

HETEROARYL COMPOUNDS FOR THE TREATMENT OF PAIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 63/592,371, filed October 23, 2023, and U.S. Provisional Application No. 63/592,715, filed October 24, 2023, each of which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Pain is a protective mechanism to avoid tissue damage and to prevent further damage to injured tissue. Nonetheless, there are many conditions where pain persists beyond its usefulness, or where patients would benefit from inhibition of pain. Acute and chronic pain are two common pain states and can be distinguished by the duration of the pain. Acute pain can arise for many reasons (e.g., a hospital procedure) and treatment options are generally limited by poor efficacy and/or adverse events. Like acute pain, chronic pain can arise for many reasons and treatment options are limited by poor efficacy and/or adverse events.

[0003] Neuropathic pain is a form of chronic pain caused by an injury to the sensory nerves (Dieleman, J.P., et al., Incidence rates and treatment of neuropathic pain conditions in the general population. *Pain*, 2008. **137**(3): p. 681-8). Neuropathic pain can be divided into two categories, pain caused by generalized metabolic damage to the nerve and pain caused by a discrete nerve injury. The metabolic neuropathies include post-herpetic neuropathy, diabetic neuropathy, and drug-induced neuropathy. Discrete nerve injury indications include post-amputation pain, post-surgical nerve injury pain, and nerve entrapment injuries like neuropathic back pain.

[0004] Voltage-gated sodium channels (Navs) are involved in pain signaling. Navs are biological mediators of electrical signaling as they mediate the rapid upstroke of the action potential of many excitable cell types, for example, neurons, skeletal myocytes, cardiac myocytes (Hille, Bertil, *Ion Channels of Excitable Membranes*, Third ed. (Sinauer Associates, Inc., Sunderland, MA, 2001)). The evidence for the role of these channels in normal physiology, the pathological states arising from mutations in sodium channel genes, preclinical work in animal models, and the clinical pharmacology of known sodium channel modulating agents all point to the central role of Navs in pain sensation (Rush, A.M. and T.R. Cummins, *Painful Research: Identification of a Small-Molecule Inhibitor that Selectively Targets Nav1.8 Sodium Channels*. Mol. Interv., 2007. **7**(4): p. 192-5); England, S., Voltage-gated sodium channels: the search for subtype-selective analgesics. *Expert Opin. Investig. Drugs* **17** (12), p. 1849-64 (2008); Krafte, D. S. and Bannion, A. W., Sodium channels and nociception: recent concepts and therapeutic opportunities. *Curr. Opin. Pharmacol.* **8** (1), p. 50-56 (2008)). Because of the role Navs play in the initiation and propagation of neuronal signals, antagonists that reduce Nav currents can prevent or reduce neural signaling and Nav channels have

been considered likely targets to reduce pain in conditions where hyper-excitability is observed (Chahine, M., Chatelier, A., Babich, O., and Krupp, J. J., Voltage-gated sodium channels in neurological disorders. *CNS Neurol. Disord. Drug Targets* 7 (2), p. 144-58 (2008)). Several clinically useful analgesics have been identified as inhibitors of Nav channels. The local anesthetic drugs such as lidocaine block pain by inhibiting Nav channels, and other compounds, such as carbamazepine, lamotrigine, and tricyclic antidepressants that have proven effective at reducing pain have also been suggested to act by sodium channel inhibition (Soderpalm, B., Anticonvulsants: aspects of their mechanisms of action. *Eur. J. Pain* 6 Suppl. A, p. 3-9 (2002); Wang, G. K., Mitchell, J., and Wang, S. Y., Block of persistent late Na⁺ currents by antidepressant sertraline and paroxetine. *J. Membr. Biol.* 222 (2), p. 79-90 (2008)).

[0005] The Navs form a subfamily of the voltage-gated ion channel super-family and comprises 9 isoforms, designated Nav1.1 – Nav1.9. The tissue localizations of the nine isoforms vary. Nav1.4 is the primary sodium channel of skeletal muscle, and Nav1.5 is primary sodium channel of cardiac myocytes. Navs 1.7, 1.8 and 1.9 are primarily localized to the peripheral nervous system, while Navs 1.1, 1.2, 1.3, and 1.6 are neuronal channels found in both the central and peripheral nervous systems. The functional behaviors of the nine isoforms are similar but distinct in the specifics of their voltage-dependent and kinetic behavior (Catterall, W. A., Goldin, A. L., and Waxman, S. G., International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. *Pharmacol. Rev.* 57 (4), p. 397 (2005)).

[0006] Upon their discovery, Nav1.8 channels were identified as likely targets for analgesia (Akopian, A.N., L. Sivilotti, and J.N. Wood, A tetrodotoxin-resistant voltage-gated sodium channel expressed by sensory neurons. *Nature*, 1996. 379(6562): p. 257-62). Since then, Nav1.8 has been shown to be a carrier of the sodium current that maintains action potential firing in small dorsal root ganglia (DRG) neurons (Blair, N.T. and B.P. Bean, Roles of tetrodotoxin (TTX)-sensitive Na⁺ current, TTX-resistant Na⁺ current, and Ca²⁺ current in the action potentials of nociceptive sensory neurons. *J. Neurosci.*, 2002. 22(23): p. 10277-90). Nav1.8 is involved in spontaneous firing in damaged neurons, like those that drive neuropathic pain (Roza, C., et al., The tetrodotoxin-resistant Na⁺ channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J. Physiol.*, 2003. 550(Pt 3): p. 921-6; Jarvis, M.F., et al., A-803467, a potent and selective Nav1.8 sodium channel blocker, attenuates neuropathic and inflammatory pain in the rat. *Proc. Natl. Acad. Sci. U S A*, 2007. 104(20): p. 8520-5; Joshi, S.K., et al., Involvement of the TTX-resistant sodium channel Nav1.8 in inflammatory and neuropathic, but not post-operative, pain states. *Pain*, 2006. 123(1-2): pp. 75-82; Lai, J., et al., Inhibition of neuropathic pain by decreased expression of the tetrodotoxin-resistant sodium channel, Nav1.8. *Pain*, 2002. 95(1-2): p. 143-52; Dong, X.W., et al., Small interfering RNA-mediated selective knockdown of Nav1.8 tetrodotoxin-resistant sodium channel reverses mechanical allodynia in neuropathic rats. *Neuroscience*. 2007. 146(2): p. 812-21; Huang, H.L., et al., Proteomic profiling of neuromas reveals alterations in protein composition and

local protein synthesis in hyper-excitability nerves. *Mol. Pain*, 2008, **4**: p. 33; Black, J.A., et al., Multiple sodium channel isoforms and mitogen-activated protein kinases are present in painful human neuromas. *Ann. Neurol.*, 2008, **64**(6): p. 644-53; Coward, K., et al., Immunolocalization of SNS/PN3 and NaN/SNS2 sodium channels in human pain states. *Pain*, 2000, **85**(1-2): p. 41-50; Yiangou, Y., et al., SNS/PN3 and SNS2/NaN sodium channel-like immunoreactivity in human adult and neonate injured sensory nerves. *FEBS Lett.*, 2000, **467**(2-3): p. 249-52; Ruangsri, S., et al., Relationship of axonal voltage-gated sodium channel 1.8 (Nav1.8) mRNA accumulation to sciatic nerve injury-induced painful neuropathy in rats. *J. Biol. Chem.* **286**(46): p. 39836-47). The small DRG neurons where Nav1.8 is expressed include the nociceptors involved in pain signaling, where Nav1.8 mediates large amplitude action potentials (Blair, N.T. and B.P. Bean, Roles of tetrodotoxin (TTX)-sensitive Na⁺ current, TTX-resistant Na⁺ current, and Ca²⁺ current in the action potentials of nociceptive sensory neurons. *J. Neurosci.*, 2002, **22**(23): p. 10277-90). Nav1.8 is necessary for rapid repetitive action potentials in nociceptors, and for spontaneous activity of damaged neurons. (Choi, J.S. and S.G. Waxman, Physiological interactions between Nav1.7 and Nav1.8 sodium channels: a computer simulation study. *J. Neurophysiol.* **106**(6): p. 3173-84; Renganathan, M., T.R. Cummins, and S.G. Waxman, Contribution of Nav1.8 sodium channels to action potential electrogenesis in DRG neurons. *J. Neurophysiol.*, 2001, **86**(2): p. 629-40; Roza, C., et al., The tetrodotoxin-resistant Na⁺ channel Nav1.8 is essential for the expression of spontaneous activity in damaged sensory axons of mice. *J. Physiol.*, 2003, **550**(Pt 3): p. 921-6). In depolarized or damaged DRG neurons, Nav1.8 appears to be a driver of hyper-excitability (Rush, A.M., et al., A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc. Natl. Acad. Sci. USA*, 2006, **103**(21): p. 8245-50). In some animal pain models, Nav1.8 mRNA expression levels have been shown to increase in the DRG (Sun, W., et al., Reduced conduction failure of the main axon of polymodal nociceptive C-fibers contributes to painful diabetic neuropathy in rats. *Brain*, **135**(Pt 2): p. 359-75; Strickland, I.T., et al., Changes in the expression of Nav1.7, Nav1.8 and Nav1.9 in a distinct population of dorsal root ganglia innervating the rat knee joint in a model of chronic inflammatory joint pain. *Eur. J. Pain*, 2008, **12**(5): p. 564-72; Qiu, F., et al., Increased expression of tetrodotoxin-resistant sodium channels Nav1.8 and Nav1.9 within dorsal root ganglia in a rat model of bone cancer pain. *Neurosci. Lett.*, **512**(2): p. 61-6).

[0007] The inventors have discovered that some voltage-gated sodium channel inhibitors have limitations as therapeutic agents due to, for example, a poor therapeutic window (e.g., due to a lack of Nav isoform selectivity, low potency, and/or other reasons). Accordingly, there remains a need to develop selective voltage-gated sodium channel inhibitors, such as selective Nav1.8 inhibitors.

SUMMARY

[0008] In one aspect, the invention relates to a compound described herein, or a pharmaceutically acceptable salt thereof.

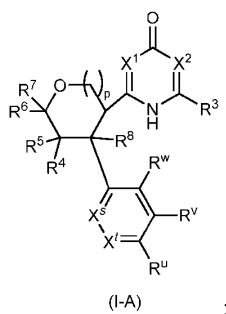
[0009] In another aspect, the invention relates to a pharmaceutical composition comprising the compound, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or vehicles.

[0010] In still another aspect, the invention relates to a method of inhibiting a voltage gated sodium channel in a subject by administering the compound, pharmaceutically acceptable salt, or pharmaceutical composition to the subject.

[0011] In yet another aspect, the invention relates to a method of treating or lessening the severity in a subject of a variety of diseases, disorders, or conditions, including, but not limited to, chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., bunionectomy pain, herniorrhaphy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, and cardiac arrhythmia, by administering the compound, pharmaceutically acceptable salt, or pharmaceutical composition to the subject.

DETAILED DESCRIPTION

[0012] In one aspect, the invention relates to a compound of formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is C- R^1 or N;

X^2 is C- R^2 or N;

X^3 is C- R^3 or N;

X^4 is C- R^4 or N;

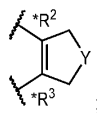
R^1 is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-(CH_2)_mO_n(CH_2)_oOCH_3$, $-(CH_2)_mR^a$, $-C(O)(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^bR^cNR^gC(O)CR^hR^iR^j$, $-NR^bC(O)CR^eR^gR^j$, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy;

R^2 and R^3 are defined as follows:

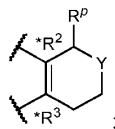
(i) R^2 is H, OH, halo, CN, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^bR^cNR^gC(O)CR^hR^iR^j$, $-O(CH_2)_mR^a$, $-CR^bR^cOR^g$, $-CR^bR^c(CH_2)_mO(CH_2)_dC(O)OR^g$, $-CR^bR^c(CH_2)_mO(CH_2)_dCR^gR^hR^a$, $-CR^bR^c(CH_2)_mO(CH_2)_dC(O)NR^gR^h$, $-CR^bR^c(CH_2)_mO(CH_2)_dR^d$, $-CR^bR^cC(R^d)(R^e)(R^f)$, $-CR^bR^cNR^gR^h$, $-CH_2C(O)NR^bR^c$, $-C(O)O_n(CH_2)_mR^a$, $-NR^b(CH_2)_mOR^c$, $-NR^b(CH_2)_mR^n$, $-(CH_2)_mNR^bC(O)R^n$, $-NR^bCR^cR^gR^h$, $-(CH_2)_mNR^bC(O)R^c$, $-SR^b$, $-S(=O)_2R^l$, $-N=S(=O)(R^b)(R^m)$, $-S(=O)(=NR^b)(R^b)$, C_3 - C_6 cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C_3 - C_6 cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, $-CH_2OH$, $-C(O)OR^b$, $-NR^bR^c$, and $-C(O)NR^bR^c$; and

R^3 is H, OH, halo, CN, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-(CH_2)_mOCH_3$, or $-(CH_2)_mR^a$;

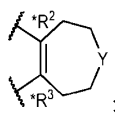
(ii) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



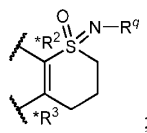
(iii) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(iv) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(v) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



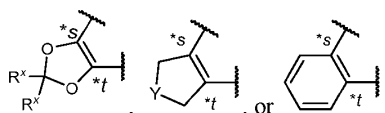
Y is O or NR^o ;

R^4 and R^5 are each independently H, OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkoxy;

R^6 and R^7 are each independently H, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or C₁-C₆ alkoxy, or R^6 and R^7 , together with the carbon atom to which they are attached, form a C₃-C₆ cycloalkyl;

R^8 is H or CH₃;

R^s and R^t are each independently H, OH, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, $-NR^bR^c$, $-NO_2$, $-SO_3H$, $-(CH_2)_mR^a$, or $-O(CH_2)_mOCH_3$, or R^s and R^t , together with the atoms to which they are attached, form a ring of formula:



Y is O or CH₂;

R^u , R^v , and R^w are each independently H, OH, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, $-NR^bR^c$, $-NO_2$, $-SO_3H$, $-(CH_2)_mR^a$, or $-O(CH_2)_mOCH_3$;

each R^x is independently H, halo, C₁-C₆ alkyl, or C₁-C₆ haloalkyl;

R^a is OH, halo, C₁-C₆ alkoxy, or $-NR^bR^c$;

R^b , R^c , R^g , R^h , R^i , and R^k are each independently H or C₁-C₆ alkyl, or R^b and R^c , together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl;

R^d , R^e , and R^f are each independently H, OH, halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R^j is H, C₁-C₆ alkyl, $-NR^bR^c$, or $-N(CH_3)_3^+$;

R^l and R^m are each independently C₁-C₆ alkyl;

R^n is C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl wherein said C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents selected from C₁-C₆ alkyl and halo;

R^o is H, C₁-C₆ alkyl, or $-C(O)O(C_1-C_6 \text{ alkyl})$;

R^p is H, C₁-C₆ alkyl, $-C(O)NR^bR^c$, or oxo;

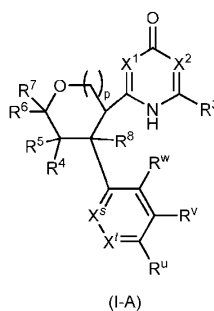
R^q is H or C₁-C₆ alkyl;

m and o are each independently 0, 1, 2, or 3;

n is 0 or 1; and

p is 0 or 1.

[0013] In another aspect, the invention relates to a compound of formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is C-R¹ or N;

X^2 is $\mathbb{C}$ - $\mathbb{R}^2$ or $\mathbb{N}$:

X^s is C-R^s or N;

 X^t is C- R^t or N:

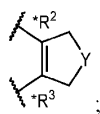
R¹ is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -(CH₂)_mO_n(CH₂)_oOCH₃, -(CH₂)_mR^a, -C(O)(CH₂)_mR^a, -C(O)OR^b, -C(O)R^b, -C(O)NR^bR^c, -NR^bR^c, -CR^dR^eR^f, -CR^bR^cNR^gC(O)CR^hRⁱR^j, -NR^bC(O)CR^hR^gRⁱ, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy;

R^2 and R^3 are defined as follows:

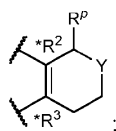
(i) R² is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, - (CH₂)_mR^a, -C(O)OR^b, -C(O)R^b, -C(O)NR^bR^c, -NR^bR^c, -CR^dR^eR^f, -CR^bR^cNR^gC(O)CR^hRⁱ, -O(CH₂)_mR^a, -CR^bR^cOR^g, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)OR^g, -CR^bR^c(CH₂)_mO(CH₂)_oCR^gR^h, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)NR^gR^h, -CR^bR^c(CH₂)_mO(CH₂)_oR^d, -CR^bR^cC(R^d)(R^e)(R^f), -CR^bR^cNR^gR^h, -CH₂C(O)NR^bR^c, -C(O)O_n(CH₂)_mR^a, -NR^b(CH₂)_mOR^c, -NR^b(CH₂)_mRⁿ, -(CH₂)_mNR^bC(O)Rⁿ, -NR^bCR^cR^gR^h, -(CH₂)_mNR^bC(O)R^c, -SR^b, -S(=O)₂Rⁱ, -N=S(=O)(R^j)(R^m), -S(=O)(=NR^b)(R^j), C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -CH₂OH, -C(O)OR^b, -NR^bR^c, and -C(O)NR^bR^c; and

R³ is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, -(CH₂)_mOCH₃, or -(CH₂)_mR^a,

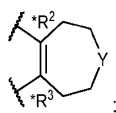
(ii) R² and R³, together with the carbon atoms to which they are attached, form a ring of formula:



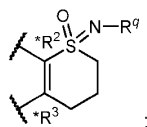
(iii) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(iv) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(v) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



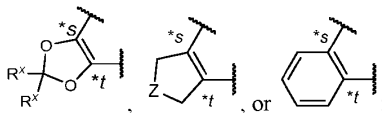
Y is O or NR^o .

R^4 and R^5 are each independently H, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_1\text{-C}_6$ alkoxy;

R^6 and R^7 are each independently H, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_1\text{-C}_6$ alkoxy, or R^6 and R^7 , together with the carbon atom to which they are attached, form a $\text{C}_3\text{-C}_6$ cycloalkyl;

R^8 is H or CH_3 ;

R^s and R^t are each independently H, OH, halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{NR}^b\text{R}^c$, $-\text{NO}_2$, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_m\text{R}^a$, or $-\text{O}(\text{CH}_2)_m\text{OCH}_3$, or R^s and R^t , together with the atoms to which they are attached, form a ring of formula:



Z is O or CH_2 ;

R^u , R^v , and R^w are each independently H, OH, halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{NR}^b\text{R}^c$, $-\text{NO}_2$, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_m\text{R}^a$, or $-\text{O}(\text{CH}_2)_m\text{OCH}_3$;

each R^x is independently H, halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl;

R^a is OH, halo, C₁-C₆ alkoxy, or $-NR^bR^c$;

R^b , R^c , R^e , R^h , R^i , and R^k are each independently H or C₁-C₆ alkyl, or R^b and R^c , together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl;

R^d , R^e , and R^f are each independently H, OH, halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R^j is H, C₁-C₆ alkyl, $-NR^bR^c$, or $-N(CH_3)_3^+$;

R^l and R^m are each independently C₁-C₆ alkyl;

R^n is C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl wherein said C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents selected from C₁-C₆ alkyl and halo;

R^o is H, C₁-C₆ alkyl, or $-C(O)O(C_1-C_6 \text{ alkyl})$;

R^p is H, C₁-C₆ alkyl, $-C(O)NR^bR^c$, or oxo;

R^q is H or C₁-C₆ alkyl;

m and o are each independently 0, 1, 2, or 3;

n is 0 or 1; and

p is 0 or 1.

[0014] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry," Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry," 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0015] As used herein, the term "compounds of the invention" refers to the compounds of formula (I-A) and all of the embodiments thereof (e.g., formulas (I-A-1), (I-A-2), etc.), as described herein, and to the compounds identified in Table A and Table B.

[0016] As described herein, the compounds of the invention comprise multiple variable groups (e.g., X^1 , R^1 , R^4 , R^u , etc.). As one of ordinary skill in the art will recognize, combinations of groups envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds. The term "stable," in this context, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0017] As used herein, the term "halo" means F, Cl, Br or I.

[0018] As used herein, the term "alkyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing no unsaturation, and having the

specified number of carbon atoms, which is attached to the rest of the molecule by a single bond. For example, a “C₁-C₆ alkyl” group is an alkyl group having between one and six carbon atoms.

[0019] As used herein, the term “cycloalkyl” refers to a stable, non-aromatic, mono- or bicyclic (fused, bridged, or spiro) saturated hydrocarbon radical consisting solely of carbon and hydrogen atoms, having the specified number of carbon ring atoms, and which is attached to the rest of the molecule by a single bond. For example, a “C₃-C₈ cycloalkyl” group is a cycloalkyl group having between three and eight carbon atoms.

[0020] As used herein, the term “alkoxy” refers to a radical of the formula -OR_a where R_a is an alkyl group having the specified number of carbon atoms. For example, a “C₁-C₆ alkoxy” group is a radical of the formula -OR_a where R_a is an alkyl group having the between one and six carbon atoms.

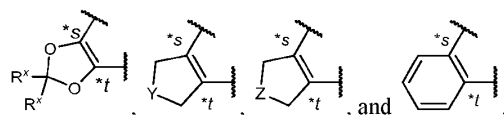
[0021] As used herein, the term “haloalkyl” refers to an alkyl group having the specified number of carbon atoms, wherein one or more of the hydrogen atoms of the alkyl group are replaced by halo groups. For example, a “C₁-C₆ haloalkyl” group is an alkyl group having between one and six carbon atoms, wherein one or more of the hydrogen atoms of the alkyl group are replaced by halo groups.

[0022] As used herein, the term “haloalkoxy” refers to an alkoxy group having the specified number of carbon atoms, wherein one or more of the hydrogen atoms of the of the alkyl group are replaced by halo groups.

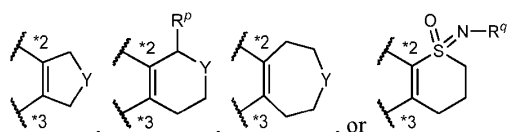
[0023] As used herein, the term “heterocyclyl” refers to a stable, non-aromatic, mono-, bi-, or tricyclic (fused, bridged, or spiro) radical in which one or more ring atoms is a heteroatom (e.g., a heteroatom independently selected from N, O, P, and S), which has the specified number of ring atoms, and which is attached to the rest of the molecule by a single bond. Heterocyclic rings can be saturated, or can contain one or more double or triple bonds. In some embodiments, the “heterocyclyl” group has the indicated number of ring members, in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, and phosphorus, and each ring in the ring system contains 3 to 7 ring members. For example, a 6-membered heterocyclyl includes a total of 6 ring members, at least one of which is a heteroatom (e.g., a heteroatom independently selected from N, O, P, and S).

[0024] As used herein, the term “heteroaryl” refers to a stable mono-, bi-, or tricyclic ring radical having the specified number of ring atoms, wherein at least one ring in the system is aromatic, at least one aromatic ring in the system contains one or more heteroatoms (e.g., one or more heteroatoms independently selected from N, O, P, and S). In some embodiments, each ring in the system contains 3 to 7 ring members. For example, a 6-membered heteroaryl includes a total of 6 ring members, at least one of which is a heteroatom selected from N, S, O, and P. The term “heteroaryl” may be used interchangeably with the term “heteroaryl ring” or the term “heteroaromatic”.

[0025] As used herein, labels such as “*s” and “*t”, such as those shown in the following structures, designate the carbon atoms to which the corresponding R groups (in this case, the R^s and R^t groups, respectively) are attached:

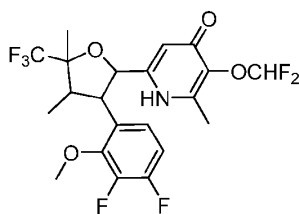


[0026] Similarly, labels such as “*2” and “*3”, such as those shown in the following structures, designate the carbon atoms to which the corresponding R groups (in this case, the R² and R³ groups, respectively) are attached:



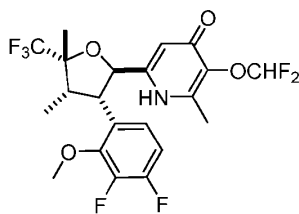
[0027] Unless otherwise specified, the compounds of the invention, whether identified by chemical name or chemical structure, include all stereoisomers (e.g., enantiomers and diastereomers), double bond isomers (e.g., (*Z*) and (*E*)), conformational isomers, and tautomers of the compounds identified by the chemical names and chemical structures provided herein. In addition, single stereoisomers, double bond isomers, conformational isomers, and tautomers as well as mixtures of stereoisomers, double bond isomers, conformational isomers, and tautomers are within the scope of the invention.

[0028] As used herein, in any chemical structure or formula, a non-bold, straight bond attached to a stereocenter of a compound, such as in



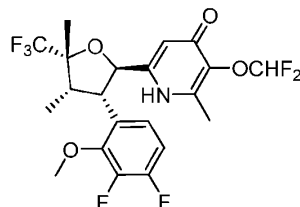
denotes that the configuration of the stereocenter is unspecified. The compound may have any configuration, or a mixture of configurations, at the stereocenter.

[0029] As used herein, in any chemical structure or formula, a bold or hashed straight bond attached to a stereocenter of a compound, such as in



denotes the relative stereochemistry of the stereocenter, relative to other stereocenter(s) to which bold or hashed straight bonds are attached.

[0030] As used herein, in any chemical structure or formula, a bold or hashed wedge bond attached to a stereocenter of a compound, such as in



denotes the absolute stereochemistry of the stereocenter, as well as the relative stereochemistry of the stereocenter, relative to other stereocenter(s) to which bold or hashed wedge bonds are attached.

[0031] As used herein, the prefix “*rac*-,” when used in connection with a chiral compound, refers to a racemic mixture of the compound. In a compound bearing the “*rac*-” prefix, the (*R*)- and (*S*)-designators in the chemical name reflect the relative stereochemistry of the compound.

[0032] As used herein, the prefix “*dia*-,” when used in connection with a chiral compound, refers to a mixture of two or more diastereomers of the compound. In a compound bearing the “*dia*-” prefix, the (*R*)- and (*S*)-designators are assigned arbitrarily and do not necessarily reflect the absolute or relative configuration of the corresponding stereocenters in any component of the mixture. In some instances, all of the diastereomers in a mixture have a single absolute configuration at one or more stereocenters. In these instances, the stereochemical designators associated with the stereocenters having a single absolute configuration are marked with an asterisk (*), *e.g.*, (*R**)- and (*S**)-. In some instances, all of the diastereomers in a mixture have the same relative stereochemistry at two or more stereocenters. In these instances, the stereochemical designators associated with such stereocenters are marked with a superscript number (ⁿ), *e.g.*, (*R*ⁿ)- and (*S*ⁿ)-. The stereochemical designators marked with a superscript number reflect the relative stereochemistry of the corresponding stereocenters with respect to other stereocenters associated with stereochemical designators having the same superscript number, *e.g.*, (*R*¹)- and (*S*¹)-, but they do not necessarily reflect the absolute configuration of such stereocenters. The stereochemical designators marked with an asterisk (*) do not necessarily reflect the relative stereochemistry of the corresponding stereocenters with respect to stereocenters associated with stereochemical designators marked with a superscript number (ⁿ) (and vice versa) or with respect to stereocenters associated with unmarked stereochemical designators. Likewise, the stereochemical designators marked with a superscript number (ⁿ) do not necessarily reflect the relative stereochemistry of the corresponding stereocenters with respect to stereocenters associated with stereochemical designators marked with a different superscript number (^m) or with respect to stereocenters associated with unmarked stereochemical designators.

[0033] As used herein, the prefix “*rel-*,” when used in connection with a chiral compound, refers to a single enantiomer of unknown absolute configuration. In a compound bearing the “*rel-*” prefix, the (*R*)- and (*S*)- designators in the chemical name reflect the relative stereochemistry of the compound, but do not necessarily reflect the absolute stereochemistry of the compound. In some instances, the absolute configuration of some stereocenters is known, while only the relative configuration of the other stereocenters is known. In these instances, the stereochemical designators associated with the stereocenters of known absolute configuration are marked with an asterisk (*), *e.g.*, (*R**)- and (*S**)-, while the stereochemical designators associated with stereocenters of unknown absolute configuration are not so marked. The unmarked stereochemical designators associated with the stereocenters of unknown absolute configuration reflect the relative stereochemistry of those stereocenters with respect to other stereocenters of unknown absolute configuration, but do not necessarily reflect the relative stereochemistry with respect to the stereocenters of known absolute configuration. Where a compound contains two or more stereocenters of unknown absolute configuration, and the relative stereochemistry of such stereocenters with respect to each other is unknown, no stereochemical designator is provided for such stereocenters.

[0034] As used herein, the term “compound,” when referring to the compounds of the invention, refers to a collection of molecules having identical chemical structures, except that there may be isotopic variation among the constituent atoms of the molecules. The term “compound” includes such a collection of molecules without regard to the purity of a given sample containing the collection of molecules. Thus, the term “compound” includes such a collection of molecules in pure form, in a mixture (*e.g.*, solution, suspension, colloid, or pharmaceutical composition, or dosage form) with one or more other substances, or in the form of a hydrate, solvate, or co-crystal.

[0035] In the specification and claims, unless otherwise specified, any atom not specifically designated as a particular isotope in any compound of the invention is meant to represent any stable isotope of the specified element. In the Examples, where an atom is not specifically designated as a particular isotope in any compound of the invention, no effort was made to enrich that atom in a particular isotope, and therefore a person of ordinary skill in the art would understand that such atom likely was present at approximately the natural abundance isotopic composition of the specified element.

[0036] As used herein, the term “stable,” when referring to an isotope, means that the isotope is not known to undergo spontaneous radioactive decay. Stable isotopes include, but are not limited to, the isotopes for which no decay mode is identified in V.S. Shirley & C.M. Lederer, *Isotopes Project*, Nuclear Science Division, Lawrence Berkeley Laboratory, *Table of Nuclides* (January 1980).

[0037] As used herein in the specification and claims, “H” refers to hydrogen and includes any stable isotope of hydrogen, namely ¹H and D. In the Examples, where an atom is designated as “H,” no effort was made to enrich that atom in a particular isotope of hydrogen, and therefore a person of

ordinary skill in the art would understand that such hydrogen atom likely was present at approximately the natural abundance isotopic composition of hydrogen.

[0038] As used herein, “¹H” refers to protium. Where an atom in a compound of the invention, or a pharmaceutically acceptable salt thereof, is designated as protium, protium is present at the specified position with at least the natural abundance concentration of protium.

[0039] As used herein, “D,” “d,” and “²H” refer to deuterium.

[0040] In some embodiments, the compounds of the invention, and pharmaceutically acceptable salts thereof, include each constituent atom at approximately the natural abundance isotopic composition of the specified element.

[0041] In some embodiments, the compounds of the invention, and pharmaceutically acceptable salts thereof, include one or more atoms having an atomic mass or mass number which differs from the atomic mass or mass number of the most abundant isotope of the specified element (“isotope-labeled” compounds and salts). Examples of stable isotopes which are commercially available and suitable for the invention include without limitation isotopes of hydrogen, carbon, nitrogen, oxygen, and phosphorus, for example ²H, ¹³C, ¹⁵N, ¹⁸O, ¹⁷O, and ³¹P, respectively.

[0042] The isotope-labeled compounds and salts can be used in a number of beneficial ways, including as medicaments. In some embodiments, the isotope-labeled compounds and salts are deuterium (²H)-labeled. Deuterium (²H)-labeled compounds and salts are therapeutically useful with potential therapeutic advantages over the non-²H-labeled compounds. In general, deuterium (²H)-labeled compounds and salts can have higher metabolic stability as compared to those that are not isotope-labeled owing to the kinetic isotope effect described below. Higher metabolic stability translates directly into an increased in vivo half-life or lower dosages, which under most circumstances would represent a preferred embodiment of the present invention. The isotope-labeled compounds and salts can usually be prepared by carrying out the procedures disclosed in the synthesis schemes, the Examples and the related description, replacing a non-isotope-labeled reactant by a readily available isotope-labeled reactant.

[0043] The deuterium (²H)-labeled compounds and salts can manipulate the rate of oxidative metabolism of the compound by way of the primary kinetic isotope effect. The primary kinetic isotope effect is a change of the rate for a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies of the covalent bonds involved in the reaction. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For example, if deuterium is bonded to a carbon atom at a non-exchangeable position, rate differences of $k_H/k_D = 2-7$ are typical. For a further discussion, see S. L. Harbeson and R. D. Tung, *Deuterium In Drug Discovery and*

Development, Ann. Rep. Med. Chem. 2011, 46, 403-417, incorporated in its entirety herein by reference.

[0044] The concentration of an isotope (e.g., deuterium) incorporated at a given position of an isotope-labeled compound of the invention, or a pharmaceutically acceptable salt thereof, may be defined by the isotopic enrichment factor. The term “isotopic enrichment factor,” as used herein, means the ratio between the abundance of an isotope at a given position in an isotope-labeled compound (or salt) and the natural abundance of the isotope.

[0045] Where an atom in a compound of the invention, or a pharmaceutically acceptable salt thereof, is designated as deuterium, such compound (or salt) has an isotopic enrichment factor for such atom of at least 3000 (~45% deuterium incorporation). In some embodiments, the isotopic enrichment factor is at least 3500 (~52.5% deuterium incorporation), at least 4000 (~60% deuterium incorporation), at least 4500 (~67.5% deuterium incorporation), at least 5000 (~75% deuterium incorporation), at least 5500 (~82.5% deuterium incorporation), at least 6000 (~90% deuterium incorporation), at least 6333.3 (~95% deuterium incorporation), at least 6466.7 (~97% deuterium incorporation), at least 6600 (~99% deuterium incorporation), or at least 6633.3 (~99.5% deuterium incorporation).

[0046] In some embodiments, the invention relates to a compound of formula (I-A), or a pharmaceutically acceptable salt thereof, wherein:

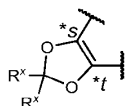
X^s is C- R^s ;

X^t is C- R^t ;

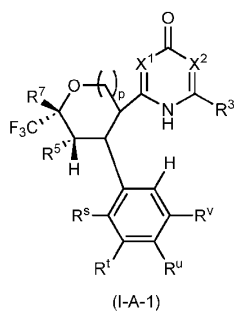
R^6 and R^7 are each independently H, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or C₁-C₆ alkoxy;

R^8 is H; and

R^s and R^t are each independently H, OH, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, $-NR^bR^c$, $-NO_2$, $-SO_3H$, $-(CH_2)_mR^a$, or $-O(CH_2)_mOCH_3$, or R^s and R^t , together with the atoms to which they are attached, form a ring of formula:



[0047] In some embodiments, the invention relates to a compound of formula (I-A-1):

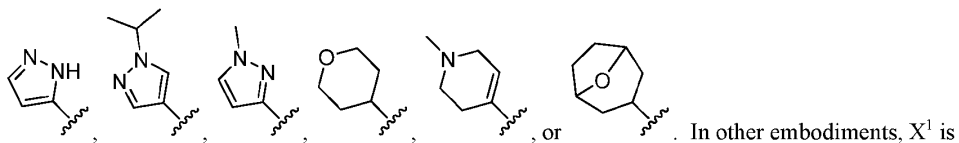
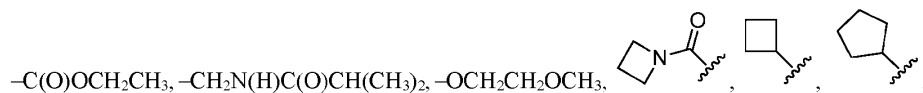


or a pharmaceutically acceptable salt thereof, wherein all variable groups are defined as they are defined for the compound of formula (I-A).

[0048] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein p is 0.

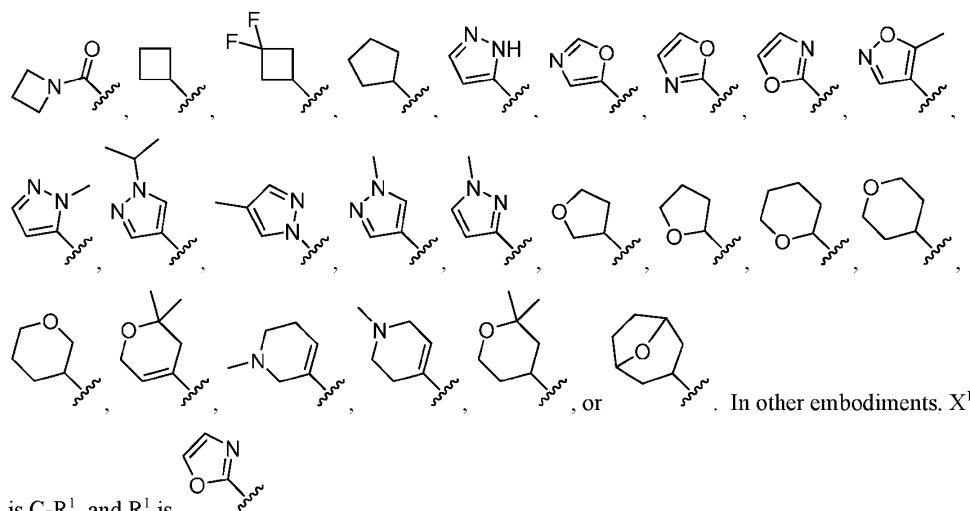
[0049] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein p is 1.

[0050] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein X¹ is N. In other embodiments, X¹ is C-R¹ and R¹ is H, halo, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -(CH₂)_mO_n(CH₂)_oOCH₃, -(CH₂)_mR^a, -C(O)(CH₂)_mR^a, -C(O)OR^b, -C(O)R^b, -C(O)NR^bR^c, -NR^bR^c, -CR^dR^eR^f, -CR^bR^cNR^gC(O)CR^bRⁱR^j, -(CH₂)_mNR^bC(O)Rⁿ, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy. In other embodiments, X¹ is C-R¹, and R¹ is H, Br, Cl, F, CN, -CH₃, -CH₂OH, -OCH₃, -OCHF₂, -CH(CH₃)₂, -CH₂OCH₃, -N(CH₃)₂, -C(O)OH, -C(O)CH₃, -C(O)OCH₃, -C(O)CH₂CH₂CH₂OH, -C(O)N(CH₃)₂, -C(O)N(H)CH₃,

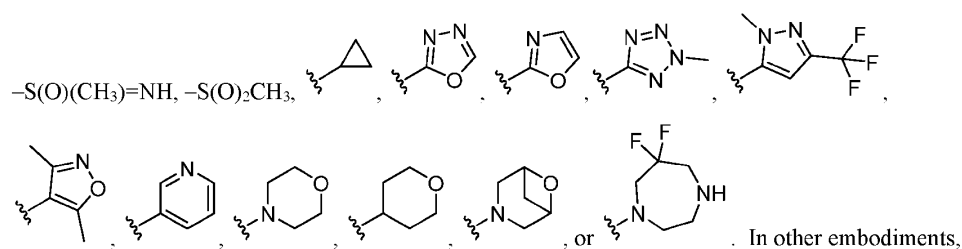


C-R¹, and R¹ is H, Br, Cl, F, CN, -CH₃, -CH₂OH, -OCH₃, -OCHF₂, -CH(CH₃)₂, -CH₂OCH₃, -N(CH₃)₂, -C(O)OH, -C(O)CH₃, -C(O)OCH₃, -C(O)CH₂CH₂CH₂OH, -C(O)N(CH₃)₂,

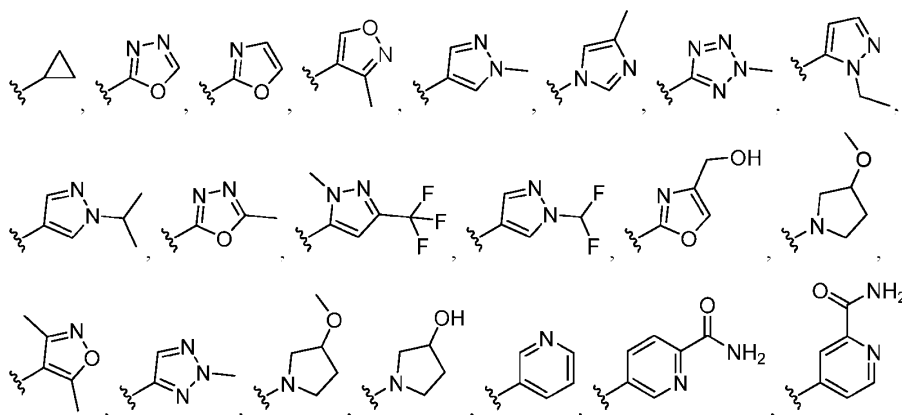


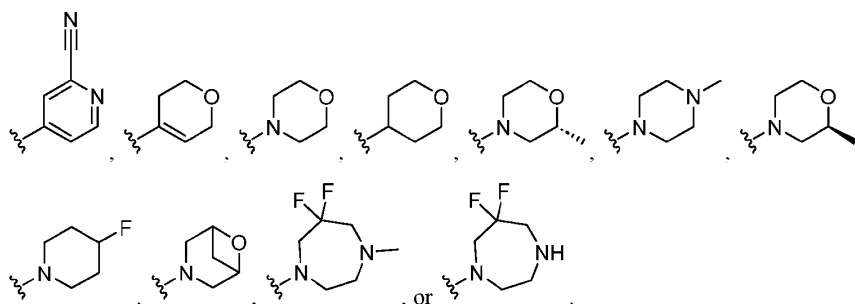


[0051] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein X² is C-R² and R² is H, halo, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CR^dR^eR^f, -CR^bR^cOR^g, -(CH₂)_mR^a, -C(O)R^b, -NR^bR^c, -O(CH₂)_mR^a, -C(O)NR^bR^c, -C(O)OR^b, -C(O)O_n(CH₂)_mR^a, -CH₂C(O)NR^bR^c, -CR^bR^cNR^gR^h, -NR^b(CH₂)_mOR^c, -NR^bCR^gR^h, -(CH₂)_mNR^bC(O)R^c, -(CH₂)_mNR^bC(O)Rⁿ, -CR^bR^c(CH₂)_mO(CH₂)_oCR^gR^h, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)NR^gR^h, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)OR^g, -CR^bR^c(CH₂)_mO(CH₂)_oR^d, -CR^bR^cC(R^d)(R^e)(R^f), -CR^bR^cNR^gC(O)CR^hRⁱR^j, -N=S(O)(R^l)(R^m), -SR^b, -S(O)(=NR^b)(R^l), -S(O)₂R^l, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -CH₂OH, -C(O)NR^bR^c. In other embodiments, X² is C-R², and R² is H, -OH, -CN, -Br, -Cl, -F, -CH₃, -OCH₃, -OCHF₂, -CH₂CH₃, -CH₂OH, -CH₂OCH₃, -CH₂CH(CH₃)₂, -CH₂CH(CH₃)OH, -CH₂CH₂OCH₃, -CH₂CH₂OH, -CH₂NH₂, -CH(CH₃)CH₂OCH₃, -CH(CH₃)CH₂OH, -CH(CH₃)₂, -CH(CH₃)CH₂OH, -CH(CH₃)N(H)CH₃, -CH(CH₃)OCH₃, -CH(OH)CH₃, -CH₂N(CH₃)₂, -OCH(CH₃)₂, -OCH₂CH₂OH, -C(OH)(CH₃)₂, -C(OCH₃)(CH₃)₂, -C(O)CH₃, -C(O)N(CH₃)₂, -C(O)N(H)CH₃, -C(O)OCH₂CH₂N(CH₃)₂, -C(O)OCH₂CH₂OH, -C(O)OCH₂CH₃, -C(O)OCH₃, -CH(CH₃)CH₂OCH₂C(CH₃)₂OH, -CH(CH₃)CH₂OCH₂C(O)NH₂, -CH(CH₃)CH₂OCH₂C(O)OCH₂CH₃, -CH(CH₃)CH₂OCH₂CH₂OH, -CH(CH₃)N(H)C(O)CH(CH₃)NH₂, -CH₂C(O)N(H)CH₃, -CH₂C(O)NH₂, -CH₂N(CH₃)C(O)CH(CH₃)N(CH₃)₂, -CH₂N(CH₃)C(O)CH(CH₃)N(H)CH₃, -CH₂N(H)C(O)CH(CH₃)₂, -CH₂N(H)C(O)CH(CH₃)NH₂, -CH₂N(H)C(O)CH₃, -N(CD₃)₂, -N(CH₃)₂, -N(CH₃)C(O)CH₃, -N(CH₃)C(O)-cyclopropyl, -N(CH₃)CH₂CH₂OCH₃, -N(CH₃)CH₂CH₂OH, -N(CH₃)₂, -N(H)CH₃, -N=S(O)(CH₃)₂, -S(CH₃), -S(O)(CH₃)=NCH₃,



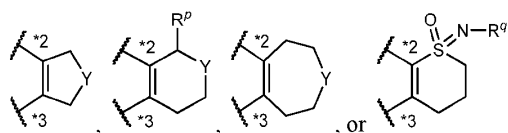
X^2 is C-R^2 , and R^2 is H, $-\text{OH}$, $-\text{CN}$, $-\text{Br}$, $-\text{Cl}$, $-\text{F}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{OCHF}_2$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OH}$,
 $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{NH}_2$,
 $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CHOH}$, $-\text{CH}(\text{CH}_3)\text{N}(\text{H})\text{CH}_3$,
 $-\text{CH}(\text{CH}_3)\text{OCH}_3$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{OH})(\text{CH}_3)_2$,
 $-\text{C}(\text{OCH}_3)(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$,
 $-\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{CH}_3)_2\text{OH}$,
 $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$,
 $-\text{CH}(\text{CH}_3)\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$,
 $-\text{CH}_2\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{N}(\text{H})\text{CH}_3$,
 $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{NH}_2$,
 $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})$ -1-methylpyrrolidine, $-\text{N}(\text{CD}_3)_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}_3$,
 $-\text{N}(\text{CH}_3)\text{C}(\text{O})$ -cyclopropyl, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{H})\text{CH}_3$,
 $-\text{N}=\text{S}(\text{=O})(\text{CH}_3)_2$, $-\text{S}(\text{CH}_3)$, $-\text{S}(\text{O})(\text{CH}_3)\text{NCH}_3$, $-\text{S}(\text{=O})(=\text{NH})(\text{CH}_3)$, $-\text{S}(\text{=O})_2\text{CH}(\text{CH}_3)_2$, $-\text{S}(\text{=O})_2\text{CH}_3$,



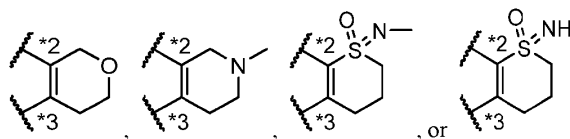


[0052] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein R³ is H, C₁-C₆ alkyl, or -(CH₂)_mOCH₃. In other embodiments, R³ is H, -CH₃, or -(CH₂)OCH₃.

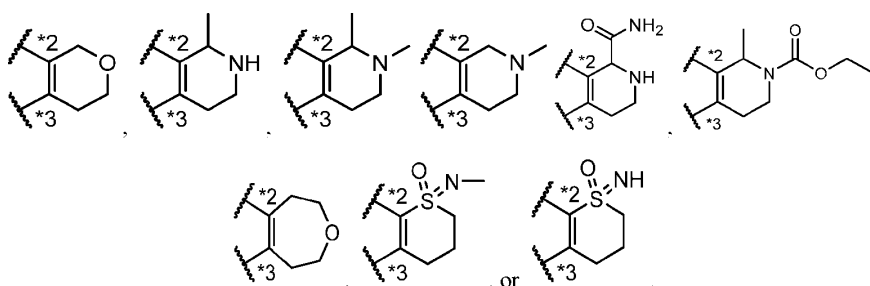
[0053] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-I), or a pharmaceutically acceptable salt thereof, wherein X^2 is CR^2 , and R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



In other embodiments, R² and R³, together with the carbon atoms to which they are attached, form a ring of formula:



In other embodiments, R² and R³, together with the carbon atoms to which they are attached, form a ring of formula:



[0054] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-I), or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

[0055] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein R^5 is H, C₁-C₆ alkyl, or C₁-C₆ alkoxy. In other embodiments, R^5 is H, -CH₃, -OCH₃.

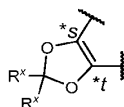
[0056] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are each independently H, C₁-C₆ alkyl, C₁-C₆ haloalkyl, or C₃-C₆ cycloalkyl, or R^6 and R^7 , together with the carbon atom to which they are attached, form a C₃-C₆ cycloalkyl. In other embodiments, R^6 is C₁-C₆ haloalkyl. In other embodiments, R^6 is -CF₃. In other embodiments, R^7 is H or C₁-C₆ alkyl. In other embodiments, R^7 is H or -CH₃.

[0057] In some embodiments, the invention relates to a compound of formula (I-A), or a pharmaceutically acceptable salt thereof, wherein R^8 is H.

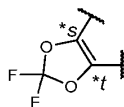
[0058] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein X^s is C-R^s, and R^s is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, or -O(CH₂)_mOCH₃. In other embodiments, X^s is C-R^s, and R^s is -CH₃, -OCH₃, -OCH(CH₃)₂, -OCH(F)₂, -OCH₂CH₂OCH₃, or -OCH₂CH₃.

[0059] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein X^t is N. In other embodiments, X^t is C-R^t, and R^t is H, halo, or C₁-C₆ haloalkyl. In other embodiments, X^t is C-R^t, and R^t is H, Cl, F, -CH₃, or -CF₃.

[0060] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein X^s is C-R^s, X^t is C-R^t, and R^s and R^t , together with the carbon atoms to which they are attached, form a ring of formula:



In other embodiments, R^s and R^t , together with the carbon atoms to which they are attached, form a ring of formula:

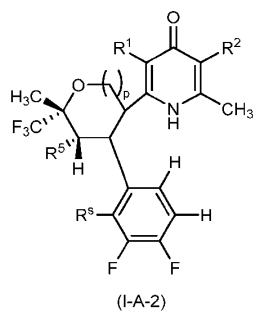


[0061] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein R^u is H, halo, C₁-C₆ alkoxy, or C₁-C₆ haloalkoxy. In other embodiments, R^u is H, F, -OCH₂CH₃, or -OCHF₂.

[0062] In some embodiments, the invention relates to a compound of formula (I-A) or (I-A-1), or a pharmaceutically acceptable salt thereof, wherein R^v is H or -NR^bR^c. In other embodiments, R^v is H or -NH₂.

[0063] In some embodiments, the invention relates to a compound of formula (I-A), or a pharmaceutically acceptable salt thereof, wherein R^w is H.

[0064] In some embodiments, the invention relates to a compound of formula (I-A-2):

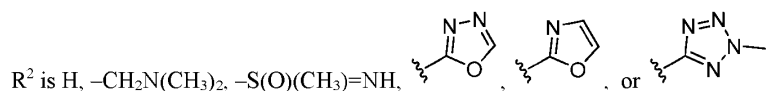


or a pharmaceutically acceptable salt thereof, wherein all variable groups are defined as they are defined for the compound of formula (I-A).

[0065] In some embodiments, the invention relates to a compound of formula (I-A), (I-A-1), or (I-A-2), or a pharmaceutically acceptable salt thereof, wherein R^1 is H or 5-6 membered heteroaryl, wherein said 5-6 membered heteroaryl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo and C_1 - C_6 alkyl. In other embodiments, R^1 is H or



[0066] In some embodiments, the invention relates to a compound of formula (I-A), (I-A-1), or (I-A-2), or a pharmaceutically acceptable salt thereof, wherein R^2 is H, $-CR^bR^cNR^eR^h$, $-S(=O)(=NR^b)(R^f)$, or 5-6 membered heteroaryl, wherein said 5-6 membered heteroaryl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, $-CH_2OH$, and $-C(O)NR^bR^c$. In other embodiments,

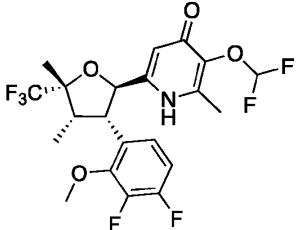
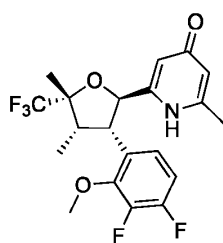
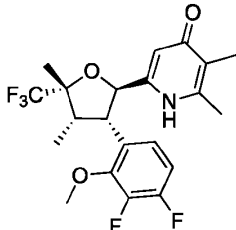
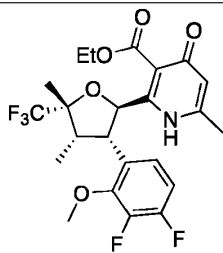
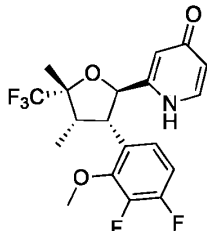
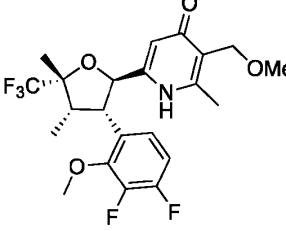


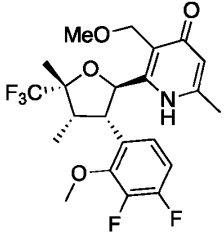
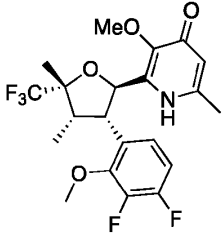
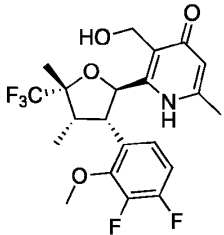
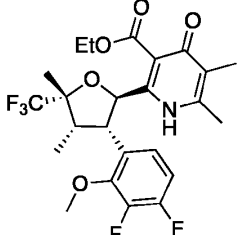
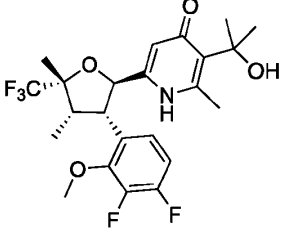
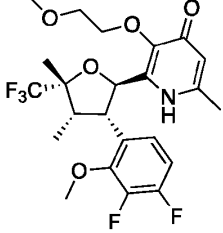
[0067] In some embodiments, the invention relates to a compound of formula (I-A), (I-A-1), or (I-A-2), or a pharmaceutically acceptable salt thereof, wherein R^5 is H, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy. In other embodiments, R^5 is H, $-CH_3$, or $-OCH_3$.

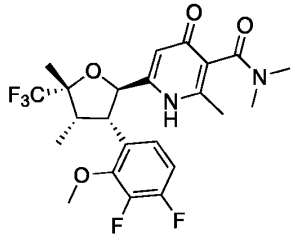
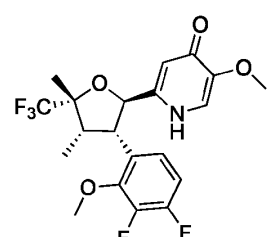
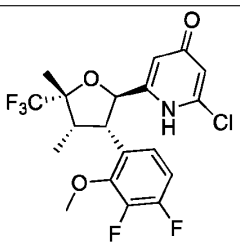
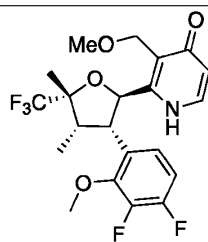
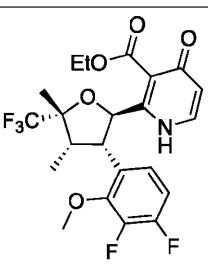
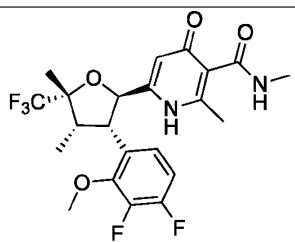
[0068] In some embodiments, the invention relates to a compound of formula (I-A), (I-A-1), or (I-A-2), or a pharmaceutically acceptable salt thereof, wherein R^5 is C_1 - C_6 alkyl or C_1 - C_6 alkoxy. In other embodiments, R^5 is $-CH_3$ or $-OCH_3$.

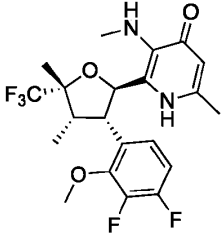
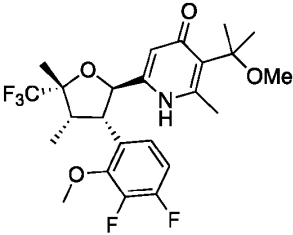
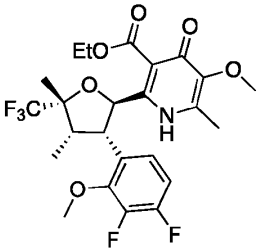
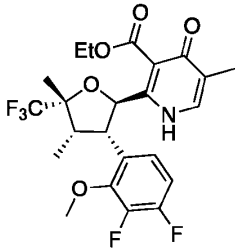
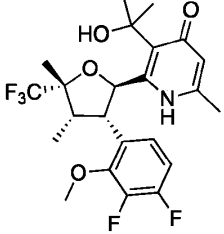
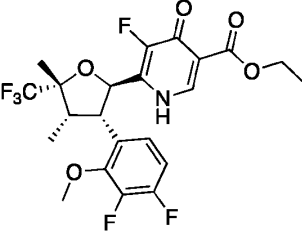
[0069] In some embodiments, the invention relates to a compound selected from Table A, or a pharmaceutically acceptable salt thereof. In other embodiments, the invention relates to a compound selected from Table A, i.e., the compound in non-salt form.

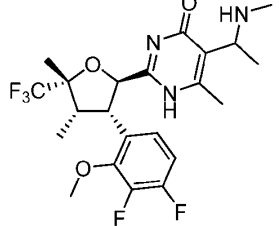
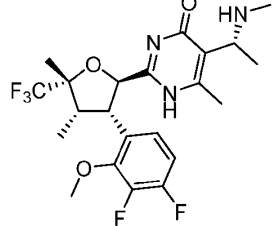
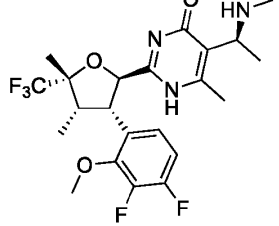
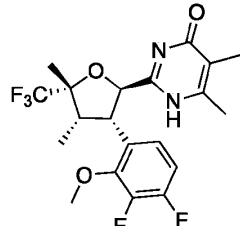
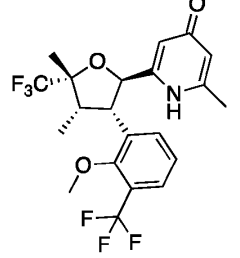
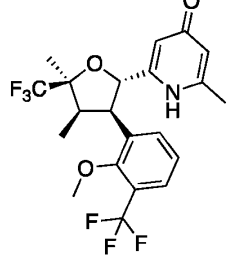
[0070] **Table A.** Compound Structures and Names.

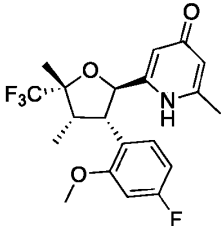
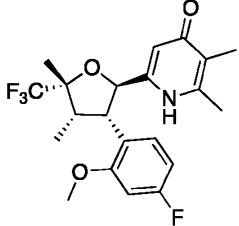
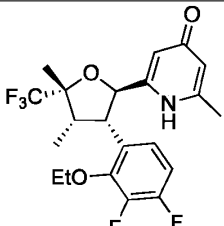
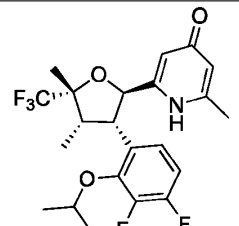
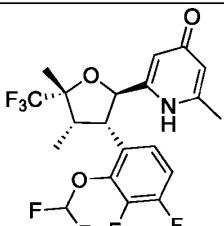
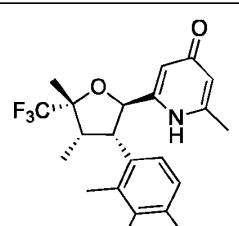
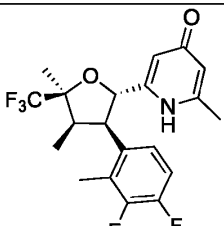
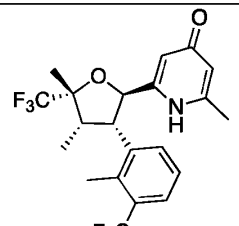
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2,3-dimethylpyridin-4(1<i>H</i>)-one	 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(methoxymethyl)-2-methylpyridin-4(1<i>H</i>)-one

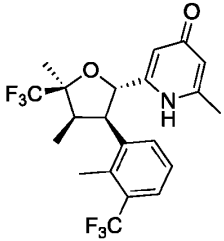
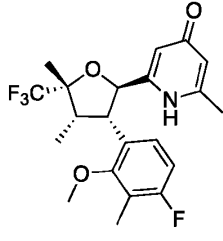
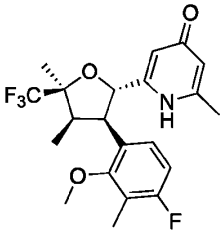
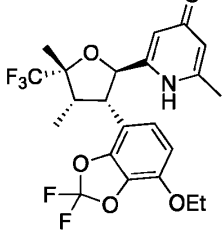
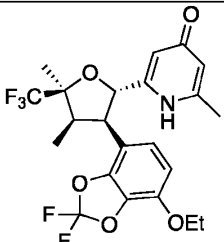
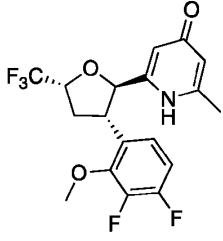
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(methoxymethyl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxy-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(hydroxymethyl)-6-methylpyridin-4(1<i>H</i>)-one	 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-hydroxypropan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-methoxyethoxy)-6-methylpyridin-4(1<i>H</i>)-one

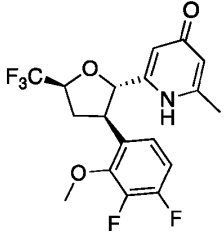
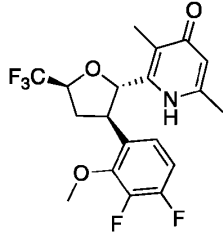
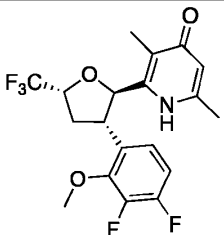
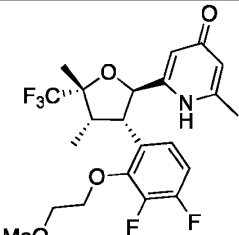
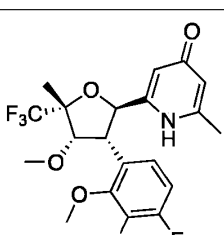
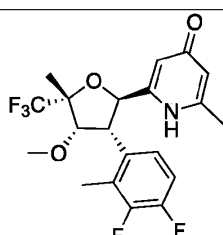
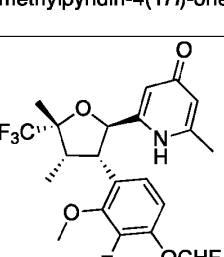
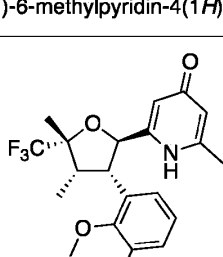
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N,N</i>,2-trimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxypyridin-4(1<i>H</i>)-one
 2-chloro-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)pyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(methoxymethyl)pyridin-4(1<i>H</i>)-one
 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N</i>,2-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide

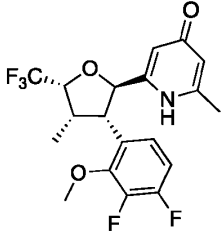
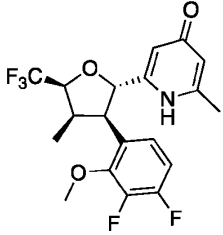
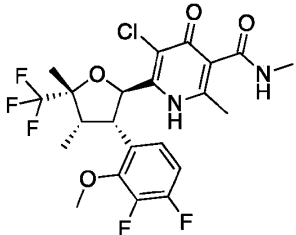
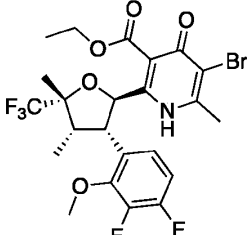
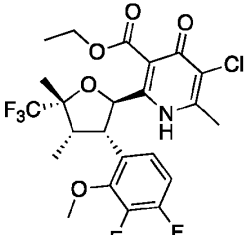
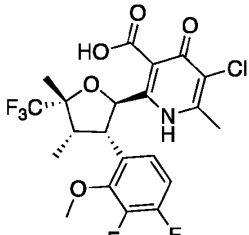
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(methylamino)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-methoxypropan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one
 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-hydroxypropan-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 ethyl 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-4-oxo-1,4-dihydropyridine-3-carboxylate

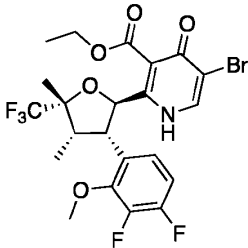
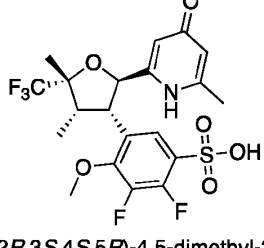
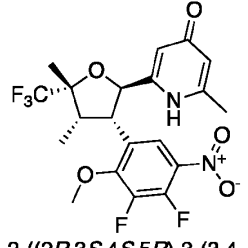
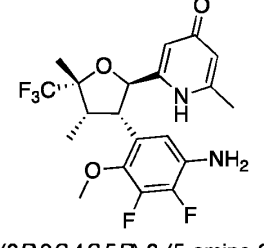
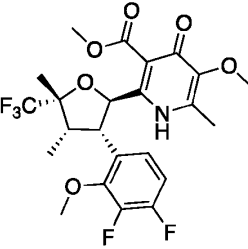
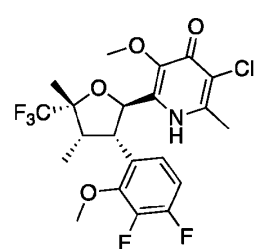
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(1-(methylamino)ethyl)pyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-((<i>R</i>)-1-(methylamino)ethyl)pyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-((<i>S</i>)-1-(methylamino)ethyl)pyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5,6-dimethylpyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(2-methoxy-3-(trifluoromethyl)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(2-methoxy-3-(trifluoromethyl)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one

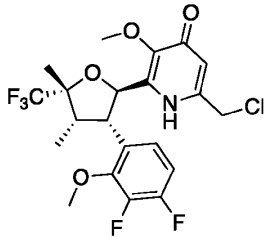
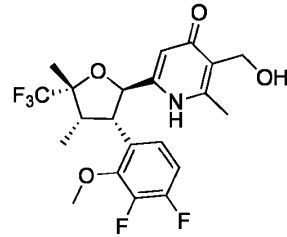
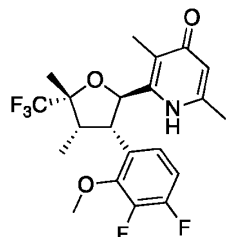
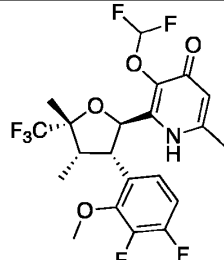
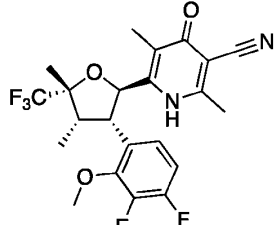
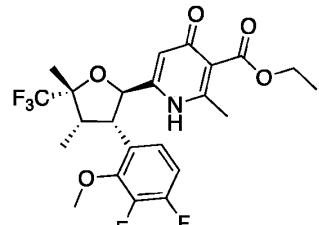
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(4-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(4-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2,3-dimethylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(2-ethoxy-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-isopropoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(2-(difluoromethoxy)-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-4,5-dimethyl-3-(2-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one

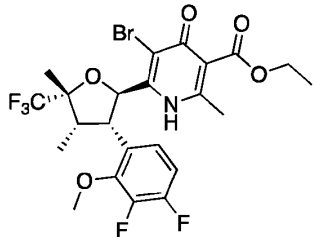
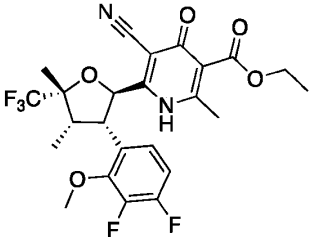
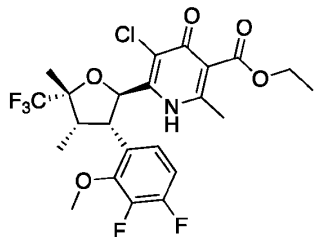
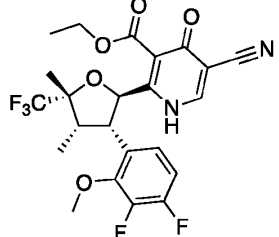
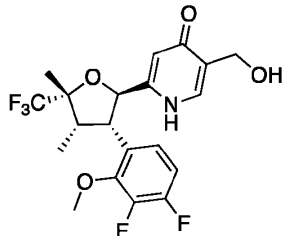
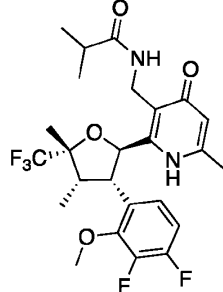
 2-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-4,5-dimethyl-3-(2-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(7-ethoxy-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(7-ethoxy-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one

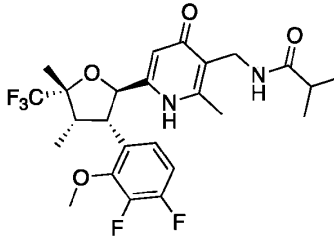
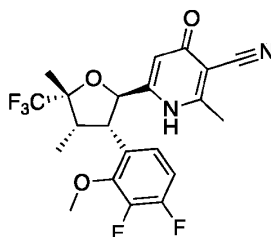
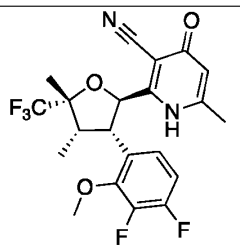
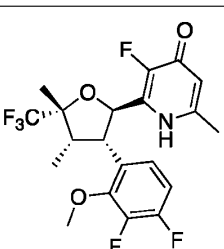
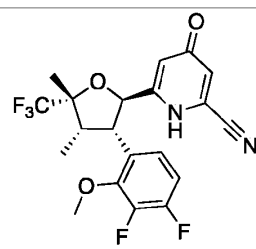
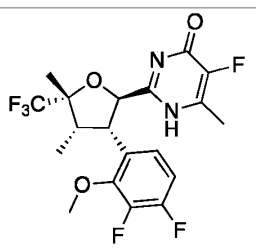
 2-((2<i>S</i>,3<i>R</i>,5<i>S</i>)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>S</i>,3<i>R</i>,5<i>S</i>)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,6-dimethylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,6-dimethylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(4-(difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one

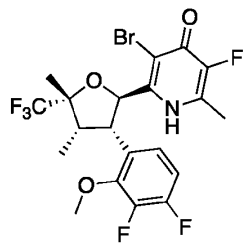
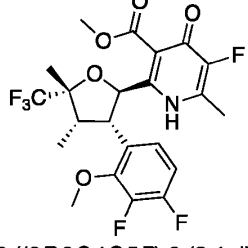
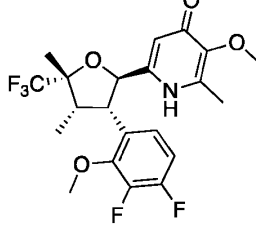
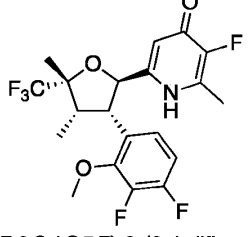
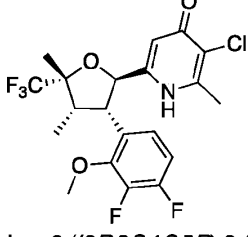
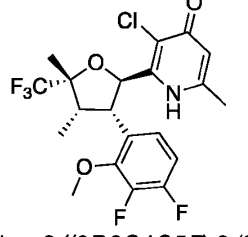
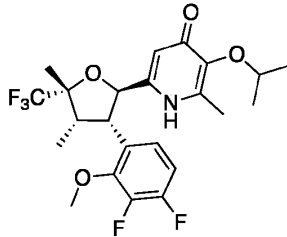
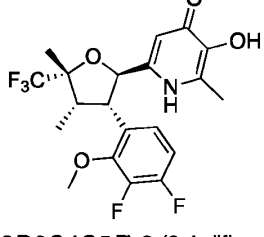
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 5-chloro-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N</i>,2-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide	 ethyl 5-bromo-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate
 ethyl 5-chloro-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 5-chloro-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid

