at room temperature then filtered through a sintered glass funnel. The filter cake was washed with EtOAc (2 x 500 mL). The filtrate was evaporated to dryness under reduced pressure. The residue was partitioned between sat'd aqueous NH₄Cl (500 mL) and extracted with
10 EtOAc (500 mL). The aqueous layer was further extracted with EtOAc (2 x 500 mL). The combined organic solution was washed with brine (750 mL) and evaporated to dryness under reduced pressure to provide **20b** (25.0 g, 99% yield) as an off-white solid which was used in next step without further purification. MS *m/z* = 358.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.90 (dd, *J* = 7.3, 2.8 Hz, 1H), 7.51 (ddd, *J* = 8.7, 4.2, 2.7 Hz, 1H), 7.16 (ddd, *J* = 12.0, 8.6, 3.0 Hz, 1H), 4.61 (t, *J* = 5.3 Hz, 1H), 4.37 (m, 1H), 4.15 (dd, *J* = 8.5, 2.8 Hz, 1H), 3.77 (dd, *J* = 8.3, 3.1 Hz, 1H), 3.68 (dt, *J* = 12.3, 6.8 Hz, 1H), 3.54 (dt, *J* = 11.1, 5.3 Hz, 1H), 3.01 (td, *J* = 8.2, 5.4 Hz, 1H), 2.34 (d, *J* = 3.1 Hz, 2H).

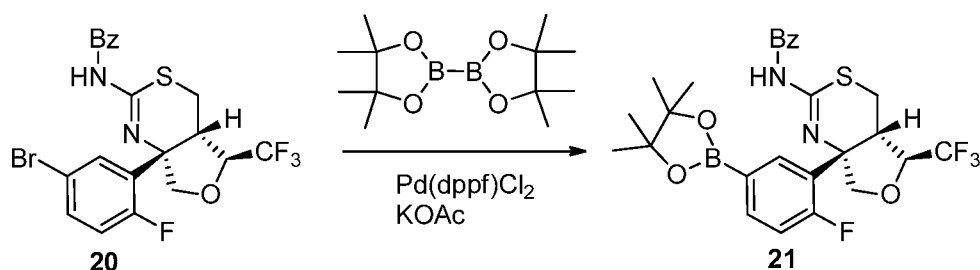
Preparation of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (20).

To a solution of **20b** (25.0 g, 69.8 mmol) in THF (250 mL) at 45 °C under a nitrogen atmosphere was added benzoyl isothiocyanate (11.5 g, 77.0 mmol) in THF (125 mL) dropwise over a period of 60 minutes. CDI (22.6 g, 139.6 mmol) was added and the resulting mixture was stirred at 65 °C for 8 hours. The reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in DCM (375.0 mL) and treated with TFA
25 (250.0 mL) dropwise. The mixture was stirred at ambient temperature for 3 hours then concentrated to dryness. The residue was diluted with EtOAc (1.0 L) and washed with 1.5 N aqueous HCl (500 mL) followed by brine (500 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 to 10% EtOAc in hexanes) to afford Intermediate **20** (26.5 g, 75% yield, 99% *ee*) as a
30 white solid. MS *m/z* = 503.0 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 7.7 Hz, 2H), 7.67 – 7.59 (m, 1H), 7.57 – 7.47 (m, 4H), 7.11 – 7.01 (m, 1H), 4.80 (p, *J* = 7.0 Hz,

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1H), 4.62 (d, $J = 8.9$ Hz, 1H), 4.06 (d, $J = 9.2$ Hz, 1H), 3.58 (dt, $J = 7.7, 3.5$ Hz, 1H), 3.18 (dd, $J = 14.0, 3.0$ Hz, 1H), 2.86 (dd, $J = 14.1, 3.9$ Hz, 1H). NH proton not observed.

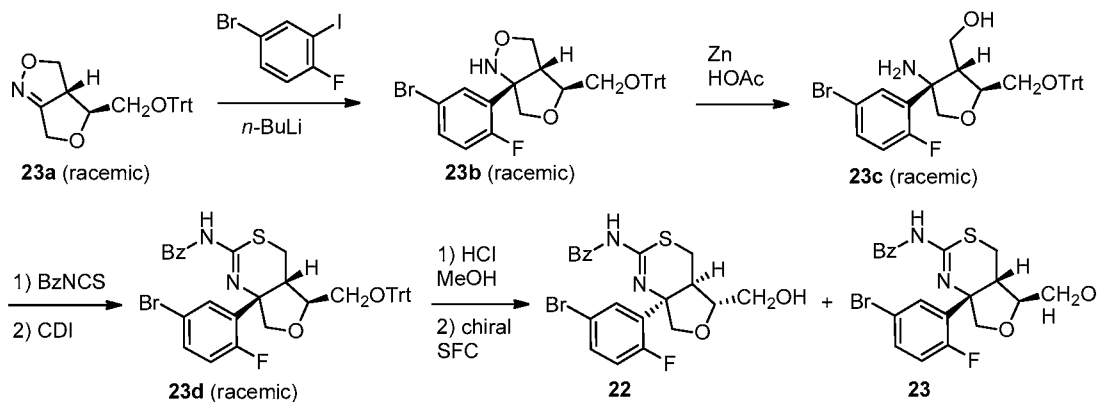
Intermediate 21: N-((4aS,5S,7aS)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.



A suspension of **20** (3.5 g, 6.95 mmol), bis(pinacolato)diboron (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA) (3.53 g, 13.91 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane adduct (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA) (0.284 g, 0.348 mmol), and potassium acetate (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA, 2.047 g, 20.86 mmol) in 1,4-dioxane (30 mL) was sparged with argon for 5 minutes then heated to 100 °C for 45 minutes. The reaction was partitioned between EtOAc (150 mL) and 5% aqueous NaHCO₃ (50 mL). The organic solution was washed with brine (20 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 to 15% EtOAc/EtOH (3/1) in heptane) to afford boronic ester **21** (3.3 g, 86% yield) as a tan foam. MS (ESI +ve ion) m/z : $[M+1] = 551.1$. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.06 (br s, 2 H), 7.81 - 7.88 (m, 1 H), 7.76 (d, $J = 8.41$ Hz, 1 H), 7.43 - 7.63 (m, 4 H), 7.15 (dd, $J = 8.22, 4.50$ Hz, 1 H), 4.79 - 4.89 (m, 1 H), 4.48 - 4.58 (m, 1 H), 4.06 - 4.19 (m, 1 H), 3.56 - 3.64 (m, 1 H), 3.29 - 3.40 (m, 1 H), 2.83 - 2.93 (m, 1 H), 1.32 - 1.36 (s, 12 H).

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Intermediate 22: N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide; and **Intermediate 23:** N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.



5

Preparation of racemic mixture of (3aS,4R)-4-((trityloxy)methyl)-3,3a,4,6-tetrahydrofuro[3,4-c]isoxazole and (3aR,4S)-4-((trityloxy)methyl)-3,3a,4,6-tetrahydrofuro[3,4-c]isoxazole (23b).

A solution of 4-bromo-1-fluoro-2-iodobenzene (Combi-Blocks, San Diego, CA, USA) (60.0 g, 197 mmol) in THF (1.0 L) at -78 °C was treated with *n*-butyl lithium (1.6 M in THF, 123.0 mL, 197 mmol) dropwise followed by borontrifluoride diethyl etherate (7.36 g, 52 mmol) dropwise. The resulting mixture was stirred for 10 minutes at -78 °C then treated with a solution of **23a** (prepared according to the methods described in WO2012098461) (40.0 g, 104 mmol) in THF (200 mL) dropwise and stirred at -78 °C for 1.5 hours. The reaction was quenched with sat'd aqueous NH₄Cl (1.0 L) and extracted with ethyl acetate (3 x 1.0 L). The combined organic solution was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to give **23b** (21.0 g, 36% yield). MS (ESI +ve ion) *m/z*: 560.2/562.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.79 – 7.72 (m, 1H), 7.55 (dt, *J* = 7.1, 3.1 Hz, 1H), 7.40 – 7.30 (m, 13H), 7.29 – 7.18 (m, 3H), 4.18 – 4.01 (m, 3H), 3.88 (d, *J* = 10.0 Hz, 1H), 3.74 – 3.68 (m, 1H), 3.29 – 3.20 (m, 3H), 3.11 – 3.06 (m, 1H).

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Preparation of racemic mixture of ((2R,3S,4R)-4-amino-4-(5-bromo-2-fluorophenyl)-2-((trityloxy)methyl)tetrahydrofuran-3-yl)methanol and ((2S,3R,4S)-4-amino-4-(5-bromo-2-fluorophenyl)-2-((trityloxy)methyl)tetrahydrofuran-3-yl)methanol (23c).

To a solution of **23b** (20.0 g, 35.7 mmol) in acetic acid (70 mL) at 0 °C was added
5 zinc(0) powder (5.9 g, 89.0 mmol) in portion-wise manner and the reaction mixture was
stirred at room temperature for 6 hours. The mixture was diluted with ethyl acetate (100 mL)
and filtered through a pad of celite. The celite bed was washed with ethyl acetate (2 x 50
mL). The filtrate was concentrated under reduced pressure. The residue was neutralized to pH
~7 with aqueous ammonia solution and extracted with ethyl acetate (5 x 100 mL). The
10 combined organic solution was dried over Na₂SO₄ and concentrated to give **23c** (18.0 g, 90%
yield) which was used without further purification. MS (ESI +ve ion) m/z: 562.2/564.2
[M+H]⁺.

**Preparation of racemic mixture of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-
((trityloxy)methyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide and
15 N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-((trityloxy)methyl)-4a,5,7,7a-
tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (23d).**

A solution of **23c** (18.0 g, 32.1 mmol) in THF (400 mL) at 0 °C was treated with
benzoyl isothiocyanate (6.27 g, 38.4 mmol) stirred at room temperature for 6 hours. The
reaction mixture was cooled to 0 °C and CDI (7.78 g, 48.0 mmol) was added in small
20 portions. The mixture was stirred at room temperature for 24 hours then quenched with
water (400 mL) and extracted with ethyl acetate (4 x 500 mL). The combined organic
solution was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel
chromatography (50% ethyl acetate in hexanes) to afford **23d** (13.5 g, 60% yield). MS (ESI
+ve ion) m/z: 707.1/709.1 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 11.82 (s, 1H), 8.88
25 (s, 1H), 8.10 (s, 1H), 7.74 – 7.68 (m, 3H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H),
7.40 – 7.37 (m, 5H), 7.31 – 7.26 (m, 10H), 5.29 (d, *J* = 10.3 Hz, 1H), 4.74 (dd, *J* = 12.0, 8.2
Hz, 1H), 4.50 (dd, *J* = 11.9, 4.6 Hz, 1H), 4.39 (d, *J* = 10.1 Hz, 1H), 4.04 (dd, *J* = 8.0, 4.0 Hz,
1H), 3.46 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.31 – 3.19 (m, 2H).

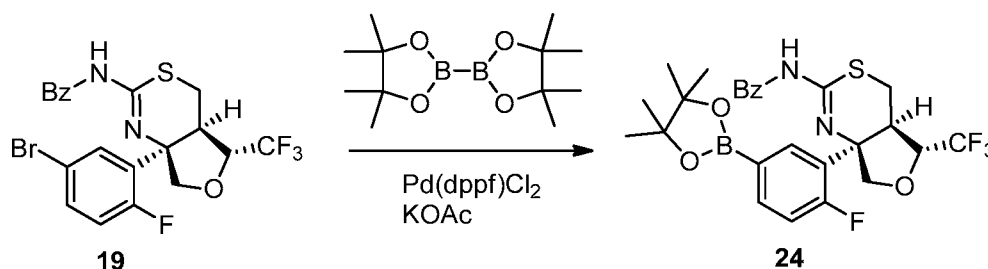
**Preparation of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-
30 4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (22) and N-**

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((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (23).

To a solution of **23d** (20.0 g, 28.3 mmol) in methanol (100 mL) at 0 °C was added HCl (35.0 mL of 4 N solution in methanol, 140 mmol) and the resulting mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The residue was diluted with water (250 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (25% ethyl acetate in hexanes) to afford a racemic mixture of **22** and **23** (4.6 g, 35%) as a white solid. MS (ESI +ve ion) m/z: 465.2/467.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.11 (s, 2H), 7.60 – 7.44 (m, 5H), 7.05 (dd, *J* = 11.7, 8.6 Hz, 1H), 4.52 (dd, *J* = 12.3, 9.0 Hz, 2H), 4.06 (s, 1H), 4.00 – 3.92 (m, 1H), 3.81 – 3.73 (m, 2H), 3.34 (s, 1H), 3.23 (d, *J* = 14.1 Hz, 1H), 2.83 (d, *J* = 13.6 Hz, 1H), 2.04 (s, 1H). The racemic mixture of **22** and **23** (4.6 g) was subjected to chiral SFC to provide 2 compounds: the 1st eluent was Intermediate **22** (1.45 g, 100% *ee*) as a white solid and the 2nd eluent was Intermediate **23** (1.45 g, 99.3% *ee*) as a white solid. Preparative SFC purification method: Chiralpak IA (250 × 30 mm, 5 μm); mobile phase (70:30) = (A:B), A = liquid CO₂, B = 20 mM ammonia in MeOH; flow rate = 100 mL/min; wave length = 250 nm; inlet pressure = 205 bar; 4.6 g of sample was dissolved in 92 mL of THF/MeOH (1/1), sample load = 1.0 mL/injection; run time = 10 minutes, cycle time = 5 minutes. The absolute stereochemistry was arbitrarily assigned.

Intermediate 24: N-((4aR,5R,7aR)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(trifluoromethyl)-4a,5,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.

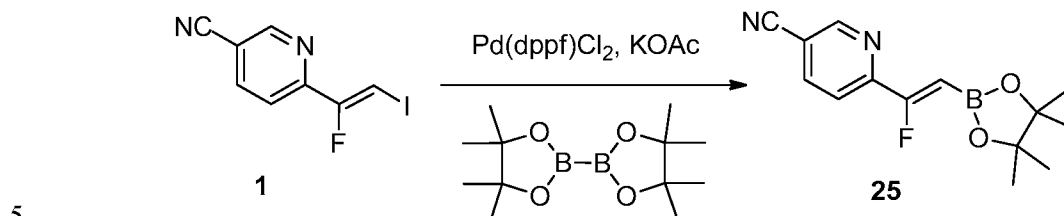


Boronic ester **24** (3.3 g, 86 % yield) as a tan foam was prepared in a fashion similar to that described for boronic ester **21**, here starting from N-((4aR,5R,7aR)-7a-(5-bromo-2-

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fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**19**) (3.5 g, 6.95 mmol). MS (ESI +ve ion) m/z : $[M+1] = 551.1$.

Intermediate 25: (Z)-6-(1-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)nicotinonitrile.



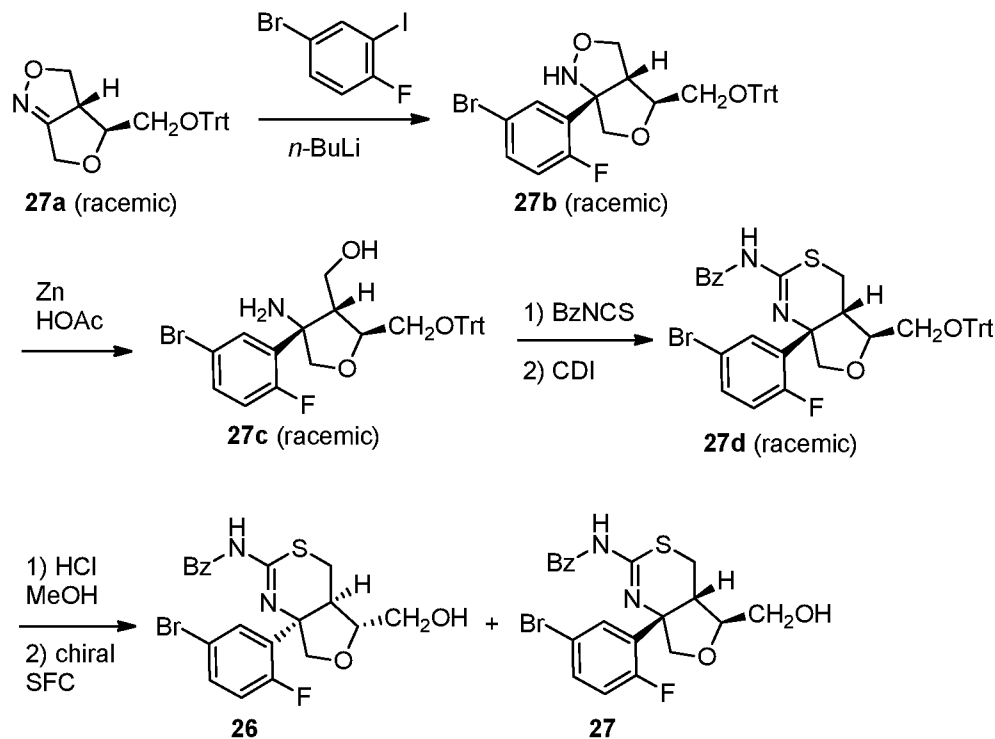
A mixture of (Z)-6-(1-fluoro-2-iodovinyl)nicotinonitrile (**1**) (1.00 g, 3.65 mmol), KOAc (0.71 g, 7.30 mmol) and bis(pinacolato)diboron (Sigma-Aldrich, St. Louis, MO, USA) (1.39 g, 5.47 mmol) in 1,4-dioxane (20 mL) was purged with nitrogen for 10 min then treated with $\text{PdCl}_2(\text{dppf})\text{-CH}_2\text{Cl}_2$ adduct (0.15 g, 0.18 mmol). The mixture was purged with nitrogen for 10 minutes then heated at 90 °C for 16 hours. After cooling to room temperature, the reaction mixture was filtered through a celite pad and washed with ethyl acetate (20 mL). The filtrate was evaporated under vacuum. The residue was purified by silica gel chromatography (20% to 30% EtOAc in hexanes) to provide (Z)-6-(1-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)nicotinonitrile (**1**) (0.50 g, 1.82 mmol, 50% yield) as an off-white solid. MS (ESI positive ion) m/z : not ionized. ^1H NMR (300 MHz, Chloroform- d) δ 8.99 – 8.63 (m, 1H), 8.20 – 7.84 (m, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 6.26 (d, $J = 52.8$ Hz, 1H), 1.37 – 1.27 (m, 12H). ^{19}F NMR (376 MHz, Chloroform- d) δ -112.82 (s).

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Intermediate 26: N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide; and **Intermediate 27:** N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.



5

Preparation of racemic mixture of (3aS,4R)-4-((trityloxy)methyl)-3,3a,4,6-tetrahydrofuro[3,4-c]isoxazole and (3aR,4S)-4-((trityloxy)methyl)-3,3a,4,6-tetrahydrofuro[3,4-c]isoxazole (27b**).**

A solution of 4-bromo-1-fluoro-2-iodobenzene (Combi-Blocks, San Diego, CA, USA) (60.0 g, 197 mmol) in THF (1.0 L) at -78 °C was treated with *n*-butyl lithium (1.6 M in THF, 123.0 mL, 197 mmol) dropwise followed by borontrifluoride diethyl etherate (7.36 g, 52 mmol) dropwise. The resulting mixture was stirred for 10 minutes at -78 °C then treated with a solution of **27a** (prepared according to the methods described in WO2012098461) (40.0 g, 104 mmol) in THF (200 mL) dropwise and stirred at -78 °C for 1.5 hours. The reaction was quenched with sat'd aqueous NH₄Cl (1.0 L) and extracted with ethyl acetate (3 x 1.0 L). The combined organic solution was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexanes) to give **27b**

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(21.0 g, 36% yield). MS (ESI +ve ion) m/z : 560.2/562.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.79 – 7.72 (m, 1H), 7.55 (dt, $J = 7.1, 3.1$ Hz, 1H), 7.40 – 7.30 (m, 13H), 7.29 – 7.18 (m, 3H), 4.18 – 4.01 (m, 3H), 3.88 (d, $J = 10.0$ Hz, 1H), 3.74 – 3.68 (m, 1H), 3.29 – 3.20 (m, 3H), 3.11 – 3.06 (m, 1H).

5 **Preparation of racemic mixture of ((2R,3S,4R)-4-amino-4-(5-bromo-2-fluorophenyl)-2-((trityloxy)methyl)tetrahydrofuran-3-yl)methanol and ((2S,3R,4S)-4-amino-4-(5-bromo-2-fluorophenyl)-2-((trityloxy)methyl)tetrahydrofuran-3-yl)methanol (27c).**

To a solution of **27b** (20.0 g, 35.7 mmol) in acetic acid (70 mL) at 0 °C was added zinc(0) powder (5.9 g, 89.0 mmol) in a portion-wise manner and the reaction mixture was
10 stirred at room temperature for 6 hours. The mixture was diluted with ethyl acetate (100 mL) and filtered through a pad of celite. The celite bed was washed with ethyl acetate (2 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was neutralized to pH ~7 with aqueous ammonia solution and extracted with ethyl acetate (5 x 100 mL). The combined organic solution was dried over Na₂SO₄ and concentrated to give **27c** (18.0 g, 90%
15 yield) which was used without further purification. MS (ESI +ve ion) m/z : 562.2/564.2 $[M+H]^+$.

Preparation of racemic mixture of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-((trityloxy)methyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide and N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-((trityloxy)methyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (27d).

A solution of **27c** (18.0 g, 32.1 mmol) in THF (400 mL) at 0 °C was treated with benzoyl isothiocyanate (6.27 g, 38.4 mmol) then stirred at room temperature for 6 hours. The reaction mixture was cooled to 0 °C and CDI (7.78 g, 48.0 mmol) was added in small portions. The mixture was stirred at room temperature for 24 hours then quenched with
25 water (400 mL) and extracted with ethyl acetate (4 x 500 mL). The combined organic solution was dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (50% ethyl acetate in hexanes) to afford **27d** (13.5 g, 60% yield). MS (ESI +ve ion) m/z : 707.1/709.1 $[M+H]^+$. 1H NMR (400 MHz, Chloroform- d) δ 11.82 (s, 1H), 8.88 (s, 1H), 8.10 (s, 1H), 7.74 – 7.68 (m, 3H), 7.63 (t, $J = 7.3$ Hz, 1H), 7.50 (t, $J = 7.8$ Hz, 2H),
30 7.40 – 7.37 (m, 5H), 7.31 – 7.26 (m, 10H), 5.29 (d, $J = 10.3$ Hz, 1H), 4.74 (dd, $J = 12.0, 8.2$

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Hz, 1H), 4.50 (dd, $J = 11.9, 4.6$ Hz, 1H), 4.39 (d, $J = 10.1$ Hz, 1H), 4.04 (dd, $J = 8.0, 4.0$ Hz, 1H), 3.46 (dd, $J = 10.6, 3.8$ Hz, 1H), 3.31 – 3.19 (m, 2H).

Preparation of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (26) and N-

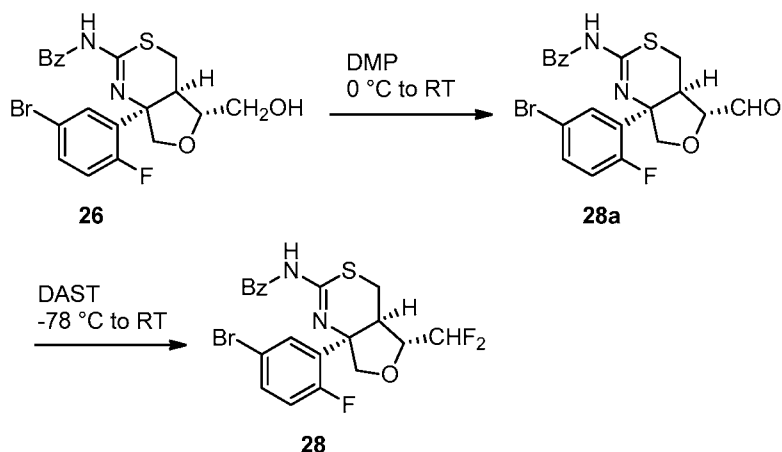
5 **((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (27).**

To a solution of **27d** (20.0 g, 28.3 mmol) in methanol (100 mL) at 0 °C was added HCl (35.0 mL of 4 N solution in methanol, 140 mmol) and the resulting mixture was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. The
10 residue was diluted with water (250 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic solution was dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (25% ethyl acetate in hexanes) to afford a racemic mixture of compounds **26** and **27** (4.6 g, 35%) as a white solid. MS (ESI +ve ion) m/z : 465.2/467.2 [M+H]⁺. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.11 (s, 2H), 7.60
15 – 7.44 (m, 5H), 7.05 (dd, $J = 11.7, 8.6$ Hz, 1H), 4.52 (dd, $J = 12.3, 9.0$ Hz, 2H), 4.06 (s, 1H), 4.00 – 3.92 (m, 1H), 3.81 – 3.73 (m, 2H), 3.34 (s, 1H), 3.23 (d, $J = 14.1$ Hz, 1H), 2.83 (d, $J = 13.6$ Hz, 1H), 2.04 (s, 1H).

The racemic mixture of compounds **26** and **27** (4.6 g) was subjected to chiral SFC to provide 2 compounds: the 1st eluent was Intermediate **26** (1.45 g, 100% *ee*) afforded as a
20 white solid and the 2nd eluent was Intermediate **27** (1.45 g, 99.3% *ee*) afforded as a white solid. Preparative SFC purification method: Chiralpak IA (250 x 30 mm, 5 μ m); mobile phase (70:30) = (A:B), A = liquid CO₂, B = 20 mM ammonia in MeOH; flow rate = 100 mL/min; wave length = 250 nm; inlet pressure = 205 bar; 4.6 g of sample was dissolved in 92 mL of THF/MeOH (1/1), sample load = 1.0 mL/injection; run time = 10 minutes, cycle time
25 = 5 minutes. The absolute stereochemistry was arbitrarily assigned.

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Intermediate 28: N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.



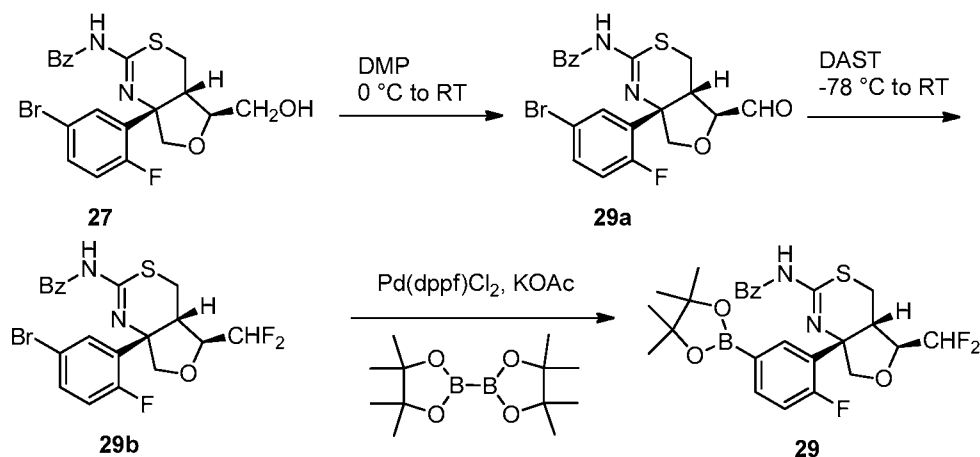
To a solution of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**26**) (1.00 g, 2.15 mmol) in DCM (15 mL) at 0 °C was added Dess-Martin periodinate (1.82 g, 4.30 mmol). After the reaction mixture was stirred at 0 °C for 2 h then at room temperature for 2 hours, it was quenched with sat'd sodium bicarbonate solution (20 mL) and extracted with DCM (2 x 20 mL). The organic solution was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to give crude N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-formyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**28a**) (0.8 g, 79% yield) as a light yellow solid. This material was used without purification.

To a solution of crude N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-formyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**28a**) (0.8 g, 1.70 mmol) in DCM (10 mL) at -78 °C was added DAST (0.57 mL, 4.32 mmol) dropwise. After the reaction mixture was stirred for 3 hours at -78 °C, it was quenched with sat'd sodium bicarbonate solution (10 mL) and extracted with DCM (2 x 50 mL). The organic solution was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified on a silica gel column (15% to 20% EtOAc in petroleum ether) to provide N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**28**) (0.15 g, 0.31 mmol, 18% yield) as an off-white solid. MS (ESI positive ion) m/z: 485.0 (M+1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (s, 2H), 7.97 – 7.72 (m, 2H), 7.52 (dt, *J* = 30.7, 8.5 Hz, 3H), 7.17 (dd, *J*

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= 12.5, 8.2 Hz, 1H), 6.03 (ddd, $J = 57.6, 54.8, 3.6$ Hz, 1H), 5.05 – 3.98 (m, 3H), 3.60 (d, $J = 6.9$ Hz, 1H), 3.49 – 3.30 (m, 1H), 3.06 – 2.80 (m, 1H), 1.56 – 1.39 (m, 1H). ^{19}F NMR (376 MHz, Chloroform- d) δ -111.05 (s, 1F), -132.12 (m, 2F).

Intermediate 29: N-((4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide.



Preparation of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (29b).