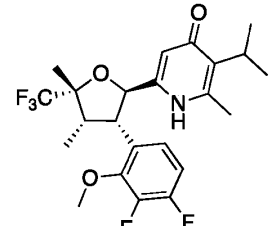
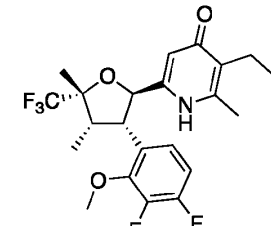
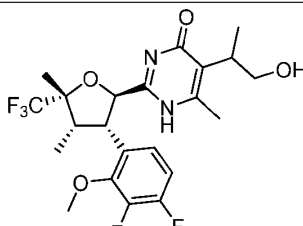
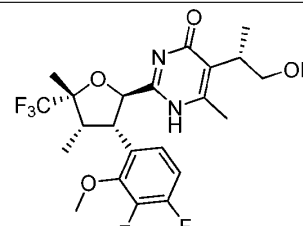
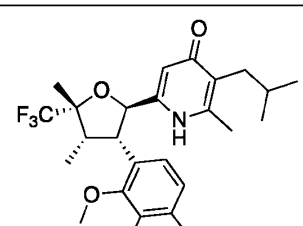
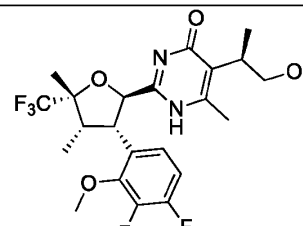
 ethyl 5-bromo-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate	 5-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-4,5-dimethyl-2-(6-methyl-4-oxo-1,4-dihydropyridin-2-yl)-5-(trifluoromethyl)tetrahydrofuran-3-yl)-2,3-difluoro-4-methoxybenzenesulfonic acid
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxy-5-nitrophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(5-amino-3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 methyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 3-chloro-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-2-methylpyridin-4(1<i>H</i>)-one

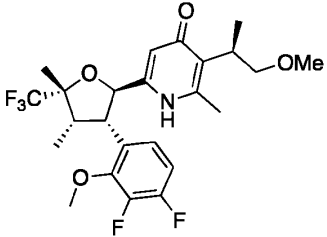
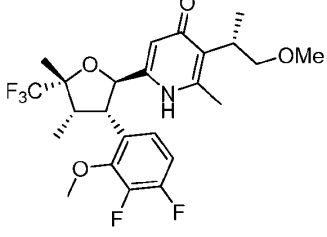
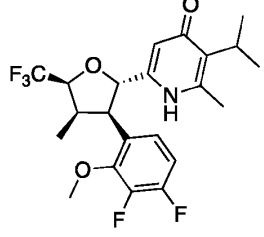
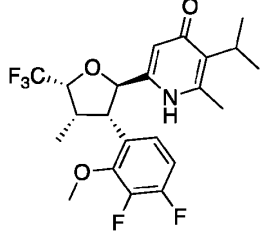
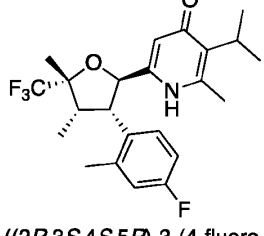
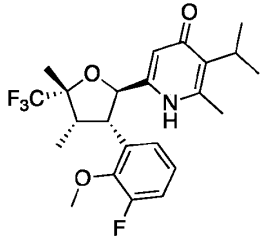
 6-(chloromethyl)-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxypyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(hydroxymethyl)-2-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,6-dimethylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-6-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2,5-dimethyl-4-oxo-1,4-dihydropyridine-3-carbonitrile	 ethyl 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate

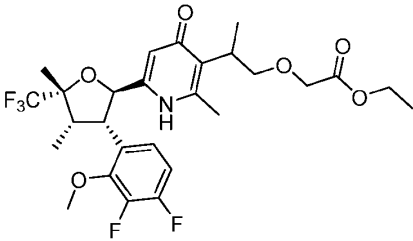
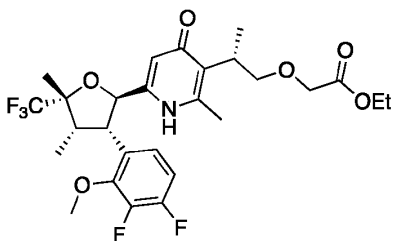
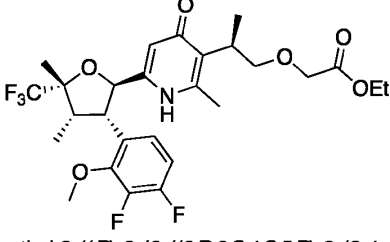
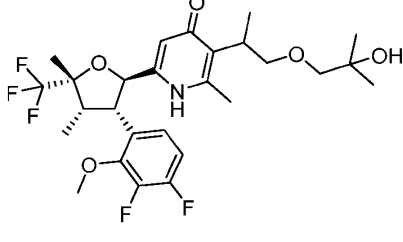
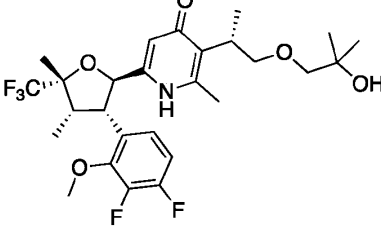
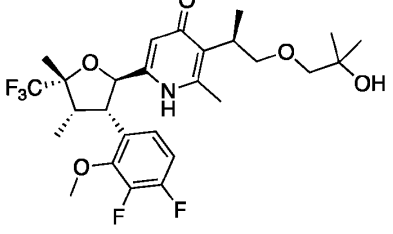
 ethyl 5-bromo-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 ethyl 5-cyano-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate
 ethyl 5-chloro-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 ethyl 5-cyano-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(hydroxymethyl)pyridin-4(1<i>H</i>)-one	 <i>N</i>-((2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)isobutyramide

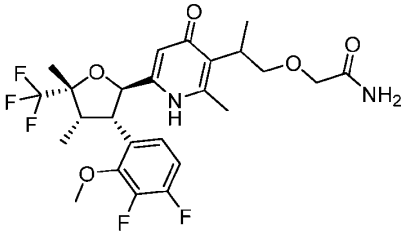
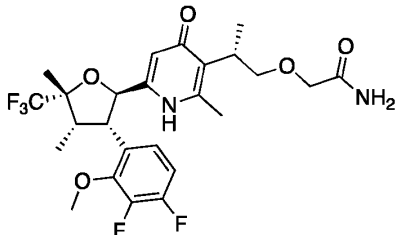
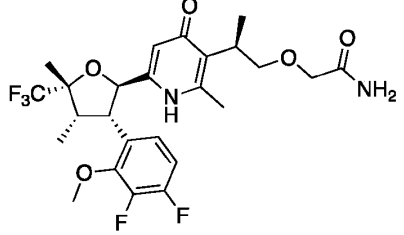
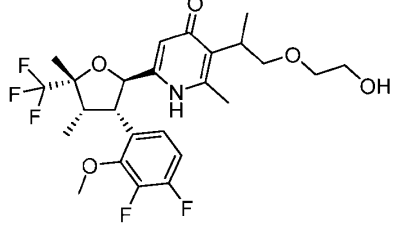
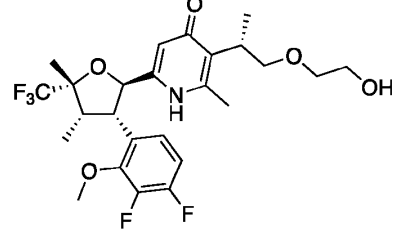
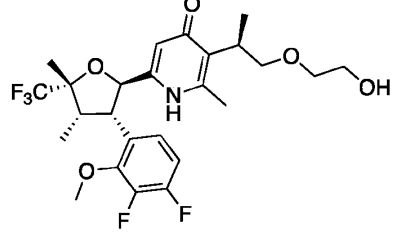
 <i>N</i>-((6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)isobutyramide	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carbonitrile
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carbonitrile	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-fluoro-6-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-2-carbonitrile	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methylpyrimidin-4(1<i>H</i>)-one

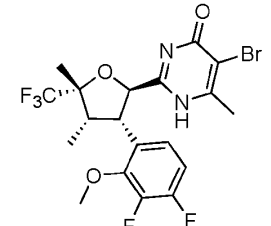
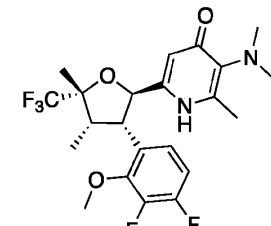
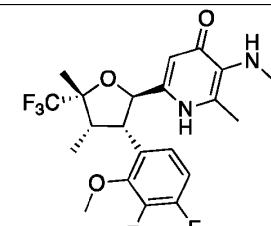
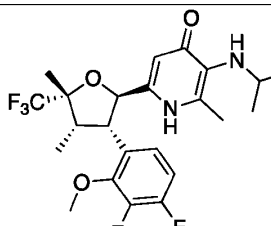
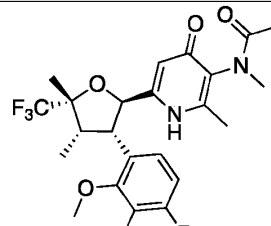
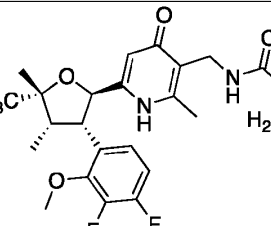
 3-bromo-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methylpyridin-4(1<i>H</i>)-one	 methyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxy-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-fluoro-2-methylpyridin-4(1<i>H</i>)-one
 3-chloro-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 3-chloro-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropoxy-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-hydroxy-2-methylpyridin-4(1<i>H</i>)-one

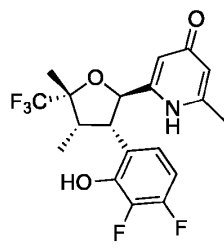
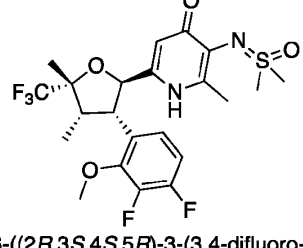
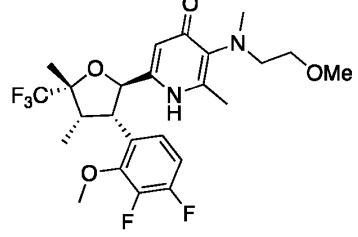
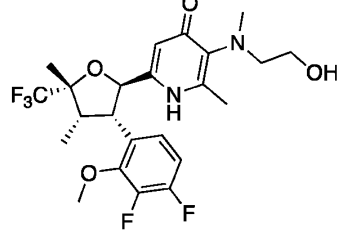
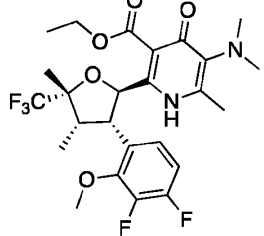
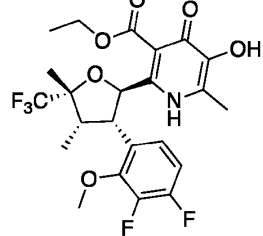
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-ethyl-2-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>S</i>)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isobutyl-2-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>R</i>)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one

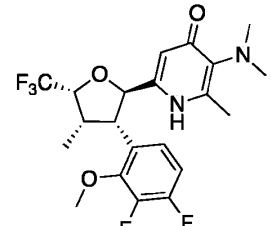
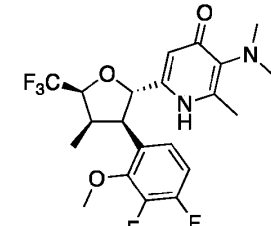
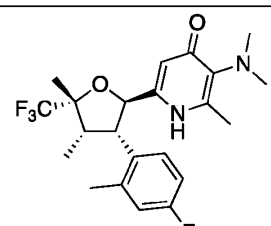
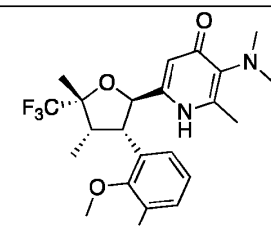
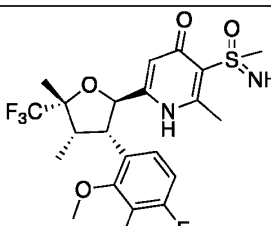
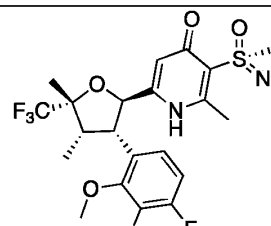
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>R</i>)-1-methoxypropan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-1-methoxypropan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(4-fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1<i>H</i>)-one

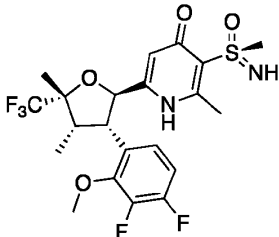
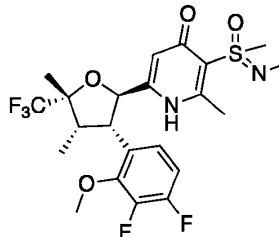
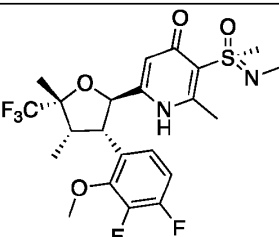
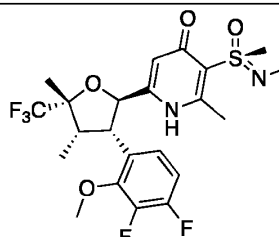
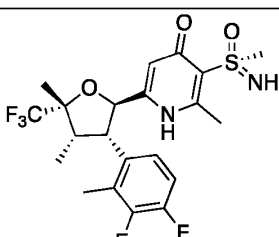
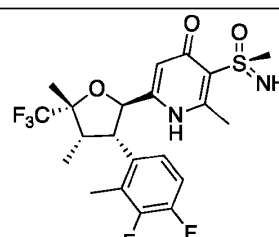
 ethyl 2-((<i>R</i>)-2-(6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetate	 ethyl 2-((<i>S</i>)-2-(6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetate
 ethyl 2-((<i>R</i>)-2-(6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetate	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-(2-hydroxy-2-methylpropoxy)propan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-1-(2-hydroxy-2-methylpropoxy)propan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>R</i>)-1-(2-hydroxy-2-methylpropoxy)propan-2-yl)-2-methylpyridin-4(1<i>H</i>)-one

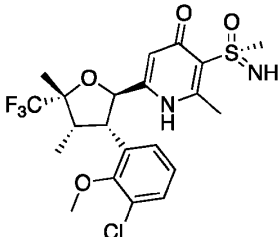
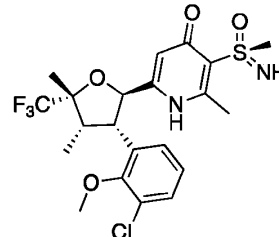
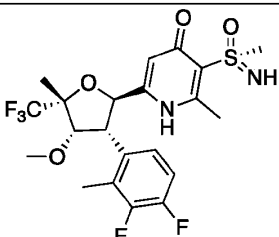
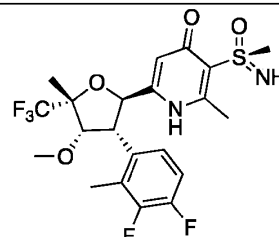
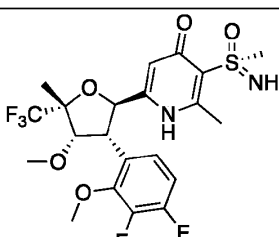
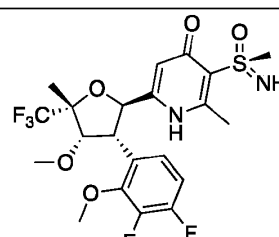
 2-(2-(6-((2R,3S,4S,5R)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetamide	 2-((S)-2-(6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetamide
 2-((R)-2-(6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetamide	 6-((2R,3S,4S,5R)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-(2-hydroxyethoxy)propan-2-yl)-2-methylpyridin-4(1H)-one
 6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((S)-1-(2-hydroxyethoxy)propan-2-yl)-2-methylpyridin-4(1H)-one	 6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((R)-1-(2-hydroxyethoxy)propan-2-yl)-2-methylpyridin-4(1H)-one

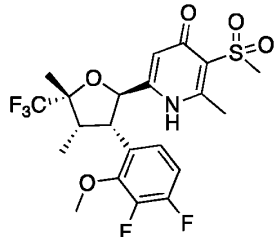
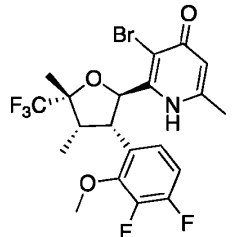
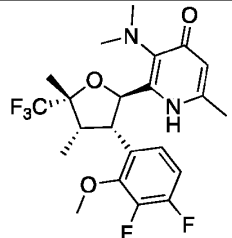
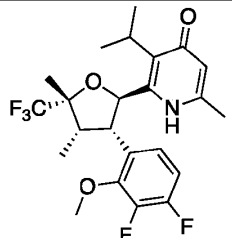
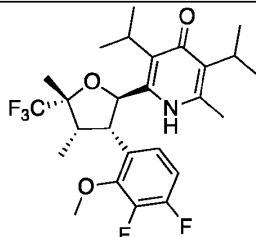
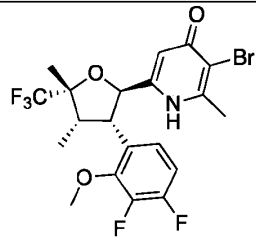
 5-bromo-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylamino)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(isopropylamino)-2-methylpyridin-4(1<i>H</i>)-one
 <i>N</i>-(6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)-<i>N</i>-methylacetamide	 (<i>R</i>)-2-amino-<i>N</i>-((6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide

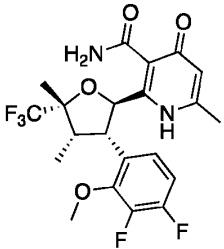
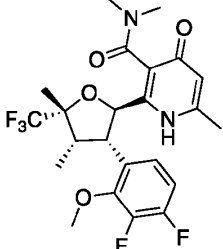
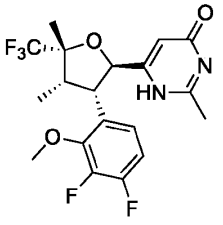
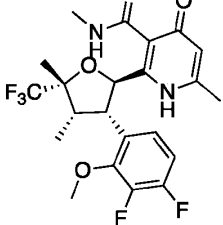
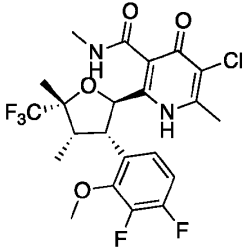
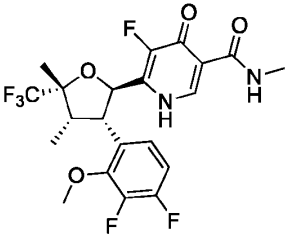
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((dimethyl(oxo)-λ⁶-sulfaneylidene)amino)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((2-methoxyethyl)(methyl)amino)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((2-hydroxyethyl)(methyl)amino)-2-methylpyridin-4(1<i>H</i>)-one
 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(dimethylamino)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-hydroxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate

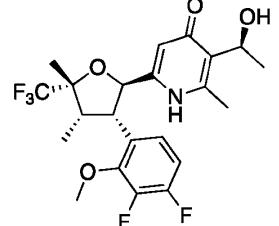
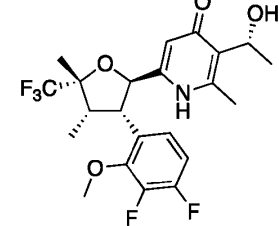
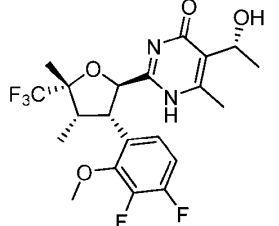
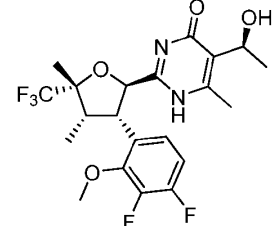
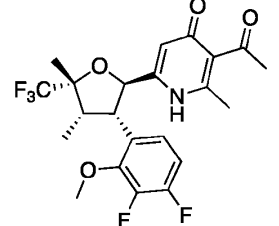
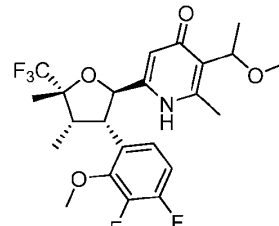
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>S</i>,3<i>R</i>,4<i>R</i>,5<i>S</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-2-methylpyridin-4(1<i>H</i>)-one
 3-(dimethylamino)-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(4-fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 3-(dimethylamino)-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one

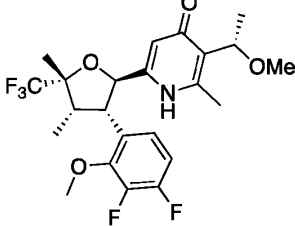
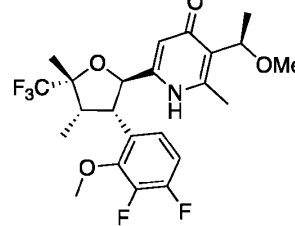
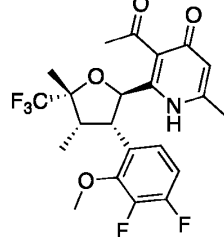
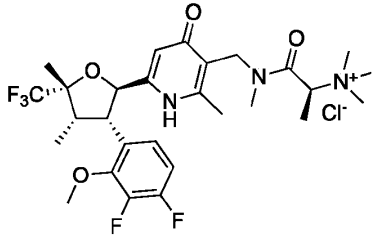
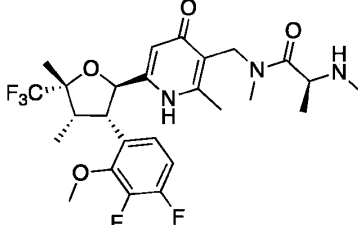
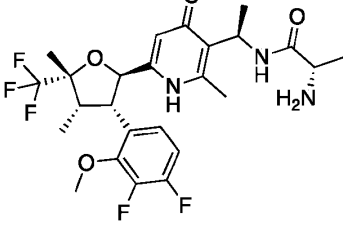
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(<i>N</i>,<i>S</i>-dimethylsulfonimidoyl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>R</i>)-<i>N</i>,<i>S</i>-dimethylsulfonimidoyl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-<i>N</i>,<i>S</i>-dimethylsulfonimidoyl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one

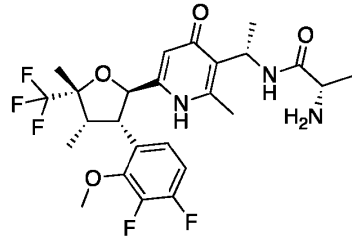
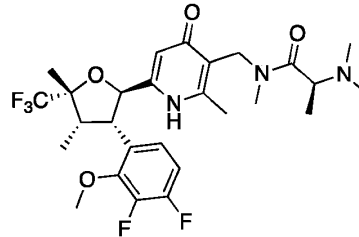
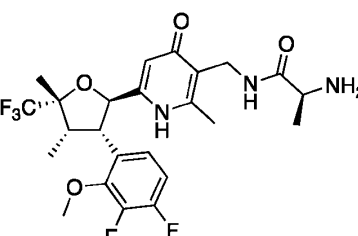
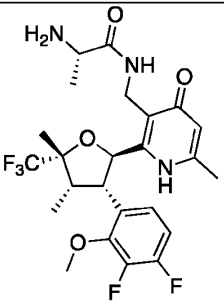
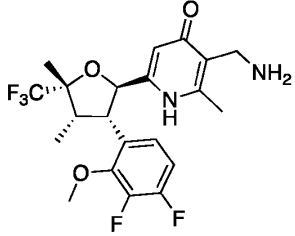
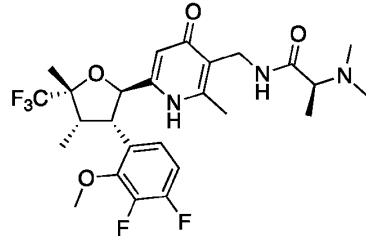
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one

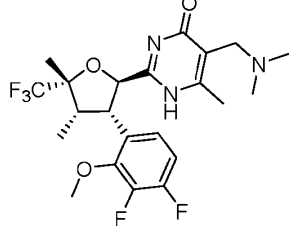
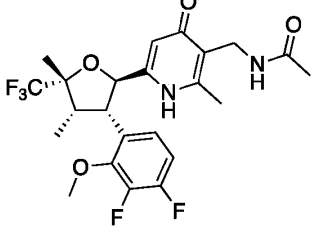
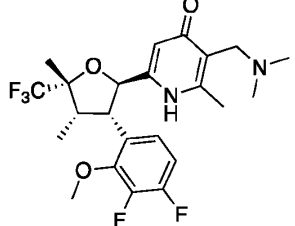
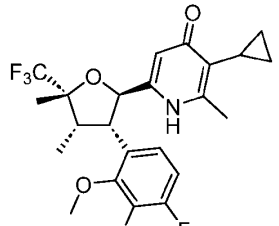
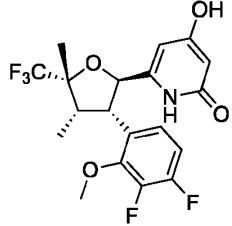
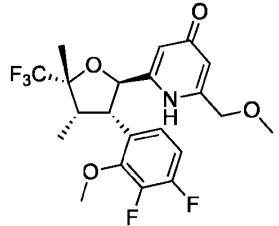
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylsulfonyl)pyridin-4(1<i>H</i>)-one	 3-bromo-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-6-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,5-diisopropyl-6-methylpyridin-4(1<i>H</i>)-one	 3-bromo-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one

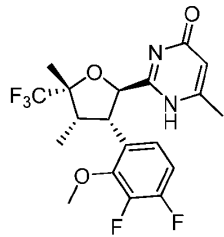
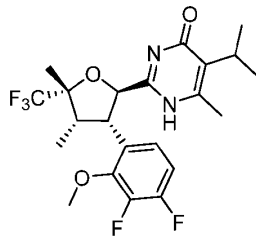
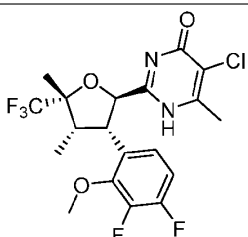
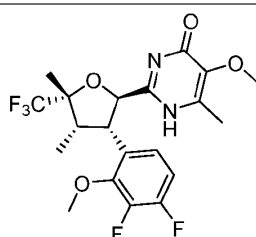
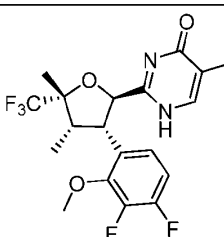
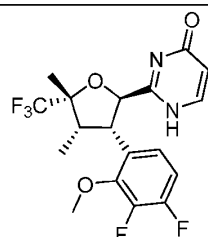
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N,N</i>,6-trimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N</i>,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide
 5-chloro-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N</i>,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-<i>N</i>-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide

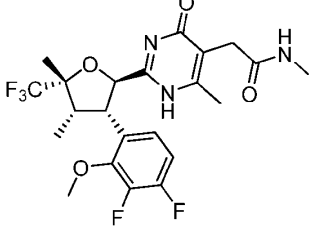
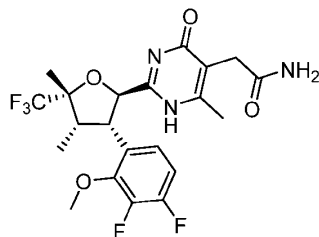
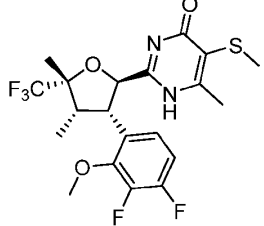
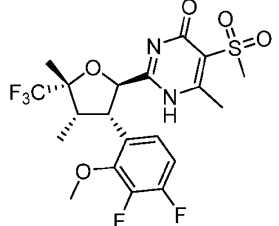
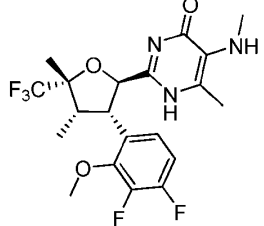
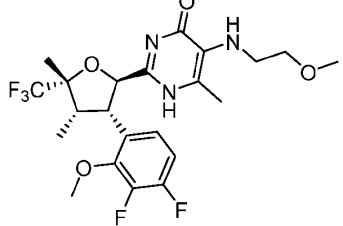
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-1-hydroxyethyl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>R</i>)-1-hydroxyethyl)-2-methylpyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>R</i>)-1-hydroxyethyl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>S</i>)-1-hydroxyethyl)-6-methylpyrimidin-4(1<i>H</i>)-one
 3-acetyl-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-methoxyethyl)-2-methylpyridin-4(1<i>H</i>)-one

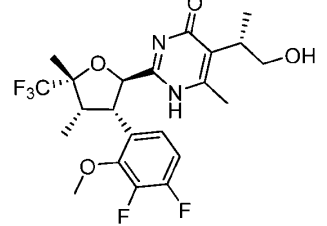
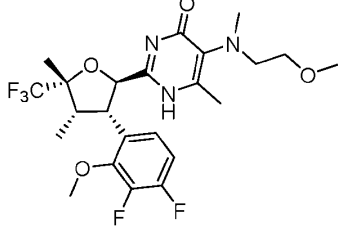
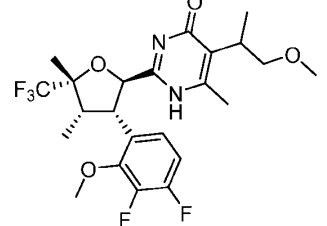
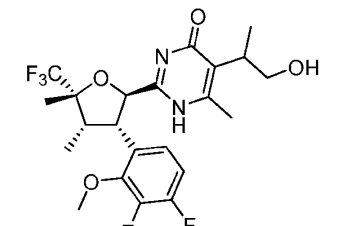
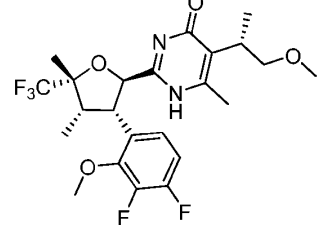
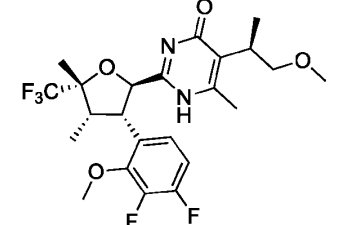
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-1-methoxyethyl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>R</i>)-1-methoxyethyl)-2-methylpyridin-4(1<i>H</i>)-one
 3-acetyl-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 (<i>S</i>)-1-(((6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)(methyl)amino)-<i>N,N,N</i>-trimethyl-1-oxopropan-2-aminium chloride
 (<i>S</i>)-<i>N</i>-(((6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-<i>N</i>-methyl-2-(methylamino)propanamide	 (<i>S</i>)-2-amino-<i>N</i>-((<i>R</i>)-1-(6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)ethyl)propanamide

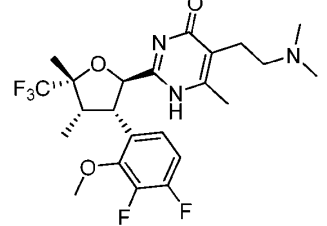
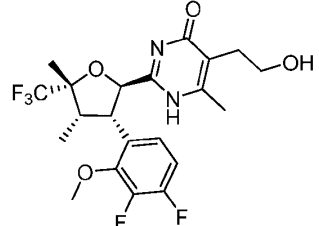
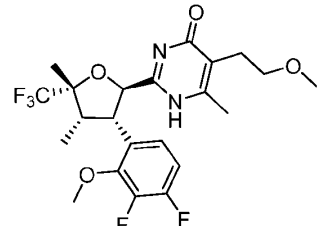
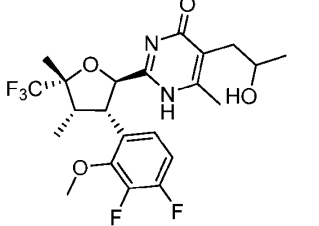
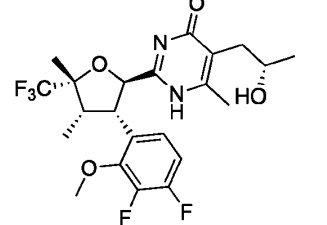
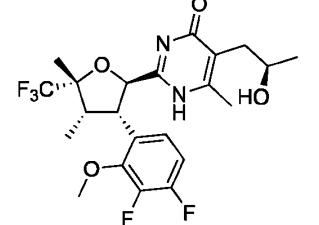
 (S)-2-amino-N-((S)-1-(6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)ethyl)propanamide	 (S)-N-((6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-2-(dimethylamino)-N-methylpropanamide
 (S)-2-amino-N-((6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide	 (S)-2-amino-N-((2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide
 3-(aminomethyl)-6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1H)-one	 (S)-N-((6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-2-(dimethylamino)propanamide

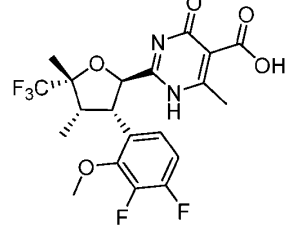
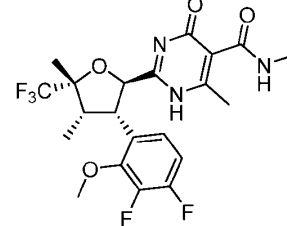
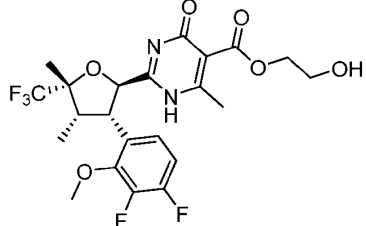
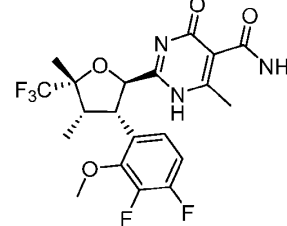
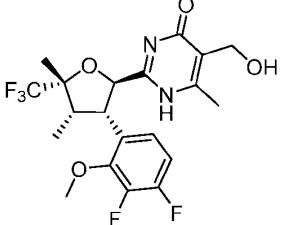
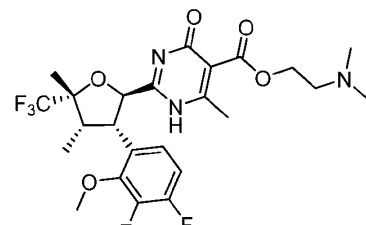
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((dimethylamino)methyl)-6-methylpyrimidin-4(1<i>H</i>)-one	 <i>N</i>-((6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)acetamide
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((dimethylamino)methyl)-2-methylpyridin-4(1<i>H</i>)-one	 3-cyclopropyl-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-hydroxypyridin-2(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-(methoxymethyl)pyridin-4(1<i>H</i>)-one

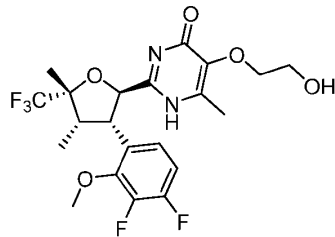
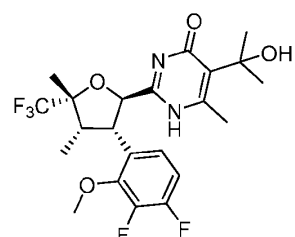
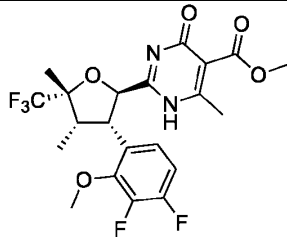
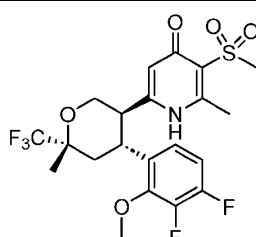
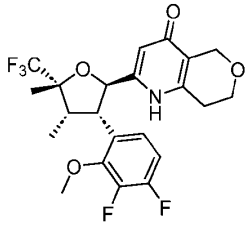
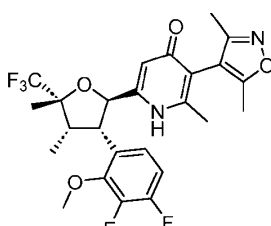
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-isopropyl-6-methylpyrimidin-4(1<i>H</i>)-one
 5-chloro-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methylpyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)pyrimidin-4(1<i>H</i>)-one

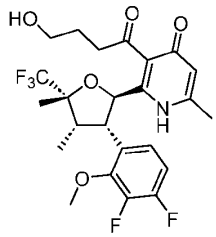
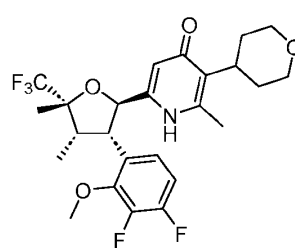
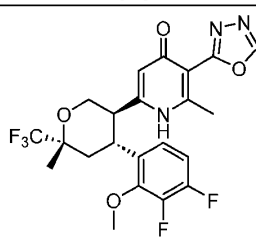
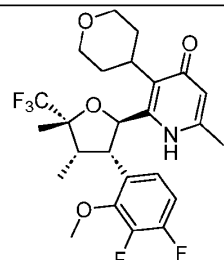
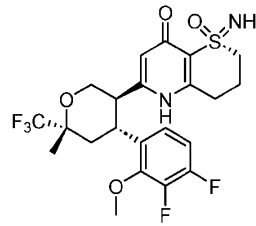
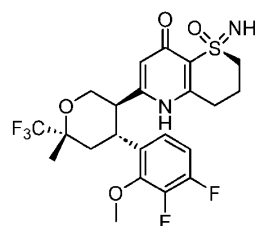
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidin-5-yl)-<i>N</i>-methylacetamide	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidin-5-yl)acetamide
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylthio)pyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylsulfonyl)pyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylamino)pyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((2-methoxyethyl)amino)-6-methylpyrimidin-4(1<i>H</i>)-one

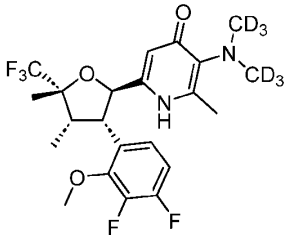
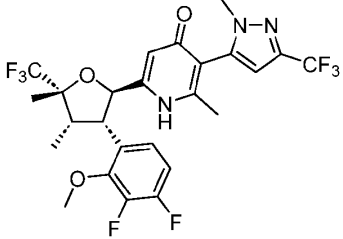
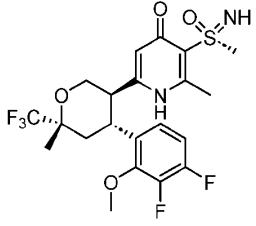
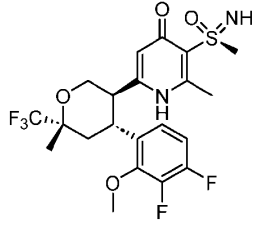
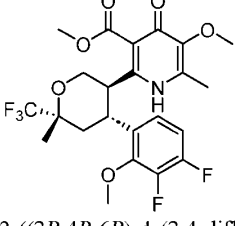
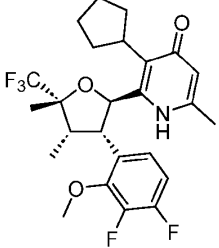
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>S</i>)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((2-methoxyethyl)(methyl)amino)-6-methylpyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-methoxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>S</i>)-1-methoxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>R</i>)-1-methoxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one

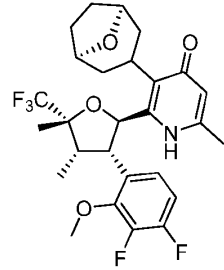
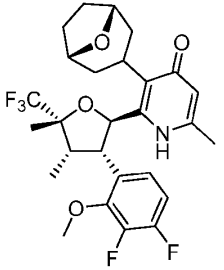
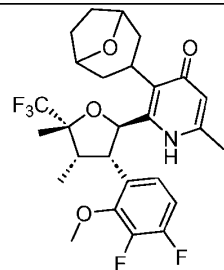
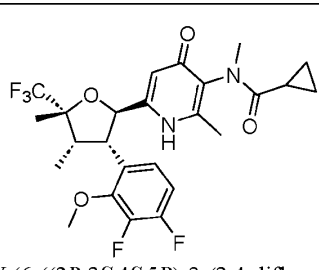
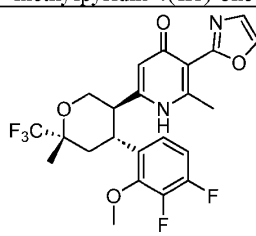
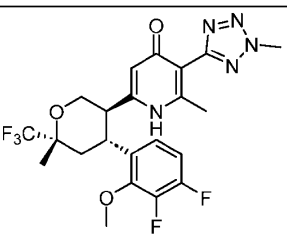
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-(dimethylamino)ethyl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxyethyl)-6-methylpyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-methoxyethyl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxypropyl)-6-methylpyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>S</i>)-2-hydroxypropyl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>R</i>)-2-hydroxypropyl)-6-methylpyrimidin-4(1<i>H</i>)-one

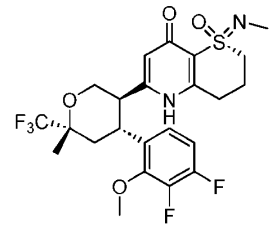
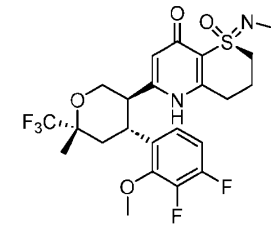
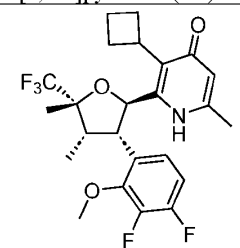
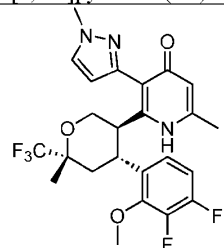
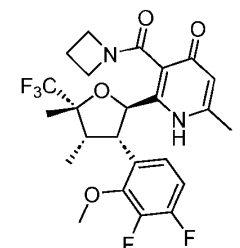
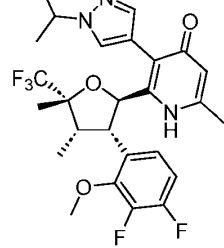
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylic acid	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-<i>N</i>,6-dimethyl-4-oxo-1,4-dihydropyrimidine-5-carboxamide
 2-hydroxyethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxamide
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(hydroxymethyl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-(dimethylamino)ethyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate

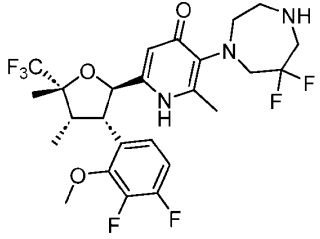
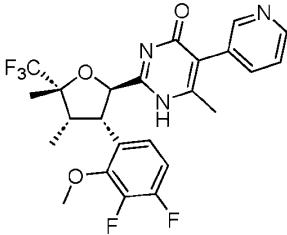
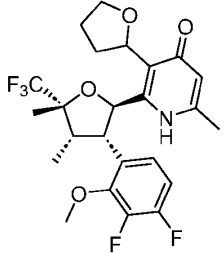
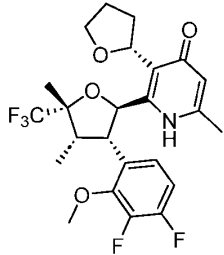
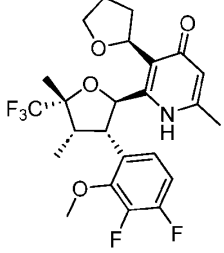
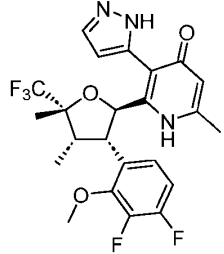
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxyethoxy)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxypropan-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one
 methyl 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate	 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-(methylsulfonyl)pyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1,5,7,8-tetrahydro-4<i>H</i>-pyrano[4,3-<i>b</i>]pyridin-4-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(3,5-dimethylisoxazol-4-yl)-2-methylpyridin-4(1<i>H</i>)-one

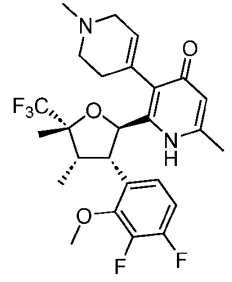
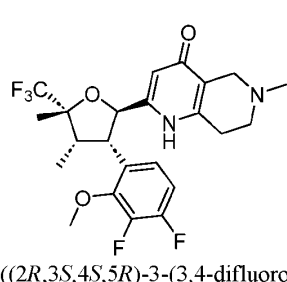
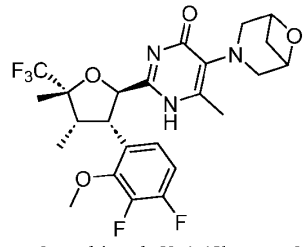
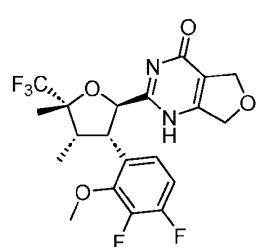
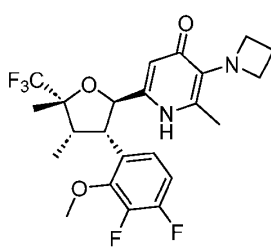
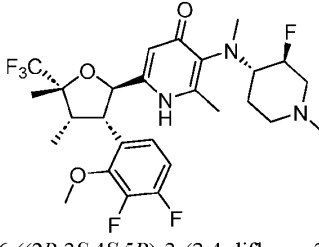
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(4-hydroxybutanoyl)-6-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(tetrahydro-2<i>H</i>-pyran-4-yl)pyridin-4(1<i>H</i>)-one
 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-(1,3,4-oxadiazol-2-yl)pyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(tetrahydro-2<i>H</i>-pyran-4-yl)pyridin-4(1<i>H</i>)-one
 (<i>R</i>)-6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-1-imino-1,3,4,5-tetrahydro-1λ^4-thiopyrano[3,2-<i>b</i>]pyridin-8(2<i>H</i>)-one 1-oxide	 (<i>S</i>)-6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-1-imino-1,3,4,5-tetrahydro-1λ^4-thiopyrano[3,2-<i>b</i>]pyridin-8(2<i>H</i>)-one 1-oxide

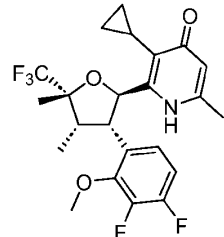
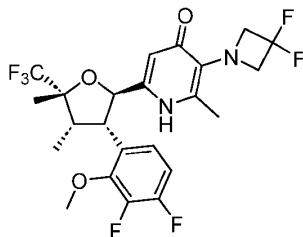
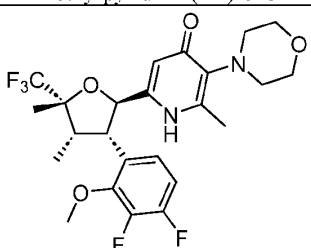
 3-(bis(methyl-d₃)amino)-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(1-methyl-3-(trifluoromethyl)-1<i>H</i>-pyrazol-5-yl)pyridin-4(1<i>H</i>)-one
 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one
 methyl 2-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	 3-cyclopentyl-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one

 3-((1R,5S)-8-oxabicyclo[3.2.1]octan-3-yl)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1H)-one	 3-((1R,5S)-8-oxabicyclo[3.2.1]octan-3-yl)-2-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1H)-one
 3-(8-oxabicyclo[3.2.1]octan-3-yl)-2-((2R*,3S*,4S*,5R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1H)-one	 N-(6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)-N-methylcyclopropanecarboxamide
 6-((3R,4R,6R)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)-2-methyl-3-(oxazol-2-yl)pyridin-4(1H)-one	 6-((3R,4R,6R)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2H-pyran-3-yl)-2-methyl-3-(2-methyl-2H-tetrazol-5-yl)pyridin-4(1H)-one

 (<i>R</i>)-6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-1-(methylimino)-1,3,4,5-tetrahydro-1λ^4-thiopyrano[3,2-<i>b</i>]pyridin-8(2<i>H</i>)-one 1-oxide	 (<i>S</i>)-6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-1-(methylimino)-1,3,4,5-tetrahydro-1λ^4-thiopyrano[3,2-<i>b</i>]pyridin-8(2<i>H</i>)-one 1-oxide
 3-cyclobutyl-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-6-methyl-3-(1-methyl-1<i>H</i>-pyrazol-3-yl)pyridin-4(1<i>H</i>)-one
 3-(azetidine-1-carbonyl)-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-isopropyl-1<i>H</i>-pyrazol-4-yl)-6-methylpyridin-4(1<i>H</i>)-one

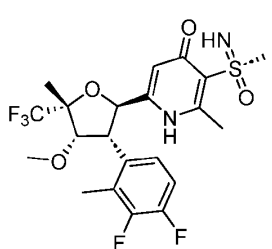
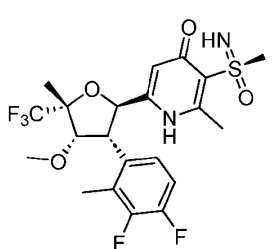
 3-(6,6-difluoro-1,4-diazepan-1-yl)-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(pyridin-3-yl)pyrimidin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(tetrahydrofuran-2-yl)pyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-((<i>R</i>)-tetrahydrofuran-2-yl)pyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-((<i>S</i>)-tetrahydrofuran-2-yl)pyridin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(1<i>H</i>-pyrazol-5-yl)pyridin-4(1<i>H</i>)-one

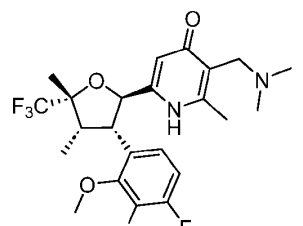
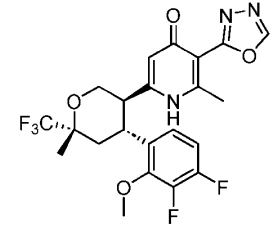
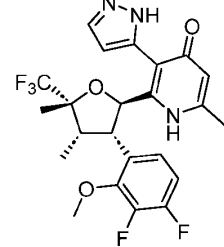
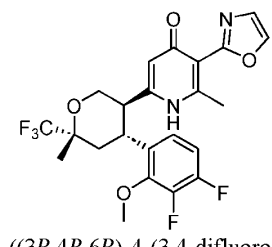
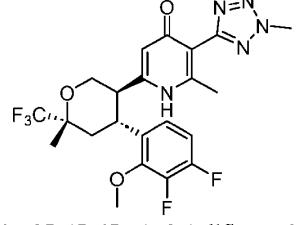
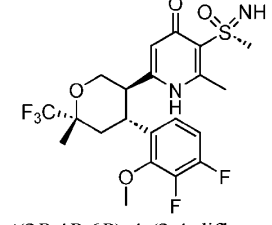
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1',6-dimethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4(1<i>H</i>)-one
 5-(6-oxa-3-azabicyclo[3.1.1]heptan-3-yl)-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1<i>H</i>)-one	 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5,7-dihydrofuro[3,4-d]pyrimidin-4(1<i>H</i>)-one
 3-(azetidin-1-yl)-6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(((3<i>S</i>,4<i>S</i>)-3-fluoro-1-methylpiperidin-4-yl)(methyl)amino)-2-methylpyridin-4(1<i>H</i>)-one

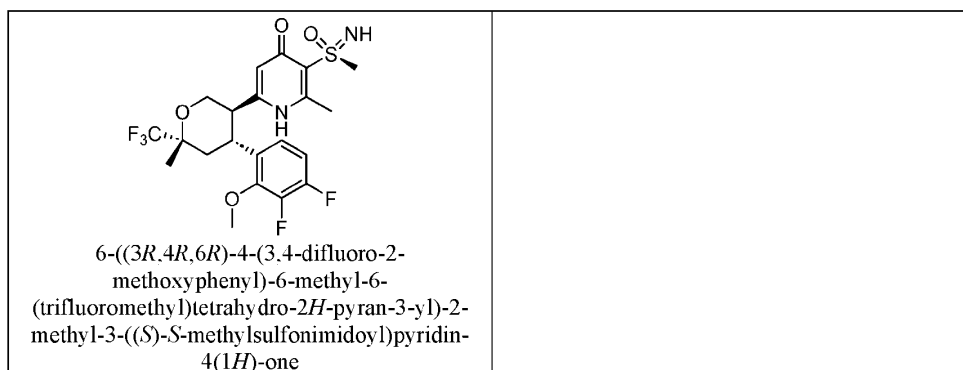
 3-cyclopropyl-2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(3,3-difluoroazetidin-1-yl)-2-methylpyridin-4(1<i>H</i>)-one
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-morpholinopyridin-4(1<i>H</i>)-one	

[0071] In some embodiments, the invention relates to a compound selected from Table B, or a pharmaceutically acceptable salt thereof. In other embodiments, the invention relates to a compound selected from Table B, i.e., the compound in non-salt form.

[0072] **Table B.** Compound Structures and Names.

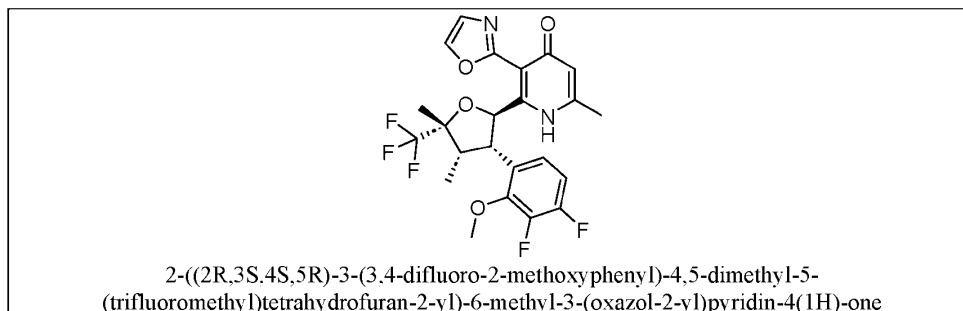
 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-Difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one	 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-Difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one
--	---

 6-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((dimethylamino)methyl)-2-methylpyridin-4(1<i>H</i>)-one	 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-(1,3,4-oxadiazol-2-yl)pyridin-4(1<i>H</i>)-one
 2-((2<i>R</i>,3<i>S</i>,4<i>S</i>,5<i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(1<i>H</i>-pyrazol-5-yl)pyridin-4(1<i>H</i>)-one	 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-(oxazol-2-yl)pyridin-4(1<i>H</i>)-one
 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-(2-methyl-2<i>H</i>-tetrazol-5-yl)pyridin-4(1<i>H</i>)-one	 6-((3<i>R</i>,4<i>R</i>,6<i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2<i>H</i>-pyran-3-yl)-2-methyl-3-((<i>R</i>)-<i>S</i>-methylsulfonimidoyl)pyridin-4(1<i>H</i>)-one



[0073] In some embodiments, the invention relates to a compound selected from Table C, or a pharmaceutically acceptable salt thereof. In other embodiments, the invention relates to a compound selected from Table C, i.e., the compound in non-salt form.

[0074] **Table C.** Compound Structures and Names.



[0075] In some embodiments, the invention relates to a compound selected from Table A or Table C, or a pharmaceutically acceptable salt thereof. In other embodiments, the invention relates to a compound selected from Table A or Table C, i.e., the compound in non-salt form.

[0076] In some embodiments, the invention relates to a compound selected from Table B or Table C, or a pharmaceutically acceptable salt thereof. In other embodiments, the invention relates to a compound selected from Table B or Table C, i.e., the compound in non-salt form.

Salts, Compositions, Uses, Formulation, Administration and Additional Agents

Pharmaceutically acceptable salts and compositions

[0077] As discussed herein, the invention provides compounds, and pharmaceutically acceptable salts thereof, that are inhibitors of voltage-gated sodium channels, and thus the present compounds, and pharmaceutically acceptable salts thereof, are useful for the treatment of diseases, disorders, and conditions including, but not limited to chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., bunionectomy

pain, herniorrhaphy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia. Accordingly, in another aspect of the invention, pharmaceutical compositions are provided, wherein these compositions comprise a compound as described herein, or a pharmaceutically acceptable salt thereof, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents. In some embodiments, the additional therapeutic agent is a sodium channel inhibitor.

[0078] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” of a compound of this invention includes any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. The salt may be in pure form, in a mixture (e.g., solution, suspension, or colloid) with one or more other substances, or in the form of a hydrate, solvate, or co-crystal. As used herein, the term “inhibitorily active metabolite or residue thereof” means that a metabolite or residue thereof is also an inhibitor of a voltage-gated sodium channel.

[0079] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compound of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N¹(C₁₋₄ alkyl)₄ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using

counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0080] As described herein, the pharmaceutically acceptable compositions of the invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soy bean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0081] In another aspect, the invention features a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0082] In another aspect, the invention features a pharmaceutical composition comprising a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers or vehicles.

Uses of Compounds and Pharmaceutically Acceptable Salts and Compositions

[0083] In another aspect, the invention features a method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject a compound of the invention or a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In another aspect, the voltage-gated sodium channel is $Na_v1.8$.

[0084] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., bunionectomy pain, herniorrhaphy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0085] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, herniorrhaphy pain, bunionectomy pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, or cardiac arrhythmia comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0086] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain, irritable bowel syndrome, endometriosis, polycystic ovarian disease, salpingitis, cervicitis or interstitial cystitis pain wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0087] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of neuropathic pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In some aspects, the neuropathic pain comprises post-herpetic neuralgia, small fiber neuropathy, diabetic neuropathy, or idiopathic small-fiber neuropathy. In some aspects, the neuropathic pain comprises diabetic neuropathy (e.g., diabetic peripheral neuropathy). As used herein, the phrase "idiopathic small-fiber neuropathy" shall be understood to include any small fiber neuropathy.

[0088] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuropathy, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve

avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, HIV-induced neuropathy; post spinal cord injury pain, spinal stenosis pain, small fiber neuropathy, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalalgia wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0089] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of musculoskeletal pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In some aspects, the musculoskeletal pain comprises osteoarthritis pain.

[0090] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0091] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain, ankylosing spondylitis or vulvodynia wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0092] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0093] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0094] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises reflex sympathetic dystrophy pain, wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0095] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of pathological cough wherein said method comprises administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0096] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of acute pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In some aspects, the acute pain comprises acute post-operative pain.

[0097] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, hemorrhoidectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain) comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0098] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of bunionectomy pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0099] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of shoulder arthroplasty pain or shoulder arthroscopy pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0100] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of herniorrhaphy pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0101] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of abdominoplasty pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0102] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of visceral pain comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In some aspects, the visceral pain comprises visceral pain from abdominoplasty.

[0103] In yet another aspect, the invention features a method of treating or lessening the severity in a subject of a neurodegenerative disease comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In some aspects, the neurodegenerative disease comprises multiple sclerosis. In some aspects, the neurodegenerative disease comprises Pitt Hopkins Syndrome (PTHS).

[0104] In yet another aspect, the invention features a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with an effective amount of the compound, pharmaceutically acceptable salt or pharmaceutical composition. In some embodiments, the additional therapeutic agent is a sodium channel inhibitor.

[0105] In another aspect, the invention features a method of inhibiting a voltage-gated sodium channel in a biological sample comprising contacting the biological sample with an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In another aspect, the voltage-gated sodium channel is Nav1.8.

[0106] In another aspect, the invention features a method of treating or lessening the severity in a subject of acute pain, sub-acute and chronic pain, nociceptive pain, neuropathic pain, inflammatory pain, nociplastic pain, arthritis, migraine, cluster headaches, tension headaches, and all other forms of headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, central neuropathic pain of multiple sclerosis and irritable bowel syndrome, incontinence, pathological cough, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, unspecific chronic back pain, head pain, neck pain, moderate pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain), cancer pain including chronic cancer pain and breakthrough cancer pain, stroke (e.g., post stroke central neuropathic pain), whiplash associated disorders, fragility fractures, spinal fractures, ankylosing spondylitis, pemphigus, Raynaud's Disease, scleroderma, systemic lupus erythematosus, Epidermolysis bullosa, gout, juvenile idiopathic arthritis, melorheostosis, polymyalgia reumatica, pyoderma gangrenosum, chronic widespread pain, diffuse idiopathic skeletal hyperostosis, disc degeneration/herniation pain, radiculopathy, facet joint syndrome, failed back surgery syndrome, burns, carpal tunnel syndrome, Paget's disease pain, spinal canal stenosis, spondylodiscitis, transverse myelitis, Ehlers-Danlos syndrome, Fabry's disease, mastocytocytosis, neurofibromatosis, ocular neuropathic pain, sarcoidosis, spondylolysis, spondylolisthesis, chemotherapy induced oral mucositis, Charcot neuropathic osteoarthritis, temporomandibular joint disorder, painful joint arthroplasties, non-cardiac chest pain, pudendal neuralgia, renal colic, biliary tract diseases, vascular leg ulcers, pain in Parkinson's disease, pain in Alzheimer's disease, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility, comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0107] In another aspect, the invention features a method of treating or lessening the severity in a subject of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache; cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal

neuralgia; Charcot-Marie-Tooth neuropathy; hereditary sensory neuropathy; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; persistent/chronic post-surgical pain (e.g., post amputation, post-thoracotomy, post-cardiac surgery), post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; phantom pain (e.g., following removal of lower extremity, upper extremity, breast); intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury pain; exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory pain, burn pain, trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain; sinusitis pain; dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebotic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease; urinary incontinence, pathological cough; hyperactive bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I, complex regional pain syndrome (CRPS) type II; widespread pain, paroxysmal extreme pain, pruritus, tinnitus, or angina-induced pain, comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

[0108] In another aspect, the invention features a method of treating or lessening the severity in a subject of trigeminal neuralgia, migraines treated with botox, cervical radiculopathy, occipital neuralgia, axillary neuropathy, radial neuropathy, ulnar neuropathy, brachial plexopathy, thoracic radiculopathy, intercostal neuralgia, lumbosacral radiculopathy, iliolumbar neuralgia, pudendal neuralgia, femoral neuropathy, meralgia paresthetica, saphenous neuropathy, sciatic neuropathy, peroneal neuropathy, tibial neuropathy, lumbosacral plexopathy, traumatic neuroma stump pain or postamputation pain, comprising administering an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof.

Compounds, Pharmaceutically Acceptable Salts, and Compositions for Use

[0109] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use as a medicament.

[0110] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting a voltage-gated sodium channel in a subject. In another aspect, the voltage-gated sodium channel is Na_v1.8.

[0111] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of

treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., herniorrhaphy pain, bunionectomy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

[0112] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, herniorrhaphy pain, bunionectomy pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, or cardiac arrhythmia.

[0113] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain, irritable bowel syndrome, endometriosis, polycystic ovarian disease, salpingitis, cervicitis or interstitial cystitis pain.

[0114] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of neuropathic pain. In some aspects, the neuropathic pain comprises post-herpetic neuralgia, small fiber neuropathy, diabetic neuropathy, or idiopathic small-fiber neuropathy. In some aspects, the neuropathic pain comprises diabetic neuropathy (e.g., diabetic peripheral neuropathy). As used herein, the phrase "idiopathic small-fiber neuropathy" shall be understood to include any small fiber neuropathy.

[0115] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton's neuroma; nerve entrapment injury; spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, HIV-induced neuropathy; post spinal cord injury pain, spinal stenosis pain, small fiber neuropathy, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic cephalgia.

[0116] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of musculoskeletal pain. In some aspects, the musculoskeletal pain comprises osteoarthritis pain.

[0117] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain.

[0118] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain, ankylosing spondylitis or vulvodynia.

[0119] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain.

[0120] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain.

[0121] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises reflex sympathetic dystrophy pain.

[0122] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of pathological cough.

[0123] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of acute pain. In some aspects, the acute pain comprises acute post-operative pain.

[0124] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, hemorrhoidectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain).

[0125] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of bunionectomy pain.

[0126] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of

treating or lessening the severity in a subject of shoulder arthroplasty pain or shoulder arthroscopy pain.

[0127] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of herniorrhaphy pain.

[0128] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of abdominoplasty pain.

[0129] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of visceral pain. In some aspects, the visceral pain comprises visceral pain from abdominoplasty.

[0130] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of a neurodegenerative disease. In some aspects, the neurodegenerative disease comprises multiple sclerosis. In some aspects, the neurodegenerative disease comprises Pitt Hopkins Syndrome (PTHS).

[0131] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method wherein the subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with an effective amount of the compound, pharmaceutically acceptable salt or pharmaceutical composition. In some embodiments, the additional therapeutic agent is a sodium channel inhibitor.

[0132] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of inhibiting a voltage-gated sodium channel in a biological sample comprising contacting the biological sample with an effective amount of a compound of the invention, a pharmaceutically acceptable salt thereof or a pharmaceutical composition thereof. In another aspect, the voltage-gated sodium channel is Nav1.8.

[0133] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of acute pain, sub-acute and chronic pain, nociceptive pain, neuropathic pain, inflammatory pain, nociplastic pain, arthritis, migraine, cluster headaches, tension headaches, and all other forms of headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, central neuropathic pain of multiple sclerosis and irritable bowel syndrome, incontinence,

pathological cough, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, unspecific chronic back pain, head pain, neck pain, moderate pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain), cancer pain including chronic cancer pain and breakthrough cancer pain, stroke (e.g., post stroke central neuropathic pain), whiplash associated disorders, fragility fractures, spinal fractures, ankylosing spondylitis, pemphigus, Raynaud's Disease, scleroderma, systemic lupus erythematosus, Epidermolysis bullosa, gout, juvenile idiopathic arthritis, melorheostosis, polymyalgia reumatica, pyoderma gangrenosum, chronic widespread pain, diffuse idiopathic skeletal hyperostosis, disc degeneration/herniation pain, radiculopathy, facet joint syndrome, failed back surgery syndrome, burns, carpal tunnel syndrome, Paget's disease pain, spinal canal stenosis, spondylodyscititis, transverse myelitis, Ehlers-Danlos syndrome, Fabry's disease, mastocytocytosis, neurofibromatosis, ocular neuropathic pain, sarcoidosis, spondylolysis, spondylolisthesis, chemotherapy induced oral mucositis, Charcot neuropathic osteoarthropathy, temporo-mandibular joint disorder, painful joint arthroplasties, non-cardiac chest pain, pudendal neuralgia, renal colic, biliary tract diseases, vascular leg ulcers, pain in Parkinson's disease, pain in Alzheimer's disease, cerebral ischemia, traumatic brain injury, amyotrophic lateral sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility.

[0134] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache; cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie-Tooth neuropathy; hereditary sensory neuropathy; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; persistent/chronic post-surgical pain (e.g., post amputation, post-thoracotomy, post-cardiac surgery), post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; phantom pain (e.g., following removal of lower extremity, upper extremity, breast); intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury pain; exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory pain, burn pain, trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute

pancreatitis; breakthrough pain; orofacial pain; sinusitis pain; dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease; urinary incontinence, pathological cough; hyperactive bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I, complex regional pain syndrome (CRPS) type II; widespread pain, paroxysmal extreme pain, pruritus, tinnitus, or angina-induced pain.

[0135] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for use in a method of treating or lessening the severity in a subject of trigeminal neuralgia, migraines treated with botox, cervical radiculopathy, occipital neuralgia, axillary neuropathy, radial neuropathy, ulnar neuropathy, brachial plexopathy, thoracic radiculopathy, intercostal neuralgia, lumbosacral radiculopathy, iliolingual neuralgia, pudendal neuralgia, femoral neuropathy, meralgia paresthetica, saphenous neuropathy, sciatic neuropathy, peroneal neuropathy, tibial neuropathy, lumbosacral plexopathy, traumatic neuroma stump pain or postamputation pain.

Manufacture of Medicaments

[0136] In another aspect, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for the manufacture of a medicament.

[0137] In another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in inhibiting a voltage-gated sodium channel. In another aspect, the voltage-gated sodium channel is $Na_v1.8$.

[0138] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain (e.g., herniorrhaphy pain, bunionectomy pain or abdominoplasty pain), visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia.

[0139] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, herniorrhaphy pain, bunionectomy pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, or cardiac arrhythmia.

[0140] In yet another aspect, the invention provides the use of the compound, pharmaceutically acceptable salt, or pharmaceutical composition described herein for the manufacture of a medicament for use in treating or lessening the severity in a subject of gut pain, wherein gut pain comprises inflammatory bowel disease pain, Crohn's disease pain, irritable bowel syndrome, endometriosis, polycystic ovarian disease, salpingitis, cervicitis or interstitial cystitis pain.

[0141] In yet another aspect, the invention provides a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of neuropathic pain. In some aspects, the neuropathic pain comprises post-herpetic neuralgia, small fiber neuropathy, diabetic neuropathy, or idiopathic small-fiber neuropathy. In some aspects, the neuropathic pain comprises diabetic neuropathy (e.g., diabetic peripheral neuropathy).

[0142] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in a treating or lessening the severity in a subject of neuropathic pain, wherein neuropathic pain comprises post-herpetic neuralgia, diabetic neuralgia, painful HIV-associated sensory neuropathy, trigeminal neuralgia, burning mouth syndrome, post-amputation pain, phantom pain, painful neuroma; traumatic neuroma; Morton's neuroma; nerve entrapment injury, spinal stenosis, carpal tunnel syndrome, radicular pain, sciatica pain; nerve avulsion injury, brachial plexus avulsion injury; complex regional pain syndrome, drug therapy induced neuralgia, cancer chemotherapy induced neuralgia, anti-retroviral therapy induced neuralgia, HIV-induced neuropathy; post spinal cord injury pain, spinal stenosis pain, small fiber neuropathy, idiopathic small-fiber neuropathy, idiopathic sensory neuropathy or trigeminal autonomic neuropathy.

[0143] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of musculoskeletal pain. In some aspects, the musculoskeletal pain comprises osteoarthritis pain.

[0144] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of musculoskeletal pain, wherein musculoskeletal pain comprises osteoarthritis pain, back pain, cold pain, burn pain or dental pain.

[0145] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain, ankylosing spondylitis or vulvodinia.

[0146] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture

of a medicament for use in treating or lessening the severity in a subject of inflammatory pain, wherein inflammatory pain comprises rheumatoid arthritis pain.

[0147] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises fibromyalgia pain.

[0148] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of idiopathic pain, wherein idiopathic pain comprises reflex sympathetic dystrophy pain.

[0149] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of pathological cough.

[0150] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of acute pain. In some aspects, the acute pain comprises acute post-operative pain.

[0151] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, hemorrhoidectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain).

[0152] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of herniorrhaphy pain.

[0153] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of bunionectomy pain.

[0154] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of shoulder arthroplasty pain or shoulder arthroscopy pain.

[0155] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity in a subject of abdominoplasty pain.

[0156] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture

of a medicament for use in treating or lessening the severity in a subject of visceral pain. In some aspects, the visceral pain comprises visceral pain from abdominoplasty.

[0157] In another aspect, the invention features a compound of the invention, or a pharmaceutically acceptable salt or pharmaceutical composition thereof, for the manufacture of a medicament for use in treating or lessening the severity in a subject of a neurodegenerative disease. In some aspects, the neurodegenerative disease comprises multiple sclerosis. In some aspects, the neurodegenerative disease comprises Pitt Hopkins Syndrome (PTHS).

[0158] In yet another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in combination with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound or pharmaceutical composition. In some embodiments, the additional therapeutic agent is a sodium channel inhibitor.