This 29b (0.15 g, 0.31 mmol) as an off-white solid was prepared from Intermediate 27 (1.00 g, 2.15 mmol) in a 2-step sequence similar to that described for Intermediate 28. MS (ESI positive ion) m/z : 485.0 ($M+1$). ^1H NMR (400 MHz, Chloroform- d) δ 8.04 (d, $J = 7.3$ Hz, 2H), 7.94 – 7.31 (m, 5H), 7.05 (dd, $J = 11.8, 8.6$ Hz, 1H), 6.02 (s, 1H), 4.51 (d, $J = 8.9$ Hz, 2H), 3.98 (s, 2H), 3.51 (s, 1H), 3.20 (d, $J = 13.9$ Hz, 1H), 2.94 – 2.82 (m, 1H). ^{19}F NMR (376 MHz, Chloroform- d) δ -111.05 (s, 1F), -132.12 (m, 2F).

Preparation of N-((4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (29).

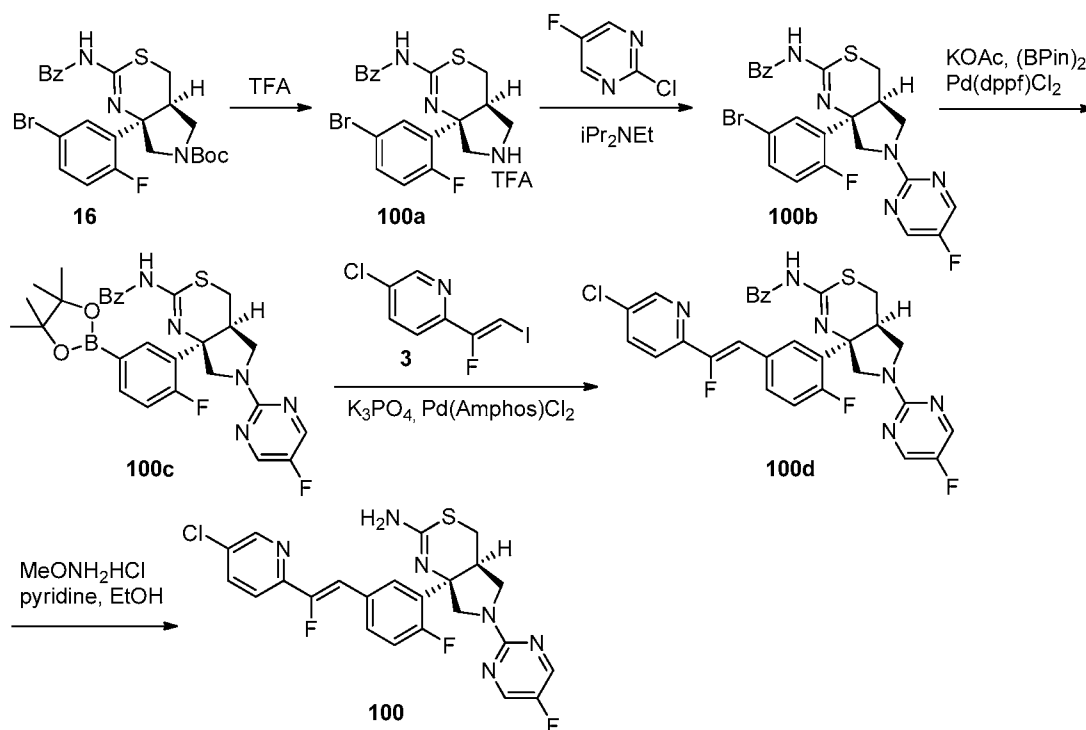
A mixture of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (29b) (0.10 g, 0.21 mmol), bis(pinacolato)diboron (65 mg, 0.25 mmol), and potassium acetate (42 mg, 0.43 mmol) in

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1,4-dioxane (10 mL) was purged with nitrogen for 2 minutes then treated with PdCl₂(dppf)-CH₂Cl₂ adduct (9 mg). The mixture was purged with nitrogen for 2 minutes then heated at 90 °C for 16 hours. After cooling to room temperature, the reaction mixture was filtered through a celite pad and the filtered cake was washed with ethyl acetate (10 mL). The filtrate was evaporated under vacuum. The crude material was purified by silica gel chromatography (20% to 30% EtOAc in petroleum ether) to Intermediate **29** (65 mg, 59% yield) as an off-white solid. MS (ESI positive ion) *m/z*: 533.1 (M+1). ¹H NMR (400 MHz, Chloroform-*d*) δ 8.12 (br s, 2H), 7.91 – 7.66 (m, 2H), 7.52 – 7.46 (m, 3H), 7.17 (dd, *J* = 12.5, 8.2 Hz, 1H), 6.03 (ddd, *J* = 57.6, 54.8, 3.6 Hz, 1H), 4.74 – 4.64 (m, 1H), 4.46 – 4.40 (m, 1H), 4.18 – 4.10 (m, 1H), 3.65 – 3.55 (m, 1H), 3.42 – 3.36 (m, 1H), 3.00 – 2.92 (m, 1H), 1.78 – 1.70 (m, 1H), 1.36 (s, 12H); ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -112.82 (s, 1F), -132.12 (d, 2F).

Examples

Example 100: (4a*S*,7a*R*)-7a-(5-((*Z*)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-*d*][1,3]thiazin-2-amine.



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Preparation of N-((4aS,7aR)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (100b).

To a solution of compound **16** (1.00 g, 1.87 mmol) in DCM (5 mL) at room temperature was added TFA (1.00 mL, 13.10 mmol) dropwise. The mixture was stirred for 18 hours then concentrated *in vacuo* to give N-((4aS,7aR)-7a-(5-bromo-2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide 2,2,2-trifluoroacetate (**100a**) (813 mg) which was used without additional purification. MS (ESI, positive ion) m/z: 434/436 (M+1).

A mixture of **100a** (813 mg, 1.87 mmol), N,N-diisopropylethylamine (2.28 mL, 13.10 mmol), and 2-chloro-5-fluoro-pyrimidine (Matrix Scientific) (1.15 mL, 9.36 mmol) in dioxane (6 mL) was heated to reflux for 2 hours. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in heptane) to provide N-((4aS,7aR)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**100b**) (0.88 g, 89% yield) as an off-white solid. MS (ESI, positive ion) m/z: 530/532 (M+1).

Preparation of N-((4aS,7aR)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (100c).

A mixture of N-((4aS,7aR)-7a-(5-bromo-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**100b**) (0.88 g, 1.66 mmol), bis(pinacolato)diboron (0.55 g, 2.16 mmol), potassium acetate (0.49 g, 4.98 mmol) in dioxane (10 mL) was purged with argon, then treated with [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (95 mg, 0.12 mmol). The mixture was heated to 90 °C for 1 hour, cooled to room temperature, and filtered through celite. The filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo*. The residue was triturated with heptane. The mixture was filtered to provide N-((4aS,7aR)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**100c**) (0.96 g, 100% yield) as a brown solid. MS (ESI, positive ion) m/z: 578 (M+1).

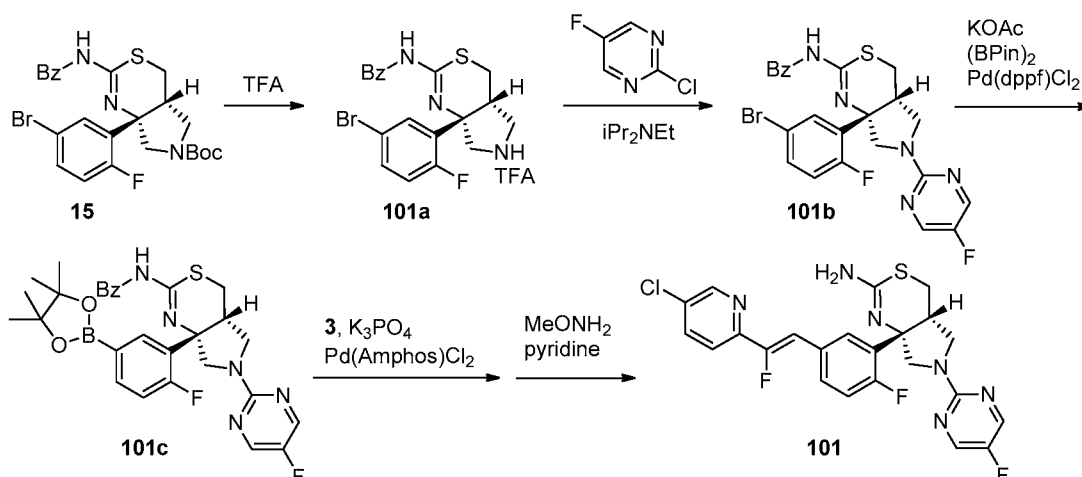
Preparation of N-((4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (100d).

A mixture of **100c** (0.15 g, 0.26 mmol), (Z)-5-chloro-2-(1-fluoro-2-iodovinyl)pyridine (**3**) (0.08 g, 0.28 mmol), Pd(Amphos)Cl₂ (0.018 g, 0.026 mmol), and potassium phosphate (0.14 g, 0.64 mmol) in dioxane (1.5 mL) and water (0.25 mL) was
5 purged with argon then heated to 80 °C for 30 minutes. The mixture was diluted with water and extracted with EtOAc. The organic solution was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in heptane)
10 to afford N-((4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**100d**) (82 mg, 52% yield) as an off-white solid. MS (ESI, positive ion) m/z: 607 (M+1).

Preparation of (4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (100).

A mixture of **100d** (0.070 g, 0.115 mmol), O-methylhydroxylamine hydrochloride (TCI America) (0.193 g, 2.306 mmol) and pyridine (0.187 mL, 2.306 mmol) in ethanol (2 mL) was heated to 70 °C for 1 hour. The mixture was concentrated *in vacuo*; the residue was
diluted with saturated Na₂CO₃ and extracted with EtOAc. The organic solution was dried
20 over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 100% EtOAc:EtOH (3:1) in heptane) to give (4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (Example **100**, 57 mg, 98% yield) as a white
solid. MS (ESI, positive ion) m/z: 503 (M+1). ¹H NMR (400 MHz, CHLOROFORM-d) δ
25 8.54 (d, *J* = 2.35 Hz, 1H), 8.23 (s, 2H), 7.67-7.75 (m, 2H), 7.67-7.75 (m, 2H), 7.61 (dd, *J* = 1.96, 8.02 Hz, 1H), 7.55 (dd, *J* = 1.37, 8.41 Hz, 1H), 6.95-7.15 (m, 2H), 4.37 (d, *J* = 11.15 Hz, 1H), 3.86 (dd, *J* = 2.64, 11.25 Hz, 1H), 3.81 (d, *J* = 8.41 Hz, 2H), 3.24 (tt, *J* = 4.23, 8.39 Hz, 1H), 3.02-3.11 (m, 1H), 2.91-2.99 (m, 1H).

Example 101: (4aR,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



- 5 **Preparation of N-((4aR,7aS)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (101c).**

Boronic ester 101c was prepared in a sequence similar to that described for boronic ester 100c, here starting from (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (15). MS (ESI, positive ion) m/z : 578 ($M+1$).

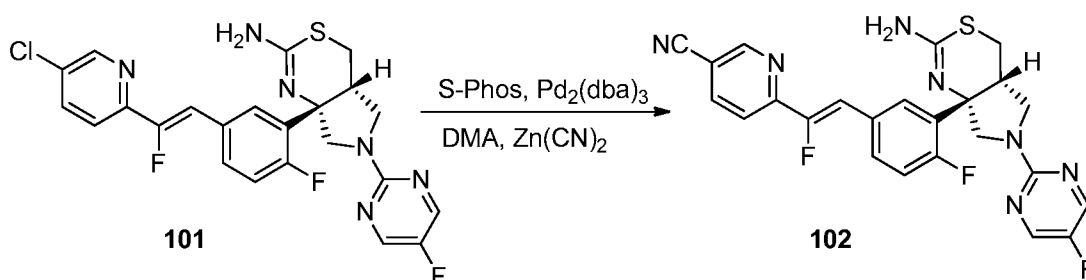
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Preparation of (4aR,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (101).

- 15 This compound (86 mg, 52% overall yield) was prepared in a fashion similar to that described for Example 100, here starting from boronic ester 101c (200 mg, 0.34 mmol) and vinyl iodide 3 (108 mg, 0.38 mmol). MS (ESI, positive ion) m/z : 503 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.54 (d, $J = 2.15$ Hz, 1H), 8.23 (s, 2H), 7.67-7.75 (m, 2H), 7.61 (dd, $J = 2.15, 8.02$ Hz, 1H), 7.55 (d, $J = 7.24$ Hz, 1H), 6.95-7.14 (m, 2H), 4.37 (d, $J = 11.15$ Hz, 1H), 3.86 (dd, $J = 2.54, 11.15$ Hz, 1H), 3.81 (d, $J = 8.22$ Hz, 2H), 3.24 (tt, $J = 4.40, 8.41$ Hz, 1H), 3.03-3.13 (m, 1H), 2.91-3.01 (m, 1H). NH_2 was not clear in NMR.
- 20

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Example 102: 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



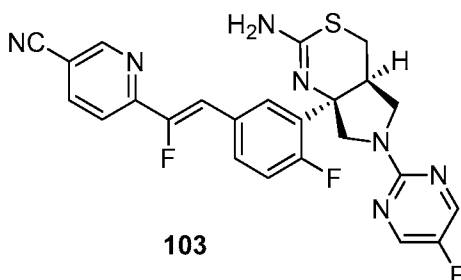
5 A 3-mL vial was charged with (4aR,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (**101**) (37.5 mg, 0.075 mmol), zinc cyanide (26 mg, 0.224 mmol), dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine (9.18 mg, 0.022 mmol), Pd₂(dba)₃ (10.2 mg, 0.011 mmol) and N, N-dimethylacetamide (0.8 mL). The vial was

10 purged with argon and sealed. The mixture was heated at 120 °C for 2 hours, cooled to room temperature, and filtered through celite. The filter cake was washed with EtOAc. The filtrate was washed with water and brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc/EtOH (3/1) in heptane) to afford Example **102** (29 mg, 78% yield) as a yellow solid. MS (ESI, positive ion) m/z: 494 (M+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.83 (s, 1 H), 8.23 (s, 2 H), 8.02 (dd, *J* = 8.31, 2.05 Hz, 1 H), 7.62 - 7.79 (m, 3 H), 7.24 (d, *J* = 38.73 Hz, 1 H), 7.12 (dd, *J* = 11.93, 8.61 Hz, 1 H), 4.37 (d, *J* = 11.35 Hz, 1 H), 3.75 - 3.93 (m, 3 H), 3.25 (tt, *J* = 8.31, 4.30 Hz, 1 H), 2.88 - 3.13 (m, 4 H). ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -109.21 (s, 1F), -125.17 (s, 1F), -158.01 (s, 1F).

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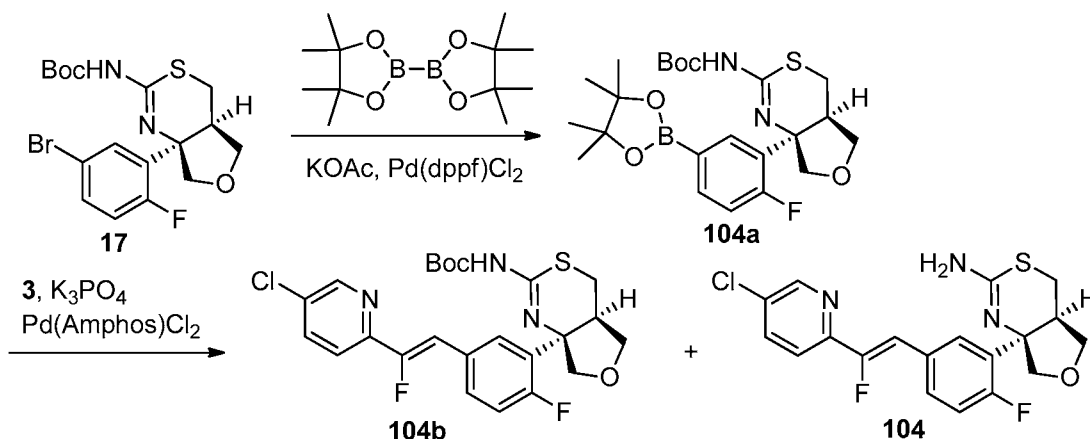
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Example 103: 6-((Z)-2-(3-((4a*S*,7a*R*)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-*d*][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



5 This compound (17 mg, 60% yield) as a yellow solid was prepared in a fashion similar to that described for **Example 102**, here starting from **Example 100** (29 mg, 0.058 mmol). MS (ESI, positive ion) *m/z*: 494 (*M*+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.82 (s, 1H), 8.23 (s, 2H), 7.96-8.09 (m, 1H), 7.61-7.78 (m, 3H), 7.03-7.27 (m, 2H), 4.36 (d, *J* = 11.15 Hz, 1H), 3.72-3.93 (m, 3H), 3.25 (tt, *J* = 4.23, 8.29 Hz, 1H), 2.88-3.12 (m, 2H),
 10 2.88-3.12 (m, 2H). ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -109.20 (d, *J* = 1.73 Hz, 1F), -125.18 (s, 1F), -158.03 (s, 1F).

Example 104: (4a*R*,7a*R*)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-amine.



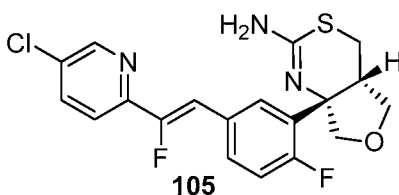
15 *Tert*-butyl ((4a*R*,7a*R*)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)carbamate (**104a**) was prepared in a fashion similar to that described for boronic ester **100c**, here starting from *tert*-butyl ((4a*R*,7a*R*)-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-

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d[[1,3]thiazin-2-yl)carbamate (**17**). MS (ESI, positive ion) m/z : 479.1 (M+1). **104a** was used without additional purification.

Using boronic ester **104a** (140 mg, 0.29 mmol) and vinyl iodide **3** (91 mg, 0.32 mmol) as the starting materials, the Suzuki coupling reaction was carried out in a fashion similar to that described for Example **100**. LCMS showed the formation of two products, the Boc-protected **104b** and the de-Boc **104**. Purification of the crude mixture via silica gel chromatography (0 to 100% EtOAc in DCM) gave Example **104** (49 mg, 41% yield) as a light yellow solid. MS (ESI, positive ion) m/z : 408 (M+1). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.55 (s, 1H), 7.64-7.78 (m, 3H), 7.57 (d, J = 8.22 Hz, 1H), 6.97-7.13 (m, 2H), 4.49 (d, J = 8.61 Hz, 1H), 4.04-4.19 (m, 2H), 3.80-3.87 (m, 1H), 2.98-3.12 (m, 2H), 2.84 (dd, J = 5.18, 12.81 Hz, 1H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -110.61 (s, 1F), -123.80 (s, 1F).

Example 105: (4a*S*,7a*S*)-7a-(5-((*Z*)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-amine.



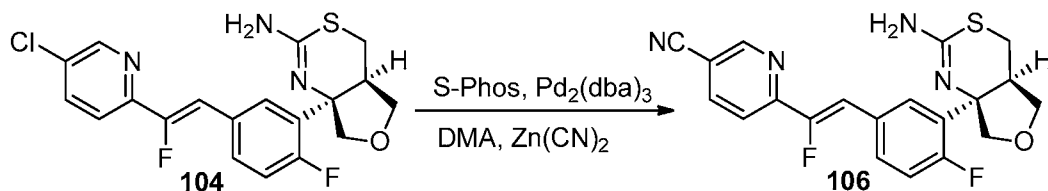
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This compound was prepared in a sequence similar to that described for Example **104**, here starting from tert-butyl ((4a*S*,7a*S*)-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)carbamate (**18**). MS (ESI, positive ion) m/z : 408 (M+1). ^1H NMR (400 MHz, CHLOROFORM-*d*) δ 8.55 (s, 1H), 7.64-7.78 (m, 3H), 7.57 (d, J = 8.41 Hz, 1H), 6.96-7.15 (m, 2H), 4.49 (d, J = 8.80 Hz, 1H), 4.03-4.22 (m, 2H), 3.90 (d, J = 8.80 Hz, 1H), 3.02-3.17 (m, 2H), 2.81-2.91 (m, 1H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM-*d*) δ -110.62 (s, 1F), -123.64 (br. s., 1F).

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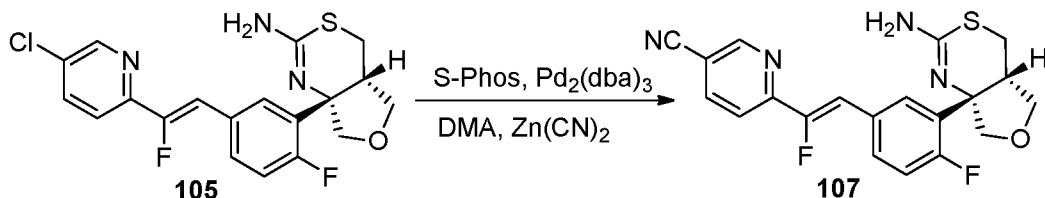
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Example 106: 6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



This compound (11 mg, 33% yield) was prepared in a fashion similar to that described for **Example 102**, here starting from **Example 104** (35 mg, 0.086 mmol). MS (ESI, positive ion) m/z : 399 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.83 (s, 1H), 8.02 (dd, $J = 2.05, 8.31$ Hz, 1H), 7.78 (dd, $J = 1.86, 7.92$ Hz, 1H), 7.68-7.75 (m, 2H), 7.26 (d, $J = 22.30$ Hz, 1H), 7.11 (dd, $J = 8.51, 11.84$ Hz, 1H), 4.49 (d, $J = 8.80$ Hz, 1H), 4.03-4.22 (m, 2H), 3.86 (dd, $J = 1.96, 8.80$ Hz, 1H), 3.02-3.14 (m, 2H), 2.80-2.92 (m, 1H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -109.12 (d, $J = 1.73$ Hz, 1F), -125.22 (d, $J = 0.87$ Hz, 1F).

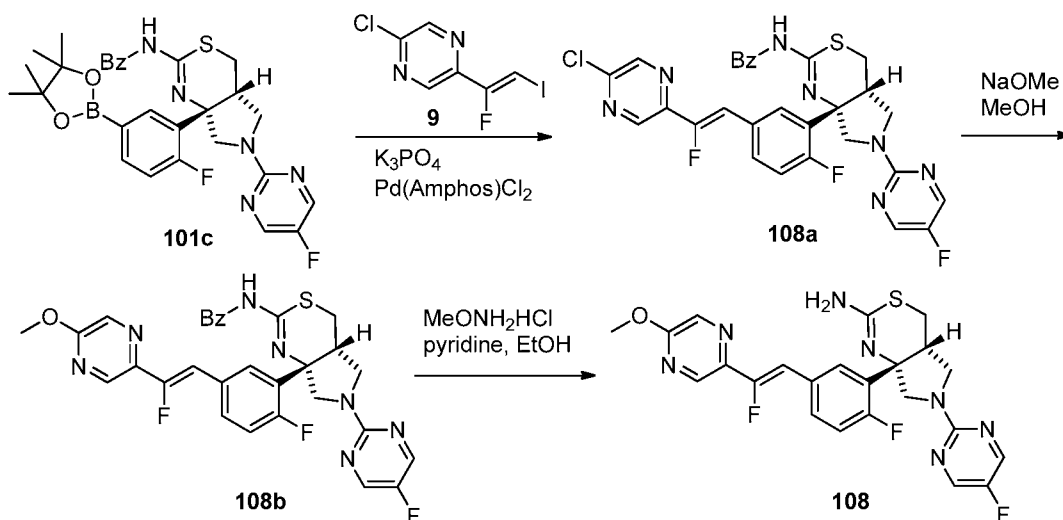
Example 107: 6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



This compound (15 mg, 32% yield) was prepared in a fashion similar to that described for **Example 102**, here starting from **Example 105** (30 mg, 0.074 mmol). MS (ESI, positive ion) m/z : 399 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.83 (s, 1H), 8.02 (dd, $J = 2.05, 8.31$ Hz, 1H), 7.78 (dd, $J = 2.05, 7.92$ Hz, 1H), 7.68-7.75 (m, 2H), 7.26 (d, $J = 37.95$ Hz, 1H), 7.11 (dd, $J = 8.51, 11.83$ Hz, 1H), 4.49 (dd, $J = 0.88, 8.71$ Hz, 1H), 4.03-4.26 (m, 2H), 3.85 (dd, $J = 2.15, 8.80$ Hz, 1H), 3.02-3.12 (m, 2H), 2.82-2.90 (m, 1H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -109.11 (d, $J = 1.73$ Hz, 1F), -125.24 (d, $J = 1.73$ Hz, 1F).

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Example 108: (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



5 Preparation of N-((4aR,7aS)-7a-(5-((Z)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (108a).

A mixture of N-((4aR,7aS)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**101c**) (0.200 g, 0.346 mmol), vinyl iodide **9** (0.207 g, 0.727 mmol), potassium phosphate (0.184 g, 0.866 mmol), and $Pd(Amphos)Cl_2$ (0.025 g, 0.035 mmol) in dioxane (3 mL) and water (0.50 mL) was purged with argon, then the vial was sealed and heated to 80 °C for 30 minutes. The mixture was diluted with water and extracted with EtOAc. The organic solution was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in heptane) to provide **108a** as an off-white solid (0.15 g, 71% yield). MS (ESI, positive ion) m/z : 608 (M+1).

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Preparation of N-((4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (108b).

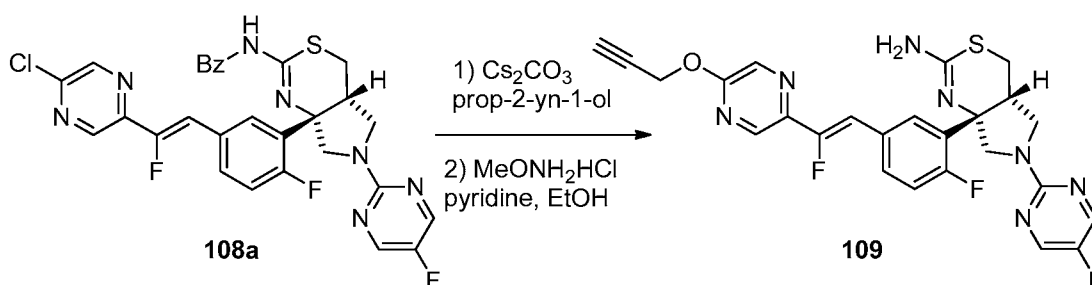
A mixture of N-((4aR,7aS)-7a-(5-((Z)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**108a**) (0.040 g, 0.064 mmol) and sodium methoxide solution (25 wt. % in methanol, 1.50 mL, 6.58 mmol) was heated to 70 °C for 2 hours. The mixture was diluted with water and extracted with EtOAc. The organic solution was dried over Na₂SO₄ and concentrated *in vacuo* to afford **108b** which was used as crude (theoretical yield was 40 mg).
MS (ESI, positive ion) m/z: 604 (M+1).

Preparation of (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (108).

A mixture of **108b** (0.040 g, 0.066 mmol), O-methylhydroxylamine hydrochloride (0.138 g, 1.657 mmol), and pyridine (0.134 mL, 1.657 mmol) in ethanol (2 mL) was heated to 70 °C for 1 hour. The mixture was concentrated *in vacuo*; the residue was diluted with EtOAc and water. The organic solution was washed sequentially with sat'd aqueous NH₄Cl, 1.0 M aqueous NaOH, and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in DCM) to afford Example **108** as a white solid (12 mg, 36% yield over two steps). MS (ESI, positive ion) m/z: 500 (M+1). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.35 (s, 1H), 8.22 (s, 2H), 8.20 (s, 1H), 7.67 (ddd, *J* = 2.35, 4.70, 8.41 Hz, 1H), 7.59 (dd, *J* = 2.15, 8.02 Hz, 1H), 7.08 (dd, *J* = 8.61, 12.13 Hz, 1H), 6.71-6.88 (m, 1H), 4.37 (d, *J* = 11.35 Hz, 1H), 4.01 (s, 3H), 3.88 (dd, *J* = 2.54, 11.15 Hz, 1H), 3.81 (d, *J* = 8.22 Hz, 2H), 3.26 (tt, *J* = 4.28, 8.34 Hz, 1H), 3.03-3.12 (m, 1H), 2.92-3.00 (m, 1H). NH₂ was not clear. ¹⁹F NMR (376 MHz, CHLOROFORM-d) δ -111.29 (s, 1F), -125.19 (s, 1F), -158.09 (s, 1F).

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Example 109: (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.

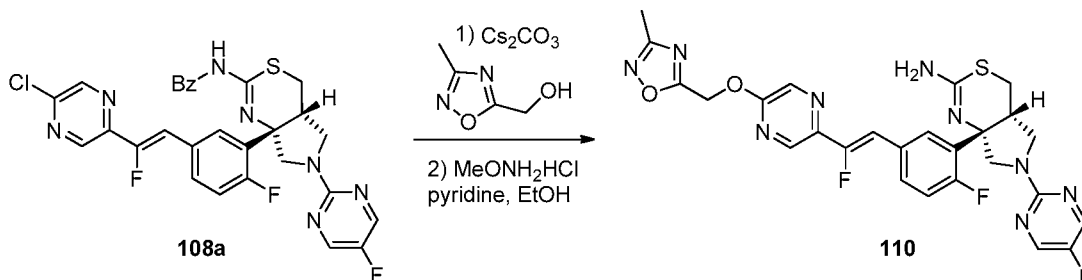


5

This compound (22 mg, 56% overall yield) as a white solid was prepared in a manner similar to that described for Example 108, here starting from **108a** (0.046 g, 0.077 mmol) and prop-2-yn-1-ol (Sigma-Aldrich) (0.045 mL, 0.768 mmol). MS (ESI, positive ion) m/z : 524 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.38 (s, 1H), 8.15-8.30 (m, 3H), 7.62-7.72 (m, 1H), 7.58 (dd, $J = 1.96, 8.02$ Hz, 1H), 7.08 (dd, $J = 8.61, 12.13$ Hz, 1H), 6.75-6.91 (m, 1H), 5.04 (d, $J = 2.35$ Hz, 2H), 4.37 (d, $J = 11.15$ Hz, 1H), 3.86 (dd, $J = 2.45, 11.05$ Hz, 1H), 3.81 (d, $J = 8.22$ Hz, 2H), 3.24 (tt, $J = 4.35, 8.26$ Hz, 1H), 3.03-3.11 (m, 1H), 2.89-3.01 (m, 1H), 2.53 (t, $J = 2.35$ Hz, 1H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -111.02 (d, $J = 1.73$ Hz, 1F), -125.44 (d, $J = 1.73$ Hz, 1F), -158.16 (s, 1F).

15

Example 110: (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



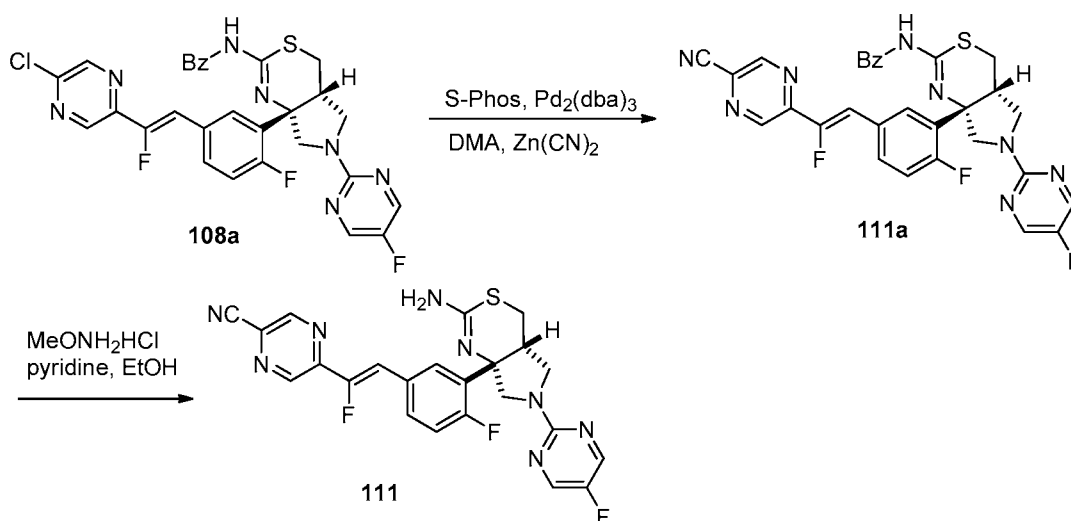
20

This compound (33 mg, 50% yield) was prepared in a fashion similar to that described for Example 109, here starting from **108a** (70 mg, 0.115 mmol) and (3-methyl-

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1,2,4-oxadiazol-5-yl)methanol (Enamine LLC., Monmouth Jct., NJ, USA) (66 mg, 0.576 mmol). MS (ESI, positive ion) m/z : 582 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.34 (d, J = 18.19 Hz, 2H), 8.22 (s, 2H), 7.62-7.68 (m, 1H), 7.60 (dd, J = 1.96, 8.02 Hz, 1H), 7.08 (dd, J = 8.51, 12.03 Hz, 1H), 6.76-6.92 (m, 1H), 5.63 (s, 2H), 4.36 (d, J = 11.15 Hz, 1H), 3.87 (dd, J = 2.45, 11.05 Hz, 1H), 3.81 (d, J = 8.41 Hz, 2H), 3.24 (tt, J = 4.25, 8.36 Hz, 1H), 2.90-3.12 (m, 2H), 2.43 (s, 3H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -110.83 (d, J = 1.73 Hz, 1F), -125.59 (s, 1F), -158.15 (s, 1F).

Example 111: 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile.



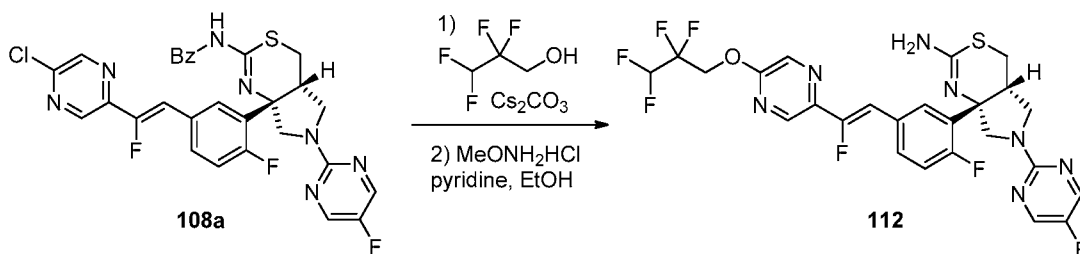
N-((4aR,7aS)-7a-(5-((Z)-2-(5-Cyanopyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**111a**) (35 mg, 36% yield) as a yellow solid was prepared in a fashion similar to that described for Example **102**, here starting from N-((4aR,7aS)-7a-(5-((Z)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**108a**) (100 mg, 0.164 mmol). MS (ESI, positive ion) m/z : 599 (M+1).

5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile (Example **111**) (16 mg, 55% yield) as a yellow solid was prepared in a fashion

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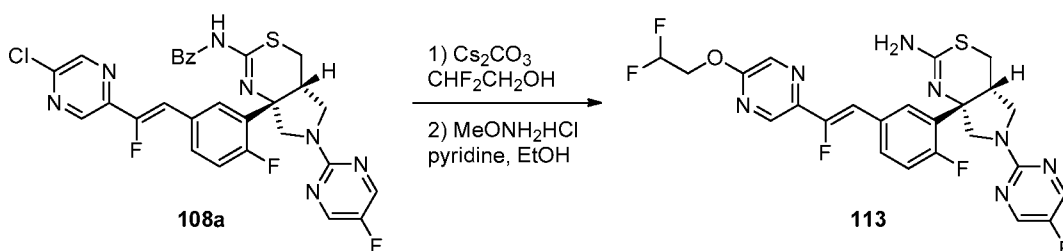
similar to that described for Example 109, here starting from 111a (35 mg, 0.058 mmol). MS (ESI, positive ion) m/z : 495 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.94 (s, 1H), 8.83 (s, 1H), 8.23 (s, 2H), 7.63-7.80 (m, 2H), 7.24 (d, J = 37.17 Hz, 1H), 7.14 (dd, J = 8.61, 11.93 Hz, 1H), 4.36 (d, J = 11.15 Hz, 1H), 3.77-3.93 (m, 3H), 3.27 (br. s., 1H), 2.92-3.12 (m, 2H). NH_2 was not clear.

Example 112: (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



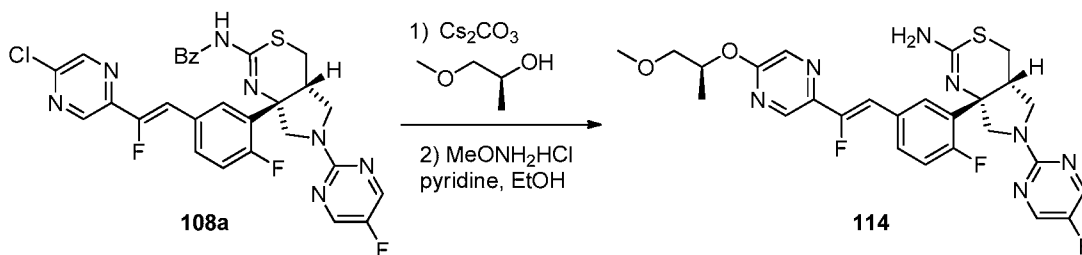
This compound (31 mg, 62% overall yield) was prepared in a fashion similar to that described for Example 109, here starting from 108a (50 mg, 0.082 mmol) and 2,2,3,3-tetrafluoropropan-1-ol (Sigma-Aldrich) (54 mg, 0.411 mmol). MS (ESI, positive ion) m/z : 600 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.36 (s, 1H), 8.31 (s, 1H), 8.23 (s, 2H), 7.64-7.72 (m, 1H), 7.60 (dd, J = 1.96, 8.02 Hz, 1H), 7.09 (dd, J = 8.51, 12.03 Hz, 1H), 6.78-6.95 (m, 1H), 5.85-6.19 (m, 1H), 4.81 (t, J = 12.62 Hz, 2H), 4.37 (d, J = 11.15 Hz, 1H), 3.73-3.94 (m, 3H), 3.25 (tt, J = 4.28, 8.34 Hz, 1H), 2.86-3.13 (m, 2H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -110.75 (s, 1F), -123.88 (t, J = 3.04 Hz, 2F), -125.61 (s, 1F), -137.85 (t, J = 3.47 Hz, 2F), -158.14 (s, 1F).

Example 113: (4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



5 This compound (12 mg, 46% overall yield) as a white solid was prepared in a fashion similar to that described for **Example 109**, here starting from 2,2-difluoroethanol (Accela Chembio Inc., San Diego, CA, USA) (22 mg, 0.271 mmol) and **108a** (27 mg, 0.045 mmol). MS (ESI, positive ion) m/z : 550 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.33 (s, 1H), 8.28 (s, 1H), 8.23 (s, 2H), 7.63-7.69 (m, 1H), 7.60 (d, $J = 7.82$ Hz, 1H), 7.08 (dd, $J =$
10 8.51, 12.03 Hz, 1H), 6.75-6.93 (m, 1H), 5.96-6.35 (m, 1H), 4.60 (dt, $J = 4.11, 13.40$ Hz, 2H), 4.36 (d, $J = 11.15$ Hz, 1H), 3.88 (d, $J = 11.15$ Hz, 1H), 3.81 (d, $J = 8.41$ Hz, 2H), 3.26 (tt, $J = 4.13, 8.19$ Hz, 1H), 2.90-3.14 (m, 2H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -110.89 (s, 1F), -125.52 (br. s., 1F), -125.66 (s, 2F), -158.09 (br. s., 1F).

15 **Example 114: (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.**

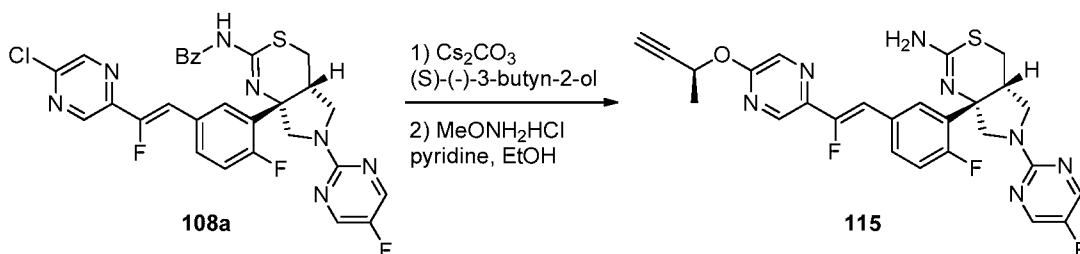


20 This compound (10 mg, 39% overall yield) as a white solid was prepared in a fashion similar to that described for **Example 109**, here starting from (S)-1-methoxy-2-propanol (Sigma-Aldrich) (24 mg, 0.271 mmol) and **108a** (27 mg, 0.045 mmol). MS (ESI, positive ion) m/z : 558 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.32 (s, 1H), 8.22 (s, 2H),

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8.19 (s, 1H), 7.66 (dd, $J = 3.03, 5.58$ Hz, 1H), 7.58 (d, $J = 7.82$ Hz, 1H), 7.07 (dd, $J = 8.51, 12.03$ Hz, 1H), 6.69-6.88 (m, 1H), 5.37-5.51 (m, 1H), 4.49 (br. s., 2H), 4.36 (d, $J = 11.15$ Hz, 1H), 3.86 (dd, $J = 1.86, 11.25$ Hz, 1H), 3.81 (d, $J = 8.41$ Hz, 2H), 3.53-3.66 (m, 2H), 3.41 (s, 3H), 3.24 (tt, $J = 4.25, 8.26$ Hz, 1H), 3.03-3.12 (m, 1H), 2.91-2.99 (m, 1H), 1.38 (d, $J = 6.26$ Hz, 3H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -111.32 (s, 1F), -125.21 (s, 1F), -158.20 (s, 1F).

Example 115: (4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



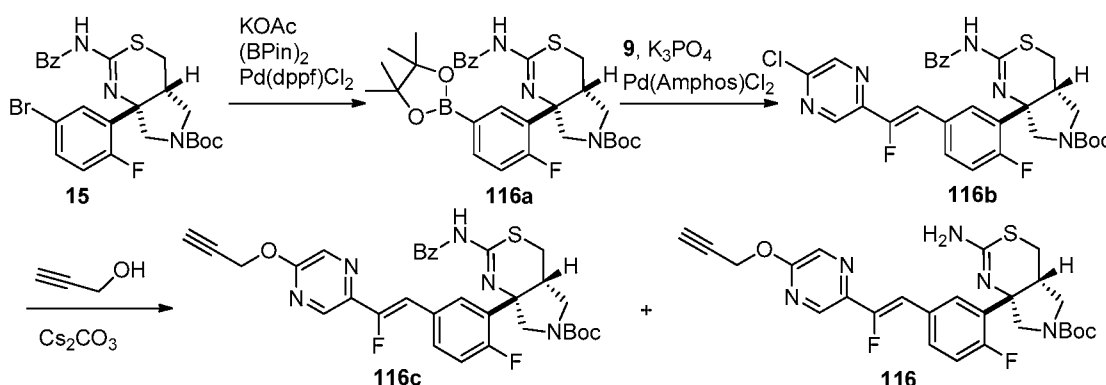
10

This compound (4.3 mg, 18% overall yield) as a white solid was prepared in a fashion similar to that described for **Example 109**, here starting from (S)-(-)-3-butyn-2-ol (Alfa Aesar) (18 mg, 0.257 mmol) and **108a** (26 mg, 0.043 mmol). MS (ESI, positive ion) m/z : 538 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.38 (s, 1H), 8.15-8.27 (m, 3H), 7.68 (dd, $J = 2.54, 6.06$ Hz, 1H), 7.58 (d, $J = 7.43$ Hz, 1H), 7.08 (dd, $J = 8.61, 12.13$ Hz, 1H), 6.71-6.90 (m, 1H), 5.76 (q, $J = 6.52$ Hz, 1H), 4.37 (d, $J = 11.15$ Hz, 1H), 3.88 (d, $J = 11.15$ Hz, 1H), 3.81 (d, $J = 8.41$ Hz, 2H), 3.25 (td, $J = 3.89, 8.07$ Hz, 1H), 3.03-3.13 (m, 1H), 2.90-3.01 (m, 1H), 2.48 (d, $J = 1.76$ Hz, 1H), 1.69 (d, $J = 6.65$ Hz, 3H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -111.13 (s, 1F), -125.31 (br. s., 1F), -158.10 (br. s., 1F).

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Example 116: (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate.



5

Preparation of (4aR,7aS)-tert-butyl 2-benzamido-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (116a).

A mixture of (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-bromo-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (**15**) (2.05 g, 3.84 mmol), bis(pinacolato)diboron (1.28 g, 5.06 mmol), potassium acetate (1.13 g, 11.51 mmol) in 1,4-dioxane (20.0 mL) was purged with argon, then [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with DCM (0.19 g, 0.23 mmol) was added. The mixture was heated to 90 °C for 1 hour then cooled to room temperature and filtered through celite. The filter cake was washed with EtOAc. The filtrate was concentrated *in vacuo* to provide boronic ester **116a** as a beige solid which was used without additional purification. MS (ESI, positive ion) *m/z*: 582 (M+1).

Preparation of (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-((Z)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (116b).

This compound (0.75 g, 46% yield) as a beige solid was prepared via a Suzuki coupling reaction similar to that described for compound **100d**, here starting from boronic

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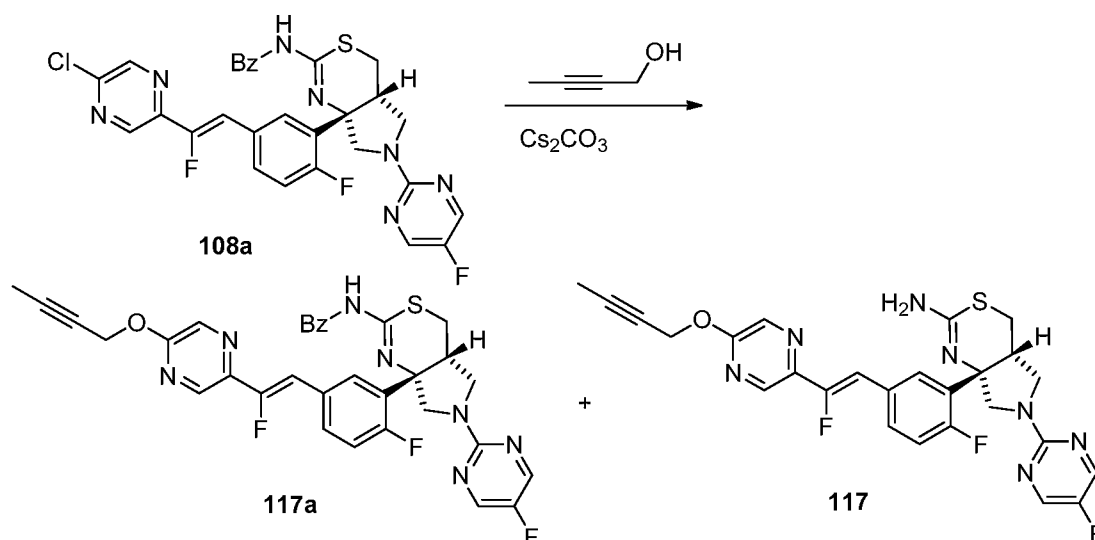
ester **116a** (1.54 g, 2.65 mmol) and vinyl iodide **9** (0.78 g, 2.75 mmol). MS (ESI, positive ion) *m/z*: 612 (M+1).

Preparation of (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (116).

A mixture of (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-((Z)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (**116b**, 0.74 g, 1.22 mmol), propargyl alcohol (0.36 mL, 6.11 mmol), and cesium carbonate (1.194 g, 3.66 mmol) in THF (10 mL) was heated to 55 °C for 8 hours then cooled to room temperature. LCMS showed the presence of two products (**116c** and **116**). The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in heptane) to give 2 compounds. The 1st eluent was (4aR,7aS)-tert-butyl 2-benzamido-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (**116c**, 0.23 g, 30% yield) as a yellow solid. MS (ESI, positive ion) *m/z*: 612 (M+1). The 2nd eluent was (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (Example **116**, 0.308 g, 48% yield) as a yellow solid. MS (ESI, positive ion) *m/z*: 528 (M+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.39 (s, 1H), 8.26 (s, 1H), 7.62-7.69 (m, 1H), 7.54-7.61 (m, 1H), 7.07 (dd, *J* = 8.51, 12.03 Hz, 1H), 6.75-6.92 (m, 1H), 5.04 (d, *J* = 2.35 Hz, 2H), 4.44 (br. s., 2H), 4.09-4.21 (m, 1H), 3.51-3.65 (m, 3H), 2.81-3.16 (m, 3H), 2.53 (t, *J* = 2.35 Hz, 1H), 1.44-1.50 (m, 9H). ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -111.64--110.37 (m, 1F), -125.85--124.75 (m, 1F).

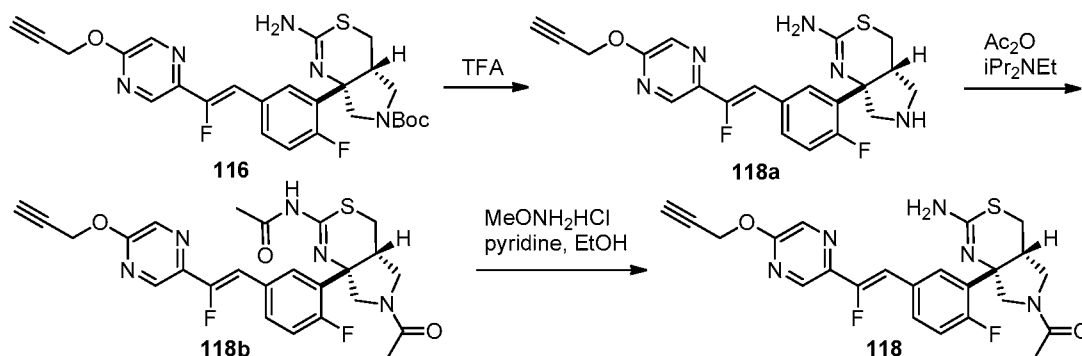
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Example 117: (4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



5 A mixture of N-((4aR,7aS)-7a-(5-((Z)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**108a**, 28 mg, 0.047 mmol), but-2-yn-1-ol (130 mg, 1.862 mmol), and cesium carbonate (45 mg, 0.140 mmol) in THF (0.2 mL) was heated to 60 °C for 3.5 hours. LCMS indicated the formation of 2 products, with MS (ESI, positive ion) *m/z*: 642.2 (*M*+1) and 538.2 (*M*+1) for **117a** and **117**, respectively. Heating was continued until the conversion to product **117** was complete. The mixture was diluted with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in DCM) to afford Example **117** (18 mg, 73% yield) as an off-white solid. MS (ESI, positive ion) *m/z*: 538.2 (*M*+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.37 (s, 1H), 8.19-8.28 (m, 3H), 7.67 (br. s., 1H), 7.58 (d, *J* = 8.22 Hz, 1H), 7.08 (dd, *J* = 8.61, 11.93 Hz, 1H), 6.72-6.92 (m, 1H), 4.99 (br. s., 2H), 4.37 (d, *J* = 11.15 Hz, 1H), 3.76-3.92 (m, 3H), 3.19-3.31 (m, 1H), 3.03-3.12 (m, 1H), 2.89-3.01 (m, 1H), 1.89 (s, 3H). NH₂ was not clear. ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -111.12 (s, 1F), -125.35 (s, 1F), -158.17 (s, 1F).

Example 118: 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone.



5 Preparation of (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (118a).

A mixture of Example 116 (0.161 g, 0.306 mmol) in TFA (0.341 mL, 4.43 mmol) and DCM (1 mL) was stirred at room temperature for 30 minutes, then cooled to 0 °C and basified by the dropwise addition of 1 M aqueous NaOH. The mixture was extracted with DCM followed by EtOAc. The combined organic solution was dried over Na₂SO₄ and concentrated *in vacuo* to provide 118a (0.131 g, 100% yield) as a yellow solid which was used without additional purification. MS (ESI, positive ion) m/z: 428 (M+1).

15 Preparation of N-((4aR,7aS)-6-acetyl-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)acetamide (118b).

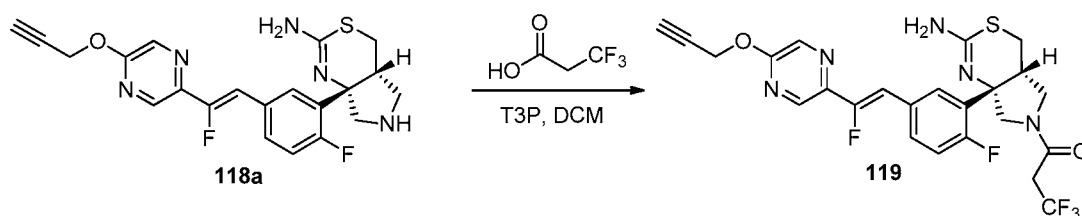
To a mixture of (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (118a) (0.020 g, 0.047 mmol) and N,N-diisopropylethylamine (0.024 mL, 0.140 mmol) in DCM (1 mL) was added acetic anhydride (4.86 μL, 0.051 mmol). The mixture was stirred at room temperature for 5 hours, then diluted with sat'd aqueous Na₂CO₃ and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in DCM) to give 118b (13 mg, 54% yield) as an off-white solid. MS (ESI, positive ion) m/z: 512 (M+1).

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Preparation of 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone (118).

A mixture of N-((4aR,7aS)-6-acetyl-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)acetamide (**118b**, 13.0 mg, 0.025 mmol), methoxylamine hydrochloride (10.61 mg, 0.127 mmol), and pyridine (10.36 μ L, 0.127 mmol) in ethanol (1 mL) was stirred at 60 °C for 2 hours, then diluted with sat'd aqueous Na₂CO₃ and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc/EtOH (3/1) in heptane) to give Example **118** (11 mg, 92% yield) as an off-white solid. MS (ESI, positive ion) *m/z*: 470 (M+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.35-8.46 (m, 1H), 8.27 (s, 1H), 7.69 (br. s., 1H), 7.51-7.61 (m, 1H), 7.03-7.14 (m, 1H), 6.77-6.92 (m, 1H), 5.04 (s, 2H), 4.17-4.30 (m, 1H), 3.62-3.88 (m, 3H), 3.13-3.32 (m, 1H), 3.04 (d, *J* = 13.30 Hz, 1H), 2.82-2.94 (m, 1H), 2.53 (br. s., 1H), 1.99-2.12 (m, 3H). NH₂ was not clear. ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -111.33 (m, 1F), -125.21 (m, 1F).

Example 119: 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-trifluoropropan-1-one.



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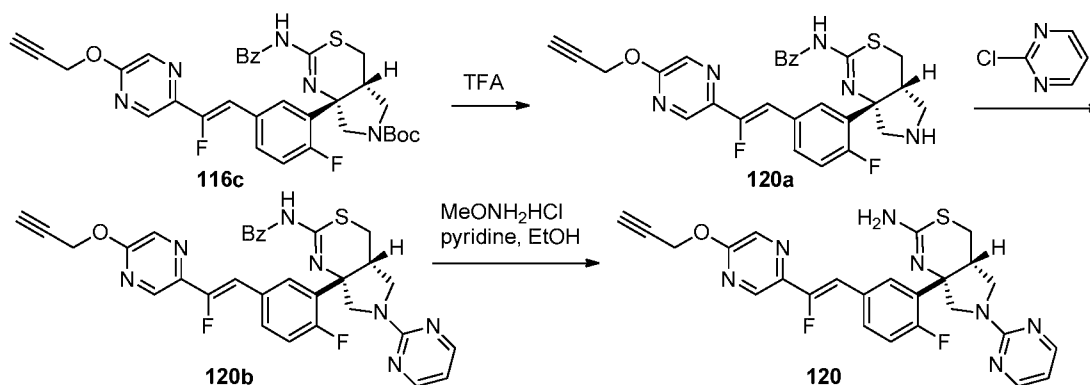
A mixture of (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (**118a**) (19.5 mg, 0.046 mmol), 3,3,3-trifluoropropanoic acid (Sigma-Aldrich) (23 mg, 0.182 mmol) in DCM (0.5 mL) at room temperature was treated with propylphosphonic anhydride solution (Sigma-Aldrich) (50 wt. % in EtOAc, 0.109 mL, 0.182 mmol) and stirred for 18 hours. The mixture was diluted with sat'd aqueous Na₂CO₃ and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by

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silica gel chromatography (0 to 100% EtOAc/EtOH (3:1) in heptane) to afford the title compound (Example 119) (10 mg, 41% yield) as a yellow solid. MS (ESI, positive ion) m/z : 538 (M+1). ^1H NMR (400 MHz, CHLOROFORM- d) δ ppm 8.36 - 8.43 (m, 1 H), 8.22 - 8.29 (m, 1 H), 7.63 - 7.74 (m, 1 H), 7.52 - 7.61 (m, 1 H), 7.03 - 7.15 (m, 1 H), 6.76 - 6.93 (m, 1 H), 5.04 (d, J = 2.35 Hz, 2 H), 4.18 - 4.35 (m, 1 H), 3.62 - 3.94 (m, 3 H), 3.10 - 3.33 (m, 3 H), 2.98 - 3.10 (m, 1 H), 2.81 - 2.93 (m, 1 H), 2.53 (t, J = 2.35 Hz, 1 H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -62.34 (m, 3F), -111.59 (m, 1F), -125.45 (m, 1F).

Example 120: (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine.



Preparation of N-((4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (120a).

A mixture of (4aR,7aS)-tert-butyl 2-benzamido-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (116c) (0.205 g, 0.325 mmol) in TFA (0.36 mL, 4.71 mmol) and DCM (1 mL) was stirred at room temperature for 30 minutes then concentrated *in vacuo*. The residue was diluted with DCM, neutralized with 1 M aqueous NaOH, and extracted with DCM. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to afford 120a (0.160 g, 93% yield) as a yellow solid which was used without additional purification. MS (ESI, positive ion) m/z : 532 (M+1).