[0159] In another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity of acute pain, sub-acute and chronic pain, nociceptive pain, neuropathic pain, inflammatory pain, nociplastic pain, arthritis, migraine, cluster headaches, tension headaches, and all other forms of headaches, trigeminal neuralgia, herpetic neuralgia, general neuralgias, epilepsy, epilepsy conditions, neurodegenerative disorders, psychiatric disorders, anxiety, depression, bipolar disorder, myotonia, arrhythmia, movement disorders, neuroendocrine disorders, ataxia, central neuropathic pain of multiple sclerosis and irritable bowel syndrome, incontinence, pathological cough, visceral pain, osteoarthritis pain, postherpetic neuralgia, diabetic neuropathy, radicular pain, sciatica, back pain, unspecific chronic back pain, head pain, neck pain, moderate pain, severe pain, intractable pain, nociceptive pain, breakthrough pain, postsurgical pain (e.g., joint replacement pain, soft tissue surgery pain, post-thoracotomy pain, post-mastectomy pain, herniorrhaphy pain, bunionectomy pain or abdominoplasty pain), cancer pain including chronic cancer pain and breakthrough cancer pain, stroke (e.g., post stroke central neuropathic pain), whiplash associated disorders, fragility fractures, spinal fractures, ankylosing spondylitis, pemphigus, Raynaud's Disease, scleroderma, systemic lupus erythematosus, Epidermolysis bullosa, gout, juvenile idiopathic arthritis, melorheostosis, polymyalgia reumatica, pyoderma gangrenosum, chronic widespread pain, diffuse idiopathic skeletal hyperostosis, disc degeneration/herniation pain, radiculopathy, facet joint syndrome, failed back surgery syndrome, burns, carpal tunnel syndrome, Paget's disease pain, spinal canal stenosis, spondylodyscititis, transverse myelitis, Ehlers-Danlos syndrome, Fabry's disease, mastocytocytosis, neurofibromatosis, ocular neuropathic pain, sarcoidosis, spondylolysis, spondylolisthesis, chemotherapy induced oral mucositis, Charcot neuropathic osteoarthropathy, temporo-mandibular joint disorder, painful joint arthroplasties, non-cardiac chest pain, pudendal neuralgia, renal colic, biliary tract diseases, vascular leg ulcers, pain in Parkinson's disease, pain in Alzheimer's disease, cerebral ischemia, traumatic brain injury, amyotrophic lateral

sclerosis, stress induced angina, exercise induced angina, palpitations, hypertension, or abnormal gastro-intestinal motility.

[0160] In another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity of femur cancer pain; non-malignant chronic bone pain; rheumatoid arthritis; osteoarthritis; spinal stenosis; neuropathic low back pain; myofascial pain syndrome; fibromyalgia; temporomandibular joint pain; chronic visceral pain, abdominal pain; pancreatic pain; IBS pain; chronic and acute headache pain; migraine; tension headache; cluster headaches; chronic and acute neuropathic pain, post-herpetic neuralgia; diabetic neuropathy; HIV-associated neuropathy; trigeminal neuralgia; Charcot-Marie-Tooth neuropathy; hereditary sensory neuropathy; peripheral nerve injury; painful neuromas; ectopic proximal and distal discharges; radiculopathy; chemotherapy induced neuropathic pain; radiotherapy-induced neuropathic pain; persistent/chronic post-surgical pain (e.g., post amputation, post-thoracotomy, post-cardiac surgery), post-mastectomy pain; central pain; spinal cord injury pain; post-stroke pain; thalamic pain; phantom pain (e.g., following removal of lower extremity, upper extremity, breast); intractable pain; acute pain, acute post-operative pain; acute musculoskeletal pain; joint pain; mechanical low back pain; neck pain; tendonitis; injury pain; exercise pain; acute visceral pain; pyelonephritis; appendicitis; cholecystitis; intestinal obstruction; hernias; chest pain, cardiac pain; pelvic pain, renal colic pain, acute obstetric pain, labor pain; cesarean section pain; acute inflammatory pain, burn pain, trauma pain; acute intermittent pain, endometriosis; acute herpes zoster pain; sickle cell anemia; acute pancreatitis; breakthrough pain; orofacial pain; sinusitis pain; dental pain; multiple sclerosis (MS) pain; pain in depression; leprosy pain; Behcet's disease pain; adiposis dolorosa; phlebitic pain; Guillain-Barre pain; painful legs and moving toes; Haglund syndrome; erythromelalgia pain; Fabry's disease pain; bladder and urogenital disease; urinary incontinence, pathological cough; hyperactive bladder; painful bladder syndrome; interstitial cystitis (IC); prostatitis; complex regional pain syndrome (CRPS), type I, complex regional pain syndrome (CRPS) type II; widespread pain, paroxysmal extreme pain, pruritus, tinnitus, or angina-induced pain.

[0161] In another aspect, the invention provides the use of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof for the manufacture of a medicament for use in treating or lessening the severity of trigeminal neuralgia, migraines treated with botox, cervical radiculopathy, occipital neuralgia, axillary neuropathy, radial neuropathy, ulnar neuropathy, brachial plexopathy, thoracic radiculopathy, intercostal neuralgia, lumbosacral radiculopathy, iliolumbar neuralgia, pudendal neuralgia, femoral neuropathy, meralgia paresthetica, saphenous neuropathy, sciatic neuropathy, peroneal neuropathy, tibial neuropathy, lumbosacral plexopathy, traumatic neuroma stump pain or postamputation pain.

Administration of Compounds, Pharmaceutically Acceptable Salts, and Compositions

[0162] In certain embodiments of the invention, an “effective amount” of a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof is that amount effective for treating or lessening the severity of one or more of the conditions recited above.

[0163] The compounds, salts, and compositions, according to the method of the invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of one or more of the pain or non-pain diseases recited herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition, the particular agent, its mode of administration, and the like. The compounds, salts, and compositions of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression “dosage unit form” as used herein refers to a physically discrete unit of agent appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compounds, salts, and compositions of the invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound or salt employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific compound or salt employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound or salt employed, and like factors well known in the medical arts. The term “subject” or “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[0164] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the condition being treated. In certain embodiments, the compound, salts, and compositions of the invention may be administered orally or parenterally at dosage levels of about 0.001 mg/kg to about 1000 mg/kg, one or more times a day, effective to obtain the desired therapeutic effect.

[0165] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compound or salt, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl

alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0166] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic 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, U.S.P. 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 can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0167] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0168] In order to prolong the effect of the compounds of the invention, it is often desirable to slow the absorption of the compounds from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-poly glycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0169] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compound or salt of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0170] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound or salt is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders

such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0171] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0172] The active compound or salt can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release-controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms, the active compound or salt may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0173] Dosage forms for topical or transdermal administration of a compound or salt of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms are

prepared by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0174] As described generally above, the compounds of the invention are useful as inhibitors of voltage-gated sodium channels. In one embodiment, the compounds are inhibitors of $\text{Na}_v1.8$ and thus, without wishing to be bound by any particular theory, the compounds, salts, and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of $\text{Na}_v1.8$ is implicated in the disease, condition, or disorder. When activation or hyperactivity of $\text{Na}_v1.8$ is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a “ $\text{Na}_v1.8$ -mediated disease, condition or disorder.” Accordingly, in another aspect, the invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation or hyperactivity of $\text{Na}_v1.8$ is implicated in the disease state.

[0175] The activity of a compound utilized in this invention as an inhibitor of $\text{Na}_v1.8$ may be assayed according to methods described generally in International Publication No. WO 2014/120808 A9 and U.S. Publication No. 2014/0213616 A1, both of which are incorporated by reference in their entirety, methods described herein, and other methods known and available to one of ordinary skill in the art.

Additional Therapeutic Agents

[0176] It will also be appreciated that the compounds, salts, and pharmaceutically acceptable compositions of the invention can be employed in combination therapies, that is, the compounds, salts, and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.” For example, exemplary additional therapeutic agents include, but are not limited to: non-opioid analgesics (indoles such as Etodolac, Indomethacin, Sulindac, Tolmetin; naphthylalkanones such as Nabumetone; oxicams such as Piroxicam; para-aminophenol derivatives, such as Acetaminophen; propionic acids such as Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Naproxen sodium, Oxaprozin; salicylates such as Aspirin, Choline magnesium trisalicylate, Diflunisal; fenamates such as meclofenamic acid, Mefenamic acid; and pyrazoles such as

Phenylbutazone); or opioid (narcotic) agonists (such as Codeine, Fentanyl, Hydromorphone, Levorphanol, Meperidine, Methadone, Morphine, Oxycodone, Oxymorphone, Propoxyphene, Buprenorphine, Butorphanol, Dezocine, Nalbuphine, and Pentazocine). Additionally, nondrug analgesic approaches may be utilized in conjunction with administration of one or more compounds of the invention. For example, anesthesiologic (intrapinal infusion, neural blockade), neurosurgical (neurolysis of CNS pathways), neurostimulatory (transcutaneous electrical nerve stimulation, dorsal column stimulation), physiatric (physical therapy, orthotic devices, diathermy), or psychologic (cognitive methods-hypnosis, biofeedback, or behavioral methods) approaches may also be utilized. Additional appropriate therapeutic agents or approaches are described generally in The Merck Manual, Nineteenth Edition, Ed. Robert S. Porter and Justin L. Kaplan, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., 2011, and the Food and Drug Administration website, www.fda.gov, the entire contents of which are hereby incorporated by reference.

[0177] In another embodiment, additional appropriate therapeutic agents are selected from the following:

[0178] (1) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmeferene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine, pentazocine, or difelikefalin;

[0179] (2) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen (including without limitation intravenous ibuprofen (e.g., Caldolor®)), indomethacin, ketoprofen, ketorolac (including without limitation ketorolac tromethamine (e.g., Toradol®)), meclofenamic acid, mefenamic acid, meloxicam, IV meloxicam (e.g., Anjeso®), nabumetone, naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

[0180] (3) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butalbital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, thiamylal or thiopental;

[0181] (4) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;

[0182] (5) a histamine (H₁) antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;

[0183] (6) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;

[0184] (7) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadrine;

[0185] (8) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2- piperidinecarboxylic acid,

budipine, EN-3231 (MorphiDex®), a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (-)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(H)-quinolinone;

[0186] (9) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmedetomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1, 2,3,4-tetrahydroisoquinolin-2-yl)-5-(2-pyridyl) quinazoline;

[0187] (10) a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;

[0188] (11) an anticonvulsant, e.g. carbamazepine (Tegretol®), lamotrigine, topiramate, lacosamide (Vimpat®) or valproate;

[0189] (12) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (alphaR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6,13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

[0190] (13) a muscarinic antagonist, e.g. oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;

[0191] (14) a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;

[0192] (15) a coal-tar analgesic, in particular paracetamol;

[0193] (16) a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonopiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine, lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclizine, Miraxion® or sarizotan;

[0194] (17) a vanilloid receptor agonist (e.g. resiniferatoxin or civamide) or antagonist (e.g. capsazepine, GRC-15300);

[0195] (18) a beta-adrenergic such as propranolol;

[0196] (19) a local anesthetic such as mexiletine;

[0197] (20) a corticosteroid such as dexamethasone;

[0198] (21) a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;

[0199] (22) a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);

- [0200] (23) a cholinergic (nicotinic) analgesic, such as ispronidine (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- [0201] (24) Tramadol®, Tramadol ER (Ultram ER®), IV Tramadol, Tapentadol ER (Nucynta®);
- [0202] (25) a PDE5 inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;
- [0203] (26) an alpha-2-delta ligand such as gabapentin (Neurontin®), gabapentin GR (Gralise®), gabapentin, enacarbil (Horizant®), pregabalin (Lyrica®), 3-methyl gabapentin, (1[alpha],3[alpha],5[alpha])(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methyamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- [0204] (27) a cannabinoid such as KHK-6188;
- [0205] (28) metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- [0206] (29) a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- [0207] (30) a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;

[0208] (31) a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethyldclomipramine, duloxetine (Cymbalta®), milnacipran and imipramine;

[0209] (32) an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)-amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-S-chloro-S-pyridinecarbonitrile; 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamide, NXN-462, or guanidinoethyldisulfide;

[0210] (33) an acetylcholinesterase inhibitor such as donepezil;

[0211] (34) a prostaglandin E2 subtype 4 (EP4) antagonist such as N-[(2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl)amino]-carbonyl]-4-methylbenzenesulfonamide or 4-[(15)-1-({5-chloro-2-(3-fluorophenoxy)pyridin-3-yl}carbonyl)amino]ethyl]benzoic acid;

[0212] (35) a leukotriene B4 antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870;

[0213] (36) a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl)-1,4-benzoquinone (CV-6504);

[0214] (37) a sodium channel blocker, such as lidocaine, lidocaine plus tetracaine cream (ZRS-201) or eslicarbazepine acetate;

[0215] (38) a Na_v1.7 blocker, such as XEN-402, XEN403, TV-45070, PF-05089771, CNV1014802, GDC-0276, RG7893 BIIB-074 (Vixotrigine), BIIB-095, ASP-1807, DSP-3905, OLP-1002, RQ-00432979, FX-301, DWP-1706, DWP-17061, IMB-110, IMB-111, IMB-112 and such as those disclosed in WO2011/140425 (US2011/306607); WO2012/106499 (US2012196869); WO2012/112743 (US2012245136); WO2012/125613 (US2012264749), WO2012/116440 (US2014187533), WO2011026240 (US2012220605), US8883840, US8466188, WO2013/109521 (US2015005304),

CN111217776, WO2020/117626, WO2021/252822, WO2021/252818, WO2021/252820, WO2014/201173, WO2012/125973, WO2013/086229, WO2013/134518, WO2014/201206, or WO2016/141035 the entire contents of each application hereby incorporated by reference;

[0216] (38a) a Na_v1.7 blocker such as (2-benzylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl)-(4-isopropoxy-3-methyl-phenyl)methanone, 2,2,2-trifluoro-1-[1'-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2,4-dimethylspiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-

piperidine]-6-yl]ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(4-isobutoxy-3-methoxy-phenyl)methanone, 1-(4-benzhydrylpiperazin-1-yl)-3-[2-(3,4-dimethylphenoxy)ethoxy]propan-2-ol, (4-butoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-(5-isopropoxy-6-methyl-2-pyridyl)methanone, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 5-[2-methyl-4-[2-methyl-6-(2,2,2-trifluoroacetyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-carbonyl]phenyl]pyridine-2-carbonitrile, (4-isopropoxy-3-methyl-phenyl)-[6-(trifluoromethyl)spiro[3,4-dihydro-2H-pyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-[3-methoxy-4-[2-(trifluoromethoxy)ethoxy]benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-3,3-dimethyl-spiro[2,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 2,2,2-trifluoro-1-[1'-(5-isopentylloxy pyridine-2-carbonyl)-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, (4-isopropoxy-3-methoxy-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopentylloxy pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[(3S)-2,3-dimethyl-1'-[4-(3,3,3-trifluoropropoxymethyl)benzoyl]spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2,2-trifluoro-ethanone, [8-fluoro-2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[3-methoxy-4-[(1R)-1-methylpropoxy]phenyl]methanone, 2,2,2-trifluoro-1-[1'-(5-isopropoxy-6-methyl-pyridine-2-carbonyl)-2,4-dimethyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]ethanone, 1-[1'-[4-methoxy-3-(trifluoromethyl)benzoyl]-2-methyl-spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-6-yl]-2,2-dimethyl-propan-1-one, (4-isopropoxy-3-methyl-phenyl)-[2-methyl-6-(trifluoromethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone, [2-methyl-6-(1-methylcyclopropanecarbonyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]-[4-(3,3,3-trifluoropropoxymethyl)phenyl]methanone, 4-bromo-N-(4-bromophenyl)-3-[(1-methyl-2-oxo-4-piperidyl)sulfamoyl]benzamide or (3-chloro-4-isopropoxy-phenyl)-[2-methyl-6-(1,1,2,2,2-pentafluoroethyl)spiro[3,4-dihydropyrrolo[1,2-a]pyrazine-1,4'-piperidine]-1'-yl]methanone.

[0217] (39) a Nav1.8 blocker, such as PF-04531083, PF-06372865 and such as those disclosed in WO2008/135826 (US2009048306), WO2006/011050 (US2008312235), WO2013/061205 (US2014296313), US20130303535, WO2013131018, US8466188, WO2013114250 (US2013274243), WO2014/120808 (US2014213616), WO2014/120815 (US2014228371), WO2014/120820 (US2014221435), WO2015/010065 (US20160152561), WO2015/089361 (US20150166589), WO2019/014352 (US20190016671), WO2018/213426, WO2020/146682, WO2020/146612, WO2020/014243, WO2020/014246, WO2020/092187, WO2020/092667

(US2020140411), WO2020/144375, WO2020/261114, WO2020/140959, WO2020/151728, WO2021/032074, WO2021/047622 (CN112479996), WO2021/257490, WO2021/257420, WO2021/257418, WO2022/263498, WO2022/235558, WO2022/235859, WO2023/138599, CN112390745, CN111808019, CN112225695, CN112457294, CN112300051, CN112300069, CN112441969, and CN114591293, the entire contents of each application hereby incorporated by reference;

[0218] (39a) a Nav1.8 blocker such as 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4,5-dichloro-2-(3-fluoro-4-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(perfluoroethyl)benzamide, 5-chloro-2-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(4-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 4-chloro-2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)benzamide, 2-((5-fluoro-2-hydroxybenzyl)oxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(o-tolyl)oxy)-5-(trifluoromethyl)benzamide, 2-(2,4-difluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(2-(trifluoromethoxy)phenoxy)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-5-(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(2-oxo-1H-pyridin-4-yl)-4-(trifluoromethyl)benzamide, [4-[[2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzoyl]amino]-2-oxo-1-pyridyl]methyl dihydrogen phosphate, 2-(4-fluoro-2-(methyl-d₃)phenoxy)-N-(2-oxo-1,2-dihydropyridin-4-yl)-4-(trifluoromethyl)benzamide, (4-(2-(4-fluoro-2-(methyl-d₃)phenoxy)-4-(trifluoromethyl)benzamido)-2-oxopyridin-1(2H)-yl)methyl dihydrogen phosphate, 3-(4-fluoro-2-methoxyphenoxy)-N-(3-(methylsulfonyl)phenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(2-chloro-4-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 3-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid, 2-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)quinoline-3-carboxamide, 3-(2,4-difluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-sulfamoylphenyl)-2-(4-

(trifluoromethoxy)phenoxy)quinoline-3-carboxamide, N-(3-sulfamoylphenyl)-3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamide, 3-(4-chloro-2-methylphenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, 5-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)picolinic acid, 3-(4-fluoro-2-methoxyphenoxy)-N-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-5-yl)quinoxaline-2-carboxamide, 3-(4-fluoro-2-methoxyphenoxy)-N-(pyridin-4-yl)quinoxaline-2-carboxamide, 3-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)quinoxaline-2-carboxamide, N-(3-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, N-(4-carbamoylphenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 4-(3-(4-(trifluoromethoxy)phenoxy)quinoxaline-2-carboxamido)benzoic acid, N-(4-cyanophenyl)-3-(4-fluoro-2-methoxyphenoxy)quinoxaline-2-carboxamide, 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 5-(2-(2,4-dimethoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4,6-bis(trifluoromethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 5-(2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)benzamido)picolinic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-(trifluoromethyl)benzamido)benzoic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 4-(2-(2-chloro-4-fluorophenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 4-(2-(4-fluoro-2-methylphenoxy)-4-(perfluoroethyl)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)benzoic acid, 4-(4,5-dichloro-2-(4-chloro-2-methylphenoxy)benzamido)benzoic acid, 5-(4-(*tert*-butyl)-2-(4-fluoro-2-methoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-(trifluoromethoxy)phenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-dimethoxyphenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(2-chloro-4-fluorophenoxy)benzamido)picolinic acid, 5-(4,5-dichloro-2-(4-fluoro-2-methylphenoxy)benzamido)picolinic acid, 4-(4,5-dichloro-2-(4-chloro-2-methoxyphenoxy)benzamido)benzoic acid, 5-(4,5-dichloro-2-(2,4-difluorophenoxy)benzamido)picolinic acid, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)-6-(trifluoromethyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-5-(difluoromethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluorophenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 2-(4-chloro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-

sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-5-(trifluoromethyl)benzamide, 5-chloro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 4,5-dichloro-2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-chloro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2,4-dichloro-6-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)-4,6-bis(trifluoromethyl)benzamide, 5-chloro-2-(2-chloro-4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethoxy)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-N-(3-sulfamoylphenyl)-4-(trifluoromethyl)benzamide, 4,5-dichloro-2-(4-fluorophenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(4-fluoro-2-methoxyphenoxy)-4-(perfluoroethyl)-N-(3-sulfamoylphenyl)benzamide, 5-fluoro-2-(4-fluoro-2-methylphenoxy)-N-(3-sulfamoylphenyl)benzamide, 2-(2-chloro-4-fluorophenoxy)-4-cyano-N-(3-sulfamoylphenyl)benzamide, N-(3-sulfamoylphenyl)-2-(4-(trifluoromethoxy)phenoxy)-4-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethoxy)benzamide, 4-[[2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, 4-[[3-chloro-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-3-(difluoromethyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethoxy)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-6-[2-chloro-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-methyl-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2,3,4-trifluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzamide, N-(2-carbamoyl-4-pyridyl)-3-fluoro-5-[2-methoxy-4-(trifluoromethoxy)phenoxy]-2-(trifluoromethyl)pyridine-4-carboxamide, 4-[[6-[2-(difluoromethoxy)-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-6-[3-chloro-4-(trifluoromethoxy)phenoxy]-2-fluoro-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(4-carbamoyl-3-fluoro-phenyl)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, 4-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-4-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-

6-[3-fluoro-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-[2-methoxy-4-(trifluoromethoxy)phenoxy]-5-(1,1,2,2,2-pentafluoroethyl)benzamide, 4-[[4-(difluoromethoxy)-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-[2-fluoro-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzamide, 4-[[4-cyclopropyl-2-fluoro-6-[2-methoxy-4-(trifluoromethoxy)phenoxy]benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-5-fluoro-2-[2-methoxy-4-(trifluoromethoxy)phenoxy]-4-(trifluoromethyl)benzamide, 5-[[2-fluoro-6-[2-(trideuteriomethoxy)-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide, N-(3-carbamoyl-4-fluoro-phenyl)-2-fluoro-6-(4-fluorophenoxy)-3-(trifluoromethyl)benzamide, or 4-[[2-fluoro-6-[3-fluoro-2-methoxy-4-(trifluoromethoxy)phenoxy]-3-(trifluoromethyl)benzoyl]amino]pyridine-2-carboxamide;

[0219] (40) a combined Na_v1.7 and Na_v1.8 blocker, such as DSP-2230, Lohocla201 or BL-1021;

[0220] (41) a 5-HT₃ antagonist, such as ondansetron;

[0221] (42) a TRPV 1 receptor agonist, such as capsaicin (NeurogesX®, Qutenza®); and the pharmaceutically acceptable salts and solvates thereof;

[0222] (43) a nicotinic receptor antagonist, such as varenicline;

[0223] (44) an N-type calcium channel antagonist, such as Z-160;

[0224] (45) a nerve growth factor antagonist, such as tanezumab;

[0225] (46) an endopeptidase stimulant, such as senrebotase;

[0226] (47) an angiotensin II antagonist, such as EMA-401;

[0227] (48) acetaminophen (including without limitation intravenous acetaminophen (e.g., Ofirmev®));

[0228] (49) bupivacaine (including without limitation bupivacaine liposome injectable suspension (e.g., Exparel®) bupivacaine ER (Posimir), bupivacaine collagen (Xaracoll) and transdermal bupivacaine (Eladur®)); and

[0229] (50) bupivacaine and meloxicam combination (e.g., HTX-011).

[0230] In one embodiment, the additional appropriate therapeutic agents are selected from V-116517, Pregabalin, controlled release Pregabalin, Ezogabine (Potiga®), Ketamine/amitriptyline topical cream (Amiket®), AVP-923, Perampanel (E-2007), Ralfinamide, transdermal bupivacaine (Eladur®), CNV1014802, JNJ-10234094 (Carisbamate), BMS-954561 or ARC-4558.

[0231] In another embodiment, the additional appropriate therapeutic agents are selected from N-(6-amino-5-(2,3,5-trichlorophenyl)pyridin-2-yl)acetamide; N-(6-amino-5-(2-chloro-5-methoxyphenyl)pyridin-2-yl)-1-methyl-1H-pyrazole-5-carboxamide; or 3-((4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-2-yl)methyl)oxetan-3-amine.

[0232] In another embodiment, the additional therapeutic agent is selected from a GlyT2/5HT2 inhibitor, such as Operanserin (VVZ149), a TRPV modulator such as CA008, CMX-020, NEO6860, FTABS, CNTX4975, MCP101, MDR16523, or MDR652, a EGR1 inhibitor such as Brivoglides

(AYX1), an NGF inhibitor such as Tanezumab, Fasinumab, ASP6294, MEDI7352, a Mu opioid agonist such as Cebranopadol, NKTR181 (oxycodol), a CB-1 agonist such as NEO1940 (AZN1940), an imidazoline 12 agonist such as CR4056 or a p75NTR-Fc modulator such as LEVI-04.

[0233] In another embodiment, the additional therapeutic agent is oliceridine or ropivacaine (TLC590).

[0234] In another embodiment, the additional therapeutic agent is a Nav1.7 blocker such as ST-2427, ST-2578 and those disclosed in WO2010/129864, WO2015/157559, WO2017/059385, WO2018/183781, WO2018/183782, WO2020/072835, and/or WO2022/036297 the entire contents of each application hereby incorporated by reference.

[0235] In another embodiment, the additional therapeutic agent is selected from ASP18071, CC-8464, ANP-230, ANP-231, NOC-100, NTX-1175, ASN008, NW3509, AM-6120, AM-8145, AM-0422, BL-017881, NTM-006, Opiranserin (UnafraTM), brivolidide, SR419, NRD.E1, LX9211, LY3016859, ISC-17536, NFX-88, LAT-8881, AP-235, NYX 2925, CNTX-6016, S-600918, S-637880, RQ-00434739, KLS-2031, MEDI 7352, and XT-150.

[0236] In another embodiment, the additional therapeutic agent is selected from Olinvyk, Zynrelef, Seglenti, Neumentum, Nevakar, HTX-034, CPL-01, ACP-044, HRS-4800, Tarlige, BAY2395840, LY3526318, Eliapixant, TRV045, RTA901, NRD1355-E1, MT-8554, LY3556050, AP-325, tetrodotoxin, Otenaproxesul, CFTX-1554, Funapide, iN1011-N17, JMKX000623/ODM-111, ETX-801, OLP-1002, ANP-230/DSP-2230, iN1011-N17, DSP-3905 and ACD440.

[0237] In another embodiment, the additional therapeutic agent is selected from HRS4800, ODM-111/JMKX000623, LX9211, LY3556050, LY3857210, CFTX01554/CFTX-1554, MEDI7352, MEDI0618, BAY3178275, BAY2395840, GSK3858279, STC-004, HALNEURON, OLP-1002, ATX01, ANP230, CC-8464, iN1011-N17, ST-2427, MSD199, FZ008, VYNAV-01, BL-017881, Profervia (Cilnidipine), LS-04, vixotrigine, FX301/PCRX-301, PF-04531083, PF-01247324, and DSP-3905.

[0238] In another embodiment, the additional therapeutic agent is a sodium channel inhibitor (also known as a sodium channel blocker), such as the Nav1.7 and Nav1.8 blockers identified above.

[0239] The amount of additional therapeutic agent present in the compositions of this invention may be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. The amount of additional therapeutic agent in the presently disclosed compositions may range from about 10% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0240] The compounds and salts of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the invention, in another aspect, includes a composition for coating an implantable device comprising a compound or salt of the invention as described generally above, and in classes and subclasses herein, and a carrier

suitable for coating said implantable device. In still another aspect, the invention includes an implantable device coated with a composition comprising a compound or salt of the invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

[0241] Another aspect of the invention relates to inhibiting $\text{Na}_v1.8$ activity in a biological sample or a subject, which method comprises administering to the subject, or contacting said biological sample with a compound of the invention, a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. The term “biological sample,” as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0242] Inhibition of $\text{Na}_v1.8$ activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, the study of sodium channels in biological and pathological phenomena; and the comparative evaluation of new sodium channel inhibitors.

Synthesis of the Compounds of the Invention

[0243] The compounds of the invention can be prepared from known materials by the methods described in the Examples, other similar methods, and other methods known to one skilled in the art. As one skilled in the art would appreciate, the functional groups of the intermediate compounds in the methods described below may need to be protected by suitable protecting groups. Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art. The use of protecting groups is described in detail in T.G.M. Wuts et al., *Greene's Protective Groups in Organic Synthesis* (4th ed. 2006).

Radiolabeled Analogs of the Compounds of the Invention

[0244] In another aspect, the invention relates to radiolabeled analogs of the compounds of the invention. As used herein, the term “radiolabeled analogs of the compounds of the invention” refers to compounds that are identical to the compounds of the invention, as described herein, including all embodiments thereof, except that one or more atoms has been replaced with a radioisotope of the atom present in the compounds of the invention.

[0245] As used herein, the term “radioisotope” refers to an isotope of an element that is known to undergo spontaneous radioactive decay. Examples of radioisotopes include ^3H , ^{14}C , ^{32}P , ^{35}S , ^{18}F , ^{36}Cl , and the like, as well as the isotopes for which a decay mode is identified in V.S. Shirley & C.M. Lederer, Isotopes Project, Nuclear Science Division, Lawrence Berkeley Laboratory, Table of Nuclides (January 1980).

[0246] The radiolabeled analogs can be used in a number of beneficial ways, including in various types of assays, such as substrate tissue distribution assays. For example, tritium (^3H)- and/or carbon-14 (^{14}C)-labeled compounds may be useful for various types of assays, such as substrate tissue distribution assays, due to relatively simple preparation and excellent detectability.

[0247] In another aspect, the invention relates to pharmaceutically acceptable salts of the radiolabeled analogs, in accordance with any of the embodiments described herein in connection with the compounds of the invention.

[0248] In another aspect, the invention relates to pharmaceutical compositions comprising the radiolabeled analogs, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle, in accordance with any of the embodiments described herein in connection with the compounds of the invention.

[0249] In another aspect, the invention relates to methods of inhibiting voltage-gated sodium channels and methods of treating or lessening the severity of various diseases and disorders, including pain, in a subject comprising administering an effective amount of the radiolabeled analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, in accordance with any of the embodiments described herein in connection with the compounds of the invention.

[0250] In another aspect, the invention relates to radiolabeled analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, for use, in accordance with any of the embodiments described herein in connection with the compounds of the invention.

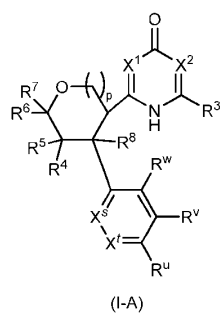
[0251] In another aspect, the invention relates to the use of the radiolabeled analogs, or pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, for the manufacture of medicaments, in accordance with any of the embodiments described herein in connection with the compounds of the invention.

[0252] In another aspect, the radiolabeled analogs, pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof, can be employed in combination therapies, in accordance with any of the embodiments described herein in connection with the compounds of the invention.

ENUMERATED EMBODIMENTS

[0253] Further embodiments of the disclosure are set out in the following numbered clauses:

1. A compound of formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is C- R^1 or N;

X^2 is C- R^2 or N;

X^3 is C- R^3 or N;

X^4 is C- R^4 or N;

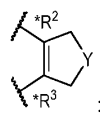
R^1 is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-(CH_2)_mO_n(CH_2)_oOCH_3$, $-(CH_2)_mR^a$, $-C(O)(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^bR^cNR^gC(O)CR^hR^iR^j$, $-NR^bC(O)CR^eR^fR^j$, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy;

R^2 and R^3 are defined as follows:

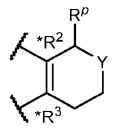
(i) R^2 is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^bR^cNR^gC(O)CR^hR^iR^j$, $-O(CH_2)_mR^a$, $-CR^bR^cOR^g$, $-CR^bR^c(CH_2)_mO(CH_2)_oC(O)OR^g$, $-CR^bR^c(CH_2)_mO(CH_2)_oCR^gR^hR^a$, $-CR^bR^c(CH_2)_mO(CH_2)_oC(O)NR^gR^h$, $-CR^bR^c(CH_2)_mO(CH_2)_oR^d$, $-CR^bR^cC(R^d)(R^e)(R^f)$, $-CR^bR^cNR^gR^h$, $-CH_2C(O)NR^bR^c$, $-C(O)O_n(CH_2)_mR^a$, $-NR^b(CH_2)_mOR^c$, $-NR^b(CH_2)_mR^n$, $-(CH_2)_mNR^bC(O)R^n$, $-NR^bCR^gR^hR^i$, $-(CH_2)_mNR^bC(O)R^c$, $-SR^b$, $-S(=O)_2R^l$, $-N=S(=O)(R^j)(R^m)$, $-S(=O)(=NR^b)(R^l)$, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, $-CH_2OH$, $-C(O)OR^b$, $-NR^bR^c$, and $-C(O)NR^bR^c$; and

R^3 is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, $-(CH_2)_mOCH_3$, or $-(CH_2)_mR^a$,

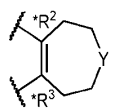
(ii) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



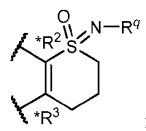
(iii) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(iv) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(v) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



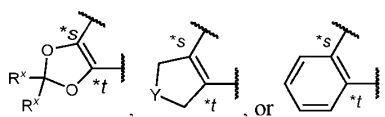
Y is O or NR^q ;

R^4 and R^5 are each independently H, OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkoxy;

R^6 and R^7 are each independently H, OH, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, or C_1 - C_6 alkoxy, or R^6 and R^7 , together with the carbon atom to which they are attached, form a C_3 - C_6 cycloalkyl;

R^8 is H or CH_3 ;

R^s and R^t are each independently H, OH, halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-NR^bR^c$, $-NO_2$, $-SO_3H$, $-(CH_2)_mR^a$, or $-O(CH_2)_mOCH_3$, or R^s and R^t , together with the atoms to which they are attached, form a ring of formula:



Y is O or CH_2 ;

R^u , R^v , and R^w are each independently H, OH, halo, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, $-NR^bR^c$, $-NO_2$, $-SO_3H$, $-(CH_2)_mR^a$, or $-O(CH_2)_mOCH_3$;

each R^x is independently H, halo, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

R^a is OH, halo, C_1 - C_6 alkoxy, or $-NR^bR^c$;

R^b , R^c , R^g , R^h , R^i , and R^k are each independently H or C_1 - C_6 alkyl, or R^b and R^c , together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl;

R^d , R^e , and R^f are each independently H, OH, halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R^j is H, C₁-C₆ alkyl, $-NR^bR^c$, or $-N(CH_3)_3^+$;

R^l and R^m are each independently C₁-C₆ alkyl;

R^n is C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl wherein said C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents selected from C₁-C₆ alkyl and halo;

R^o is H, C₁-C₆ alkyl, or $-C(O)O(C_1-C_6 \text{ alkyl})$;

R^p is H, C₁-C₆ alkyl, $-C(O)NR^bR^c$, or oxo;

R^q is H or C₁-C₆ alkyl;

m and o are each independently 0, 1, 2, or 3;

n is 0 or 1; and

p is 0 or 1.

2. The compound of clause 1, or a pharmaceutically acceptable salt thereof, wherein:

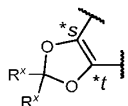
X^s is C- R^s ;

X^t is C- R^t ;

R^6 and R^7 are each independently H, OH, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₃-C₆ cycloalkyl, or C₁-C₆ alkoxy;

R^8 is H; and

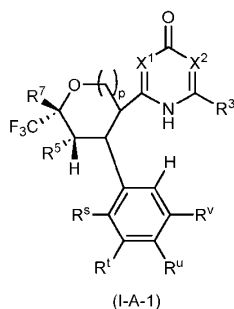
R^s and R^t are each independently H, OH, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, $-NR^bR^c$, $-NO_2$, $-SO_3H$, $-(CH_2)_mR^a$, or $-O(CH_2)_mOCH_3$, or R^s and R^t , together with the atoms to which they are attached, form a ring of formula:



3. The compound of clause 1 or 2, or pharmaceutically acceptable salt thereof, wherein p is 0.

4. The compound of clause 1 or 2, or pharmaceutically acceptable salt thereof, wherein p is 1.

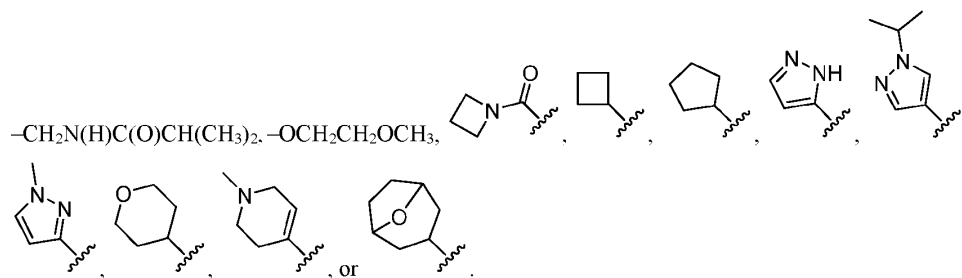
5. The compound of any one of clauses 1 to 4, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula (I-A-1):



6. The compound of any one of clauses 1 to 5, or a pharmaceutically acceptable salt thereof, wherein X^1 is N.

7. The compound of any one of clauses 1 to 5, or a pharmaceutically acceptable salt thereof, wherein X^1 is $C-R^1$ and R^1 is H, halo, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-(CH_2)_mO_n(CH_2)_oOCH_3$, $-(CH_2)_mR^a$, $-C(O)(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^bR^cNR^gC(O)CR^bR^j$, $-(CH_2)_mNR^bC(O)R^n$, C_3 - C_6 cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C_3 - C_6 cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, and C_1 - C_6 haloalkoxy.

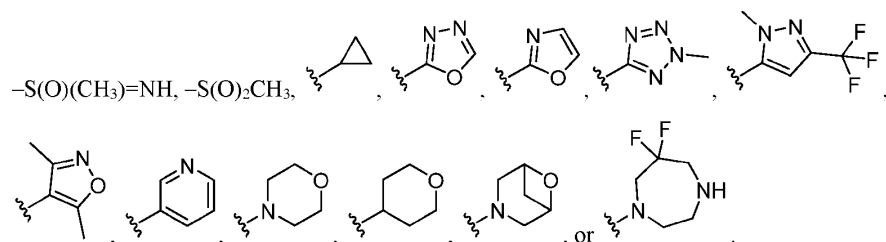
8. The compound of clause 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is H, Br, Cl, F, CN, $-CH_3$, $-CH_2OH$, $-OCH_3$, $-OCHF_2$, $-CH(CH_3)_2$, $-CH_2OCH_3$, $-N(CH_3)_2$, $-C(O)OH$, $-C(O)CH_3$, $-C(O)OCH_3$, $-C(O)CH_2CH_2CH_2OH$, $-C(O)N(CH_3)_2$, $-C(O)N(H)CH_3$, $-C(O)OCH_2CH_3$,



9. The compound of any one of clauses 1 to 8, or a pharmaceutically acceptable salt thereof, wherein X^2 is $C-R^2$ and R^2 is H, halo, CN, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $-CR^dR^eR^f$, $-CR^bR^cOR^g$, $-(CH_2)_mR^a$, $-C(O)R^b$, $-NR^bR^c$, $-O(CH_2)_mR^a$, $-C(O)NR^bR^c$, $-C(O)OR^b$, $-C(O)O_n(CH_2)_mR^a$, $-CH_2C(O)NR^bR^c$, $-CR^bR^cNR^gR^h$, $-NR^b(CH_2)_mOR^c$, $-NR^bCR^eR^gR^h$, $-(CH_2)_mNR^bC(O)R^c$, $-(CH_2)_mNR^bC(O)R^n$, $-CR^bR^c(CH_2)_mO(CH_2)_oCR^gR^hR^a$, $-CR^bR^c(CH_2)_mO(CH_2)_oC(O)NR^gR^h$, $-CR^bR^c(CH_2)_mO(CH_2)_oC(O)OR^g$, $-CR^bR^c(CH_2)_mO(CH_2)_oR^d$, $-CR^bR^cC(R^d)(R^e)(R^f)$, $-CR^bR^cNR^gC(O)CR^bR^j$, $-N=S(O)(R^i)(R^m)$, $-SR^b$, $-S(O)(=NR^b)(R^i)$,

$-\text{S}(=\text{O})_2\text{R}^f$, C_3 - C_6 cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C_3 - C_6 cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{NR}^b\text{R}^c$.

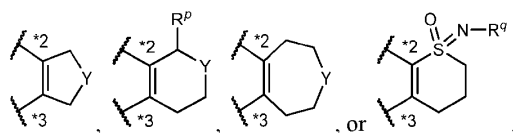
10. The compound of clause 9, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, $-\text{OH}$, $-\text{CN}$, $-\text{Br}$, $-\text{Cl}$, $-\text{F}$, $-\text{CH}_3$, $-\text{OCH}_3$, $-\text{OCHF}_2$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{OH}$, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)\text{N}(\text{H})\text{CH}_3$, $-\text{CH}(\text{CH}_3)\text{OCH}_3$, $-\text{CH}(\text{OH})\text{CH}_3$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{OCH}(\text{CH}_3)_2$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{OH})(\text{CH}_3)_2$, $-\text{C}(\text{OCH}_3)(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{CH}_3)_2\text{OH}$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{C}(\text{O})\text{OCH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{CH}(\text{CH}_3)\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{N}(\text{H})\text{CH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{N}(\text{H})\text{CH}_3$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}(\text{CH}_3)\text{NH}_2$, $-\text{CH}_2\text{N}(\text{H})\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CD}_3)_2$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{CH}_3)\text{C}(\text{O})\text{CH}_3$, $-\text{N}(\text{CH}_3)\text{C}(\text{O})$ -cyclopropyl, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OH}$, $-\text{N}(\text{CH}_3)_2$, $-\text{N}(\text{H})\text{CH}_3$, $-\text{N}=\text{S}(=\text{O})(\text{CH}_3)_2$, $-\text{S}(\text{CH}_3)$, $-\text{S}(\text{O})(\text{CH}_3)=\text{NCH}_3$,



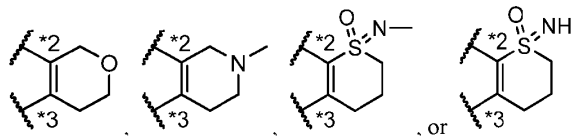
11. The compound of any of clauses 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, C_1 - C_6 alkyl, or $-(\text{CH}_2)_m\text{OCH}_3$.

12. The compound of clause 11, or a pharmaceutically acceptable salt thereof, wherein R^3 is H, $-\text{CH}_3$, or $-(\text{CH}_2)\text{OCH}_3$.

13. The compound of any one of clauses 1 to 8, or a pharmaceutically acceptable salt thereof, wherein X^2 is CR^2 , and R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



14. The compound of clause 13, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



15. The compound of any one of clauses 1 to 4 and 6 to 14, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

16. The compound of any one of clauses 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^5 is H, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.

17. The compound of clause 16, or a pharmaceutically acceptable salt thereof, wherein R^5 is H, $-CH_3$, $-OCH_3$.

18. The compound of any one of clause 1 to 17, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are each independently H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_3 - C_6 cycloalkyl, or R^6 and R^7 , together with the carbon atom to which they are attached, form a C_3 - C_6 cycloalkyl.

19. The compound of any one of clauses 1 to 4 and 6 to 18, or a pharmaceutically acceptable salt thereof, wherein R^6 is $-CF_3$.

20. The compound of any one of clauses 1 to 19, or a pharmaceutically acceptable salt thereof, wherein R^7 is H or C_1 - C_6 alkyl.

21. The compound of clause 20, or a pharmaceutically acceptable salt thereof, wherein R^7 is H or $-CH_3$.

22. The compound of any one of clauses 1 to 21, or a pharmaceutically acceptable salt thereof, wherein R^8 is H.

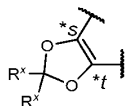
23. The compound of any one of clauses 1 to 22, or a pharmaceutically acceptable salt thereof, wherein X^s is $C-R^s$, and R^s is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, or $-O(CH_2)_mOCH_3$.

24. The compound of clause 23, or a pharmaceutically acceptable salt thereof, wherein R^s is $-CH_3$, $-OCH_3$, $-OCH(CH_3)_2$, $-OCH(F)_2$, $-OCH_2CH_2OCH_3$, or $-OCH_2CH_3$.

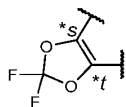
25. The compound of any one of clauses 1 to 24, or a pharmaceutically acceptable salt thereof, wherein X^t is $C-R^t$, and R^t is H, halo, or C_1 - C_6 haloalkyl.

26. The compound of clause 25, or a pharmaceutically acceptable salt thereof, wherein R^t is H, Cl, F, $-\text{CH}_3$, or $-\text{CF}_3$.

27. The compound of any one of clauses 1 to 22, or a pharmaceutically acceptable salt thereof, wherein X^s is $\text{C}-R^s$, X^t is $\text{C}-R^t$, and R^s and R^t , together with the carbon atoms to which they are attached, form a ring of formula:



28. The compound of clause 27, or a pharmaceutically acceptable salt thereof, wherein R^s and R^t , together with the carbon atoms to which they are attached, form a ring of formula:



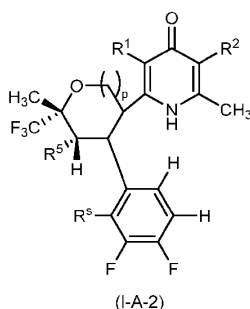
29. The compound of any one of clauses 1 to 28, or a pharmaceutically acceptable salt thereof, wherein R^u is H, halo, $\text{C}_1\text{-C}_6$ alkoxy, or $\text{C}_1\text{-C}_6$ haloalkoxy.

30. The compound of clause 29, or a pharmaceutically acceptable salt thereof, wherein R^u is H, F, $-\text{OCH}_2\text{CH}_3$, or $-\text{OCHF}_2$.

31. The compound of any one of clauses 1 to 30, or a pharmaceutically acceptable salt thereof, wherein R^v is H or $-\text{NR}^b\text{R}^c$.

32. The compound of clause 31, or a pharmaceutically acceptable salt thereof, wherein R^v is H or $-\text{NH}_2$.

33. The compound of any one of clauses 1 to 4, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula (I-A-2):



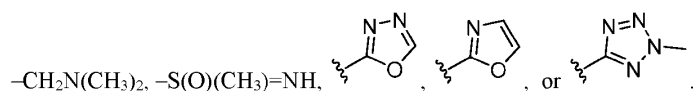
34. The compound of any one of clauses 1 to 4 and 33, or a pharmaceutically acceptable salt thereof, wherein R^1 is H or 5-6 membered heteroaryl, wherein said 5-6 membered heteroaryl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo and C_1 - C_6 alkyl.

35. The compound of clause 34, or a pharmaceutically acceptable salt thereof, wherein R^1 is H or



36. The compound of any one of clauses 1 to 4 and 33 to 35, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, $-CR^bR^cNR^sR^h$, $-S(=O)(=NR^b)(R^h)$, or 5-6 membered heteroaryl, wherein said 5-6 membered heteroaryl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, $-CH_2OH$, and $-C(O)NR^bR^c$.

37. The compound of clause 36, or a pharmaceutically acceptable salt thereof, wherein R^2 is H,



38. The compound of any one of clauses 1 to 4 and 33 to 37, or a pharmaceutically acceptable salt thereof, wherein R^5 is H, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.

39. The compound of clause 38, or a pharmaceutically acceptable salt thereof, wherein R^5 is H, $-CH_3$, or $-OCH_3$.

40. The compound of any one of clauses 1 to 4 and 33 to 39, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_1 - C_6 alkyl or C_1 - C_6 alkoxy.

41. The compound of clause 40, or a pharmaceutically acceptable salt thereof, wherein R^5 is $-CH_3$ or $-OCH_3$.

42. A compound selected from Table A, or a pharmaceutically acceptable salt thereof.

43. A compound selected from Table B, or a pharmaceutically acceptable salt thereof.

44. The compound of any one of clauses 1 to 43 in non-salt form.

45. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of clauses 1 to 43, or a pharmaceutically acceptable salt thereof, or the compound of clause 44, and one or more pharmaceutically acceptable carriers or vehicles.
46. A pharmaceutical composition comprising the compound of any one of clauses 1 to 43, or a pharmaceutically acceptable salt thereof, or the compound of clause 44, and one or more pharmaceutically acceptable carriers or vehicles.
47. A method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject the compound of any one of clauses 1 to 43, or a pharmaceutically acceptable salt thereof, the compound of clause 44, or the pharmaceutical composition of clause 45 or 46.
48. The method of clause 47, wherein the voltage-gated sodium channel is $Na_v1.8$.
49. A method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprising administering to the subject an effective amount of the compound of any one of clauses 1 to 43, or a pharmaceutically acceptable salt thereof, the compound of clause 44, or the pharmaceutical composition of clause 45 or 46.
50. The method of clause 49, where the method comprises treating or lessening the severity in the subject of neuropathic pain.
51. The method of clause 50, wherein the neuropathic pain comprises post-herpetic neuralgia.
52. The method of clause 50, wherein the neuropathic pain comprises small-fiber neuropathy.
53. The method of clause 50, wherein the neuropathic pain comprises idiopathic small-fiber neuropathy.
54. The method of clause 50, wherein the neuropathic pain comprises diabetic neuropathy.
55. The method of clause 54, wherein the diabetic neuropathy comprises diabetic peripheral neuropathy.
56. The method of clause 49, wherein the method comprises treating or lessening the severity in the subject of musculoskeletal pain.
57. The method of clause 56, wherein the musculoskeletal pain comprises osteoarthritis pain.

58. The method of clause 49, wherein the method comprises treating or lessening the severity in the subject of acute pain.
59. The method of clause 58, wherein the acute pain comprises acute post-operative pain.
60. The method of clause 49, wherein the method comprises treating or lessening the severity in the subject of postsurgical pain.
61. The method of clause 60, wherein the postsurgical pain comprises bunionectomy pain.
62. The method of clause 60, wherein the postsurgical pain comprises abdominoplasty pain.
63. The method of clause 60, wherein the postsurgical pain comprises herniorrhaphy pain.
64. The method of clause 49, wherein the method comprises treating or lessening the severity in the subject of visceral pain.
65. The method of any one of clauses 47 to 64, wherein said subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound, pharmaceutically acceptable salt, or pharmaceutical composition.
66. Use of the compound of any one of clauses 1 to 43, or a pharmaceutically acceptable salt thereof, the compound of clause 44, or the pharmaceutical composition of clause 45 or 46, as a medicament.

EXAMPLES

[0254] General methods. ¹H NMR spectra were obtained as solutions in an appropriate deuterated solvent such as dimethyl sulfoxide-*d*₆ (DMSO-*d*₆).

[0255] Compound purity, retention time, and electrospray mass spectrometry (ESI-MS) data were determined by LC/MS analysis.

[0256] LC/MS Method: The compounds were analysed by LC/MS according to one of the following methods, as shown in Table 1

Table 1. Description of LC/MS Methods

LC/MS Method	Method Description
A	Waters™ Acquity BEH C ₈ , 1.7 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (10 mM Ammonium Formate, pH 9), 45 °C. Flow rate 0.6 mL/min over 5.0 min
B	Kinetex® EVO C ₁₈ , 2.6 μm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (10 mM Ammonium Formate, pH 9), 45 °C, Flow rate 0.7 mL/min over 4.0 min

LC/MS Method	Method Description
C	Kinetex® EVO C ₁₈ , 2.6 µm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (10 mM Ammonium Formate, pH 9), 45 °C, Flow rate 1.0 mL/min over 1.5 min
D	Waters™ Acquity BEH C ₁₈ , 1.7 µm 2.1 x 50 mm, 1 to 99% MeCN in H ₂ O (0.05% Trifluoroacetic acid), 60°C, Flow rate 1.2 ml/min over 2.9 min
E	Kinetex® Polar C ₁₈ , 2.6 µm 3.0 x 50 mm, 5 to 95% MeCN in H ₂ O (0.1% Formic Acid), Flow rate 1.2 mL/min over 6 min
F	SunFire C ₁₈ , 3.5 µm 75 x 4.6 mm, initial gradient 5 to 95% MeCN in H ₂ O (0.1% Formic Acid) for 1 min then linear gradient to 95% MeCN for 5 min. 45 °C, Flow rate 1.5 mL/min over 6 min
G	XBridge C ₁₈ , 5 µm 4.6 x 75 mm, initial gradient 5 to 95% MeCN (NH ₄ HCO ₃), 6 min run with 1 min equilibration gradient 0 to 3 min at 95% MeCN and hold for 3 min, Flow rate 1.5 mL/min
H	Waters™ Acquity CSH C ₁₈ , 1.7 µm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (0.1% TFA, pH 2), 45 °C, Flow rate 0.6 mL/min over 5.0 min
I	Waters™ Acquity CSH C ₁₈ , 1.7 µm 2.1 x 50 mm, 2 to 95% MeCN in H ₂ O (0.1% Formic Acid), 40 °C, Flow rate 0.8 mL/min over 4.6 min
J	Waters™ Acquity BEH C ₁₈ , 2.5 µm 2.1 x 50 mm, 2 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 4.6 min
K	SunFire C ₁₈ , 3.5 µm 75 x 4.6 mm, initial gradient 5 to 95% MeCN in H ₂ O (0.1% Formic acid) then linear gradient to 95% MeCN for 4 min, hold for 2 min at 95% MeCN, 45 °C, Flow rate 1.5mL/min over 6 min
L	Waters™ Acquity BEH C ₁₈ , 2.5 µm 2.1 x 50 mm, 2 to 50% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 4.6 min
M	Waters™ Acquity CSH C ₁₈ , 1.7 µm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (0.1% TFA), 45 °C, Flow rate 1.0 mL/min over 1.5 min
N	Waters™ Acquity CSH C ₁₈ , 1.7 µm 2.1 x 50 mm, 2 to 95% MeCN in water (0.1% Formic Acid), 40 °C, Flow rate 0.8 mL/min over 1.4 min
O	YMC Triart C ₁₈ , 3 µm 33 x 2.1 mm, 2 to 98% MeCN in H ₂ O (5 mM NH ₄ OAc), Flow rate 1.0 mL/min over 3 min
P	Waters™ Acquity BEH C ₁₈ , 2.5 µm 2.1 x 50 mm, 2 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 1.4 min
Q	Waters™ Acquity BEH C ₁₈ , 1.7 µm 2.1 x 50 mm, 1 to 99% MeCN in H ₂ O (0.05% Trifluoroacetic acid), 60°C, Flow rate 1.2 ml/min over 4.5 min
R	Waters™ Acquity BEH C ₁₈ , 2.5 µm 2.1 x 50 mm, 20 to 70% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 4.6 min
S	Kinetex® Polar C ₁₈ , 2.6 µm 3.0 x 50 mm, 5 to 95% MeCN in H ₂ O (0.1% Formic Acid), Flow rate 1.2 mL/min over 3 min
T	Waters™ Acquity BEH C ₁₈ , 1.7 µm 2.1 x 30 mm, 1 to 99% MeCN in H ₂ O (0.05% Trifluoroacetic acid), 60°C, Flow rate 1.5 ml/min over 1.0 min
U	YMC Triart C ₁₈ , 3 µm 33 x 2.1 mm, 2 to 98% MeCN in H ₂ O (0.05% Formic Acid), Flow rate 1.0 mL/min over 3 min
V	Waters™ Acquity BEH, C ₁₈ 1.7 µm 2.1 x 50 mm, 1 to 99% MeCN in H ₂ O (10 mM Ammonium formate), 60°C, Flow rate 1.2 ml/min over 4.5 min
W	Waters™ CSH C ₁₈ , 1.7 µm 2.1 x 50 mm, 2 to 98% MeCN in H ₂ O (0.1% TFA), 45 °C, Flow rate 0.6 mL/min over 4.0 min
X	Waters™ Acquity BEH C ₈ , 1.7 µm 50 x 2.1 mm, 2 to 98% 90:10 MeCN:H ₂ O (0.05% Formic Acid), Flow rate 0.8 mL/min over 3 min
Y	XBridge C ₁₈ , 5 µm 50 x 4.6 mm, 10 to 90% MeCN in H ₂ O (10 mM NH ₄ OAc), Flow rate 1.2 mL/min over 6 min
Z	YMC Triart C ₁₈ , 3 µm 33 x 2.1 mm, 5 to 95% MeCN in H ₂ O (0.05% Formic Acid), Flow rate 1.0 mL/min over 12 min

LC/MS Method	Method Description
AA	Waters™ Acquity BEH C ₈ , 1.7 μm 2.1 x 50 mm, 50 to 95% MeCN in H ₂ O (0.1% NH ₃), 40 °C, Flow rate 0.8 mL/min over 1.4 min
AB	Waters™ Acquity BEH C ₈ , 1.7 μm 50 x 2.1 mm, 5 to 95% 90:10 MeCN:H ₂ O (0.05% Formic Acid), Flow rate 0.8 mL/min over 5 min
AC	Waters™ Acquity HSS T3 C ₁₈ , 1.8 μm, 50 x 2.1 mm, 2 to 95% MeCN in H ₂ O (0.1% Formic Acid), 40 °C, Flow rate 0.8 mL/min over 1.4 min

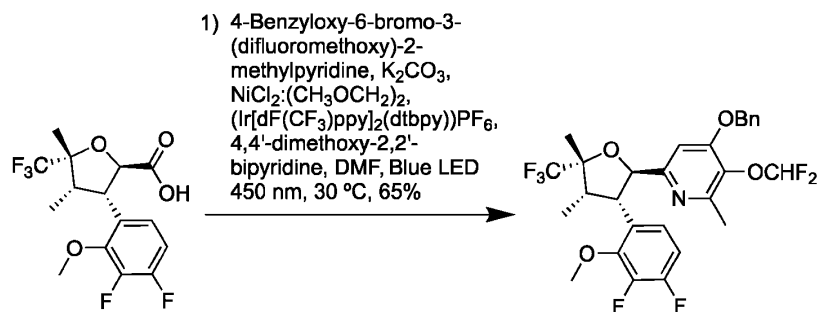
Abbreviations

[0257] Unless otherwise noted, or where the context dictates otherwise, the following abbreviations shall be understood to have the following meanings:

<u>Abbreviation</u>	<u>Meaning</u>
NMR	Nuclear magnetic resonance
ESI-MS	Electrospray mass spectrometry
LC/MS	Liquid chromatography-mass spectrometry
UPLC	Ultra performance liquid chromatography
HPLC/MS/MS	High performance liquid chromatography/tandem mass spectrometry
IS	Internal standard
HPLC	High performance liquid chromatography
SFC	Supercritical fluid chromatography
ESI	Electrospray ionization
cm	centimeters
g	grams
mg	milligrams
L	Liter(s)
mL	Milliliters
μL	Microliters
nL	nanoliters
mmol	millimoles
hr, h	hours
min	Minutes
ms	millisecond
mm	Millimeters
μm	Micrometers
nm	nanometer
MHz	Megahertz
Hz	Hertz
N	Normal (concentration)
M	Molar (concentration)
mM	Millimolar (concentration)
μM	Micromolar (concentration)
μW	Microwave
ppm	Parts per million
% w/v	Weight-volume concentration
% w/w	Weight-weight concentration
AcOH	Acetic acid
B ₂ Pin ₂	Bis(pinacolato)diboron
<i>t</i> BuOH	<i>tert</i> -butyl alcohol
CPME	Cyclopentyl methyl ether
DCM	Dichloromethane
DCE	Dichloroethane
DIC	<i>N,N'</i> -Diisopropylcarbodiimide

<u>Abbreviation</u>	<u>Meaning</u>
DIEA, DIPEA	N, N-Diisopropyl ethyl amine
DIPA	Diisopropyl amine
DMA	N,N-Dimethyl acetamide
DMAP	4-(Dimethylamino)pyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DRG	Dorsal root ganglia
EtOH	Ethanol
EtOAc	ethyl acetate
IMS	Industrial methylated spirit
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
TFA	Trifluoroacetic acid
T3P	Propylphosphonic anhydride, i.e., 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide
Ru(BPY) ₃ .6H ₂ O	Tris(2,2'-bipyridyl)dichlororuthenium(II) hexahydrate
LiHMDS	Lithium hexamethyldisilazane
MeOH	Methanol
MeCN, ACN	Acetonitrile
mCPBA	3-chloroperbenzoic acid
2-MeTHF	2-Methyltetrahydrofuran
MTBE	Methyl <i>tert</i> -butyl ether
NMP	N-Methylpyrrolidone
Proton-sponge [®]	1,8-Bis(dimethylamino)naphthalene
STAB	Sodium triacetoxymethylborohydride
TBAF	Tetrabutylammonium fluoride
TEA	Triethylamine
THF	Tetrahydrofuran
TBME	Methyl <i>tert</i> -butyl ether or <i>tert</i> -Butyl methyl ether
RB	Round bottom (flask)
RT	Ambient temperature
r.t.	Retention time
LED	Light Emitting Diode
4CzIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
ca.	Circa (approximately)
E-VIPR	Electrical stimulation voltage ion probe reader
HEK	Human embryonic kidney
KIR2.1	Inward-rectifier potassium ion channel 2.1
DMEM	Dulbecco's Modified Eagle's Medium
FBS	Fetal bovine serum
NEAA	Non-essential amino acids
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
DiSBAC ₆ (3)	Bis-(1,3-diethylthiobarbituric acid) trimethine oxonol
CC2-DMPE	Chlorocoumarin-2-dimyristoyl phosphatidylethanolamine
VABSC-1	Voltage Assay Background Suppression Compound
HS	Human serum
BSA	Bovine Serum Albumin

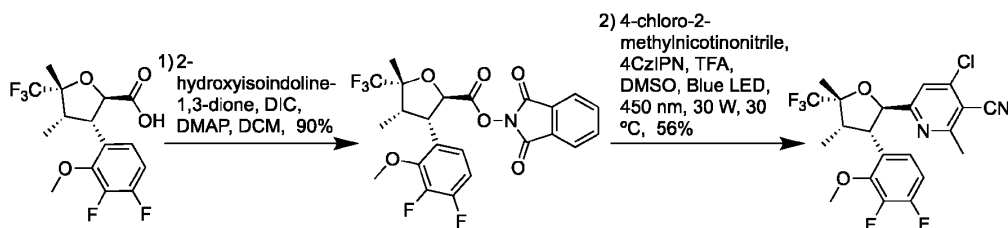
GENERAL METHOD A:



[0258] Step 1:

[0259] A 8-mL dram vial, equipped with a stir bar, was charged with (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 100 mg, 0.282 mmol), 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine (98 mg, 0.285 mmol), K_2CO_3 (59 mg, 0.43 mmol), $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (32 mg, 0.029 mmol), $NiCl_2 \cdot (CH_3OCH_2)_2$ (10 mg, 0.046 mmol) and 4,4'-dimethoxy-2,2'-bipyridine (10 mg, 0.046 mmol). DMF (5.0 mL) was injected into the tube via syringe under a nitrogen atmosphere. The mixture was degassed for 15 min by bubbling nitrogen through, then sealed with parafilm. The solution was stirred at 30 °C under the irradiation of a blue LED (450 nm) using a Penn OC Photoreactor M1 for 15 h. Upon reaction completion, the mixture was poured over a saturated $NaHCO_3$ solution (10 mL) and extracted with MTBE (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$) filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO_2 , 0 to 100% EtOAc in heptane) gave 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridine (106 mg, 65%) as a colourless oil. ESI-MS *m/z* calc. 573.175, found 574.6 ($M+1$)⁺; Retention time: 4.33 minutes using LC/MS method A.

GENERAL METHOD B:



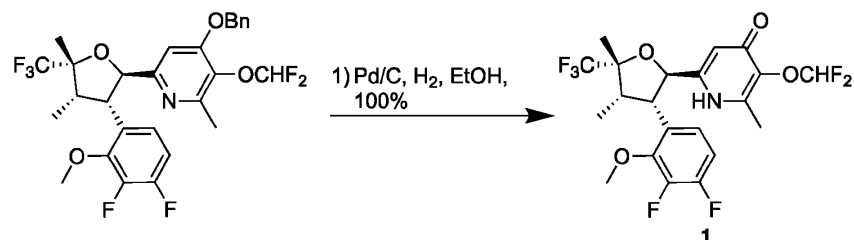
[0260] Step 1:

[0261] In a reaction vessel, a mixture of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 1.618 g, 4.567 mmol) and 2-

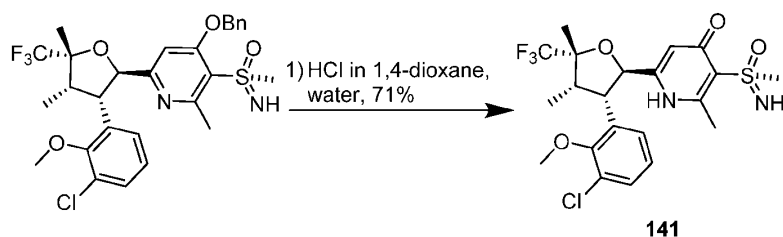
hydroxyisoindoline-1,3-dione (920 mg, 5.640 mmol) were dissolved in DCM (25 mL). DMAP (687 mg, 5.62 mmol) was added and the reaction mixture was stirred for 10 min at ambient temperature. DIC (760 μ L, 4.85 mmol) was added and the mixture was stirred at ambient temperature for 1 h. On reaction completion, the mixture was treated with 2 M HCl (40 mL). The aqueous layer was separated and extracted with DCM (2 x 40 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. After adding DCM to the residue, a white precipitate formed. The solid was filtered, and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (40 g SiO_2 , 0 to 40% EtOAc in heptane) gave 1,3-dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2.06 g, 90%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, J = 5.5, 3.1 Hz, 2H), 7.81 (dd, J = 5.5, 3.1 Hz, 2H), 7.07 - 6.98 (m, 1H), 6.92 (td, J = 9.2, 7.3 Hz, 1H), 5.33 (d, J = 0.8 Hz, 1H), 4.46 (t, J = 8.9 Hz, 1H), 4.10 (d, J = 2.4 Hz, 3H), 2.81 (q, J = 7.7 Hz, 1H), 1.69 (q, J = 1.2 Hz, 3H), 0.89 - 0.82 (m, 3H) ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -74.46, -136.60, -153.83 ppm. ESI-MS m/z calc. 499.105, found 500.0 ($\text{M}+1$) $^+$; Retention time: 1.12 minutes using LC/MS method M.

[0262] Step 2

[0263] A 5-mL microwave vial, equipped with a teflon cap and a stir bar, was charged with 1,3-dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (51 mg, 0.102 mmol), DMSO (650 μ L), TFA (13 μ L, 0.17 mmol), 4-chloro-2-methylnicotinonitrile (13 mg, 0.085 mmol) and 4CzIPN (0.8 mg, 0.001 mmol). Nitrogen gas was vigorously bubbled through the solution for 5 min. The vial was sealed, and placed in a Hepatochem photoreactor (450 nM, 30W). The reaction was stirred and irradiated with blue light for 1 h at ambient temperature. Purification by flash chromatography (SiO_2 , 1 to 100% EtOAc in hexanes) gave 4-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinonitrile (22 mg, 56%) as a clear oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.51 (s, 1H), 7.19 - 7.07 (m, 1H), 6.95 - 6.75 (m, 1H), 5.47 (d, J = 11.0 Hz, 1H), 4.04 - 3.97 (m, 1H), 3.94 (d, J = 2.7 Hz, 3H), 2.87 - 2.73 (m, 1H), 2.66 (s, 3H), 1.74 (s, 3H), 0.84 (d, J = 7.7, 2.3 Hz, 3H) ppm. ESI-MS m/z calc. 460.098, found 461.1 ($\text{M}+1$) $^+$; Retention time: 2.26 minutes using LC/MS method D.

GENERAL METHOD C: (E.G., 1)**[0264] Step 1**

[0265] A solution of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridine (**Product of Example 1, Step 1**, 106 mg, 0.185 mmol) in EtOH (2.0 mL) was added to a 20-mL vial containing Pd/C (10 wt % loading, wet, Degussa, 5 mg, 0.005 mmol). The reaction mixture was degassed with nitrogen for 5 min and stirred under a hydrogen atmosphere (balloon) for 5 min. The mixture was stirred under a hydrogen atmosphere for a further 10 min. Upon reaction completion, the mixture was sparged with nitrogen for 5 min and filtered through a 0.45 micron syringe filter. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100% EtOAc in heptane) gave 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridin-4(1*H*)-one (**1**, 92 mg, 100%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 6.41 - 6.36 (m, 1H), 6.34 - 6.26 (m, 1H), 6.21 (t, *J* = 76.6 Hz, 1H), 5.79 (s, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 3.50 (dd, *J* = 11.1, 8.3 Hz, 1H), 2.67 - 2.62 (m, 3H), 2.18 (dq, *J* = 8.3, 7.9 Hz, 1H), 1.74 (s, 3H), 1.00 (s, 3H), 0.23 - 0.17 (m, 3H) ppm; NH pyridone not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.41, -84.37, -139.52, -156.35 ppm. ESI-MS *m/z* calc. 483.128, found 484.5 (M+1)⁺; 482.40 (M-1)⁻; Retention time: 3.17 minutes using LC/MS method A.

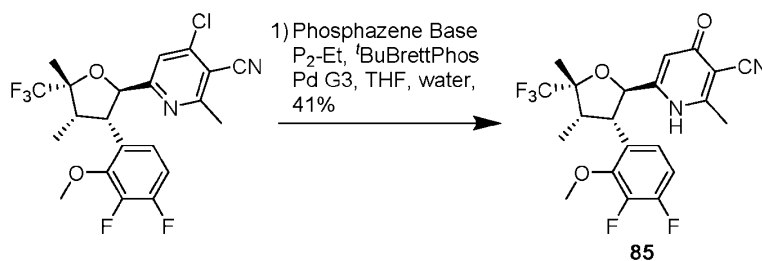
GENERAL METHOD D: (E.G., 141)**[0266] Step 1:**

[0267] To a suspension of *rel*-(*R*)-4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl(imino)(methyl)-λ⁶-sulfanone (**Product of Step 4 in the synthesis of 141**, 5 mg, 0.007 mmol) in

water (0.5 mL) was added HCl (50 μ L, 4 M solution in 1,4-dioxane, 0.2 mmol). The reaction mixture was heated to reflux for 4 h. Upon reaction completion, the mixture was concentrated *in vacuo*.

Purification by preparative reverse phase HPLC (C₁₈ X-bridge column, 38 to 53% MeCN in H₂O containing 1% NH₄OH) gave *rel*-6-((2*R**,3*S**,4*S**,5*R**)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((*R*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**141**, 2.5 mg, 71%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.27 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 6.52 (s, 1H), 5.35 (d, *J* = 11.2 Hz, 1H), 4.31 - 4.22 (m, 1H), 3.84 (s, 3H), 3.30 (s, 3H), 2.88 (p, *J* = 7.8 Hz, 1H), 2.73 (s, 3H), 1.68 (d, *J* = 1.1 Hz, 3H), 0.88 (dq, *J* = 7.5, 2.3 Hz, 3H) ppm; NH pyridone and sulfoximine not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.44 ppm. ESI-MS *m/z* calc. 492.110, found 493.2 (M+1)⁺; 491.2 (M-1)⁻; Retention time: 2.83 minutes using LC/MS method A.