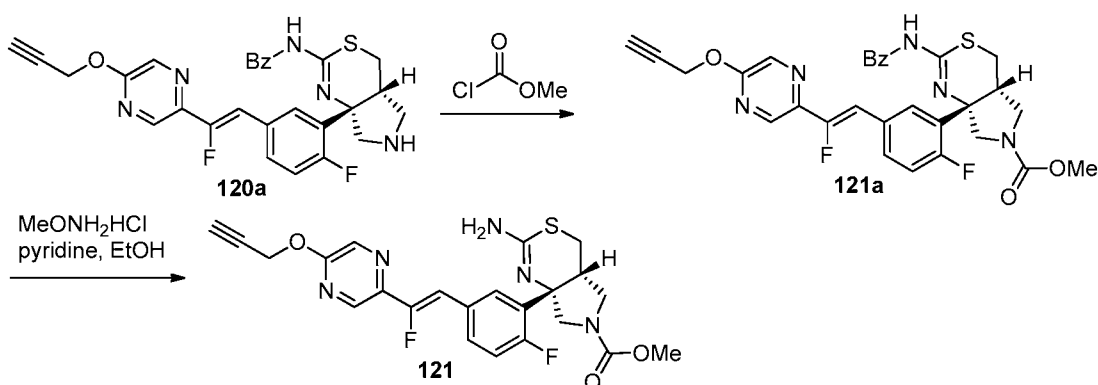
Preparation of N-((4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (120b).

A mixture of N-((4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**120a**) (0.040 g, 0.075 mmol), 2-chloropyrimidine (Acros Organics) (0.043 g, 0.376 mmol) and N,N-diisopropylethylamine (0.105 mL, 0.602 mmol) in dimethyl sulfoxide (1 mL) was heated in a sealed vial at 110 °C for 2 hours. After cooling to room temperature, the mixture was diluted with sat'd aqueous Na₂CO₃ and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in heptane) to give **120b** (36.8 mg, 80% yield) as an off-white solid. MS (ESI, positive ion) m/z: 610 (M+1).

Preparation of (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine (120).

A mixture of N-((4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**120b**) (36.8 mg, 0.060 mmol), methoxylamine hydrochloride (55 mg, 0.664 mmol) and pyridine (0.054 mL, 0.664 mmol) in ethanol (2 mL) was stirred at 70 °C for 2 hours. The mixture was concentrated *in vacuo*. The residue was diluted with EtOAc then sequentially washed with NH₄Cl, 1.0 M aqueous NaOH, and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 100% EtOAc in DCM) to give Example **120** (22.2 mg, 73% yield) as a white solid. MS (ESI, positive ion) m/z: 506 (M+1). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.36 (s, 1H), 8.33 (d, *J* = 4.69 Hz, 2H), 8.25 (s, 1H), 7.65 (ddd, *J* = 2.25, 4.60, 8.41 Hz, 1H), 7.60 (dd, *J* = 2.05, 7.92 Hz, 1H), 7.07 (dd, *J* = 8.61, 12.13 Hz, 1H), 6.73-6.90 (m, 1H), 6.50 (t, *J* = 4.79 Hz, 1H), 5.03 (d, *J* = 2.35 Hz, 2H), 4.40 (d, *J* = 11.15 Hz, 1H), 3.74-3.98 (m, 3H), 3.24 (tt, *J* = 4.35, 8.26 Hz, 1H), 2.89-3.12 (m, 2H), 2.53 (t, *J* = 2.45 Hz, 1H). NH₂ was not clear. ¹⁹F NMR (376 MHz, CHLOROFORM-d) δ -110.99 (d, *J* = 1.73 Hz, 1F), -125.44 (d, *J* = 1.73 Hz, 1F).

Example 121: (4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate.



5 Preparation of (4aR,7aS)-methyl 2-benzamido-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (121a).

A mixture of N-((4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**120a**) (33.5 mg, 0.063 mmol) and methyl chloroformate (0.024 mL, 0.315 mmol, Aldrich) in DCM (1 mL) at room temperature was treated with N,N-diisopropylethylamine (0.077 mL, 0.441 mmol) and stirred for 2.5 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography (0 to 100% EtOAc in heptane) to give **121a** (34.8 mg, 94% yield) as an off-white solid. MS (ESI, positive ion) m/z: 590 (M+1).

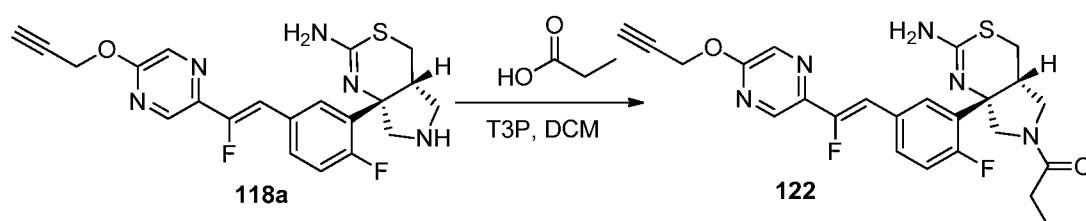
Preparation of (4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (121).

This compound (22.3 mg, 78%) as a white solid was prepared in a fashion similar to that described for Example **120**, here starting from **121a** (34.8 mg, 0.059 mmol) and methoxylamine hydrochloride (0.054 g, 0.649 mmol). MS (ESI, positive ion) m/z: 486 (M+1). ¹H NMR (400 MHz, CHLOROFORM-d) δ 8.39 (s, 1H), 8.27 (s, 1H), 7.62-7.72 (m, 1H), 7.56 (dd, *J* = 2.05, 7.92 Hz, 1H), 7.07 (dd, *J* = 8.51, 12.03 Hz, 1H), 6.74-6.91 (m, 1H),

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5.04 (d, $J = 2.54$ Hz, 2H), 4.44 (d, $J = 7.63$ Hz, 2H), 4.13-4.23 (m, 1H), 3.58-3.75 (m, 6H), 3.11 (td, $J = 4.25, 8.31$ Hz, 1H), 2.97-3.04 (m, 1H), 2.80-2.92 (m, 1H), 2.53 (t, $J = 2.45$ Hz, 1H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -111.23 (d, $J = 18.21$ Hz, 1F), -125.32 (d, $J = 13.01$ Hz, 1F).

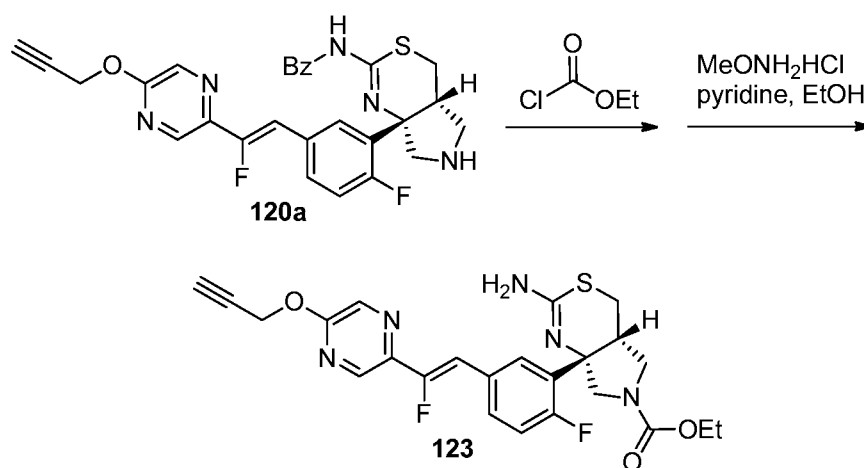
- 5 **Example 122: 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one.**



This compound (7 mg, 27% yield) as an off-white solid was prepared in a fashion similar to that described for Example 119, here starting from **118a** (22 mg, 0.05 mmol) and propionic acid (19 mg, 0.25 mmol). MS (ESI, positive ion) m/z : 484 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.36-8.46 (m, 1H), 8.27 (br. s., 1H), 7.67 (br. s., 1H), 7.58 (d, $J = 7.63$ Hz, 1H), 7.02-7.15 (m, 1H), 6.74-6.94 (m, 1H), 4.99-5.08 (m, 2H), 5.04 (s, 2H), 4.17-4.29 (m, 1H), 3.59-3.89 (m, 3H), 3.08-3.28 (m, 1H), 3.03 (d, $J = 13.30$ Hz, 1H), 2.80-2.94 (m, 1H), 2.53 (s, 1H), 2.21-2.38 (m, 2H), 1.18 (q, $J = 6.98$ Hz, 3H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -111.27 (d, $J = 34.68$ Hz, 1F), -125.22 (d, $J = 76.29$ Hz, 1F).

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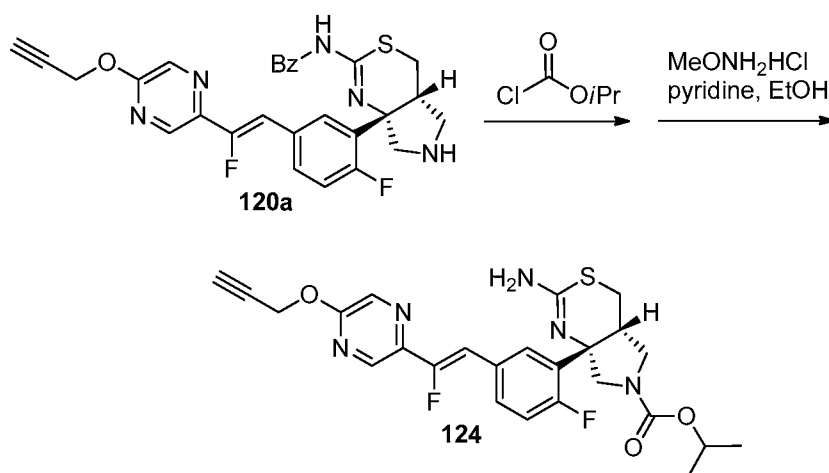
Example 123: (4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate.



5 This compound (18 mg, 91% yield) as a white solid was prepared in a fashion similar to that described for Example **121**, here starting from **120a** (21 mg, 0.04 mmol) and ethyl chloroformate (21 mg, 0.20 mmol). MS (ESI, positive ion) m/z : 500 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM- d) δ 8.39 (s, 1H), 8.26 (s, 1H), 7.62-7.70 (m, 1H), 7.57 (d, J = 7.82 Hz, 1H), 7.07 (dd, J = 8.71, 12.03 Hz, 1H), 6.75-6.92 (m, 1H), 5.04 (d, J = 2.35 Hz, 2H),
 10 4.46 (br. s., 2H), 4.13-4.23 (m, 3H), 3.56-3.73 (m, 3H), 3.11 (tt, J = 4.28, 8.44 Hz, 1H), 2.97-3.05 (m, 1H), 2.80-2.93 (m, 1H), 2.53 (t, J = 2.45 Hz, 1H), 1.26-1.29 (m, 3H). ^{19}F NMR (376 MHz, CHLOROFORM- d) δ -111.11 (m, 1F), -125.35 (m, 1F).

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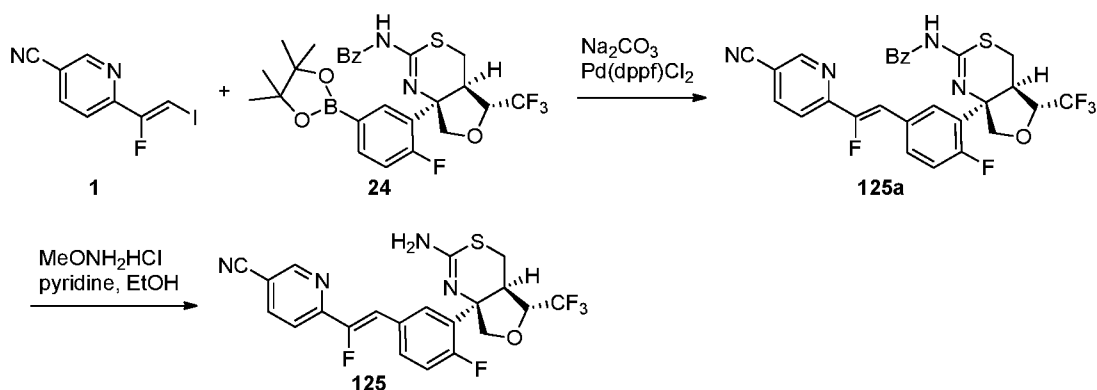
Example 124: (4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate.



5 This compound (16 mg, 76% yield) as a white solid was prepared in a fashion similar to that described for Example 121, here starting from **120a** (21 mg, 0.04 mmol) and isopropyl chloroformate (Sigma-Aldrich) (0.20 mL of 1.0 M solution in toluene, 0.20 mmol). MS (ESI, positive ion) m/z : 514 ($M+1$). ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.39 (s, 1H), 8.27 (s, 1H), 7.67 (br. s., 1H), 7.57 (d, $J = 7.82$ Hz, 1H), 7.08 (dd, $J = 8.51, 12.03$ Hz, 1H), 6.75-6.93 (m, 1H), 5.04 (d, $J = 2.35$ Hz, 2H), 4.88-5.01 (m, 1H), 4.08-4.23 (m, 1H), 3.55-3.77 (m, 3H), 3.16 (dd, $J = 4.40, 8.12$ Hz, 1H), 2.96-3.06 (m, 1H), 2.82-2.95 (m, 1H), 2.53 (t, $J = 2.35$ Hz, 1H), 1.23-1.29 (m, 6H). NH_2 was not clear. ^{19}F NMR (376 MHz, CHLOROFORM-d) δ -111.20 (m, 1F), -125.67 (m, 1F).

10

Example 125: 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



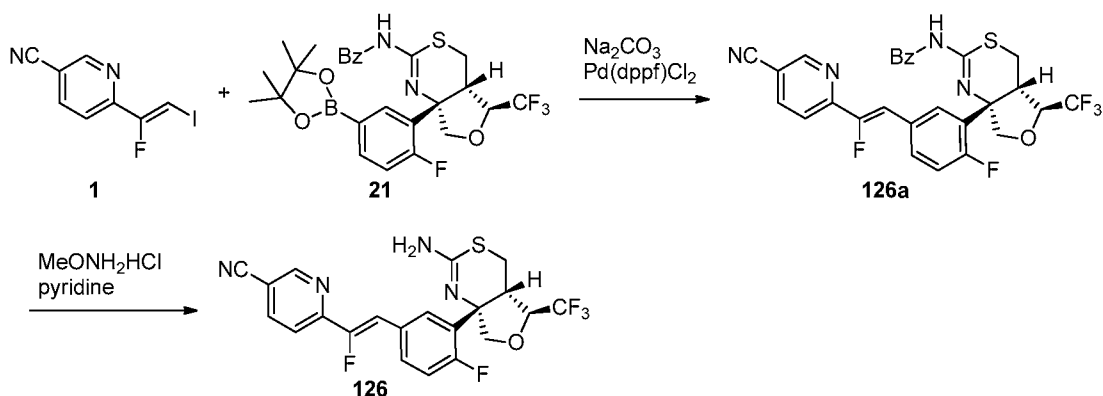
5 Preparation of N-((4aR,5R,7aR)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (125a).

A suspension of boronic ester **24** (1.30 g, 2.36 mmol), vinyl iodide **1** (0.97 g, 3.54 mmol), 1,1'-bis(diphenylphosphino)ferrocene palladium(II)dichloride dichloromethane adduct (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA) (58 mg, 0.07 mmol), sodium carbonate (0.75 g, 7.09 mmol) in 1,4-dioxane (10 mL) and water (5 mL) was sparged with argon for 5 minutes. The suspension was heated to 70 °C with rapid stirring for 45 minutes. The reaction mixture was partitioned between EtOAc (60 mL) and 5% aqueous NaHCO₃ (30 mL). The organic solution was washed with brine (10 mL), dried over MgSO₄, then purified via silica gel chromatography (0 to 15% EtOAc/EtOH (3:1) in heptane) to afford N-((4aR,5R,7aR)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**125a**, 0.95 g, 70% yield) as a tan foam. MS (ESI +ve ion) m/z: [M+1] = 571.1. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.83 (s, 1 H), 7.98 - 8.10 (m, 3 H), 7.77 - 7.86 (m, 1 H), 7.65 - 7.73 (m, 2 H), 7.55 - 7.63 (m, 1 H), 7.46 - 7.54 (m, 2 H), 7.16 - 7.33 (m, 3 H), 4.77 - 4.89 (m, 1 H), 4.66 (d, *J* = 8.80 Hz, 1 H), 4.04 (br d, *J* = 8.02 Hz, 1 H), 3.52 - 3.64 (m, 1 H), 3.23 (br d, *J* = 14.09 Hz, 1 H), 2.87 (br dd, *J* = 13.89, 3.52 Hz, 1 H).

Preparation of Example 125.

A suspension of N-((4aR,5R,7aR)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**125a**) (900 mg, 1.57 mmol), methoxylamine hydrochloride (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA, 659 mg, 7.89 mmol), and pyridine (643 μ L, 7.89 mmol) in EtOH (6 mL) was heated to 50 °C for 4 hours. The reaction mixture was partitioned between EtOAc (60 mL) and sat'd aqueous NaHCO₃ (40 mL). The organic solution was washed with brine (5 mL), dried over MgSO₄, filtered, and then concentrated under reduced pressure to afford a white solid. The solid was then suspended in boiling EtOH (5 mL), and after cooling the liquid was discarded. The resulting white solid was dried overnight at 50 °C with a gentle stream of argon to afford 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (Example **125**) (375 mg, 51% yield) as a white solid. MS (ESI +ve ion) m/z: [M+1] = 467.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.08 (s, 1 H), 8.44 (dd, *J* = 8.41, 1.96 Hz, 1 H), 7.87 (br d, *J* = 8.02 Hz, 2 H), 7.74 - 7.80 (m, 1 H), 7.24 - 7.40 (m, 2 H), 6.33 (s, 2 H), 4.68 (quin, *J* = 7.38 Hz, 1 H), 4.40 (d, *J* = 8.02 Hz, 1 H), 3.84 (br d, *J* = 6.26 Hz, 1 H), 3.21 - 3.28 (m, 1 H), 3.08 (dd, *J* = 13.99, 2.84 Hz, 1 H), 2.88 (dd, *J* = 13.99, 3.81 Hz, 1 H).

Example 126: 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



Preparation of N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (126a).

This compound (2.0 g, 69 % yield) as a tan foam was prepared in a fashion similar to that described for compound **125a**, here using boronic ester **21** (2.80 g, 5.09 mmol) and (Z)-6-(1-fluoro-2-iodovinyl)nicotinonitrile (**1**) (1.81 g, 6.61 mmol) as starting materials. MS (ESI +ve ion) m/z: [M+1] = 571.1. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.77-8.80 (m, 1H), 7.95-8.06 (m, 3H), 7.74-7.81 (m, 1H), 7.62-7.69 (m, 2H), 7.56 (t, *J* = 14.90 Hz, 1H), 7.47 (t, *J* = 15.10 Hz, 2H), 7.12-7.29 (m, 3H), 4.74-4.84 (m, 1H), 4.62 (d, *J* = 8.80 Hz, 1H), 4.00 (d, *J* = 6.85 Hz, 1H), 3.50-3.58 (m, 1H), 3.19 (d, *J* = 13.69 Hz, 1H), 2.82 (dd, *J* = 2.74, 13.69 Hz, 1H).

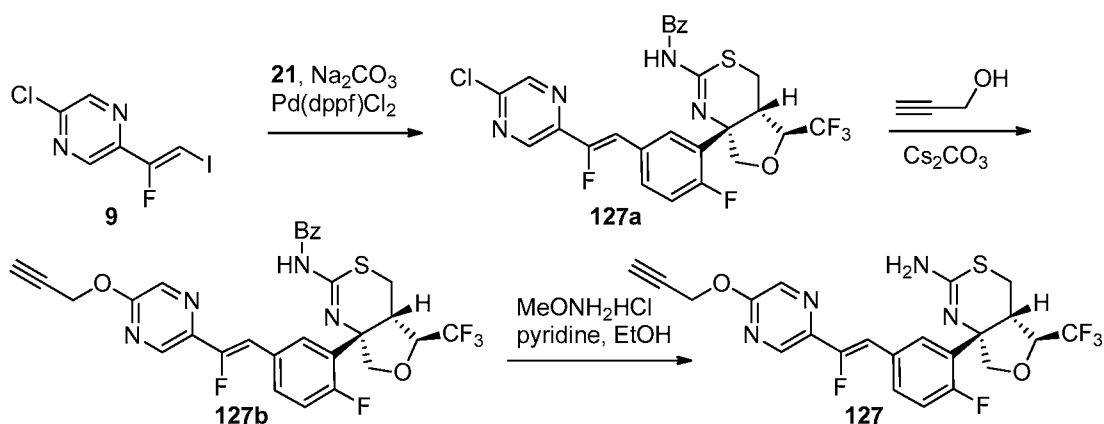
Preparation of Example 126.

A suspension of N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**126a**) (2.00 g, 3.51 mmol) and methoxylamine hydrochloride (1.46 g, 17.53 mmol) in pyridine (11.93 mL, 140 mmol) was heated to 60 °C for 90 minutes. After cooling to room temperature, the reaction mixture was partitioned between DCM (75 mL) and sat'd aqueous NaHCO₃ (50 mL). The aqueous was further extracted with DCM (25 mL). The combined organic solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography (10 to 25% EtOH/EtOAc (1:3) in DCM) to give the desired product (MS (ESI +ve ion) m/z: [M+1] = 467.0) as a brown solid containing a small amount of impurity. The material was dissolved in DCM/MeOH then adsorbed onto silica gel (20 g) after removal of solvent under reduced pressure. The material was further purified by silica gel chromatography (0 to 100% EtOAc (0.3% AcOH) in heptane (0.3% AcOH)) to give the desired product as a white solid. The resulting white solid was then partitioned between EtOAc (75 mL) and 1 M aqueous NaOH (50 mL). The separated aqueous was extracted once with EtOAc (20 mL). The combined organic solution was washed with brine (20 mL), dried over MgSO₄, filtered, then concentrated under reduced pressure to afford 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (Example **126**) (0.75 g, 46% yield) as a white solid. MS (ESI +ve ion) m/z: [M+1] = 467.0. ¹H NMR (400 MHz,

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DMSO-*d*₆) δ ppm 9.08 (s, 1 H), 8.45 (dd, *J* = 8.31, 1.66 Hz, 1 H), 7.88 (br d, *J* = 8.22 Hz, 2 H), 7.79 (br d, *J* = 3.52 Hz, 1 H), 7.25 - 7.41 (m, 2 H), 6.33 (s, 2 H), 4.68 (quin, *J* = 7.48 Hz, 1 H), 4.40 (d, *J* = 7.82 Hz, 1 H), 3.85 (br d, *J* = 7.04 Hz, 1 H), 3.21 - 3.29 (m, 1 H), 3.04 - 3.14 (m, 1 H), 2.89 (dd, *J* = 13.79, 3.42 Hz, 1 H).

- 5 **Example 127: (4a*S*,5*S*,7a*S*)-7a-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-(prop-2-ynyloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-amine.**



- 10 **Preparation of 127a: N-((4a*S*,5*S*,7a*S*)-7a-(5-((*Z*)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide.**

This compound (1.3 g, 77% yield) as a white solid was prepared in a fashion similar to that described for compound **125a**, here starting from boronic ester **21** (1.60 g, 2.91 mmol) and vinyl iodide **9** (1.24 g, 4.36 mmol). MS (ESI +ve ion) *m/z*: [*M*+1] = 581.0.

- 15 **Preparation of 127b: N-((4a*S*,5*S*,7a*S*)-7a-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-(prop-2-ynyloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide.**

- 20 A suspension of N-((4a*S*,5*S*,7a*S*)-7a-(5-((*Z*)-2-(5-chloropyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide (**127a**) (1.30 g, 2.24 mmol), propargyl alcohol (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA) (0.66 mL, 11.19 mmol), cesium carbonate (Sigma-

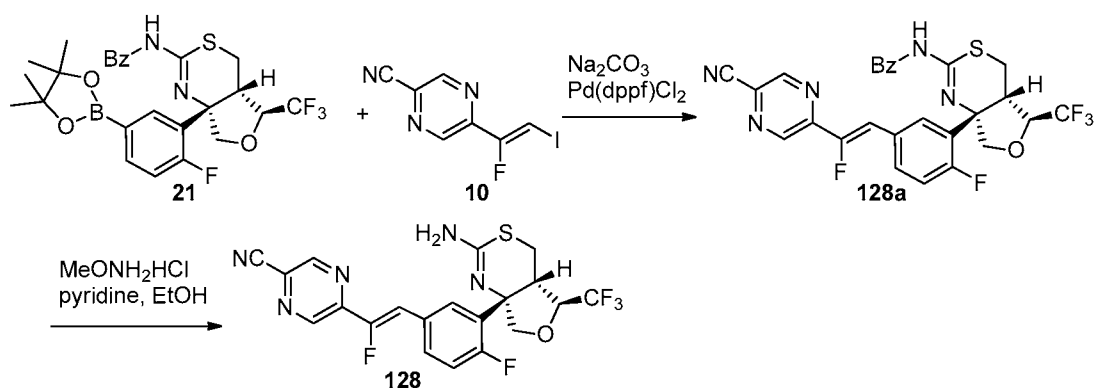
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Aldrich Chemical Company, Inc., St. Louis, Missouri, USA) (2.18 g, 6.71 mmol) in THF (10 mL) was stirred for 18 hours at 20 °C. The reaction was partitioned between EtOAc (40 mL) and sat'd aqueous NaHCO₃ (20 mL). The organic solution was washed with brine (5 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 to 20% EtOAc/ EtOH (3:1) in heptane) to afford N-
5-((4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**127b**) (780 mg, 58% yield) as a white foam. MS (ESI +ve ion) m/z: [M+1] = 601.1.

Preparation of (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine acetate (127).

A suspension of **127b** (780 mg, 1.30 mmol), methoxylamine hydrochloride (1085 mg, 12.99 mmol) and pyridine (1.06 mL, 12.99 mmol) in EtOH (5 mL) was heated to 70 °C for 1 hour. The reaction was then partitioned between EtOAc (40 mL) and sat'd aqueous NaHCO₃ (25 mL). The organic solution was washed with brine (5 mL), dried over MgSO₄, filtered, and then concentrated under reduced pressure. Purification of the residue via silica gel chromatography (0 to 100% EtOAc (0.3% AcOH) in heptane (0.3% AcOH)) afforded (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine acetate (Example **127**) (425 mg, 59% yield) as a white solid. MS (ESI +ve ion) m/z: [M+1] = 497.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.96 (br s, 1 H), 8.53 (s, 1 H), 8.46 (s, 1 H), 7.81 (br d, *J* = 8.02 Hz, 1 H), 7.66 - 7.74 (m, 1 H), 7.29 (dd, *J* = 12.23, 8.51 Hz, 1 H), 6.95 (d, *J* = 41.28 Hz, 1 H), 6.33 (br s, 2 H), 5.09 (d, *J* = 2.15 Hz, 2 H), 4.68 (quin, *J* = 7.43 Hz, 1 H), 4.41 (d, *J* = 8.02 Hz, 1 H), 3.84 (br d, *J* = 6.65 Hz, 1 H), 3.62 (t, *J* = 2.25 Hz, 1 H), 3.21 - 3.29 (m, 1 H), 3.09 (dd, *J* = 13.79, 2.84 Hz, 1 H), 2.89 (dd, *J* = 13.99, 3.81 Hz, 1 H), 1.91 (s, 3 H).

Example 128: 5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile.



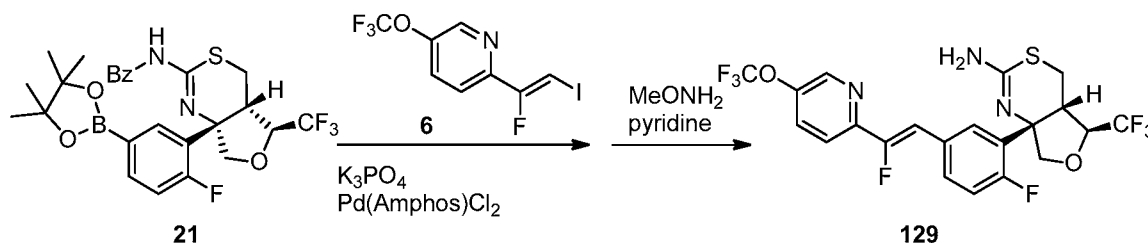
5 N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-Cyanopyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**128a**) (320 mg, 62% yield) as a white solid was prepared in a fashion similar to that described for compound **125a**, here starting from boronic ester **21** (500 mg, 0.91 mmol) and (Z)-5-(1-fluoro-2-iodovinyl)pyrazine-2-carbonitrile (**10**) (375 mg, 1.36 mmol). MS (ESI +ve ion)
 10 m/z: $[\text{M}+1] = 572.0$. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.96 (s, 1H), 8.84 (s, 1H), 8.06 (br s, 2H), 7.81-7.89 (m, 1H), 7.71 (d, $J = 7.24$ Hz, 1H), 7.62 (t, $J = 14.70$ Hz, 1H), 7.53 (t, $J = 15.30$ Hz, 2H), 7.20-7.35 (m, 3H), 4.78-4.88 (m, 1H), 4.67 (d, $J = 8.80$ Hz, 1H), 4.00-4.08 (m, 1H), 3.54-3.64 (m, 1H), 3.22 (d, $J = 14.67$ Hz, 1H), 2.83-2.94 (m, 1H).

15 5-((Z)-2-(3-((4aS,5S,7aS)-2-Amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile (Example **128**) (70 mg, 26% yield) as a white solid was prepared in a fashion similar to that described for Example **125** here starting from N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**128a**) (320 mg, 0.56 mmol) and methoxyamine
 20 hydrochloride (187 mg, 2.24 mmol). MS (ESI +ve ion) m/z: $[\text{M}+1] = 480.0$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.25 (s, 1H), 9.16 (s, 1H), 7.92 (d, $J = 8.22$ Hz, 1H), 7.77-7.84 (m, 1H), 7.30-7.48 (m, 2H), 6.33 (br s, 2H), 4.63-4.73 (m, 1H), 4.41 (d, $J = 8.22$ Hz, 1H), 3.84 (d, $J = 7.43$ Hz, 1H), 3.21-3.28 (m, 1H), 3.08 (d, $J = 13.89$ Hz, 1H), 2.89 (dd, $J = 13.50, 14.28$ Hz,

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1H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -125.87 (s, 1 F), -108.23 (s, 1 F), -76.24 (s, 3 F).

Example 129: (4a*S*,5*S*,7a*S*)-7a-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-amine.



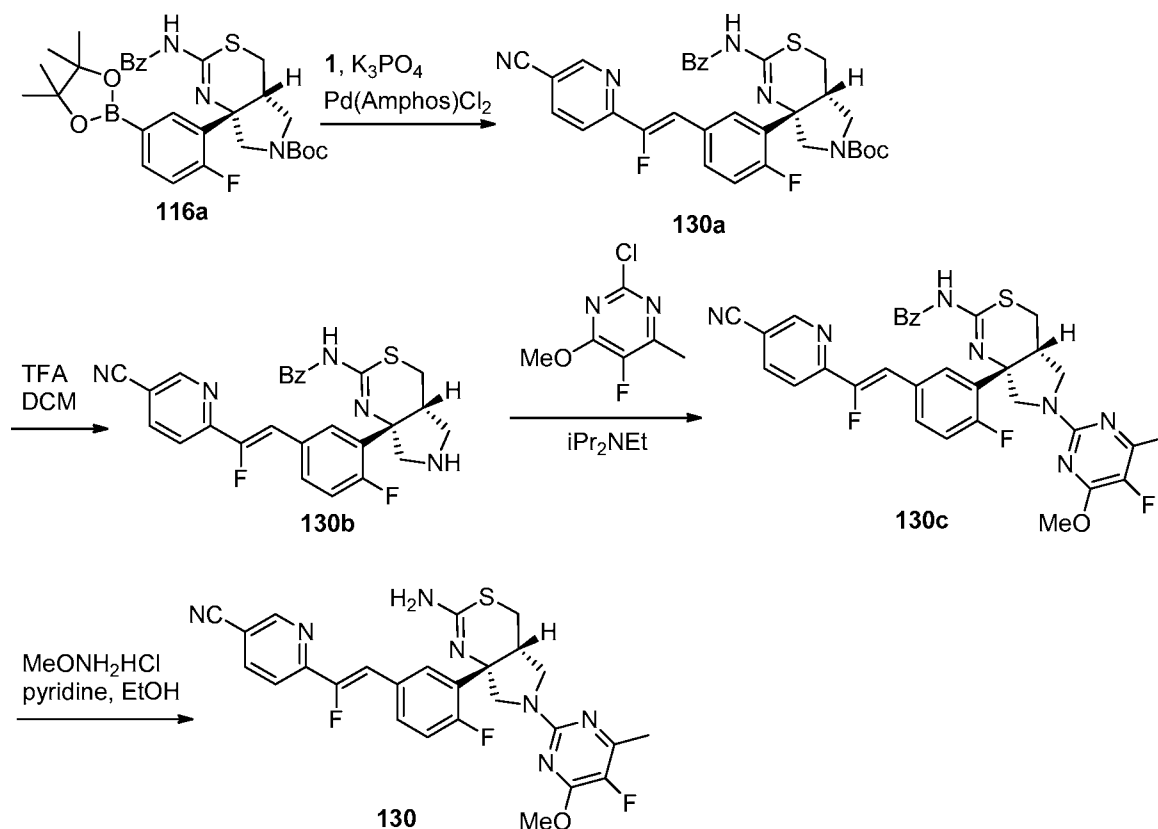
A suspension of boronic ester **21** (247 mg, 0.45 mmol), (*Z*)-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethoxy)pyridine (**6**) (115 mg, 0.345 mmol), bis-(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (20 mg, 0.03 mmol), potassium phosphate tribasic monohydrate (239 mg, 1.04 mmol) in 1,4-dioxane (3 mL) and water (1.5 mL) was sparged with argon for 2 minutes. The reaction was then heated to 90 °C for 45 minutes, then cooled to room temperature and partitioned between EtOAc (10 mL) and sat'd aqueous NaHCO₃ (2 mL). The EtOAc layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (15 to 35% EtOAc in heptane) to afford a brown amorphous solid that contained N-((4a*S*,5*S*,7a*S*)-7a-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide (160 mg) as an off-white amorphous solid. MS *m/z* = 630.1 [M+H]⁺.

A suspension of N-((4a*S*,5*S*,7a*S*)-7a-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide (160 mg) and methoxylamine hydrochloride (115 mg, 1.38 mmol) in pyridine (0.88 mL, 10.36 mmol) was heated to 60 °C for 90 minutes. The reaction mixture was partitioned between EtOAc (35 mL) and water (5 mL). The aqueous was discarded. The EtOAc layer was concentrated and the residue was purified silica gel chromatography twice (20 to 35% EtOAc in heptane) to give (4a*S*,5*S*,7a*S*)-7a-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-

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4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine (Example 129) (24 mg, 13% yield) as a brown crystalline solid. MS m/z = 526.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.75 (d, J = 2.35 Hz, 1H), 8.04 (d, J = 8.88 Hz, 1H), 7.83 (m, 2H), 7.74 (m, 1H), 7.30 (dd, J = 8.61, 12.32 Hz, 1H), 7.15 (d, J = 39.55 Hz, 1H), 6.32 (br., 2H), 4.67 (m, 1H), 4.40 (d, J = 8.02 Hz, 1H), 3.83 (m, 1H), 3.26 (m, 1H), 3.08 (dd, J = 2.93, 13.89 Hz, 1H), 2.88 (dd, J = 3.81, 13.99 Hz, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -57.14 (s, 3F), -76.21 (s, 3F), -109.96 (s, 1F), -122.79 (s, 1F).

Example 130: 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



Preparation of (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (130a).

A mixture of (4aR,7aS)-tert-butyl 2-benzamido-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (**116a**) (1.00 g, 1.72 mmol), vinyl iodide **1** (0.56 g, 2.06 mmol), Pd(Amphos)Cl₂ (0.12 g, 0.17 mmol) and potassium phosphate tribasic monohydrate (919 mg, 4.00 mmol) in 1,4-dioxane (7.8 mL) and water (1.3 mL) was purged with argon, then the flask was sealed and heated to 80 °C for 1.5 hours. The mixture was diluted with water and extracted with EtOAc (3 x). The organic solution was dried over Na₂SO₄ and concentrated *in vacuo*. The crude was purified by silica gel chromatography (0 to 50% EtOAc in heptane) to give (4aR,7aS)-tert-butyl 2-benzamido-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate (**130a**) (0.79 g, 76% yield) as a beige solid. MS (ESI +ve ion) m/z: [M+1] = 602.2.

Preparation of N-((4aR,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (130b).

To a solution of **130a** (0.78 g, 1.3 mmol) in DCM (6.5 mL) was added trifluoroacetic acid (2.1 mL, 27 mmol) dropwise. The reaction mixture was stirred for 2 hours. The mixture was evaporated *in vacuo* and the residue was added DCM and evaporated again *in vacuo*. The residue was partitioned between DCM and sat'd aqueous NaHCO₃. The aqueous layer was extracted with DCM (2 x) and the combined DCM extracts were dried over Na₂SO₄ and concentrated to give **130b** as a light yellow solid which was used without additional purification, assuming theoretical yield. MS (ESI +ve ion) m/z: [M+1] = 502.1.

Preparation of N-((4aR,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (130c).

A mixture of N-((4aR,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (**130b**) (0.19 g, 0.38 mmol), N,N-diisopropylethylamine (0.46 mL, 2.65 mmol), and 2-chloro-5-fluoro-4-methoxy-6-methylpyrimidine (Enamine) (0.33 g, 1.89 mmol) in dioxane (1.2 mL)

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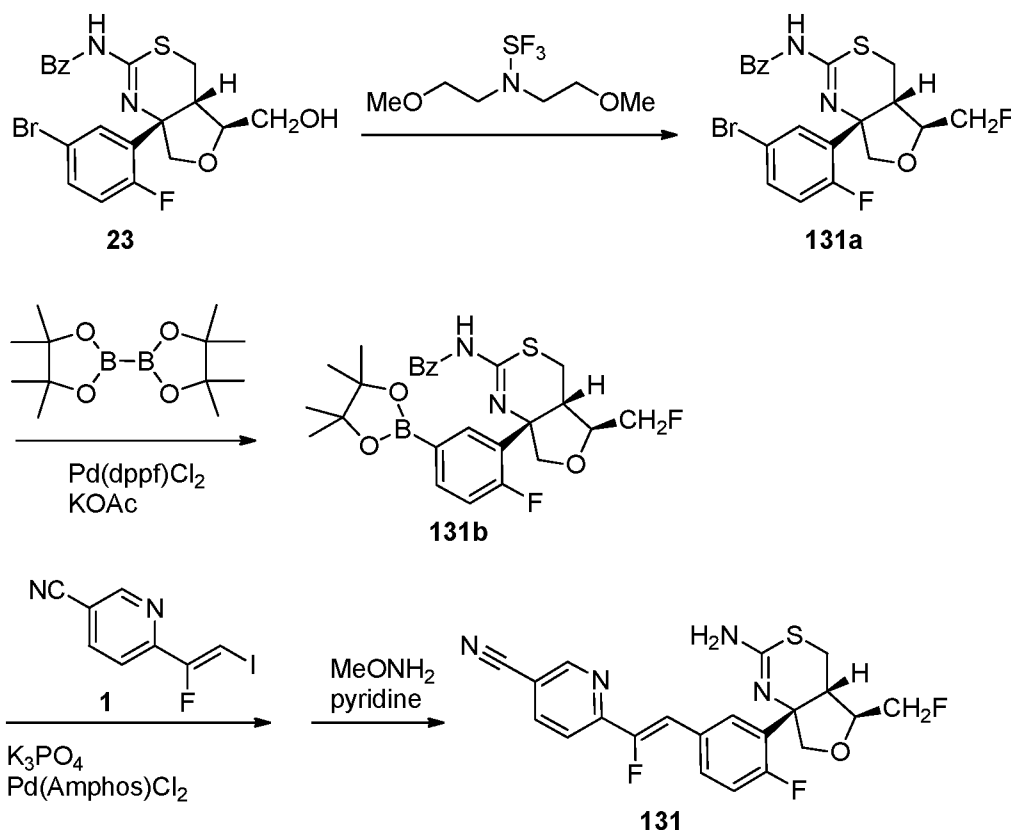
was heated to reflux for 2 hours. The mixture was diluted with water and extracted with EtOAc. The organic layer was concentrated *in vacuo*. The crude was purified by silica gel chromatography (0 to 40% EtOAc in heptane) to give N-((4aR,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (130c) (90 mg, 37% yield) as an off-white solid. MS (ESI +ve ion) m/z: [M+1] = 642.2.

Preparation of 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (130).

A mixture of N-((4aR,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (130c) (90 mg, 0.14 mmol), O-methylhydroxylamine hydrochloride (117 mg, 1.40 mmol), pyridine (113 μ L, 1.4 mmol) and EtOH (1.8 mL) was heated to 70 °C for 1 hour. The mixture was diluted with EtOAc and water. The organic solution was washed with NH₄Cl, and brine, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 40% (3:1) EtOAc/EtOH in heptane) followed by reverse phase HPLC (Phenomenex Gemini column, 10 micron, C18, 110 Å, 150 x 30 mm, 0.1% TFA in CH₃CN/H₂O, gradient 10 to 70% over 15 minutes, then neutralized with aqueous NaHCO₃ and extracted with DCM) to provide 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (Example 130) (20 mg, 26% yield) as a white solid. MS (ESI +ve ion) m/z: [M+1] = 538.1. ¹H NMR (CHLOROFORM-*d*) δ : 8.92 (br s, 1H), 8.12 (br d, *J* = 7.4 Hz, 1H), 7.78 (br d, *J* = 6.8 Hz, 3H), 7.14-7.30 (m, 2H), 4.44 (br d, *J* = 11.7 Hz, 1H), 4.05 (br s, 3H), 3.79-3.99 (m, 3H), 3.30 (br s, 1H), 2.96-3.19 (m, 2H), 2.40 (br s, 3H). NH₂ peak was not observed. ¹⁹F NMR (CHLOROFORM-*d*) δ : -109.05 (br s, 1F), -125.23 (br s, 1F), -176.34 (m, 1F).

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Example 131: 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



Preparation of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (131a).

A solution of bis(2-methoxyethyl)aminosulfur trifluoride (123 μL , 0.55 mmol) in 1 mL of DCM was added to a solution of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**23**) (225 mg, 0.48 mmol) in 2 mL of DCM at 0 °C. The mixture was stirred at 0 °C for 45 minutes then room temperature for 18 hours. It was cooled with an ice bath and treated with 10 mL of sat'd aqueous NaHCO_3 followed by 35 mL of DCM. The mixture was stirred for 15 minutes. The solution was separated. The DCM layer was concentrated and the residue was purified on a silica gel column (30 to 65% EtOAc in heptane) to give 2 compounds: 85 mg (0.18 mmol, 37% yield) of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**131a**) (MS m/z = 467/469

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[M+H]⁺) and 100 mg of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**23**) (MS m/z = 465/467 [M+H]⁺).

5 **Preparation of N-((4aS,5S,7aS)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (131b).**

A suspension of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**131a**) (125 mg, 0.27 mmol), bis(pinacolato)diboron (88 mg, 0.35 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(ii) complex with dichloromethane (9 mg, 10.7 μmol), potassium acetate (79 mg, 0.82 mmol) in 1,4-dioxane (3 mL) was sparged with argon for 10 minutes then heated to 100 °C for 1 hour. Additional bis(pinacolato)diboron (25 mg) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane (3 mg) were added to the reaction mixture which was heated again at 100 °C for 20 minutes. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and the filter cake was rinsed with (2 x 3 mL) of EtOAc. The filtrate was concentrated under reduced pressure to give N-((4aS,5S,7aS)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**131b**) as a brown solid which was used without additional purification. MS m/z = 515.0 [M+H]⁺.

Preparation of 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (131).

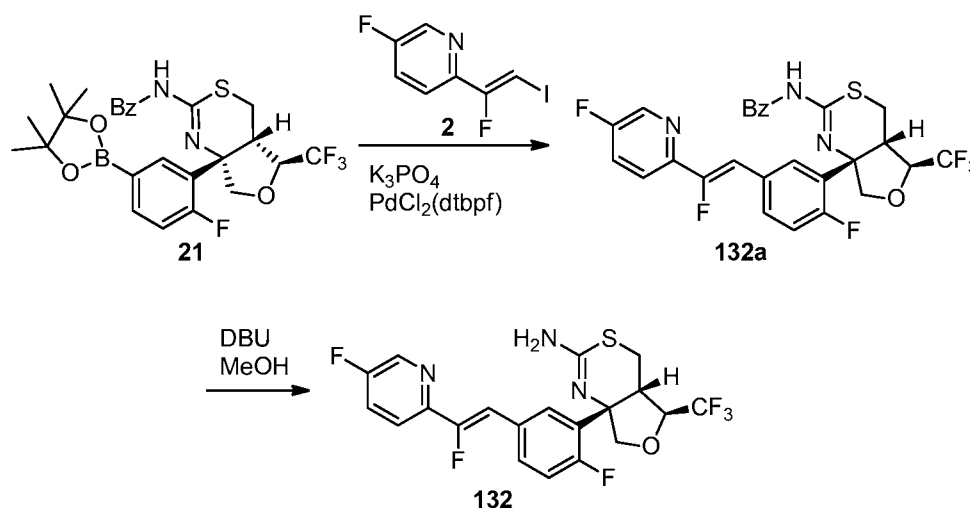
A mixture of the above obtained crude boronic ester **131b**, potassium phosphate tribasic (170 mg, 0.80 mmol), (Z)-6-(1-fluoro-2-iodovinyl)nicotinonitrile (**1**) (70 mg, 0.25 mmol), and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine)dichloropalladium(II) (15 mg, 0.02 mmol) in 2 mL of dioxane and 1 mL of water was purged with argon for 2 minutes and then heated in an oil bath at 90 °C for 90 minutes. The mixture was partitioned between EtOAc (10 mL) and sat'd aqueous NaHCO₃ (2 mL). The organic layer was concentrated under reduced pressure. The residue was purified by silica gel chromatography (25 to 55%

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EtOAc in heptane) to afford N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (56 mg) as a brown amorphous solid. MS m/z = 535.1 $[M+H]^+$.

- 5 A suspension of N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (56 mg, 0.10 mmol) and methoxylamine hydrochloride (34 mg, 0.41 mmol) in pyridine (0.5 mL) was heated to 60 °C for 90 minutes. The mixture was partitioned between EtOAc (35 mL) and water (5 mL). The aqueous portion was discarded. The EtOAc layer was
- 10 concentrated and the residue purified via silica gel chromatography twice (35 to 85% EtOAc in heptane) to give 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (Example
- 15 **131**) (20 mg, 17% overall yield) an off-white crystalline solid. MS m/z = 431.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.08 (s, 1H), 8.44 (dd, J = 2.15, 8.22 Hz, 1H), 7.82-7.89 (m, 2H), 7.74 (m, 1H), 7.24-7.37 (m, 2H), 6.14 (br., 2H), 4.45-4.69 (m, 2H), 4.28-4.41 (m, 2H), 3.75 (dd, J = 2.74, 8.22 Hz, 1H), 3.01 (m, 2H), 2.80 (m, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -108.74 (s, 1F), -124.33 (s, 1F), -225.47 (s, 1F).

- Example 132: (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-**
- 20 **amine.**



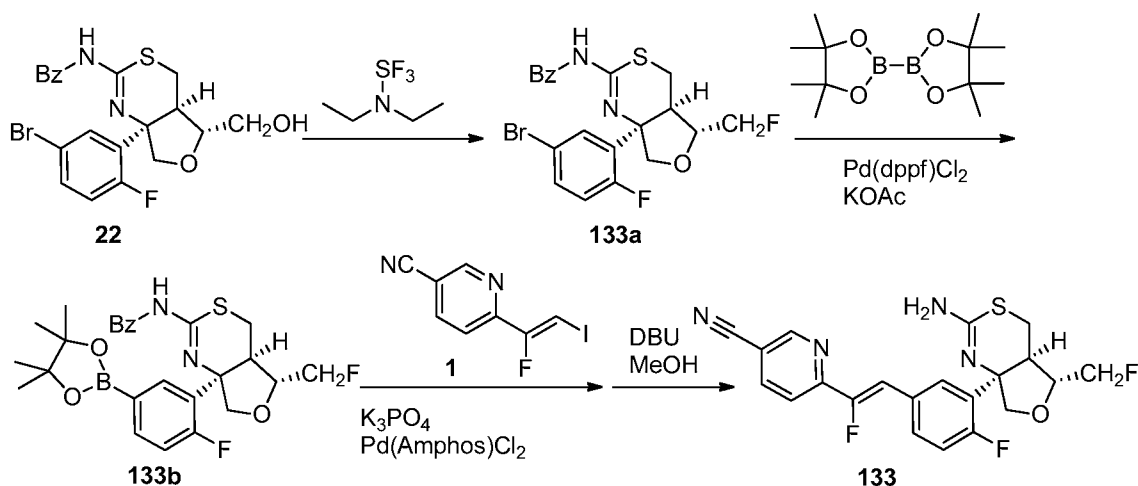
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A solution of boronic ester **21** (200 mg, 0.36 mmol), vinyl iodide **2** (97 mg, 0.36 mmol) and potassium phosphate tribasic (193 mg, 0.91 mmol) in 1,4-dioxane:water (5:1, 6 mL) was degassed with nitrogen for 10 minutes then treated with 1,1'-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (25.7 mg, 0.036 mmol). The reaction mixture
5 was degassed with nitrogen for 10 minutes then heated at 80 °C for 1.5 hours. After cooling to room temperature, the mixture was partitioned between water (50 mL) and EtOAc (150 mL). The organic layer was washed with brine (50 mL) and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 to 15% EtOAc in hexanes) to afford N-((4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**132a**) 150 mg, 73% yield) as an off-white solid. MS *m/z* = 564.2 [M+H]⁺.
10

A mixture of **132a** (150 mg, 0.27 mmol) and DBU (60 µL, 0.40 mmol) in methanol (3 mL) was stirred at 70 °C for 3 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (0 to 30% EtOAc in hexanes) to provide (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine (Example **132**) (50 mg, 41%) as a
20 white solid. MS *m/z* = 460.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.67 (d, *J* = 2.8 Hz, 1H), 7.89 - 7.84 (m, 1H), 7.80 (td, *J* = 9.6, 8.7, 3.4 Hz, 2H), 7.71 (ddd, *J* = 7.2, 4.7, 2.3 Hz, 1H), 7.28 (dd, *J* = 12.3, 8.5 Hz, 1H), 7.06 (d, *J* = 40.3 Hz, 1H), 6.33 (s, 2H), 4.66 (m, 1H), 4.40 (d, *J* = 8.1 Hz, 1H), 3.83 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.24 (dd, *J* = 7.9, 4.1 Hz, 1H), 3.08 (dd, *J* = 13.8, 3.1 Hz, 1H), 2.88 (dd, *J* = 13.8, 3.9 Hz, 1H). ¹⁹F NMR (400 MHz, DMSO-*d*₆) δ
25 -76.213 (s, 3F), -110.498 (s, 1F), -122.269 (s, 1F), -126.210 (s, 1F).

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Example 133: 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



5

Preparation of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (133a).

A solution of (diethylamino)trifluorosulfur (76 mg, 0.47 mmol) in 1 mL of DCM was added to a solution of N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(hydroxymethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**22**) (176 mg, 0.38 mmol) in 2 mL of DCM at -30 °C. The mixture was slowly warmed to room temperature and stirred 18 hours. It was cooled with an ice bath and treated with 10 mL of sat'd aqueous NaHCO₃ followed by 35 mL of DCM. The mixture was stirred for 15 minutes. The solution was separated. The DCM layer was concentrated and the residue was purified on a silica gel column (30 to 65% EtOAc in heptane) to give N-((4aR,5R,7aR)-7a-(5-bromo-2-fluorophenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**133a**) (65 mg, 36% yield). MS m/z = 467/469 [M+H]⁺.

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Preparation of N-((4aR,5R,7aR)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (133b).

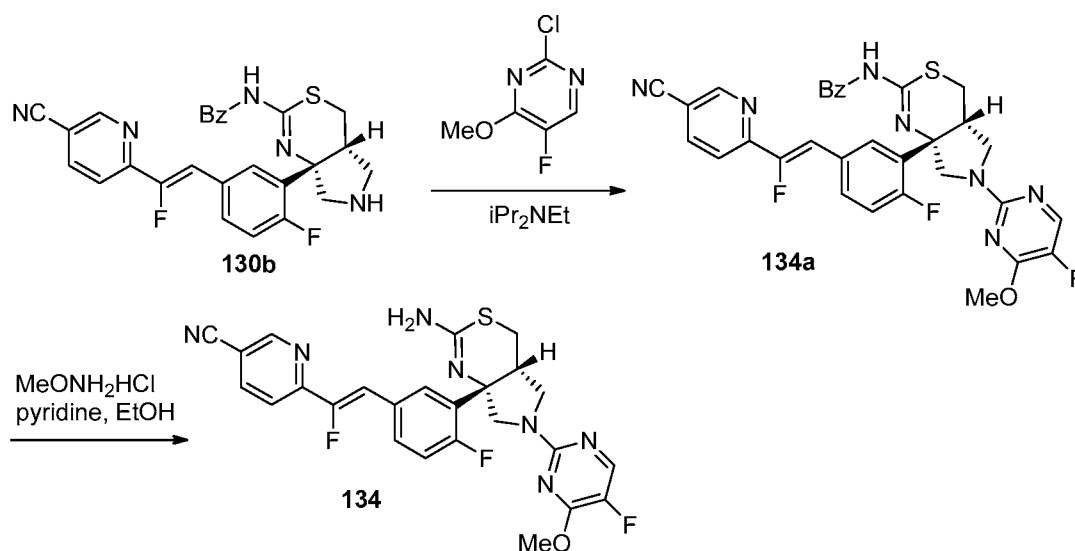
A suspension of **133a** (122 mg, 0.26 mmol), bis(pinacolato)diboron (86 mg, 0.34 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(ii) complex with dichloromethane (9 mg, 10.7 μ mol), potassium acetate (77 mg, 0.78 mmol) in 1,4-dioxane (3 mL) was sparged with argon for 10 minutes then heated to 100 °C for 1 hour. After cooling to room temperature, the reaction mixture was filtered through a pad of celite and the filter cake was rinsed with (2 x 3 mL) of EtOAc. The filtrate was concentrated under reduced pressure to give N-((4aR,5R,7aR)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**133b**) as a brown solid which was used without additional purification, assuming theoretical yield. MS m/z = 515.0 $[M+H]^+$.

Preparation of 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (133).

This compound (20 mg, 18% overall yield) as a white solid was prepared via a 2-step protocol similar to that described for Example **132**, here starting from boronic ester **133b** (133 mg, 0.26 mmol) and vinyl iodide **1** (68 mg, 0.25 mmol). MS m/z = 431.9 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.08 (s, 1H), 8.44 (dd, J = 2.15, 8.22 Hz, 1H), 7.82-7.89 (m, 2H), 7.74 (m, 1H), 7.24-7.37 (m, 2H), 6.14 (br., 2H), 4.45-4.69 (m, 2H), 4.28-4.41 (m, 2H), 3.75 (dd, J = 2.74, 8.22 Hz, 1H), 3.01 (m, 2H), 2.80 (m, 1H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -108.74 (s, 1F), -124.33 (s, 1F), -225.47 (s, 1F).

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Example 134: 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile



5 Preparation of N-((4aR,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-yl)benzamide (134a).

This compound (97 mg, 57 % yield) as an off-white solid was prepared in a manner similar to that described for compound **130c**, here starting from **130b** (0.13 g, 0.27 mmol) and 2-chloro-5-fluoro-4-methoxypyrimidine (SynQuest Laboratories, Inc., Alachua, FL, USA) (0.22 g, 1.36 mmol). MS (ESI +ve ion) m/z : $[M+1] = 628.1$.

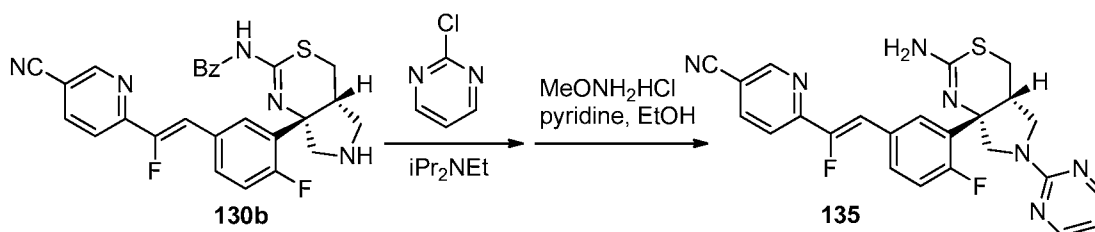
Preparation of 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (134).

A mixture of **134a** (97 mg, 0.16 mmol), O-methylhydroxylamine hydrochloride (129 mg, 1.55 mmol), pyridine (125 μL , 1.55 mmol) and EtOH (2 mL) was heated to 70 $^{\circ}\text{C}$ for 1 hour. The mixture was diluted with EtOAc and water. The organic layer was washed with sat'd aqueous NH_4Cl followed by brine, and concentrated *in vacuo*. The residue was purified by HPLC using 5-95% gradient of 0.1% NH_4OH in acetonitrile and water as mobile phase to give 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-

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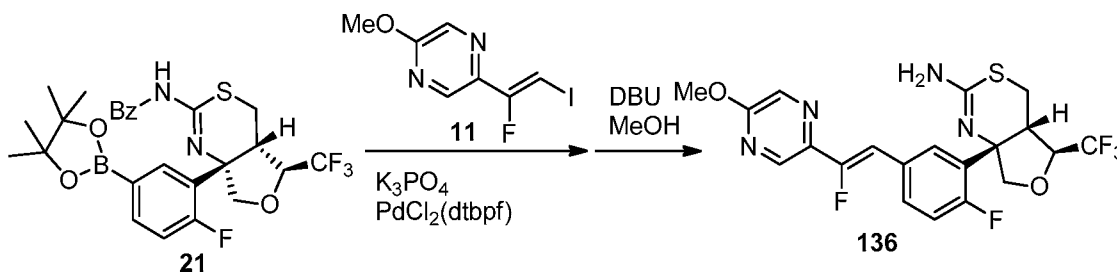
hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (Example **134**) (6 mg, 7% yield) as an off-white solid. MS (ESI +ve ion) m/z : $[M+1] = 524.0$.

Example 135: 6-((*Z*)-2-(3-((4*R*,7*aS*)-2-amino-6-(pyrimidin-2-yl)-4,4*a*,5,6,7,7*a*-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



This compound (32 mg, 27% overall yield) as an off-white solid was prepared in a 2-step protocol similar to that described for Example **134**, here starting from **130b** (0.13 g, 0.26 mmol) and 2-chloropyrimidine (Acros Organics) (0.15 g, 1.28 mmol). MS (ESI +ve ion) m/z : $[M+1] = 476.0$. ^1H NMR (DMSO- d_6) δ : 9.07 (d, $J = 2.1$ Hz, 1H), 8.40-8.46 (m, 1H), 8.34 (d, $J = 4.7$ Hz, 2H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.71-7.78 (m, 2H), 7.26-7.35 (m, 1H), 7.28 (d, $J = 32$ Hz, 1H), 6.62 (t, $J = 4.8$ Hz, 1H), 6.18 (s, 2H), 4.13 (d, $J = 11.2$ Hz, 1H), 3.68-3.81 (m, 2H), 3.54-3.65 (m, 1H), 3.01-3.12 (m, 2H), 2.90-2.98 (m, 1H).