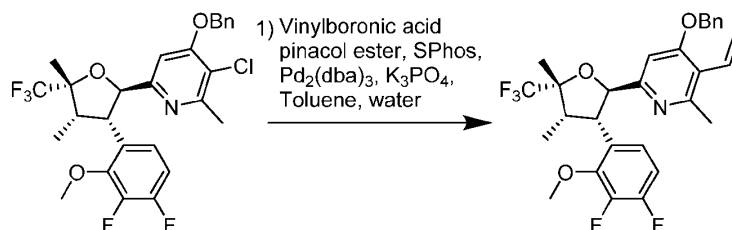
GENERAL METHOD E: (E.G., 85)



[0268] Step 1:

[0269] A stirred mixture of 4-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinonitrile (**Product of Step 1 of Example 4**, 10 mg, 0.022 mmol) and *t*BuBrettPhos Pd G3 (2 mg, 0.002 mmol) in THF (500 μ L) and water (6 μ L) was degassed with nitrogen for 5 min. Phosphazene Base P₂-Et (22 μ L, 0.066 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 h. Upon reaction completion, the mixture was diluted with DMSO (500 μ L) and filtered. Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in H₂O containing 5 mM HCl) gave 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-carbonitrile (**85**, 4 mg, 41%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.15 - 7.03 (m, 1H), 7.03 - 6.92 (m, 1H), 6.47 (d, *J* = 17.3 Hz, 1H), 5.54 - 5.32 (m, 1H), 4.18 (t, *J* = 11.2, 8.4 Hz, 1H), 3.99 (d, *J* = 2.6 Hz, 3H), 2.93 - 2.79 (m, 1H), 2.63 (s, 3H), 1.66 (s, 3H), 0.86 (d, 3H) ppm. ESI-MS *m/z* calc. 442.132, found 443.1 (M+1)⁺; Retention time: 1.58 minutes using LC/MS method D.

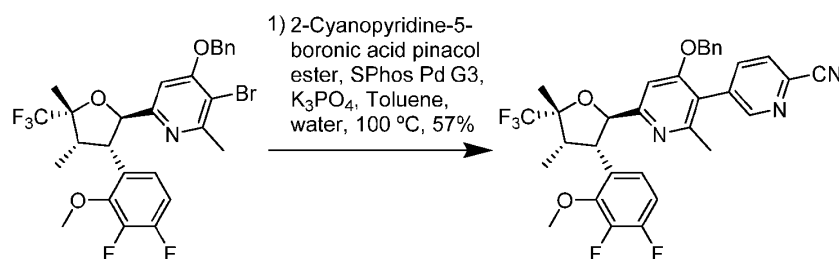
GENERAL METHOD F:



[0270] Step 1:

[0271] $\text{Pd}_2(\text{dba})_3$ (2 mg, 0.002 mmol), SPhos (3 mg, 0.007 mmol) and K_3PO_4 (60 mg, 0.28 mmol) were successively added to a degassed and stirred solution of 4-(benzyloxy)-3-chloro-6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (**Product of Step 2, Example 6**, 50 mg, 0.092 mmol) in toluene (2 mL) and water (200 μL). Vinylboronic acid pinacol ester (25 mg, 0.16 mmol) was added and the reaction mixture was heated to 100 °C for 2 h. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO_2 , 0 to 100% EtOAc in heptane) gave 4-(benzyloxy)-6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-vinylpyridine, which was used without further purification in the next step. ESI-MS m/z calc. 533.199, found 534.6 ($\text{M}+1$)⁺; Retention time: 1.28 minutes using LC/MS method C.

GENERAL METHOD G:

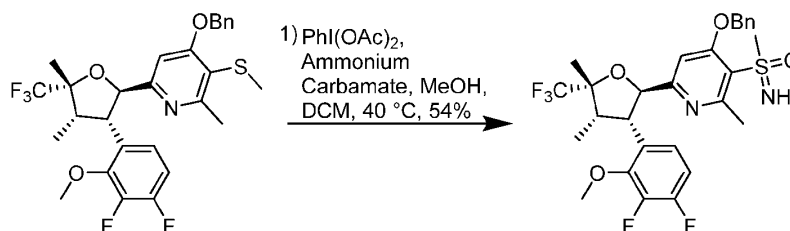


[0272] Step 1:

A vial containing a mixture of 4-(benzyloxy)-3-bromo-6-((2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (**Product of Step 3, Example 11**, 150 mg, 0.253 mmol), 2-cyanopyridine-5-boronic acid pinacol ester (88 mg, 0.383 mmol), SPhos Pd G3 (24 mg, 0.031 mmol) and K_3PO_4 (322 mg, 1.517 mmol) in toluene (1.5 mL) and water (150 μL) was sealed and nitrogen was flushed through the solution for 10 min. The reaction mixture was stirred and heated at 100 °C for 1 h. The mixture was diluted with DMSO (500 μL) and filtered. Purification by reverse phase preparative chromatography (C_{18} column, 1 to 99%

MeCN in H₂O containing 5 mM HCl) gave 4'-(benzyloxy)-6'-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2'-methyl-[3,3'-bipyridine]-6-carbonitrile (88 mg, 57%), which was used without further purification in the next step. ESI-MS *m/z* calc. 609.590, found 610.1 (M+1)⁺; Retention time: 1.91 minutes using LC/MS method D.

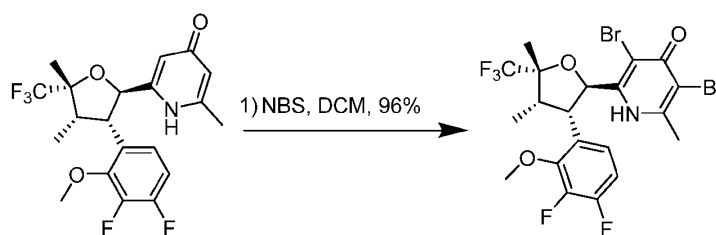
GENERAL METHOD H:



[0273] Step 1:

[0274] Ammonium carbamate (25 mg, 0.320 mmol) was added to a solution of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylthio)pyridine (**Product of Step 2, Example 9**, 70 mg, 0.116 mmol) in MeOH (2 mL) and DCM (2 mL). PhI(OAc)₂ (110 mg, 0.342 mmol) was added and the reaction mixture was heated for 2 h at 40 °C. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was diluted with DCM, filtered and the filtrates were concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100 % EtOAc in heptane) gave *rac*-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (45 mg, 54%). ESI-MS *m/z* calc. 584.177, found 585.5 (M+1)⁺; Retention time: 3.75 minutes using LC/MS method A.

GENERAL METHOD I:

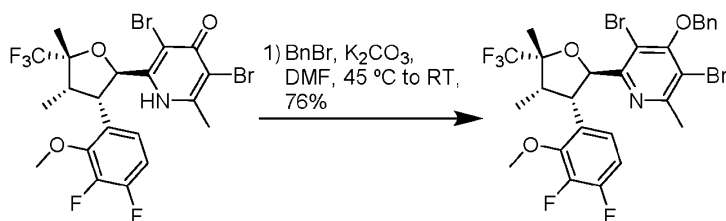


[0275] Step 1:

[0276] 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 1 g, 2.4 mmol) was suspended in DCM (25 mL), cooled in an ice bath and treated with NBS (940 mg, 5.28 mmol). The mixture was

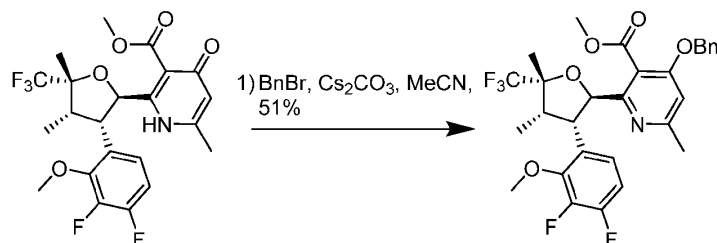
stirred in the ice bath for 5 min and at ambient temperature for 1 h to give a pale-yellow clear solution. The solution was treated with water (50 mL) and a sodium thiosulfate solution (380 mg, 2.40 mmol), and stirred at ambient temperature for 0.5 h to give a 3 phases mixture. The DCM was removed *in vacuo* and the suspension was stirred at ambient temperature for 1 h, after which it was filtered, washing the solid with copious amounts of water. The solid was dried overnight to give 3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (1.33 g, 97%) as a colourless solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.11 (t, *J* = 6.9 Hz, 1H), 6.97 (td, *J* = 9.4, 7.6 Hz, 1H), 5.87 (d, *J* = 10.9 Hz, 1H), 4.47 (t, *J* = 10.5 Hz, 1H), 3.90 (d, *J* = 2.4 Hz, 3H), 3.03 - 2.90 (m, 1H), 2.59 (s, 3H), 1.70 (s, 3H), 0.85 (dt, *J* = 7.9, 2.2 Hz, 3H) ppm; NH pyridone not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -74.70, -139.38, -156.46 (d, *J* = 18.9 Hz) ppm. ESI-MS *m/z* calc. 572.957, found 576.0 (M+1)⁺; Retention time: 2.53 minutes using LC/MS method Q.

GENERAL METHOD J:

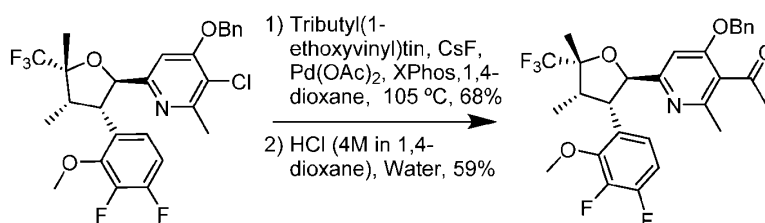


[0277] Step 1:

[0278] K₂CO₃ (270 mg, 1.954 mmol), followed by benzyl bromide (170 μL, 1.429 mmol) were added to a solution of 3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**Product of Step 2, Example 11**, 750 mg, 1.304 mmol) in DMF (7.5 mL) and the mixture was heated at 45 °C for 6.5 h. Another portion of benzyl bromide (31 μL, 0.26 mmol) was added at 45 °C, after which the reaction mixture was cooled to ambient temperature and left stirring for 14 h. The suspension was concentrated *in vacuo* and the residue was partitioned between MTBE (20 mL) and water (20 mL). The organic phase was separated, washed with 1 M K₂CO₃ (20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 50% EtOAc in hexane) gave 4-(benzyloxy)-3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (658 mg, 76%) as a colourless solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.59 - 7.49 (m, 2H), 7.45 - 7.30 (m, 3H), 6.95 - 6.83 (m, 2H), 6.00 (d, *J* = 10.8 Hz, 1H), 5.09 (s, 2H), 4.83 - 4.76 (m, 1H), 3.98 (d, *J* = 2.0 Hz, 3H), 2.85 (p, *J* = 7.6 Hz, 1H), 2.60 (s, 3H), 1.61 (s, 3H), 0.88 (dq, *J* = 7.2, 2.4 Hz, 3H) ppm. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.76, -140.40 (d, *J* = 18.8 Hz), -156.73 (d, *J* = 18.8 Hz) ppm. ESI-MS *m/z* calc. 663.004, found 666.0 (M+1)⁺; Retention time: 3.84 minutes using LC/MS method Q.

GENERAL METHOD K:**[0279] Step 1:**

[0280] Benzyl bromide (190 μ L, 1.597 mmol) was added to a stirring suspension of methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**Product of Step 1 Example 12**, 750 mg, 1.58 mmol) and Cs_2CO_3 (515 mg, 1.58 mmol) in MeCN (3.8 mL). The reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was diluted with DMSO (500 μ L) and filtered. Purification by reverse phase preparative chromatography (C_{18} column, 1 to 99% MeCN in H_2O containing 5 mM HCl) gave methyl 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylnicotinate (460 mg, 51%) as a white semi-solid. ^1H NMR (400 MHz, Methanol- d_4) δ 7.41 - 7.27 (m, 5H), 7.11 - 7.00 (m, 1H), 6.95 (s, 1H), 6.94 - 6.86 (m, 1H), 5.57 - 5.41 (m, 1H), 5.17 (s, 2H), 4.66 (dd, J = 10.7, 8.5 Hz, 1H), 3.91 (d, J = 1.9 Hz, 3H), 3.87 (s, 3H), 2.79 (p, J = 7.8 Hz, 1H), 2.40 (s, 3H), 1.57 (s, 3H), 0.90 - 0.73 (m, 3H) ppm. ESI-MS m/z calc. 565.189, found 566.3 ($\text{M}+1$) $^+$; Retention time: 2.14 minutes using LC/MS method D.

GENERAL METHOD L:**[0281] Step 1:**

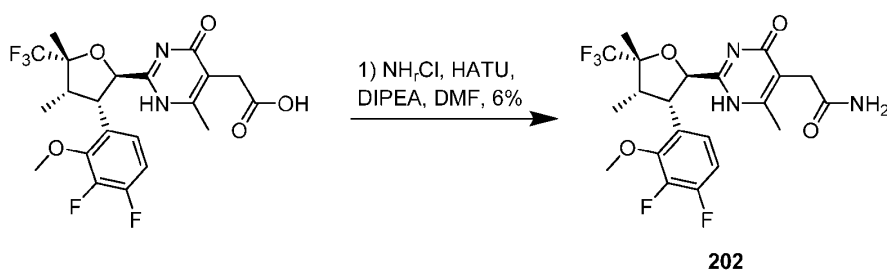
[0282] A 4-mL screw-top vial containing 4-(benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (**Product of Step 2 Example 6**, 65 mg, 0.120 mmol), $\text{Pd}(\text{OAc})_2$ (2.7 mg, 0.012 mmol), XPhos (5.7 mg, 0.012 mmol) and CsF (64 mg, 0.42 mmol) was purged with nitrogen. Nitrogen flushed 1,4-dioxane (1 mL) and tributyl(1-ethoxyvinyl)tin (65 μ L, 0.192 mmol) were added and nitrogen was passed through the mixture for a further 2 min. The vial was sealed and the mixture was heated at 105

°C for 2 h. The mixture was cooled to ambient temperature and filtered through a Celite® pad, washing with EtOAc. The filtrate was concentrated *in vacuo* to give a yellow oil (120 mg). Purification by flash chromatography gave 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-ethoxyvinyl)-2-methylpyridine (47 mg, 68%) as a colourless gum. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.44 - 7.29 (m, 5H), 7.12 (td, *J* = 6.0, 2.8 Hz, 1H), 7.04 (s, 1H), 6.88 (td, *J* = 9.5, 9.1, 7.6 Hz, 1H), 5.40 (d, *J* = 11.1 Hz, 1H), 5.24 (s, 2H), 4.52 (d, *J* = 2.3 Hz, 1H), 4.14 (d, *J* = 2.2 Hz, 1H), 4.10 (dd, *J* = 11.1, 7.8 Hz, 1H), 3.90 (d, *J* = 7.0 Hz, 2H), 3.86 (d, *J* = 2.2 Hz, 3H), 2.80 (p, *J* = 7.5 Hz, 1H), 2.41 (s, 3H), 1.66 (d, *J* = 1.2 Hz, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 0.88 - 0.81 (m, 3H) ppm. ESI-MS *m/z* calc. 577.225, found 578.7 (M+1)⁺; Retention time: 1.28 minutes using LC/MS method C.

[0283] Step 2:

[0284] A mixture of hydrogen chloride (0.5 mL, 4 M solution in 1,4-dioxane, 2 mmol) and water (10 µL, 0.56 mmol) (one drop) was added to 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-ethoxyvinyl)-2-methylpyridine (45 mg) and the resulting mixture was stirred at ambient temperature for 25 min. The mixture was quenched by addition of a saturated NaHCO₃ solution (4 mL). The mixture was diluted with water (6 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with a saturated brine solution, dried (MgSO₄), filtered and concentrated *in vacuo* to give 1-(4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-one (39 mg, 59%) as a light yellow oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.45 - 7.34 (m, 5H), 7.19 - 7.13 (m, 2H), 6.90 (ddd, *J* = 10.0, 8.9, 7.6 Hz, 1H), 5.44 (d, *J* = 11.0 Hz, 1H), 5.30 (s, 2H), 4.19 - 4.10 (m, 1H), 3.89 (d, *J* = 2.2 Hz, 3H), 2.81 (p, *J* = 7.6 Hz, 1H), 2.48 (s, 3H), 2.33 (s, 3H), 1.66 (d, *J* = 1.2 Hz, 3H), 0.89 - 0.82 (m, 3H) ppm. ESI-MS *m/z* calc. 549.194, found 550.6 (M+1)⁺; Retention time: 1.20 minutes using LC/MS method C.

GENERAL METHOD M: (E.G., 202)



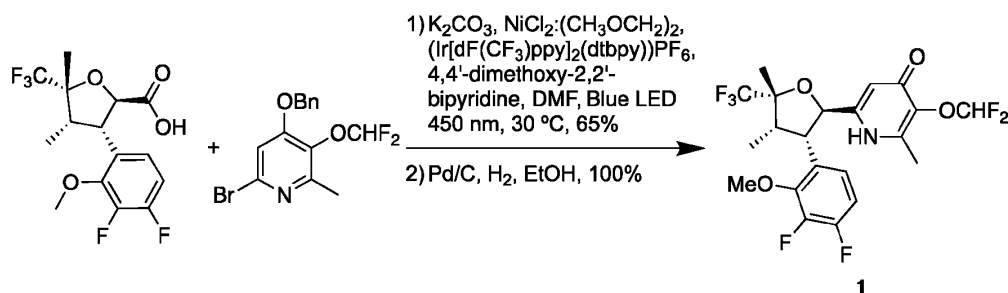
[0285] Step 1:

[0286] 2-(2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidin-5-yl)acetic acid (49 mg,

0.094 mmol) was dissolved in DMF (1 mL). NH_4Cl (15 mg, 0.28 mmol), HATU (72 mg, 0.19 mmol) and DIPEA (61 mg, 82 μL , 0.47 mmol) were successively added and the mixture was stirred at ambient temperature overnight. The mixture was partitioned between EtOAc and an aqueous NaHCO_3 solution, and the aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (4 g C_{18} column, 10 to 80% MeCN in H_2O containing 0.1% NH_4OH) followed by reverse phase HPLC (XBridge C_{18} column, 10 to 60% MeCN in H_2O containing 0.1% NH_4OH) gave 2-(2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidin-5-yl)acetamide (**202**, 2.8 mg, 6%) as a colourless solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.15 - 7.11 (m, 1H), 6.86 (td, J = 9.2, 7.5 Hz, 1H), 6.51 (br s, 1H), 5.27 (d, J = 10.5 Hz, 1H), 5.13 (br s, 1H), 3.99 - 3.94 (m, 4H), 3.41 (s, 2H), 2.81 - 2.73 (m, 1H), 2.27 (s, 3H), 1.65 (s, 3H), 0.81 - 0.78 (m, 3H) ppm; NH pyrimidine not observed. ESI-MS m/z calc. 475.153, found 476.1 ($\text{M}+1$) $^+$; Retention time: 1.33 minutes using LC/MS method J.

Example 1

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridin-4(1*H*)-one (**1**)



[0287] Step 1:

[0288] (2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 100 mg, 0.282 mmol) and 4-benzyloxy-6-bromo-3-(difluoromethoxy)-2-methylpyridine (**Int-21**, 98 mg, 0.285 mmol) were treated via the method described in General Method A to give 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridine (106 mg, 65%) as a colourless oil. ESI-MS m/z calc. 573.175, found 574.6 ($\text{M}+1$) $^+$; Retention time: 4.33 minutes using LC/MS Method A.

[0289] Step 2:

[0290] 4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridine (106 mg, 0.185 mmol)

was treated via the method described in General Method C to give 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-2-methylpyridin-4(1*H*)-one (**1**) (92 mg, 100%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 6.41 - 6.36 (m, 1H), 6.34 - 6.26 (m, 1H), 6.21 (t, *J* = 76.6 Hz, 1H), 5.79 (s, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 3.50 (dd, *J* = 11.1, 8.3 Hz, 1H), 2.67 - 2.62 (m, 3H), 2.18 (dq, *J* = 8.3, 7.9 Hz, 1H), 1.74 (s, 3H), 1.00 (s, 3H), 0.23 - 0.17 (m, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 483.128, found 484.5 (M+1)⁺; 482.4 (M-1)⁻; Retention time: 3.17 minutes using LC/MS Method A.

[0291] The following compounds were made using the methods described in Example 1 except that different halide coupling partners were used in Step 1 in place of 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**. In the case of **25**, EtOAc was used as the solvent in place of EtOH in Step 2:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
2	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	417.136	418.5	1.87	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 14.85 - 13.22 (m, 1H), 7.27 (ddd, <i>J</i> = 7.4, 5.3, 1.6 Hz, 1H), 7.22 (s, 1H), 7.13 (td, <i>J</i> = 9.4, 8.9, 7.7 Hz, 1H), 6.93 (s, 1H), 5.67 (d, <i>J</i> = 11.2 Hz, 1H), 4.32 (dd, <i>J</i> = 11.3, 8.0 Hz, 1H), 3.93 (d, <i>J</i> = 2.1 Hz, 3H), 2.88 (p, <i>J</i> = 7.7 Hz, 1H), 2.55 (s, 3H), 1.69 (s, 3H), 0.76 (dd, <i>J</i> = 7.5, 2.5 Hz, 3H) ppm.
3	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2,3-dimethylpyridin-4(1 <i>H</i>)-one	431.152	432.4	1.83	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.44 (s, 1H), 7.27 (ddd, <i>J</i> = 8.3, 5.8, 2.0 Hz, 1H), 7.17 - 7.06 (m, 1H), 7.02 (s, 1H), 5.62 (d, <i>J</i> = 11.2 Hz, 1H), 4.23 (dd, <i>J</i> = 11.3, 7.8 Hz, 1H), 3.93 (d, <i>J</i> = 2.1 Hz, 3H), 2.84 (p, <i>J</i> = 7.6 Hz, 1H), 2.48 (s, 3H), 2.00 (s, 3H), 1.66 (s, 3H), 0.77 (d, 3H) ppm.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
4	Ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (Hydrochloride salt)	489.157	490.1	1.69	D	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.20 - 7.08 (m, 1H), 7.08 - 6.96 (m, 1H), 6.59 (s, 1H), 5.37 (dd, <i>J</i> = 11.2, 3.0 Hz, 1H), 4.63 (t, <i>J</i> = 9.8 Hz, 1H), 4.37 - 4.29 (m, 2H), 3.89 (d, <i>J</i> = 1.9 Hz, 3H), 2.80 (t, <i>J</i> = 8.2 Hz, 1H), 2.34 (s, 3H), 1.56 (s, 3H), 1.26 (t, <i>J</i> = 7.2, 2.3 Hz, 3H), 0.72 (d, 3H) ppm; NH pyridone not observed.
5	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)pyridine-4(1 <i>H</i>)-one	403.121	404.5	1.81	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.43 (d, <i>J</i> = 6.9 Hz, 1H), 7.26 (ddd, <i>J</i> = 8.2, 5.6, 2.3 Hz, 1H), 7.20 (dd, <i>J</i> = 6.9, 2.6 Hz, 1H), 7.07 (ddd, <i>J</i> = 9.9, 8.9, 7.5 Hz, 1H), 6.99 (s, 1H), 5.80 (d, <i>J</i> = 11.3 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.4 Hz, 1H), 3.96 (s, 3H), 2.88 (p, <i>J</i> = 7.8 Hz, 1H), 1.73 (s, 3H), 0.91 (d, <i>J</i> = 7.4, 3H) ppm; NH pyridone not observed.
6	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(methoxymethyl)-2-methylpyridine-4(1 <i>H</i>)-one	461.163	462.5	2.93	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.06 (ddd, <i>J</i> = 8.0, 5.6, 2.1 Hz, 1H), 6.98 (ddd, <i>J</i> = 9.9, 8.9, 7.4 Hz, 1H), 6.38 (s, 1H), 5.35 (d, <i>J</i> = 11.3 Hz, 1H), 4.40 (s, 2H), 4.19 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.98 (d, <i>J</i> = 2.4 Hz, 3H), 3.34 (s, 3H), 2.86 (p, <i>J</i> = 7.8 Hz, 1H), 2.45 (s, 3H), 1.68 (d, <i>J</i> = 1.2 Hz, 3H), 0.88 (dt, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
7	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-3- (methoxymethyl)- 6- methylpyridin- 4(1 <i>H</i>)-one	461.163	462.4	2.03	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.15 (ddd, <i>J</i> = 8.2, 5.6, 2.2 Hz, 1H), 7.05 - 6.99 (m, 1H), 6.98 (s, 1H), 5.87 (d, <i>J</i> = 10.8 Hz, 1H), 4.52 (t, <i>J</i> = 10.6 Hz, 1H), 4.46 (s, 2H), 3.91 (s, 3H), 3.32 (s, 3H), 3.06 (dq, <i>J</i> = 10.4, 7.8 Hz, 1H), 2.66 (s, 3H), 1.82 (s, 3H), 0.87 (dt, <i>J</i> = 7.8, 2.2 Hz, 3H) ppm; NH pyridone not observed.
8	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-3- methoxy-6- methylpyridin- 4(1 <i>H</i>)-one	447.147	448.1	2.05	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.12 - 7.03 (m, 1H), 7.03 - 6.91 (m, 2H), 5.78 (d, <i>J</i> = 11.2 Hz, 1H), 4.48 (t, <i>J</i> = 11.1, 9.5 Hz, 1H), 3.95 (d, <i>J</i> = 2.6 Hz, 3H), 3.84 (s, 3H), 3.07 - 2.89 (m, 1H), 2.59 (s, 3H), 1.73 (d, <i>J</i> = 1.3 Hz, 3H), 0.86 (d, <i>J</i> = 7.5, 2.2 Hz, 3H) ppm; NH pyridone not observed.
9	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-3- (hydroxymethyl)- 6- methylpyridin- 4(1 <i>H</i>)-one	447.147	448.1	1.81	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.20 (ddd, <i>J</i> = 8.2, 5.6, 2.2 Hz, 1H), 7.03 - 6.93 (m, 2H), 5.97 (d, <i>J</i> = 10.9 Hz, 1H), 4.68 - 4.48 (m, 3H), 3.90 (s, 3H), 3.04 (dq, <i>J</i> = 10.3, 7.8 Hz, 1H), 2.63 (s, 3H), 1.73 (s, 3H), 0.87 (dq, <i>J</i> = 7.5, 2.2 Hz, 3H) ppm; NH pyridone and OH alcohol not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
10	Ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxylate	503.173	504.1	2.46	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.08 - 6.98 (m, 1H), 7.04 - 6.92 (m, 1H), 5.42 (d, <i>J</i> = 10.9 Hz, 1H), 4.50 (t, <i>J</i> = 10.4 Hz, 1H), 4.35 (dq, <i>J</i> = 10.8, 7.2 Hz, 1H), 4.23 (dq, <i>J</i> = 10.8, 7.1 Hz, 1H), 3.88 (d, <i>J</i> = 2.3 Hz, 3H), 2.97 - 2.82 (m, 1H), 2.42 (s, 3H), 2.02 (s, 3H), 1.64 (s, 3H), 1.32 (t, <i>J</i> = 7.2 Hz, 3H), 0.81 (dt, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.
11	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-hydroxypropan-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	475.178	476.2	2.01	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.15 - 7.06 (m, 2H), 7.06 - 6.96 (m, 1H), 5.62 (d, <i>J</i> = 11.3 Hz, 1H), 4.28 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 4.01 (s, 3H), 2.93 (q, <i>J</i> = 7.8 Hz, 1H), 2.83 (s, 3H), 1.69 (s, 9H), 0.89 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.
12	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-methoxyethoxy)-6-methylpyridin-4(1 <i>H</i>)-one	491.173	492.2	2.14	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.22 (ddd, <i>J</i> = 8.3, 5.6, 2.2 Hz, 1H), 6.92 (td, <i>J</i> = 9.5, 7.7 Hz, 1H), 6.71 (s, 1H), 6.03 (d, <i>J</i> = 11.2 Hz, 1H), 4.40 - 4.27 (m, 2H), 4.12 (ddd, <i>J</i> = 10.8, 7.1, 2.4 Hz, 1H), 3.94 (s, 3H), 3.73 (ddd, <i>J</i> = 11.4, 7.0, 2.4 Hz, 1H), 3.61 (ddd, <i>J</i> = 11.3, 5.4, 2.3 Hz, 1H), 3.42 (s, 3H), 2.95 (p, <i>J</i> = 8.0 Hz, 1H), 2.53 (s, 3H), 1.74 (s, 3H), 0.84 (dd, <i>J</i> = 7.5, 2.4 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
13	6- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)- <i>N,N</i> ,2- trimethyl-4-oxo- 1,4- dihydropyridine- 3-carboxamide	488.173	489.1	1.90	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.21 - 7.09 (m, 1H), 7.07 - 6.96 (m, 1H), 6.88 (d, <i>J</i> = 17.2 Hz, 1H), 5.64 (d, <i>J</i> = 11.1 Hz, 1H), 4.26 (dd, <i>J</i> = 11.2, 8.4 Hz, 1H), 4.00 (s, 3H), 3.10 (s, 3H), 2.91 (dd, <i>J</i> = 7.6, 4.0 Hz, 4H), 2.53 (s, 3H), 1.70 (s, 3H), 0.90 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm.
14	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-5- methoxypyridin- 4(1 <i>H</i>)-one	433.131	434.1	1.87	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.04 (s, 1H), 7.20 (t, <i>J</i> = 7.3 Hz, 1H), 7.10 - 6.98 (m, 1H), 6.95 (s, 1H), 5.68 (d, <i>J</i> = 11.3 Hz, 1H), 4.15 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.98 (d, <i>J</i> = 1.7 Hz, 3H), 3.96 (d, <i>J</i> = 2.5 Hz, 3H), 2.87 (p, <i>J</i> = 7.8 Hz, 1H), 1.72 (s, 3H), 0.90 (dd, <i>J</i> = 7.7, 2.4 Hz, 3H) ppm; NH pyridone not observed.
15	2-Chloro-6- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)pyridine- 4(1 <i>H</i>)-one	437.082	438.1	2.65	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.21 (ddd, <i>J</i> = 8.3, 5.6, 2.2 Hz, 1H), 7.01 (ddd, <i>J</i> = 10.0, 8.9, 7.6 Hz, 1H), 6.73 (d, <i>J</i> = 1.2 Hz, 1H), 6.51 (d, <i>J</i> = 1.2 Hz, 1H), 5.41 (d, <i>J</i> = 11.2 Hz, 1H), 3.93 (dd, <i>J</i> = 11.3, 8.1 Hz, 1H), 3.87 (d, <i>J</i> = 2.3 Hz, 3H), 2.73 (p, <i>J</i> = 7.7 Hz, 1H), 1.66 (d, <i>J</i> = 1.4 Hz, 3H), 0.87 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
16	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl) -4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-3- (methoxymethyl))pyridin-4(1 <i>H</i>)- one	447.147	448.3	2.02	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.34 (d, <i>J</i> = 6.6 Hz, 1H), 7.19 - 7.01 (m, 3H), 5.79 (d, <i>J</i> = 10.8 Hz, 1H), 4.62 (t, <i>J</i> = 10.0 Hz, 1H), 4.43 (q, <i>J</i> = 11.3 Hz, 2H), 3.88 (d, <i>J</i> = 1.9 Hz, 4H), 3.25 (s, 3H), 3.05 - 2.91 (m, 1H), 1.69 (s, 3H), 0.82 - 0.72 (m, 3H) ppm.
17	Ethyl 2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-difluoro- 2- methoxyphenyl) -4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-4-oxo-1,4- dihydropyridine- 3-carboxylate	475.142	476.1	1.61	D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.43 - 8.24 (m, 1H), 7.19 - 6.95 (m, 3H), 5.63 (d, <i>J</i> = 10.4 Hz, 1H), 4.48 - 4.24 (m, 2H), 4.21 - 4.05 (m, 1H), 3.88 (d, <i>J</i> = 2.4 Hz, 3H), 3.02 - 2.85 (m, 1H), 1.70 (s, 3H), 1.29 (t, <i>J</i> = 7.1 Hz, 3H), 0.83 (d, <i>J</i> = 7.2, 2.3 Hz, 3H) ppm; NH pyridone not observed.
18	6- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl) -4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)- <i>N</i> ,2- dimethyl-4-oxo- 1,4- dihydropyridine- 3-carboxamide	474.158	475.1	1.96	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.17 (ddd, <i>J</i> = 8.1, 5.6, 2.1 Hz, 1H), 7.08 - 6.98 (m, 2H), 5.68 (d, <i>J</i> = 11.2 Hz, 1H), 4.25 (dd, <i>J</i> = 11.2, 8.4 Hz, 1H), 4.00 (s, 3H), 2.90 (s, 4H), 2.63 (s, 3H), 1.71 (s, 3H), 0.91 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone and amide not observed.
19	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl) -4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-6-methyl- 3- (methylamino)p yridin-4(1 <i>H</i>)- one	446.163	447.2	2.00	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 6.94 - 6.88 (m, 2H), 6.86 (s, 1H), 5.82 (d, <i>J</i> = 11.4 Hz, 1H), 4.52 - 4.40 (m, 1H), 4.01 (d, <i>J</i> = 2.8 Hz, 3H), 3.07 - 2.99 (m, 1H), 2.97 (s, 3H), 2.55 (s, 3H), 1.74 (s, 3H), 0.91 - 0.81 (m, 3H) ppm; NH pyridone and amine not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
20	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(2-methoxypropan-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	489.194	490.1	2.05	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.11 (ddd, <i>J</i> = 8.0, 5.6, 2.1 Hz, 1H), 7.07 (s, 1H), 7.05 - 6.97 (m, 1H), 5.65 (d, <i>J</i> = 11.3 Hz, 1H), 4.27 (dd, <i>J</i> = 11.2, 8.2 Hz, 1H), 4.02 (s, 3H), 3.18 (s, 3H), 2.98 - 2.89 (m, 1H), 2.86 (s, 3H), 1.68 (d, <i>J</i> = 1.3 Hz, 3H), 1.66 (d, <i>J</i> = 4.1 Hz, 6H), 0.90 (dq, <i>J</i> = 7.5, 2.4 Hz, 3H) ppm; NH pyridone not observed.
21	Ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	519.168	520.5	3.50	H	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 6.99 (tt, <i>J</i> = 9.8, 6.4 Hz, 2H), 5.37 (d, <i>J</i> = 11.0 Hz, 1H), 4.50 (s, 1H), 4.36 (dq, <i>J</i> = 10.9, 7.2 Hz, 1H), 4.24 (p, <i>J</i> = 7.2 Hz, 1H), 3.91 (d, <i>J</i> = 2.1 Hz, 3H), 3.76 (s, 3H), 2.88 (p, <i>J</i> = 8.0 Hz, 1H), 2.34 (s, 3H), 1.63 (s, 3H), 1.33 (t, <i>J</i> = 7.1 Hz, 3H), 0.80 (dt, <i>J</i> = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed.
22	Ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	489.157	490.5	3.15	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.69 (s, 1H), 7.03 - 6.98 (m, 2H), 5.44 (d, <i>J</i> = 10.7 Hz, 1H), 4.37 - 4.26 (m, 2H), 4.16 (d, <i>J</i> = 9.3 Hz, 1H), 3.89 (d, <i>J</i> = 2.2 Hz, 3H), 2.95 - 2.85 (m, 1H), 2.01 (s, 3H), 1.68 (s, 3H), 1.31 (t, <i>J</i> = 7.1 Hz, 3H), 0.83 (dt, <i>J</i> = 7.4, 2.2 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
23	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-3-(2- hydroxypropan- 2-yl)-6- methylpyridin- 4(1 <i>H</i>)-one	475.178	476.2	2.00	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.36 - 7.25 (m, 2H), 7.03 - 6.93 (m, 1H), 6.92 (s, 1H), 4.30 (t, <i>J</i> = 10.5 Hz, 1H), 3.83 (d, <i>J</i> = 2.4 Hz, 3H), 3.06 - 2.94 (m, 1H), 2.67 (s, 3H), 1.73 (s, 3H), 1.64 (s, 3H), 1.37 (s, 3H), 0.85 (dd, <i>J</i> = 7.9, 2.1 Hz, 3H) ppm; NH pyridone and OH alcohol not observed.
24	Ethyl 6- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-5-fluoro-4- oxo-1,4- dihydropyridine- 3-carboxylate	493.132	494.1	2.55	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.49 (s, 1H), 7.05 (ddd, <i>J</i> = 8.1, 5.6, 1.9 Hz, 1H), 6.96 (td, <i>J</i> = 9.4, 7.4 Hz, 1H), 5.78 (d, <i>J</i> = 11.2 Hz, 1H), 4.36 (q, <i>J</i> = 7.1 Hz, 3H), 3.94 (s, 3H), 2.88 (p, <i>J</i> = 7.8 Hz, 1H), 1.70 (s, 3H), 1.35 (t, <i>J</i> = 7.1 Hz, 3H), 0.89 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.
25	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-5,6- dimethylpyrimidin- 4(1 <i>H</i>)-one	432.147	434.0	3.32	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.51 (s, 1H), 7.15 (ddd, <i>J</i> = 10.1, 8.9, 7.7 Hz, 1H), 7.03 (ddd, <i>J</i> = 8.6, 5.8, 2.0 Hz, 1H), 5.19 (d, <i>J</i> = 11.0 Hz, 1H), 4.48 (dd, <i>J</i> = 11.0, 8.0 Hz, 1H), 3.94 (d, <i>J</i> = 2.0 Hz, 3H), 2.81 (p, <i>J</i> = 7.6 Hz, 1H), 2.17 (d, <i>J</i> = 1.0 Hz, 3H), 1.87 (d, <i>J</i> = 0.9 Hz, 3H), 1.61 (s, 3H), 0.72 (dt, <i>J</i> = 7.5, 2.4 Hz, 3H) ppm.
26	2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)- 3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl) tetrahydrofuran- 2-yl)-1,5,7,8- tetrahydro-4 <i>H</i> - pyrano[4,3- b]pyridin-4-one	459.410	460.9	1.88	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.14 (ddd, <i>J</i> = 8.1, 5.5, 2.1 Hz, 1H), 7.01 (td, <i>J</i> = 9.3, 7.4 Hz, 1H), 6.75 (s, 1H), 5.60 (d, <i>J</i> = 11.2 Hz, 1H), 4.62 (s, 2H), 4.22 (dd, <i>J</i> = 11.2, 8.4 Hz, 1H), 4.03 - 3.93 (m, 5H), 2.99 (t, <i>J</i> = 5.6 Hz, 2H), 2.89 (p, <i>J</i> = 7.8 Hz, 1H), 1.69 (s, 3H), 0.90 (dq, <i>J</i> = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
27	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4(1 <i>H</i>)-one	472.45	473.2	1.22	D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.24 - 7.11 (m, 1H), 7.10 - 6.95 (m, 1H), 6.92 - 6.65 (m, 1H), 5.78 - 5.56 (m, 1H), 4.53 - 4.49 (m, 1H), 4.29 - 4.19 (m, 1H), 4.15 - 4.09 (m, 1H), 3.99 (d, <i>J</i> = 2.6 Hz, 3H), 3.93 - 3.69 (m, 1H), 3.60 (s, 1H), 3.46 - 3.35 (m, 2H), 3.10 (s, 3H), 2.96 - 2.83 (m, 1H), 1.70 (s, 3H), 0.95 - 0.84 (m, 3H) ppm; NH pyridone not observed.

[0292] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(2-methoxy-3-(trifluoromethyl)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. Between Step 1 and Step 2, a step was introduced to separate the enantiomers by chiral SFC using a Chiralpak® IA column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
28	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(2-Methoxy-3-(trifluoromethyl)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IA, rt = 2.42 min)	449.143	450.2	2.98	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.81 (d, <i>J</i> = 7.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.7 Hz, 1H), 7.34 (t, <i>J</i> = 7.8 Hz, 1H), 6.65 (d, <i>J</i> = 112.0 Hz, 2H), 5.47 (d, <i>J</i> = 10.7 Hz, 1H), 4.48 (s, 1H), 3.84 (s, 3H), 2.89 (t, <i>J</i> = 7.6 Hz, 1H), 2.29 (s, 3H), 1.70 (s, 3H), 0.82 (dd, <i>J</i> = 7.8, 2.5 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
29	<i>rel</i> -2-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(2-Methoxy-3-(trifluoromethyl)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak [®] IA, rt = 2.90 min)	449.143	450.2	2.98	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.81 (d, <i>J</i> = 7.9 Hz, 1H), 7.62 (d, <i>J</i> = 7.8 Hz, 1H), 7.34 (t, <i>J</i> = 7.9 Hz, 1H), 6.80 (s, 1H), 6.52 (s, 1H), 5.48 (d, <i>J</i> = 10.7 Hz, 1H), 4.48 (s, 1H), 3.84 (s, 3H), 2.89 (s, 1H), 2.29 (s, 3H), 1.70 (s, 3H), 0.82 (dd, <i>J</i> = 7.5, 2.5 Hz, 3H) ppm; NH pyridone not observed.

[0293] The following compounds were made using methods described in Example 1 except that, in Step 1, different halide coupling partners were used in place of 4-benzyloxy-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21** and (2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
30	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-Fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	399.146	401.0	2.84	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.20 (dd, <i>J</i> = 8.6, 6.4 Hz, 1H), 6.80 (dd, <i>J</i> = 10.9, 2.5 Hz, 1H), 6.66 (td, <i>J</i> = 8.4, 2.5 Hz, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 5.40 (d, <i>J</i> = 11.3 Hz, 1H), 4.17 (dd, <i>J</i> = 11.3, 8.1 Hz, 1H), 3.85 (s, 3H), 2.87 (t, <i>J</i> = 7.8 Hz, 1H), 2.35 (s, 3H), 1.69 - 1.62 (m, 3H), 0.81 (dt, <i>J</i> = 7.4, 2.4 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
31	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-Fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2,3-dimethylpyridin-4(1 <i>H</i>)-one	413.161	413.8	2.92	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.18 (dd, <i>J</i> = 8.5, 6.4 Hz, 1H), 6.80 (dd, <i>J</i> = 11.0, 2.5 Hz, 1H), 6.65 (td, <i>J</i> = 8.4, 2.6 Hz, 1H), 6.44 (s, 1H), 5.42 (d, <i>J</i> = 11.3 Hz, 1H), 4.18 (dd, <i>J</i> = 11.4, 8.0 Hz, 1H), 3.85 (s, 3H), 2.87 (p, <i>J</i> = 7.7 Hz, 1H), 2.42 (s, 3H), 2.00 (s, 3H), 1.64 (d, <i>J</i> = 1.3 Hz, 3H), 0.81 (dq, <i>J</i> = 7.4, 2.4 Hz, 3H) ppm; NH pyridone not observed.

[0294] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(2-ethoxy-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
32	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(2-Ethoxy-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	431.152	432.5	3.06	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.12 - 7.06 (m, 1H), 6.83 (td, <i>J</i> = 9.1, 7.3 Hz, 1H), 6.35 (s, 1H), 6.32 (s, 1H), 5.49 (dd, <i>J</i> = 11.1, 5.5 Hz, 1H), 4.27 - 4.16 (m, 1H), 4.16 - 4.06 (m, 2H), 2.75 (p, <i>J</i> = 7.7 Hz, 1H), 2.36 (s, 3H), 1.64 (s, 3H), 1.34 (t, <i>J</i> = 7.1 Hz, 3H), 0.82 (dd, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

[0295] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-isopropoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
33	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-isopropoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	445.168	446.5	3.19	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.34 - 7.28 (m, 1H), 6.86 (q, <i>J</i> = 8.6 Hz, 1H), 6.57 (s, 1H), 6.45 (s, 1H), 5.69 (d, <i>J</i> = 11.3 Hz, 1H), 4.62 (p, <i>J</i> = 6.1 Hz, 1H), 4.21 - 4.09 (m, 1H), 2.79 (p, <i>J</i> = 7.6 Hz, 1H), 2.47 (d, <i>J</i> = 3.6 Hz, 3H), 1.66 (s, 3H), 1.34 (d, <i>J</i> = 6.1 Hz, 3H), 1.17 - 1.09 (m, 3H), 0.90 - 0.76 (m, 3H) ppm; NH pyridone not observed.

[0296] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(2-(difluoromethoxy)-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
34	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(2-(Difluoromethoxy)-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	453.118	454.5	2.98	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.53 - 7.47 (m, 1H), 7.08 (q, <i>J</i> = 8.6 Hz, 1H), 6.59 (d, <i>J</i> = 2.2 Hz, 1H), 6.54 (t, <i>J</i> = 7.4 Hz, 1H), 6.48 (s, 1H), 5.71 (d, <i>J</i> = 11.1 Hz, 1H), 4.18 - 4.08 (m, 1H), 2.77 (p, <i>J</i> = 7.7 Hz, 1H), 2.45 (s, 3H), 1.61 (s, 3H), 0.83 - 0.78 (m, 3H) ppm; NH pyridone not observed.

[0297] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-4** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. The enantiomers of Step 1 were further separated by chiral SFC using a Chiralcel® OJ-H column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
----------	---------------	---------------------------	-------------------	-------------------	--------------	---------------------

35	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralcel® OJ-H, rt = 2.98 min)	401.141	402.2	2.86	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.03 - 6.94 (m, 2H), 6.21 (s, 1H), 6.11 (s, 1H), 5.33 (d, <i>J</i> = 11.1 Hz, 1H), 3.95 (dd, <i>J</i> = 11.0, 8.2 Hz, 1H), 2.79 (t, <i>J</i> = 7.8 Hz, 1H), 2.25 (d, <i>J</i> = 0.7 Hz, 3H), 2.19 (t, <i>J</i> = 1.2 Hz, 3H), 1.58 (d, <i>J</i> = 1.1 Hz, 3H), 0.78 - 0.68 (m, 3H) ppm; NH pyridone not observed.
36	<i>rel</i> -2-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(3,4-Difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralcel® OJ-H, rt = 3.21 min)	401.141	402.2	2.87	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.02 - 6.94 (m, 2H), 6.21 (s, 1H), 6.11 (s, 1H), 5.33 (d, <i>J</i> = 11.1 Hz, 1H), 3.95 (dd, <i>J</i> = 11.0, 8.2 Hz, 1H), 2.84 - 2.72 (m, 1H), 2.25 (d, <i>J</i> = 0.8 Hz, 3H), 2.19 (t, <i>J</i> = 1.2 Hz, 3H), 1.58 (d, <i>J</i> = 1.2 Hz, 3H), 0.77 - 0.69 (m, 3H) ppm; NH pyridone not observed.

[0298] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-4,5-dimethyl-3-(2-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. Between Step 1 and Step 2, a step was introduced to separate the enantiomers by chiral SFC using a Chiralpak® IA column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
37	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-4,5-Dimethyl-3-(2-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IA, rt = 1.84 min)	433.148	434.2	3.06	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.50 (d, <i>J</i> = 7.8 Hz, 1H), 7.43 (d, <i>J</i> = 7.8 Hz, 1H), 7.25 (t, <i>J</i> = 7.9 Hz, 1H), 6.23 (s, 1H), 6.11 (s, 1H), 5.43 (d, <i>J</i> = 11.0 Hz, 1H), 4.11 (dd, <i>J</i> = 11.0, 8.2 Hz, 1H), 2.92 - 2.83 (m, 1H), 2.36 (s, 3H), 2.25 (d, <i>J</i> = 0.7 Hz, 3H), 1.60 (s, 3H), 0.72 (dd, <i>J</i> = 7.6, 2.2 Hz, 3H) ppm; NH pyridone not observed.
38	<i>rel</i> -2-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-4,5-Dimethyl-3-(2-methyl-3-(trifluoromethyl)phenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IA, rt = 2.2 min)	433.148	434.2	3.06	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.50 (d, <i>J</i> = 7.7 Hz, 1H), 7.43 (d, <i>J</i> = 7.8 Hz, 1H), 7.25 (s, 1H), 6.22 (s, 1H), 6.11 (s, 1H), 5.43 (d, <i>J</i> = 11.0 Hz, 1H), 4.11 (dd, <i>J</i> = 11.0, 8.2 Hz, 1H), 2.86 (t, <i>J</i> = 7.9 Hz, 1H), 2.36 (s, 3H), 2.25 (d, <i>J</i> = 0.8 Hz, 3H), 1.60 (d, <i>J</i> = 1.2 Hz, 3H), 0.72 (dd, <i>J</i> = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed.

[0299] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-11** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. Between Step 1 and Step 2, a step was introduced to separate the enantiomers by chiral SFC using a Chiralpak® IG column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
39	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-Fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IG, rt = 3.00 min)	413.161	414.2	2.93	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.17 (dd, <i>J</i> = 8.7, 6.3 Hz, 1H), 6.89 (t, <i>J</i> = 8.8 Hz, 1H), 6.26 (d, <i>J</i> = 30.3 Hz, 2H), 5.33 (d, <i>J</i> = 11.3 Hz, 1H), 4.18 (dd, <i>J</i> = 11.3, 8.4 Hz, 1H), 3.71 (s, 3H), 2.85 (p, <i>J</i> = 7.8 Hz, 1H), 2.36 (d, <i>J</i> = 0.7 Hz, 3H), 2.21 (d, <i>J</i> = 2.2 Hz, 3H), 1.70 (d, <i>J</i> = 1.2 Hz, 3H), 0.89 (dt, <i>J</i> = 7.6, 2.4 Hz, 3H) ppm; NH pyridone not observed.
40	<i>rel</i> -2-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(4-Fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IG, rt = 4.02 min)	413.161	414.7	2.93	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.18 (dd, <i>J</i> = 8.7, 6.3 Hz, 1H), 6.89 (t, <i>J</i> = 8.8 Hz, 1H), 6.33 (s, 1H), 6.26 (d, <i>J</i> = 2.4 Hz, 1H), 5.34 (d, <i>J</i> = 11.3 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.5 Hz, 1H), 3.71 (s, 3H), 2.86 (q, <i>J</i> = 7.9 Hz, 1H), 2.37 (d, <i>J</i> = 0.7 Hz, 3H), 2.21 (d, <i>J</i> = 2.1 Hz, 3H), 1.71 (d, <i>J</i> = 1.1 Hz, 3H), 0.89 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

[0300] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(7-ethoxy-2,2-difluorobenzo[*d*][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-14** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. Between Step 1 and Step 2, a step was introduced to separate the enantiomers by chiral SFC using a Chiralpak® IA column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
41	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(7-Ethoxy-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IA, rt = 2.90 min)	475.142	476.2	3.26	A	
42	<i>rel</i> -2-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(7-Ethoxy-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IA, rt = 3.4 min)	475.142	476.2	3.26	A	

[0301] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-15** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. Between Step 1 and Step 2, a step was introduced to separate the enantiomers by chiral SFC using a Chiralpak® IA, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation or Chiralpak® IC column, 5 µm particle size, 25 cm x 20 mm from Daicel Corporation respectively:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
43	rel -2-((2 <i>R</i> ,3 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IA, rt = 2.66 min)	389.105	390.5	2.59	A	
44	rel -2-((2 <i>S</i> ,3 <i>R</i> ,5 <i>S</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IA, rt = 3.09 min)	389.105	390.7	2.58	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.17 (ddd, <i>J</i> = 8.2, 5.7, 2.3 Hz, 1H), 7.07 - 6.99 (m, 1H), 6.23 (s, 1H), 5.96 (s, 1H), 4.91 (d, <i>J</i> = 9.2 Hz, 1H), 3.91 - 3.81 (m, 1H), 3.76 (d, <i>J</i> = 2.4 Hz, 3H), 2.73 (dt, <i>J</i> = 12.8, 7.5 Hz, 1H), 2.48 (td, <i>J</i> = 12.4, 8.7 Hz, 2H), 2.39 (d, <i>J</i> = 0.7 Hz, 3H) ppm; NH pyridone not observed.
45	rel -2-((2 <i>S</i> ,3 <i>R</i> ,5 <i>S</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,6-dimethylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IC, rt = 2.7 min)	403.121	404.5	2.72	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.22 (ddd, <i>J</i> = 8.3, 5.7, 2.3 Hz, 1H), 7.03 (td, <i>J</i> = 9.3, 7.5 Hz, 1H), 6.22 (s, 1H), 5.32 (d, <i>J</i> = 10.4 Hz, 1H), 4.96 (q, <i>J</i> = 7.4 Hz, 1H), 3.90 - 3.79 (m, 1H), 3.69 (d, <i>J</i> = 2.5 Hz, 3H), 2.74 (dt, <i>J</i> = 12.8, 7.6 Hz, 1H), 2.62 (td, <i>J</i> = 12.5, 8.6 Hz, 1H), 2.43 (d, <i>J</i> = 0.7 Hz, 3H), 1.44 (s, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
46	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,6-dimethylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak [®] IC, rt = 3.4 min)	403.121	404.0	2.72	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.22 (ddd, <i>J</i> = 8.2, 5.6, 2.3 Hz, 1H), 7.07 - 6.98 (m, 1H), 6.22 (s, 1H), 5.32 (d, <i>J</i> = 10.4 Hz, 1H), 4.96 (q, <i>J</i> = 7.6 Hz, 1H), 3.91 - 3.80 (m, 1H), 3.69 (d, <i>J</i> = 2.5 Hz, 3H), 2.77 - 2.69 (m, 1H), 2.62 (td, <i>J</i> = 12.5, 8.6 Hz, 1H), 2.43 (d, <i>J</i> = 0.7 Hz, 3H), 1.44 (s, 3H) ppm; NH pyridone not observed.

[0302] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-16** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
47	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	461.163	463.0	2.97	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.30 - 7.02 (m, 2H), 6.75 (s, 1H), 6.50 (s, 1H), 5.37 (d, <i>J</i> = 11.1 Hz, 1H), 4.38 - 4.20 (m, 2H), 4.14 (d, <i>J</i> = 7.1 Hz, 1H), 3.74 - 3.53 (m, 2H), 3.32 (s, 3H), 2.87 (p, <i>J</i> = 7.3 Hz, 1H), 2.26 (s, 3H), 1.62 (s, 3H), 0.74 (dt, <i>J</i> = 4.7, 2.6 Hz, 3H) ppm; NH pyridone not observed.

[0303] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-2** and 4-(benzyloxy)-2-bromo-6-methylpyridine were respectively used as starting materials in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1** and 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
48	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	433.131	434.7	1.67	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.26 (ddd, <i>J</i> = 8.4, 5.8, 2.3 Hz, 1H), 7.00 (ddd, <i>J</i> = 10.0, 9.0, 7.5 Hz, 1H), 6.26 (d, <i>J</i> = 2.4 Hz, 1H), 6.21 (d, <i>J</i> = 2.4 Hz, 1H), 5.36 - 5.27 (m, 1H), 4.05 - 3.96 (m, 2H), 3.91 (d, <i>J</i> = 2.1 Hz, 3H), 3.02 (s, 3H), 2.31 (s, 3H), 1.64 (d, <i>J</i> = 1.2 Hz, 3H) ppm; NH pyridone not observed.

[0304] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid and 4-(benzyloxy)-2-bromo-6-methylpyridine were respectively used as starting materials in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1** and 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
49	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	417.136	418.6	1.70	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.33 (ddd, <i>J</i> = 9.0, 4.8, 1.7 Hz, 1H), 7.16 (d, 1H), 6.96 (d, <i>J</i> = 2.4 Hz, 1H), 6.92 (d, <i>J</i> = 2.5 Hz, 1H), 5.67 (d, <i>J</i> = 11.2 Hz, 1H), 4.16 (d, <i>J</i> = 4.9 Hz, 1H), 3.93 (dd, <i>J</i> = 11.3, 4.9 Hz, 1H), 2.95 (s, 3H), 2.60 (s, 3H), 2.32 (d, <i>J</i> = 2.5 Hz, 3H), 1.69 (d, <i>J</i> = 1.2 Hz, 3H) ppm; NH pyridone not observed.

[0305] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(4-(difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-10** and 4-(benzyloxy)-2-bromo-6-methylpyridine were respectively used as starting materials in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1** and 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**. In Step 2, EtOAc was used as the solvent in place of EtOH:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
50	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-(difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	465.137	466.5	2.98	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.45 (s, 1H), 7.24 (d, <i>J</i> = 8.6 Hz, 1H), 7.21 (t, <i>J</i> = 74 Hz, 1H), 7.00 (t, <i>J</i> = 8.1 Hz, 1H), 6.77 (s, 1H), 6.52 (s, 1H), 5.40 (d, <i>J</i> = 11.0 Hz, 1H), 4.32 (dd, <i>J</i> = 11.0, 7.4 Hz, 1H), 3.88 (d, <i>J</i> = 1.7 Hz, 3H), 2.76 (t, <i>J</i> = 7.4 Hz, 1H), 2.28 (s, 3H), 1.62 (s, 3H), 0.79 (d, <i>J</i> = 7.5 Hz, 3H) ppm.

[0306] The following compound was made using methods described in Example 1 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-9** and 4-(benzyloxy)-2-bromo-6-methylpyridine were respectively used as starting materials in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1** and 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**. The debenzoylation Step 2 was carried out using the conditions described in General Method D:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
51	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3-Chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	415.116	416.5	2.90	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.34 (ddd, <i>J</i> = 11.3, 7.9, 1.6 Hz, 1H), 7.14 (d, <i>J</i> = 7.9 Hz, 1H), 7.09 - 6.95 (m, 2H), 6.15 - 5.94 (m, 1H), 5.51 - 5.33 (m, 1H), 4.27 - 4.02 (m, 1H), 3.77 - 3.78 (m, 3H), 2.89 - 2.68 (m, 1H), 2.46 - 2.30 (m, 3H), 1.70 - 1.64 (m, 3H), 0.85 (td, <i>J</i> = 9.0, 7.7, 2.4 Hz, 3H) ppm; NH pyridone not observed.

[0307] The following compounds were made using methods described in Example 1 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-3** and 4-(benzyloxy)-2-bromo-6-methylpyridine were respectively used as starting materials in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1** and 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**. Between Step 1 and Step 2, a

step was introduced to separate the enantiomers by chiral SFC using a Chiralpak® IG column, 5 µm particle size, 25 cm x 20 mm from Daicel Corporation:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
52	<i>rel</i> -2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IG, rt = 2.23 min)	403.121	404.5	2.77	A	
53	<i>rel</i> -2-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IG, rt = 2.88 min)	403.121	404.4	2.77	A	

[0308] The following compound was made using methods described in Example 1, except that 4-(benzyloxy)-6-chloro-*N*,2-dimethylnicotinamide was used as the coupling partner in Step 1. The product of Step 2 (**18**) was chlorinated, as outlined below:

[0309] *Chlorination reaction:* NCS (5.1 mg, 0.038 mmol) was added to a stirred solution of 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,2-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**18**, 15 mg, 0.031 mmol) in DCM (500 µL) and MeOH (100 µL). The mixture was stirred at ambient temperature for 70 min. The mixture was diluted with EtOAc, washed with a 10% aqueous Na₂S₂O₃ solution, water, and brine. The organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl modifier over 15 min) gave 5-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-

(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,2-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**54**, 2 mg, 12%) as an off-white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.10 (t, *J* = 6.8 Hz, 1H), 6.98 (q, *J* = 8.9 Hz, 1H), 5.83 (d, *J* = 11.0 Hz, 1H), 4.47 (t, *J* = 10.5 Hz, 1H), 3.91 (s, 3H), 3.00 - 2.94 (m, 1H), 2.85 (s, 3H), 2.55 (s, 3H), 1.71 (s, 3H), 0.88 - 0.84 (m, 3H) ppm; NH pyridone and amide not observed. ESI-MS *m/z* calc. 508.118, found 509.1 (M+1)⁺; Retention time: 2.26 minutes using LC/MS method Q.

[0310] The following compound was made using methods described in Example 1, except that ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate **Int-18a** was used as the coupling partner in Step 1. The product of Step 2 (**4**) was brominated, as outlined below:

[0311] *Bromination reaction:* To a solution of ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**4**, 63 mg, 0.13 mmol) in DCM (1 mL) and acetic acid (500 μL) was added NBS (27.5 mg, 0.155 mmol) in a single portion. The mixture was stirred at ambient temperature for 16 h and concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with a 10% aqueous Na₂S₂O₃ solution and a saturated NaHCO₃ solution. The organic layer was dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by reverse phase preparative chromatography (C₁₈ column, 30 to 99% MeCN in water containing 5 mM HCl modifier) gave ethyl 5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**55**, 58.8 mg, 80%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.06 - 6.94 (m, 2H), 5.39 (dd, *J* = 10.9, 6.2 Hz, 1H), 4.55 - 4.45 (m, 1H), 4.36 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.90 (s, 3H), 2.95 - 2.85 (m, 1H), 2.54 (d, *J* = 13.6 Hz, 3H), 1.64 (s, 3H), 1.32 (td, *J* = 7.1, 1.5 Hz, 3H), 0.81 (dq, *J* = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 567.068, found 569.9 (M+1)⁺; Retention time: 2.54 minutes using LC/MS method Q.

[0312] The following compound was made using methods described in Example 1, except that ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate **Int-18a** was used as the coupling partner in Step 1. The product of Step 2 (**4**) was chlorinated, as outlined below:

[0313] *Chlorination reaction:* Ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**4**, 20 mg, 0.035 mmol) was dissolved in DCM (1 mL) and MeOH (300 μL). NCS (10 mg, 0.075 mmol) was added in one portion and the reaction mixture was stirred at ambient temperature for 24 h. The mixture was quenched by addition of a saturated aqueous Na₂S₂O₃ solution (1 mL) and poured onto water (10 mL). The mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO₂, 0 to 100 % EtOAc in heptane) gave ethyl 5-chloro-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**56**, 8.3 mg, 43%) as a white solid. ¹H NMR (400 MHz, Chloroform-

d) δ 12.19 (s, 1H), 6.80 - 6.69 (m, 1H), 6.64 (t, $J = 7.0$ Hz, 1H), 6.21 (d, $J = 10.4$ Hz, 1H), 4.88 (t, $J = 9.3$ Hz, 1H), 4.54 (t, $J = 7.4$ Hz, 2H), 4.02 (d, $J = 2.0$ Hz, 3H), 2.79 (p, $J = 7.7$ Hz, 1H), 2.50 (s, 3H), 1.56 (s, 3H), 1.47 (t, $J = 7.1$ Hz, 3H), 0.92 - 0.82 (m, 3H) ppm. ESI-MS m/z calc. 523.118, found 524.1 (M+1)⁺; 522.1 (M-1)⁻; Retention time: 2.85 minutes using LC/MS method A.

[0314] The following compound was made using methods described in Example 1, except that ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate **Int-18a** was used as the coupling partner in Step 1. The product of Step 2 (**4**) was saponified, as outlined below:

[0315] *Ester hydrolysis*: A solution of ethyl 5-chloro-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**4**, 2.9 mg, 0.005 mmol) in EtOH (250 μ L) was treated with NaOH (20 μ L, 2 M solution in water, 0.04 mmol) and heated at 50 °C for 1 h. Additional NaOH (20 μ L, 2 M solution in water, 0.04 mmol) was added and the mixture was heated at 100 °C for 1 h. Purification by reverse phase HPLC (C₁₈ X-bridge column, 31% to 45% MeCN in H₂O containing 0.1% NH₄OH) gave 5-chloro-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylic acid (Ammonium salt) (**57**, 1.61 mg, 58%). ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.22 (ddd, $J = 8.4, 5.6, 2.3$ Hz, 1H), 7.07 (s, 1H), 6.92 (q, $J = 8.9$ Hz, 1H), 4.44 (s, 1H), 3.92 (d, $J = 2.2$ Hz, 3H), 2.91 (t, $J = 8.4$ Hz, 1H), 2.62 (s, 3H), 1.72 (s, 3H), 0.86 (dq, $J = 7.4, 2.2$ Hz, 3H) ppm; NH pyridone and OH acid not observed. ESI-MS m/z calc. 495.087, found 496.1 (M+1)⁺; Retention time: 2.79 minutes using LC/MS method A.

[0316] The following compound was made using methods described in Example 1, except that ethyl 4-(benzyloxy)-2-bromonicotinate was used as the coupling partner in Step 1. The product of Step 2 (**17**) was brominated, as outlined below:

[0317] *Bromination reaction*: To a solution of ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate (**17**, 50 mg, 0.103 mmol) in DCM (780 μ L) and acetic acid (390 μ L) was added NBS (22 mg, 0.123 mmol) in a single portion. The reaction mixture was stirred at ambient temperature for 2 h. Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl modifier) gave ethyl 5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate (**58**, 41 mg, 70%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.16 (s, 1H), 7.09 - 6.91 (m, 2H), 5.42 (d, $J = 10.7$ Hz, 1H), 4.37 - 4.23 (m, 2H), 4.19 - 4.05 (m, 1H), 3.89 (d, $J = 2.4$ Hz, 3H), 3.01 - 2.74 (m, 1H), 1.66 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.81 (dd, $J = 8.1, 2.2$ Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 553.052, found 553.9 (M+1)⁺; Retention time: 1.73 minutes using LC/MS method D.

[0318] The following compound was made using methods described in Example 1, except that 4-(benzyloxy)-2-bromo-6-methylpyridine was used as the coupling partner in Step 1. The product of Step 2 (2) was sulfonylated, as outlined below:

[0319] *Sulfonylation reaction:* A 20 mL scintillation vial, charged with 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (2, 542 mg, 1.286 mmol), was cooled down in an ice/brine bath. Concentrated H₂SO₄, cooled in an ice/brine bath, was added to the solid and the mixture was stirred at 0 °C for 35 min. The ice/brine bath was removed. The mixture was warmed to ambient temperature and stirred overnight. The reaction mixture was added to a flask containing water (30 mL) cooled at -2 °C, at such a rate to keep the internal temperature below 5 °C. A tan precipitate formed. The mixture was stirred for 15 min, filtered, and the solid was rinsed with water (3 x 8 mL). The solid was air-dried under suction for 30 min then in a vacuum oven at 42 °C. Purification by flash column chromatography (40g SiO₂, 0 to 10 % MeOH in MeCN) gave 5-((2*R*,3*S*,4*S*,5*R*)-4,5-dimethyl-2-(6-methyl-4-oxo-1,4-dihydropyridin-2-yl)-5-(trifluoromethyl)tetrahydrofuran-3-yl)-2,3-difluoro-4-methoxybenzenesulfonic acid (59, 472 mg, 73%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.30 (s, 1H), 7.37 - 7.22 (m, 2H), 7.07 (d, *J* = 2.3 Hz, 1H), 5.61 (d, *J* = 11.0 Hz, 1H), 4.31 (dd, *J* = 11.0, 8.2 Hz, 2H), 3.93 (d, *J* = 2.4 Hz, 3H), 2.96 (p, *J* = 7.7 Hz, 1H), 2.61 (s, 3H), 1.66 (s, 3H), 0.81 (dd, 3H) ppm. ESI-MS *m/z* calc. 497.093, found 498.2 (M+1)⁺; Retention time: 1.41 minutes using LC/MS method Q.

[0320] The following compound was made using methods described in Example 1, except that 4-(benzyloxy)-2-bromo-6-methylpyridine was used as the coupling partner in Step 1. The product of Step 2 (2) was nitrated, as outlined below:

[0321] *Nitration:* 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (2, 1 g, 2.4 mmol) was slowly added to HNO₃ (5 mL, 65 % w/w solution in water, 72 mmol) under stirring at ambient temperature. Another portion of HNO₃ (5 mL, 65 % w/w solution in water, 72 mmol) was added and the mixture was stirred at ambient temperature for 0.5 h. The resulting solution was slowly added to cold H₂SO₄ (5 mL, 94 mmol), causing a strong exotherm. The internal temperature was kept between -5 and -20 °C by cooling in a dry-ice/acetone bath. At the end of addition, the mixture was warmed to ambient temperature and stirred for 1 h. The yellow solution was slowly added to ice/water (250 mL) and stirred for 1 h. The solid was collected by filtration, washed with water and dried *in vacuo*. The solid was dissolved in EtOAc, dried (MgSO₄) and concentrated *in vacuo*. Purification by flash column chromatography (24g SiO₂, 0 to 100 % EtOAc in heptane) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxy-5-nitrophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (60, 671 mg, 59%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.90 (dd, *J* = 7.6, 2.2 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 5.57 (d, *J* = 10.9 Hz, 1H), 4.25 (dd, *J* = 10.9, 8.5 Hz, 1H), 4.20 (d, *J* = 4.6 Hz, 3H), 2.97 (p, *J* = 7.8 Hz, 1H), 2.50 (s, 3H), 1.68 (d, *J* = 1.2 Hz, 3H), 0.91

(dq, $J = 7.4, 2.3$ Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 462.121, found 463.0 (M+1)⁺; Retention time: 1.81 minutes using LC/MS method Q.

[0322] 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxy-5-nitrophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**60**, 100 mg, 0.216 mmol) was reduced using the method described in General Method C to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(5-amino-3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (Hydrochloride salt) (**61**, 60 mg, 58%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.05 - 6.98 (m, 2H), 6.74 (dd, $J = 8.6, 2.3$ Hz, 1H), 5.58 (d, $J = 11.2$ Hz, 1H), 4.22 (dd, $J = 11.2, 8.5$ Hz, 1H), 3.84 (d, $J = 1.5$ Hz, 3H), 2.89 (p, $J = 7.8$ Hz, 1H), 2.67 (s, 3H), 1.69 (s, 3H), 0.94 (dq, $J = 7.4, 2.4$ Hz, 3H) ppm; NH pyridone and NH₂ amine not observed. ESI-MS m/z calc. 432.147, found 433.0 (M+1)⁺; Retention time: 1.62 minutes using LC/MS method Q.

[0323] The following compound was made by transesterification of ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate **21** as outlined below:

[0324] *Transesterification:* To a solution of ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (6 mg, 0.006 mmol) in MeOH (1 mL) was added NH₃ (200 μ L, 7 M solution in MeOH, 1.4 mmol). The mixture was heated at 60 °C for 16 h. The mixture was concentrated *in vacuo* then re-suspended in MeOH and filtered. The filtrate was concentrated *in vacuo*. After purification by reverse phase HPLC (C₁₈ X-bridge column, 38% to 53% MeCN in H₂O containing 0.1% NH₄OH), the residue was partitioned between EtOAc (5 mL) and a saturated NaHCO₃ solution (10 mL). The organic phase was separated and washed with a saturated NaHCO₃ solution (2 x 10 mL), dried (MgSO₄), filtered, concentrated *in vacuo* and lyophilized to give methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**62**, 1.2 mg, 40%) as a white solid. ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.05 - 6.99 (m, 2H), 5.37 (s, 1H), 4.50 (s, 1H), 3.91 (d, $J = 2.1$ Hz, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 2.88 (p, $J = 8.0$ Hz, 1H), 2.36 (s, 3H), 1.65 (s, 3H), 0.82 (dt, $J = 7.5, 2.3$ Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 505.152, found 506.5 (M+1)⁺; 504.4 (M-1)⁻; Retention time: 2.98 minutes using LC/MS method A.

[0325] The following compound was made using the method described in Example 1, except that 4-(benzyloxy)-2-bromo-3-methoxy-6-methylpyridine **Int-19** was used as the coupling partner in Step 1. The product of Step 2 (**8**) was chlorinated using two different methods, as outlined below:

[0326] *Chlorination method 1:* To a solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxy-6-methylpyridin-4(1*H*)-one (**8**) (280 mg, 0.626 mmol) in MeOH (3 mL) at 40 °C, DMSO (10 μ L, 0.141 mmol) and NCS (200 mg, 1.498 mmol) were added and the mixture was stirred at 40 °C. When reasonable conversion to the main product was observed, the reaction was stopped. Purification by flash

chromatography (24 g SiO₂, 0 to 100 % EtOAc in heptane) gave 3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-2-methylpyridin-4(1*H*)-one (**63**, 10.6 mg, 3%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.17 - 7.08 (m, 1H), 6.96 (ddd, *J* = 8.6, 5.6, 2.0 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 4.59 - 4.48 (m, 1H), 3.92 (d, *J* = 2.1 Hz, 3H), 3.73 (s, 3H), 2.86 (p, *J* = 7.8 Hz, 1H), 2.40 (s, 3H), 1.64 (s, 3H), 0.75 (dd, *J* = 7.7, 2.2 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 481.107, found 482.5 (M+1)⁺; 480.4 (M-1)⁻; Retention time: 3.06 minutes using LC/MS method A.

[0327] *Chlorination method 2*: To a solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxy-6-methylpyridin-4(1*H*)-one (**8**) (100 mg, 0.07 mmol) in CHCl₃ (342 μL) at 35 °C, DMSO (1 mg, 1 μL, 0.014 mmol) and NCS (11 mg, 0.084 mmol) were added and the mixture was stirred at 35 °C under air until full conversion (about 30 min). The reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography gave 6-(chloromethyl)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxypyridin-4(1*H*)-one (**64**, 2.2 mg, 6%). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.86 (td, *J* = 9.2, 7.3 Hz, 1H), 6.80 - 6.73 (m, 1H), 6.55 (s, 1H), 4.69 (ddd, *J* = 11.2, 6.3, 3.2 Hz, 1H), 3.97 (d, *J* = 2.8 Hz, 3H), 3.82 (s, 3H), 3.53 (dd, *J* = 11.3, 8.1 Hz, 1H), 3.03 (dd, *J* = 15.3, 3.2 Hz, 1H), 2.83 - 2.73 (m, 1H), 2.58 (p, *J* = 7.8 Hz, 1H), 1.52 (d, *J* = 1.1 Hz, 3H), 0.74 (dq, *J* = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 481.108, found 482.5 (M+1)⁺; 480.4 (M-1)⁻; Retention time: 3.42 minutes using LC/MS method A.

[0328] The following compound was made using the method described in Example 1, except that ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate was used as the coupling partner in Step 1. Between Step 1 and Step 2, a step was introduced to reduce the ester group, as outlined below:

[0329] *Ester reduction*: A reaction vial, equipped with a stir bar and containing a solution of ethyl 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinate (335 mg, 0.57 mmol) in THF (8 mL), was cooled to -40 °C. LiAlH₄ (600 μL, 2 M solution in THF, 1.2 mmol) was added dropwise and the reaction mixture was stirred at -40 °C for 1 h. The mixture was warmed up to 0 °C for 30 min, and then stirred at ambient temperature for 30 min. The reaction mixture was cooled to 0 °C, quenched by addition of water (300 μL), 4 M NaOH (300 μL) and water (900 μL) and allowed to stir at ambient temperature for 15 min. The mixture was filtered through a pad of Celite®, washing with EtOAc. The mother liquors were concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 40 % EtOAc in heptane) gave (4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methanol (170 mg, 55%) as a colourless solid. ESI-MS *m/z* calc. 537.193, found 538.1 (M+1)⁺; Retention time: 1.23 minutes using LC/MS method D.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
65	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(hydroxymethyl)-2-methylpyridin-4(1 <i>H</i>)-one	447.147	448.1	1.74	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.06 (ddd, <i>J</i> = 7.9, 5.6, 2.0 Hz, 1H), 6.98 (td, <i>J</i> = 9.4, 7.4 Hz, 1H), 6.56 (s, 1H), 5.42 (d, <i>J</i> = 11.3 Hz, 1H), 4.58 (s, 2H), 4.19 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.97 (d, <i>J</i> = 2.5 Hz, 3H), 2.86 (p, <i>J</i> = 7.8 Hz, 1H), 2.55 (s, 3H), 1.70 - 1.64 (m, 3H), 0.88 (dt, <i>J</i> = 7.7, 1.9 Hz, 3H) ppm; NH pyridone and OH alcohol not observed.

[0330] The following compounds were made using methods described in Example 1 except that, in Step 1, different halide coupling partners were used. General method D was used instead of General Method C to carry out the debenylation in Step 2:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
66	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,6-dimethylpyridin-4(1 <i>H</i>)-one	431.152	432.3	1.93	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 14.10 (s, 1H), 7.25 - 7.05 (m, 2H), 5.80 (d, <i>J</i> = 11.1 Hz, 1H), 4.66 (t, <i>J</i> = 10.3 Hz, 1H), 3.85 (d, <i>J</i> = 1.9 Hz, 3H), 3.01 (t, 1H), 2.60 (s, 3H), 2.16 (s, 3H), 2.07 (s, 1H), 1.72 (s, 3H), 0.79 (d, 3H) ppm.
67	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(difluoromethoxy)-6-methylpyridin-4(1 <i>H</i>)-one	483.128	484.5	3.29	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.56 (s, 1H), 7.54 - 6.79 (m, 3H), 6.24 (s, 1H), 5.73 (d, <i>J</i> = 10.4 Hz, 1H), 4.06 (s, 1H), 3.89 (d, <i>J</i> = 2.6 Hz, 3H), 2.74 (p, <i>J</i> = 8.0 Hz, 1H), 2.32 (d, <i>J</i> = 0.7 Hz, 3H), 1.70 - 1.66 (m, 3H), 0.84 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
68	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2,5-dimethyl-4-oxo-1,4-dihydropyridine-3-carbonitrile	456.147	457.5	2.96	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.23 (s, 1H), 7.26 - 7.10 (m, 1H), 7.04 (d, <i>J</i> = 7.3 Hz, 1H), 5.48 (d, <i>J</i> = 11.1 Hz, 1H), 4.39 (t, <i>J</i> = 10.4 Hz, 1H), 3.86 (d, <i>J</i> = 1.9 Hz, 3H), 2.93 (s, 1H), 2.50 (d, <i>J</i> = 1.9 Hz, 3H), 1.90 (s, 3H), 1.68 (s, 3H), 0.89 - 0.67 (m, 3H) ppm.

[0331] The following compounds were made using methods described in Example 1 except that, in Step 1, (3*S*,4*R*,6*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylic acid **Int-34** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. Different halide coupling partners were used in Step 1 in place of 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine **Int-21**. The halide coupling partner for compound **75** was **Int-39** (SFC Peak 1) and the halide coupling partner for **76** was **Int-40** (SFC peak 2). In the case of **71**, **72**, **74**, and **73**, MeOH was used as the solvent in place of EtOH in Step 2:

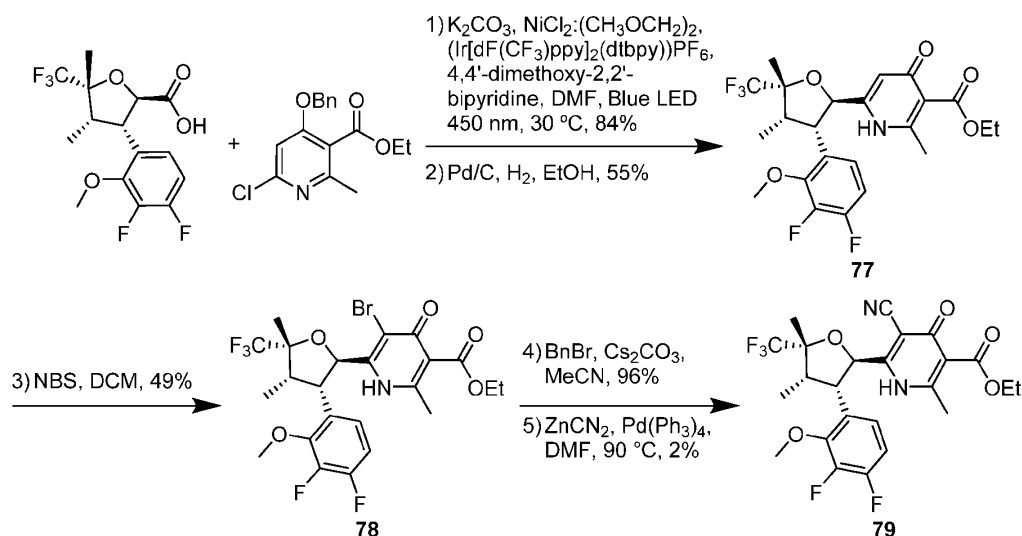
Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
69	6-((3 <i>R</i> ,4 <i>R</i> ,6 <i>R</i>)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-2-methyl-3-(methylsulfonyl)pyridin-4(1 <i>H</i>)-one	495.114	496.2	1.97	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.39 (s, 1H), 7.19 - 7.06 (m, 2H), 6.34 (d, <i>J</i> = 1.7 Hz, 1H), 4.02 (dd, <i>J</i> = 11.5, 4.3 Hz, 1H), 3.93 (d, <i>J</i> = 1.8 Hz, 3H), 3.87 - 3.75 (m, 2H), 3.24 (td, <i>J</i> = 11.4, 4.2 Hz, 1H), 3.17 (s, 3H), 2.52 (s, 3H), 1.88 - 1.75 (m, 2H), 1.63 (s, 3H) ppm.
70	6-((3 <i>R</i> ,4 <i>R</i> ,6 <i>R</i>)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-2-methyl-3-(1,3,4-oxadiazol-2-yl)pyridin-4(1 <i>H</i>)-one	485.137	486.3	1.83	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.75 (s, 1H), 9.28 (s, 1H), 7.24 - 7.16 (m, 1H), 7.16 - 7.06 (m, 1H), 6.35 (s, 1H), 4.05 (dd, <i>J</i> = 11.5, 4.4 Hz, 1H), 3.96 - 3.88 (m, 4H), 3.91 - 3.82 (m, 1H), 3.29 (dd, <i>J</i> = 11.4, 4.1 Hz, 1H), 2.23 (s, 3H), 1.90 - 1.75 (m, 2H), 1.65 (s, 3H) ppm.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
71	Methyl 2-((3 <i>R</i> ,4 <i>R</i> ,6 <i>R</i>)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-5-methoxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	505.152	506.4	2.03	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 11.32 (s, 1H), 6.74 - 6.62 (m, 2H), 4.29 - 4.14 (m, 2H), 4.08 (s, 3H), 4.05 - 4.00 (m, 1H), 3.92 - 3.86 (m, 1H), 3.89 (d, <i>J</i> = 1.7 Hz, 3H), 3.78 (s, 3H), 2.36 (s, 3H), 1.91 (t, <i>J</i> = 12.5 Hz, 1H), 1.84 - 1.76 (m, 1H), 1.65 (s, 3H) ppm.
72	6-((3 <i>R</i> ,4 <i>R</i> ,6 <i>R</i>)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-2-methyl-3-(oxazol-2-yl)pyridin-4(1 <i>H</i>)-one	484.142	485.5	2.05	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 12.72 (br s, 1H), 7.76 (s, 1H), 7.26 (s, 1H), 6.91 - 6.85 (m, 1H), 6.82 - 6.69 (m, 1H), 6.59 (s, 1H), 4.08 - 3.93 (m, 3H), 3.90 (d, <i>J</i> = 1.8 Hz, 3H), 3.33 - 3.21 (m, 1H), 2.79 (s, 3H), 1.94 (t, <i>J</i> = 12.9 Hz, 1H), 1.81 (dd, <i>J</i> = 13.1, 4.0 Hz, 1H), 1.66 (s, 3H) ppm.
73	6-((3 <i>R</i> ,4 <i>R</i> ,6 <i>R</i>)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-2-methyl-3-(2-methyl-2 <i>H</i> -tetrazol-5-yl)pyridin-4(1 <i>H</i>)-one	499.164	500.3	1.82	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 11.10 (br s, 1H), 6.91 (s, 1H), 6.80 - 6.71 (m, 1H), 6.62 (s, 1H), 4.46 (s, 3H), 4.10 - 3.96 (m, 3H), 3.94 - 3.87 (m, 3H), 3.33 - 3.24 (m, 1H), 2.80 (s, 3H), 2.01 - 1.88 (m, 1H), 1.86 - 1.78 (m, 1H), 1.67 (s, 3H) ppm.
74	2-((3 <i>R</i> ,4 <i>R</i> ,6 <i>R</i>)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-6-methyl-3-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyridin-4(1 <i>H</i>)-one	497.174	498.6	1.93	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 10.66 (br s, 1H), 7.58 (d, <i>J</i> = 2.4 Hz, 1H), 6.61 (d, <i>J</i> = 2.4 Hz, 1H), 6.57 - 6.52 (m, 1H), 6.51 (s, 1H), 6.43 (s, 1H), 4.26 - 4.17 (m, 1H), 4.16 - 4.10 (m, 2H), 4.00 (s, 3H), 3.92 - 3.85 (m, 1H), 3.84 (d, <i>J</i> = 1.6 Hz, 3H), 2.35 (s, 3H), 1.87 - 1.74 (m, 2H), 1.70 (s, 3H) ppm.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
75	<i>rel</i> -(<i>R</i>)-6-((3 <i>R</i> *,4 <i>R</i> *,6 <i>R</i> *)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-1-(methylimino)-1,3,4,5-tetrahydro-1 <i>λ</i> ⁴ -thiopyrano[3,2- <i>b</i>]pyridin-8(2 <i>H</i>)-one 1-oxide	520.146	521.1	1.75	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.90 (s, 1H), 7.26 - 7.19 (m, 1H), 7.17 - 7.08 (m, 1H), 6.49 (s, 1H), 4.25 - 4.14 (m, 1H), 4.04 - 3.87 (m, 7H), 3.07 - 2.98 (m, 2H), 2.78 (s, 3H), 2.35 - 2.17 (m, 2H), 1.84 - 1.74 (m, 2H), 1.68 (s, 3H) ppm; one proton obscured by solvent.
76	<i>rel</i> -(<i>S</i>)-6-((3 <i>R</i> *,4 <i>R</i> *,6 <i>R</i> *)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-1-(methylimino)-1,3,4,5-tetrahydro-1 <i>λ</i> ⁴ -thiopyrano[3,2- <i>b</i>]pyridin-8(2 <i>H</i>)-one 1-oxide	520.146	521.1	1.74	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.92 (s, 1H), 7.29 - 7.19 (m, 1H), 7.17 - 7.07 (m, 1H), 6.49 (s, 1H), 4.27 - 4.15 (m, 1H), 4.05 - 3.86 (m, 7H), 3.39 (td, <i>J</i> = 11.2, 4.5 Hz, 1H), 3.14 - 2.90 (m, 2H), 2.78 (s, 3H), 2.40 - 2.13 (m, 2H), 1.90 - 1.72 (m, 2H), 1.67 (s, 3H) ppm.

Example 2

Ethyl 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**77**), ethyl 5-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**78**) and ethyl 5-cyano-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**79**)



[0332] Step 1:

[0333] (2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 400 mg, 1.13 mmol) and ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate (345 mg, 1.13 mmol) were treated via the method described in General Method A to give ethyl 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinate (550 mg, 84%). ESI-MS *m/z* calc. 579.200, found 580.4 (*M*+1)⁺; Retention time: 2.22 minutes using LC/MS Method D.

[0334] Step 2:

[0335] Ethyl 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinate (550 mg, 0.95 mmol) was treated via the method described in General Method C to give ethyl 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**77**, 302 mg, 55%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.12 - 7.01 (m, 1H), 7.02 - 6.88 (m, 1H), 6.47 (s, 1H), 5.38 (d, *J* = 11.2 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.18

(dd, $J = 11.2, 8.3$ Hz, 1H), 3.97 (d, $J = 2.5$ Hz, 3H), 3.01 - 2.75 (m, 1H), 2.43 (s, 3H), 1.66 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H), 0.86 (d, $J = 7.5, 2.3$ Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 489.157, found 490.1 ($M+1$)⁺; Retention time: 1.67 minutes using LC/MS Method Q.

[0336] Step 3:

[0337] Ethyl 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**77**, 240 mg, 0.490 mmol) was treated via the method described in General Method I to give ethyl 5-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**78**, 140 mg, 49%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.22 - 7.07 (m, 1H), 7.06 - 6.92 (m, 1H), 5.87 (d, $J = 10.9$ Hz, 1H), 4.54 - 4.38 (m, 1H), 4.32 (q, $J = 7.2$ Hz, 2H), 3.91 (s, 3H), 3.07 - 2.89 (m, 1H), 2.41 (s, 3H), 1.71 (s, 3H), 1.32 (t, $J = 6.7$ Hz, 3H), 0.86 (d, $J = 7.6, 2.4$ Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 567.068, found 570.0 ($M+1$)⁺; Retention time: 1.91 minutes using LC/MS Method D.

[0338] Step 4:

[0339] Ethyl 5-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**78**, 140 mg, 0.241 mmol) was treated via the method described General Method K to give ethyl 4-(benzyloxy)-5-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinate (153 mg, 96%). ESI-MS m/z calc. 657.115, found 659.9 ($M+1$)⁺; Retention time: 2.17 minutes using LC/MS Method D.

[0340] Step 5:

[0341] A microwave vessel, loaded with ethyl 4-(benzyloxy)-5-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinate (120 mg, 0.182 mmol), zinc cyanide (32 mg, 0.27 mmol), and Pd(PPh₃)₄ (42 mg, 0.036 mmol) was capped and purged with nitrogen. DMF (1.9 mL) was added via syringe to the reaction vessel and the reaction was sparged by bubbling nitrogen through the solution for 10 min. The reaction mixture was heated at 90 °C for 1 h, cooled to ambient temperature, filtered, and concentrated *in vacuo*.

Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl modifier) gave ethyl 5-cyano-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**79**, 2 mg, 2%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.15 - 7.06 (m, 1H), 7.07 - 6.95 (m, 1H), 5.47 (d, $J = 11.1$ Hz, 1H), 4.57 (t, $J = 10.4$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 3.95 (d, $J = 2.4$ Hz, 3H), 3.05 - 2.85 (m, 1H), 2.40 (s, 3H), 1.73 (s, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 0.87 (dd, $J = 7.7, 2.3$ Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 514.150, found 515.1 ($M+1$)⁺; Retention time: 1.73 minutes using LC/MS Method D.

[0342] The following compound was made using the method described in Example 2 except that, Steps 3, 4 and 5 were omitted. The product of Step 2 (**77**) was chlorinated using the conditions

described for the synthesis of ethyl 5-chloro-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (56):

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
80	Ethyl 5-chloro-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	523.118	524.0	2.62	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.08 (ddd, <i>J</i> = 8.0, 5.6, 2.1 Hz, 1H), 6.97 (td, <i>J</i> = 9.4, 7.5 Hz, 1H), 5.84 (d, <i>J</i> = 10.9 Hz, 1H), 4.49 (t, <i>J</i> = 10.4 Hz, 1H), 4.34 (q, <i>J</i> = 7.1 Hz, 2H), 3.92 (s, 3H), 2.99 - 2.90 (m, 1H), 2.45 (s, 3H), 1.74 - 1.66 (m, 3H), 1.33 (t, <i>J</i> = 7.1 Hz, 3H), 0.86 (dq, <i>J</i> = 7.6, 2.2 Hz, 3H) ppm; NH pyridone not observed.

[0343] The following compound was made using the methods described in Example 2 except that, in Step 1, ethyl 4-(benzyloxy)-2-bromonicotinate was used as the halide coupling partner in place of ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
81	Ethyl 5-cyano-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-3-carboxylate	500.137	501.1	1.68	D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.22 (s, 1H), 7.06 - 6.84 (m, 2H), 5.34 (d, <i>J</i> = 10.7 Hz, 1H), 4.46 (t, <i>J</i> = 9.9 Hz, 1H), 4.41 - 4.29 (m, 1H), 4.29 - 4.15 (m, 1H), 3.91 (d, <i>J</i> = 2.1 Hz, 3H), 2.96 - 2.76 (m, 1H), 1.61 (s, 3H), 1.32 (t, <i>J</i> = 6.8 Hz, 3H), 0.78 (dd, <i>J</i> = 7.4, 2.4 Hz, 3H) ppm; NH pyridone not observed.

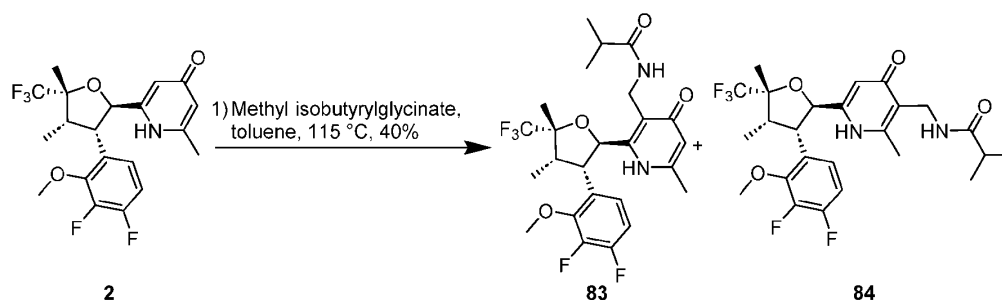
[0344] The following compound was made using methods described in Example 2, except that Steps 2, 3, 4 and 5 were omitted. In Step 1, (6-chloro-4-methoxypyridin-3-yl)methanol was used as the halide coupling partner in place of ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate. The product of Step 1 was demethylated in the presence of BBr₃, as outlined below:

[0345] *Demethylation*: A reaction vial, containing a solution of 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-methoxypyridin-3-yl)methanol (25.1 mg, 0.056 mmol) in DCM (1 mL), was degassed under an atmosphere of N₂ for 5

min. The vial was sealed and cooled to 0 °C. BBr₃ (170 µL, 1 M solution in DCM, 0.170 mmol) was added slowly, the reaction mixture was warmed to ambient temperature and stirred for 6 h. The mixture was poured into ice-water and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative chromatography (C₁₈ column, 10 to 99% MeCN in water containing 5 mM HCl modifier) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(hydroxymethyl)pyridin-4(1*H*)-one (**82**, 13.4 mg, 55%) as a solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.47 (s, 1H), 7.32 (s, 1H), 7.19 (ddd, *J* = 8.2, 5.6, 2.2 Hz, 1H), 6.87 - 6.75 (m, 1H), 5.92 (d, *J* = 11.3 Hz, 1H), 4.66 (d, *J* = 1.1 Hz, 2H), 4.22 (dd, *J* = 11.4, 8.2 Hz, 1H), 4.00 (s, 3H), 2.96 (p, *J* = 7.7 Hz, 1H), 2.66 (s, 1H), 1.81 - 1.71 (m, 3H), 0.95 (dq, *J* = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 433.131, found 434.4 (M+1)⁺; Retention time: 1.52 minutes using LC/MS method Q.

Example 3

N-((2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)isobutyramide (**83**) and *N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)isobutyramide (**84**)



[0346] Step 1:

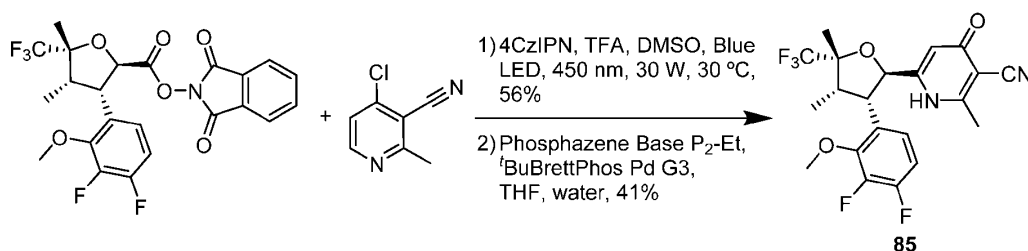
[0347] In a sealed vial, a solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 398 mg, 0.954 mmol) and methyl isobutyrylglycinate (465 mg, 2.92 mmol) in toluene (6 mL) was heated at 115 °C for 20 h. The reaction mixture was concentrated *in vacuo*. Purification by flash chromatography (40 g SiO₂, 0 to 10% MeOH in DCM) gave *N*-((2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)isobutyramide (**83**, 148 mg, 30%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.21 (s, 1H), 6.98 (d, *J* = 10.1 Hz, 1H), 6.23 (s, 1H), 5.75 (d, *J* = 11.0 Hz, 1H), 4.34 (s, 1H), 4.27 (dd, *J* = 14.1, 5.5 Hz, 1H), 4.06 (d, *J* = 14.5 Hz, 1H), 3.85 (s, 3H), 3.07 - 2.78 (m, 1H), 2.41 (p, *J* = 7.1 Hz, 1H), 2.35 (s,

3H), 1.70 (s, 3H), 1.10 (dd, $J = 6.9, 2.6$ Hz, 6H), 0.87 (dd, $J = 7.4, 2.3$ Hz, 3H) ppm; NH pyridone and NH amide not observed. ESI-MS m/z calc. 516.205, found 517.5 ($M+1$)⁺; Retention time: 2.26 minutes using LC/MS method V.

[0348] Also obtained *N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)isobutyramide (**84**, 52 mg, 10%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.04 (dt, $J = 8.0, 5.5, 1.9$ Hz, 1H), 6.95 (ddd, $J = 9.4, 7.4$ Hz, 1H), 6.34 (s, 1H), 5.32 (d, $J = 11.3$ Hz, 1H), 4.21 (s, 2H), 4.17 (dd, $J = 11.3, 8.3$ Hz, 1H), 3.96 (d, $J = 2.4$ Hz, 3H), 2.83 (p, $J = 7.7$ Hz, 1H), 2.48 (s, 3H), 2.42 - 2.29 (m, 1H), 1.65 (s, 3H), 1.04 (d, $J = 6.9$ Hz, 6H), 0.86 (dq, $J = 7.3, 2.3$ Hz, 3H) ppm; NH pyridone and NH amide not observed. ESI-MS m/z calc. 516.205, found 517.4 ($M+1$)⁺; Retention time: 2.20 minutes using LC/MS method V.

Example 4

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridine-3-carbonitrile (**85**)



[0349] Step 1:

[0350] 1,3-Dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (**Product from Step 1 of General Method B**, 13 mg, 0.085 mmol) and 4-chloro-2-methylnicotinonitrile (13 mg, 0.085 mmol) were treated via the method described in General Method B Step 2 to give 4-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinonitrile (22 mg, 56%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.51 (s, 1H), 7.19 - 7.07 (m, 1H), 6.95 - 6.75 (m, 1H), 5.47 (d, $J = 11.0$ Hz, 1H), 4.04 - 3.97 (m, 1H), 3.94 (d, $J = 2.7$ Hz, 3H), 2.87 - 2.73 (m, 1H), 2.66 (s, 3H), 1.74 (s, 3H), 0.84 (d, $J = 7.7, 2.3$ Hz, 3H) ppm. ESI-MS m/z calc. 460.098, found 461.1 ($M+1$)⁺; Retention time: 2.26 minutes using LC/MS method D.

[0351] Step 2:

[0352] 4-Chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinonitrile (10 mg, 0.022 mmol) was treated via the method described in General Method E to give 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-

dihydropyridine-3-carbonitrile (**85**, 4 mg, 41%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.15 - 7.03 (m, 1H), 7.03 - 6.92 (m, 1H), 6.47 (d, *J* = 17.3 Hz, 1H), 5.54 - 5.32 (m, 1H), 4.18 (t, *J* = 11.2, 8.4 Hz, 1H), 3.99 (d, *J* = 2.6 Hz, 3H), 2.93 - 2.79 (m, 1H), 2.63 (s, 3H), 1.66 (s, 3H), 0.86 (d, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 442.132, found 443.1 (M+1)⁺; Retention time: 1.58 minutes using LC/MS method D.

[0353] The following compounds were made using methods described in Example 4 using different coupling partners in Step 1:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
86	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carbonitrile	442.132	443.3	2.16	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 (ddd, <i>J</i> = 9.0, 5.6, 2.1 Hz, 1H), 7.01 (ddd, <i>J</i> = 9.8, 8.9, 7.4 Hz, 1H), 6.39 (s, 1H), 5.50 (d, <i>J</i> = 11.0 Hz, 1H), 4.57 (dd, <i>J</i> = 11.0, 9.8 Hz, 1H), 3.93 (s, 3H), 2.96 (dq, <i>J</i> = 9.7, 7.7 Hz, 1H), 2.37 (s, 3H), 1.73 (s, 3H), 0.87 (dq, <i>J</i> = 7.6, 2.2 Hz, 3H) ppm; NH pyridone not observed.
87	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-fluoro-6-methylpyridine-4(1 <i>H</i>)-one	435.127	436.4	2.90	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.14 - 7.09 (m, 1H), 7.01 - 6.97 (m, 1H), 5.63 (d, <i>J</i> = 10.8 Hz, 1H), 4.63 - 4.56 (m, 1H), 3.92 (d, <i>J</i> = 1.8 Hz, 3H), 2.82 - 2.76 (m, 1H), 2.63 - 2.60 (m, 1H), 2.25 (s, 3H), 1.59 (s, 3H), 0.78 (d, <i>J</i> = 6.8 Hz, 3H) ppm; NH pyridone not observed.
88	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-oxo-1,4-dihydropyridine-2-carbonitrile	428.116	429.1	2.49	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.52 (s, 1H), 7.12 (s, 1H), 7.16 - 7.07 (m, 1H), 6.95 - 6.83 (m, 1H), 5.78 (d, <i>J</i> = 11.4 Hz, 1H), 4.28 (dd, <i>J</i> = 11.4, 7.9 Hz, 1H), 3.92 (d, <i>J</i> = 2.3 Hz, 3H), 2.83 (p, <i>J</i> = 7.5 Hz, 1H), 1.68 (s, 3H), 0.86 (dd, <i>J</i> = 7.8, 2.4 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
89	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methylpyrimidin-4(1 <i>H</i>)-one	454.088	455.1	1.82	D	

[0354] The following compound was made using methods described in Example 4, except that 4-chloro-3-fluoro-2-methylpyridine was used as the coupling partner in Step 1. The product of Step 2 was further brominated using the conditions described for compound 58:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
90	3-Bromo-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methylpyridin-4(1 <i>H</i>)-one	514.037	513.9	2.42	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.07 - 7.01 (m, 1H), 6.99 - 6.90 (m, 1H), 5.89 (d, <i>J</i> = 10.9 Hz, 1H), 4.55 (dd, <i>J</i> = 10.9, 9.5 Hz, 1H), 3.92 (s, 3H), 2.99 - 2.88 (m, 1H), 2.42 (s, 3H), 1.68 (s, 3H), 0.89 - 0.81 (m, 3H) ppm; NH pyridone not observed.

[0355] The following compound was made using methods described in Example 4, except that 4-chloro-3-fluoro-2-methylpyridine was used as the coupling partner in Step 1. The product of Step 2 was further brominated using the conditions described for compound 58. A final carbonylation step was carried out as outlined below:

[0356] *Carbonylation reaction:* A suspension of 3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methylpyridin-4(1*H*)-one (90, 25 mg, 0.048 mmol), Et₃N (25 μL, 0.179 mmol) and PdCl₂(dppf)·DCM (5.9 mg, 0.007 mmol) in MeOH (500 μL) was sparged with carbon monoxide for 15 min at ambient temperature. The reaction mixture was stirred under a carbon monoxide atmosphere (balloon) at 65 °C over the weekend. The solution was filtered and purified by preparative reverse phase HPLC (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl modifier over 20 min) to give methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-fluoro-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (91, 12.1 mg, 44%) as a brown solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.05 - 6.96 (m, 2H), 5.44 (d, *J* = 10.8 Hz, 1H), 4.52 (t, *J* = 10.3 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 2.94 - 2.82 (m, 1H), 2.42 (s, 3H), 1.62 (s, 3H), 0.85 - 0.78 (m, 3H)

ppm; NH pyridone not observed. ESI-MS m/z calc. 493.132, found 494.1 ($M+1$)⁺; Retention time: 2.29 minutes using LC/MS method Q.

[0357] The following compounds were made using methods described in Example 4 except that different coupling partners were used in Step 1. Step 2 was omitted. A final benzyl deprotection step was introduced using the conditions described in General Method C:

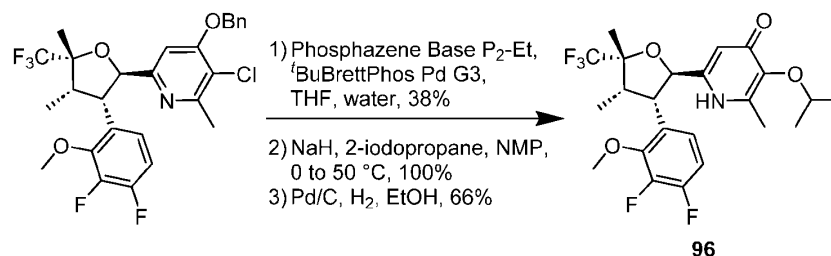
Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found $M+1$	MS retention time	LC/MS Method	NMR (shifts in ppm)
92	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-methoxy-2-methylpyridin-4(1 <i>H</i>)-one	447.147	448.5	2.94	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.05 - 7.01 (m, 1H), 6.99 - 6.93 (m, 1H), 6.43 (s, 1H), 5.33 (d, J = 11.3 Hz, 1H), 4.15 (dd, J = 11.3, 8.3 Hz, 1H), 3.97 (d, J = 2.4 Hz, 3H), 3.74 (s, 3H), 2.84 (dq, J = 7.8, 7.8 Hz, 1H), 2.36 (s, 3H), 1.66 (s, 3H), 0.88 - 0.84 (m, 3H) ppm; NH pyridone not observed.
93	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-fluoro-2-methylpyridin-4(1 <i>H</i>)-one	435.127	436.5	2.85	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.08 - 7.03 (m, 1H), 7.00 - 6.93 (m, 1H), 6.54 (d, J = 7.5 Hz, 1H), 5.35 (d, J = 11.2 Hz, 1H), 4.15 (dd, J = 11.2, 8.3 Hz, 1H), 3.96 (d, J = 2.5 Hz, 3H), 2.84 (dq, J = 8.3, 7.7 Hz, 1H), 2.38 (d, J = 3.1 Hz, 3H), 1.66 (d, J = 1.1 Hz, 3H), 0.89 - 0.85 (m, 3H) ppm; NH pyridone not observed.

[0358] The following compounds were made using methods described in Example 4 except that different coupling partners were used in Step 1. Step 2 was omitted. A final benzyl deprotection step was carried out at 80 °C, using a 4 M HCl solution in 1,4-dioxane:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
94	3-Chloro-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	451.097	452.4	2.95	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.17 - 7.14 (m, 1H), 7.08 - 7.03 (m, 1H), 6.52 (s, 1H), 5.24 (d, <i>J</i> = 11.0 Hz, 1H), 4.21 (dd, <i>J</i> = 11.1, 7.5 Hz, 1H), 3.87 (d, <i>J</i> = 1.8 Hz, 3H), 2.71 (dq, <i>J</i> = 7.5, 7.5 Hz, 1H), 2.31 (s, 3H), 1.56 (s, 3H), 0.73 (d, <i>J</i> = 6.2 Hz, 3H) ppm; NH pyridone not observed.
95	3-Chloro-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	451.815	452.3	3.04	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.10 - 7.06 (m, 1H), 7.00 - 6.94 (m, 1H), 6.34 (s, 1H), 5.86 (d, <i>J</i> = 11.0 Hz, 1H), 4.46 (dd, <i>J</i> = 11.0, 9.9 Hz, 1H), 3.90 (d, <i>J</i> = 2.3 Hz, 3H), 2.95 (dq, <i>J</i> = 9.9, 7.8 Hz, 1H), 2.38 (d, <i>J</i> = 0.7 Hz, 3H), 1.71 (s, 3H), 0.88 - 0.85 (m, 3H) ppm; NH pyridone not observed.

Example 5

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropoxy-2-methylpyridin-4(1*H*)-one (96)



[0359] Step 1:

[0360] 4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-ol (Product of Step 2 in Example 6, 35 mg, 0.064 mmol) was treated via the method described in General Method E to give 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-ol (13 mg, 38%) as a light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.90 (s, 1H), 7.52 - 7.45 (m, 2H), 7.42 - 7.29 (m, 3H), 7.11 (s, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.05 - 6.97

(m, 1H), 5.33 (d, $J = 11.1$ Hz, 1H), 5.24 (s, 2H), 4.24 (dd, $J = 11.1, 7.3$ Hz, 1H), 3.87 (d, $J = 2.0$ Hz, 3H), 2.73 (t, $J = 7.5$ Hz, 1H), 2.25 (s, 3H), 1.58 (s, 3H), 0.74 (d, $J = 7.5$ Hz, 3H) ppm.

[0361] Step 2:

[0362] Sodium hydride (1.7 mg, 60% dispersion in mineral oil, 0.042 mmol) was added to a solution of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-ol (12 mg, 0.022 mmol) in NMP (0.5 mL) at 0 °C and the reaction mixture was stirred for 5 min. 2-Iodopropane (4.6 µL, 0.046 mmol) was added, the mixture was warmed to ambient temperature and then heated at 50 °C overnight. The mixture was cooled to ambient temperature and allowed to stand for 1.5 days. The mixture was partitioned between EtOAc (5 mL), a half-saturated brine solution (3 mL), water (2 mL) and a saturated brine solution (2 mL). The organic layer was dried (MgSO₄), filtered concentrated *in vacuo* to give 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropoxy-2-methylpyridine (16 mg, 100%) as a yellow oil. ESI-MS m/z calc. 565.225, found 566.6 (M+1)⁺; Retention time: 1.28 minutes using LC/MS method C.

[0363] Step 3:

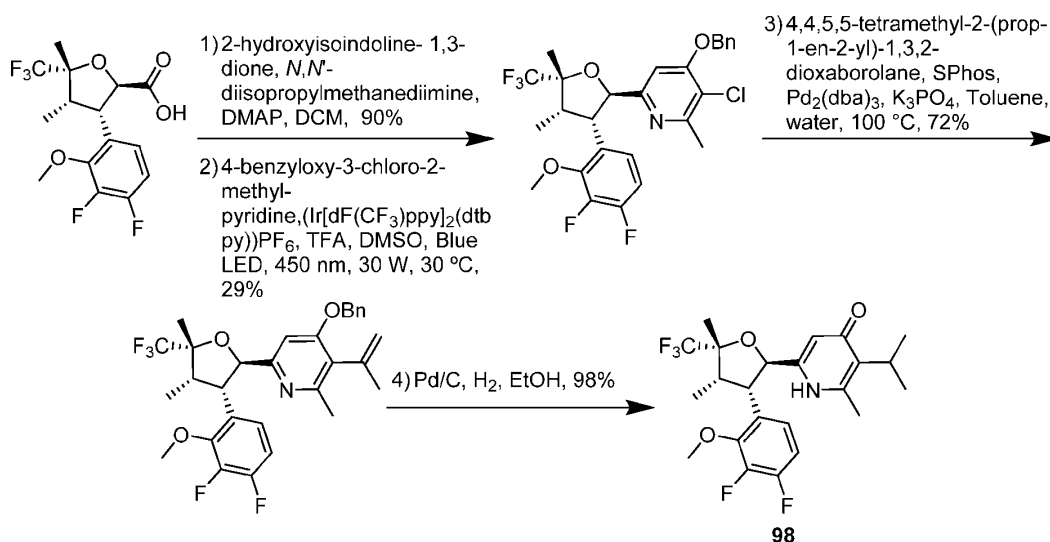
[0364] 4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropoxy-2-methylpyridine (16 mg, 0.028 mmol) was treated via the method described in General Method C to give 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropoxy-2-methylpyridin-4(1*H*)-one (**96**, 9 mg, 66%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.05 (ddd, $J = 7.8, 5.6, 2.0$ Hz, 1H), 7.02 - 6.94 (m, 1H), 6.41 (s, 1H), 5.35 (d, $J = 11.3$ Hz, 1H), 4.69 (p, $J = 6.1$ Hz, 1H), 4.18 (dd, $J = 11, 8.3$ Hz, 1H), 3.98 (d, $J = 2.5$ Hz, 3H), 2.86 (p, $J = 7.6$ Hz, 1H), 2.36 (s, 3H), 1.68 (d, $J = 1.1$ Hz, 3H), 1.23 (dd, $J = 6.2, 1.6$ Hz, 6H), 0.91 - 0.84 (m, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 475.178, found 476.5 (M+1)⁺; Retention time: 3.18 minutes using LC/MS method A.

[0365] The following compound was made using methods described in Example 5 except that, in Step 1, 4-(benzyloxy)-3-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine was used as the starting material in place of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylnicotinonitrile and ^tBuXPhos Pd G3 was used as the catalyst in place of ^tBuBrettPhos Pd G3. Step 2 was omitted:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
97	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-hydroxy-2-methylpyridin-4(1 <i>H</i>)-one	433.131	434.1	1.81	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.11 (ddd, <i>J</i> = 8.0, 5.6, 2.1 Hz, 1H), 7.06 - 6.96 (m, 2H), 5.60 (d, <i>J</i> = 11.3 Hz, 1H), 4.21 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.99 (s, 3H), 2.90 (p, <i>J</i> = 7.8 Hz, 1H), 2.57 (s, 3H), 1.72 - 1.66 (m, 3H), 0.89 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; OH alcohol and NH pyridone not observed.

Example 6

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1*H*)-one (**98**)



[0366] Step 1:

[0367] DMAP (6.86 g, 56.2 mmol) was added to a solution of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 1.618 g, 4.567 mmol) and 2-hydroxyisoindoline-1,3-dione (920 mg, 5.64 mmol) in DCM (25 mL) and the reaction mixture was stirred for 10 min at ambient temperature. DIPEA (760 μL, 4.85 mmol) was added and the mixture was stirred at ambient temperature for 1 h. The mixture was treated with 2M HCl (40 mL) and extracted with DCM (2 x 40 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. The oil was diluted with DCM and a white precipitate formed. The solid was filtered and the mother liquors were concentrated *in vacuo*. Purification by

flash chromatography (SiO₂, 0 to 40% EtOAc in heptane) gave 1,3-dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2.06 g, 90%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.07 - 6.98 (m, 1H), 6.92 (td, *J* = 9.2, 7.3 Hz, 1H), 5.33 (d, *J* = 0.8 Hz, 1H), 4.46 (t, *J* = 8.9 Hz, 1H), 4.10 (d, *J* = 2.4 Hz, 3H), 2.81 (q, *J* = 7.7 Hz, 1H), 1.69 (q, *J* = 1.2 Hz, 3H), 0.89 - 0.82 (m, 3H) ppm.

[0368] Step 2:

[0369] 1,3-Dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2.00 g, 4.005 mmol) and 4-(benzyloxy)-3-chloro-2-methylpyridine (816 mg, 3.49 mmol) were treated via the method described in General Method B Step 2 to give 4-(benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (634 mg, 29%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.49 - 7.30 (m, 5H), 7.09 (ddd, *J* = 8.4, 5.7, 2.3 Hz, 1H), 6.94 (s, 1H), 6.86 - 6.73 (m, 1H), 5.39 (d, *J* = 10.8 Hz, 1H), 5.25 (d, *J* = 5.5 Hz, 2H), 4.06 - 3.99 (m, 1H), 3.90 (d, *J* = 2.4 Hz, 3H), 2.76 (t, *J* = 7.6 Hz, 1H), 2.52 (d, *J* = 0.4 Hz, 3H), 1.64 (d, *J* = 1.3 Hz, 3H), 0.89 - 0.74 (m, 3H) ppm. ESI-MS *m/z* calc. 541.144, found 542.1 (M+1)⁺; Retention time: 1.24 minutes using LC/MS method C.

[0370] Step 3:

[0371] 4-(Benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (1.04 g, 1.77 mmol) was treated via the method described in General Method F to give 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(prop-1-en-2-yl)pyridine (728 mg, 72%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.41 - 7.26 (m, 5H), 7.14 - 7.06 (m, 1H), 7.01 (s, 1H), 6.91 - 6.81 (m, 1H), 5.38 (d, *J* = 11.1 Hz, 1H), 5.31 - 5.25 (m, 1H), 5.20 (s, 2H), 4.83 - 4.77 (m, 1H), 4.09 (dd, *J* = 11.1, 7.8 Hz, 1H), 3.85 (d, *J* = 2.2 Hz, 3H), 2.79 (p, *J* = 7.6 Hz, 1H), 2.37 (s, 3H), 1.96 (s, 3H), 1.64 (s, 3H), 0.89 - 0.76 (m, 3H) ppm. ESI-MS *m/z* calc. 547.215, found 548.6 (M+1)⁺; Retention time: 2.48 minutes using LC/MS method Q.

[0372] Step 4:

[0373] 4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(prop-1-en-2-yl)pyridine (7.4 g, 13.5 mmol) was treated via the method described in General Method C to give 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1*H*)-one (**98**, 6.15 g, 98%) as an off-white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.02 (t, *J* = 7.3 Hz, 1H), 7.00 - 6.89 (m, 1H), 6.24 (s, 1H), 5.30 (d, *J* = 11.3 Hz, 1H), 4.16 (dd, *J* = 11.4, 8.2 Hz, 1H), 3.97 (d, *J* = 2.4 Hz, 3H), 3.16 (p, *J* = 7.0 Hz, 1H), 2.83 (p, *J* = 7.7 Hz, 1H), 2.39 (s, 3H), 1.67 - 1.62 (m, 3H), 1.26 (dd, *J* = 7.1, 2.4 Hz, 6H), 0.85 (dq, *J* = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.46, -139.63 (d, *J* = 18.9 Hz), -156.37 (d, *J* = 18.8

Hz) ppm. ESI-MS *m/z* calc. 459.183, found 460.5 ($M+1$)⁺; Retention time: 1.97 minutes using LC/MS method Q.

[0374] The following compounds were made using methods described in Example 6 except that different Suzuki coupling partners were used in Step 3. In the case of **104**, EtOAc was used as the solvent in Step 4 in place of EtOH. Step 4 was omitted for compounds **103** and **105**. In the case of **106**, 4-(benzyloxy)-3-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine was used in place of 4-(benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine, dichloro[1,1'-ferrocenylbis(diphenylphosphane)]palladium dichloromethane was used as the catalyst, K₂CO₃ was used as the base, and dioxane as the solvent:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
99	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-ethyl-2-methylpyridin-4(1 <i>H</i>)-one	445.168	446.5	3.09	A	
100	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isobutyl-2-methylpyridin-4(1 <i>H</i>)-one	473.199	474.6	3.35	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.20 (s, 1H), 6.82 (td, <i>J</i> = 9.3, 7.5 Hz, 1H), 6.55 (s, 1H), 5.59 (d, <i>J</i> = 11.1 Hz, 1H), 4.13 - 4.01 (m, 1H), 3.92 (d, <i>J</i> = 2.6 Hz, 3H), 2.75 (h, <i>J</i> = 8.2, 7.7 Hz, 1H), 2.49 (s, 3H), 2.41 (d, <i>J</i> = 7.3 Hz, 2H), 1.92 (hept, <i>J</i> = 6.8 Hz, 1H), 1.63 (s, 3H), 0.89 (dd, <i>J</i> = 6.6, 1.6 Hz, 6H), 0.85 - 0.74 (m, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
101	<i>rel</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>R</i>)-1-methoxypropan-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	489.194	490.5	3.17	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.07 - 7.02 (m, 1H), 6.97 (td, <i>J</i> = 9.3, 7.4 Hz, 1H), 6.26 (s, 1H), 5.33 (d, <i>J</i> = 11.3 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.99 (d, <i>J</i> = 2.4 Hz, 3H), 3.86 (t, <i>J</i> = 8.4 Hz, 1H), 3.61 (dd, <i>J</i> = 9.0, 6.6 Hz, 1H), 3.27 (s, 3H), 3.14 (d, <i>J</i> = 16.0 Hz, 1H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.41 (s, 3H), 1.67 (d, <i>J</i> = 1.1 Hz, 3H), 1.26 (d, <i>J</i> = 7.0 Hz, 3H), 0.88 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.
102	<i>rel</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-1-methoxypropan-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	489.194	490.5	3.16	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.04 (d, <i>J</i> = 6.3 Hz, 1H), 6.98 (q, <i>J</i> = 8.8 Hz, 1H), 6.23 (s, 1H), 5.33 (d, <i>J</i> = 11.3 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.99 (d, <i>J</i> = 2.4 Hz, 3H), 3.86 (t, <i>J</i> = 8.5 Hz, 1H), 3.62 (dd, <i>J</i> = 9.0, 6.6 Hz, 1H), 3.28 (s, 3H), 3.19 - 3.08 (m, 1H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.41 (s, 3H), 1.67 (d, <i>J</i> = 1.1 Hz, 3H), 1.25 (d, <i>J</i> = 7.1 Hz, 3H), 0.88 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.
103	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(3,5-dimethylisoxazol-4-yl)-2-methylpyridin-4(1 <i>H</i>)-one	512.477	513.5	3.06	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 (t, <i>J</i> = 7.3 Hz, 1H), 7.05 - 6.95 (m, 1H), 6.43 (s, 1H), 5.42 (d, <i>J</i> = 11.3 Hz, 1H), 4.26 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 4.02 (dd, <i>J</i> = 2.6, 1.1 Hz, 3H), 2.90 (p, <i>J</i> = 7.7 Hz, 1H), 2.23 (s, 3H), 2.20 (d, <i>J</i> = 6.7 Hz, 3H), 2.05 (d, <i>J</i> = 7.2 Hz, 3H), 1.70 (s, 3H), 0.95 - 0.85 (m, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
104	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(tetrahydro-2 <i>H</i> -pyran-4-yl)pyridin-4(1 <i>H</i>)-one	501.494	502.6	3.09	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 6.85 (qd, <i>J</i> = 10.9, 9.0, 5.7 Hz, 2H), 5.99 (s, 1H), 5.30 (d, <i>J</i> = 11.0 Hz, 1H), 3.98 (d, <i>J</i> = 24.2 Hz, 4H), 1.43 - 1.13 (m, 4H), 3.92 - 3.74 (m, 1H), 3.52 - 3.33 (m, 2H), 3.09 (t, <i>J</i> = 12.3 Hz, 1H), 2.70 (p, <i>J</i> = 7.7 Hz, 1H), 2.53 - 2.42 (m, 1H), 2.40 (s, 3H), 1.62 (d, <i>J</i> = 1.2 Hz, 3H), 0.79 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.
105	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(1-methyl-3-(trifluoromethyl)-1 <i>H</i> -pyrazol-5-yl)pyridin-4(1 <i>H</i>)-one	565.464	566.5	3.36	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 (d, <i>J</i> = 6.8 Hz, 1H), 7.00 (q, <i>J</i> = 8.7 Hz, 1H), 6.57 (d, <i>J</i> = 6.7 Hz, 1H), 6.45 (s, 1H), 5.42 (dd, <i>J</i> = 11.3, 2.3 Hz, 1H), 4.31 - 4.21 (m, 1H), 4.03 (t, <i>J</i> = 2.2 Hz, 3H), 3.69 (d, <i>J</i> = 6.3 Hz, 3H), 2.97 - 2.84 (m, 1H), 2.27 (d, <i>J</i> = 2.5 Hz, 3H), 1.70 (s, 3H), 0.90 (dd, <i>J</i> = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed.
106	3-Cyclopropyl-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	457.17	458.3	1.98	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 - 6.79 (m, 2H), 6.30 (s, 1H), 5.31 (d, <i>J</i> = 11.3 Hz, 1H), 4.15 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.96 (d, <i>J</i> = 2.5 Hz, 3H), 2.83 (p, <i>J</i> = 7.7 Hz, 1H), 2.49 (s, 3H), 1.64 (s, 3H), 1.41 (q, <i>J</i> = 7.5, 6.8 Hz, 1H), 0.95 - 0.88 (m, 2H), 0.85 (dq, <i>J</i> = 7.5, 2.4 Hz, 3H), 0.61 - 0.40 (m, 2H) ppm; NH pyridone not observed.

[0375] The following compounds were made using methods described in Example 6 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic **Int-3** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-

carboxylic acid **Int-1**. A final step was introduced to separate the enantiomers by chiral SFC using a Lux[®] Cellulose-5 column, 5 μ m particle size, 25 cm x 10 mm from Phenomenex, Inc:

[0376] First Eluting Isomer (rt = 4.79 minutes): *rel*-6-((2*S*,3*R*,4*R*,5*S*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1*H*)-one (**107**, 15 mg, 16%). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.95 (t, *J* = 7.3 Hz, 1H), 6.86 - 6.75 (m, 1H), 6.23 (s, 1H), 5.38 (d, *J* = 10.8 Hz, 1H), 4.77 (p, *J* = 8.0, 7.3 Hz, 1H), 4.10 (dt, *J* = 7.9, 4.3 Hz, 1H), 3.94 (d, *J* = 2.6 Hz, 3H), 3.15 (p, *J* = 7.1 Hz, 1H), 2.95 (hept, *J* = 7.0 Hz, 1H), 2.39 (s, 3H), 1.32 (dd, *J* = 7.0, 2.2 Hz, 6H), 0.81 - 0.79 (m, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 445.168, found 446.2 (M+1)⁺; 444.2 (M-1)⁻; Retention time: 3.07 minutes using LC/MS Method A.

[0377] Second Eluting Isomer (rt = 5.46 minutes): *rel*-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1*H*)-one (**108**, 9 mg, 9%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.22 - 7.13 (m, 1H), 6.83 (td, *J* = 9.0, 7.2 Hz, 1H), 6.04 (s, 1H), 5.34 (d, *J* = 10.6 Hz, 1H), 4.69 (p, *J* = 7.2 Hz, 1H), 3.99 (d, *J* = 10.3 Hz, 1H), 3.96 (d, *J* = 2.8 Hz, 3H), 3.15 (p, *J* = 7.1 Hz, 1H), 2.95 (h, *J* = 7.1 Hz, 1H), 2.37 (s, 3H), 1.30 (dd, *J* = 7.1, 1.1 Hz, 6H), 0.88 - 0.78 (m, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 445.167, found 446.3 (M+1)⁺; 444.2 (M-1)⁻; Retention time: 3.08 minutes using LC/MS Method A.

[0378] The following compound was made using methods described in Example 6 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

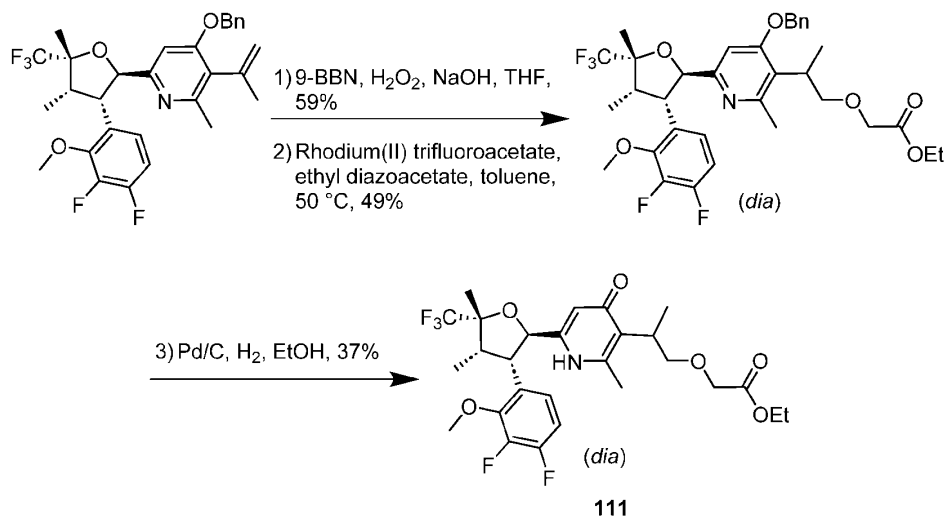
Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
109	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-Fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1 <i>H</i>)-one	425.198	426.3	3.15	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.24 (dd, <i>J</i> = 8.6, 5.6 Hz, 1H), 6.98 (ddd, <i>J</i> = 9.8, 2.8, 0.7 Hz, 1H), 6.90 (td, <i>J</i> = 8.5, 2.8 Hz, 1H), 6.34 (s, 1H), 5.42 (d, <i>J</i> = 11.1 Hz, 1H), 4.05 (dd, <i>J</i> = 11.2, 8.0 Hz, 1H), 3.23 - 3.10 (m, 1H), 2.87 (p, <i>J</i> = 7.6 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 1.70 - 1.64 (m, 3H), 1.27 (dd, <i>J</i> = 7.1, 3.8 Hz, 6H), 0.83 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.

[0379] The following compound was made using methods described in Example 6 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
110	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3-Fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-2-methylpyridin-4(1 <i>H</i>)-one	441.192	442.6	3.20	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.11 - 7.05 (m, 1H), 7.05 - 7.01 (m, 2H), 6.27 (s, 1H), 5.33 (d, <i>J</i> = 11.3 Hz, 1H), 4.23 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.91 (d, <i>J</i> = 2.2 Hz, 3H), 3.23 - 3.08 (m, 1H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.40 (s, 3H), 1.66 (d, <i>J</i> = 1.3 Hz, 3H), 1.27 (dd, <i>J</i> = 7.1, 3.3 Hz, 6H), 0.86 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Example 7

Ethyl *dia*-2-(2-(6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetate (**111**)



[0380] Step 1:

[0381] To a solution of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(prop-1-en-2-yl)pyridine (**Product of**

Step 3 in Example 6, 700 mg, 1.28 mmol) in THF (14 mL) under a nitrogen atmosphere, was added 9-BBN (40 mL, 0.5 M solution in THF, 20 mmol). The reaction mixture was heated at 30 °C for 2 days. The mixture was cooled to ambient temperature, quenched by addition of NaOH (14 mL, 1 M aqueous solution, 14 mmol) and stirred for 30 min. H₂O₂ (5 mL, 30% aqueous solution, 163 mmol) was added and the mixture was stirred for a further 30 min. The reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 100% EtOAc in heptane) gave *dia*-2-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propan-1-ol (430 mg, 59%) as a mixture of epimers. ESI-MS *m/z* calc. 565.225, found 566.7 (M+1)⁺; Retention time: 1.17 minutes using LC/MS Method C.

[0382] Step 2:

[0383] Ethyl diazoacetate (180 µL, 1.71 mmol) was added dropwise to a degassed solution of *dia*-2-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propan-1-ol (300 mg, 0.53 mmol) and rhodium(II) 2,2,2-trifluoroacetate (20 mg, 0.03 mmol) in toluene (5 mL) at 50 °C. The reaction mixture was stirred for 10 min at 50 °C and then concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100% EtOAc in heptane) gave ethyl *dia*-2-(2-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)acetate (171 mg, 49%) as a mixture of epimers. ESI-MS *m/z* calc. 651.262, found 652.5 (M+1)⁺; Retention time: 1.27 minutes using LC/MS Method C.

[0384] Step 3:

[0385] Ethyl *dia*-2-(2-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)acetate (15 mg, 0.023 mmol) was treated via the method described in General Method C to give ethyl *dia*-2-(2-(6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetate (111, 5.6 mg, 37%) as a mixture of epimers. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.90 (s, 1H), 6.83 (q, *J* = 8.6 Hz, 1H), 5.30 (dd, *J* = 11.0, 2.3 Hz, 1H), 4.27 - 4.20 (m, 3H), 4.17 (qd, *J* = 7.2, 0.8 Hz, 2H), 4.03 (d, *J* = 2.4 Hz, 2H), 3.95 (t, *J* = 2.5 Hz, 3H), 3.83 (ddd, *J* = 8.5, 5.8, 2.5 Hz, 1H), 3.12 (s, 1H), 2.72 (h, *J* = 7.9 Hz, 1H), 2.35 (d, *J* = 4.6 Hz, 3H), 1.64 - 1.60 (m, 3H), 1.32 - 1.22 (m, 6H), 0.80 (dd, *J* = 7.7, 2.4 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 561.214, found 563.3 (M+1)⁺; 560.2 (M-1)⁻; Retention time: 3.26 minutes using LC/MS Method A.

[0386] The following compound was made using methods described in Example 7 except that, an additional Grignard reaction step was introduced between Step 2 and Step 3, as outlined below:

[0387] Grignard reaction: MeMgBr (100 μ L, 3 M in Et₂O, 0.3 mmol) was added to a stirred solution of ethyl *dia*-2-(2-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)acetate (50 mg, 0.076 mmol) in THF (1 mL) at 0 °C and the reaction mixture was warmed to ambient temperature. Upon reaction completion, the mixture was quenched by addition of a saturated NH₄Cl solution (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO₂, 0 to 100 % EtOAc in heptane) gave *dia*-1-(2-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)-2-methylpropan-2-ol (32 mg, 65%). ESI-MS *m/z* calc. 637.282, found 638.2 (M+1)⁺; Retention time: 1.24 minutes using LC/MS Method C.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS retention time	LC/MS Method	NMR (shifts in ppm)
112	<i>dia</i> -6-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-(2-hydroxy-2-methylpropoxy)propan-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	547.236	546.2	3.09	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.33 (q, <i>J</i> = 8.5, 7.9 Hz, 1H), 6.86 (td, <i>J</i> = 9.2, 7.4 Hz, 1H), 6.82 - 6.74 (m, 1H), 5.73 (dd, <i>J</i> = 17.9, 11.2 Hz, 1H), 4.18 - 4.04 (m, 1H), 3.93 (dd, <i>J</i> = 3.9, 2.6 Hz, 3H), 3.86 (dt, <i>J</i> = 9.1, 7.4 Hz, 1H), 3.77 (dt, <i>J</i> = 9.1, 5.8 Hz, 1H), 3.31 - 3.08 (m, 3H), 2.76 (h, <i>J</i> = 7.7 Hz, 1H), 2.61 (d, <i>J</i> = 3.5 Hz, 3H), 1.66 (d, <i>J</i> = 7.1 Hz, 3H), 1.31 (d, <i>J</i> = 7.1 Hz, 3H), 1.11 (d, <i>J</i> = 8.2 Hz, 3H), 1.05 (d, <i>J</i> = 8.2 Hz, 3H), 0.83 (dt, <i>J</i> = 8.0, 2.3 Hz, 3H) ppm; OH alcohol and NH pyridone not observed.

[0388] The following compound was made using methods described in Example 7 except that an additional amidation step was introduced between Step 2 and Step 3 as outlined below:

[0389] Amidation: Ethyl *dia*-2-(2-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)acetate (35 mg, 0.053 mmol) was dissolved in NH₃ (3 mL, 7 M solution in MeOH, 21 mmol) under N₂ and stirred for 16 h. The solution was concentrated *in vacuo*. Purification by flash chromatography (4 g SiO₂, 0 to 100 % EtOAc in heptane) gave *dia*-2-(2-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)acetamide (22 mg, 66%). ESI-MS *m/z* calc. 622.247, found 623.3 (M+1)⁺; Retention time: 1.11 minutes using LC/MS Method C.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
113	<i>dia</i> -2-(2-(6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)propoxy)acetamide	532.200	533.1	2.84	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.65 (s, 1H), 6.96 (s, 1H), 6.83 - 6.75 (m, 2H), 5.82 (s, 1H), 5.40 (s, 1H), 5.26 - 5.18 (m, 1H), 4.15 (t, <i>J</i> = 8.6 Hz, 1H), 3.89 (dd, <i>J</i> = 2.9, 2.0 Hz, 4H), 3.76 (dd, <i>J</i> = 16.0, 3.2 Hz, 1H), 3.65 - 3.54 (m, 1H), 3.05 (s, 1H), 2.64 (p, <i>J</i> = 7.9 Hz, 1H), 2.28 (s, 3H), 1.56 (s, 3H), 1.23 - 1.12 (m, 3H), 0.74 (dq, <i>J</i> = 7.6, 2.4 Hz, 3H) ppm; NH pyridone not observed.

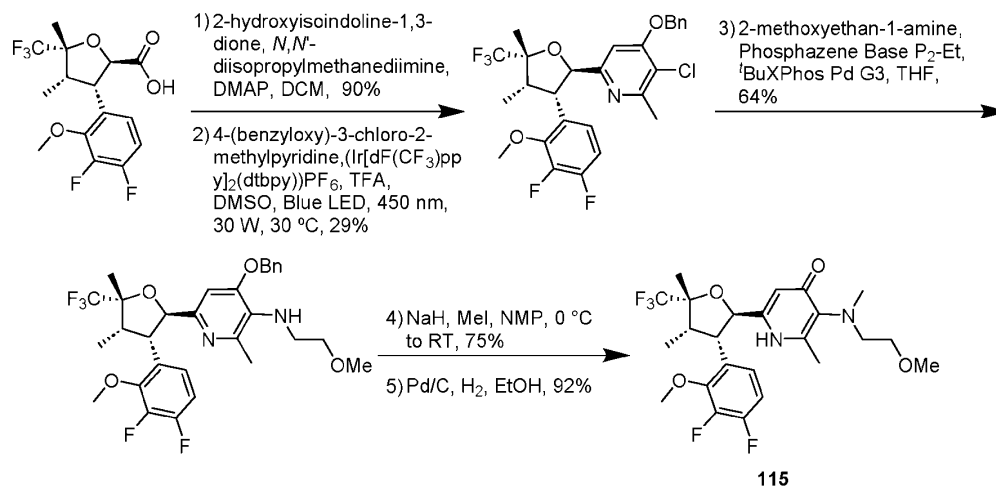
[0390] The following compound was made using methods described in Example 7 except that an additional ester reduction step was introduced between Step 2 and Step 3 as outlined below:

[0391] *Ester reduction:* LiAlH₄ (100 μL of 1 M, 0.1 mmol) was added to a stirred solution of ethyl *dia*-2-(2-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)acetate (60 mg, 0.092 mmol) in THF (1.2 mL) at -78 °C, and the mixture warmed to 0 °C. Upon reaction completion, the reaction mixture was quenched by addition of a saturated NH₄Cl solution (10 mL) and diluted with DCM (10 mL). The organic extract was dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO₂, 0 to 100 % EtOAc in heptane) gave *dia*-2-(2-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)propoxy)ethan-1-ol (21 mg, 37%). ESI-MS *m/z* calc. 609.251, found 610.3 (M+1)⁺; Retention time: 1.16 minutes using LC/MS Method C.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
114	<i>dia</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-(2-hydroxyethoxy)propan-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	519.501	520.4	2.89	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 6.93 (s, 1H), 6.81 (td, <i>J</i> = 9.2, 7.3 Hz, 1H), 5.35 - 5.27 (m, 1H), 4.06 - 3.96 (m, 2H), 3.95 (t, <i>J</i> = 2.7 Hz, 3H), 3.76 - 3.62 (m, 3H), 3.60 - 3.45 (m, 2H), 3.14 (s, 1H), 2.72 (p, <i>J</i> = 7.7 Hz, 1H), 2.35 (s, 3H), 1.64 - 1.60 (m, 3H), 1.31 - 1.17 (m, 4H), 0.79 (dq, <i>J</i> = 7.6, 2.4 Hz, 3H) ppm; OH alcohol and NH pyridone not observed.

Example 8

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((2-methoxyethyl)(methyl)amino)-2-methylpyridin-4(1*H*)-one (**115**)



[0392] Step 1:

[0393] *N,N*-Diisopropylmethanediimine (6.86 g, 56.2 mmol) was added to a mixture of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 1.618 g, 4.567 mmol) and 2-hydroxyisoindoline-1,3-dione (920 mg, 5.64 mmol) in DCM (25 mL) and the reaction mixture was stirred for 10 min at ambient temperature. DIPEA (760 μL , 4.85 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h. On reaction completion, the mixture was treated with 2 M HCl (40 mL) and extracted with DCM (2 x 40 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. The oil was taken up in DCM and a white precipitate formed. The precipitate was filtered and the mother liquors were concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 0 to 40% EtOAc in heptane) gave 1,3-dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2.06 g, 90%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.81 (dd, $J = 5.5, 3.1$ Hz, 2H), 7.07 - 6.98 (m, 1H), 6.92 (td, $J = 9.2, 7.3$ Hz, 1H), 5.33 (d, $J = 0.8$ Hz, 1H), 4.46 (t, $J = 8.9$ Hz, 1H), 4.10 (d, $J = 2.4$ Hz, 3H), 2.81 (q, $J = 7.7$ Hz, 1H), 1.69 (q, $J = 1.2$ Hz, 3H), 0.89 - 0.82 (m, 3H) ppm.

[0394] Step 2:

[0395] 1,3-Dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2 g, 4 mmol) and 4-(benzyloxy)-3-chloro-2-methylpyridine (1.47 g, 6.28 mmol) were treated via the method described in General Method B Step 2 to give 4-(benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (634 mg, 29%). ^1H NMR (400 MHz,

Chloroform-*d*) δ 7.49 - 7.30 (m, 5H), 7.09 (ddd, J = 8.4, 5.7, 2.3 Hz, 1H), 6.94 (s, 1H), 6.86 - 6.73 (m, 1H), 5.39 (d, J = 10.8 Hz, 1H), 5.25 (d, J = 5.5 Hz, 2H), 4.06 - 3.99 (m, 1H), 3.90 (d, J = 2.4 Hz, 3H), 2.76 (t, J = 7.6 Hz, 1H), 2.52 (d, J = 0.4 Hz, 3H), 1.64 (d, J = 1.3 Hz, 3H), 0.89 - 0.74 (m, 3H), 0.82 - 0.75 (m, 1H) ppm. Retention time: 1.24 minutes using LC/MS Method C.

[0396] Step 3:

[0397] 4-(Benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (100 mg, 0.175 mmol), 2-methoxyethan-1-amine (31 μ L, 0.36 mmol) and 'BuXPhos Pd G3 (15 mg, 0.019 mmol) were added to a 4-mL screw-top vial and the vessel was purged with nitrogen. A nitrogen purged solution of phosphazene base P2-Et (175 μ L, 0.526 mmol) in THF (0.85 mL) was added and the resulting mixture was purged with nitrogen for a further 3 min. The vial was sealed and the mixture was stirred and heated at 50 °C in a pre-heated heating block for 6 h. The mixture was cooled to ambient temperature and allowed to stand for a further 10 h. The reaction mixture was stirred at 50 °C for 6 h, then cooled to ambient temperature and allowed to stand for 1.5 days. The mixture was diluted with EtOAc (10 mL), washed with a half-saturated aqueous NH₄Cl solution (7 mL) and a saturated aqueous brine solution, dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography gave 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-2-methylpyridin-3-amine (65 mg, 64%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.50 - 7.44 (m, 2H), 7.40 (ddd, J = 7.7, 6.8, 1.0 Hz, 2H), 7.37 - 7.32 (m, 1H), 7.12 (d, J = 7.4 Hz, 2H), 7.08 - 7.00 (m, 1H), 5.36 (d, J = 11.1 Hz, 1H), 5.21 (d, J = 2.4 Hz, 2H), 4.32 (dd, J = 11.1, 7.4 Hz, 1H), 4.14 (t, J = 6.7 Hz, 1H), 3.90 (d, J = 2.0 Hz, 3H), 3.33 (t, J = 5.5 Hz, 2H), 3.18 (s, 5H), 2.76 (t, J = 7.4 Hz, 1H), 2.32 (s, 3H), 1.61 (s, 3H), 0.76 (d, J = 7.4 Hz, 3H) ppm. ESI-MS *m/z* calc. 580.236, found 581.4 (M+1)⁺; Retention time: 1.19 minutes using LC/MS method C.

[0398] Step 4:

[0399] Sodium hydride (5.5 mg, 60 % w/w dispersion in mineral oil, 0.14 mmol) was added to a stirred solution of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-2-methylpyridin-3-amine (64 mg, 0.11 mmol) in NMP (1 mL) at 0 °C and the mixture was stirred at 0 °C for 10 min. MeI (10 μ L, 0.16 mmol) was added and the mixture was warmed to ambient temperature. After 16 h, the mixture was cooled to 0 °C and additional amounts of sodium hydride (2 x 5.5 mg, 60 % w/w dispersion in mineral oil, 0.14 mmol) and MeI (2 x 10 μ L, 0.16 mmol) were added until reaction completion. The reaction was quenched by addition of a saturated aqueous NH₄Cl solution (1 mL), diluted with EtOAc (10 mL) and washed with a half-saturated aqueous NH₄Cl solution (5 mL), water (5 mL) and a saturated aqueous brine solution. Purification by flash chromatography gave 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-*N*,2-dimethylpyridin-3-amine (49 mg, 75%) as a colourless oil. ¹H NMR (400

MHz, DMSO- d_6) δ 7.51 - 7.47 (m, 2H), 7.42 (ddd, J = 8.0, 7.0, 1.0 Hz, 2H), 7.38 - 7.33 (m, 1H), 7.19 (d, J = 5.8 Hz, 2H), 7.11 - 7.01 (m, 1H), 5.41 (d, J = 11.0 Hz, 1H), 5.27 - 5.18 (m, 2H), 4.33 (dd, J = 11.1, 7.3 Hz, 1H), 3.90 (d, J = 2.0 Hz, 3H), 3.26 (t, J = 6.0 Hz, 2H), 3.13 (s, 3H), 3.05 (t, J = 5.9 Hz, 2H), 2.78 (t, J = 7.4 Hz, 1H), 2.64 (s, 3H), 2.36 (s, 3H), 1.62 (s, 3H), 0.77 (d, J = 7.4 Hz, 3H) ppm. ^{19}F NMR (376 MHz, DMSO- d_6) δ -73.47, -138.68, -155.30 ppm. ESI-MS m/z calc. 594.252, found 595.4 (M+1) $^+$; Retention time: 1.29 minutes using LC/MS method C.