Example 136: (4*aS*,5*S*,7*aS*)-7*a*-(2-fluoro-5-((*Z*)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4*a*,5,7,7*a*-tetrahydro-4*H*-furo[3,4-d][1,3]thiazin-2-amine.



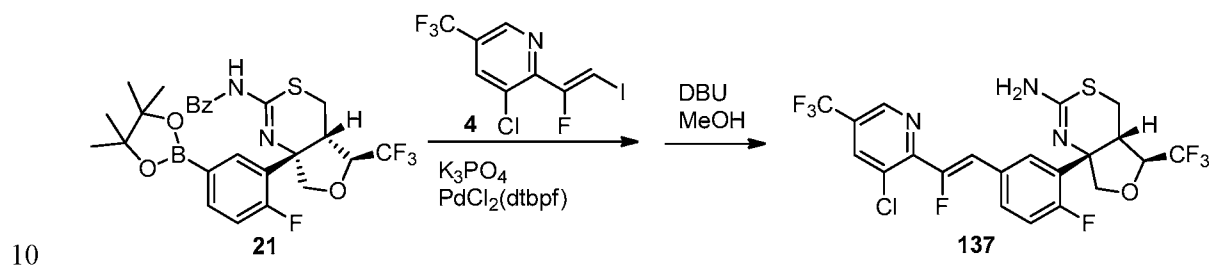
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This compound (45 mg, 25% overall yield) as a white solid was prepared via a 2-step protocol similar to that described for Example **132**, here starting from boronic ester **21** (200

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mg, 0.36 mmol) and vinyl iodide **11** (102 mg, 0.36 mmol). MS $m/z = 473.2$ $[M+H]^+$. 1H NMR (300 MHz, DMSO- d_6) δ 8.50 (s, 1H), 8.40 (d, $J = 1.3$ Hz, 1H), 7.80 (dd, $J = 8.1, 2.4$ Hz, 1H), 7.75 - 7.65 (m, 1H), 7.28 (dd, $J = 12.3, 8.5$ Hz, 1H), 6.93 (d, $J = 40.9$ Hz, 1H), 6.34 (s, 2H), 4.67 (q, $J = 7.5$ Hz, 1H), 4.41 (d, $J = 8.0$ Hz, 1H), 3.98 (s, 3H), 3.83 (dd, $J = 8.4, 2.8$ Hz, 1H), 3.27 - 3.23 (m, 1H), 3.08 (dd, $J = 13.9, 3.2$ Hz, 1H), 2.88 (dd, $J = 14.0, 3.9$ Hz, 1H). ^{19}F NMR (400 MHz, DMSO- d_6) δ -76.213 (s, 3F), -110.700 (s, 1F), -124.383 (s, 1F).

Example 137: (4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.



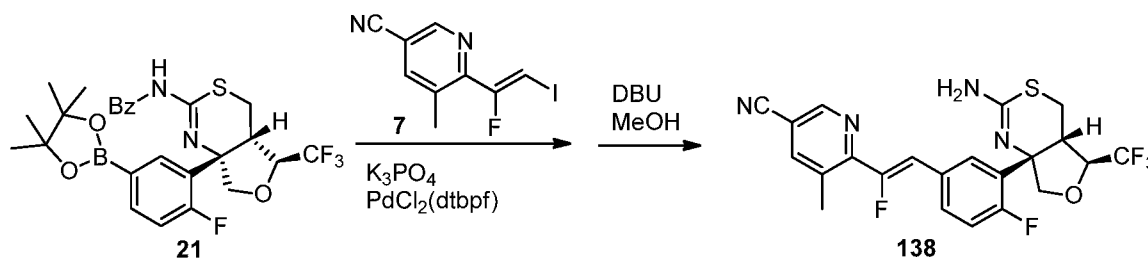
This compound (45 mg, 23% overall yield) as a white solid was prepared via a 2-step protocol similar to that described for Example **132**, here starting from boronic ester **21** (200 mg, 0.36 mmol) and vinyl iodide **4** (128 mg, 0.36 mmol). MS $m/z = 544.1$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 9.03 (d, $J = 1.8$ Hz, 1H), 8.61 (d, $J = 1.8$ Hz, 1H), 7.86 - 7.81 (m, 1H), 7.74 (ddd, $J = 7.0, 4.5, 2.3$ Hz, 1H), 7.32 (dd, $J = 12.3, 8.5$ Hz, 1H), 7.00 (d, $J = 38.3$ Hz, 1H), 6.33 (s, 2H), 4.67 (q, $J = 7.5$ Hz, 1H), 4.41 (d, $J = 8.1$ Hz, 1H), 3.86 - 3.79 (m, 1H), 3.25 (dd, $J = 7.7, 3.9$ Hz, 1H), 3.07 (dd, $J = 14.2, 3.1$ Hz, 1H), 2.88 (dd, $J = 14.0, 3.9$ Hz, 1H). ^{19}F NMR (400 MHz, DMSO- d_6) δ -60.759 (s, 3F), -76.206 (s, 3F), -109.315 (s, 1F), -113.235 (s, 1F).

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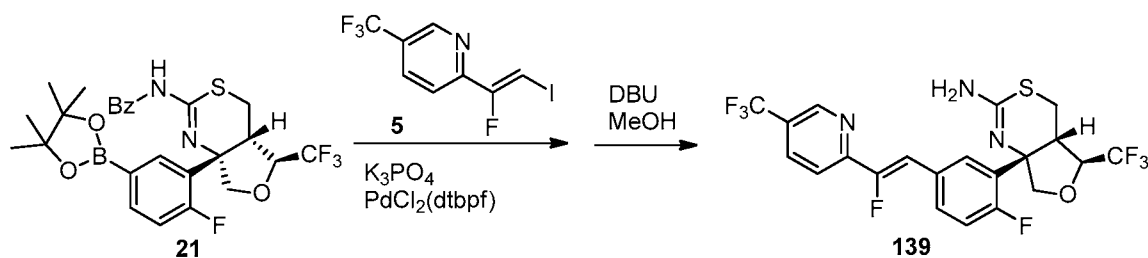
Example 138: 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile.



5

This compound (55 mg, 34% overall yield) as a white solid was prepared via a 2-step protocol similar to that described for Example 132, here starting from boronic ester **21** (188 mg, 0.33 mmol) and vinyl iodide **7** (98 mg, 0.33 mmol). MS $m/z = 481.2$ $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.94 – 8.87 (m, 1H), 8.31 (d, $J = 2.1$ Hz, 1H), 7.81 (dd, $J = 8.0, 2.4$ Hz, 1H), 7.75 (ddd, $J = 8.7, 4.7, 2.4$ Hz, 1H), 7.31 (dd, $J = 12.3, 8.6$ Hz, 1H), 7.03 (d, $J = 39.2$ Hz, 1H), 6.33 (s, 2H), 4.68 (m, 1H), 4.40 (d, $J = 8.1$ Hz, 1H), 3.84 (dd, $J = 8.1, 2.8$ Hz, 1H), 3.26 (dt, $J = 7.9, 3.7$ Hz, 1H), 3.09 (dd, $J = 13.9, 3.2$ Hz, 1H), 2.89 (dd, $J = 13.9, 4.0$ Hz, 1H), 2.54 (d, $J = 6.3$ Hz, 3H). ^{19}F NMR (400 MHz, DMSO- d_6) δ -76.220 (s, 3F), -109.740 (s, 1F), -113.575 (s, 1F).

Example 139: (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.



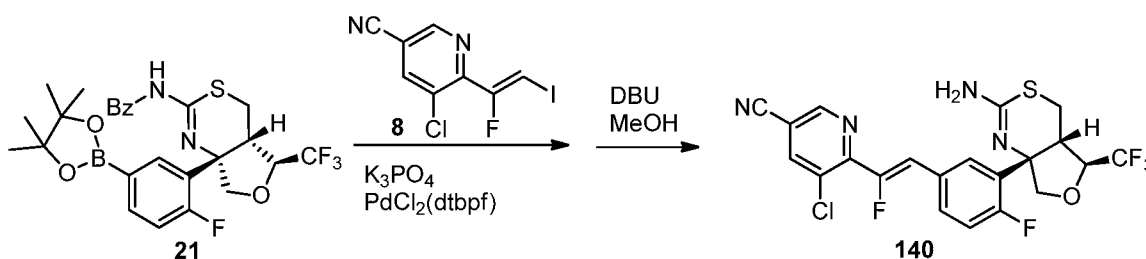
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This compound (55 mg, 28% overall yield) as a white solid was prepared via a 2-step protocol similar to that described for Example 132, here starting from boronic ester **21** (214 mg, 0.39 mmol) and vinyl iodide **5** (124 mg, 0.39 mmol). MS $m/z = 510.2$ $[M+H]^+$. 1H NMR

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(400 MHz, DMSO-*d*₆) δ 9.04 (s, 1H), 8.39 – 8.32 (m, 1H), 7.95 – 7.84 (m, 2H), 7.82 – 7.74 (m, 1H), 7.38 – 7.24 (m, 2H), 6.35 (s, 2H), 4.68 (m, 1H), 4.41 (d, *J* = 8.1 Hz, 1H), 3.84 (dd, *J* = 8.0, 2.7 Hz, 1H), 3.26 (dd, *J* = 7.7, 3.9 Hz, 1H), 3.09 (dd, *J* = 14.2, 3.1 Hz, 1H), 2.89 (dd, *J* = 14.0, 3.9 Hz, 1H). ¹⁹F NMR (400 MHz, DMSO-*d*₆) δ -60.825 (s, 3F), -76.217 (s, 3F), -109.449 (s, 1F), -123.777 (s, 1F).

Example 140: 6-((*Z*)-2-(3-((4*a*S,5*S*,7*a*S)-2-amino-5-(trifluoromethyl)-4*a*,5,7,7*a*-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-7*a*-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile.



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This compound (60 mg, 11% overall yield) as a white solid was prepared via a 2-step protocol similar to that described for Example **132**, here starting from boronic ester **21** (600 mg, 1.09 mmol) and vinyl iodide **8** (335 mg, 1.09 mmol). MS *m/z* = 501.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.06 (d, *J* = 3.2 Hz, 1H), 8.74 (d, *J* = 1.8 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.75 (q, *J* = 4.8, 3.2 Hz, 1H), 7.33 (dd, *J* = 12.3, 8.5 Hz, 1H), 7.08 (dd, *J* = 38.1, 2.7 Hz, 1H), 6.33 (s, 2H), 4.68 (m, 1H), 4.41 (d, *J* = 8.1 Hz, 1H), 3.88 – 3.80 (m, 1H), 3.25 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.09 (dd, *J* = 14.0, 3.2 Hz, 1H), 2.89 (dd, *J* = 13.9, 3.9 Hz, 1H). ¹⁹F NMR (400 MHz, DMSO-*d*₆) δ -76.214 (s, 3F), -108.987 (s, 1F), -114.129 (s, 1F).

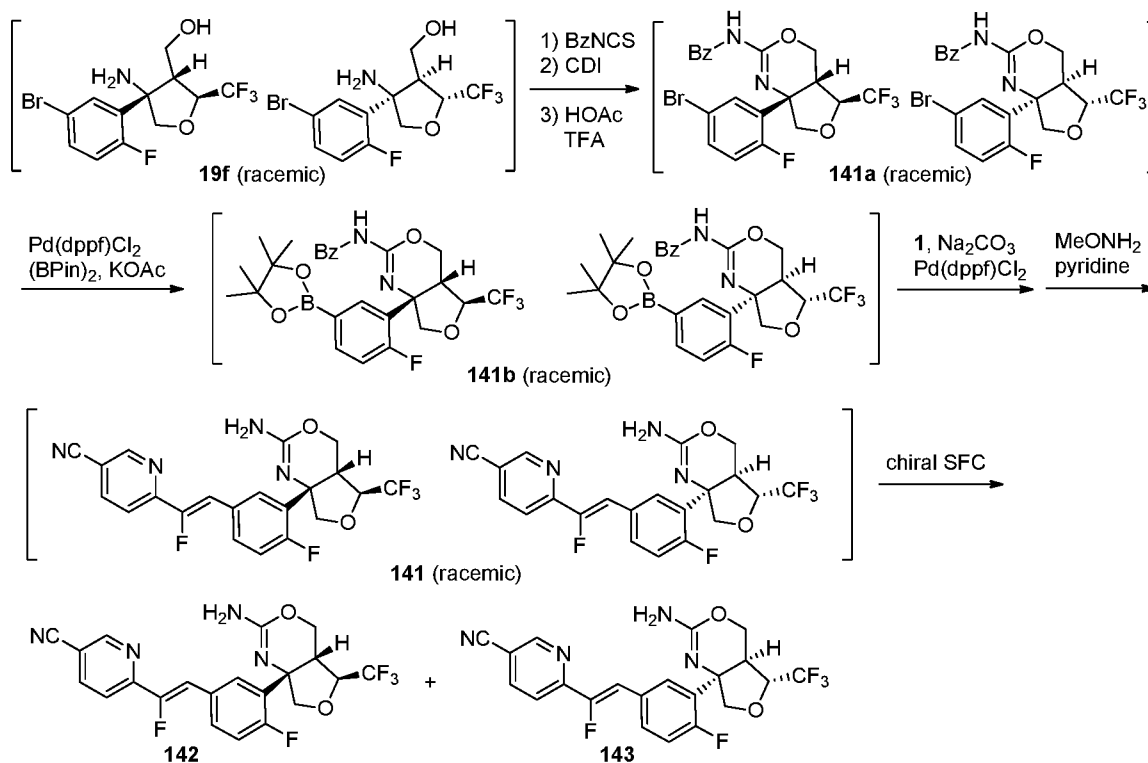
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Example 141: 6-((*Z*)-2-(3-((4*a*R,5*S*,7*a*S)-2-amino-5-(trifluoromethyl)-4*a*,5,7,7*a*-tetrahydro-4*H*-furo[3,4-*d*][1,3]oxazin-7*a*-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile and 6-((*Z*)-2-(3-((4*a*S,5*R*,7*a*R)-2-amino-5-(trifluoromethyl)-4*a*,5,7,7*a*-tetrahydro-4*H*-furo[3,4-*d*][1,3]oxazin-7*a*-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; and **Example 142:** 6-((*Z*)-2-(3-((4*a*R,5*S*,7*a*S)-2-amino-5-(trifluoromethyl)-4*a*,5,7,7*a*-tetrahydro-4*H*-furo[3,4-*d*][1,3]oxazin-7*a*-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; and **Example 143:** 6-((*Z*)-2-(3-

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((4a*S*,5*R*,7a*R*)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-
d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



5 Preparation of 141a.

To a solution of racemic **19f** (2.46 g, 6.87 mmol) in THF (25 mL) under a nitrogen atmosphere at 45 °C was added a solution of benzoyl isothiocyanate (Sigma-Aldrich, St. Louis, MO, USA) (0.92 mL, 6.88 mmol) in THF (12 mL) dropwise in a period of 45 minutes. Once the addition was complete, the mixture was stirred for another 10 minutes. CDI (Sigma-Aldrich, St. Louis, MO, USA) (1.25 g, 7.71 mmol) was added in one portion and the reaction stirred for another 90 minutes. The mixture was evaporated to dryness under reduced pressure and the crude was suspended in DCM (50 mL). It was stirred for 5 minutes after which a thick white precipitate formed. Heptane (30 mL) was added slowly and the mixture stirred for another 20 minutes. The slurry was filtered through a sintered glass frit and the solid was washed with DCM/heptane (1/1, 10 mL). The solid was collected and dried to give a racemic mixture of ((2*S*,3*R*,4*S*)-4-(3-benzoylthioureido)-4-(5-bromo-2-

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fluorophenyl)-2-(trifluoromethyl)tetrahydrofuran-3-yl)methyl 1H-imidazole-1-carboxylate and ((2R,3S,4R)-4-(3-benzoylthioureido)-4-(5-bromo-2-fluorophenyl)-2-(trifluoromethyl)tetrahydrofuran-3-yl)methyl 1H-imidazole-1-carboxylate (2.83 g, 4.60 mmol, 67 % yield) which was used without further purification. MS m/z = 637.4/639.4 [M+Na]⁺.

The above obtained racemic mixture of ((2S,3R,4S)- and ((2R,3S,4R)-4-(3-benzoylthioureido)-4-(5-bromo-2-fluorophenyl)-2-(trifluoromethyl)tetrahydrofuran-3-yl)methyl 1H-imidazole-1-carboxylate (2.40 g, 3.90 mmol) was dissolved in acetic acid (50 mL) and heated to reflux for 2 hours. The mixture was then evaporated to dryness under reduced pressure. The residue was dissolved in TFA (50 mL) and heated at 80 °C bath for 2 hours. The mixture was evaporated to dryness under reduced pressure. The residue was dissolved in EtOAc (150 mL) then washed with 0.5 N aqueous NaOH (75 mL) followed by brine (50 mL) and concentrated *in vacuo*. Purification of the residue using silica gel chromatography (25 to 75% EtOAc in heptane) gave **141a** (0.39 g, 21% yield). MS m/z = 487.2/489.2 [M+H]⁺.

Preparation of 141b.

A solution of **141a** (200 mg, 0.41 mmol) in 1,4-dioxane (3 mL) was sparged with argon for 5 minutes then treated with bis(pinacolato)diboron (136 mg, 0.53 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane (17 mg, 0.02 mmol), potassium acetate (121 mg, 1.23 mmol) and heated at 100 °C for 1 hour. Additional bis(pinacolato)diboron (136 mg, 0.53 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane (17 mg) and potassium acetate (121 mg) were added in and heating was continued at 100 °C for an additional 2 hours. After cooling to room temperature, the reaction mixture was partitioned between EtOAc (20 mL) and sat'd aqueous NaHCO₃ (10 mL). The organic solution was dried over MgSO₄, concentrated under reduced pressure, then purified by silica gel chromatography (0 to 20% EtOAc in heptane) to afford boronic ester **141b** (150 mg, 0.28 mmol, 68% yield) as a colorless film. MS (ESI +ve ion) m/z : [M+1] = 535.0

Preparation of Example 141.

A suspension of boronic ester **141b** (150 mg, 0.42 mmol), vinyl iodide **1** (115mg, 0.42 mmol), [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane (Sigma-Aldrich Chemical Company, Inc., St. Louis, Missouri, USA, 12 mg, 0.014 mmol), sodium carbonate (89 mg, 0.84 mmol) in 1,4-dioxane (2 mL) and water (1 mL) was sparged with argon for 3 minutes then heated to 70 °C for 1 hour. The reaction mixture was partitioned between EtOAc (15 mL) and sat'd aqueous NaHCO₃ (7 mL). The organic was concentrated under reduced pressure then purified by silica gel chromatography (0 to 20% EtOAc in heptane) to afford a racemic mixture of N-((4aR,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-2-yl)benzamide and N-((4aS,5R,7aR)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-2-yl)benzamide (75 mg, 48% yield) as a brown solid. MS (ESI +ve ion) m/z: [M+1] = 555.0.

To the above obtained brown solid (75 mg, 0.13 mmol) was added methoxylamine hydrochloride (40 mg, 0.41 mmol) and pyridine (460 µL, 5.41 mmol) and the resulting mixture was heated to 70 °C for 45 minutes. The reaction was partitioned between EtOAc (15 mL) and sat'd aqueous NaHCO₃ (10 mL). The organic solution was concentrated *in vacuo*. The residue was purified by silica gel chromatography (0 to 80% EtOAc (0.3% AcOH) in heptane (0.3% AcOH)) to afford Example **141** as an AcOH salt (30 mg, 0.06 mmol, 44% yield) as a white solid. MS (ESI +ve ion) m/z: [M+1] = 451.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.99 (br s, 1H), 9.07 (d, *J* = 1.17 Hz, 1H), 8.45 (dd, *J* = 1.96, 8.22 Hz, 1H), 8.10 (dd, *J* = 1.96, 7.82 Hz, 1H), 7.88 (d, *J* = 8.22 Hz, 1H), 7.73-7.80 (m, 1H), 7.26-7.40 (m, 2H), 5.85 (br s, 2H), 4.50-4.59 (m, 1H), 4.31 (d, *J* = 8.02 Hz, 1H), 3.99-4.05 (m, 1H), 3.86-3.92 (m, 1H), 3.75-3.81 (m, 1H), 3.18-3.23 (m, 1H), 1.89-1.91 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ ppm -76.63 (s, 3F), -109.73 (s, 1F), -124.23 (s, 1F).

Preparation of Examples 142 and 143.

Example **141** as an AcOH salt (20 mg) was subjected to chiral SFC to provide two compounds: the 1st eluent was Example **142** (8 mg) as a white solid and the 2nd eluent was Example **143** (8 mg) as a white solid. Preparative SFC purification method: (OD-H (250 × 30 mm, 5 µm)); mobile phase (65 : 35 (A : B), A = liquid CO₂, B = 20 mM ammonia in

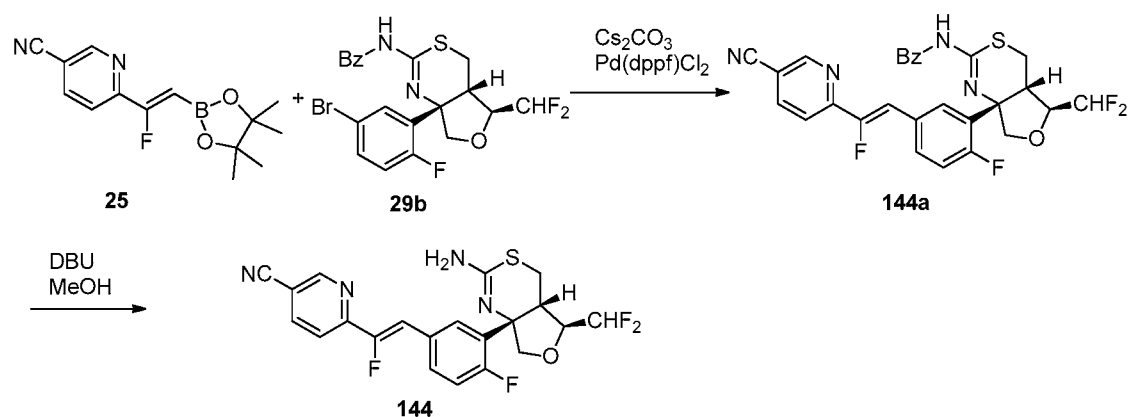
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MeOH); flow rate 75 mL/min; wave length 210 nm; BPI(Bar) 102; Sample conc. 10 mg/mL; Inj. Vol. 2.0 mL; run time 5 minutes. The absolute stereochemistry was arbitrarily assigned.

6-((Z)-2-(3-((4aR,5S,7aS)-2-Amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (**142**): MS (ESI +ve ion) m/z: [M+1] = 451.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.44 (dd, *J* = 1.96, 8.22 Hz, 1H), 8.10 (dd, *J* = 1.96, 7.63 Hz, 1H), 7.87 (d, *J* = 8.22 Hz, 1H), 7.73-7.80 (m, 1H), 7.26-7.40 (m, 2H), 5.84 (s, 2H), 4.49-4.60 (m, 1H), 4.31 (d, *J* = 8.41 Hz, 1H), 4.01 (d, *J* = 11.54 Hz, 1H), 3.89 (d, *J* = 11.35 Hz, 1H), 3.78 (d, *J* = 8.02 Hz, 1H), 3.20 (d, *J* = 7.24 Hz, 1H).

6-((Z)-2-(3-((4aS,5R,7aR)-2-Amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (**143**): MS (ESI +ve ion) m/z: [M+1] = 451.1. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.07 (s, 1H), 8.44 (dd, *J* = 1.96, 8.22 Hz, 1H), 8.10 (dd, *J* = 1.96, 7.63 Hz, 1H), 7.87 (d, *J* = 8.22 Hz, 1H), 7.73-7.80 (m, 1H), 7.26-7.40 (m, 2H), 5.84 (s, 2H), 4.49-4.60 (m, 1H), 4.31 (d, *J* = 8.41 Hz, 1H), 4.01 (d, *J* = 11.54 Hz, 1H), 3.89 (d, *J* = 11.35 Hz, 1H), 3.78 (d, *J* = 8.02 Hz, 1H), 3.20 (d, *J* = 7.24 Hz, 1H).

Example 144: 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



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Preparation of N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (144a).

A mixture of N-((4aS,5S,7aS)-7a-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**29b**) (0.10 g, 0.21 mmol), boronic ester **25** (0.17 g, 0.62 mmol) and cesium carbonate (0.20 g, 0.62 mmol) in 1,4-dioxane (9 mL) and water (3 mL) was purged with nitrogen for 2 minutes then treated with Pd(dppf)Cl₂-CH₂Cl₂ adduct (9 mg). The mixture was heated at 80 °C for 5 hours. After cooling to room temperature, the reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 x 20 mL). The organic solution was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified via silica gel chromatography (10% to 20% EtOAc in petroleum ether) to afford **144a** (0.08 g, 70% yield) as an off-white solid. MS (ESI positive ion) m/z: 553.1 (M+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.84 (s, 1H), 8.11 (d, *J* = 7.5 Hz, 2H), 8.04 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.86 – 7.78 (m, 1H), 7.77 – 7.68 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.32 (s, 1H), 7.26 – 7.20 (m, 1H), 6.03 (td, *J* = 55.6, 3.2 Hz, 1H), 4.70 – 4.56 (m, 1H), 4.61 – 4.52 (m, 1H), 4.08 – 4.06 (m, 1H), 3.58 (s, 1H), 3.31 – 3.22 (m, 1H), 2.91 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.00 – 1.90 (m, 1H); ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -109.09 (s, 1F), -120.96 (s, 1F), -132.12 (d, 2F).

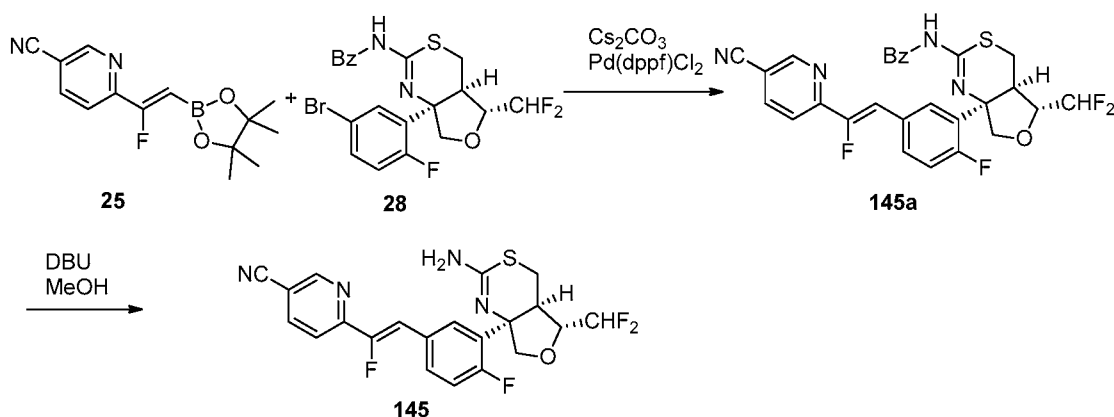
Preparation of 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (144).

A solution of N-((4aS,5S,7aS)-7a-(5-((Z)-2-(5-cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**144a**) (0.08 g, 0.14 mmol) and DBU (0.07 mL, 0.44 mmol) in methanol (2 mL) was stirred at 70 °C for 3 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic solution was washed with brine (20 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by reverse-phase preparative HPLC [Phenomenex Luna C8(2), (150 x 21.2 mm, 5 micron); mobile phase: 0.1% TFA in CH₃CN/H₂O, gradient 2% to 5%; flow rate: 15 mL/min;

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run time: 30 min] to provide 6-((Z)-2-(3-((4a*S*,5*S*,7a*S*)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (**144**) as a TFA salt (25 mg, 39% yield) as an off-white solid. MS (ESI positive ion) *m/z*: 449.1 (*M*+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 9.45 – 8.27 (m, 3H), 8.33 – 7.68 (m, 3H), 7.65 – 7.22 (m, 2H), 6.27 (td, *J* = 54.8, 3.6 Hz, 1H), 5.32 – 3.79 (m, 4H), 3.71 – 3.39 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -73.57 (s, 3F), -109.60 (s, 1F), -123.57 (s, 1F), -126.71 (dd, 1F), -130.19 (dd, 1F).

Example 145: 6-((Z)-2-(3-((4a*R*,5*R*,7a*R*)-2-Amino-5-(difluoromethyl)-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.