[0400] Step 5:

[0401] Pd/C (35 mg, 5 % w/w, 0.016 mmol) was added to 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-*N*,2-dimethylpyridin-3-amine (48 mg, 0.081 mmol) and the vessel was purged with nitrogen. EtOH (1.5 mL) was added and the suspension was flushed with nitrogen for 3 min. The atmosphere was replaced by a hydrogen atmosphere and the mixture stirred at ambient temperature for 8 min. The vessel was purged with nitrogen and the reaction mixture was filtered through a PTFE syringe filter (0.45 μm), washing with EtOAc. The filtrate was concentrated *in vacuo* to give a colourless oil. Purification by reverse phase preparative HPLC gave 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((2-methoxyethyl)(methyl)amino)-2-methylpyridin-4(1*H*)-one (**115**, 38 mg, 92%) as a white solid. ^1H NMR (400 MHz, Methanol- d_4) δ 7.04 (d, J = 6.4 Hz, 1H), 7.02 - 6.94 (m, 1H), 6.32 (s, 1H), 5.33 (d, J = 11.3 Hz, 1H), 4.18 (dd, J = 11.3, 8.3 Hz, 1H), 3.99 (d, J = 2.5 Hz, 3H), 3.31 (s, 2H), 3.27 (s, 3H), 3.21 (d, J = 5.7 Hz, 2H), 2.85 (p, J = 7.7 Hz, 1H), 2.71 (s, 3H), 2.45 - 2.40 (m, 3H), 1.67 (d, J = 1.2 Hz, 3H), 0.93 - 0.83 (m, 3H) ppm; NH pyridone not observed. ^{19}F NMR (376 MHz, Methanol- d_4) δ -75.44, -139.66, -156.44 ppm. ESI-MS m/z calc. 504.205, found 505.7 (M+1) $^+$; Retention time: 3.26 minutes using LC/MS method A.

[0402] The following compounds were made using methods described in Example 8 except that, in Step 3, different amines were used in place of 2-methoxyethan-1-amine. Step 4 was omitted in all cases. In the case of compound **123**, *tert*-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate was used as the amine in Step 3, and the Boc-protecting group was removed using HCl in 1,4-dioxane prior to Step 5:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
116	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-2-methylpyridin-4(1 <i>H</i>)-one	460.179	461.5	3.21	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.09 - 6.93 (m, 2H), 6.30 (s, 1H), 5.32 (d, <i>J</i> = 11.3 Hz, 1H), 4.17 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.99 (d, <i>J</i> = 2.5 Hz, 3H), 2.85 (p, <i>J</i> = 7.5 Hz, 1H), 2.72 (s, 6H), 2.41 (s, 3H), 1.67 (d, <i>J</i> = 1.2 Hz, 3H), 0.92 - 0.84 (m, 3H) ppm; NH pyridone not observed.
117	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylamino)pyridin-4(1 <i>H</i>)-one	446.163	447.5	2.91	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.04 (ddd, <i>J</i> = 7.9, 5.6, 2.0 Hz, 1H), 6.98 (td, <i>J</i> = 9.3, 7.4 Hz, 1H), 6.37 (s, 1H), 5.34 (d, <i>J</i> = 11.3 Hz, 1H), 4.18 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.98 (d, <i>J</i> = 2.4 Hz, 3H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.72 (s, 3H), 2.44 (s, 3H), 1.68 (t, <i>J</i> = 1.2 Hz, 3H), 0.88 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.
118	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(isopropylamino)-2-methylpyridin-4(1 <i>H</i>)-one	474.194	475.5	3.1	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.05 (ddd, <i>J</i> = 7.8, 5.6, 2.0 Hz, 1H), 7.02 - 6.95 (m, 1H), 6.37 (s, 1H), 5.35 (d, <i>J</i> = 11.3 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.98 (d, <i>J</i> = 2.4 Hz, 3H), 3.39 - 3.34 (m, 1H), 2.86 (p, <i>J</i> = 7.7 Hz, 1H), 2.40 (s, 3H), 1.68 (d, <i>J</i> = 1.1 Hz, 3H), 1.09 (dd, <i>J</i> = 6.3, 3.2 Hz, 6H), 0.88 (dt, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
119	<i>N</i> -(6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)- <i>N</i> -methylacetamide	488.173	489.5	2.79	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.75 (br-s, 1H), 7.18 (s, 1H), 7.07 (q, <i>J</i> = 8.9 Hz, 1H), 6.68 (br-s, 1H), 5.35 (d, <i>J</i> = 11.0 Hz, 1H), 4.32 - 4.19 (m, 1H), 3.92 (d, <i>J</i> = 2.1 Hz, 3H), 2.90 (s, 3H), 2.83 (t, <i>J</i> = 7.8 Hz, 1H), 2.22 (d, <i>J</i> = 2.0 Hz, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 0.81 (d, <i>J</i> = 7.5 Hz, 3H) ppm.
120	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((dimethyl(oxo)-λ ⁶ -sulfaneylidene)amino)-2-methylpyridin-4(1 <i>H</i>)-one	508.146	509.5	2.79	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.05 (dd, <i>J</i> = 8.5, 6.1 Hz, 1H), 6.98 (td, <i>J</i> = 9.3, 7.3 Hz, 1H), 6.38 (s, 1H), 5.35 (d, <i>J</i> = 11.3 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.99 (d, <i>J</i> = 2.4 Hz, 3H), 3.23 (s, 6H), 2.86 (p, <i>J</i> = 7.8 Hz, 1H), 2.42 (s, 3H), 1.68 (d, <i>J</i> = 1.1 Hz, 3H), 0.88 (dt, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.
121	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((2-hydroxyethyl)(methyl)amino)-2-methylpyridin-4(1 <i>H</i>)-one	490.189	491.3	3.00	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.04 (s, 1H), 6.98 (q, <i>J</i> = 8.7 Hz, 1H), 6.34 (s, 1H), 5.34 (d, <i>J</i> = 11.3 Hz, 1H), 4.18 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.99 (d, <i>J</i> = 2.5 Hz, 3H), 3.50 (td, <i>J</i> = 4.5, 2.9 Hz, 2H), 3.18 - 3.08 (m, 2H), 2.86 (p, <i>J</i> = 7.9 Hz, 1H), 2.74 (s, 3H), 2.44 (s, 3H), 1.67 (d, <i>J</i> = 1.2 Hz, 3H), 0.93 - 0.83 (m, 3H) ppm; OH alcohol and NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
122	3-(Bis(methyl- <i>d</i> ₃)amino)-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	466.482	467.5	3.21	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.03 (d, <i>J</i> = 6.6 Hz, 1H), 6.98 (q, <i>J</i> = 8.8 Hz, 1H), 6.30 (s, 1H), 5.32 (d, <i>J</i> = 11.2 Hz, 1H), 4.17 (dd, <i>J</i> = 11.3, 8.3 Hz, 1H), 3.99 (d, <i>J</i> = 2.4 Hz, 3H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.41 (s, 3H), 1.67 (d, <i>J</i> = 1.1 Hz, 3H), 0.87 (dt, <i>J</i> = 7.4, 2.4 Hz, 3H) ppm; NH pyridone not observed.
123	3-(6,6-Difluoro-1,4-diazepan-1-yl)-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	551.506	552.7	3.19	A	
124	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(3,3-difluoroazetidin-1-yl)-2-methylpyridin-4(1 <i>H</i>)-one	508.437	509.5	3.31	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.03 (t, <i>J</i> = 7.5 Hz, 1H), 6.97 (q, <i>J</i> = 8.8 Hz, 1H), 6.30 (s, 1H), 5.31 (d, <i>J</i> = 11.4 Hz, 1H), 4.36 (t, <i>J</i> = 12.6 Hz, 4H), 4.16 (dd, <i>J</i> = 11.4, 8.3 Hz, 1H), 3.99 (d, <i>J</i> = 2.4 Hz, 3H), 2.85 (p, <i>J</i> = 7.8 Hz, 1H), 2.40 (s, 3H), 1.67 (d, <i>J</i> = 1.1 Hz, 3H), 0.87 (dt, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
125	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-morpholinopyridine-4(1 <i>H</i>)-one	502.19	503.5	3.12	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.04 (t, <i>J</i> = 7.3 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.31 (s, 1H), 5.32 (d, <i>J</i> = 11.3 Hz, 1H), 4.17 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.99 (d, <i>J</i> = 2.5 Hz, 3H), 3.73 (t, <i>J</i> = 4.6 Hz, 4H), 3.10 (s, 4H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.47 (s, 3H), 1.67 (d, <i>J</i> = 1.2 Hz, 3H), 0.91 – 0.84 (m, 3H) ppm; NH pyridone not observed.

[0403] The following compound was made using methods described in Example 8 except that, in Step 3, *tert*-butyl (3*S*,4*S*)-4-amino-3-fluoro-piperidine-1-carboxylate was used in place of 2-methoxyethan-1-amine and the Boc-protecting group was subsequently removed using HCl in 1,4-dioxane. Prior to Steps 4 and 5, an additional methylation step (via reductive amination) was introduced as outlined below:

[0404] *Methylation*: Formaldehyde (10 μ L, 37 % w/w solution in water, 0.14 mmol) and acetic acid (7.75 μ L, 0.1363 mmol) were added to a solution of 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-((3*S*,4*S*)-3-fluoropiperidin-4-yl)-2-methylpyridin-3-amine (34 mg, 0.055 mmol) in 2-MeTHF (1 mL) and the mixture was stirred at ambient temperature for 10 min. STAB (35 mg, 0.17 mmol) was added in a single portion and the resulting suspension stirred at ambient temperature for 140 min. Additional portions of formaldehyde (5 μ L, 0.07 mmol), acetic acid (4 μ L, 0.07 mmol) and STAB (17 mg, 0.08 mmol) were added and the mixture stirred for 16 h. The mixture was quenched with a saturated aqueous NH₄Cl solution (0.5 mL), basified with a 50% saturated aqueous NaHCO₃ solution (5 mL) and extracted with EtOAc (2 x 7 mL). The combined extracts were washed with saturated brine, dried (MgSO₄), filtered and concentrated *in vacuo* to afford 4-benzyloxy-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-((3*S*,4*S*)-3-fluoro-1-methylpiperidin-4-yl)-2-methylpyridin-3-amine (33 mg, 95%) as a yellow oil. ESI-MS *m/z* calc. 637.274, found 638.4 (*M*+1)⁺; Retention time: 1.18 minutes using LC/MS method C.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
126	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(((3 <i>S</i> ,4 <i>S</i>)-3-fluoro-1-methylpiperidin-4-yl)(methylamino)-2-methylpyridin-4(1 <i>H</i>)-one	561.569	562.3	2.87	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.14 (t, <i>J</i> = 7.9 Hz, 1H), 7.09 - 7.00 (m, 1H), 6.02 (s, 1H), 5.03 (d, <i>J</i> = 10.9 Hz, 1H), 4.77 (d, <i>J</i> = 45.8 Hz, 1H), 4.33 - 4.25 (m, 1H), 4.19 (d, <i>J</i> = 11.8 Hz, 1H), 4.03 (s, 1H), 3.93 (d, <i>J</i> = 1.9 Hz, 3H), 3.74 (d, <i>J</i> = 43.5 Hz, 1H), 3.19 (s, 3H), 3.11 (s, 4H), 2.74 - 2.67 (m, 1H), 2.65 - 2.59 (m, 1H), 2.55 (s, 1H), 2.11 (s, 3H), 1.79 (s, 1H), 1.57 (s, 3H), 0.72 (d, <i>J</i> = 7.4 Hz, 3H) ppm. NH pyridone not observed.

[0405] The following compound was made using methods described in Example 8 except that, in Step 3, methylamine was used as the amine coupling partner in place of 2-methoxyethan-1-amine.

Step 4 was replaced with an acylation step using cyclopropanecarbonyl chloride to provide intermediate *N*-(4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)-*N*-methylcyclopropanecarboxamide:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
127	<i>N</i> -(6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)- <i>N</i> -methylcyclopropanecarboxamide	514.493	515.5	2.94	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 10.77 (s, 1H), 7.19 (d, <i>J</i> = 9.6 Hz, 1H), 7.07 (q, <i>J</i> = 9.6 Hz, 1H), 6.73 (s, 1H), 5.35 (d, <i>J</i> = 10.9 Hz, 1H), 4.30 (t, <i>J</i> = 9.6 Hz, 0.5H), 4.22 (dd, <i>J</i> = 10.8, 8.1 Hz, 0.5H), 3.92 (t, <i>J</i> = 2.6 Hz, 3H), 2.94 (s, 3H), 2.82 (q, <i>J</i> = 7.2 Hz, 1H), 2.24 (d, <i>J</i> = 3.2 Hz, 3H), 1.65 (s, 3H), 1.20 (s, 1H), 0.81 (d, <i>J</i> = 7.5 Hz, 3H), 0.77 - 0.72 (m, 1H), 0.66 (d, <i>J</i> = 6.3 Hz, 1H), 0.51 (dd, <i>J</i> = 19.2, 10.2 Hz, 2H) ppm; showing a mixture of rotamers.

[0406] The following compounds were made using methods described in Example 8 except that, the starting material of Step 3 was prepared by treating ethyl 5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (**55**) via the method described in General method K and dimethylamine was used in place of 2-methoxyethan-1-amine. Step 4 was omitted. Ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-hydroxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate **129** was also obtained as a side-product in the synthesis of ethyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(dimethylamino)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate **128**:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
128	Ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(dimethylamino)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	532.200	533.0	1.97	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 6.98 (dd, <i>J</i> = 11.9, 6.8 Hz, 2H), 5.29 (s, 1H), 4.45 (s, 1H), 4.31 (d, <i>J</i> = 8.4 Hz, 1H), 4.22 (s, 1H), 3.90 (s, 3H), 2.87 (t, <i>J</i> = 8.6 Hz, 1H), 2.71 (s, 6H), 2.38 (s, 3H), 1.63 (s, 3H), 1.37 - 1.27 (m, 3H), 0.79 (dq, <i>J</i> = 7.4, 2.2 Hz, 3H) ppm; NH pyridone not observed.
129	Ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-hydroxy-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate	505.152	506.1	2.32	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 - 6.99 (m, 2H), 5.57 (d, <i>J</i> = 10.8 Hz, 1H), 4.55 (t, <i>J</i> = 10.5 Hz, 1H), 4.43 (dq, <i>J</i> = 10.8, 7.1 Hz, 1H), 4.29 (dq, <i>J</i> = 10.8, 7.1 Hz, 1H), 3.89 (s, 3H), 2.94 (dq, <i>J</i> = 10.1, 7.7 Hz, 1H), 2.57 (s, 3H), 1.66 (s, 3H), 1.35 (t, <i>J</i> = 7.1 Hz, 3H), 0.83 (dq, <i>J</i> = 7.7, 2.2 Hz, 3H) ppm; OH alcohol and NH pyridone not observed.

[0407] The following compounds were made using methods described in Example 8 except that, in Step 1, *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-

(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-3** was used as the starting material in place of in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-

(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. In Step 3, dimethylamine was used in place of 2-methoxyethan-1-amine. Step 4 was omitted. Before carrying out Step 5, an additional step was introduced to separate the enantiomers by chiral SFC using a Chiralart Amylose-SA column, 5 μ m particle size, 25 cm x 20 mm from YMC Co., Ltd.:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
130	<i>rel</i> -6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-2-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralart Amylose-SA, <i>rt</i> = 1.45 min)	446.163	447.5	3.06	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.06 (d, <i>J</i> = 8.2 Hz, 1H), 6.82 (dd, <i>J</i> = 19.9, 11.5 Hz, 2H), 5.33 (d, <i>J</i> = 10.0 Hz, 1H), 4.76 (s, 1H), 4.15 (d, <i>J</i> = 19.0 Hz, 1H), 4.03 - 3.87 (m, 3H), 3.03 (t, <i>J</i> = 16.2 Hz, 1H), 2.72 (s, 6H), 2.42 (d, <i>J</i> = 2.3 Hz, 3H), 0.85 - 0.81 (m, 3H) ppm; NH pyridone not observed.
131	<i>rel</i> -6-((2 <i>S</i> ,3 <i>R</i> ,4 <i>R</i> ,5 <i>S</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-2-methylpyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralart Amylose-SA, <i>rt</i> = 2.64 min)	446.163	447.5	3.06	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.06 (d, <i>J</i> = 7.4 Hz, 1H), 6.91 - 6.76 (m, 2H), 5.33 (d, <i>J</i> = 10.1 Hz, 1H), 4.76 (s, 1H), 4.17 (s, 1H), 3.95 (d, <i>J</i> = 2.4 Hz, 3H), 3.04 (q, <i>J</i> = 10.1, 9.0 Hz, 1H), 2.72 (s, 6H), 2.42 (s, 3H), 0.85 - 0.80 (m, 3H) ppm; NH pyridone not observed.

[0408] The following compound was made using methods described in Example 8 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-

methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. In Step 3, dimethylamine was used in place of 2-methoxyethan-1-amine. Step 4 was omitted:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
132	3-(Dimethylamino)-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	426.193	427.5	3.15	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.24 (dd, <i>J</i> = 8.7, 5.6 Hz, 1H), 6.98 (dd, <i>J</i> = 9.9, 2.8 Hz, 1H), 6.90 (td, <i>J</i> = 8.5, 2.9 Hz, 1H), 6.43 (s, 1H), 5.43 (d, <i>J</i> = 11.2 Hz, 1H), 4.05 (dd, <i>J</i> = 11.1, 8.0 Hz, 1H), 2.87 (p, <i>J</i> = 7.7 Hz, 1H), 2.73 (s, 6H), 2.43 (s, 3H), 2.35 (s, 3H), 1.67 (d, <i>J</i> = 1.1 Hz, 3H), 0.82 (dt, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.

[0409] The following compound was made using methods described in Example 8 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. In Step 3, dimethylamine was used in place of 2-methoxyethan-1-amine. Step 4 was omitted:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
133	3-(Dimethylamino)-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	442.188	443.5	3.13	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.12 - 7.05 (m, 1H), 7.04 (q, <i>J</i> = 3.2, 2.6 Hz, 2H), 6.30 (s, 1H), 5.33 (d, <i>J</i> = 11.4 Hz, 1H), 4.21 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 3.91 (d, <i>J</i> = 2.2 Hz, 3H), 2.85 (p, <i>J</i> = 7.7 Hz, 1H), 2.70 (s, 6H), 2.39 (s, 3H), 1.66 (d, <i>J</i> = 1.2 Hz, 3H), 0.85 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.

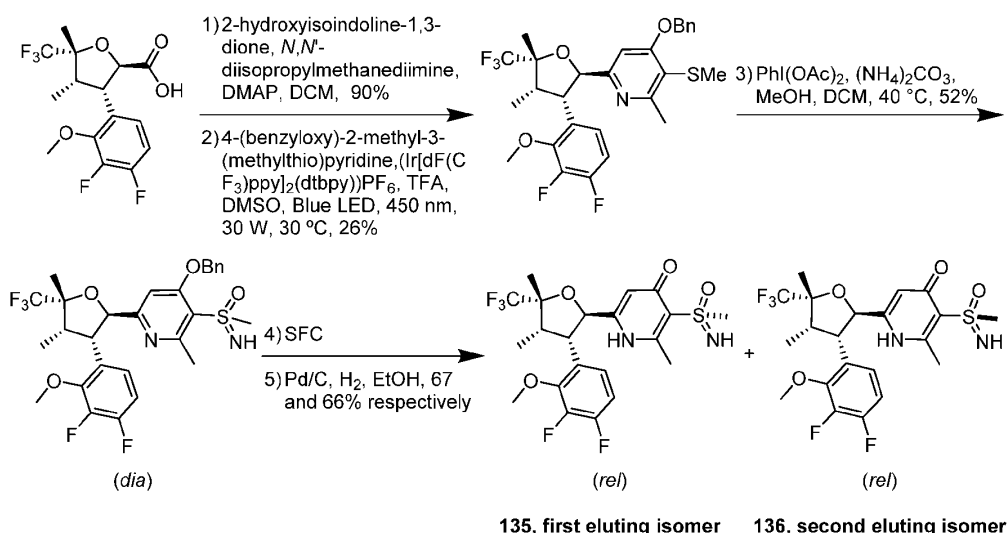
[0410] The following compound was made using methods described in Example 8 using Steps 3 and 5, except that the starting material in Step 3 was 4-(benzyloxy)-3-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (prepared in Example 11, *debromination*). In Step 3, dichloro[9,9-dimethyl-4,5-

bis(diphenylphosphino)xanthene] palladium(II) was used as the catalyst in place of *t*BuXPhos Pd G3, and NaO*t*Bu used in place of phosphazene base P2-Et. Step 4 was omitted.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
134	3-(Azetidin-1-yl)-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	472.456	473.2	1.762	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 (ddd, <i>J</i> = 8.0, 5.6, 2.0 Hz, 1H), 7.05 - 6.96 (m, 1H), 6.94 (s, 1H), 5.58 (d, <i>J</i> = 11.2 Hz, 1H), 4.21 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 4.00 (s, 3H), 3.64 (t, <i>J</i> = 6.2 Hz, 2H), 3.43 (t, <i>J</i> = 6.9 Hz, 2H), 2.90 (p, <i>J</i> = 7.7 Hz, 1H), 2.62 (s, 3H), 2.02 (p, <i>J</i> = 6.5 Hz, 2H), 1.68 (s, 3H), 0.89 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm. NH pyridone not observed.

Example 9

rel-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((*R*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (135) and *rel*-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((*S*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (136)



[0411] Step 1:

[0412] (2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 1.618 g, 4.567 mmol) and 2-hydroxyisoindoline-1,3-dione (920 mg, 5.640 mmol) were treated via the method described in General Method B Step 1, to give 1,3-dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2.06 g, 90%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.81 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.07 - 6.98 (m, 1H), 6.92 (td, *J* = 9.2, 7.3 Hz, 1H), 5.33 (d, *J* = 0.8 Hz, 1H), 4.46 (t, *J* = 8.9 Hz, 1H), 4.10 (d, *J* = 2.4 Hz, 3H), 2.81 (q, *J* = 7.7 Hz, 1H), 1.69 (q, *J* = 1.2 Hz, 3H), 0.89 - 0.82 (m, 3H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -74.46, -136.60, -153.83 ppm. ESI-MS *m/z* calc. 499.105, found 500.0 (M+1)⁺; Retention time: 1.12 minutes using LC/MS method M.

[0413] Step 2:

[0414] 1,3-Dioxoisindolin-2-yl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.65 g, 2.81 mmol) and 4-(benzyloxy)-2-methyl-3-(methylthio)pyridine (620 mg, 2.53 mmol) were treated via the method described in General Method B Step 2, to give 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylthio)pyridine (490 mg, 26%) as a colourless oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.52 - 7.46 (m, 2H), 7.44 - 7.39 (m, 2H), 7.38 - 7.30 (m, 1H), 7.23 (s, 1H), 7.19 - 7.10 (m, 1H), 7.05 (td, *J* = 9.4, 7.7 Hz, 1H), 5.45 (d, *J* = 10.9 Hz, 1H), 5.40 - 5.21 (m, 2H), 4.30 (dd, *J* = 11.0, 7.4 Hz, 1H), 3.89 (d, *J* = 1.8 Hz, 3H), 2.77 (p, *J* = 7.4 Hz, 1H), 2.54 (s, 3H), 2.25 (s, 3H), 1.62 (s, 3H), 0.76 (dd, *J* = 7.5, 2.4 Hz, 3H) ppm. ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ -73.34, -136.92 - -139.88 (m), -155.14 (d, *J* = 32.0 Hz) ppm. ESI-MS *m/z* calc. 553.171, found 554.6 (M+1)⁺; Retention time: 1.31 minutes using LC/MS method C.

[0415] Step 3:

[0416] 4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylthio)pyridine (1 g, 1.55 mmol) was treated via the method described in General Method H to give *dia*-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (510 mg, 52%) as a mixture of diastereoisomers. ESI-MS *m/z* calc. 584.177, found 586.3 (M+1)⁺; Retention time: 3.70 minutes using LC/MS method A.

[0417] Step 4:

[0418] The diastereomers of *dia*-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone were separated by chiral SFC using a Chiralpak® IC column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation to give:

[0419] **First Eluting Isomer (rt = 4.59 minutes):** *rel*-(*R*)-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (157.6 mg, 32%). ESI-MS *m/z* calc. 584.177, found 585.2 (M+1)⁺; Retention time: 3.68 minutes using LC/MS method A.

[0420] **Second Eluting Isomer (rt = 6.14 minutes):** *rel*-(*S*)-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (173.9 mg, 37%). ESI-MS *m/z* calc. 584.177, found 585.2 (M+1)⁺; Retention time: 3.67 minutes using LC/MS method A.

[0421] **Step 5:**

[0422] *rel*-(*R*)-(4-(Benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (142.6 mg, 0.227 mmol) (First Eluting Isomer, rt = 4.59 minutes) was treated via the method described in General Method C to give *rel*-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((*R*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**135**, 113.9 mg, 67%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.06 (ddd, *J* = 8.2, 5.6, 2.1 Hz, 1H), 6.96 (ddd, *J* = 9.9, 8.9, 7.4 Hz, 1H), 6.51 (s, 1H), 5.36 (d, *J* = 11.2 Hz, 1H), 4.19 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.99 (d, *J* = 2.5 Hz, 3H), 2.85 (p, *J* = 7.7 Hz, 1H), 2.74 (s, 3H), 1.66 (d, *J* = 1.2 Hz, 3H), 0.86 (dq, *J* = 7.3, 2.3 Hz, 3H) ppm; NH pyridone and sulfoximine not observed. ESI-MS *m/z* calc. 494.130, found 496.0 (M+1)⁺; 493.1 (M-1)⁻; Retention time: 2.85 minutes using LC/MS method A.

[0423] *rel*-(*S*)-(4-(Benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (250 mg, 0.428 mmol) (Second Eluting Isomer (rt = 6.14 minutes) was treated via the method described in General Method C to give *rel*-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((*S*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**136**, 138.7 mg, 66%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.06 (dd, *J* = 8.3, 5.9 Hz, 1H), 6.96 (td, *J* = 9.3, 7.5 Hz, 1H), 6.51 (s, 1H), 5.35 (d, *J* = 11.2 Hz, 1H), 4.20 (dd, *J* = 11.3, 8.2 Hz, 1H), 3.99 (d, *J* = 2.5 Hz, 3H), 3.30 (d, *J* = 1.8 Hz, 3H), 2.85 (p, *J* = 7.8 Hz, 1H), 2.75 (s, 3H), 1.66 (d, *J* = 1.2 Hz, 3H), 0.86 (dq, *J* = 7.4, 2.3 Hz, 3H) ppm; NH pyridone and sulfoximine not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.47, -136.33 - -142.38 (m), -156.44 ppm. ESI-MS *m/z* calc. 494.130, found 496.0 (M+1)⁺; 493.1 (M-1)⁻; Retention time: 2.85 minutes using LC/MS method A.

[0424] The following compound was made using the methods described in Example 9 except that Step 4 was omitted:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
137	<i>dia</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(<i>S</i> -methylsulfonyl)pyridin-4(1 <i>H</i>)-one	494.130	495.5	2.70	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.06 (s, 1H), 6.96 (td, <i>J</i> = 9.4, 7.4 Hz, 1H), 6.51 (s, 1H), 5.35 (dd, <i>J</i> = 11.2, 1.7 Hz, 1H), 4.19 (dd, <i>J</i> = 11.3, 8.1 Hz, 1H), 4.01 - 3.96 (m, 3H), 3.30 (s, 3H), 2.84 (p, <i>J</i> = 7.7 Hz, 1H), 2.74 (d, <i>J</i> = 1.0 Hz, 3H), 1.66 (t, <i>J</i> = 1.2 Hz, 3H), 0.86 (dq, <i>J</i> = 7.3, 2.3 Hz, 3H) ppm; NH pyridone and sulfoximine not observed.

[0425] The following compound was made using methods described in Example 9 except that an additional methylation step was introduced after Step 3, as outlined below. Step 4 was omitted:

[0426] *N*-Methylation of sulfoximine: To a solution of *dia*-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (18 mg, 0.024 mmol) in MeCN (1.5 mL) was added formaldehyde (25 μL, 37 % w/w solution in water, 0.33 mmol), triethylsilane (30 μL, 0.18 mmol) and TFA (15 μL, 0.19 mmol). The reaction mixture was stirred at ambient temperature for 18 h and then quenched by addition of a NaHCO₃ solution. The mixture was extracted with EtOAc. The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give *dia*-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)(methyl)(methylimino)-λ⁶-sulfanone (25 mg, 35%) as a colourless oil and as a mixture of diastereoisomers. ESI-MS *m/z* calc. 598.192, found 599.2 (*M*+1)⁺; Retention time: 1.12 minutes using LC/MS Method C.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
138	<i>dia</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(<i>N,S</i> -dimethylsulfonimido-2-methylpyridin-4(1 <i>H</i>))-one	508.502	509.5	3.09	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.08 (s, 1H), 6.94 (q, <i>J</i> = 8.8 Hz, 1H), 6.50 (s, 1H), 5.32 (d, <i>J</i> = 11.2 Hz, 1H), 4.25 - 4.13 (m, 1H), 3.96 (dd, <i>J</i> = 2.4, 1.0 Hz, 3H), 3.38 (dd, <i>J</i> = 8.4, 4.2 Hz, 3H), 2.83 (t, <i>J</i> = 7.7 Hz, 1H), 2.67 (s, 3H), 2.61 (d, <i>J</i> = 7.5 Hz, 3H), 1.65 (s, 3H), 0.88 - 0.82 (m, 3H) ppm; NH pyridone not observed.

[0427] The following compounds were made using methods described in Example 9 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid Int-1:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
139	<i>rel</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)- <i>S</i> -methylsulfonimidoyl)pyridin-4(1 <i>H</i>))-one (Precursor was the first eluting peak by SFC on Chiralpak® IC column, rt = 4.23 min)	478.135	479.3	2.82	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.15 - 6.98 (m, 2H), 6.53 (s, 1H), 5.40 (d, <i>J</i> = 11.0 Hz, 1H), 4.08 (dd, <i>J</i> = 11.0, 8.0 Hz, 1H), 3.28 (s, 3H), 2.86 (p, <i>J</i> = 7.6 Hz, 1H), 2.71 (s, 3H), 2.29 (d, <i>J</i> = 2.1 Hz, 3H), 1.67 (d, <i>J</i> = 1.2 Hz, 3H), 0.82 (dt, <i>J</i> = 7.4, 2.4 Hz, 3H) ppm; NH pyridone and sulfoximine not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
140	<i>rel</i> -6- ((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *) -3-(3,4-Difluoro- 2-methylphenyl)- 4,5-dimethyl-5- (trifluoromethyl)te- trahydrofuran-2- yl)-2-methyl-3- ((<i>S</i>)- <i>S</i> - methylsulfonimid- oyl)pyridin- 4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IC column, rt = 5.36 min)	478.135	479.3	2.82	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.12 - 6.99 (m, 2H), 6.53 (s, 1H), 5.41 (d, <i>J</i> = 11.0 Hz, 1H), 4.08 (dd, <i>J</i> = 11.0, 8.0 Hz, 1H), 3.27 (s, 3H), 2.87 (p, <i>J</i> = 7.7 Hz, 1H), 2.72 (s, 3H), 2.29 (d, <i>J</i> = 1.9 Hz, 3H), 1.68 (d, <i>J</i> = 1.1 Hz, 3H), 0.82 (dt, <i>J</i> = 7.3, 2.3 Hz, 3H) ppm; NH pyridone and sulfoximine not observed.

[0428] The following compounds were made using methods described in Example 9 except that, in Step 1, (2*R*,3*S*,4*S*,5*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-9** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. In Step 5, the debenzylolation step was carried out using the method described in General Method D:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
141	<i>rel</i> -6- ((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *) -3-(3-Chloro-2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl)te- trahydrofuran-2- yl)-2-methyl-3- ((<i>R</i>)- <i>S</i> - methylsulfonimid- oyl)pyridin- 4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IC column, rt = 4.67 min)	492.110	493.2	2.83	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.36 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.27 (dd, <i>J</i> = 7.9, 1.6 Hz, 1H), 7.10 (t, <i>J</i> = 7.9 Hz, 1H), 6.52 (s, 1H), 5.35 (d, <i>J</i> = 11.2 Hz, 1H), 4.31 - 4.22 (m, 1H), 3.84 (s, 3H), 3.30 (s, 3H), 2.88 (p, <i>J</i> = 7.8 Hz, 1H), 2.73 (s, 3H), 1.68 (d, <i>J</i> = 1.1 Hz, 3H), 0.88 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone and sulfoximine not observed.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
142	<i>rel</i> -6- ((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *) - 3-(3-Chloro-2-methoxyphenyl)- 4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)- <i>S</i> -methylsulfonimidoyl)pyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IC column, <i>rt</i> = 6.08 min)	492.110	493.2	2.82	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.34 (dd, <i>J</i> = 8.0, 1.5 Hz, 1H), 7.27 (dd, <i>J</i> = 10.7, 8.2 Hz, 1H), 7.09 (t, <i>J</i> = 7.9 Hz, 1H), 6.54 (d, <i>J</i> = 13.6 Hz, 1H), 5.40 - 5.30 (m, 1H), 4.26 (dd, <i>J</i> = 11.2, 8.2 Hz, 1H), 3.83 (s, 3H), 3.27 (s, 3H), 2.86 (p, <i>J</i> = 7.8 Hz, 1H), 2.71 (s, 3H), 1.68 (d, <i>J</i> = 1.2 Hz, 3H), 0.88 - 0.86 (m, 3H) ppm; NH pyridone and sulfoximine not observed.

[0429] The following compounds were made using methods described in Example 9 except that the product of Step 2 was made using General Method A using (2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid and 4-(benzyloxy)-6-chloro-2-methyl-3-(methylthio)pyridine **Int-28** as the starting materials. In Step 4, the diastereomers were separated by chiral SFC using a Chiralpak® IB column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation. Step 5 was carried out in EtOAc in place of EtOH as the solvent:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
143	<i>rel</i> -6- ((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *) -3-(3,4-Difluoro- 2-methylphenyl)- 4-methoxy-5- methyl-5- (trifluoromethyl)te- trahydrofuran-2- yl)-2-methyl-3- ((<i>R</i>)- <i>S</i> - methylsulfonyl)pyridin- 4(<i>1H</i>)-one (Precursor was the first eluting peak by SFC on Chiralpak® IB column, rt = 9.07 min)	494.130	495.6	2.55	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.27 - 7.24 (m, 1H), 7.13 - 7.07 (m, 1H), 6.47 (s, 1H), 5.42 (d, <i>J</i> = 11.2 Hz, 1H), 4.09 (d, <i>J</i> = 4.8 Hz, 1H), 3.89 (dd, <i>J</i> = 11.2, 4.8 Hz, 1H), 3.28 (s, 3H), 2.93 (s, 3H), 2.71 (s, 3H), 2.34 (d, <i>J</i> = 2.4 Hz, 3H), 1.64 (s, 3H) ppm; NH pyridone and sulfoximine not observed.
144	<i>rel</i> -6- ((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *) -3-(3,4-Difluoro- 2-methylphenyl)- 4-methoxy-5- methyl-5- (trifluoromethyl)te- trahydrofuran-2- yl)-2-methyl-3- ((<i>S</i>)- <i>S</i> - methylsulfonyl)pyridin- 4(<i>1H</i>)-one (Precursor was the second eluting peak by SFC on Chiralpak® IB column, rt = 10.86 min)	494.130	495.6	2.54	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.27 - 7.23 (m, 1H), 7.13 - 7.07 (m, 1H), 6.48 (s, 1H), 5.42 (d, <i>J</i> = 11.2 Hz, 1H), 4.09 (d, <i>J</i> = 4.8 Hz, 1H), 3.89 (dd, <i>J</i> = 11.2, 4.8 Hz, 1H), 3.30 (s, 3H), 2.93 (s, 3H), 2.70 (s, 3H), 2.34 (d, <i>J</i> = 2.5 Hz, 3H), 1.63 (s, 3H) ppm; NH pyridone and sulfoximine not observed.

[0430] The following compounds were made using methods described in Example 9 except that, in Step 1, (2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-2** was used as the starting material in place of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1**. In Step 4, the diastereomers were separated by chiral SFC using a Chiralcel® OJ-H column, 5 μm particle size, 25 cm x 20 mm from Daicel Corporation:

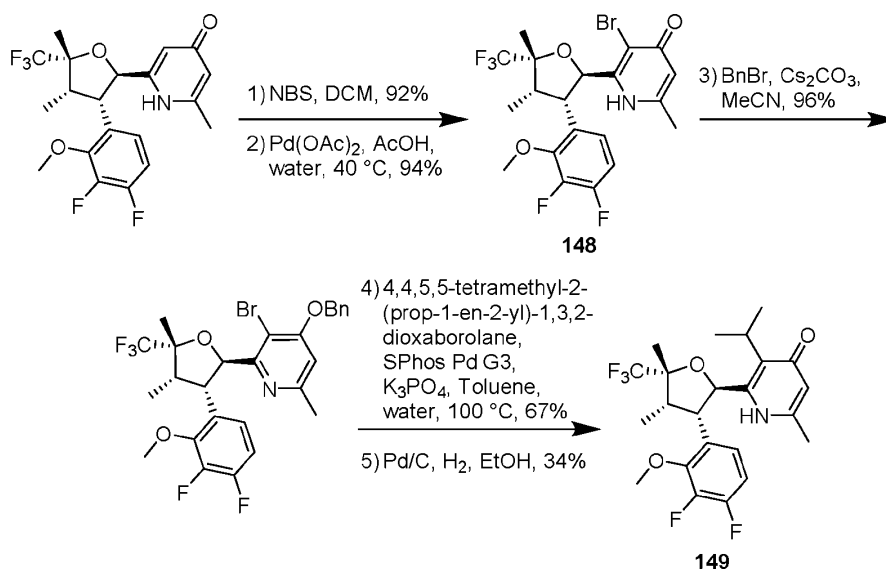
Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
145	<i>rel</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>R</i>)- <i>S</i> -methylsulfonimidoyl)pyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralcel® OJ-H column, <i>rt</i> = 2.51 min)	510.125	511.6	2.53	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.27 - 7.23 (m, 1H), 7.03 - 6.97 (m, 1H), 6.48 (s, 1H), 5.37 - 5.33 (m, 1H), 4.06 - 4.02 (m, 2H), 3.96 (d, <i>J</i> = 2.2 Hz, 3H), 3.30 (s, 3H), 3.02 (s, 3H), 2.70 (s, 3H), 1.62 (s, 3H) ppm; NH pyridone and sulfoximine not observed.
146	<i>rel</i> -6-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-((<i>S</i>)- <i>S</i> -methylsulfonimidoyl)pyridin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralcel® OJ-H column, <i>rt</i> = 5.23 min)	510.125	511.6	2.51	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.27 - 7.23 (m, 1H), 7.03 - 6.97 (m, 1H), 6.47 (s, 1H), 5.37 - 5.33 (m, 1H), 4.07 - 4.02 (m, 2H), 3.96 (d, <i>J</i> = 2.2 Hz, 3H), 3.29 (s, 3H), 3.02 (s, 3H), 2.71 (s, 3H), 1.62 (s, 3H) ppm; NH pyridone and sulfoximine not observed.

[0431] The following compound was made using methods described in Example 9 except that in Step 2, 4-chloro-2-methyl-3-(methylthio)pyridine **Int-30** was used as the coupling partner in place of 4-(benzyloxy)-2-methyl-3-(methylthio)pyridine. Steps 3, 4 and 5 were omitted. The product of Step 2 was further hydroxylated using the conditions described in Example 4 Step 2. A final oxidation step was introduced, as outlined below:

[0432] *Oxidation:* To a solution of 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylthio)pyridin-4(1*H*)-one (25 mg, 0.052 mmol) in DCM (1 mL) was added *m*CPBA (20 mg, 0.11 mmol) in one portion and the mixture was stirred at -20 °C for 4 h. The mixture was quenched by addition of a NaHCO₃ solution (2 mL) and extracted with DCM (3 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100 % EtOAc in heptane) gave the crude product. The residue was diluted with EtOAc (10 mL) and washed with a saturated aqueous NaHCO₃ solution (3 x 10 mL). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The product was lyophilized to give 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-3-(methylsulfonyl)pyridin-4(1*H*)-one (**147**, 6.7 mg, 25%). ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.04 (ddd, *J* = 7.9, 5.6, 2.0 Hz, 1H), 6.97 (td, *J* = 9.4, 7.4 Hz, 1H), 6.42 (s, 1H), 5.35 (d, *J* = 11.2 Hz, 1H), 4.19 (dd, *J* = 11.2, 8.2 Hz, 1H), 4.00 (d, *J* = 2.5 Hz, 3H), 3.25 (s, 3H), 2.86 (p, *J* = 7.7 Hz, 1H), 2.73 (s, 3H), 1.65 (d, *J* = 1.2 Hz, 3H), 0.86 (dd, *J* = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 495.114, found 496.4 (M+1)⁺; 494.4 (M-1)⁻; Retention time: 2.74 minutes using LC/MS method A.

Example 10

3-Bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**148**) and 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-6-methylpyridin-4(1*H*)-one (**149**)



[0433] Step 1:

[0434] 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 6 g, 14.4 mmol) was treated via the method described in General Method I to give 3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (7.69 g, 92%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.09 (s, 1H), 6.84 (dd, *J* = 9.2, 7.4 Hz, 1H), 5.81 (d, *J* = 10.0 Hz, 1H), 4.53 (t, *J* = 9.9 Hz, 1H), 3.88 (d, *J* = 2.4 Hz, 3H), 2.82 (p, 1H), 2.53 (s, 3H), 1.66 (s, 3H), 0.82 (dd, *J* = 7.7, 2.4 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 572.957, found 575.9 (M+1)⁺; Retention time: 2.53 minutes using LC/MS method Q.

[0435] Step 2:

[0436] A suspension of 3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (2.5 g, 4.35 mmol) in acetic acid (38 mL) was heated with a heat gun to 100 °C. Only partial dissolution occurred. Additional acetic acid (26 mL) was added and the mixture was heated to 106 °C with a heat gun. Upon cooling to 45 °C, some cloudiness was observed. Additional acetic acid (10 mL) was added and the mixture was reheated to dissolve the suspension. The solution was maintained at 35 °C to ensure precipitation did not occur. Under N₂ atmosphere, palladium (371 mg, 5 % w/w, 0.174 mmol) was added and the nitrogen atmosphere was replaced with hydrogen using a balloon. The mixture was stirred at 45 °C for 2.5 h. The reaction mixture cooled to ambient temperature. A minor amount of precipitation was observed. The mixture was re-heated to 40 °C and then filtered through a pad of Celite[®]. The filtrate was concentrated *in vacuo*. The residue was slowly added to a solution of NaOAc (1g, ~3eq) in ice water (30 mL) to give a cream suspension. The suspension was stirred at ambient temperature for 1 h, filtered, washed with water and air dried under suction over weekend to give 3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**148**, 2.10 g, 94%) as a light purple solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.11 (s, 1H), 7.02 - 6.87 (m, 1H), 6.31 (s, 1H), 5.91 (d, *J* = 10.9 Hz, 1H), 4.45 (s, 1H), 3.90 (d, *J* = 2.4 Hz, 3H), 3.05 - 2.86 (m, 1H), 2.37 (s, 3H), 1.70 (s, 3H), 0.86 (ddd, *J* = 7.9, 2.1 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 496.266, found 498.0 (M+1)⁺; Retention time: 2.34 minutes using LC/MS method Q.

[0437] Step 3:

[0438] 3-Bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**148**, 3 g, 5.9 mmol) was treated via the method described in General Method K to give 4-(benzyloxy)-3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (3.350 g, 96%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.50 - 7.42 (m, 2H), 7.42 - 7.28 (m, 3H), 6.94 - 6.81 (m, 3H), 6.05 (d, *J* = 10.8 Hz, 1H), 5.21 (dd, *J* = 2.7 Hz, 2H), 4.81 (dd, *J* = 10.9, 8.0 Hz, 1H), 3.95 (d, *J* = 1.9 Hz, 3H), 2.84 (p, *J* = 7.6 Hz, 1H), 2.42 (s, 3H), 1.63 (s, 3H), 0.90 - 0.81

(m, 3H) ppm. ESI-MS m/z calc. 585.093, found 587.6 (M+1)⁺; Retention time: 2.45 minutes using LC/MS method D.

[0439] Step 4:

[0440] 4-(Benzyloxy)-3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (17 mg, 0.029 mmol) and 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (7.6 mg, 0.045 mmol) were treated via the method described in General Method G to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(prop-1-en-2-yl)pyridine (10.7 mg, 67%). ESI-MS m/z calc. 547.215, found 548.5 (M+1)⁺; Retention time: 1.82 minutes using LC/MS method Q.

[0441] Step 5:

[0442] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(prop-1-en-2-yl)pyridine (10.7 mg) was treated via the method described in General Method C. Purification by reverse phase HPLC (10 to 100 % MeCN in H₂O containing 5 mM HCl over 20 min) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-isopropyl-6-methylpyridin-4(1*H*)-one (**149**, 4.1 mg, 46%). ¹H NMR (400 MHz, Methanol-*d*₃) δ 7.26 - 7.17 (m, 1H), 7.13 - 7.02 (m, 1H), 6.92 (s, 1H), 5.77 (d, J = 10.5 Hz, 1H), 4.37 (t, J = 10.9 Hz, 1H), 3.86 (d, J = 2.5 Hz, 3H), 3.24 - 3.12 (m, 1H), 3.11 - 2.98 (m, 1H), 2.63 (s, 3H), 1.75 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.89 (dd, J = 7.8, 2.3 Hz, 3H) ppm; NH pyridone not observed. ESI-MS m/z calc. 459.183, found 460.3 (M+1)⁺; Retention time: 2.11 minutes using LC/MS method Q.

[0443] The following compounds were made using methods described in Example 10 except that different boronate coupling partners were used in Step 4. For compound **155**, Pd(OH)₂ was used in place of Pd/C in Step 5. For compound **154**, *tert*-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazole-1-carboxylate was used as the boronate coupling partner in Step 4, and Step 5 was replaced with acidic deprotection conditions (20 eq TFA in toluene, 70 °C, 2 h) to afford the final compound **154**.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
150	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(tetrahydro-2 <i>H</i> -pyran-4-yl)pyridin-4(1 <i>H</i>)-one	501.494	502.5	1.89	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.32 - 7.24 (m, 1H), 7.18 - 7.07 (m, 1H), 6.96 (s, 1H), 5.85 (d, <i>J</i> = 10.1 Hz, 1H), 4.34 (t, <i>J</i> = 10.7 Hz, 1H), 3.97 (dd, 1H), 3.87 (d, <i>J</i> = 2.7 Hz, 3H), 3.82 (dd, <i>J</i> = 11.5, 4.5 Hz, 1H), 3.47 - 3.37 (m, 1H), 3.16 - 2.90 (m, 3H), 2.65 (s, 3H), 2.56 - 2.35 (m, 2H), 1.78 (s, 3H), 1.44 (d, <i>J</i> = 13.3 Hz, 1H), 0.89 (d, 3H), 0.66 (d, <i>J</i> = 13.1 Hz, 1H) ppm; NH pyridone not observed.
151	3-Cyclopentyl-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	485.495	486.4	2.22	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.17 - 7.09 (m, 1H), 7.09 - 6.98 (m, 1H), 6.13 (s, 1H), 5.60 (d, <i>J</i> = 10.5 Hz, 1H), 4.31 (t, <i>J</i> = 10.7 Hz, 1H), 3.77 (d, <i>J</i> = 2.0 Hz, 3H), 3.06 - 2.81 (m, 2H), 2.33 (s, 3H), 2.11 - 1.96 (m, 1H), 1.94 - 1.74 (m, 3H), 1.70 (s, 3H), 1.66 - 1.51 (m, 3H), 1.49 - 1.33 (m, 1H), 0.85 (dd, <i>J</i> = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed.
152	<i>dia</i> -3-(8-Oxabicyclo[3.2.1]octan-3-yl)-2-((2 <i>R'</i> ,3 <i>S'</i> ,4 <i>S'</i> ,5 <i>R'</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	527.532	528.3	1.85	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 - 7.06 (m, 1H), 6.94 - 6.85 (m, 1H), 5.84 - 5.64 (m, 1H), 4.54 - 4.33 (m, 2H), 3.94 - 3.86 (m, 3H), 3.41 - 3.32 (m, 1H), 3.14 - 2.98 (m, 1H), 2.68 - 2.54 (m, 4H), 2.50 (t, <i>J</i> = 12.6 Hz, 1H), 2.12 - 1.89 (m, 2H), 1.85 - 1.72 (m, 4H), 1.69 - 1.56 (m, 1H), 1.45 - 1.28 (m, 2H), 0.98 - 0.84 (m, 5H) ppm; NH pyridone not observed.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
153	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-isopropyl-1 <i>H</i> -pyrazol-4-yl)-6-methylpyridin-4(1 <i>H</i>)-one	525.520	526.15	2.09	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.81 (s, 1H), 7.51 (s, 1H), 7.10 (s, 1H), 6.84 - 6.75 (m, 1H), 6.32 - 6.25 (m, 1H), 5.68 (d, <i>J</i> = 11.0 Hz, 1H), 4.68 - 4.57 (m, 1H), 4.46 (t, <i>J</i> = 10.5 Hz, 1H), 3.93 (s, 3H), 3.05 - 2.94 (m, 1H), 2.74 (s, 3H), 1.73 (s, 3H), 1.57 (d, <i>J</i> = 4.8 Hz, 3H), 1.55 (d, <i>J</i> = 4.8 Hz, 3H), 0.77 - 0.67 (m, 3H) ppm; NH pyridone not observed.
154	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(1 <i>H</i> -pyrazol-5-yl)pyridin-4(1 <i>H</i>)-one	483.439	484.1	1.85	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.84 (s, 1H), 7.13 (s, 1H), 6.79 - 6.70 (m, 1H), 6.40 - 6.28 (m, 2H), 5.91 (d, <i>J</i> = 10.7 Hz, 1H), 4.31 (t, <i>J</i> = 10.6 Hz, 1H), 3.89 (s, 3H), 3.00 - 2.87 (m, 1H), 2.76 (s, 3H), 1.69 (s, 3H), 0.74 - 0.65 (m, 3H); NH pyridone not observed.
155	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-1',6'-dimethyl-1',2',3',6'-tetrahydro-[3,4'-bipyridin]-4(1 <i>H</i>)-one	512.512	513.4	1.41	Q	

[0444] The following compound was made using methods described in Example 10 except that Step 4 was replaced by a Buchwald coupling step using the conditions outlined below:

[0445] *Buchwald coupling*: Me₂NH (700 μL, 2 M solution in THF, 1.4 mmol) and LiHMDS (700 μL, 1.0 M solution in THF, 0.7 mmol) were successively added to a suspension of 4-(benzyloxy)-3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (85 mg, 0.14 mmol) in THF (1 mL) and the reaction mixture was degassed for 5 min. ^tBuBrettPhos Pd G3 (15 mg, 0.018 mmol) was added and the mixture was stirred at ambient temperature for 30 min. The reaction mixture was quenched by addition of a NH₄Cl solution and extracted with EtOAc. The organic extracts were dried and

concentrated *in vacuo*. Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 M HCl modifier over 20 min) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N,N*,6-trimethylpyridin-3-amine (20 mg, 16%) as a clear glassy solid. ESI-MS *m/z* calc. 550.225, found 551.1 (M+1)⁺; Retention time: 0.65 minutes using LC/MS method T.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
156	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(dimethylamino)-6-methylpyridin-4(1 <i>H</i>)-one	460.179	461.2	2.18	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.14 (ddd, <i>J</i> = 8.3, 5.6, 2.1 Hz, 1H), 7.01 (td, <i>J</i> = 9.4, 7.5 Hz, 1H), 6.95 (s, 1H), 6.10 (d, <i>J</i> = 11.0 Hz, 1H), 4.42 (t, <i>J</i> = 10.6 Hz, 1H), 3.95 (d, <i>J</i> = 2.7 Hz, 3H), 3.06 - 2.93 (m, 1H), 2.64 (s, 3H), 2.62 (s, 6H), 1.72 (s, 3H), 0.84 (dt, <i>J</i> = 7.8, 2.2 Hz, 3H) ppm; NH pyridone not observed.

[0446] The following compounds were made using methods described in Example 10 except that Step 4 was replaced by a Negishi coupling step using the conditions outlined below. In the case of 157, the Negishi coupling step was carried out using cyclopropylzinc bromide in place of cyclobutylzinc bromide:

[0447] *Negishi coupling*: A vial containing 4-(benzyloxy)-3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (26.4 mg, 0.045 mmol) and Pd(*t*Bu₃P)₂ (2.6 mg, 0.005 mmol) was purged with nitrogen. Cyclobutylzinc bromide (1 mL, 0.5 M solution in THF, 0.5 mmol) was added and the mixture was sparged with nitrogen for 1 min. The mixture was stirred at ambient temperature for 4 h, then diluted with MeOH (500 μL), filtered, and purified by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in 5 mM HCl) to provide 4-(benzyloxy)-3-cyclobutyl-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine. ESI-MS *m/z* calc. 561.230, found 562.6 (M+1)⁺; Retention time: 2.01 minutes using LC/MS method D.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
157	3-Cyclopropyl-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	457.441	458.5	2.19	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.14 - 6.82 (m, 2H), 6.28 - 6.07 (m, 2H), 4.43 - 4.18 (m, 1H), 3.88 (d, <i>J</i> = 2.3 Hz, 3H), 2.95 (p, <i>J</i> = 8.0 Hz, 1H), 2.35 (s, 3H), 1.70 (s, 3H), 1.24 - 1.09 (m, 1H), 1.09 - 0.95 (m, 2H), 0.86 (dd, 3H), 0.72 - 0.54 (m, 1H), 0.44 - 0.30 (m, 1H) ppm; NH pyridone not observed.
158	3-Cyclobutyl-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	471.468	472.4	2.39	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.18 - 6.86 (m, 2H), 6.11 (s, 1H), 5.54 (d, <i>J</i> = 10.9 Hz, 1H), 4.41 - 4.09 (m, 1H), 3.80 (d, <i>J</i> = 2.1 Hz, 3H), 3.55 - 3.37 (m, 1H), 2.99 - 2.87 (m, 1H), 2.75 - 2.61 (m, 1H), 2.46 - 2.37 (m, 1H), 2.32 (s, 3H), 2.24 - 2.13 (m, 1H), 1.96 - 1.80 (m, 3H), 1.71 (s, 3H), 0.92 - 0.75 (m, 3H) ppm; NH pyridone not observed.

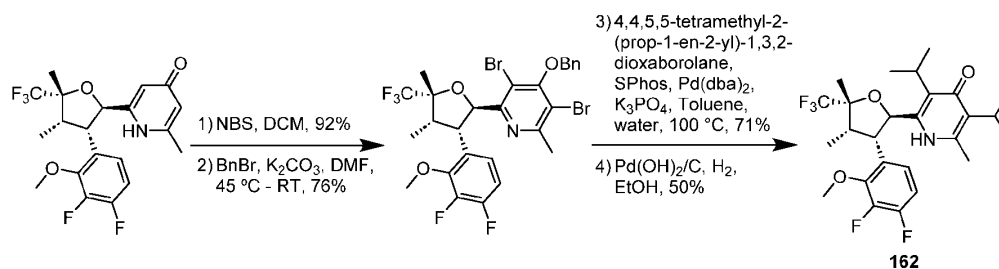
[0448] The following compounds were made using methods described in Example 10 except that Step 4 was replaced by a Stille coupling step using the conditions outlined below. In Step 5, (Pd(OH)₂ was used in place of Pd/C. In the case of compound **161**, 2-(tributylstannyl)oxazole was used as the Stille coupling partner in place of tributyl(2,3-dihydrofuran-5-yl)stannane and Step 5 was replaced by a benzyl deprotection step carried out at 70 °C, using an excess of TFA in toluene.

[0449] *Stille coupling:* A solution of tributyl(2,3-dihydrofuran-5-yl)stannane (20 mg, 0.056 mmol), Pd(PPh₃)₄ (3.1 mg, 0.003 mmol) and 4-(benzyloxy)-3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (30 mg, 0.051 mmol) in toluene (1 mL) was sparged with nitrogen for 3 min. The reaction was stirred at 100 °C for 30 min and then concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 30% EtOAc in hexanes) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(4,5-dihydrofuran-2-yl)-6-methylpyridine.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
159	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(4-hydroxybutanoyl)-6-methylpyridin-4(1 <i>H</i>)-one	503.466	504.3	1.84	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.14 - 7.05 (m, 1H), 7.05 - 6.93 (m, 1H), 6.26 (s, 1H), 5.28 (d, <i>J</i> = 11.0 Hz, 1H), 4.51 (t, <i>J</i> = 10.3 Hz, 1H), 3.90 (d, <i>J</i> = 2.0 Hz, 3H), 3.64 - 3.50 (m, 2H), 3.01 - 2.89 (m, 1H), 2.83 (p, <i>J</i> = 7.9 Hz, 1H), 2.64 - 2.52 (m, 1H), 2.29 (s, 3H), 1.98 - 1.74 (m, 2H), 1.59 (s, 3H), 0.78 (dd, <i>J</i> = 7.7, 2.3 Hz, 3H) ppm; exchangeable protons not observed.
160	<i>dia</i> -2-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(tetrahydrofuran-2-yl)pyridin-4(1 <i>H</i>)-one	487.467	488.6	1.89	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.25 - 6.67 (m, 2H), 6.47 - 5.81 (m, 2H), 5.17 - 4.91 (m, 1H), 4.62 - 4.20 (m, 1H), 4.10 (q, <i>J</i> = 7.4 Hz, 1H), 3.99 - 3.50 (m, 4H), 3.07 - 2.80 (m, 1H), 2.35 (s, 3H), 2.22 - 2.03 (m, 1H), 2.03 - 1.71 (m, 2H), 1.71 (s, 3H), 1.24 - 0.94 (m, 1H), 0.85 (dd, 3H) ppm; NH pyridone not observed.
161	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3-(oxazol-2-yl)pyridin-4(1 <i>H</i>)-one	484.142	485.1	2.18	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.09 (s, 1H), 7.43 (s, 1H), 7.14 (s, 1H), 6.94 - 6.85 (m, 1H), 6.68 - 6.61 (m, 1H), 5.87 (d, <i>J</i> = 10.5 Hz, 1H), 4.39 (t, <i>J</i> = 10.6 Hz, 1H), 3.88 (s, 3H), 2.99 - 2.87 (m, 1H), 2.75 (s, 3H), 1.62 (s, 3H), 0.79 - 0.72 (m, 3H) ppm; NH pyridone not observed.

Example 11

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,5-diisopropyl-6-methylpyridin-4(1*H*)-one (**162**)



[0450] Step 1:

[0451] 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 6 g, 14.4 mmol) was treated via the method described in General Method J to give 3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (7.69 g, 92%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.09 (s, 1H), 6.84 (dd, *J* = 9.2, 7.4 Hz, 1H), 5.81 (d, *J* = 10.0 Hz, 1H), 4.53 (t, *J* = 9.9 Hz, 1H), 3.88 (d, *J* = 2.4 Hz, 3H), 2.82 (p, 1H), 2.53 (s, 3H), 1.66 (s, 3H), 0.82 (dd, *J* = 7.7, 2.4 Hz, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 572.957, found 575.9 (M+1)⁺; Retention time: 2.53 minutes using LC/MS method Q.

[0452] Step 2:

[0453] 3,5-Dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (750 mg, 1.304 mmol) was treated via the method described in General Method J to give 4-(benzyloxy)-3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (658 mg, 76%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.59 - 7.49 (m, 2H), 7.45 - 7.30 (m, 3H), 6.95 - 6.83 (m, 2H), 6.00 (d, *J* = 10.8 Hz, 1H), 5.09 (s, 2H), 4.83 - 4.76 (m, 1H), 3.98 (d, *J* = 2.0 Hz, 3H), 2.85 (p, *J* = 7.6 Hz, 1H), 2.60 (s, 3H), 1.61 (s, 3H), 0.88 (dq, *J* = 7.2, 2.4 Hz, 3H) ppm. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.76, -140.40 (d, *J* = 18.8 Hz), -156.73 (d, *J* = 18.8 Hz) ppm. ESI-MS *m/z* calc. 663.004, found 666.0 (M+1)⁺; Retention time: 3.84 minutes using LC/MS Method Q.

[0454] Step 3:

[0455] SPhos (7 mg, 0.017 mmol) was added to a stirring mixture of 4-(benzyloxy)-3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (132 mg, 0.198 mmol) and K₃PO₄ (127 mg, 0.598 mmol) in toluene (2.64 mL) and water (264 μL) and the reaction mixture was flushed with nitrogen for 20 min. 4,4,5,5-

Tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (47 μ L) and Pd(dba)₂ (4 mg, 0.007 mmol) were successively added to the mixture. The reaction mixture was flushed with nitrogen for 5 min and heated at 100 °C for 17 h. Additional amounts of 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (0.11 mL) were added and the heating was continued for a further 90 min. The mixture was diluted with water and EtOAc. The organic phase was separated, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 10% MTBE in hexanes) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3,5-di(prop-1-en-2-yl)pyridine (83 mg, 71%), which was used without further purification in the next step.

[0456] Step 4:

[0457] A mixture of 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-3,5-di(prop-1-en-2-yl)pyridine (83 mg, 0.14 mmol) and Pd(OH)₂ (21 mg, 20% w/w, 50% wet, 0.015 mmol) in ethanol (1.5 mL) was stirred under hydrogen for 19 h. The mixture was filtered and additional amounts of Pd(OH)₂ (30 mg, 20% w/w, 50% wet, 0.021 mmol) were added. The reaction mixture was stirred under hydrogen for 24 h. The mixture was filtered and purified by reverse phase HPLC (MeCN in H₂O containing 5 mM HCl) to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3,5-diisopropyl-6-methylpyridin-4(1*H*)-one (Hydrochloride salt) (**162**, 38 mg, 50%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.25 - 7.14 (m, 1H), 7.12 - 6.99 (m, 1H), 5.70 (d, *J* = 10.5 Hz, 1H), 4.39 (t, *J* = 10.8 Hz, 1H), 3.85 (d, *J* = 2.4 Hz, 3H), 3.42 - 3.32 (m, 1H), 3.23 - 3.09 (m, 1H), 3.09 - 2.96 (m, 1H), 2.64 (s, 3H), 1.72 (s, 3H), 1.37 - 1.29 (m, 9H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 - 0.83 (m, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 501.230, found 502.6 (M+1)⁺; Retention time: 2.52 minutes using LC/MS method Q.

[0458] The following compound was made using methods described in Example 11 except that, an additional debromination step was introduced after Step 2, using the conditions outlined below. Step 3 was omitted:

[0459] Debromination:

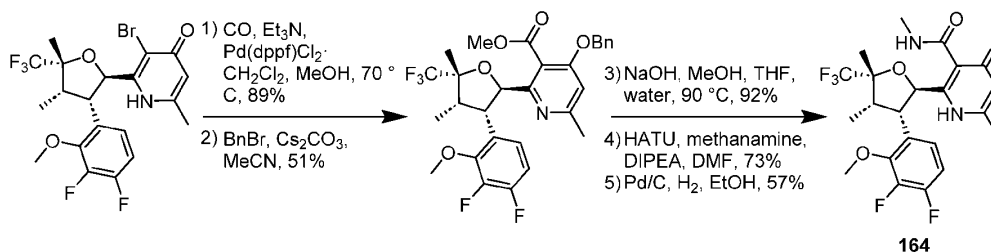
A solution of 4-(benzyloxy)-3,5-dibromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridine (5 g, 7.516 mmol) in THF (50 mL) was placed under a nitrogen atmosphere and cooled in a dry ice/acetone bath. When the internal temperature reached -71 °C, PhMgBr (5 mL, 3 M solution in Et₂O, 15 mmol) was added via syringe. After stirring the mixture for 20 min, ⁿBuLi (8.1 mL, 1.4 M in cyclohexane, 11 mmol) was slowly added via syringe. After stirring the mixture at -60 °C for 1 h, the reaction mixture was quenched by addition of a mixture of acetic acid (21 mL, 370 mmol) and water (5.25 mL). The mixture was warmed to ambient temperature and concentrated *in vacuo* (10 mBar, 35 °C) to remove most of the THF. The residue was partitioned between EtOAc (200 mL) and water (50 mL). The organic layer was separated, washed with brine (30 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* (10

mBar, 45 °C). Purification by flash chromatography gave 4-(benzyloxy)-3-bromo-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (3.20 g, 72%) as a colourless oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.50 - 7.25 (m, 5H), 7.10 (ddd, *J* = 8.4, 5.6, 2.3 Hz, 1H), 7.05 (s, 1H), 6.86 (ddd, *J* = 10.0, 8.9, 7.6 Hz, 1H), 5.39 (d, *J* = 11.0 Hz, 1H), 5.31 (s, 2H), 4.17 - 4.09 (m, 1H), 3.85 (d, *J* = 2.2 Hz, 3H), 2.78 (p, *J* = 7.6 Hz, 1H), 2.54 (s, 3H), 1.63 (d, *J* = 1.3 Hz, 3H), 0.83 (ddd, *J* = 7.5, 2.3 Hz, 3H) ppm. ESI-MS *m/z* calc. 585.094, found 587.9 (M+1)⁺; Retention time: 2.66 minutes using LC/MS Method Q.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
163	3-Bromo-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one	495.047	496.3	2.99	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.06 - 7.02 (m, 1H), 6.99 - 6.93 (m, 1H), 6.40 (s, 1H), 5.36 (d, <i>J</i> = 11.2 Hz, 1H), 4.18 (dd, <i>J</i> = 11.2, 7.8 Hz, 1H), 3.97 (d, <i>J</i> = 2.5 Hz, 3H), 2.85 (dq, <i>J</i> = 7.8, 7.8 Hz, 1H), 2.55 (s, 3H), 1.66 (s, 3H), 0.88 - 0.83 (m, 3H) ppm; NH pyridone not observed.

Example 12

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (164)



[0460] Step 1:

[0461] A suspension of 3-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (148, 500.2 mg, 0.988 mmol), Et₃N (0.44 mL, 3.2 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (81 mg, 0.099 mmol) in MeOH (9.8 mL) was stirred under a carbon monoxide atmosphere at 18 bar in a steel bomb, in a 70 °C oil bath. Additional Pd(dppf)Cl₂·CH₂Cl₂ (41 mg, 0.05 mmol) was added and the mixture was sparged with CO for 15 min at ambient temperature, then stirred under a carbon monoxide atmosphere (balloon) at 65

°C over the weekend. The reaction mixture was filtered through a disposable filter, washing through with MeOH. The filtrate was concentrated *in vacuo*. The residue was dissolved in DCM, washed with 1 M citric acid (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (40 g SiO₂, 0 to 8% MeOH in DCM) gave methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (474 mg, 89%). ESI-MS *m/z* calc. 475.142, found 476.3 (M+1)⁺; Retention time: 2.16 minutes using LC/MS Method Q.

[0462] Step 2:

[0463] Methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxylate (750 mg, 1.58 mmol) was treated via the method described in General Method K to give methyl 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylnicotinate (460 mg, 51%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.41 - 7.27 (m, 5H), 7.11 - 7.00 (m, 1H), 6.95 (s, 1H), 6.94 - 6.86 (m, 1H), 5.57 - 5.41 (m, 1H), 5.17 (s, 2H), 4.66 (dd, *J* = 10.7, 8.5 Hz, 1H), 3.91 (d, *J* = 1.9 Hz, 3H), 3.87 (s, 3H), 2.79 (p, *J* = 7.8 Hz, 1H), 2.40 (s, 3H), 1.57 (s, 3H), 0.90 - 0.73 (m, 3H) ppm. ESI-MS *m/z* calc. 565.189, found 566.3 (M+1)⁺; Retention time: 2.14 minutes using LC/MS Method D.

[0464] Step 3:

[0465] A mixture of methyl 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylnicotinate (450 mg, 0.796 mmol) and NaOH (160 mg, 4 mmol) in a mixture of MeOH (1.4 mL), water (1.4 mL) and THF (1.4 mL) was heated at 90 °C for 3 h. The reaction mixture was diluted with MeOH (500 μL), filtered, and purified by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl) to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylnicotinic acid (411 mg, 92%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.46 - 7.39 (m, 2H), 7.39 - 7.24 (m, 3H), 7.21 - 7.06 (m, 1H), 6.98 (s, 1H), 6.95 - 6.81 (m, 1H), 5.57 (d, *J* = 10.8 Hz, 1H), 5.20 (s, 2H), 4.71 (dd, *J* = 10.9, 8.6 Hz, 1H), 3.89 (d, *J* = 1.9 Hz, 3H), 2.98 - 2.77 (m, 1H), 2.44 (s, 3H), 2.03 (s, 1H), 1.63 (s, 3H), 0.87 - 0.73 (m, 3H) ppm. ESI-MS *m/z* calc. 551.173, found 552.3 (M+1)⁺; Retention time: 1.14 minutes using LC/MS Method D.

[0466] Step 4:

[0467] Methanamine (186 μL, 33 wt % solution in ethanol, 4.53 mmol) was added to a solution of 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylnicotinic acid (275 mg, 0.499 mmol), HATU (190 mg, 0.500 mmol) and DIPEA (261 μL, 1.50 mmol) in DMF (2.7 mL), under nitrogen and the reaction mixture was stirred at ambient temperature for 1 h. Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl) gave 4-(benzyloxy)-2-

((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethylnicotinamide (210 mg, 73%).

[0468] Step 5:

[0469] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethylnicotinamide (210 mg) was treated via the method described in General Method C to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**164**, 138 mg, 57%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.16 - 6.91 (m, 2H), 6.72 (s, 1H), 5.80 (d, *J* = 10.9 Hz, 1H), 4.47 (t, *J* = 10.5 Hz, 1H), 3.92 (d, *J* = 2.4 Hz, 3H), 3.01 - 2.85 (m, 1H), 2.82 (s, 3H), 2.54 (s, 3H), 1.68 (s, 3H), 0.88 - 0.69 (m, 3H) ppm; NH pyridone and amide not observed. ESI-MS *m/z* calc. 474.158, found 475.1 (M+1)⁺; Retention time: 1.38 minutes using LC/MS method D.

[0470] The following compounds were made using methods described in Example 12 except that, in Step 4, different amines were used as the amide coupling partner:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
165	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)- <i>N</i> ,6-trimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide	488.173	489.1	1.38	D	
166	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridine-3-carboxamide	460.142	461.1	1.32	D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.19 - 7.07 (m, 1H), 7.07 - 6.89 (m, 2H), 5.79 - 5.60 (m, 1H), 4.68 - 4.54 (m, 1H), 3.93 (d, <i>J</i> = 2.5 Hz, 3H), 2.99 (t, <i>J</i> = 8.8 Hz, 1H), 2.64 (s, 3H), 1.72 (s, 3H), 0.87 - 0.74 (m, 3H) ppm; NH pyridone and NH ₂ amide not observed.

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
167	3-(Azetidine-1-carbonyl)-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1 <i>H</i>)-one	500.466	501.1	1.38	D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.09 (s, 2H), 7.00 (d, <i>J</i> = 3.2 Hz, 1H), 5.57 (s, 1H), 4.60 (t, <i>J</i> = 10.5 Hz, 1H), 4.36 - 3.66 (m, 7H), 2.99 (s, 1H), 2.64 (d, <i>J</i> = 1.5 Hz, 3H), 2.42 - 2.05 (m, 2H), 1.72 (s, 3H), 0.90 - 0.72 (m, 3H) ppm; NH pyridone not observed.

[0471] The following compound was made using methods described in Example 12 except that a final chlorination step was carried out as outlined below:

[0472] *Chlorination*: NCS (5.2 mg, 0.039 mmol) was added in a single portion to a solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (15.4 mg, 0.032 mmol) in a mixture of DCM (0.5 mL) and AcOH (10 μL, 0.18 mmol). The reaction mixture was stirred at ambient temperature for 2 h. The mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with a 10% Na₂S₂O₃ solution and a saturated NaHCO₃ solution. The organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase HPLC (30 to 99% MeCN in water containing 5 mM HCl) gave 5-chloro-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethyl-4-oxo-1,4-dihydropyridine-3-carboxamide (**168**, 9.9 mg, 60%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.05 (ddd, *J* = 8.0, 5.7, 2.0 Hz, 1H), 6.96 (td, *J* = 9.4, 7.4 Hz, 1H), 5.79 (d, *J* = 10.9 Hz, 1H), 4.44 (t, *J* = 10.4 Hz, 1H), 3.92 (s, 3H), 2.93 (dd, *J* = 9.8, 7.6 Hz, 1H), 2.82 (s, 3H), 2.60 (s, 3H), 1.67 (s, 3H), 0.79 (dq, *J* = 7.8, 2.2 Hz, 3H) ppm; NH pyridone and amide not observed. ESI-MS *m/z* calc. 508.119, found 509.1 (*M*+1)⁺; Retention time: 2.14 minutes using LC/MS method Q.