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N-((4a*R*,5*R*,7a*R*)-7a-(5-((Z)-2-(5-Cyanopyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide (**145a**, 120 mg, 70% yield) as a light-yellow solid was prepared in a fashion similar to that described for compound **144a**, here starting from N-((4a*R*,5*R*,7a*R*)-7a-(5-bromo-2-fluorophenyl)-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*d*][1,3]thiazin-2-yl)benzamide (**28**) (150 mg, 0.31 mmol) and boronic ester **25** (169 mg, 0.62 mmol). MS (ESI positive ion) *m/z*: 553.10 (*M*+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ 8.84 (s, 1H), 8.12 – 8.02 (m, 3H), 7.86 – 7.80 (m, 1H), 7.74 – 7.68 (m, 2H), 7.62 – 7.56 (m, 1H), 7.54 – 7.48 (m, 2H), 7.28 (s, 1H), 7.25 – 7.20 (m, 1H), 6.04 (td, *J* = 55.6, 3.2 Hz, 1H), 4.72 – 4.64 (m, 1H), 4.60 – 4.56 (m, 1H), 4.08 – 4.04 (m, 1H), 3.58 – 3.54 (m, 1H), 3.30 – 3.24 (m, 1H), 2.92 (d, *J* = 13.6 Hz, 1H), 2.01 – 1.92 (m, 1H); ¹⁹F NMR (376 MHz, CHLOROFORM-*d*) δ -112.12 (s, 1F), -121.06 (s, 1F), -132.12 (d, 2F).

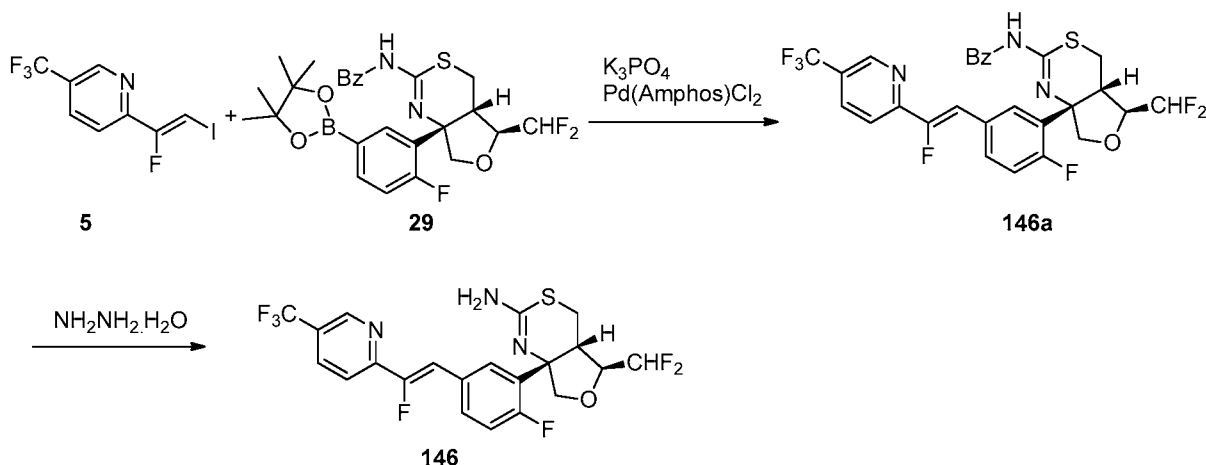
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Preparation of 6-((Z)-2-(3-((4aR,5R,7aR)-2-Amino-5-(difluoromethyl)-4a,5-dihydro-4H-furo[3,4-d][1,3]thiazin-7a(7H)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile (145).

6-((Z)-2-(3-((4aR,5R,7aR)-2-Amino-5-(difluoromethyl)-4a,5-dihydro-4H-furo[3,4-d][1,3]thiazin-7a(7H)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile as a TFA salt (**145**) (12 mg, 12% yield) as an off-white solid was prepared in a fashion similar to that described for compound **144**, here starting from **145a** (120 mg, 0.22 mmol) and DBU (66 mg, 0.43 mmol) in methanol (5 mL). MS (ESI positive ion) m/z: 449.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 9.45 – 8.27 (m, 3H), 8.33 – 7.68 (m, 3H), 7.65 – 7.22 (m, 2H), 6.27 (td, *J* = 54.8, 3.6 Hz, 1H), 5.32 – 3.79 (m, 4H), 3.71 – 3.39 (m, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) -73.57 (s, 3F), -110.99 (s, 1F), -125.87 (s, 1F), -127.87 (dd, 1F), -132.97 (dd, 1F).

Example 146: (4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a,5,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.



Preparation of N-((4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a,5,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (146a).

A mixture of N-((4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4a,5,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**29**) (65 mg, 0.12 mmol), potassium phosphate tribasic (52 mg, 0.24 mmol)

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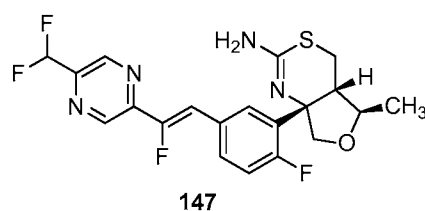
and (Z)-2-(1-fluoro-2-iodovinyl)-5-(trifluoromethyl)pyridine (**5**) (47 mg, 0.14 mmol) in 1,4-dioxane (6 mL) and water (2 mL) was degassed for 5 minutes then treated with Pd(Amphos)Cl₂ (5 mg). The mixture was degassed for 2 minutes and heated at 90 °C for 4 hours. The reaction mixture was allowed to cool to room temperature, diluted with water (5 mL) and extracted with EtOAc (2 x 20 mL). The organic solution was washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting yellow oil was purified on silica gel column (20% to 30% EtOAc in hexanes) to provide **145a** (35 mg, 48% yield) as an off-white solid. MS (ESI positive ion) m/z: 596.1 (M+1).

Preparation of (4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine (146).

A solution of N-((4aS,5S,7aR)-5-(difluoromethyl)-7a-(3-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-yl)benzamide (**146a**) (35 mg, 0.06 mmol) and hydrazine hydrate (10 µL, 0.30 mmol) in ethanol (2 mL) was stirred for 4 hours at ambient temperature. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 20 mL). The organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting yellow oil was purified by reverse-phase preparative HPLC [Phenomenex Luna C8(2), (150 x 21.2 mm, 5 micron); mobile phase: 0.1% TFA in CH₃CN/H₂O, gradient 80% to 100%; flow rate: 15 mL/min; run time: 30 min] to give (4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine as a TFA salt (**146**) (12 mg, 42% yield) as an off-white solid. MS (ESI positive ion) m/z: 492.1 (M+1). ¹H NMR (400 MHz, METHANOL-*d*₄) δ 8.92 (s, 1H), 8.26 – 8.14 (m, 1H), 7.92 – 7.67 (m, 3H), 7.26 – 7.15 (m, 1H), 6.10 (dd, *J* = 55.7, 4.0 Hz, 1H), 4.60 (d, *J* = 8.3 Hz, 1H), 4.46 (qd, *J* = 8.9, 4.5 Hz, 1H), 3.87 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.26 (dd, *J* = 8.1, 3.9 Hz, 1H), 3.19 – 3.08 (m, 2H), 2.94 (dd, *J* = 13.5, 4.1 Hz, 1H). ¹⁹F NMR (376 MHz, METHANOL-*d*₄) δ -63.94 (s, 3F), -111.06 (s, 1F), -125.82 (s, 2F), -126.91 (d, 2F), -132.10 (d, 2F).

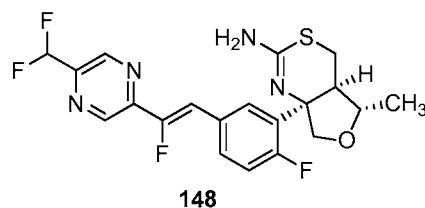
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Example 147: (4aS,5R,7aS)-7a-(5-((Z)-2-(5-(difluoromethyl)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.



5 (4aS,5R,7aS)-7a-(5-((Z)-2-(5-(difluoromethyl)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine (**146**) is synthesized by methods disclosed herein or methods known to the person of ordinary skill in the art.

Example 148: (4aR,5S,7aR)-7a-(5-((Z)-2-(5-(difluoromethyl)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.



(4aR,5S,7aR)-7a-(5-((Z)-2-(5-(difluoromethyl)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-methyl-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine (**147**) is synthesized by methods disclosed herein or methods known to the person of ordinary skill in the art.

Biological Evaluation

Provided in this section is the biological evaluation of the specific examples provided herein. In particular, Table 2 contains biological activity data. The data presented in Table 2 provides the IC₅₀ (μM) for the specific examples obtained in a BACE1 enzyme assay,

5 BACE1 cell assay, BACE2 enzyme assay and CatD assay.

Table 2

Ex. No.	BACE1 Enzyme IC ₅₀ (μM)	BACE1 Cell IC ₅₀ (μM)	BACE2 Enzyme IC ₅₀ (μM)	Cat D Enzyme IC ₅₀ (μM)
100	0.84667	1.245	0.495	544.3
101	0.0018417	0.00194	0.001033	49.1
102	0.00024133	0.00068175	0.00308	117.5
103	0.00186	0.005445	0.02715	246
104	0.804	2.26	7.48	654.4
105	0.0644	0.129	0.0569	181
106	0.5025	0.9845	6.39	815
107	0.011685	0.041	0.279	> 400.0
108	0.00271	0.016	0.034	14.8
109	0.0001495	0.0003115	0.00549	7.6
110	0.001565	0.004105	0.0855	4.5
111	0.00032	0.000807	0.00518	19.6
112	0.108	0.02005	0.136	1.32
113	0.0226	0.00935	0.0381	26.6
114	0.00896	0.00257	0.0306	38.7
115	0.0010065	0.000542	0.0153	18.9
116	0.00253	0.00188	0.052	28.6
117	0.0002865	0.00038	0.00279	13.2
118	0.0074525	0.019775	0.39433	125
119	0.009445	0.0265	0.51	105
120	0.0001865	0.0007605	0.034	6.3
121	0.00159	0.006795	0.258	47.9
122	0.00236	0.0086	0.353	87.9
123	0.004495	0.00478	0.214	36.5
124	0.002615	0.00269	0.0922	23.8
125	2.54	1.385	18	30.6
126	0.020067	0.0057417	0.33383	292.4
127	0.1029	0.0243	2.9	160
128	0.015333	0.0036367	0.34133	417.9
129	0.1075	0.0151	2.215	> 44.4
130	0.000405	0.000906	0.00178	25.8

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131	0.003835	0.01145	0.427	> 400.0
132	0.4265	0.112	0.427	> 400.0
133	1.215	1.995	28	139
134	0.0014	0.0009	0.0043	59.3
135	0.0043	0.0018	0.0223	106
136	0.622	2.03	6.63	> 400.0
137	0.015	0.2	0.605	382
138	0.0272	0.116	1.14	> 400.0
139	0.0158	0.117	1.5	> 400.0
140	0.0087	0.0482	0.22	333
141	0.08625	0.1605	9.725	237
142	0.03715	0.05885	3.54	> 400.0
143	9.01	53.5	139.5	95.6
144	0.0216	0.01805	0.74133	> 400.0
145	0.04845	0.041	1.4	> 400.0

The results presented in Table 2 have been generated with the *in vitro* assays described below. These assays may be used to test any of the compounds described herein to assess and characterize a compound's ability to modulate BACE activity and to regulate the cleavage of A β precursor protein, thereby reducing or inhibiting the production of A β protein.

In Vitro Enzymatic BACE1 and BACE2 FRET (Fluorescence Resonance Energy Transfer) Assays

The cDNAs for both human recombinant BACE1 and 2 with C-terminal 6-His Tags were cloned into transient protein expression vectors, which were subsequently transfected into mammalian cell lines. These recombinant proteins were further purified using Ni-NTA affinity chromatography (Qiagen). The assay buffer used in these screens was 0.05 M acetate, pH 4.5, 8% DMSO final, 100 μ M genapol (which is a nonionic detergent, below its Critical Micelle Concentration). The β -secretase enzyme (0.02 nM for BACE1 and 0.64 nM for BACE2), which was pre-incubated for one hour with the test compound, typically in about 1 μ L of DMSO according to a serial dilution, was added thereto. The assay was effectively started by the addition of FRET substrate (50 nM) and the combination was incubated for one hour. The FRET assay was terminated by the addition of tris buffer, which raised the pH to neutrality, and the fluorescence was determined. The FRET substrate was a

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peptide with commercially available fluorophore and quencher, on opposite sides of the BACE cleavage site. The specific FRET substrate used in this assay was made by Amgen in-house. Commercially available FRET substrates, for example, the FRET substrate offered with the BACE1 FRET Assay Kit sold by ThermoFisher Scientific (Catalog Number P2985), may be used in this assay with the appropriate modifications, which are within the purview of the ability of a person with ordinary skill in the art. Proteolytic cleavage of the FRET substrate released quenching of fluorescence (excitation 488 nm and emission 590 nm).

The *in vitro* BACE FRET enzyme data for each of the Examples is provided in Table 2.

In Vitro BACE1 cell-based assay

The cell-based assay measures inhibition or reduction of A β 40 in conditioned medium of test compound treated cells expressing amyloid precursor protein. Cells stably expressing Amyloid Precursor Protein (APP) were plated at a density of 45K cells/well in 384 well plates (Corning/BioCoat 354663). The test compounds were then added to cells in 22-point dose response concentrations with the starting concentration being 62.5 μ M. The compounds were diluted from stock solutions in DMSO and the final DMSO concentration of the test compounds on cells was 0.625%. The cells were cultivated overnight at 37°C and 5% CO₂ in DMEM supplemented with 10% FBS. After 24 h of incubation with the test compounds, the conditioned media was collected and the A β 40 levels were determined using HTRF (Homogeneous Time Resolved Fluorescence). The IC₅₀ of the compound was calculated from the percent of control or percent inhibition of A β 40 as a function of the concentration of the test compound.

The HTRF to detect A β 40 was performed in 384 well plates (Costar 3658). The antibody pair that were used to detect A β 40 from cell supernatants were ConfAb40 antibody (Amgen in-house) and biotinylated 6E10 (BIOLEGEND). As an alternative to ConfAb40, a commercially available antibody, Anti-beta Amyloid 1-40 antibody [BDI350] from Abcam, Cambridge, MA 02139-1517 (Product code: ab20068), may be used in this assay. The concentrations were 0.35 μ g/mL of ConfAb40 antibody and 1.33 μ g/mL of 6E10-biotinylated antibody, as well as 4.5 μ g/mL of Streptavidin Allophycocyanin Conjugate (ThermoFisher Scientific) in HTRF Buffer (1M Hepes pH 7.5, 1M NaCl, 1% BSA, 0.5% Tween 20).

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The conditioned media was incubated with above antibodies and Streptavidin Allophycocyanin Conjugate for 30-60 minutes at 23°C. The final readout was performed on Envision from PerkinElmer.

The *in vitro* BACE cell-based data for each of the Examples is provided in Table 2.

5 *In Vitro* Enzymatic Cathepsin D (CatD) FRET Assay

Recombinant CatD was expressed in CHO cells. The assay buffer for CatD was 0.05 M citrate pH 3.5, 10% DMSO final, 5 mM CHAPS. The CatD enzyme (9 nM) was pre-incubated for one hour with inhibitors, typically in about 1uL of DMSO according to a serial dilution, is added thereto. The assays was effectively started by the addition of different
10 FRET substrates (20 nM for CatD) and the combination was incubated for one hour. The FRET assay was terminated with by addition of tris buffer, which raises the pH to neutrality, and the fluorescence was determined. The FRET substrate was a peptide with commercially available fluorophore and quencher, on opposite sides of the CatD cleavage site. The CatD substrate peptide sequence was based on sequence #1 of Table 1 from Gulnik *et al.*, *FEBS Lett.* 413(2):379-384 (1997). Proteolytic cleavage of the FRET substrate released quenching
15 of fluorescence (CatD excitation 500 nm and emission 580 nm).

Alternatively, a CatD assay may also be run according to the procedure described in Yasuda *et al.*, *J. Biochem.* 125(6):1137-1143 (1999). In addition, the CatD and Cathepsin E assays are described in International Patent Application Publication No. WO2011069934.

20 The *in vitro* CatD FRET assay data for each of the Examples is provided in Table 2, conducted by the first procedure described above. As shown by the high micromolar CatD data (very poorly active or inactive against CatD), the compounds disclosed herein possess the unexpected property of little to no ability to inhibit the activity of CatD. Thus, with this surprising selectivity profile, the compounds provided herein are believed to minimize,
25 reduce or completely eliminate any risk of retinal atrophy and abnormal development of the eye and of the retinal pigmented epithelium as it relates to the normal function and activity of CatD.

In vivo Inhibition of β -Secretase

Several animal models, including mouse, rat, dog, and monkey, may be used to
30 screen for inhibition of β -secretase activity *in vivo* following administration of a test

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compound. This procedure may be used to show that the compounds provided herein reduce the formation and/or deposition of A β peptide in the cerebrospinal fluid (CSF) as well as in the brain. Animals to be used in this experiment can be wild type, transgenic, or gene knockout animals. For example, the Tg2576 mouse model, prepared and conducted as
5 described in Hsiao *et al.*, *Science* 274:99-102 (1996), and other non-transgenic or gene knockout animals are useful to analyze *in vivo* inhibition of A β peptide production in the presence of test compounds.

Generally, 2 to 18 month old Tg2576 mice, gene knockout mice or non-transgenic animals are administered test compounds formulated in vehicles, such as cyclodextran,
10 phosphate buffers, hydroxypropyl methylcellulose or other suitable vehicles. One to twenty-four hours following the administration of compound, animals are sacrificed, and brains as well as cerebrospinal fluid (CSF) and plasma are removed for analysis of A β levels and test compound concentrations (Dovey *et al.*, *J. Neurochem.*, 76(1):173-181 (2001)) Beginning at
15 time 0, animals are administered by oral gavage, or other means of delivery such as intravenous injection, an inhibitory test compound of up to 100 mg/kg in a standard, conventional formulation, such as 2% hydroxypropyl methylcellulose, 1% Tween80. A separate group of animals receive 2% hydroxypropyl methylcellulose, 1% Tween80 alone, containing no test compound, and serve as a vehicle-control group. At the end of the test
20 period, animals are sacrificed and brain tissues, plasma or cerebrospinal fluid are collected. Brains are either homogenized in 10 volumes (w/v) of 0.2% diethylamine (DEA) in 50 mM NaCl (Best *et al.*, *J. Pharmacol. Exp. Ther.* 313(2):902-908 (2005)), or in 10 volumes of 0.5% TritonX-100 in Tris-buffered saline (pH at about 7.6). Homogenates are centrifuged at 355,000g, 4°C for 30 minutes. CSF or brain supernatants are then analyzed for the presence of A β by specific sandwich ELISA assays based on ECL (Electrochemiluminescence)
25 technology. For example, rat A β 40 is measured using biotinylated-4G8 (Signet) as a capture antibody and Fab40 (an in-house antibody specific to the C-terminal of A β 40) as a detection antibody. For example, 4 hours after administration of 30 mg/kg oral dose of the test compound in 2% hydroxypropyl methylcellulose, 1% Tween80 (pH2.2) to 200g male Sprague Dawley rats, A β peptide levels are measured for reduction by X% and Y% in
30 cerebrospinal fluid and brain, respectively, when compared to the levels measured in the vehicle-treated or control mice. Alternatively, the antibody sold with the V-PLEX abeta40

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Peptide (4G8) Kit, commercially available from Meso Scale Diagnostics (MSD), Rockville, Maryland 20850-3173 (Catalog NO. K150SJE-1) may be used in this assay.

This procedure may be used to show that the compounds provided herein reduce the formation and/or deposition of A β peptide in the cerebrospinal fluid (CSF) as well as in the brain of a mouse or rat at either 3mpk, 10 mpk or 30 mpk (mpk = mg compound per kg weight of the animal) dosing concentrations after 4hrs.

The results presented in Table 3 were obtained using certain compounds described herein in the *in vivo* protocol described above.

Table 3

Ex. No.	% A β reduction in rat CSF at 10 mpk	% A β reduction in rat brain at 10 mpk
118	43	43
126	83	80
128	79	77

METHODS OF USE

According to the amyloid cascade hypothesis, cerebral deposition of amyloid-beta (A β) peptide is critical for Alzheimer's disease (AD) pathogenesis. A β peptide generation is initiated when β -secretase (BACE1) cleaves the amyloid precursor protein. De Meyer *et al.* re-affirm the putative role that the accumulation of A β peptide in cerebral spinal fluid (CSF) in a subject plays in the progression of symptoms, initially revealed as mild cognitive impairment, which ultimately leads to AD. *Arch Neurol.* 67(8):949-956 (2010). A β peptides generated from amyloid precursor protein (APP) by proteolytic cleavage, such as by aspartyl protease enzymes, including β -secretase (BACE) and γ -secretase, likely play a causal role in AD pathogenesis (Tanzi *et al.*, *Cell* 120(4):545-555 (2005); Walsh *et al.*, *Neuron* 44(1):181-193 (2004)). Although the precise mechanisms of A β toxicity are unclear, oligomeric forms of A β may contribute to cognitive decline by altering synaptic structure and function (Palop *et al.*, *Nat. Neurosci.* 13(7):812-818 (2010); Selkoe, *Behav. Brain Res.* 192(1):106-113 (2008); Shankar *et al.*, *Nat. Med.* 14(8):837-842 (2008)). Transgenic mouse models that overexpress mutant APP and produce high levels of A β show amyloid plaque deposition, synaptic deficits, learning and memory impairments, and other behavioral abnormalities (Games *et al.*, *Nature* 373:523-527 (1995); Götz *et al.*, *Mol. Psychiatry* 9(7):664-683 (2004);

Hsia *et al.*, *Proc. Natl. Academy of Science USA* (96): 3228-3233, 1999; Hsiao *et al.*, *Science* (274): 99-102, 1996, citing Harris *et al.*, *Neuron* (68): 428-441, 2010).

For many years now, BACE1 has been a prime target for designing drugs to prevent or treat AD. Vassar *et al.*, *Lancet Neurol.* 13:319-329 (2014). Several pharmaceutical
5 companies are presently pursuing BACE1 inhibitors in human clinical trials. *Id.* at abstract.

For example, MK-8931, a small molecule inhibitor of BACE1, was the first molecule to enter phase I clinical trials. Yan, *Transl. Neurodegener.* 5(13):1-11 (2016) at page 4. MK-8931 was shown to have an excellent safety profile with no immediately noticeable side effects. *Id.* Merck was able to show that MK-8931 enters the brain and blocks β -secretase
10 by showing that MK-8931 significantly reduced CSF A β peptide concentrations in a sustained and dose-dependent manner. Vassar *et al.*, *Lancet Neurol.* 13:319-329 (2014) at page 323. MK-8931 is currently evaluated in a phase II/III clinical trial to assess the efficacy and safety of the compound for the treatment of AD patients with amnesic mild cognitive impairment (prodromal AD). Yan, *Transl. Neurodegener.* 5(13):1-11 (2016) at page 4.

Further, E2609, a BACE inhibitor identified by Eisai, showed significant reduction in
15 A β peptide levels in the CSF and plasma in nonhuman primates. Yan, *Transl. Neurodegener.* 5(13):1-11 (2016) at page 7. E2609 did not show clinical significant safety concerns after repeated doses up to 200 mg in a phase I clinical trial. *Id.* After 14d dosing the A β peptide level reduction in the CSF was statistically significant compared to baseline (46.2% (25mg),
20 61.9% (50 mg), 73.8% (100 mg), 79.9% (200 mg)). *Id.* In November 2014, Eisai stated that a phase II dose-finding study in patients with mild cognitive impairment (MCI) due to AD or prodromal AD and a positive amyloid PET-scan will be conducted in collaboration with Biogen.

Additionally, companies are also developing therapies targeting asymptomatic
25 patients. JNJ-54861911, which was first developed by Shionogi & Co. in Japan and later in collaboration with Janssen, demonstrated an ability to cross the blood-brain barrier and to dose-dependently reduce A β peptide concentrations. Yan, *Transl. Neurodegener.* 5(13):1-11 (2016) at pages 5-7. For example, an oral dose of 95 mg once daily achieved A β peptide reduction of up to 95% in CSF. *Id.* In October 2015, Janssen and Shionogi launched a phase
30 II/III trial targeting asymptomatic subjects that are at risk for developing Alzheimer's dementia. *Id.*

Similarly, Amgen and Novartis announced in late 2015 a collaboration to co-develop Novartis' BACE inhibitor CNP520. *Yan, Transl. Neurodegener.* 5(13):1-11 (2016) at page 8. The study that started in November 2015 is aimed at, *inter alia*, showing that CNP520 "can slow down the onset and progression of clinical symptoms associated with Alzheimer's disease (AD) in participants at the risk to develop clinical symptoms based on their age and genotype." <https://clinicaltrials.gov/ct2/show/NCT02565511> (last visited October 23, 2016).

The compounds disclosed herein have been shown to modulate, and specifically inhibit the activity of the β -secretase enzymes as shown in Table 2 for specific examples disclosed herein, thereby reducing the generation of A β peptide. Accordingly, the compounds provided herein are useful for, for example, the prevention or treatment of β -secretase related diseases, including, but not limited to, AD. The compounds provided herein have the ability to modulate the activity of the β -secretase enzyme, thereby regulating the production of A β peptide and reducing the formation and deposition of A β peptide in both the cerebral spinal fluid as well as in the brain, resulting in a decrease of A β plaque in the brain.

More specifically, provided are the following uses for the compounds disclosed herein:

Provided are the compounds disclosed herein for reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

Provided are the compounds disclosed herein for treating AD, cognitive impairment, or a combination thereof in a subject. In one embodiment, the compounds provided herein are useful for treating various stages and degrees of AD, including without limitation, mild, moderate and severe AD. In another embodiment, the compounds provided herein are useful for treating preclinical AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD. In yet another embodiment, the compounds provided herein may be used to treat prodromal subjects.

Provided are the compounds disclosed herein for treating a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia

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associated with cortical basal degeneration, diffuse Lewy body type of AD, or a combination thereof in a subject.

Provided are the compounds disclosed herein for reducing formation of plaque in the brain of a subject.

5 As previously discussed, in certain embodiments, the compounds described herein are to be understood to include all stereoisomers, tautomers, isotopically-labelled forms thereof or pharmaceutically acceptable salts of any of the foregoing or solvates of any of the foregoing or amorphous and crystalline forms (polymorphs) of any of the foregoing. Accordingly, the scope of the methods and uses provided in the instant disclosure is to be
10 understood to encompass also methods and uses employing all such forms.

Besides being useful for human treatment, the compounds provided herein may be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. For example, animals including horses, dogs, and cats may be treated with compounds provided herein.

15 **DOSAGE, FORMULATION, AND ROUTE OF ADMINISTRATION**

The amount of compound(s) which is/are administered and the dosage regimen for treating neurological disorders and β -secretase mediated diseases with the compounds and/or compositions disclosed herein depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route
20 and frequency of administration, and the particular compound employed. A daily dose of about 0.01 to 500 mg/kg, or in some embodiments, between about 0.01 and about 50 mg/kg, and in still other embodiments between about 0.01 and about 30 mg/kg body weight may be appropriate. In yet other embodiments, a daily dose of between about 0.1 and about 10 mg/kg body weight may be appropriate and should be useful for all uses disclosed herein.
25 The daily dose can be administered a number of times a day such as from one to four doses per day.

While it may be possible to administer a compound disclosed herein alone in the uses described, the compound administered normally will be present as an active ingredient in a pharmaceutical composition. Thus, in another embodiment, provided herein is a
30 pharmaceutical composition comprising a compound disclosed herein in combination with a pharmaceutically acceptable excipient, such as diluents, carriers, adjuvants and the like, and,

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if desired, other active ingredients. In one embodiment, a pharmaceutical composition may comprise a therapeutically effective amount of a compound disclosed herein.

The compound(s) disclosed herein may be administered by any suitable route in the form of a pharmaceutical composition adapted to such a route and in a dose effective for the treatment intended. The compounds and compositions present herein may, for example, be administered orally, mucosally, topically, rectally, pulmonarily, such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly, intrasternally, and by infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable excipients such as carriers, adjuvants, and vehicles.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is typically made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 1 to 2000 mg, from about 1 to 500 mg, and from about 5 to 150 mg.

For therapeutic purposes, the compounds provided herein are ordinarily combined with one or more diluents or other “excipients” appropriate to the indicated route of administration.

If orally administered on a per dose basis, the compounds provided herein may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, to form the final formulation. For example, the active compound(s) and excipient(s) may be tableted or encapsulated by known and accepted methods for convenient administration. Examples of suitable formulations include, without limitation, pills, tablets, soft and hard-shell gel capsules, troches, orally-dissolvable forms and delayed or controlled-release formulations thereof. Particularly, capsule or tablet formulations may contain one or more controlled-release agents, such as hydroxypropylmethyl cellulose, as a dispersion with the active compound(s).

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Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules using one or more of the carriers or diluents mentioned for use in the formulations for oral administration or by using other
5 suitable dispersing or wetting agents and suspending agents. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum, and/or various buffers. Other excipients and modes of administration are well and widely known in the pharmaceutical art. The active ingredient may also be administered by injection as a
10 composition with suitable excipients including saline, dextrose, or water, and optionally comprising one or more of a cosolvent such as propylene glycol or emulsifier such as, for example, Tween 80. Such formulations may also include compounds such as a cyclodextrin (for example, Captisol).

The sterile injectable preparation may also be a sterile injectable solution or
15 suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty
20 acids such as oleic acid find use in the preparation of injectables.

The active ingredient may also be administered by injection as a composition with suitable carriers including saline, dextrose, or water. The daily parenteral dosage regimen will be from about 0.1 to about 30 mg/kg of total body weight, and in some embodiments may be from about 0.1 to about 10 mg/kg.

25 For pulmonary administration, the pharmaceutical composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional excipients, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can
30 additionally be prepared with enteric coatings. Such compositions may also comprise excipients, such as wetting, sweetening, flavoring, and perfuming agents. Accordingly, in yet

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another embodiment of the present disclosure, there is provided a method of manufacturing a medicament, the method comprising combining an amount of a compound according to Formula I with a pharmaceutically acceptable diluent to manufacture the medicament.

5 In yet another embodiment, the provided herein is a method of manufacturing a medicament for the treatment of AD, the method comprising combining an amount of a compound provided herein with a pharmaceutically acceptable excipient to manufacture the medicament.

COMBINATIONS

10 While the compounds disclosed herein can be dosed or administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds provided herein or in conjunction with other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered simultaneously or sequentially at different times, or the therapeutic agents can be given as a single composition.

15 The phrase “co-therapy” (or “combination-therapy”), in defining use of a compound provided herein and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these
20 active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds provided herein may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of β -secretase, γ -secretase and/or other reagents known to influence the formation and/or deposition of A β peptide, otherwise responsible for the formation of plaque in the brain.

25 If formulated as a fixed dose, such combination products employ the compounds disclosed herein within the accepted dosage ranges. The compounds provided herein may also be administered sequentially with other known medicinal agents. This disclosure is not limited in the sequence of administration; compounds provided herein may be administered either prior to, simultaneous with or after administration of the known anti-inflammatory
30 agent.

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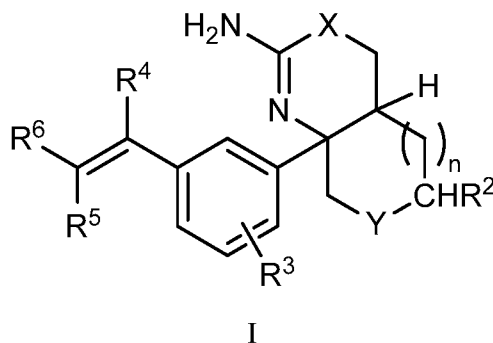
The foregoing description is merely illustrative and is not intended to limit the disclosure to the described compounds, compositions and methods. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, as defined in the appended claims. From the foregoing description, one skilled
5 in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

All references, for example, a scientific publication or patent application publication, cited herein are incorporated herein by reference in their entirety and for all purposes to the
10 same extent as if each reference was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

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What is claimed is:

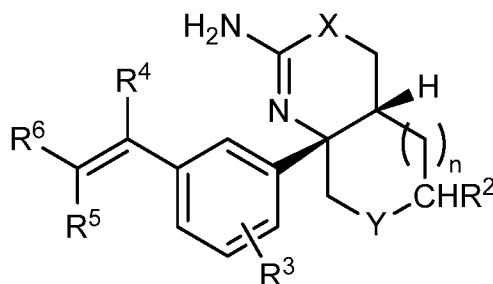
1. A compound of Formula I



- 5 or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein
- X is S or O;
- Y is O or NR¹;
- R¹ is -C(O)C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, or 6-membered nitrogen-containing
- 10 heteroaryl,
- wherein the C₁₋₆alkyl of -C(O)C₁₋₆alkyl and -C(O)OC₁₋₆alkyl is optionally substituted with 1 to 3 fluoro substituents, and
- wherein the heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy;
- 15 R² is H or C₁₋₆alkyl, wherein the C₁₋₆alkyl is optionally substituted with 1 to 3 fluoro substituents;
- R³ is halogen;
- R⁴ is H or F;
- one of R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is a 6-membered nitrogen-
- 20 containing heteroaryl, which heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butynyloxy, 3-butyln-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,
- wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy; and
- 25 n is 0 or 1.

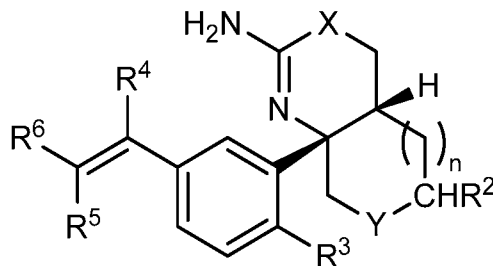
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2. The compound according to Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound of Formula I is a compound of Formula II



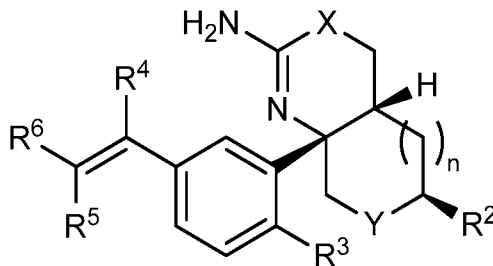
II.

3. The compound according to Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound of Formula I is a compound of Formula III



III.

4. The compound according to Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound of Formula I is a compound of Formula III'



III'.

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5. The compound according to any one of Claims 1 to 4, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein n is 0.

6. The compound according to any one of Claims 1 to 4, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein n is 1.

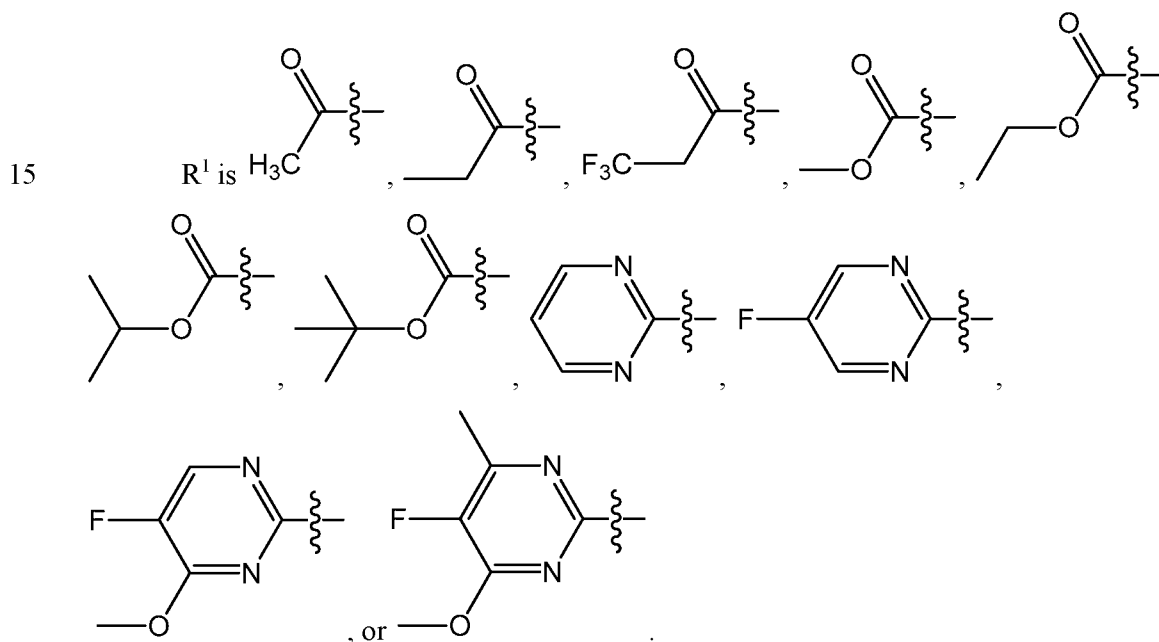
5 7. The compound according to any one of Claims 1 to 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein X is O.

8. The compound according to any one of Claims 1 to 6, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein X is S.

9. The compound according to any one of Claims 1 to 8, or a tautomer thereof,
10 or a pharmaceutically acceptable salt of said compound or tautomer, wherein Y is O.

10. The compound according to any one of Claims 1 to 8, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein Y is NR¹.

11. The compound according to any one of Claims 1 to 8 and 10, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein



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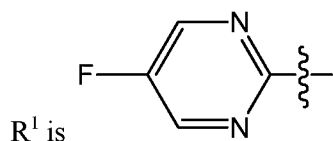
12. The compound according to any one of Claims 1 to 8 and 10, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R¹ is a 6-membered nitrogen-containing heteroaryl, wherein the heteroaryl is optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy.

13. The compound according to any one of Claims 1 to 8, 10, and 12, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R¹ is pyrimidinyl optionally substituted with 1 to 3 substituents independently selected from halogen, C₁₋₆alkyl, or C₁₋₆alkoxy.

14. The compound according to any one of Claims 1 to 8 and 10 to 13, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein



15. The compound according to any one of Claims 1 to 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R² is H, methyl, monofluoromethyl, difluoromethyl, or trifluoromethyl.

16. The compound according to any one of Claims 1 to 9, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R² is trifluoromethyl.

17. The compound according to any one of Claims 1 to 17, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein R³ is F.

18. The compound according to any one of Claims 1 to 17, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is pyridyl or pyrazinyl, which pyridyl or pyrazinyl is

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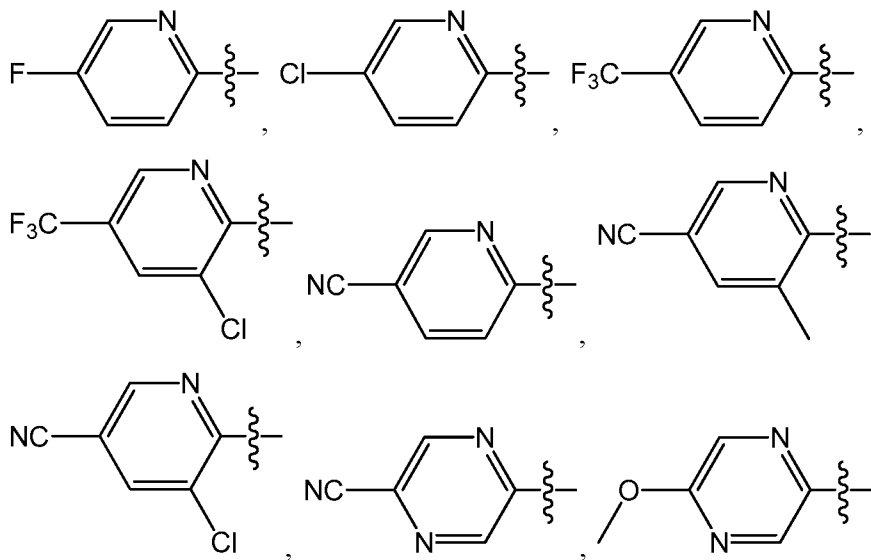
optionally substituted with 1 to 3 substituents independently selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butyloxy, 3-buten-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,

wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy.

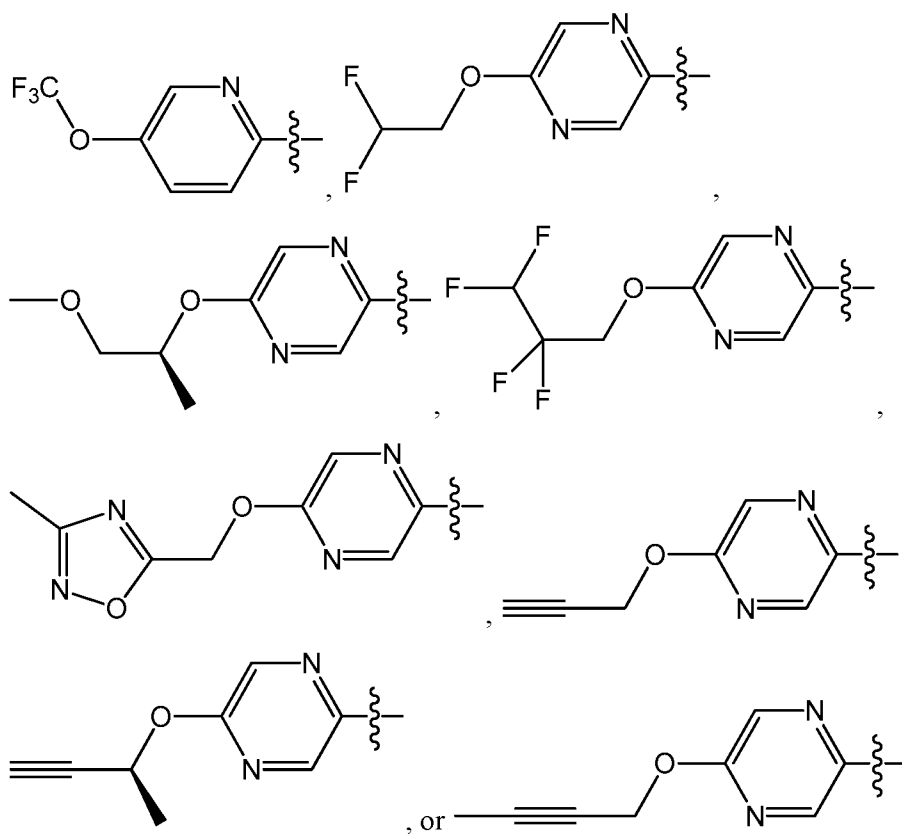
19. The compound according to any one of Claims 1 to 17, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein R⁵ and R⁶ is F or H and the other of R⁵ and R⁶ is pyridyl or pyrazinyl, which pyridyl or pyrazinyl is optionally substituted with 1 to 3 substituents independently selected from -CN, C₁₋₆alkyl, C₁₋₆alkoxy, 2-propynyloxy, 2-butyloxy, 3-buten-2-yloxy, or (3-methyl-1,2,4-oxadiazol-5-yl)methoxy,

wherein the C₁₋₆alkyl or C₁₋₆alkoxy is optionally substituted with 1 to 4 substituents independently selected from F or methoxy.

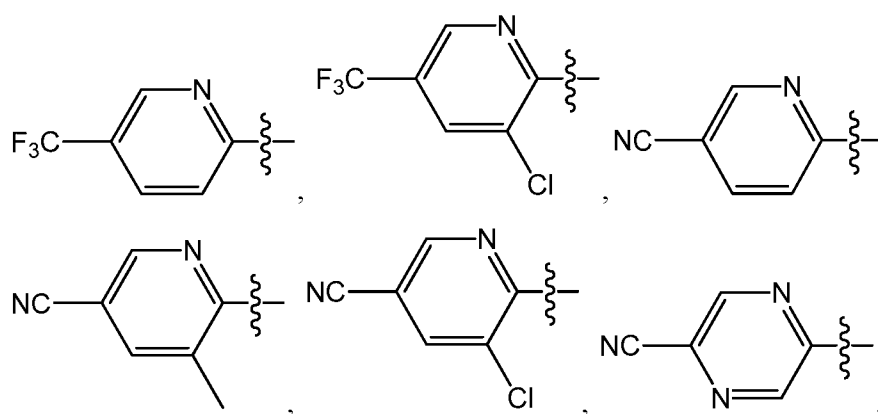
20. The compound according to any one of Claims 1 to 18, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein one of R⁶ and R⁷ is



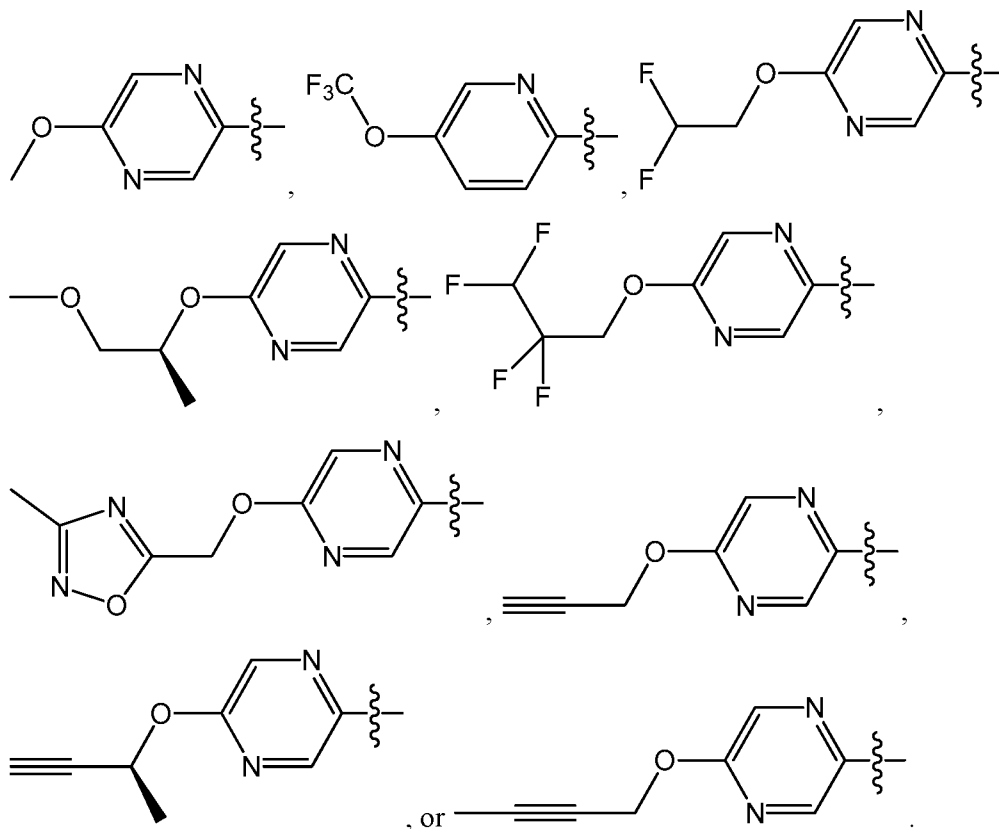
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- 5 21. The compound according to any one of Claims 1 to 19, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein one of R⁶ and R⁷ is



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- 5 22. The compound according to any one of Claims 1 to 21, or a tautomer thereof,
or a pharmaceutically acceptable salt of said compound or tautomer, wherein
 R⁴ is H; and
 R⁵ is H.
- 10 23. The compound according to any one of Claims 1 to 21, or a tautomer thereof,
or a pharmaceutically acceptable salt of said compound or tautomer, wherein
 R⁴ is H; and
 R⁶ is H.
- 15 24. The compound according to any one of Claims 1 to 21, or a tautomer thereof,
or a pharmaceutically acceptable salt of said compound or tautomer, wherein
 R⁴ is F; and
 R⁵ is H.

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25. The compound according to any one of Claims 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R⁴ is F; and

R⁶ is H.

5 26. The compound according to any one of Claims 1 to 21, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R⁴ is H; and

R⁵ is F.

10 27. The compound according to any one of Claims 1 to 21 or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein

R⁴ is H; and

R⁶ is F.

28. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

15 (4aS,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

20 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,7aR)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aR,7aR)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

25 (4aS,7aS)-7a-(5-((Z)-2-(5-chloropyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

5 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

10 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

20 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

25 (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

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1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-

5 trifluoropropan-1-one;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one;

(4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

20 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

30

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

5 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
10 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;
15 (4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile;
20 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile;
25 6-((Z)-2-(3-((4aR,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;
30 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

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6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(difluoromethyl)-4a,5-dihydro-4H-furo[3,4-d][1,3]thiazin-7a(7H)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; or
 (4aS,5S,7aS)-5-(difluoromethyl)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine.

29. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, selected from

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

10 6-((Z)-2-(3-((4aS,7aR)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aR)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

15 6-((Z)-2-(3-((4aS,7aS)-2-amino-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-methoxypyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-((3-methyl-1,2,4-oxadiazol-5-yl)methoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

25 5-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(2,2,3,3-tetrafluoropropoxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-(2,2-difluoroethoxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

5 (4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(((S)-1-methoxypropan-2-yl)oxy)pyrazin-2-yl)vinyl)phenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

(4aR,7aS)-7a-(5-((Z)-2-(5-((S)-but-3-yn-2-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

10 (4aR,7aS)-tert-butyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-7a-(5-((Z)-2-(5-(but-2-yn-1-yloxy)pyrazin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-6-(5-fluoropyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

15 1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)ethanone;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)-3,3,3-trifluoropropan-1-one;

(4aR,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-2-amine;

25 (4aR,7aS)-methyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

1-((4aR,7aS)-2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazin-6(4H)-yl)propan-1-one;

30 (4aR,7aS)-ethyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

(4aR,7aS)-isopropyl 2-amino-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-yn-1-yloxy)pyrazin-2-yl)vinyl)phenyl)-4a,5,7,7a-tetrahydropyrrolo[3,4-d][1,3]thiazine-6(4H)-carboxylate;

5 6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

10 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(prop-2-ynyloxy)pyrazin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

5-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)pyrazine-2-carbonitrile;

15 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethoxy)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxy-6-methylpyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

20 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

(4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-fluoropyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(fluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

25 6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(5-fluoro-4-methoxypyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aR,7aS)-2-amino-6-(pyrimidin-2-yl)-4,4a,5,6,7,7a-hexahydropyrrolo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

30 5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

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(4aS,5S,7aS)-7a-(5-((Z)-2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)-2-fluorovinyl)-2-fluorophenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-methylnicotinonitrile;

5 (4aS,5S,7aS)-7a-(2-fluoro-5-((Z)-2-fluoro-2-(5-(trifluoromethyl)pyridin-2-yl)vinyl)phenyl)-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-2-amine;

6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)-5-chloronicotinonitrile;

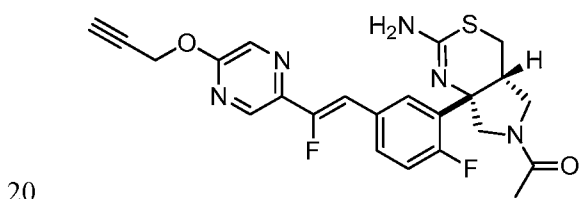
10 6-((Z)-2-(3-((4aR,5S,7aS)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

6-((Z)-2-(3-((4aS,5R,7aR)-2-amino-5-(trifluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]oxazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile;

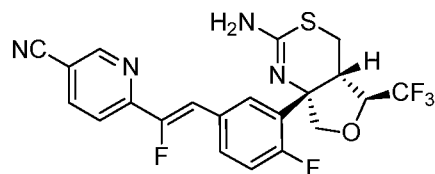
15 6-((Z)-2-(3-((4aS,5S,7aS)-2-amino-5-(difluoromethyl)-4a,5,7,7a-tetrahydro-4H-furo[3,4-d][1,3]thiazin-7a-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile; or

6-((Z)-2-(3-((4aR,5R,7aR)-2-amino-5-(difluoromethyl)-4a,5-dihydro-4H-furo[3,4-d][1,3]thiazin-7a(7H)-yl)-4-fluorophenyl)-1-fluorovinyl)nicotinonitrile.

30. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is

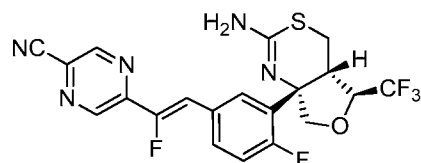


31. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is

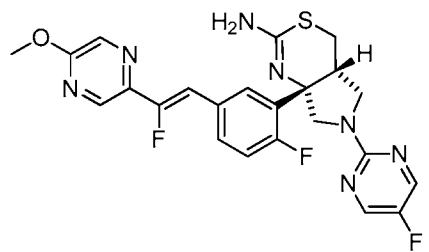


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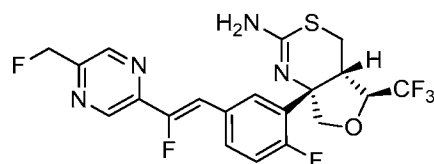
32. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is



33. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is



34. The compound of Claim 1, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, wherein the compound is



35. A pharmaceutical composition comprising the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, and a pharmaceutically acceptable excipient.

36. A compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 for use as a medicament.

37. A compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical

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composition according to Claim 35 for use in reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

38. A compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 for use in treating Alzheimer's disease, cognitive impairment, or a combination thereof in a subject.

39. A compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 for use in treating a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject.

40. A compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 for use in reducing formation of plaque on the brain of a subject.

41. Use of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 in the preparation of a medicament for reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject.

42. Use of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 in the preparation of a medicament for treating Alzheimer's disease, cognitive impairment, or a combination thereof in a subject.

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43. Use of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 in the preparation of a medicament for the treatment of a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject.

44. Use of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer, or the pharmaceutical composition according to Claim 35 in the preparation of a medicament for the reduction of formation of plaque on the brain of a subject.

45. A method of reducing beta amyloid peptide levels in the cerebral spinal fluid of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

46. A method of treating Alzheimer's disease, cognitive impairment or a combination thereof in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

47. A method of treating a neurological disorder selected from mild cognitive impairment, Down's syndrome, hereditary cerebral hemorrhage with Dutch-type amyloidosis, cerebral amyloid angiopathy, degenerative dementia, dementia associated with Parkinson's disease, dementia associated with supranuclear palsy, dementia associated with cortical basal degeneration, diffuse Lewy body type of Alzheimer's disease, or a combination thereof in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

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48. A method of reducing the formation of plaque on the brain of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the compound according to any one of Claims 1 to 34, or a tautomer thereof, or a pharmaceutically acceptable salt of said compound or tautomer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2017/066180

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/04 C07D513/04 A61P25/00 A61P25/28 A61K31/542
A61K31/5365

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/093999 A1 (MOTOKI TAKAFUMI [JP] ET AL) 15 April 2010 (2010-04-15) the whole document; in particular the claims and the examples -----	1-48
Y	WO 2011/009898 A1 (EISAI R&D MAN CO LTD [JP]; ELLARD JOHN MARK [GB]; FARTHING CHRISTOPHER) 27 January 2011 (2011-01-27) the whole document, in particular the claims and the examples -----	1-48
Y	WO 2014/143579 A1 (LILLY CO ELI [US]) 18 September 2014 (2014-09-18) cited in the application the whole document ----- -/-	1-48



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

26 February 2018

Date of mailing of the international search report

15/03/2018

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Hanisch, Inken

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2017/066180

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/098213 A1 (EISAI R&D MAN CO LTD [JP]; HALL ADRIAN [GB]; FARTHING CHRISTOPHER NEIL) 26 July 2012 (2012-07-26) in particular the claims -----	1-48
Y,P	WO 2017/024180 A1 (AMGEN INC [US]) 9 February 2017 (2017-02-09) the claims -----	1-48

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/066180

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2010093999	A1	15-04-2010	AR 073406 A1	03-11-2010
			AU 2009300836 A1	08-04-2010
			CA 2738150 A1	08-04-2010
			CN 102171221 A	31-08-2011
			EP 2332943 A1	15-06-2011
			ES 2539859 T3	06-07-2015
			IL 211933 A	31-03-2015
			JP 5666304 B2	12-02-2015
			JP WO2010038686 A1	01-03-2012
			KR 20110076965 A	06-07-2011
			NZ 591878 A	29-06-2012
			PE 03072011 A1	21-05-2011
			TW 201016708 A	01-05-2010
			US 2010093999 A1	15-04-2010
			US 2011207723 A1	25-08-2011
			WO 2010038686 A1	08-04-2010
			ZA 201102172 B	31-10-2012

WO 2011009898	A1	27-01-2011	EP 2456774 A1	30-05-2012
			EP 2653473 A1	23-10-2013
			ES 2433229 T3	10-12-2013
			JP 5651692 B2	14-01-2015
			JP 2012533603 A	27-12-2012
			US 2012202804 A1	09-08-2012
			WO 2011009898 A1	27-01-2011

WO 2014143579	A1	18-09-2014	AR 094918 A1	09-09-2015
			AU 2014228351 A1	17-09-2015
			CA 2898500 A1	18-09-2014
			CL 2015002529 A1	28-03-2016
			CN 105026404 A	04-11-2015
			CR 20150418 A	16-09-2015
			DK 2970336 T3	13-11-2017
			EA 201591491 A1	29-01-2016
			EP 2970336 A1	20-01-2016
			ES 2653421 T3	07-02-2018
			HK 1212694 A1	17-06-2016
			HR P20171851 T1	12-01-2018
			JP 6095844 B2	15-03-2017
			JP 2016512252 A	25-04-2016
			KR 20150119070 A	23-10-2015
			LT 2970336 T	10-01-2018
			PE 15422015 A1	28-10-2015
			PH 12015502031 A1	18-01-2016
			PT 2970336 T	21-12-2017
			SG 11201507499X A	29-10-2015
			SI 2970336 T1	30-11-2017
			TN 2015000340 A1	03-01-2017
			TW 201520217 A	01-06-2015
			UA 112941 C2	10-11-2016
			US 2014275044 A1	18-09-2014
			US 2014350245 A1	27-11-2014
			US 2015157641 A1	11-06-2015
			WO 2014143579 A1	18-09-2014

WO 2012098213	A1	26-07-2012	AR 084903 A1	10-07-2013
			AU 2012208526 A1	02-05-2013
			CA 2828738 A1	26-07-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2017/066180

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CL 2013002083 A1	06-12-2013
		CN 103328486 A	25-09-2013
		EP 2665732 A1	27-11-2013
		ES 2575914 T3	04-07-2016
		IL 226596 A	21-04-2016
		JP 5947815 B2	06-07-2016
		JP 2014502987 A	06-02-2014
		KR 20140002724 A	08-01-2014
		NZ 611365 A	24-04-2015
		PE 11822014 A1	14-09-2014
		RU 2013138717 A	27-02-2015
		SG 190908 A1	31-07-2013
		TW 201309710 A	01-03-2013
		UA 109927 C2	26-10-2015
		US 2012190672 A1	26-07-2012
		US 2013203740 A1	08-08-2013
		US 2014142091 A1	22-05-2014
		WO 2012098213 A1	26-07-2012
		ZA 201303801 B	30-07-2014

WO 2017024180	A1	09-02-2017	NONE