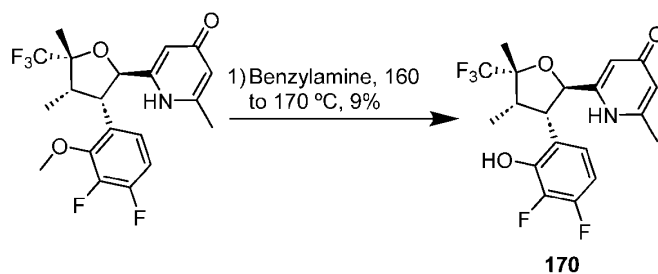
[0473] The following compound was made using methods described in Example 12 except that the product of Step 2 was made using the method described in Example 1 Step 1 by combining (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**) and ethyl 4-(benzyloxy)-6-chloro-5-fluoronicotinate:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
169	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-	478.133	479.1	2.22	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.48 (s, 1H), 7.08 (ddd, <i>J</i> = 8.3, 5.7, 1.7 Hz, 1H), 6.98 (td, <i>J</i> = 9.3, 7.4 Hz, 1H), 5.77 (d, <i>J</i> = 11.2 Hz, 1H), 4.21

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
	yl)-5-fluoro- <i>N</i> -methyl-4-oxo-1,4-dihydropyridine-3-carboxamide					(dd, <i>J</i> = 11.3, 8.9 Hz, 1H), 3.92 (s, 3H), 2.92-2.85 (m, 4H), 1.75 - 1.66 (m, 3H), 0.89 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone and amide not observed.

Example 13

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**170**)

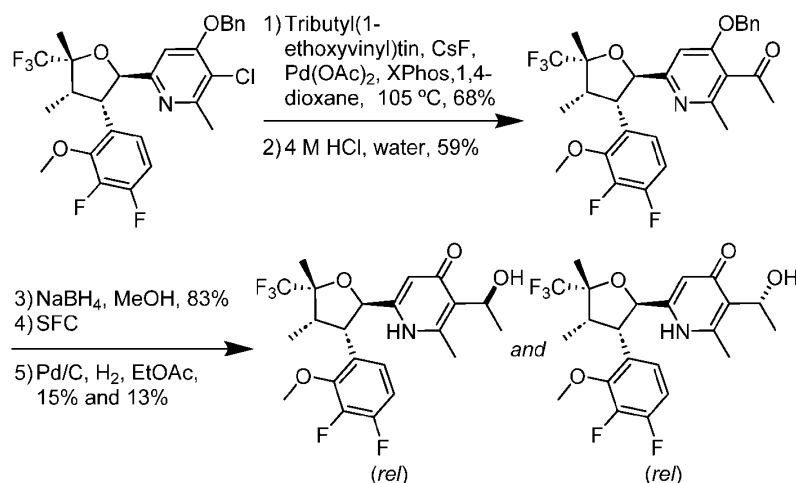


[0474] Step 1:

[0475] 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 100 mg, 0.240 mmol) was dissolved in benzylamine (1 mL, 9.2 mmol) and heated at 160 - 170 °C for 7 h. The brown solution was left standing at ambient temperature overnight and then concentrated under high vacuum at 60 °C. Part of the crude was dissolved in methanol, filtered and purified by reverse phase HPLC (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl over 30 min) to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (Hydrochloride salt) (**170**, 10 mg, 9%) as an off-white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.05 - 6.96 (m, 1H), 6.92 - 6.84 (m, 2H), 6.79 - 6.68 (m, 1H), 5.65 (d, *J* = 11.2 Hz, 1H), 4.25 (dd, *J* = 11.3, 8.3 Hz, 1H), 2.96 (p, *J* = 7.7 Hz, 1H), 2.60 (s, 3H), 1.68 (s, 3H), 0.90 (dq, *J* = 7.6, 2.4 Hz, 3H) ppm; NH pyridone and OH alcohol not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.43, -140.66 (d, *J* = 20.1 Hz), -162.79 (d, *J* = 20.1 Hz) ppm. ESI-MS *m/z* calc. 403.121, Retention time: 1.59 minutes; no mass ionisation observed using LC/MS Method Q.

Example 14

rel-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((*S*)-1-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (**171**) and
rel-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((*R*)-1-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (**172**)



[0476] Step 1 and Step 2:

[0477] 4-(Benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (**Product of Example 6, Step 2**, 65 mg, 0.120 mmol) was treated via the method described in General Method L to give 1-(4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-one (39 mg, 59%) as a light-yellow oil. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.45 - 7.34 (m, 5H), 7.19 - 7.13 (m, 2H), 6.90 (ddd, *J* = 10.0, 8.9, 7.6 Hz, 1H), 5.44 (d, *J* = 11.0 Hz, 1H), 5.30 (s, 2H), 4.19 - 4.10 (m, 1H), 3.89 (d, *J* = 2.2 Hz, 3H), 2.81 (p, *J* = 7.6 Hz, 1H), 2.48 (s, 3H), 2.33 (s, 3H), 1.66 (d, *J* = 1.2 Hz, 3H), 0.89 - 0.82 (m, 3H) ppm. ESI-MS *m/z* calc. 549.194, found 550.6 (M+1)⁺; Retention time: 1.20 minutes using LC/MS method C.

[0478] Step 3:

[0479] 1-(4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-one (24 mg, 0.044 mmol) was dissolved in MeOH (1 mL) at ambient temperature. NaBH₄ (5 mg, 0.13 mmol) was added in one portion and the reaction mixture was stirred for 10 min. Upon reaction completion, the mixture was quenched by addition of a half-saturated NH₄Cl solution (10 mL) and extracted with DCM (2 x 5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give

dia-1-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (20 mg, 83%). ESI-MS *m/z* calc. 551.210, found 592.6 (M+1)⁺; Retention time: 3.96 minutes using LC/MS method A.

[0480] Step 4:

[0481] The diastereoisomers of *dia*-1-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (20 mg) were separated by chiral SFC using a Chiralpak® IB column, 5µm particle size, 25 cm x 21.2 mm from Daicel Corporation:

[0482] First eluting isomer (rt = 1.75 min): *rel*-(*S*)-1-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (10 mg, 42%) ESI-MS *m/z* calc. 551.210, found 552.2 (M+1)⁺; 550.3 (M-1)⁻; Retention time: 3.91 minutes using LC/MS method A.

[0483] Second eluting isomer (rt = 3.73 min): *rel*-(*R*)-1-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (8 mg, 33%) ESI-MS *m/z* calc. 551.210, found 552.3 (M+1)⁺; 550.3 (M-1)⁻; Retention time: 3.91 minutes using LC/MS method A.

[0484] Step 5:

[0485] *rel*-(*S*)-1-(4-(Benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (10 mg, 42%) was treated via the method described in General Method C, using EtOAc as the solvent in place of EtOH, to give *rel*-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((*S*)-1-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (**171**, 3.1 mg, 15%). ESI-MS *m/z* calc. 461.163, found 462.5 (M+1)⁺; 460.4 (M-1)⁻; Retention time: 2.98 minutes using LC/MS method A.

[0486] *rel*-(*R*)-1-(4-(Benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (8 mg, 33%) was treated via the method described in General Method C, using EtOAc as the solvent in place of EtOH, to give *rel*-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((*R*)-1-hydroxyethyl)-2-methylpyridin-4(1*H*)-one (**172**, 2.6 mg, 13%). ESI-MS *m/z* calc. 461.163, found 462.5 (M+1)⁺; 460.4 (M-1)⁻; Retention time: 2.98 minutes using LC/MS method A.

[0487] The following compounds were made using methods described in Example 14 except that, in Step 1, 4-(benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2 Example 22**) was used as the starting material in place of 4-(benzyloxy)-3-chloro-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridine (**Product of Example 6 Step 2**). In Step 4, the diastereoisomers were separated by chiral SFC using a

Chiralcel® OD-H column, 5 µm particle size, 25 cm x 10 mm from Daicel Corporation. In Step 5, a 1:1 mixture of EtOH and AcOH was used as the solvent in place of EtOAc:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
173	<i>rel</i> -2-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>R</i>)-1-hydroxyethyl)-6-methylpyrimidin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on Chiralcel® OD-H, rt = 1.84 min)	462.158	463.5	3.05	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.05 - 7.01 (m, 1H), 6.97 - 6.90 (m, 1H), 5.26 (d, <i>J</i> = 10.7 Hz, 1H), 5.01 (q, <i>J</i> = 6.7 Hz, 1H), 4.50 (dd, <i>J</i> = 10.7, 8.1 Hz, 1H), 3.99 (d, <i>J</i> = 2.2 Hz, 3H), 2.85 (dq, <i>J</i> = 8.1, 7.7 Hz, 1H), 2.32 (s, 3H), 1.63 (s, 3H), 1.41 (d, <i>J</i> = 6.7 Hz, 3H), 0.84 - 0.81 (m, 3H) ppm; NH pyridone not observed.
174	<i>rel</i> -2-((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((<i>S</i>)-1-hydroxyethyl)-6-methylpyrimidin-4(1 <i>H</i>)-one (Precursor was the second eluting peak by SFC on Chiralcel® OD-H, rt = 3.10 min)	462.158	463.5	3.04	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.06 - 7.01 (m, 1H), 6.98 - 6.89 (m, 1H), 5.27 (d, <i>J</i> = 10.7 Hz, 1H), 5.01 (q, <i>J</i> = 6.7 Hz, 1H), 4.50 (dd, <i>J</i> = 10.7, 8.2 Hz, 1H), 3.99 (d, <i>J</i> = 2.2 Hz, 3H), 2.85 (dq, <i>J</i> = 8.2, 7.7 Hz, 1H), 2.33 (s, 3H), 1.63 (s, 3H), 1.41 (d, <i>J</i> = 6.7 Hz, 3H), 0.86 - 0.81 (m, 3H) ppm; NH pyridone not observed.

[0488] The following compound was made using methods described in Example 14 except that Steps 3 and 4 were omitted:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
175	3-Acetyl-6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-	459.147	460.5	2.98	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.10 - 7.04 (m, 1H), 6.99 (td, <i>J</i> = 9.3, 7.4 Hz, 1H), 6.39 (s, 1H), 5.36 (d, <i>J</i> = 11.3 Hz, 1H),

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS retention time	LC/MS Method	NMR (shifts in ppm)
	(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1 <i>H</i>)-one					4.20 (dd, <i>J</i> = 11.2, 8.3 Hz, 1H), 4.01 (d, <i>J</i> = 2.5 Hz, 3H), 2.87 (p, <i>J</i> = 7.8 Hz, 1H), 2.47 (s, 3H), 2.36 (s, 3H), 1.68 (d, <i>J</i> = 1.2 Hz, 3H), 0.88 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm: NH pyridone not observed.

[0489] The following compounds were made using methods described in Example 14 except that an additional alkylation step was introduced between Step 3 and Step 4, as outlined below. In the case of **176**, Step 4 was omitted. In the case of **177** and **178**, Step 5 was carried out before Step 4 and, in Step 4, the diastereoisomers of **176** were separated by chiral SFC using a ChiralPak[®] IC column, 5 μ m particle size, 25 cm x 21.2 mm from Daicel Corporation:

[0490] *Alkylation*: MeI (30 μ L, 0.48 mmol) was added dropwise to a mixture of *dia*-1-(4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethan-1-ol (18 mg), and NaH (10 mg, 60% dispersion in mineral oil, 0.25 mmol) in THF and stirred at 22 °C for 2 h. The mixture was concentrated *in vacuo*. Purification by reverse phase preparative chromatography (C₁₈ column, 1 to 99% MeCN in water containing 5 mM HCl modifier over 20 min) gave *dia*-4-(benzyloxy)-6-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-methoxyethyl)-2-methylpyridine (1.5 mg, 5%) as a clear solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.42 - 7.30 (m, 5H), 7.16 (s, 1H), 7.10 - 7.06 (m, 1H), 6.90 (q, *J* = 8.8 Hz, 1H), 5.46 (d, *J* = 11.2 Hz, 1H), 5.32 (s, 2H), 5.04 (qd, *J* = 6.6, 3.1 Hz, 1H), 4.17 (q, *J* = 10.6 Hz, 1H), 3.89 (d, *J* = 2.4 Hz, 3H), 3.34 (s, 3H), 3.17 (d, *J* = 4.5 Hz, 3H), 2.85 (t, *J* = 7.7 Hz, 1H), 2.63 (s, 3H), 1.66 (s, 3H), 1.44 (dd, *J* = 6.8, 4.2 Hz, 3H), 0.88 - 0.81 (m, 3H) ppm. ESI-MS *m/z* calc. 565.225, found 566.6 (*M*+1)⁺; Retention time: 2.36 minutes using LC/MS method Q.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
176	<i>dia</i> -6-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-methoxyethyl)-2-methylpyridin-4(1 <i>H</i>)-one	475.178	476.1	1.92	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.08 - 7.00 (m, 1H), 7.03 - 6.92 (m, 1H), 6.47 (s, 1H), 5.40 (dd, <i>J</i> = 11.3, 3.1 Hz, 1H), 4.95 (qd, <i>J</i> = 6.7, 2.3 Hz, 1H), 4.20 (ddd, <i>J</i> = 11.1, 8.3, 2.6 Hz, 1H), 3.98 (d, <i>J</i> = 2.5 Hz, 3H), 3.19 (d, <i>J</i> = 6.2 Hz, 3H), 2.86 (p, <i>J</i> = 7.8 Hz, 1H), 2.56 (d, <i>J</i> = 0.9 Hz, 3H), 1.66 (s, 3H), 1.36 (dd, <i>J</i> = 6.7, 5.4 Hz, 3H), 0.87 (dt, <i>J</i> = 7.6, 2.3 Hz, 3H) ppm; NH pyridone not observed.
177	<i>rel</i> -6-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((<i>S</i>)-1-methoxyethyl)-2-methylpyridin-4(1 <i>H</i>)-one (Precursor was the first eluting peak by SFC on ChiralPak [®] IC, rt = 3.88 min)	475.178	476.186	1.94	Q	

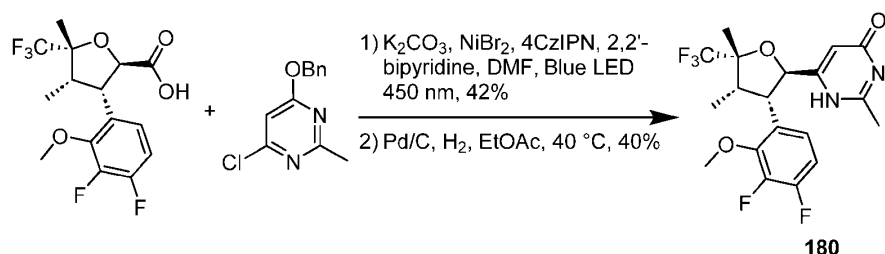
Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
178	<i>rel</i> -6- ((2 <i>R</i> *,3 <i>S</i> *,4 <i>S</i> *,5 <i>R</i> *) -3-(3,4-Difluoro- 2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl)te- trahydrofuran-2- yl)-3-((<i>R</i>)-1- methoxyethyl)-2- methylpyridin- 4(<i>1H</i>)-one (Precursor was the first eluting peak by SFC on ChiralPak® IC, rt = 4.71 min)	475.178	476.2	1.93	Q	

[0491] The following compound was made using methods described in Example 14 except that the starting material in Step 1 was made by combining (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid **Int-1** and 4-(benzyloxy)-5-chloro-2-methylpyridine using methods described in General Method B. Steps 3 and 4 were omitted:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
179	3-Acetyl-2- ((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3- (3,4-difluoro-2- methoxyphenyl)- 4,5-dimethyl-5- (trifluoromethyl)te- trahydrofuran-2- yl)-6- methylpyridin- 4(<i>1H</i>)-one	459.147	460.4	3.03	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.10 (ddd, <i>J</i> = 8.1, 5.6, 2.2 Hz, 1H), 7.00 (td, <i>J</i> = 9.3, 7.5 Hz, 1H), 6.27 (s, 1H), 5.33 (d, <i>J</i> = 10.9 Hz, 1H), 4.49 (t, <i>J</i> = 10.4 Hz, 1H), 3.89 (d, <i>J</i> = 1.9 Hz, 3H), 2.82 (dq, <i>J</i> = 9.8, 7.7 Hz, 1H), 2.37 (s, 3H), 2.34 - 2.24 (m, 3H), 1.64 - 1.52 (m, 3H), 0.79 (dt, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Example 15

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyrimidin-4(1*H*)-one (**180**)

**[0492] Step 1:**

[0493] In an oven-dried 20-mL vial, equipped with a stir bar, a mixture of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 62 mg, 0.175 mmol), 4-benzyloxy-6-chloro-2-methylpyrimidine (92 mg, 0.39 mmol), K₂CO₃ (48 mg, 0.35 mmol), 2,2'-bipyridine (4 mg, 0.026 mmol), NiBr₂ (4 mg, 0.018 mmol) and 4CzIPN (11 mg, 0.014 mmol) in DMF (8.7 mL) was degassed for 15 min. The vial was sealed and the solution was stirred at ambient temperature under the irradiation of a blue LED (450 nm) using a Penn OC Photoreactor M1 for 18 h. Upon reaction completion, the mixture was quenched by addition of H₂O (10 mL) and brine (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by preparative reverse phase HPLC (C₁₈ column, 1 to 99% MeCN in water containing HCl modifier over 15 min) gave 4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyrimidine (62.8 mg, 42%) as a pale yellow solid, which was used without further purification in the next step. ESI-MS *m/z* calc. 508.179, found 509.5 (M+1)⁺; Retention time: 3.42 minutes using LC/MS method Q.

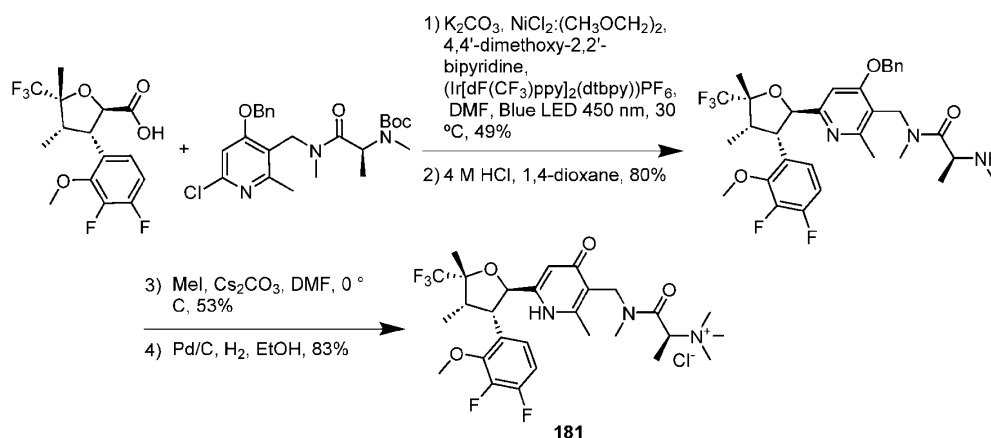
[0494] Step 2:

[0495] 4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyrimidine (62.8 mg) was treated via the method described in General Method C using EtOAc as the solvent in place of EtOH. The reaction was carried out at 40 °C. Purification by preparative reverse phase HPLC (C₁₈ column, 1 to 99% MeCN in H₂O containing HCl modifier over 30 min) gave 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyrimidin-4(1*H*)-one (**180**, 29.1 mg, 40%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.39 (s, 1H), 7.22 (ddd, *J* = 8.3, 5.9, 2.0 Hz, 1H), 7.15 - 7.06 (m, 1H), 6.37 (s, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 4.26 (dd, *J* = 10.9, 7.4 Hz, 1H), 3.90 (d, *J* = 1.9 Hz, 3H), 2.71 (p, *J* = 7.5 Hz, 1H), 2.23 (s, 3H), 1.60 (s, 3H), 0.75 (dd, *J* = 7.6, 2.8 Hz, 3H).

ppm. ESI-MS m/z calc. 418.132, found 419.5 ($M+1$)⁺; Retention time: 2.36 minutes using LC/MS method Q.

Example 16

(*S*)-1-(((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)(methyl)amino)-*N,N,N*-trimethyl-1-oxopropan-2-aminium chloride (**181**)



[0496] Step 1:

[0497] (2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 60 mg, 0.17 mmol) and *tert*-butyl (*S*)-1-(((4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methyl)(methyl)amino)-1-oxopropan-2-yl)methyl carbamate (**Int-27**, 95.3 mg, 0.204 mmol) were treated via the method described in General Method A to give *tert*-butyl ((*S*)-1-(((4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methyl)(methyl)amino)-1-oxopropan-2-yl)methyl carbamate (61.8 mg, 49%) as an off-white solid. ESI-MS m/z calc. 735.331, found 736.3 ($M+1$)⁺; Retention time: 1.53 minutes using LC/MS method D.

[0498] Step 2:

[0499] In a vial, HCl (400 μ L, 4 M solution in 1,4-dioxane, 1.6 mmol) was added to stirring solution of *tert*-butyl ((*S*)-1-(((4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methyl)(methyl)amino)-1-oxopropan-2-yl)methyl carbamate (40.1 mg, 0.053 mmol) in 1,4-dioxane (1 mL) and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C_{18} column, 1 to 99% MeCN in water containing HCl modifier over 15 min) gave (*S*)-*N*-(((4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-

methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methyl)-*N*-methyl-2-(methylamino)propanamide (Hydrochloride salt) (28.6 mg, 80%) as an off-white solid. ESI-MS *m/z* calc. 635.278, found 636.2 (M+1)⁺; Retention time: 1.09 minutes using LC/MS method D.

[0500] Step 3:

[0501] MeI (5 μ L, 0.08 mmol) was added dropwise to a suspension of (*S*)-*N*-((4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methyl)-*N*-methyl-2-(methylamino)propanamide (Hydrochloride salt) (28.6 mg, 0.045 mmol) and Cs₂CO₃ (52.2 mg, 0.160 mmol) in DMF (1 mL) at 0 °C and the mixture was stirred for 30 min at 0 °C. The mixture was partitioned between EtOAc and a saturated NH₄Cl solution. The organic phase was separated, washed with brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C₁₈ column, 1 to 99% MeCN in water containing HCl modifier over 15 min) gave (*S*)-1-(((4-(benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methyl)(methyl)amino)-*N,N,N*-trimethyl-1-oxopropan-2-aminium chloride (20.1 mg, 53%) as a white solid. ESI-MS *m/z* calc. 664.317, found 665.2 (M+1)⁺; Retention time: 1.12 minutes using LC/MS method D.

[0502] Step 4:

[0503] (*S*)-1-(((4-(Benzyloxy)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)methyl)(methyl)amino)-*N,N,N*-trimethyl-1-oxopropan-2-aminium chloride (20.1 mg, 0.028 mmol) was treated via the method described in General Method C to give (*S*)-1-(((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)(methyl)amino)-*N,N,N*-trimethyl-1-oxopropan-2-aminium chloride (**181**, 14.6 mg, 83%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.20 - 7.16 (m, 1H), 7.11 (s, 1H), 7.03 (td, *J* = 9.4, 7.6 Hz, 1H), 5.70 (d, *J* = 11.1 Hz, 1H), 4.73 - 4.61 (m, 3H), 4.27 (dd, *J* = 11.3, 8.3 Hz, 1H), 4.00 (s, 3H), 3.25 (s, 9H), 3.17 (s, 3H), 2.94 (q, *J* = 7.8 Hz, 1H), 2.79 (s, 3H), 1.70 (s, 3H), 1.57 (d, *J* = 6.8 Hz, 3H), 0.92 - 0.89 (m, 3H) ppm; NH pyridone not observed. ESI-MS *m/z* calc. 574.270, found 574.1 (M+0)⁺; Retention time: 1.66 minutes using LC/MS method Q.

[0504] The following compound was made using methods described in Example 16, except that Step 3 was omitted and Step 4 was carried out before Step 2:

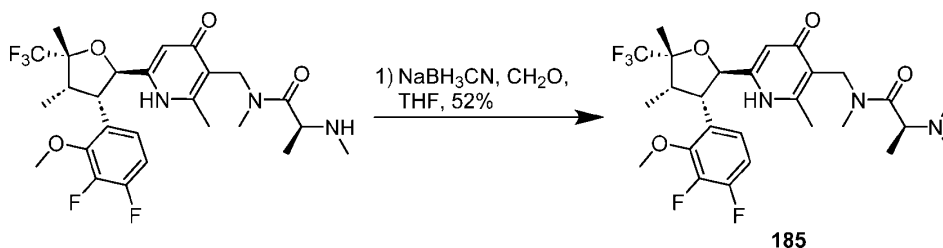
Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
182	(<i>S</i>)- <i>N</i> -((6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)- <i>N</i> -methyl-2-(methylamino)propanamide (Hydrochloride salt)	545.231	546.1	1.60	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.2 - 7.16 (m, 1H), 7.12 (s, 1H), 7.10 - 6.98 (m, 1H), 5.70 (d, <i>J</i> = 11.2 Hz, 1H), 4.73 (d, <i>J</i> = 14.8 Hz, 1H), 4.60 (d, <i>J</i> = 14.8 Hz, 1H), 4.35 (q, <i>J</i> = 6.8 Hz, 1H), 4.27 (dd, <i>J</i> = 11.3, 8.2 Hz, 1H), 4.01 (s, 3H), 3.08 (s, 3H), 2.93 (p, <i>J</i> = 7.7 Hz, 1H), 2.79 (s, 3H), 2.64 (s, 3H), 1.70 (s, 3H), 1.44 (d, <i>J</i> = 6.8 Hz, 3H), 0.92 - 0.88 (m, 3H) ppm; NH amine and pyridone not observed.

[0505] The following compounds were made using methods described in Example 16, except that in Step 1, *tert*-butyl *dia*-((*S*^{*})-1-(((*S*¹)-1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethyl)amino)-1-oxopropan-2-yl)carbamate (**Int-32**) was used as the cross-coupling partner in place of *tert*-butyl (*S*)-1-(((4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methyl)(methyl)amino)-1-oxopropan-2-yl(methyl)carbamate (**Int-27**). The products of Step 1 were separated by reverse phase flash chromatography (150 g C₁₈ column, 5 to 100% MeCN in water containing 0.1% formic acid) to give *tert*-butyl *rel*-((*S*^{*})-1-(((*R*)-1-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethyl)amino)-1-oxopropan-2-yl)carbamate (first eluting isomer) and *tert*-butyl *rel*-((*S*^{*})-1-(((*S*)-1-(4-(benzyloxy)-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-3-yl)ethyl)amino)-1-oxopropan-2-yl)carbamate (second eluting isomer), which were respectively used in the following Steps to form **183** and **184**. Step 3 was omitted and Step 4 was carried out before Step 2:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
183	<i>rel</i> -(<i>S</i> [*])-2-Amino- <i>N</i> -((<i>R</i>)-1-(6-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)ethyl)propanamide (Hydrochloride salt)	531.216	532.2	2.60	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.89 (br s, 1H), 7.96 (d, <i>J</i> = 3.3 Hz, 3H), 7.27 (br s, 1H), 7.17 - 7.09 (m, 2H), 5.66 (br s, 1H), 5.02 - 4.95 (m, 1H), 4.26 (dd, <i>J</i> = 11.2, 8.0 Hz, 1H), 3.97 (d, <i>J</i> = 2.0 Hz, 3H), 3.77 - 3.73 (m, 1H), 2.90 - 2.83 (m, 1H), 2.69 - 2.62 (m, 3H), 1.65 (s, 3H), 1.41 (d, <i>J</i> = 7.0 Hz, 3H), 1.33 (d, <i>J</i> = 6.8 Hz, 3H), 0.76 (d, <i>J</i> = 6.2 Hz, 3H) ppm.
184	<i>rel</i> -(<i>S</i> [*])-2-Amino- <i>N</i> -((<i>S</i>)-1-(6-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)ethyl)propanamide (Hydrochloride salt)	531.216	532.2	2.61	K	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.90 (br s, 1H), 8.03 - 7.96 (m, 3H), 7.30 - 7.24 (m, 1H), 7.12 (q, <i>J</i> = 8.8 Hz, 1H), 6.89 (br s, 1H), 5.59 (br s, 1H), 5.01 - 4.92 (m, 1H), 4.22 (dd, <i>J</i> = 11.3, 7.9 Hz, 1H), 3.95 (d, <i>J</i> = 1.8 Hz, 3H), 3.91 - 3.84 (m, 1H), 2.90 - 2.80 (m, 1H), 2.58 (br s, 3H), 1.65 (s, 3H), 1.40 (d, <i>J</i> = 7.1 Hz, 3H), 1.18 (d, <i>J</i> = 7.0 Hz, 3H), 0.75 (d, <i>J</i> = 6.7 Hz, 3H) ppm.

Example 17

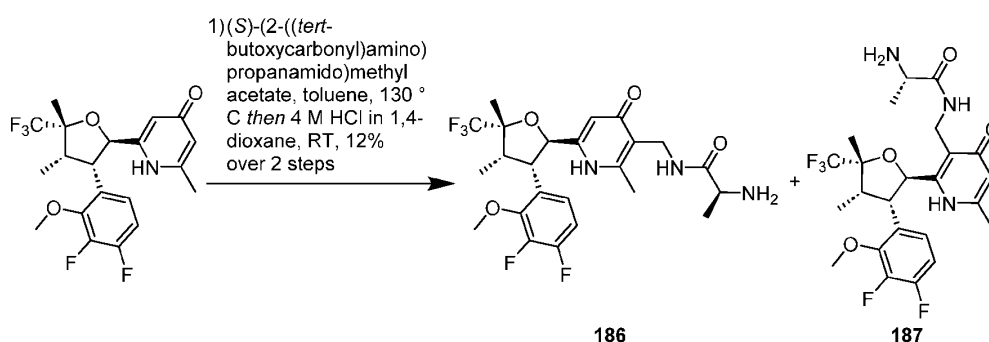
(*S*)-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-2-(dimethylamino)-*N*-methylpropanamide (**185**)

**[0506] Step 1:**

[0507] Formaldehyde (16.5 mg, 0.015 mL, 37% w/w in water, 0.203 mmol) and NaBH₃CN (12 mg, 0.19 mmol) were added to a stirred solution of (*S*)-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-*N*-methyl-2-(methylamino)propanamide (Hydrochloride salt) (**182**, 19.4 mg, 0.033 mmol) in THF (1 mL) at ambient temperature and the mixture was stirred overnight at ambient temperature. The mixture was concentrated *in vacuo*. Purification by reverse phase flash chromatography (30 g C₁₈ column, 2 to 100% MeCN in water containing 0.1% formic acid) gave after concentration, co-evaporation with MeCN (6 x 20 mL) and lyophilization (*S*)-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-2-(dimethylamino)-*N*-methylpropanamide (**185**, 10 mg, 52%) as a white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.14 - 6.96 (m, 3H), 5.64 (d, *J* = 11.2 Hz, 1H), 4.78 - 4.70 (m, 1H), 4.66 - 4.58 (m, 1H), 4.45 - 4.37 (m, 1H), 4.30 - 4.21 (m, 1H), 4.03 - 3.97 (m, 3H), 3.09 (s, 3H), 2.95 - 2.75 (m, 10H), 1.69 (s, 3H), 1.60 - 1.45 (m, 3H), 0.91 (d, *J* = 6.1 Hz, 3H) ppm; NH pyridone not observed. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -75.28 - -75.53 (m, 3F), -139.40 - -139.65 (m, 1F), -156.35 (d, *J* = 17.7 Hz, 1F) ppm. ESI-MS *m/z* calc. 559.247, found 560.2 (M+1)⁺; Retention time: 2.47 minutes using LC/MS method K.

Example 18

(*S*)-2-Amino-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide (**186**) and (*S*)-2-amino-*N*-((2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide (**187**)

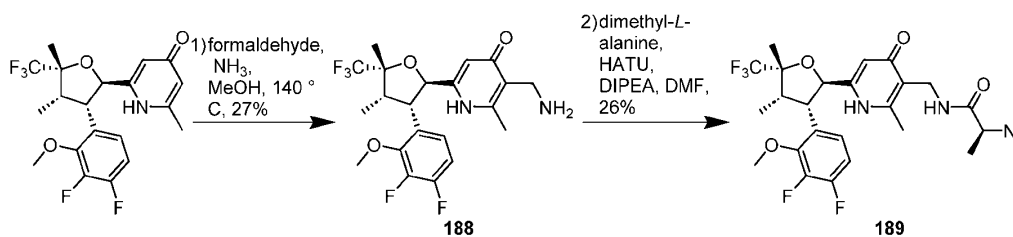


[0508] Step 1:

[0509] A solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 100 mg, 0.24 mmol) and (*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)methyl acetate (**Int-33**, 141 mg, 0.542 mmol) in toluene (1.5 mL) was heated at 130 °C overnight then at 145 °C for a further 4.25 h. Additional (*S*)-2-((*tert*-butoxycarbonyl)amino)propanamido)methyl acetate (**Int-33**, 47 mg, 0.18 mmol) was added and the reaction mixture was heated at 145 °C for 1.25 h then, at 130 °C overnight. The mixture was cooled to ambient temperature and HCl (~2-3 mL, 4 M solution in 1,4-dioxane) was added. The reaction mixture was stirred at ambient temperature overnight and concentrated *in vacuo*. The mixture was dissolved in MeOH and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C₁₈ column, 1 to 50% MeCN in water containing HCl modifier over 15 min) gave, after lyophilization, (*S*)-2-amino-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide (Hydrochloride salt) (**186**, 7.9 mg, 5%)(ESI-MS *m/z* calc. 517.200, found 518.2 (M+1)⁺; Retention time: 1.62 minutes using LC/MS method Q) and (*S*)-2-amino-*N*-((2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide (Hydrochloride salt) (**187**, 10 mg, 7%)(ESI-MS *m/z* calc. 517.200, found 518.2 (M+1)⁺; Retention time: 1.48 minutes using LC/MS method Q).

Example 19

3-(Aminomethyl)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1*H*)-one (**188**) and (*S*)-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-2-(dimethylamino)propanamide (**189**)

**[0510] Step 1:**

[0511] In a 20-mL microwave vial, formaldehyde (434 mg, 14.45 mmol) and ammonia (10 mL, 7 M solution in MeOH, 70.0 mmol) were added to a solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**, 500 mg, 1.198 mmol) in methanol (10 mL) and the mixture was irradiated at 140 °C for 2 h. The mixture was concentrated *in vacuo*. Purification by reverse phase flash chromatography (10 to 70% MeCN in water containing HCl) gave 3-(aminomethyl)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1*H*)-one (Hydrochloride salt) (**188**, 162 mg, 27%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.19 (t, *J* = 5.8 Hz, 3H), 7.44 (td, *J* = 8.3, 5.7, 2.0 Hz, 1H), 7.32 (s, 1H), 7.12 (dd, *J* = 9.7, 7.9 Hz, 1H), 5.83 (d, *J* = 11.3 Hz, 1H), 4.29 (dd, *J* = 11.4, 7.8 Hz, 1H), 3.95 (d, *J* = 2.0 Hz, 3H), 3.88 (q, *J* = 5.7 Hz, 2H), 2.87 (p, *J* = 7.6 Hz, 1H), 2.71 (s, 3H), 1.70 (s, 3H), 0.76 (d, 3H) ppm. ESI-MS *m/z* calc. 446.163, found 447.3 (*M*+1)⁺; Retention time: 1.63 minutes using LC/MS method Q.

[0512] Step 2:

[0513] DIPEA (27 μL, 0.155 mmol) was added to a stirred solution of 3-(aminomethyl)-6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methylpyridin-4(1*H*)-one (Hydrochloride salt) (46 mg, 0.103 mmol) and dimethyl-*L*-alanine (19 mg, 0.16 mmol) in DMF (1 mL) and the mixture was stirred at ambient temperature for 5 min. HATU (86 mg, 0.226 mmol) was added and the mixture was stirred at ambient temperature. Upon reaction completion, the mixture was partitioned between a saturated aqueous NaHCO₃ solution (20 mL) and EtOAc (30 mL). The organic phase was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO₂, 0 to 10% MeOH in DCM then, 12 g SiO₂, 0 to 20% MeOH in DCM) gave (*S*)-*N*-((6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)-2-(dimethylamino)propanamide (**189**, 15 mg, 26%). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.11 - 7.04 (m,

1H), 7.04 - 6.95 (m, 1H), 6.84 (s, 1H), 5.59 (d, $J = 11.2$ Hz, 1H), 5.49 (s, 2H), 4.43 (dd, 2H), 4.23 (dd, $J = 11.2$, 8.3 Hz, 1H), 4.00 (d, $J = 2.6$ Hz, 3H), 3.79 (q, $J = 6.9$ Hz, 1H), 2.91 (p, $J = 7.8$ Hz, 1H), 2.84 (s, 6H), 2.76 (s, 3H), 1.67 (s, 3H), 1.49 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 7.3$ Hz, 3H) ppm. ESI-MS m/z calc. 545.231, found 546.4 ($M+1$)⁺; Retention time: 1.62 minutes using LC/MS method Q.

[0514] The following compound was made using methods described in Example 19, except that, in Step 2, (*tert*-butoxycarbonyl)-*D*-alanine was used as the amide coupling partner in place of dimethyl-*L*-alanine. A final deprotection step was carried out using the conditions described in Example 3 Step 2:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found $M+1$	MS r.t.	LC/MS Method	NMR (shifts in ppm)
190	(<i>R</i>)-2-Amino- <i>N</i> -((6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)propanamide (Hydrochloride salt)	517.200	518.3	1.58	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.19 (td, $J = 8.4$, 5.5, 2.1 Hz, 1H), 7.09 (s, 1H), 7.02 (ddd, $J = 9.3$, 7.5 Hz, 1H), 5.68 (dd, $J = 11.3$, 4.0 Hz, 1H), 4.43 (s, 2H), 4.26 (dd, $J = 11.3$, 8.4 Hz, 1H), 4.00 (d, $J = 2.6$ Hz, 3H), 3.89 (q, $J = 7.1$ Hz, 1H), 3.34 (s, 2H), 2.92 (p, $J = 7.8$ Hz, 1H), 2.83 (s, 3H), 1.70 (s, 3H), 1.43 (d, $J = 7.0$ Hz, 3H), 0.90 (dd, $J = 7.2$, 2.4 Hz, 3H) ppm; NH amide and pyridone not observed.

[0515] The following compound was made using methods described in Example 19 except that, in Step 1, 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (**196**, below) and dimethylamine (2 M solution in MeOH) were respectively used in place of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyridin-4(1*H*)-one (**2**) and ammonia and the reaction was carried out at 80 °C in EtOH as the solvent. Step 2 was omitted:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS <i>r.t.</i>	LC/MS Method	NMR (shifts in ppm)
191	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((dimethylamino)methyl)-6-methylpyrimidin-4(1 <i>H</i>)-one	475.189	477.4	2.70	A	¹ H NMR (500 MHz, Acetonitrile- <i>d</i> ₃) δ 7.16 - 7.01 (m, 1H), 6.93 (q, <i>J</i> = 8.9 Hz, 1H), 5.28 (d, <i>J</i> = 10.9 Hz, 1H), 4.48 (dd, <i>J</i> = 10.9, 7.8 Hz, 1H), 3.98 (d, <i>J</i> = 2.1 Hz, 3H), 3.58 (s, 2H), 2.86 (p, <i>J</i> = 7.6 Hz, 1H), 2.34 (s, 6H), 2.25 (s, 3H), 1.65 (s, 3H), 0.83 (dq, <i>J</i> = 7.4, 2.4 Hz, 3H) ppm; NH pyrimidone not observed.

[0516] The following compound was made using methods described in Example 19, except that Step 2 was omitted. The product of Step 1 was further acetylated at ambient temperature using an excess of acetic anhydride in pyridine:

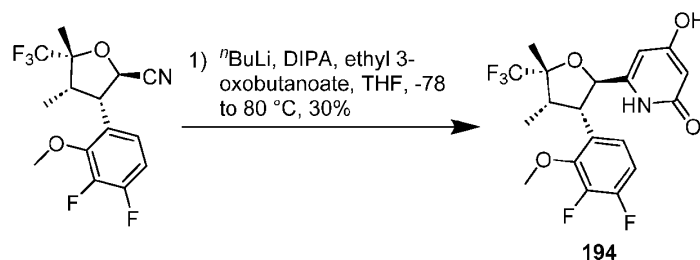
Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS <i>r.t.</i>	LC/MS Method	NMR (shifts in ppm)
192	<i>N</i> -((6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-2-methyl-4-oxo-1,4-dihydropyridin-3-yl)methyl)acetamide	488.173	489.3	1.82	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.03 (s, 1H), 7.21 (ddd, <i>J</i> = 8.2, 5.8, 1.9 Hz, 1H), 7.11 (dd, 1H), 6.76 (s, 1H), 5.46 (d, <i>J</i> = 11.2 Hz, 1H), 4.26 (dd, <i>J</i> = 11.3, 7.7 Hz, 1H), 4.09 (d, <i>J</i> = 5.2 Hz, 2H), 3.94 (d, <i>J</i> = 2.0 Hz, 3H), 2.80 (p, <i>J</i> = 7.6 Hz, 1H), 2.44 (s, 3H), 1.77 (s, 3H), 1.64 (s, 3H), 0.76 (d, 3H) ppm; NH amide not observed.

[0517] The following compound was made using methods described in Example 19, except that Step 2 was omitted. In Step 1, dimethylamine was used in place of ammonia and the reaction was carried out at reflux in EtOH as the solvent:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found <i>M</i> +1	MS <i>r.t.</i>	LC/MS Method	NMR (shifts in ppm)
193	6-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-((dimethylamino)methyl)-2-methylpyridin-4(1 <i>H</i>)-one	474.194	475.5	3.04	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.07 (ddd, <i>J</i> = 8.1, 5.5, 2.2 Hz, 1H), 6.93 (ddd, <i>J</i> = 10.0, 8.9, 7.5 Hz, 1H), 6.46 (s, 1H), 5.31 (d, <i>J</i> = 11.2 Hz, 1H), 4.17 (dd, <i>J</i> = 11.2, 8.1 Hz, 1H), 3.95 (d, <i>J</i> = 2.3 Hz, 3H), 3.62 (s, 2H), 2.83 (p, <i>J</i> = 7.7 Hz, 1H), 2.41 (s, 3H), 2.36 (s, 6H), 1.66 (d, <i>J</i> = 1.3 Hz, 3H), 0.86 (dq, <i>J</i> = 7.5, 2.3 Hz, 3H) ppm; NH pyridone not observed.

Example 20

6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-hydroxypyridin-2(1*H*)-one (**194**)



[0518] ⁿBuLi (263 μ L, 2.5 M solution in hexanes, 0.658 mmol) was added to a stirred solution of DIPA (92 μ L, 92 μ L, 0.656 mmol) in THF (1 mL) cooled in an ice bath. The colourless solution was stirred for 30 min in the ice bath allowing the solution to warm to 15 °C. The solution was cooled back down to 0 °C. Ethyl 3-oxobutanoate (42 μ L, 0.330 mmol) was slowly added and the solution was stirred in the ice bath for another 45 min. The resulting solution was slowly added to a stirred solution of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carbonitrile (100 mg, 0.298 mmol) in THF (1 mL) cooled in a dry ice bath. The solution was slowly warmed to ambient temperature over 20 h, keeping the dry ice bath in place. The mixture was then heated to 80 °C for 2.5 h. The reaction was partitioned between EtOAc (25 mL) and a 1 M citric acid solution (25 mL). The organic phase was separated, washed with brine (10 mL), dried, filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂) gave 6-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-4-hydroxypyridin-2(1*H*)-one (**194**, 38 mg, 30%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.03 (s, 1H), 10.59 (s, 1H), 7.39 - 6.91 (m, 2H), 6.05

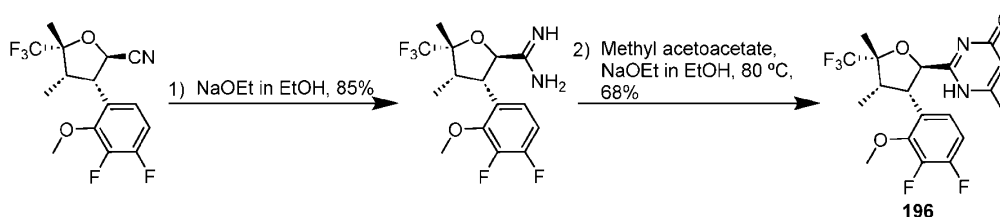
(s, 1H), 5.44 (s, 1H), 5.21 (d, $J = 11.4$ Hz, 1H), 4.24 (dd, $J = 11.4, 8.2$ Hz, 1H), 3.90 (d, $J = 1.9$ Hz, 3H), 2.76 (p, $J = 7.7$ Hz, 1H), 1.64 (s, 3H), 0.71 (dd, $J = 7.3, 2.6$ Hz, 3H) ppm. ESI-MS m/z calc. 419.116, found 420.2 ($M+1$)⁺; Retention time: 2.14 minutes using LC/MS method Q.

[0519] The following compound was made using methods described in Example 20, except that the reaction was carried out using 1-methoxypentane-2,4-dione in place of ethyl 3-oxobutanoate:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found $M+1$	MS r.t.	LC/MS Method	NMR (shifts in ppm)
195	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-(methoxymethyl)pyridin-4(1 <i>H</i>)-one	447.147	448.5	2.05	Q	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.16 - 7.05 (m, 1H), 7.04 - 6.87 (m, 1H), 6.46 (s, 2H), 5.43 (d, $J = 11.2$ Hz, 1H), 4.40 (s, 2H), 4.15 (dd, $J = 11.3, 8.1$ Hz, 1H), 3.94 (d, $J = 2.4$ Hz, 3H), 3.38 (s, 3H), 2.82 (p, $J = 7.7$ Hz, 1H), 1.67 (s, 3H), 0.91 - 0.82 (m, 3H) ppm; NH pyridone not observed.

Example 21

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (196)



[0520] Step 1:

[0521] A solution of NaOEt (45 mL, 21 % w/v solution in ethanol, 139 mmol) was added dropwise over 10 min to a solution of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carbonitrile (17.443 g, 52.03 mmol) in ethanol (175 mL) (slight exotherm from 22 °C to 27 °C) and the reaction mixture was stirred at ambient temperature for 30 min. The mixture was quenched by dropwise addition of a saturated aqueous NH₄Cl solution (100 mL). The mixture was diluted with water (100 mL) and EtOAc (100 mL) and stirred for 20 min. The aqueous layer was separated and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (1 x 100 mL), passed through a Whatman[®] phase separation filter paper and concentrated *in vacuo* to give a pale yellow oily solid. The solid was triturated from MTBE to give (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboximidamide (Hydrochloride salt) (17.163 g, 85%) as a cream solid. ¹H NMR (400 MHz, DMSO-

d_6) δ 9.14 (s, 4H), 7.26 - 7.12 (m, 2H), 5.12 (d, J = 11.1 Hz, 1H), 4.26 - 4.14 (m, 1H), 3.96 (d, J = 2.2 Hz, 3H), 2.82 (p, J = 7.8 Hz, 1H), 1.65 (s, 3H), 0.77 - 0.62 (m, 3H) ppm. ^{19}F NMR (376 MHz, DMSO- d_6) δ -73.40, -137.32 (d, J = 22.1 Hz), -154.46 (d, J = 21.6 Hz) ppm. ESI-MS m/z calc. 352.121, found 353.6 ($M+1$) $^+$; Retention time: 0.80 minutes using LC/MS Method C.

[0522] Step 2:

[0523] A solution of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboximidamide (Hydrochloride salt) (13 g, 33.4 mmol) and methylacetoacetate (7.5 mL, 69.5 mmol) in EtOH (100 mL) was treated with NaOEt (22 mL, 21 % w/v solution in ethanol, 68 mmol) and heated at 80 °C for 2 h. The reaction mixture was cooled to ambient temperature, quenched by addition of a saturated aqueous NH_4Cl solution (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were passed through a Whatman[®] phase separation filter paper and concentrated *in vacuo*. Purification by flash chromatography (120 g SiO_2 , 0 to 100% EtOAc in heptane) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (**196**, 10.023 g, 68%). ^1H NMR (400 MHz, Methanol- d_4) δ 7.04 (ddd, J = 8.2, 5.7, 2.2 Hz, 1H), 6.94 (ddd, J = 10.0, 8.9, 7.5 Hz, 1H), 6.17 (s, 1H), 5.29 (d, J = 10.6 Hz, 1H), 4.49 (dd, J = 10.6, 8.2 Hz, 1H), 3.98 (dd, J = 3.8, 2.3 Hz, 3H), 2.85 (p, J = 7.7 Hz, 1H), 2.22 (s, 3H), 1.66 - 1.58 (m, 3H), 0.82 (dq, J = 7.3, 2.3 Hz, 3H) ppm; NH pyrimidine not observed. ^{19}F NMR (376 MHz, Methanol- d_4) δ -75.68 (d, J = 83.0 Hz), -138.79 - -140.21 (m), -155.68 - -156.80 (m) ppm. ESI-MS m/z calc. 418.132, found 419.0 ($M+1$) $^+$; Retention time: 0.99 minutes using LC/MS Method M.

[0524] The following compounds were made using methods described in Example 21 except that, in Step 2, different cyclisation partners were used in place of methylacetoacetate:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
197	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-isopropyl-6-methylpyrimidin-4(1 <i>H</i>)-one	460.179	462.0	3.71	A	^1H NMR (400 MHz, Chloroform- d) δ 10.20 (s, 1H), 7.17 (ddd, J = 8.4, 5.6, 2.2 Hz, 1H), 6.87 (td, J = 9.2, 7.4 Hz, 1H), 5.26 (d, J = 10.8 Hz, 1H), 4.10 (dd, J = 10.9, 8.4 Hz, 1H), 4.00 (d, J = 2.8 Hz, 3H), 3.07 (p, J = 7.0 Hz, 1H), 2.82 (p, J = 7.8 Hz, 1H), 2.24 (s, 3H), 1.72 (s, 3H), 1.30 (td, J = 6.7, 6.3, 2.9 Hz, 6H), 0.82 (dq, J = 7.4, 2.4 Hz, 3H) ppm.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
198	5-Chloro-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1 <i>H</i>)-one	452.093	453.1	2.62	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.23 (s, 1H), 7.17 (q, <i>J</i> = 9.0 Hz, 1H), 7.04 (t, <i>J</i> = 7.5 Hz, 1H), 5.25 (d, <i>J</i> = 10.7 Hz, 1H), 4.46 (dd, <i>J</i> = 10.8, 8.0 Hz, 1H), 3.94 (d, <i>J</i> = 2.1 Hz, 3H), 2.89 - 2.75 (m, 1H), 2.31 (s, 3H), 1.62 (s, 3H), 0.73 (d, <i>J</i> = 7.4 Hz, 3H) ppm.

[0525] The following compounds were made using methods described in Example 21 except that, in Step 2, different cyclisation partners were used in place of methylacetoacetate and NaOMe (solution in MeOH) was used in instead of NaOEt (solution in EtOH). In the case of **200**, Step 2 was carried out at 70 °C:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
199	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methoxy-6-methylpyrimidin-4(1 <i>H</i>)-one	448.142	449.5	3.14	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 12.81 (s, 1H), 7.16 (ddd, <i>J</i> = 10.1, 8.9, 7.6 Hz, 1H), 7.02 (ddd, <i>J</i> = 8.6, 5.7, 1.9 Hz, 1H), 5.21 (d, <i>J</i> = 10.9 Hz, 1H), 4.47 (dd, <i>J</i> = 10.9, 8.0 Hz, 1H), 3.95 (d, <i>J</i> = 1.9 Hz, 3H), 3.73 (s, 3H), 2.81 (p, <i>J</i> = 7.6 Hz, 1H), 2.13 (s, 3H), 1.61 (s, 3H), 0.72 (dd, <i>J</i> = 7.6, 2.4 Hz, 3H) ppm.
200	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-methylpyrimidin-4(1 <i>H</i>)-one	418.132	419.1	1.37	J	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 9.69-10.11 (br s, 1H), 7.63 (d, <i>J</i> = 0.9 Hz, 1H), 7.11-7.07 (m, 1H), 6.87 (td, <i>J</i> = 9.2, 7.3 Hz, 1H), 5.27 (d, <i>J</i> = 10.5 Hz, 1H), 4.01 (dd, <i>J</i> = 10.8, 8.5 Hz, 1H), 3.95 (d, <i>J</i> = 2.7 Hz, 3H), 2.77 (t, <i>J</i> = 8.0 Hz, 1H), 2.02 (d, <i>J</i> = 0.9 Hz, 3H), 1.66 (s, 3H), 0.79 (td, <i>J</i> = 4.8, 2.4 Hz, 3H) ppm.

[0526] The following compound was made using methods described in Example 21 except that, the conditions outlined below were used in Step 2:

[0527] *DBU Cyclisation*: A solution of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboximidamide (hydrochloride salt) (30 mg, 0.072

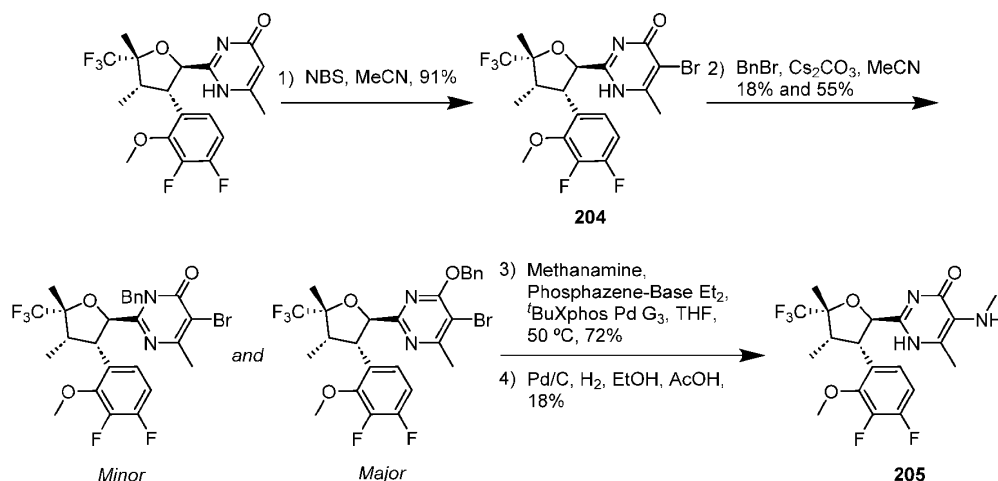
mmol), methyl (*E*)-3-methoxyacrylate (9 mg, 0.078 mmol) and DBU (30.5 mg, 30 μ L, 0.20 mmol) was stirred at 65 °C for 4 h. The mixture was partitioned between EtOAc (20 mL) and water (5 mL). The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (12 g C₁₈ column, 10 to 80% MeCN in water containing 0.1% formic acid) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)pyrimidin-4(1*H*)-one (**201**, 7 mg, 23%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 6.4 Hz, 1H), 7.10-7.06 (m, 1H), 6.87 (td, *J* = 9.3, 7.5 Hz, 1H), 6.30 (d, *J* = 6.9 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 4.05 (dd, *J* = 10.8, 8.5 Hz, 1H), 3.95 (d, *J* = 2.7 Hz, 3H), 2.78 (t, *J* = 7.8 Hz, 1H), 1.66 (s, 3H), 0.79 (td, *J* = 4.9, 2.3 Hz, 3H) ppm; NH pyrimidone not observed. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -74.3 (s, 3F), -136.7 (qd, *J* = 9.6, 5.7 Hz, 1F), -154.2--154.3 (m, 1F) ppm; ESI-MS *m/z* calc. 404.116, found 405.1 (M+1)⁺; Retention time: 1.18 minutes using LC/MS Method J.

[0528] The following compounds were made using methods described in Example 21, except that in Step 2, dimethyl 2-acetylsuccinate was used as the cyclisation partner in place of methylacetoacetate and NaOMe (solution in MeOH) was used in place of NaOEt (solution in EtOH). The reaction was carried out at 70 °C. A final amide coupling step was introduced using the conditions described in General Method M except that, in the case of **202**, methylamine was used as the amine coupling partner in place of ammonium chloride:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
202	2-(2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidin-5-yl)- <i>N</i> -methylacetamide	489.169	490.1	1.92	L	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 9.54 (br s, 1H), 7.15-7.11 (m, 1H), 6.86 (dd, <i>J</i> = 16.5, 9.2 Hz, 1H), 6.51 (br s, 1H), 5.27 (d, <i>J</i> = 11.0 Hz, 1H), 3.99-3.92 (m, 4H), 3.38 (s, 2H), 2.81-2.74 (m, 1H), 2.72 (d, <i>J</i> = 4.6 Hz, 3H), 2.29 (s, 3H), 1.64 (s, 3H), 0.82-0.76 (m, 3H) ppm.
203	2-(2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-Dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidin-5-yl)acetamide	475.153	476.1	1.33	J	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.15-7.11 (m, 1H), 6.86 (td, <i>J</i> = 9.2, 7.5 Hz, 1H), 6.51 (br s, 1H), 5.27 (d, <i>J</i> = 10.5 Hz, 1H), 5.13 (br s, 1H), 3.99-3.94 (m, 4H), 3.41 (s, 2H), 2.81-2.73 (m, 1H), 2.27 (s, 3H), 1.65 (s, 3H), 0.81-0.78 (m, 3H) ppm; NH pyrimidone not observed.

Example 22

5-Bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (**204**) and 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylamino)pyrimidin-4(1*H*)-one (**205**)



[0529] Step 1:

[0530] 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (**196**, 7.553 g, 17.15 mmol) was treated via the method described in General Method I, except that MeCN was used as the solvent instead of DCM, to give 5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (**204**, 8.201 g, 91%) as a foamy off-white solid. ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.04 (ddd, *J* = 8.1, 5.5, 2.1 Hz, 1H), 6.94 (ddd, *J* = 10.0, 8.8, 7.4 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 4.50 (dd, *J* = 10.6, 8.1 Hz, 1H), 3.99 (dd, *J* = 3.2, 2.2 Hz, 3H), 2.86 (p, *J* = 7.7 Hz, 1H), 2.41 (s, 3H), 1.69 - 1.59 (m, 4H), 0.83 (dq, *J* = 7.5, 2.3 Hz, 3H) ppm. ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -73.55 - -78.79 (m), -139.02 - -142.01 (m), -155.61 - -158.82 (m) ppm. ESI-MS *m/z* calc. 496.042, found 499.0 (M+1)⁺; 497.0 (M-1)⁻; Retention time: 0.79 minutes using LC/MS Method C.

[0531] Step 2:

[0532] 5-Bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1*H*)-one (8 g, 16.09 mmol) was treated via the method described in General Method K to give:

[0533] **Minor Product:** 3-Benzyl-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(3*H*)-one (1.693 g, 18%) a pale yellow oil, which solidified on standing. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.38 (d, *J* = 7.0

Hz, 3H), 7.24 - 7.21 (m, 2H), 6.40 - 6.31 (m, 1H), 6.15 (d, $J = 15.6$ Hz, 1H), 5.39 (t, $J = 6.7$ Hz, 1H), 5.24 (d, $J = 10.8$ Hz, 1H), 5.01 (d, $J = 15.6$ Hz, 1H), 4.71 (dd, $J = 10.8, 8.3$ Hz, 1H), 3.97 (d, $J = 2.0$ Hz, 3H), 2.67 (p, $J = 7.7$ Hz, 1H), 2.36 (s, 3H), 1.57 - 1.55 (m, 3H), 0.67 - 0.57 (m, 3H) ppm. ^{19}F NMR (376 MHz, Chloroform- d) δ -74.46, -137.61 (d, $J = 19.6$ Hz), -153.94 (d, $J = 19.7$ Hz) ppm. ESI-MS m/z calc. 586.089, found 587.1 ($M+1$) $^{+}$; Retention time: 1.28 minutes using LC/MS Method C.

[0534] Major product: 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (5.216 g, 55%) as a colourless oil. ^1H NMR (400 MHz, Chloroform- d) δ 7.48 - 7.30 (m, 5H), 6.93 (ddd, $J = 8.4, 5.7, 2.1$ Hz, 1H), 6.73 (td, $J = 9.3, 7.5$ Hz, 1H), 5.49 (d, $J = 2.7$ Hz, 2H), 5.44 (d, $J = 11.0$ Hz, 1H), 4.40 (dd, $J = 11.0, 7.4$ Hz, 1H), 3.94 (d, $J = 2.4$ Hz, 3H), 2.81 (p, $J = 7.5$ Hz, 1H), 2.56 (s, 3H), 1.73 - 1.66 (m, 3H), 0.91 - 0.86 (m, 3H) ppm. ^{19}F NMR (376 MHz, Chloroform- d) δ -74.60, -137.75 (d, $J = 19.6$ Hz), -154.66 (d, $J = 19.5$ Hz) ppm. ESI-MS m/z calc. 586.089, found 587.1 ($M+1$) $^{+}$; Retention time: 1.33 minutes using LC/MS Method C.

[0535] Step 3:

[0536] 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (60 mg, 0.102 mmol) and $t\text{BuXPhos Pd G3}$ (8.1 mg, 0.010 mmol) were added to a screw-top vial and the vessel was purged with nitrogen. A solution of methanamine (255 μL , 2 M solution in THF, 0.5 mmol) and phosphazene base $\text{P}_2\text{-Et}$ (84 μL , 0.25 mmol) in THF (1.2 mL) was added and the resulting mixture was flushed with nitrogen for an additional 2 min. The vial was sealed, and the mixture was stirred at 50 $^{\circ}\text{C}$ for 16 h. The mixture was cooled to ambient temperature and partitioned between EtOAc (10 mL) and a saturated NH_4Cl solution (10 mL). The aqueous layer was separated and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO_2 , 0 to 100% EtOAc in heptane) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethylpyrimidin-5-amine (45 mg, 72%). ESI-MS m/z calc. 537.205, found 539.4 ($M+1$) $^{+}$; 536.2 ($M-1$) $^{-}$; Retention time: 1.23 minutes using LC/MS method C.

[0537] Step 4:

[0538] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethylpyrimidin-5-amine (45 mg, 0.074 mmol) was treated via the method described in General Method C, except that a 1:1 mixture of EtOH and acetic acid was used as the solvent, to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methy lamino)pyrimidin-4(1*H*)-one (**205**, 6.2 mg, 18%) as a white solid. ^1H NMR (500 MHz, Acetonitrile- d_3) δ 9.93 (br s, 1H), 7.09 (ddd, $J = 8.5, 5.7, 2.2$ Hz, 1H), 6.97 (ddd, $J = 10.1, 8.9, 7.7$ Hz, 1H), 5.21 (d, $J = 10.9$ Hz, 1H), 4.34 (dd, $J =$

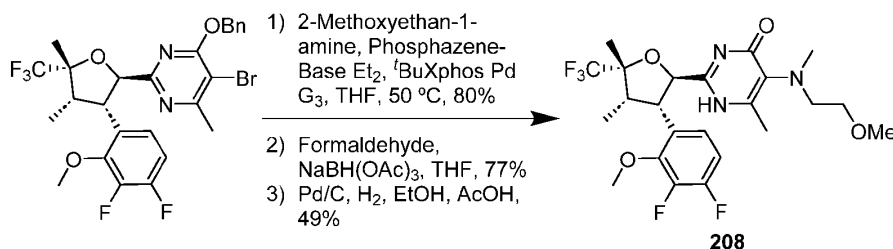
10.9, 8.2 Hz, 1H), 3.98 (d, $J = 2.2$ Hz, 3H), 2.83 (s, 4H), 2.21 (s, 3H), 1.65 (q, $J = 1.2$ Hz, 3H), 0.81 (dq, $J = 7.4$, 2.4 Hz, 3H) ppm; NH pyrimidone or amine not observed. ESI-MS m/z calc. 447.15814, found 448.9 (M+1)⁺; Retention time: 3.19 minutes using LC/MS Method C.

[0539] The following compounds were made using methods described in Example 22 except that in Step 3, different amine coupling partners were used in place of methanamine:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
206	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((2-methoxyethyl)amino)-6-methylpyrimidin-4(1 <i>H</i>)-one	491.184	493.2	3.25	A	¹ H NMR (500 MHz, Acetonitrile- <i>d</i> ₃) δ 7.10 (ddd, $J = 8.4$, 5.7, 2.2 Hz, 1H), 6.97 (ddd, $J = 10.2$, 8.9, 7.6 Hz, 1H), 5.21 (d, $J = 10.9$ Hz, 1H), 4.34 (dd, $J = 10.8$, 8.2 Hz, 2H), 3.97 (d, $J = 2.1$ Hz, 3H), 3.43 (dd, $J = 5.6$, 4.8 Hz, 2H), 3.30 (s, 5H), 2.95 - 2.77 (m, 1H), 2.17 (s, 4H), 1.66 (q, $J = 1.2$ Hz, 3H), 0.81 (dq, $J = 7.4$, 2.4 Hz, 3H) ppm.
207	5-(6-oxa-3-Azabicyclo[3.1.1]heptan-3-yl)-2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-4(1 <i>H</i>)-one	515.481	516.5	3.44	A	¹ H NMR (500 MHz, Methanol- <i>d</i> ₄) δ 7.06 (ddd, $J = 8.2$, 5.6, 2.1 Hz, 1H), 6.97 (td, $J = 9.3$, 7.4 Hz, 1H), 5.30 (d, $J = 10.7$ Hz, 1H), 4.61 - 4.57 (m, 2H), 4.52 (dd, $J = 10.8$, 8.2 Hz, 1H), 4.02 (d, $J = 2.2$ Hz, 3H), 3.79 (d, $J = 11.0$ Hz, 2H), 3.14 (dt, $J = 8.1$, 6.4 Hz, 1H), 3.02 - 2.97 (m, 2H), 2.87 (p, $J = 7.7$ Hz, 1H), 2.50 (d, $J = 8.2$ Hz, 1H), 2.32 (s, 3H), 1.66 (d, $J = 1.2$ Hz, 3H), 0.85 (dq, $J = 7.4$, 2.3 Hz, 3H) ppm; NH pyrimidone not observed.

Example 23

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((2-methoxyethyl)(methyl)amino)-6-methylpyrimidin-4(1*H*)-one (208)



[0540] Step 1:

[0541] 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2 Example 22**, 90 mg, 0.153 mmol) and ^tBuXPhos Pd G₃ (6 mg, 0.008 mmol) were added to a screw-top vial and the vessel was purged with nitrogen. A solution of 2-methoxyethan-1-amine (33 μL, 0.38 mmol) and phosphazene base P₂-Et (63 μL, 0.19 mmol) in THF (1.5 mL) was added and the resulting mixture was flushed with nitrogen for an additional 1 min. The vial was sealed, and the mixture was stirred at 50 °C for 16 h. The mixture was cooled to ambient temperature and partitioned between EtOAc (10 mL) and a saturated NH₄Cl solution (10 mL). The aqueous layer was separated and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (4 g SiO₂, 0 to 100% EtOAc in heptane) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-6-methylpyrimidin-5-amine (71 mg, 80%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.45 - 7.39 (m, 2H), 7.39 - 7.28 (m, 3H), 7.07 - 6.98 (m, 2H), 5.51 - 5.38 (m, 2H), 5.35 (d, *J* = 11.0 Hz, 1H), 4.50 (dd, *J* = 11.1, 7.3 Hz, 1H), 4.45 - 4.38 (m, 1H), 3.91 (d, *J* = 1.9 Hz, 3H), 3.29 (d, *J* = 3.1 Hz, 4H), 3.14 (s, 3H), 2.77 (p, *J* = 7.4 Hz, 1H), 2.31 (s, 3H), 1.57 (s, 3H), 0.85 - 0.68 (m, 3H) ppm. ESI-MS *m/z* calc. 581.2313, found 583.3 (M+1)⁺; Retention time: 1.24 minutes using LC/MS method C.

[0542] Step 2:

[0543] Formaldehyde (18 μL, 37 % w/w solution in water, 0.22 mmol) and NaBH(OAc)₃ (93 mg, 0.44 mmol) were successively added to a solution of 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-6-methylpyrimidin-5-amine (128 mg, 0.220 mmol) in THF (3.8 mL) and the reaction was stirred at ambient temperature for 16 h. Additional amounts of formaldehyde (18 μL, 0.65 mmol) and NaBH(OAc)₃ (93 mg, 0.44 mmol) were added and the mixture was stirred for a further 16 h. The last operation was repeated once more. The reaction mixture was quenched by dropwise addition of MeOH (2 mL) and stirred at ambient temperature for 30 min. The mixture was concentrated *in vacuo*.

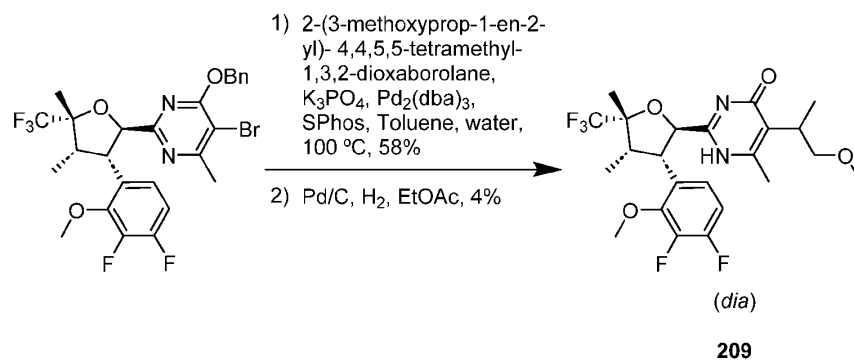
Purification by flash chromatography (12 g column, 0 to 100 % EtOAc in heptane) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-*N*,6-dimethylpyrimidin-5-amine (101 mg, 77%) as a white solid. ESI-MS *m/z* calc. 595.247, found 597.6 (M+1)⁺; Retention time: 1.3 minutes using LC/MS method C.

[0544] Step 3:

[0545] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*-(2-methoxyethyl)-*N*,6-dimethylpyrimidin-5-amine (100 mg, 0.1679 mmol) was treated via the method described in General Method C, except that a 1:1 mixture of EtOH and acetic acid was used as the solvent, to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((2-methoxyethyl)(methyl)amino)-6-methylpyrimidin-4(1*H*)-one (**208**, 43 mg, 49%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.72 (s, 1H), 7.32 (q, *J* = 9.1 Hz, 1H), 7.17 (ddd, *J* = 8.9, 5.8, 1.9 Hz, 1H), 5.35 (d, *J* = 10.9 Hz, 1H), 4.63 (dd, *J* = 11.0, 8.0 Hz, 1H), 4.09 (d, *J* = 1.8 Hz, 2H), 3.46 - 3.38 (m, 3H), 3.28 (s, 3H), 3.21 (t, *J* = 5.8 Hz, 2H), 2.96 (p, *J* = 7.6 Hz, 1H), 2.76 (s, 3H), 2.34 (s, 3H), 1.76 (s, 3H), 0.96 - 0.77 (m, 3H) ppm. ESI-MS *m/z* calc. 505.200, found 506.6 (M+1)⁺; 504.5 (M-1)⁻; Retention time: 3.60 minutes using LC/MS method A.

Example 24

dia-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-methoxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (**209**)



[0546] Step 1:

[0547] 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2, Example 22**, 60 mg, 0.096 mmol) and 2-(3-methoxyprop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (24.26 mg, 0.123 mmol) were treated via the method described in General Method F to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-

(trifluoromethyl)tetrahydrofuran-2-yl)-5-(3-methoxyprop-1-en-2-yl)-6-methylpyrimidine (32 mg, 58%), which was used without further purification in the next step. ESI-MS m/z calc. 578.220, found 579.6 (M+1)⁺; Retention time: 1.26 minutes using LC/MS Method C.

[0548] Step 2:

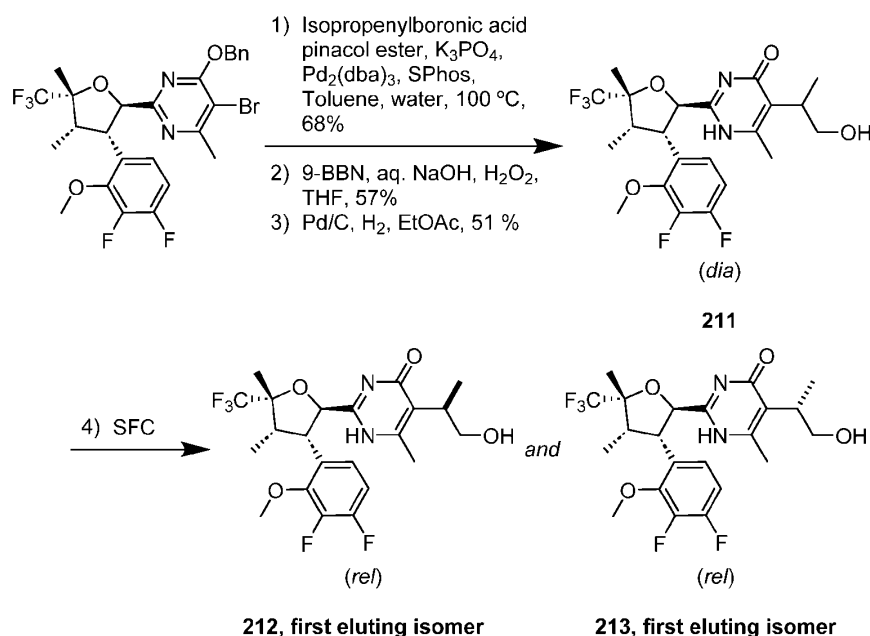
[0549] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(3-methoxyprop-1-en-2-yl)-6-methylpyrimidine was treated via the method described in General Method C, except that EtOAc was used as the solvent in place of EtOH, to give *dia*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-methoxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (**209**, 2 mg, 4%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.11 - 7.05 (m, 1H), 6.85 - 6.74 (m, 1H), 5.15 (d, J = 10.7 Hz, 1H), 3.98 - 3.84 (m, 3H), 3.77 (ddd, J = 45.3, 9.0, 7.9 Hz, 1H), 3.50 (ddd, J = 10.1, 9.0, 6.6 Hz, 1H), 3.22 (s, 3H), 3.07 - 2.96 (m, 1H), 2.71 (p, J = 7.7 Hz, 1H), 2.10 (d, J = 17.9 Hz, 3H), 1.59 - 1.55 (m, 3H), 1.20 - 1.14 (m, 3H), 0.72 (ddq, J = 6.9, 4.6, 2.2 Hz, 3H) ppm; NH pyrimidone not observed. ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -72.81 - -76.77 (m), -136.97 - -137.33 (m), -154.54 - -154.84 (m) ppm. ESI-MS m/z calc. 490.189, found 491.6 (M+1)⁺; 489.4 (M-1)⁻; Retention time: 3.60 minutes using LC/MS Method A.

[0550] The following compound was made using methods described in Example 24 except that 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was used in Step 1 in place of 2-(3-methoxyprop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. In Step 2, Et₃SiH (20 eq.) was used in place of hydrogen and methanol used as solvent in place of EtOAc:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
210	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(pyridin-3-yl)pyrimidin-4(1 <i>H</i>)-one	495.450	496.5	3.08	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 12.97 (s, 1H), 8.52 (dd, J = 4.8, 1.6 Hz, 1H), 8.46 (d, J = 1.6 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.42 (dd, J = 7.5, 5.1 Hz, 1H), 7.22 - 7.17 (m, 1H), 7.10 - 7.07 (m, 1H), 5.28 (d, J = 10.9 Hz, 1H), 4.56 (dd, J = 10.8, 8.0 Hz, 1H), 3.97 (d, J = 1.9 Hz, 3H), 2.85 (dt, J = 15.3, 7.7 Hz, 1H), 2.09 (s, 3H), 1.64 (s, 3H), 0.74 (d, J = 6.9 Hz, 3H) ppm.

Example 25

dia-2-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (211), *rel*-2-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((*R*)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (212) and *rel*-2-((2*R**,3*S**,4*S**,5*R**)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((*S*)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (213)



[0551] Step 1:

[0552] 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (Product of Step 2 Example 22, 710 mg, 1.21 mmol) and isopropenylboronic acid pinacol ester (230 μL, 1.22 mmol) were treated via the method described in General Method F to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(prop-1-en-2-yl)pyrimidine (450 mg, 68%), which was used without further purification in the next step. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.40 - 7.29 (m, 5H), 6.96 (ddd, *J* = 8.3, 5.5, 2.1 Hz, 1H), 6.78 - 6.66 (m, 1H), 5.53 - 5.39 (m, 3H), 5.28 (p, *J* = 1.6 Hz, 1H), 4.84 (dt, *J* = 1.9, 1.0 Hz, 1H), 4.49 (dd, *J* = 10.9, 7.4 Hz, 1H), 3.95 (d, *J* = 2.5 Hz, 3H), 2.82 (p, *J* = 7.5 Hz, 1H), 2.38 (s, 3H), 1.93 (dd, *J* = 1.5, 1.0 Hz, 3H), 1.69 (d, *J* = 1.1 Hz, 3H), 0.87 - 0.81 (m, 3H) ppm. ¹⁹F NMR (471 MHz, Chloroform-*d*) δ

-74.57, -136.28 - -140.46 (m), -152.18 - -157.66 (m) ppm. ESI-MS m/z calc. 548.210, found 549.5 (M+1)⁺; Retention time: 1.34 minutes using LC/MS Method C.

[0553] Step 2:

[0554] 9-BBN (2.8 mL, 0.5 M in THF, 1.4 mmol) was added to a stirring solution of 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(prop-1-en-2-yl)pyrimidine (50 mg, 0.091 mmol) in THF (2.5 mL) at ambient temperature under nitrogen. The reaction mixture was heated at 45 °C for 12 h. Upon reaction completion, the mixture was cooled to 0 °C, quenched by addition of a 1 M NaOH solution (1 mL) and stirred for 30 min. H₂O₂ (1 mL, 30 % w/w aqueous solution, 32.6 mmol) was added, and the mixture was stirred for 30 min at ambient temperature. The mixture was diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100% EtOAc in heptane) gave *dia*-2-(4-(benzyloxy)-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)propan-1-ol (30 mg, 57%) which was used in the next step without further purification. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.39 - 7.32 (m, 5H), 6.97 (dtd, *J* = 7.7, 5.3, 2.1 Hz, 1H), 6.75 (tdd, *J* = 9.2, 7.4, 1.6 Hz, 1H), 5.52 - 5.38 (m, 3H), 4.48 (ddd, *J* = 11.7, 7.3, 5.3 Hz, 1H), 3.96 (dd, *J* = 4.8, 2.5 Hz, 3H), 3.88 (dddd, *J* = 10.8, 8.2, 5.4, 3.0 Hz, 1H), 3.76 (dtd, *J* = 10.5, 6.6, 1.2 Hz, 1H), 3.28 - 3.17 (m, 1H), 2.82 (p, *J* = 7.5 Hz, 1H), 2.48 (s, 3H), 1.69 (dd, *J* = 3.9, 1.1 Hz, 3H), 1.20 (dd, *J* = 7.1, 0.8 Hz, 3H), 0.84 (dt, *J* = 7.4, 2.4 Hz, 3H) ppm; OH alcohol not observed. ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -74.56, -135.97 - -141.22 (m), -154.39 - -155.68 (m) ppm. ESI-MS m/z calc. 566.220, found 567.6 (M+1)⁺; Retention time: 4.05 minutes using LC/MS Method A.

[0555] Step 3:

[0556] *dia*-2-(4-(Benzyloxy)-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)propan-1-ol (30 mg) was treated via the method described in General Method C, except that EtOAc was used as the solvent in place of EtOH, to give *dia*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (**211**, 23 mg, 51%) as a mixture of epimers. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.12 (ddd, *J* = 8.1, 5.5, 2.2 Hz, 1H), 6.90 - 6.81 (m, 1H), 5.26 (dd, *J* = 10.8, 2.4 Hz, 1H), 4.05 (dt, *J* = 10.8, 8.5 Hz, 1H), 3.99 (dd, *J* = 2.8, 1.4 Hz, 3H), 3.91 (td, *J* = 11.3, 6.9 Hz, 1H), 3.81 (dd, *J* = 11.1, 3.7 Hz, 1H), 3.06 - 2.98 (m, 1H), 2.84 - 2.74 (m, 1H), 2.22 (d, *J* = 0.9 Hz, 3H), 1.65 (s, 3H), 1.28 - 1.25 (m, 3H), 0.80 (dp, *J* = 6.4, 2.1 Hz, 3H) ppm; OH alcohol and NH pyrimidone not observed. ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -74.50, -137.04 (dt, *J* = 31.0, 9.3 Hz), -154.60 (t, *J* = 23.3 Hz) ppm. ESI-MS m/z calc. 476.173, found 477.5 (M+1)⁺; 475.4 (M-1)⁻; Retention time: 3.23 minutes using LC/MS Method A.

[0557] Step 4:

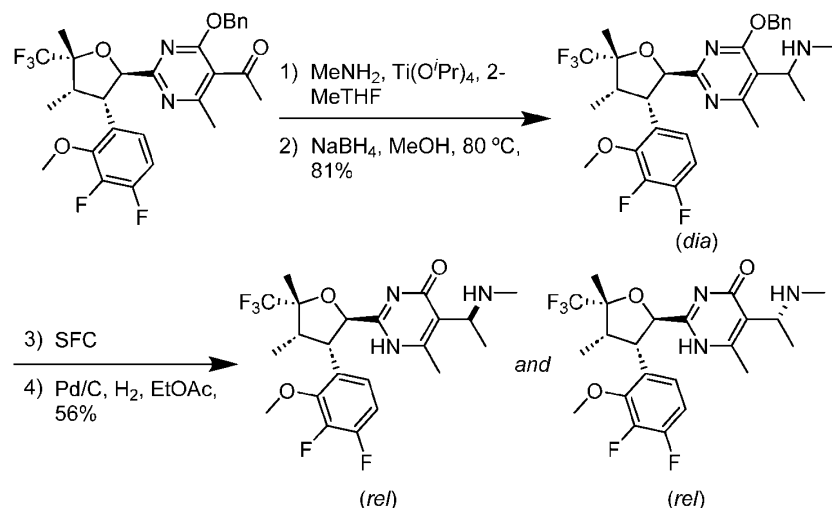
[0558] The epimers of *dia*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (**210**, 23 mg) were separated by chiral SFC using a Chiralpak[®] IG column, 5 μm particle size, 25 cm x 10 mm form Daicel Corporation:

[0559] First eluting isomer (rt = 3.31 min): *rel*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((*R*)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (**212**, 5.7 mg, 13%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.45 (s, 1H), 7.20 - 7.12 (m, 1H), 7.01 (ddd, *J* = 8.5, 5.7, 1.9 Hz, 1H), 5.19 (d, *J* = 11.0 Hz, 1H), 4.50 (dd, *J* = 11.0, 7.9 Hz, 2H), 3.95 (d, *J* = 1.8 Hz, 3H), 3.68 (d, *J* = 10.9 Hz, 1H), 3.51 (dt, *J* = 10.2, 5.2 Hz, 1H), 2.88 (q, *J* = 7.0 Hz, 1H), 2.81 (p, *J* = 7.7 Hz, 1H), 2.21 (s, 3H), 1.61 (s, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.73 - 0.68 (m, 3H) ppm. ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ -73.27, -137.60 - -137.96 (m), -154.49 (d, *J* = 29.0 Hz) ppm. ESI-MS *m/z* calc. 476.173, found 477.3 (M+1)⁺; 475.2 (M-1)⁻; Retention time: 3.16 minutes using LC/MS Method A.

[0560] Second eluting isomer (rt = 4.03 min): *rel*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-((*S*)-1-hydroxypropan-2-yl)-6-methylpyrimidin-4(1*H*)-one (**213**, 6.3 mg, 15%). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.44 (s, 1H), 7.16 (q, *J* = 8.9 Hz, 1H), 7.02 (ddd, *J* = 8.7, 5.8, 1.9 Hz, 1H), 5.19 (d, *J* = 11.0 Hz, 1H), 4.51 (dd, *J* = 11.1, 8.0 Hz, 2H), 3.95 (d, *J* = 1.8 Hz, 3H), 3.73 - 3.64 (m, 1H), 3.51 (dt, *J* = 10.7, 5.7 Hz, 1H), 2.88 (d, *J* = 6.8 Hz, 1H), 2.81 (p, *J* = 7.7 Hz, 1H), 2.21 (s, 3H), 1.61 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.78 - 0.60 (m, 3H) ppm. ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ -73.27, -136.81 - -139.09 (m), -154.46 (d, *J* = 29.2 Hz) ppm. ESI-MS *m/z* calc. 476.173, found 477.2 (M+1)⁺; 475.2 (M-1)⁻; Retention time: 3.16 minutes using LC/MS Method A.

Example 26

rel-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-((*S*)-1-(methylanino)ethyl)pyrimidin-4(1*H*)-one (214) and *rel*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-((*R*)-1-(methylanino)ethyl)pyrimidin-4(1*H*)-one (215)



214, first eluting isomer

215, second eluting isomer

[0561] Step 1:

[0562] 1-(4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)ethan-1-one (Step 2 product in synthesis of 173 and 174, 36 mg, 0.065 mmol) was dissolved in 2-MeTHF (1.0 mL) before addition of Ti(OiPr)₄ (50 μ L, 0.169 mmol). The reaction mixture was stirred at ambient temperature for 10 min after which, MeNH₂ (170 μ L, 2 M solution in THF, 0.34 mmol) was added and the mixture was stirred at ambient temperature for 4 h. The mixture was poured over water (5 mL) and diluted with EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give 1-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-imine as a colourless oil, which was used without further purification in the next step.

[0563] Step 2:

[0564] 1-(4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-imine was dissolved in MeOH (1 mL) and NaBH₄ (50 mg, 1.3 mmol) was added in one portion. The reaction mixture was

heated to 80 °C and stirred for 24 h. The mixture was poured over water (5 mL) and diluted with EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale yellow oil. The oil was dissolved in MeOH and loaded onto a 2-g SCX-2 cartridge, washing with MeOH (20 mL) before eluting the desired product with NH₃ (20 mL, 2 M solution in MeOH). The basic eluent was concentrated *in vacuo* to give *dia*-1-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-amine (30.0 mg, 81%) as a mixture of epimers, which was used in the next step without further purification.

[0565] Step 3:

[0566] The diastereoisomers of *dia*-1-(4-(benzyloxy)-2-((2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-amine (30.0 mg, 81%) were separated by chiral SFC using a Chiralpak[®] IG column, 5 μm particle size, 25 cm x 10 mm from Daicel Corporation:

[0567] First eluting isomer (r.t. = 3.35 min): *rel*-(*S*)-1-(4-(benzyloxy)-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-amine (9 mg, 49%). ESI-MS *m/z* calc. 565.236, found 566.2 (M+1)⁺; Retention time: 3.99 minutes using LC/MS Method A.

[0568] Second eluting isomer (r.t. = 3.96 min): *rel*-(*R*)-1-(4-(benzyloxy)-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-amine (10 mg, 54%). ESI-MS *m/z* calc. 565.236, found 566.2 (M+1)⁺; Retention time: 4.00 minutes using LC/MS Method A.

[0569] Step 4:

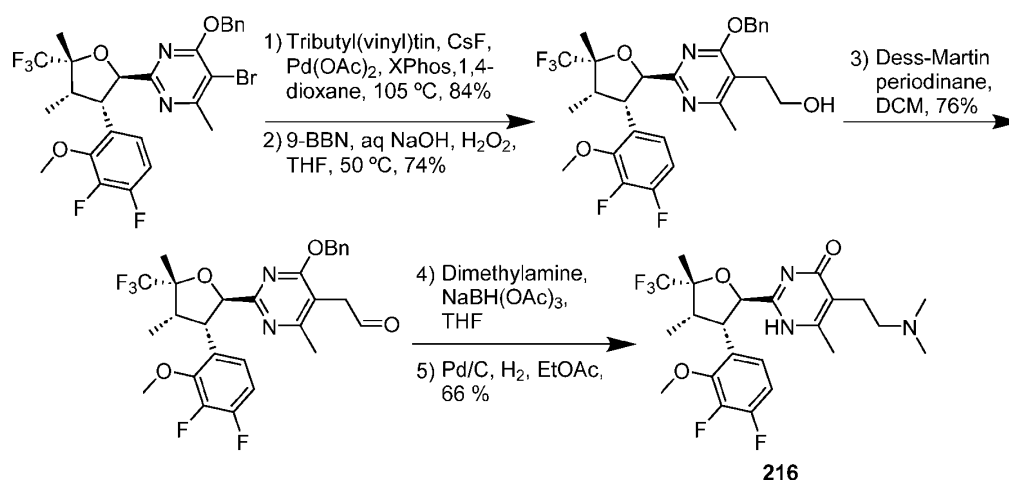
[0570] *rel*-(*S*)-1-(4-(Benzyloxy)-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-amine (9 mg, 0.016 mmol) was treated via the method described in General Method C except that EtOAc was used as the solvent in place of EtOH. Purification by reverse phase HPLC (C₁₈ X-bridge column, 38 to 53% MeCN in H₂O containing 0.1% NH₄OH) gave *rel*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-((*S*)-1-(methylamino)ethyl)pyrimidin-4(1*H*)-one (**214**, 4.2 mg, 56%). ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.01 - 6.98 (m, 1H), 6.89 - 6.82 (m, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.55 (dd, *J* = 11.0, 7.9 Hz, 1H), 4.26 (q, *J* = 6.8 Hz, 1H), 3.98 (d, *J* = 2.2 Hz, 3H), 2.84 (dq, *J* = 7.9, 7.6 Hz, 1H), 2.51 (s, 3H), 2.27 (s, 3H), 1.64 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H), 0.83 - 0.79 (m, 3H) ppm; NH amine and pyrimidone not observed. ¹⁹F NMR (471 MHz, Methanol-*d*₄) δ -75.67, -140.93, -157.41 ppm. ESI-MS *m/z* calc. 475.189, found 476.5 (M+1)⁺; 474.4 (M-1)⁻; Retention time: 2.78 minutes using LC/MS Method A.

[0571] *rel*-(*R*)-1-(4-(Benzyloxy)-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N*-methylethan-1-amine

(10 mg, 0.018 mmol) was treated via the method described in General Method C except that EtOAc was used as the solvent in place of EtOH. Purification by reverse phase HPLC (C₁₈ X-bridge column, 38 to 53% MeCN in H₂O containing 0.1% NH₄OH) *rel*-2-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-((*R*)-1-(methylamino)ethyl)pyrimidin-4(1*H*)-one (**215**, 4.7 mg, 55%). ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.04 - 7.00 (m, 1H), 6.90 - 6.84 (m, 1H), 5.24 (d, *J* = 11.0 Hz, 1H), 4.56 (dd, *J* = 11.0, 7.9 Hz, 1H), 4.28 (q, *J* = 6.7 Hz, 1H), 4.00 (d, *J* = 2.2 Hz, 3H), 2.86 (dq, *J* = 7.9, 7.6 Hz, 1H), 2.50 (s, 3H), 2.29 (s, 3H), 1.66 (s, 3H), 1.53 (d, *J* = 6.7 Hz, 3H), 0.85 - 0.81 (m, 3H) ppm; NH amine and pyrimidone not observed. ¹⁹F NMR (471 MHz, Methanol-*d*₄) δ -75.68, -140.95, -157.42 ppm. ESI-MS *m/z* calc. 475.189, found 476.5 (M+1)⁺; 474.4 (M-1)⁻; Retention time: 2.79 minutes using LC/MS Method A.

Example 27

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-(dimethylamino)ethyl)-6-methylpyrimidin-4(1*H*)-one (**216**)



[0572] Step 1:

[0573] 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2, Example 25**, 1.2 g, 2.04 mmol) was treated via the method described in General Method L Step 1, except that tributyl(vinyl)stannane was used as the Stille coupling partner in place of tributyl(1-ethoxyvinyl)stannane to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-vinylpyrimidine (920 mg, 84%). ESI-MS *m/z* calc. 534.194, found 536.6 (M+1)⁺; Retention time: 1.31 minutes using LC/MS Method C.

[0574] Step 2:

[0575] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-vinylpyrimidine (920 mg, 1.72 mmol) was treated via the method described in Example 29 Step 2, except that the reaction was carried out at 50 °C for 2 h. to give 2-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)ethan-1-ol (700 mg, 74%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.39 - 7.29 (m, 5H), 6.97 (ddd, *J* = 8.2, 5.5, 2.2 Hz, 1H), 6.74 (ddd, *J* = 9.6, 8.9, 7.5 Hz, 1H), 5.47 - 5.39 (m, 3H), 4.48 (dd, *J* = 11.0, 7.3 Hz, 1H), 3.95 (d, *J* = 2.4 Hz, 3H), 3.75 (tdd, *J* = 6.8, 5.6, 1.8 Hz, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.82 (p, *J* = 7.5 Hz, 1H), 2.46 (s, 3H), 1.69 (d, *J* = 1.1 Hz, 3H), 0.84 (dq, *J* = 7.4, 2.4 Hz, 3H) ppm; OH alcohol and NH pyrimidine not observed. ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -74.57, -136.66 - -140.00 (m), -152.86 - -159.03 (m) ppm. ESI-MS *m/z* calc. 552.205, found 554.3 (M+1)⁺; Retention time: 1.15 minutes using LC/MS Method C.

[0576] Step 3:

[0577] 2-(4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)ethan-1-ol (100 mg, 0.181 mmol) was dissolved in DCM (2.0 mL) and Dess-Martin periodinane (154 mg, 0.363 mmol) was added in one portion. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was diluted with water (20 mL) and poured over a mixture containing a saturated Na₂S₂O₃ solution (10 mL) and MTBE (30 mL). The aqueous layer was separated and extracted with MTBE (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a cloudy oil (145 mg). Purification by flash column chromatography (12 g SiO₂, 0 to 100% EtOAc in heptane) gave 2-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)acetaldehyde (114 mg, 76%) as a colourless oil. ESI-MS *m/z* calc. 550.189, found 551.6 (M+1)⁺; 549.5 (M-1)⁻; Retention time: 4.10 minutes using LC/MS Method C.

[0578] Step 4:

[0579] 2-(4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)acetaldehyde (46 mg, 0.055 mmol) was dissolved in THF (500 μL) before addition of dimethylamine (110 μL, 2 M solution in THF, 0.22 mmol) and STAB (35 mg, 0.165 mmol). The resulting mixture was stirred at ambient temperature for 8 days. The mixture was poured over a saturated NaHCO₃ solution (10 mL) and diluted with MTBE (10 mL). The aqueous layer was separated and extracted with MTBE (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give 2-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N,N*-dimethylethan-1-amine as a colourless oil, which was used in the next step without further purification.

[0580] Step 5:

[0581] 2-(4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)-*N,N*-dimethylethan-1-amine was treated via the method described in General Method C, except that EtOAc was used as the solvent in place of EtOH. Purification by preparative reverse phase HPLC (C₁₈ column, MeCN in water containing 0.05% TFA) to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-(dimethylamino)ethyl)-6-methylpyrimidin-4(1*H*)-one (trifluoroacetate salt) (**216**, 23.0 mg, 66%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.83 (s, 1H), 9.38 (s, 1H), 7.20 - 7.15 (m, 1H), 7.06 - 7.01 (m, 1H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.49 (dd, *J* = 11.0, 8.0 Hz, 1H), 3.94 (d, *J* = 2.0 Hz, 3H), 3.13 - 3.06 (m, 2H), 2.84 - 2.80 (m, 6H), 2.77 - 2.72 (m, 2H), 2.24 (s, 3H), 1.61 (s, 3H), 0.75 - 0.70 (m, 3H) ppm. ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -73.40, -137.90, -154.63 ppm. ESI-MS *m/z* calc. 489.205, found 490.6 (M+1)⁺; 488.5 (M-1)⁻; Retention time: 3.04 minutes using LC/MS Method C.

[0582] The following compound was made using methods described in Example 27 except that Steps 3 and 4 were omitted:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
217	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxyethyl)-6-methylpyrimidin-4(1 <i>H</i>)-one	462.158	463.5	3.04	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.19 - 7.13 (m, 1H), 7.04 - 7.00 (m, 1H), 5.19 (d, <i>J</i> = 10.9 Hz, 1H), 4.49 (dd, <i>J</i> = 10.9, 8.0 Hz, 1H), 3.94 (d, <i>J</i> = 1.9 Hz, 3H), 3.43 (t, <i>J</i> = 6.9 Hz, 2H), 2.80 (dq, <i>J</i> = 8.0, 6.3 Hz, 1H), 2.53 (t, <i>J</i> = 6.9 Hz, 3H), 2.20 (s, 3H), 1.61 (s, 3H), 0.71 (d, <i>J</i> = 6.3 Hz, 3H) ppm; NH pyrimidone not observed.

[0583] The following compound was made using methods described in Example 27 except that the conditions used in Step 1 were those described in Example 6 Step 3, using vinylboronic acid pinacol ester as the Suzuki coupling partner in place of 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane. Step 2 was carried out at ambient temperature. Steps 3 and 4 were omitted. An additional alkylation step was introduced before Step 5, as outlined below:

[0584] *Alkylation:* Sodium hydride (2 mg, 60% dispersion in mineral oil, 0.05 mmol) was added to a stirring suspension of 2-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)ethan-1-ol (20 mg, 0.036 mmol) in DMF (400 μL) and the reaction mixture was stirred at ambient temperature for 30 min. MeI (10 μL, 0.16 mmol) was added and the mixture stirred at 80 °C for 30 min. The reaction mixture was cooled to ambient temperature. Purification by flash chromatography gave 4-(benzyloxy)-2-

((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-methoxyethyl)-6-methylpyrimidine (12 mg, 59%). ESI-MS *m/z* calc. 566.220, found 567.6 (M+1)⁺; Retention time: 1.29 minutes using LC/MS Method C.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
218	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-methoxyethyl)-6-methylpyrimidin-4(1 <i>H</i>)-one	476.173	477.5	3.4	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.14 (ddd, <i>J</i> = 8.3, 5.5, 2.2 Hz, 1H), 6.86 (td, <i>J</i> = 9.3, 7.5 Hz, 1H), 5.24 (d, <i>J</i> = 10.8 Hz, 1H), 4.01 (dd, <i>J</i> = 10.8, 8.3 Hz, 1H), 3.97 (d, <i>J</i> = 2.7 Hz, 3H), 3.50 (qt, <i>J</i> = 9.2, 6.8 Hz, 2H), 3.31 (s, 3H), 2.83 - 2.70 (m, 3H), 2.20 (s, 3H), 1.65 (d, <i>J</i> = 1.2 Hz, 3H), 0.80 (dq, <i>J</i> = 7.4, 2.3 Hz, 3H) ppm; NH pyrimidine not observed.

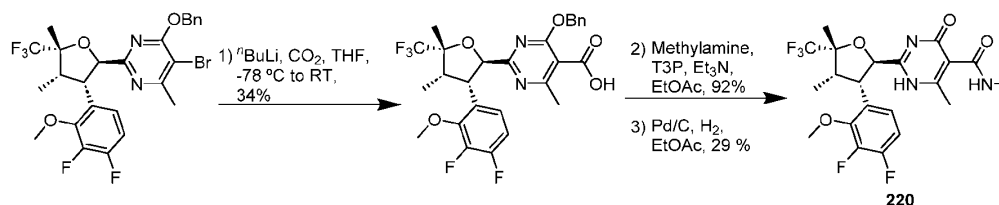
[0585] The following compound was made using methods described in Example 27 except that, Step 4 was replaced by a Grignard reaction, as outlined below:

[0586] *Grignard reaction:* 2-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)acetaldehyde (68 mg, 0.082 mmol) was dissolved in THF (1 mL) and cooled to -78 °C. MeMgBr (35 µL, 3 M solution in Et₂O, 0.11 mmol) was added dropwise and the mixture was stirred at -78 °C for 20 min. Another portion of MeMgBr (35 µL, 3 M solution in Et₂O, 0.11 mmol) was added and the reaction mixture stirred at -78 °C for 40 min. The mixture was quenched at -78 °C by dropwise addition of a saturated aqueous NH₄Cl solution (5 mL) and warmed to ambient temperature. The mixture was diluted with water (10 mL) and MTBE (10 mL). The aqueous layer was separated and extracted with MTBE (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a colourless oil to give 1-(4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)propan-2-ol.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
219	<i>dia</i> -2-((2 <i>R</i> [*] ,3 <i>S</i> [*] ,4 <i>S</i> [*] ,5 <i>R</i> [*])-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxypropyl)-6-methylpyrimidin-4(1 <i>H</i>)-one	476.173	477.2	3.16	A	

Example 28

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethyl-4-oxo-1,4-dihydropyrimidine-5-carboxamide (**220**)



[0587] Step 1:

[0588] *t*BuLi (105 μ L, 1.6 M solution in hexanes, 0.17 mmol) was added dropwise over 5 min to a stirring solution of 4-(benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2, Example 22**, 104 mg, 0.177 mmol) in THF (2 mL) at -78 °C under nitrogen and the reaction mixture was stirred for 15 min. THF-washed CO₂ pellets (2.14 g, 48.63 mmol) were added to the mixture and the suspension was stirred at -78 °C under nitrogen for 10 min. The mixture was quenched by addition of water (2 mL), warmed to ambient temperature and further diluted with water (8 mL). The aqueous layer was separated and extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a pale orange oil. Purification by flash column chromatography (SiO₂, 0 to 100 % EtOAc in heptane, then isocratic run with 1:1 EtOAc in 95:5 EtOAc:AcOH) gave 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine-5-carboxylic acid (34 mg, 34%) as a white solid. ESI-MS *m/z* calc. 552.168, found 551.5 (M-1)⁻; Retention time: 0.78 minutes using LC/MS Method C.

[0589] Step 2:

[0590] To a stirring a solution of 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine-5-

carboxylic acid (17 mg, 0.030 mmol) and Et₃N (16 μ L, 0.115 mmol) in EtOAc (0.75 mL) was added T3P (35 μ L, 0.12 mmol) in one portion and the reaction mixture was stirred at ambient temperature under nitrogen for 25 min. Methylamine (30 μ L, 2 M solution in THF, 0.06 mmol) was added in one portion and the reaction mixture was stirred at ambient temperature under nitrogen for 2 h. Additional amounts of T3P (35 μ L, 0.12 mmol) and methylamine (30 μ L, 2 M solution in THF, 0.06 mmol) were added and the reaction mixture was stirred at ambient temperature for 15 h. The mixture was diluted with water (5 mL) and a saturated NaHCO₃ solution (5 mL). The aqueous layer was separated and extracted with DCM (2 x 10 mL). The combined organic extracts were passed through a phase separation cartridge and concentrated *in vacuo* to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethylpyrimidine-5-carboxamide (20 mg, 92%) as an orange gum. ESI-MS *m/z* calc. 565.200, found 566.6 (M+1)⁺; Retention time: 1.12 minutes using LC/MS Method C.

[0591] Step 3:

[0592] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethylpyrimidine-5-carboxamide (20 mg, 0.035 mmol) was treated via the method described in General Method C. Purification by preparative reverse phase HPLC (C₁₈ X-bridge column, 47.4 to 97.4% MeCN in H₂O containing 1% TFA) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-*N*,6-dimethyl-4-oxo-1,4-dihydropyrimidine-5-carboxamide (**220**, 5 mg, 29%) as an off-white solid. ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.05 (ddd, *J* = 8.2, 5.5, 2.1 Hz, 1H), 7.02 - 6.94 (m, 1H), 5.31 (d, *J* = 10.5 Hz, 1H), 4.50 (dd, *J* = 10.6, 8.2 Hz, 1H), 3.99 (d, *J* = 2.3 Hz, 3H), 2.85 (s, 4H), 2.38 (s, 3H), 1.64 (d, *J* = 1.3 Hz, 3H), 0.84 (dq, *J* = 7.4, 2.3 Hz, 3H) ppm; NH amide and pyrimidone not observed. ESI-MS *m/z* calc. 475.153, found 476.5 (M+1)⁺; 474.4 (M-1)⁻; Retention time: 2.60 minutes using LC/MS Method A.

[0593] The following compound was made using methods described in Example 28 except that Step 2 was omitted. In Step 3, MeOH was used as the solvent in place of EtOAc:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
221	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylic acid (Trifluoroacetate salt)	462.121	463.5	2.63	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.40 (s, 2H), 7.26 - 7.12 (m, 1H), 7.12 - 7.04 (m, 1H), 5.35 (d, <i>J</i> = 10.4 Hz, 1H), 4.50 (dd, <i>J</i> = 10.5, 8.0 Hz, 1H), 3.95 (d, <i>J</i> = 2.0 Hz, 3H), 2.85 (p, <i>J</i> = 7.6 Hz, 1H), 2.47 (s, 3H), 1.62 (s, 3H), 0.75 (dt, <i>J</i> = 7.6, 2.5 Hz, 3H) ppm.

[0594] The following compound was made using a similar method to that described in Example 28 except that, the conditions used in Step 2 were those described in General Method M using TBTU as the coupling agent in place of HATU and ammonium hydroxide as the amine coupling partner in place of ammonium chloride. In Step 3, MeOH was used as the solvent in place of EtOAc:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
222	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxamide	461.137	462.2	2.49	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.97 (s, 1H), 7.97 (s, 1H), 7.43 (s, 1H), 7.17 (ddd, <i>J</i> = 10.0, 8.9, 7.6 Hz, 1H), 7.05 (ddd, <i>J</i> = 8.6, 5.7, 2.0 Hz, 1H), 5.26 (d, <i>J</i> = 10.8 Hz, 1H), 4.50 (dd, <i>J</i> = 10.8, 7.9 Hz, 1H), 3.95 (d, <i>J</i> = 2.0 Hz, 3H), 2.83 (t, <i>J</i> = 7.6 Hz, 1H), 2.29 (s, 3H), 1.63 (s, 3H), 0.73 (dt, <i>J</i> = 7.5, 2.5 Hz, 3H) ppm.

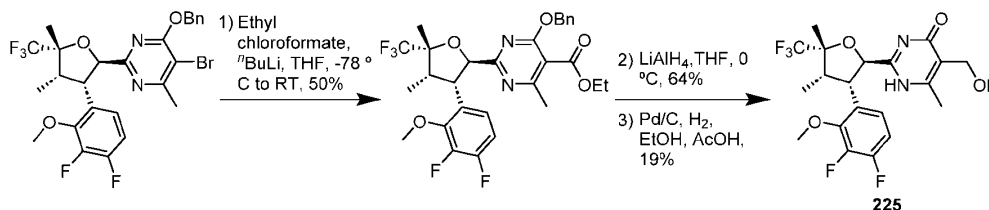
[0595] The following compounds were made using methods described in Example 28 except that Step 2 was replaced by an esterification step, using the conditions described in General Method J using different alkylating agents in place of benzyl bromide. The reaction was carried out at 110 °C in THF as the solvent in place of DMF. In Step 3, MeOH was used as the solvent in place of EtOAc:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
223	2-Hydroxyethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate (Trifluoroacetate salt)	506.148	507.6	2.72	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 13.19 (s, 1H), 7.25 - 7.13 (m, 1H), 7.06 (ddd, <i>J</i> = 8.7, 5.8, 2.0 Hz, 1H), 5.27 (d, <i>J</i> = 10.7 Hz, 1H), 4.47 (dd, <i>J</i> = 10.7, 8.0 Hz, 1H), 4.21 (dd, <i>J</i> = 5.7, 4.3 Hz, 2H), 3.95 (d, <i>J</i> = 2.1 Hz, 3H), 3.62 (dd, <i>J</i> = 5.8, 4.2 Hz, 2H), 3.50 (br s, 2H), 2.84 (t, <i>J</i> = 7.7 Hz, 1H), 2.21 (s, 3H), 1.63 (s, 3H), 0.74 (dd, <i>J</i> = 7.9, 2.7 Hz, 3H) ppm.

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
224	2-(Dimethylamino)ethyl 2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate (Trifluoroacetate salt)	533.195	535.2	2.89	A	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.83 (s, 1H), 7.18 (ddd, <i>J</i> = 10.0, 8.9, 7.5 Hz, 1H), 7.07 (ddd, <i>J</i> = 8.7, 5.8, 1.9 Hz, 1H), 5.30 (d, <i>J</i> = 10.7 Hz, 1H), 4.56 - 4.52 (m, 2H), 4.48 (dd, <i>J</i> = 10.7, 7.9 Hz, 1H), 3.96 (d, <i>J</i> = 2.0 Hz, 3H), 3.75 (br s, 1H), 2.84 (t, <i>J</i> = 7.7 Hz, 1H), 3.52 - 3.42 (m, 2H), 2.84 (s, 6H), 2.26 (s, 3H), 1.62 (s, 3H), 0.81 - 0.69 (m, 3H) ppm.

Example 29

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(hydroxymethyl)-6-methylpyrimidin-4(1*H*)-one (**225**)



[0596] Step 1:

[0597] 4-(Benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2, Example 22**, 82 mg, 0.115 mmol) was dissolved in THF (1.4 mL) and cooled to -78 °C. *n*-BuLi (86 µL, 1.6 M solution in hexanes, 0.14 mmol) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 15 min. Ethyl chloroformate (13 µL, 0.14 mmol) was added and the mixture was stirred at -78 °C for 30 min. The reaction was quenched by addition of water (1 mL) and warmed to ambient temperature. The mixture was poured over water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100% EtOAc in heptane) gave ethyl 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine-5-carboxylate (55 mg, 50%), which was used without further purification the next step. ESI-MS *m/z* calc. 580.200, found 581.6 (M+1)⁺; Retention time: 4.33 minutes using LC/MS Method A.

[0598] Step 2:

[0599] Ethyl 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine-5-carboxylate (22 mg, 0.023 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. LiAlH₄ (30 µL, 1 M solution in THF, 0.03 mmol) was added at 0 °C and the mixture was stirred for 15 min at 0 °C. The reaction mixture was quenched by addition of a saturated Rochelle's salt solution (5 mL) and diluted with EtOAc (5 mL). The resulting mixture was stirred at ambient temperature for 10 min. The organic layer was separated, washed with brine (5 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give (4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)methanol (21.5 mg, 64%) as a colourless oil, which was used in the next step without further purification.

[0600] Step 3:

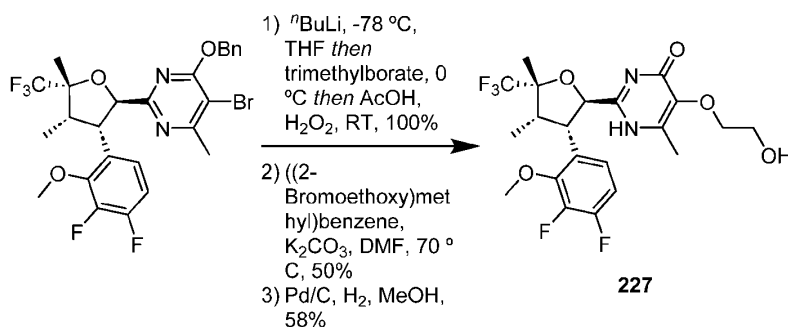
[0601] (4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-yl)methanol (21.5 mg) was treated via the method described in General method C using a 1:1 mixture of ethanol and AcOH as the solvent. After purification by preparative reverse phase HPLC (C₁₈ X-bridge column, 47 to 95% MeCN in H₂O containing 0.1% TFA), the residue was partitioned between EtOAc (5 mL) and a saturated aqueous NaHCO₃ solution (5 mL). The aqueous layer was separated and extracted with EtOAc (2 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(hydroxymethyl)-6-methylpyrimidin-4(1*H*)-one (**225**, 2.0 mg, 19%) as a white solid. ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.07 - 7.03 (m, 1H), 6.98 - 6.91 (m, 1H), 5.28 (d, *J* = 10.6 Hz, 1H), 4.51 (s, 2H), 4.48 (t, *J* = 10.6, 8.3 Hz, 1H), 3.99 (d, *J* = 2.3 Hz, 3H), 2.85 (dq, *J* = 8.3, 7.7 Hz, 1H), 2.34 (s, 3H), 1.64 (s, 3H), 0.85 - 0.82 (m, 3H) ppm. ¹⁹F NMR (471 MHz, Methanol-*d*₄) δ -75.59, -140.05, -156.78 ppm; OH alcohol and NH pyrimidone not observed. ESI-MS *m/z* calc. 448.142, found 449.5 (M+1)⁺; 447.4 (M-1)⁻; Retention time: 2.91 minutes using LC/MS Method A.

[0602] The following compound was made using methods described in Example 29 except that Step 2 was replaced by a Grignard reaction step, using the conditions described in the synthesis of *dia*-6-((2*R*^{*},3*S*^{*},4*S*^{*},5*R*^{*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-3-(1-(2-hydroxy-2-methylpropoxy)propan-2-yl)-2-methylpyrimidin-4(1*H*)-one (**112**):

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
226	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxypropan-2-yl)-6-methylpyrimidin-4(1 <i>H</i>)-one	476.173	477.5	3.13	A	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.05 - 6.99 (m, 1H), 6.98 - 6.91 (m, 1H), 5.27 (d, <i>J</i> = 10.6 Hz, 1H), 4.51 (dd, <i>J</i> = 10.6, 8.1 Hz, 1H), 4.00 (d, <i>J</i> = 2.3 Hz, 3H), 2.85 (dq, <i>J</i> = 8.1, 7.4 Hz, 1H), 2.46 (s, 3H), 1.63 (s, 3H), 1.56 (s, 6H), 0.86 - 0.80 (m, 3H) ppm: OH alcohol and NH pyrimidone not observed.

Example 30

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxyethoxy)-6-methylpyrimidin-4(1*H*)-one (**227**)



[0603] Step 1:

[0604] ⁿBuLi (200 μL, 2.5 M in hexanes, 0.50 mmol) was added to a stirring solution of 4-(benzyloxy)-5-bromo-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (**Product of Step 2 Example 22**, 250 mg, 0.426 mmol) in THF (10 mL) at -78 °C under nitrogen. After 10 min, trimethyl borate (100 μL, 0.881 mmol) was added and the mixture was gradually warmed to 0 °C. After stirring for 4 h, AcOH (75 μL, 1.32 mmol) followed by H₂O₂ (100 μL, 30 % w/v in water, 0.88 mmol) were added and the mixture was stirred for 16 h. The reaction was quenched by addition of water. The organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo* to give 4-(benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-ol (233.4 mg, 100%). ESI-MS *m/z* calc. 524.173, found 553.7 (M+1)⁺; Retention time: 1.17 minutes using LC/MS Method C.

[0605] Step 2:

[0606] 4-(Benzyloxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidin-5-ol (112 mg, 0.214 mmol) and ((2-

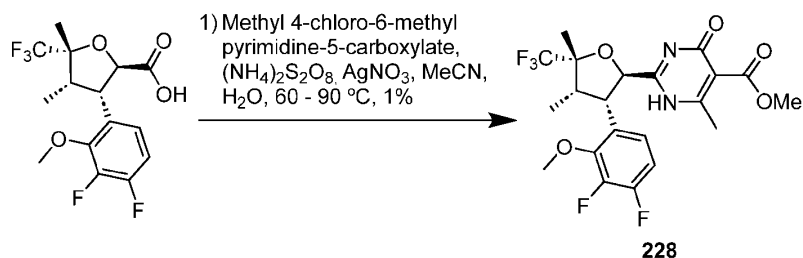
bromoethoxy)methyl)benzene (55 μ L, 0.35 mmol) were treated via the method described in General Method J except that the reaction was carried out at 70 °C. Purification by reverse phase HPLC (C_{18} X-bridge column, 47 to 95% MeCN in H_2O containing 0.1% NH_4OH) gave 4-(benzyloxy)-5-(2-(benzyloxy)ethoxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (69.6 mg, 50%). ESI-MS m/z calc. 658.247, found 659.8 ($M+1$)⁺; Retention time: 1.34 minutes using LC/MS Method A.

[0607] Step 3:

[0608] 4-(Benzyloxy)-5-(2-(benzyloxy)ethoxy)-2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methylpyrimidine (69.6 mg, 0.106 mmol) was treated via the method described in General Method C using MeOH as the solvent in place of EtOH. Purification by reverse phase HPLC (C_{18} X-bridge column, 38 to 53% MeCN in H_2O containing 0.1% NH_4OH) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5-(2-hydroxyethoxy)-6-methylpyrimidin-4(1*H*)-one (**227**, 31.9 mg, 58%). ¹H NMR (400 MHz, $DMSO-d_6$) δ 12.74 (s, 1H), 7.17 (ddd, J = 10.0, 8.9, 7.6 Hz, 1H), 7.02 (ddd, J = 8.5, 5.7, 2.1 Hz, 1H), 5.21 (d, J = 10.9 Hz, 1H), 4.77 (s, 1H), 4.48 (dd, J = 11.0, 8.1 Hz, 1H), 4.01 (dd, J = 5.5, 4.4 Hz, 2H), 3.95 (d, J = 2.0 Hz, 3H), 3.56 (dd, J = 5.5, 4.4 Hz, 2H), 2.82 (t, J = 7.7 Hz, 1H), 2.17 (s, 3H), 1.61 (s, 3H), 0.78 - 0.63 (m, 3H) ppm. ESI-MS m/z calc. 478.153, found 479.2 ($M+1$)⁺; Retention time: 2.91 minutes using LC/MS Method A.

Example 31

Methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate (**228**)



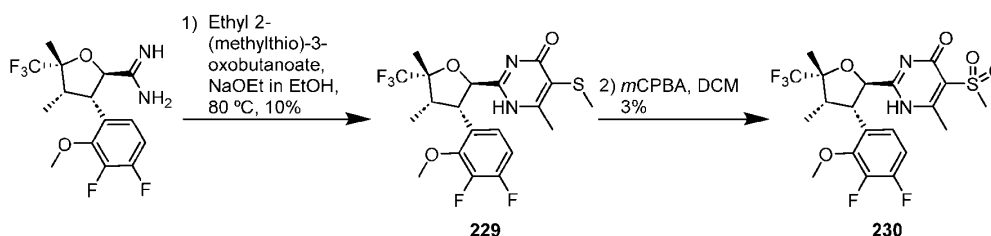
[0609] Step 1:

[0610] Methyl 4-chloro-6-methylpyrimidine-5-carboxylate (116 mg, 0.622 mmol), (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 300 mg, 0.847 mmol), silver nitrate (1.5 g, 8.83 mmol) and ammonium persulfate (709 mg, 3.11 mmol) were combined in a mixture of MeCN (5 mL) and water (5 mL). The reaction mixture was sealed and heated at 60 °C overnight then, at 90 °C for 6 h. The reaction mixture was cooled to ambient temperature. Purification by reverse phase HPLC (C_{18} column, 47 to 95% MeCN in H_2O containing 0.1% NH_4OH) gave methyl 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-

methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-4-oxo-1,4-dihydropyrimidine-5-carboxylate (**228**, 3.32 mg, 1%). ^1H NMR (500 MHz, Methanol- d_4) δ 7.05 (ddd, $J = 8.1, 5.6, 2.1$ Hz, 1H), 6.95 (ddd, $J = 9.9, 8.9, 7.5$ Hz, 1H), 5.34 - 5.27 (m, 1H), 4.49 (dd, $J = 10.5, 8.2$ Hz, 1H), 3.99 (d, $J = 2.3$ Hz, 3H), 3.84 (s, 3H), 2.94 - 2.80 (m, 1H), 2.27 (s, 3H), 1.64 (d, $J = 1.1$ Hz, 3H), 0.83 (dq, $J = 7.4, 2.3$ Hz, 3H) ppm; NH pyrimidone not observed. ESI-MS m/z calc. 476.390, found 478.1 ($M+1$) $^+$; Retention time: 2.56 minutes using LC/MS Method A.

Example 32

2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylthio)pyrimidin-4(1*H*)-one (**229**) and 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylsulfonyl)pyrimidin-4(1*H*)-one (**230**)



[0611] Step 1:

[0612] A solution of (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboximidamide (hydrochloride salt) (**Product of Step 1 Example 21**, 1.18 g, 3.04 mmol) and ethyl *rac*-(methylthio)-3-oxobutanoate (**Int-31**, 900 mg, 4.85 mmol) in EtOH (10 mL) was treated with NaOEt (2 mL, 21 % w/v solution in EtOH, 6.2 mmol) and heated at 80 °C for 2 h. An additional amount of NaOEt (1 mL, 21 % w/v solution in EtOH, 3.1 mmol) was added and the reaction mixture was stirred at 80 °C overnight. The mixture was partitioned between a saturated aqueous NH_4Cl solution (15 mL) and EtOAc (30 mL). The aqueous phase was separated and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (80 g SiO_2 , 0 to 100 % EtOAc in heptane) followed by reverse phase HPLC (C_{18} X-bridge column, 47.4 to 94.7% MeCN in water containing 0.1% NH_4OH) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylthio)pyrimidin-4(1*H*)-one (**229**, 335 mg, 10%) as a white solid. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.16 (dt, $J = 10.0, 8.4$ Hz, 1H), 7.03 (ddd, $J = 8.7, 5.7, 1.9$ Hz, 1H), 5.23 (d, $J = 10.8$ Hz, 1H), 4.48 (dd, $J = 10.8, 8.0$ Hz, 1H), 3.94 (d, $J = 2.0$ Hz, 3H), 2.82 (p, $J = 7.7$ Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H), 1.61 (s, 3H), 0.74 - 0.69 (m, 3H) ppm; NH pyrimidone not observed. ^{19}F NMR (471 MHz, $\text{DMSO}-d_6$) δ -73.39 (d, $J = 14.4$

Hz), -137.83 - -138.03 (m), -154.56 - -154.77 (m) ppm. ESI-MS m/z calc. 464.119, found 465.5

($M+1$)⁺; 463.4 ($M-1$)⁻; Retention time: 3.44 minutes using LC/MS method A.

[0613] Step 2:

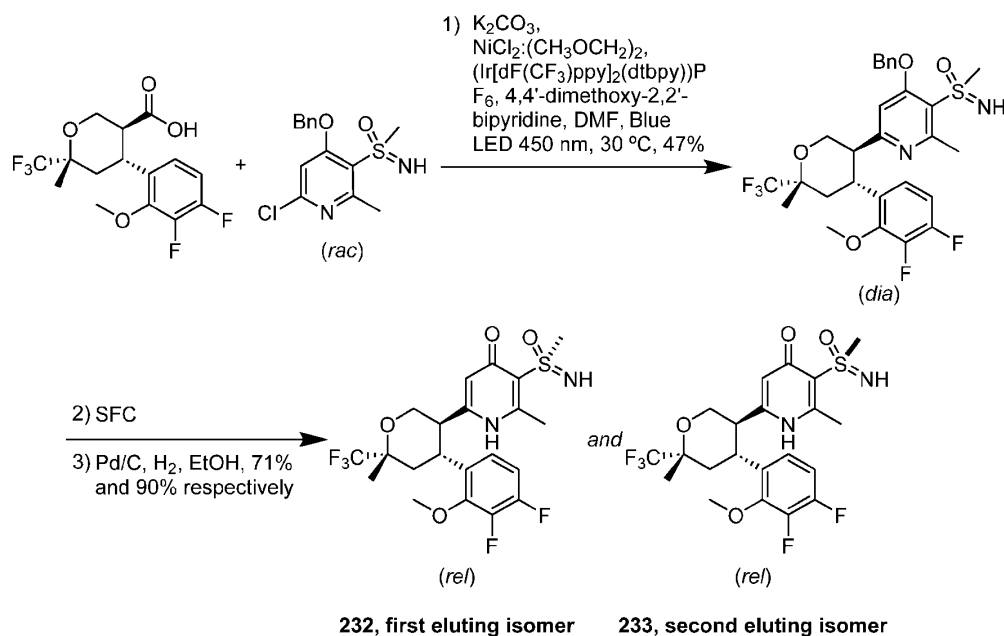
[0614] *m*CPBA (30 mg, 0.13 mmol) was added to a stirred solution of 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylthio)pyrimidin-4(1*H*)-one (20 mg, 0.043 mmol) in DCM (2 mL) and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was diluted with water and Na₂S₂O₃. The aqueous layer was separated and extracted with DCM (3 x). The combined organic extracts were passed through a Whatman[®] phase separation filter paper and concentrated *in vacuo*. Purification by reverse phase chromatography HPLC (C₁₈ X-bridge column, 38 to 53% MeCN in H₂O containing 1% NH₄OH) gave 2-((2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-6-methyl-5-(methylsulfonyl)pyrimidin-4(1*H*)-one (**230**, 0.6 mg, 3%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.57 (s, 1H), 7.21 - 7.14 (m, 1H), 7.06 (t, *J* = 7.1 Hz, 1H), 5.25 (d, *J* = 10.6 Hz, 1H), 4.48 (dd, *J* = 10.6, 7.8 Hz, 1H), 3.96 (d, *J* = 2.0 Hz, 3H), 3.25 (s, 3H), 2.82 (t, *J* = 7.6 Hz, 1H), 2.55 (s, 3H), 1.61 (s, 3H), 0.74 (d, *J* = 7.4 Hz, 3H) ppm. ¹⁹F NMR (471 MHz, DMSO-*d*₆) δ -73.40, -138.05, -154.85 ppm. ESI-MS m/z calc. 496.110, found 497.5 ($M+1$)⁺; 495.4 ($M-1$)⁻; Retention time: 2.58 minutes using LC/MS method A.

[0615] The following compound was made using the method described in Example 32, Step 1, except that ethyl 2-(methylthio)-3-oxobutanoate was replaced with ethyl 4-oxotetrahydrofuran-3-carboxylate. The reaction was carried out at 70 °C and KOH was used in place of NaOEt:

Cmpd No.	Compound Name	LC/MS (m/z calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
231	2-((2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl)-5,7-dihydrofuro[3,4- <i>d</i>]pyrimidin-4(1 <i>H</i>)-one	446.374	445.1	1.22	J	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.09 - 7.05 (m, 1H), 6.86 (q, <i>J</i> = 8.5 Hz, 1H), 5.31 (d, <i>J</i> = 11.0 Hz, 1H), 5.02 (d, <i>J</i> = 3.4 Hz, 2H), 4.88 - 4.71 (m, 2H), 4.06 - 4.00 (m, 1H), 3.97 (q, <i>J</i> = 2.7 Hz, 3H), 2.80 - 2.67 (m, 1H), 1.65 (d, <i>J</i> = 10.5 Hz, 3H), 0.80 - 0.78 (m, 3H) ppm; NH pyridone not observed.

Example 33

rel-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methyl-3-((*R*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**232**) and *rel*-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methyl-3-((*S*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**233**)



[0616] Step 1:

[0617] A vial was charged with (3*S*,4*R*,6*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylic acid (120 mg, 0.330 mmol), *rac*-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)(imino)(methyl)- λ^6 -sulfanone (111 mg, 0.357 mmol), K_2CO_3 (70 mg, 0.51 mmol), $(Ir[dF(CF_3)ppy]_2(dtbbpy))PF_6$ (35 mg, 0.031 mmol), $NiCl_2$ glyme (12 mg, 0.055 mmol), 4,4'-dimethoxy-2,2'-bipyridine (12 mg, 0.055 mmol) and DMF (6 mL). The mixture was sparged with N_2 for 5 min and the vial was sealed with parafilm. The solution was stirred at 30 °C under the irradiation of a blue LED (450 nm) using a Penn OC Photoreactor M1 for 18 h. The reaction mixture was partitioned between water and EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by preparative reverse phase HPLC (C_{18} column, 10 to 99% MeCN in water containing 5 mM HCl) provided *dia*-(4-(benzyloxy)-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methylpyridin-3-yl)(imino)(methyl)- λ^6 -sulfanone (90 mg, 47%). ESI-MS m/z calc. 584.177, found 585.4 ($M+1$)⁺; Retention time: 1.62 minutes using method D.

[0618] Step 2:

[0619] The diastereomers of *dia*-(4-(benzyloxy)-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone were separated by chiral SFC using a Lux[®] Cellulose-4 column, 5 μm particle size, 25 cm x 21 mm from Phenomenex, Inc. to give:

[0620] First Eluting Isomer (rt = 3.55 minutes): *rel*-(*R*)-(4-(benzyloxy)-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (32.8 mg, 34%). ESI-MS *m/z* calc. 584.177, found 585.3 (M+1)⁺; Retention time: 1.77 minutes using method D.

[0621] Second Eluting Isomer (rt = 5.20 minutes): *rel*-(*S*)-(4-(benzyloxy)-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (26.3 mg, 27%). ESI-MS *m/z* calc. 584.177, found 585.3 (M+1)⁺; Retention time: 1.77 minutes using method D.

[0622] Step 3:

[0623] *rel*-(*R*)-(4-(Benzyloxy)-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (32.5 mg, 0.056 mmol) (First Eluting Isomer, rt = 3.55 minutes) was treated via the method described in General Method C to give *rel*-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methyl-3-((*R*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**232**, 20 mg, 71%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.51 (s, 1H), 9.29 (s, 1H), 7.27 - 7.20 (m, 1H), 7.18 - 7.09 (m, 1H), 6.56 (s, 1H), 4.01 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.99 - 3.84 (m, 5H), 3.78 - 3.72 (m, 3H), 2.62 (s, 3H), 1.87 - 1.74 (m, 2H), 1.67 (s, 3H) ppm; 1H obscured by water peak. ESI-MS *m/z* calc. 494.130, found 495.2 (M+1)⁺; Retention time: 1.85 minutes using method Q.

[0624] *rel*-(*S*)-(4-(Benzyloxy)-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone (26.3 mg, 0.045 mmol) (Second Eluting Isomer, rt = 5.20 minutes) was treated via the method described in General Method C to give *rel*-6-((3*R**,4*R**,6*R**)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-2-methyl-3-((*S*)-*S*-methylsulfonimidoyl)pyridin-4(1*H*)-one (**233**, 20 mg, 90%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.64 (s, 1H), 9.25 (s, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.19 - 7.08 (m, 1H), 6.59 (s, 1H), 4.07 - 3.98 (m, 1H), 3.98 - 3.81 (m, 5H), 3.78 (s, 3H), 3.54 - 3.48 (m, 1H), 2.61 (s, 3H), 1.89 - 1.74 (m, 2H), 1.66 (s, 3H) ppm. ESI-MS *m/z* calc. 494.130, found 495.2 (M+1)⁺; Retention time: 1.86 minutes using method Q.

[0625] The following compounds were made using methods described in Example 33 except that, in Step 1, *rac*-8-(benzyloxy)-6-chloro-1-imino-1,2,3,4-tetrahydro-1λ⁴-thiopyrano[3,2-*b*]pyridine 1-oxide **Int-38** was used as the halide coupling partner in place of *rac*-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)(imino)(methyl)-λ⁶-sulfanone. In Step 2, the diastereomers were separated by

chiral SFC using a Chiralpak[®] IG column, 5 μ m particle size, 25 cm x 21 mm from Daicel Corporation to give

[0626] First Eluting Isomer (rt = 3.6 minutes): *rel*-(*R*)-8-(benzyloxy)-6-((3*R*^{*},4*R*^{*},6*R*^{*})-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-1-imino-1,2,3,4-tetrahydro-1 λ ⁴-thiopyrano[3,2-*b*]pyridine 1-oxide (12.5 mg, 20%). ESI-MS *m/z* calc. 596.613, found 597.2 (M+1)⁺; Retention time: 1.81 minutes using method D.

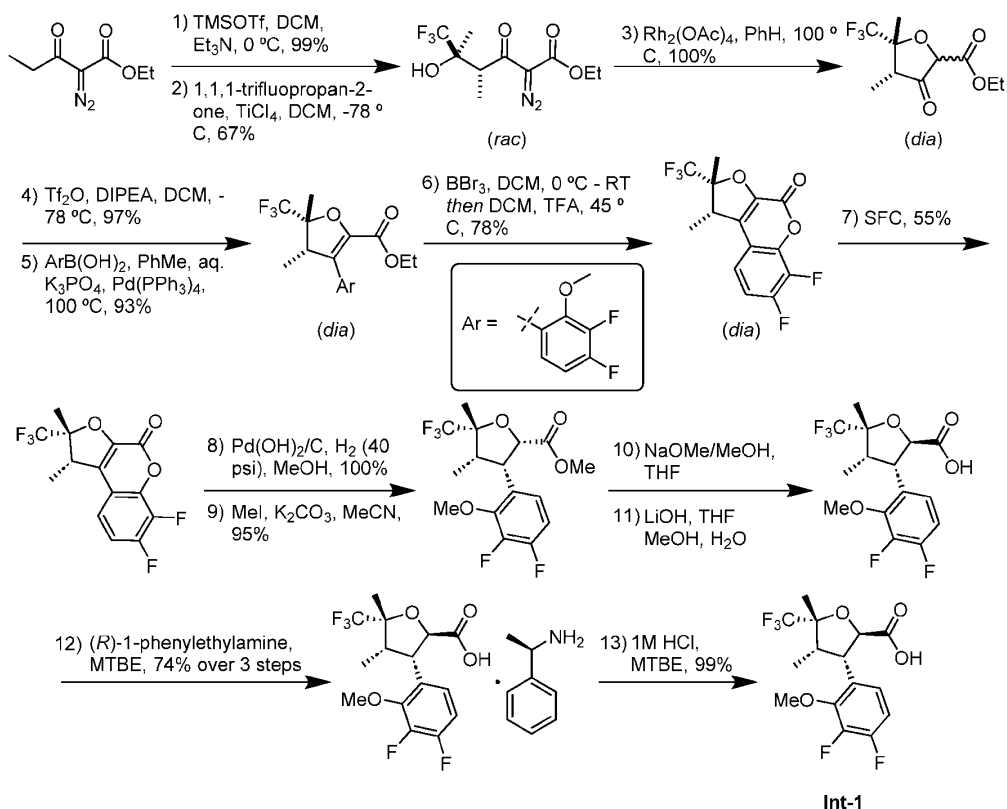
[0627] Second Eluting Isomer (rt = 5.5 minutes): *rel*-(*S*)-8-(benzyloxy)-6-((3*R*^{*},4*R*^{*},6*R*^{*})-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-yl)-1-imino-1,2,3,4-tetrahydro-1 λ ⁴-thiopyrano[3,2-*b*]pyridine 1-oxide (11.5 mg, 12%). ESI-MS *m/z* calc. 596.613, found 597.2 (M+1)⁺; Retention time: 1.82 minutes using method D.

[0628] In Step 3, MeOH was used as the solvent in place of EtOH:

Cmpd No.	Compound Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS retention time	LC/MS Method	NMR (shifts in ppm)
234	<i>rel</i> -(<i>R</i>)-6-((3 <i>R</i> [*] ,4 <i>R</i> [*] ,6 <i>R</i> [*])-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-1-imino-1,3,4,5-tetrahydro-1 λ ⁴ -thiopyrano[3,2- <i>b</i>]pyridin-8(2 <i>H</i>)-one 1-oxide	506.488	507.1	1.76	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 6.95 (s, 1H), 6.81 (q, <i>J</i> = 8.7 Hz, 1H), 6.32 (s, 1H), 4.05 - 3.85 (m, 4H), 3.85 - 3.67 (m, 2H), 3.44 - 3.29 (m, 3H), 3.15 - 3.00 (m, 1H), 2.99 - 2.83 (m, 1H), 2.60 - 2.42 (m, 1H), 2.41 - 2.25 (m, 1H), 1.95 (t, <i>J</i> = 13.0 Hz, 1H), 1.83 - 1.70 (m, 1H), 1.58 (s, 3H) ppm; exchangeable protons not observed.
235	<i>rel</i> -(<i>S</i>)-6-((3 <i>R</i> [*] ,4 <i>R</i> [*] ,6 <i>R</i> [*])-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2 <i>H</i> -pyran-3-yl)-1-imino-1,3,4,5-tetrahydro-1 λ ⁴ -thiopyrano[3,2- <i>b</i>]pyridin-8(2 <i>H</i>)-one 1-oxide	506.488	507.1	1.74	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.00 - 6.90 (m, 1H), 6.87 - 6.74 (m, 1H), 6.29 (s, 1H), 4.06 (dd, <i>J</i> = 11.7, 4.2 Hz, 1H), 3.96 (d, 3H), 3.83 - 3.63 (m, 2H), 3.42 - 3.23 (m, 3H), 3.11 - 2.99 (m, 1H), 2.99 - 2.82 (m, 1H), 2.55 - 2.40 (m, 1H), 2.41 - 2.25 (m, 1H), 1.94 - 1.70 (m, 2H), 1.54 (s, 3H) ppm; exchangeable protons not observed.

Intermediate 1

(2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**)



[0629] Step 1:

[0630] Et₃N (7.7 mL, 55.2 mmol) was added to a stirred solution of ethyl 2-diazo-3-oxopentanoate (6.69 g, 39.3 mmol) in DCM (80 mL) with stirring at 0 °C under nitrogen. TMSOTf (8.5 mL, 47.0 mmol) was added dropwise over 5 min and the mixture was stirred for a further 30 min at 0 °C. The reaction mixture was diluted with pentane (100 mL). The layers were separated and the organic phase was washed with a diluted aqueous NaHCO₃ solution (100 mL) and brine (100 mL). The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo* to give ethyl (Z)-2-diazo-3-(trimethylsilyloxy)pent-3-enoate (9.4 g, 99%) as a red oil. ¹H NMR (500 MHz, Chloroform-*d*) δ 5.33 (q, *J* = 7.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.67 (d, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.22 (s, 9H) ppm.

[0631] Step 2:

[0632] To a stirring solution of 1,1,1-trifluoropropan-2-one (8 mL, 89.4 mmol) in DCM (80 mL) at -78 °C was added TiCl₄ (70 mL, 1 M solution in DCM, 70.00 mmol) *via* cannula. A solution of

ethyl (Z)-2-diazo-3-trimethylsilyloxy-pent-3-enoate (36.1 g, 31.3 % w/w solution in DCM, 46.6 mmol) in DCM (40 mL) was added dropwise over 15 min and the mixture was stirred for 100 min at -78 °C. The reaction was carefully quenched with water, allowing the temperature to rise slowly to ambient temperature. The aqueous phase was separated and extracted with DCM. The combined organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (330 g SiO₂, 0 to 20% EtOAc in heptane) gave ethyl rac-(4*R*,5*R*)-2-diazo-6,6,6-trifluoro-5-hydroxy-4,5-dimethyl-3-oxo-hexanoate (8.82 g, 67%), which was stored as a solution in toluene. ¹H NMR (500 MHz, Chloroform-*d*) δ 4.33 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.0 Hz, 1H), 3.98 (s, 1H), 1.43 (q, *J* = 1.2 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.31 (dq, *J* = 7.0, 1.4 Hz, 3H) ppm. ESI-MS *m/z* calc. 282.083, found 283.1 (M+1)⁺; 281.0 (M-1)⁻; Retention time: 0.76 minutes using LC/MS method C.

[0633] Step 3:

[0634] A solution of rhodium tetraacetate (245 mg, 0.55 mmol) in benzene (32 mL) was heated at reflux for 10 min before a solution of ethyl rac-(4*R*,5*R*)-2-diazo-6,6,6-trifluoro-5-hydroxy-4,5-dimethyl-3-oxo-hexanoate (10 g, 35.4 mmol) in benzene (13 mL) was added slowly *via* additional funnel while refluxing for 60 min. The mixture was then concentrated *in vacuo* to give ethyl dia-(2*S*¹,4*R*²,5*R*³)-4,5-dimethyl-3-oxo-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (9.0 g, 100%) as a green coloured residue containing residual catalyst, and as a mixture of epimers at the position next to the ester. This material was used without further purification in the next step. ¹H NMR (500 MHz, Chloroform-*d*) δ 4.83 - 4.57 (m, 1H), 4.38 - 4.16 (m, 2H), 2.60 (dddd, *J* = 9.3, 8.2, 5.6, 1.4 Hz, 1H), 1.73 - 1.63 (m, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.24 (ddq, *J* = 6.4, 4.1, 1.9 Hz, 3H) ppm.

[0635] Step 4:

[0636] To a stirred solution of ethyl dia-(2*S*¹,4*R*²,5*R*³)-4,5-dimethyl-3-oxo-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (48 g, 189 mmol) in DCM (400 mL) at -78 °C was added DIPEA (29.7 g, 40 mL, 229 mmol). A solution of Tf₂O (53.4 g, 32 mL, 189 mmol) in DCM (200 mL) was added to the reaction mixture at the same temperature over 1 h. The reaction mixture was stirred for 30 min at 0 °C before being quenched with a saturated aqueous NaHCO₃ solution (100 mL). The aqueous layer was separated and extracted with DCM (160 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to give ethyl rac-(4*R*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-3-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydrofuran-2-carboxylate (71 g, 97%). ¹H NMR (400 MHz, Chloroform-*d*) δ 4.38 - 4.32 (m, 2H), 3.29 - 3.23 (m, 1H), 1.64 (s, 3H), 1.37 - 1.33 (m, 6H) ppm.

[0637] Step 5:

[0638] To stirring a solution of ethyl rac-(4*R*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-3-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydrofuran-2-carboxylate (26 g, 67 mmol) in toluene (130 mL) was added (3,4-difluoro-2-methoxy-phenyl)boronic acid (14 g, 74.5 mmol) followed by K₃PO₄ (100 mL, 2 M aqueous solution, 200 mmol) under an argon atmosphere. The reaction was degassed

before Pd(PPh₃)₄ (4 g, 3.5 mmol) was added. After further degassing, the reaction was heated at 100 °C for 2 h. The reaction was diluted with water and the aqueous layer was extracted with EtOAc (2 x100 mL). The combined organic layers were concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 10% EtOAc in heptane) gave ethyl *dia*-(4*S*^{*l*},5*R*^{*l*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (24.4 g, 93%) as a 6:1 diastereomeric mixture, with the major isomer believed to be ethyl *rac*-(4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate. Major isomer: ¹H NMR (400 MHz, Chloroform-*d*) δ 6.88 - 6.79 (m, 2H), 4.17 - 4.09 (m, 2H), 3.90 (s, 3H), 3.46 (q, *J* = 7.4 Hz, 1H), 1.67 (s, 3H), 1.12 (t, *J* = 7.4 Hz, 3H), 1.06 (dd, *J* = 5.4, 2.7 Hz, 3H) ppm. Minor isomer: ¹H NMR (400 MHz, Chloroform-*d*) δ 6.88 - 6.79 (m, 2H), 4.17 - 4.09 (m, 2H), 3.88 (s, 3H), 3.76 - 3.71 (m, 1H), 1.51 (s, 3H), 1.12 (t, *J* = 7.4 Hz, 3H), 0.99 (dd, *J* = 5.4, 2.7 Hz, 3H) ppm. ESI-MS *m/z* calc. 380.105, found 381.0 (M+1)⁺; Retention time: 2.09 minutes using LC/MS method O.

[0639] Step 6:

[0640] To an ice-cold solution of ethyl *dia*-(4*S*^{*l*},5*R*^{*l*})-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (110 g, 243 mmol) in DCM (360 mL) was added BBr₃ (370 mL, 1 M solution in DCM, 370 mmol) dropwise. Upon reaction completion, the mixture was quenched by addition of water and an aqueous sodium NaHCO₃. The aqueous layer was separated and extracted with DCM and the combined organic layers dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was dissolved in DCM (430 mL) at ambient temperature and TFA (40 mL, 519 mmol) was added. The reaction was heated to 45 °C. Upon reaction completion, the mixture was quenched by addition of an aqueous NaHCO₃ solution. The aqueous layer was separated and extracted with DCM, dried (MgSO₄), filtered and concentrated *in vacuo* to give the desired product as a 5:1 mixture of diastereomers. Recrystallization was carried out by solubilizing the crude in the smallest possible amount of DCM and adding a layer of heptane on top of this solution (liquid-liquid diffusion). After approximately 1 h, 56.5 g (*d.r.* 97:3 *syn:anti*) of product from the first and second crystallization was obtained, together with a further 4.6 g (*d.r.* 96:4 *syn:anti*) from the third crystallization. The batches were combined to give *dia*-(1*S*^{*l*},2*R*^{*l*})-6,7-difluoro-1,2-dimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (61 g, 78%), with the major isomer believed to be *rac*-(1*S*,2*R*)-6,7-difluoro-1,2-dimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one. ESI-MS *m/z* calc. 320.047, found 321.5 (M+1)⁺; 319.6 (M-1)⁻; Retention time: 3.17 minutes using LC/MS method A.

[0641] Step 7:

[0642] The isomers of *rac*-(1*S*,2*R*)-6,7-difluoro-1,2-dimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (1348 g, 4.366 mol) were separated by chiral SFC using a (*R,R*)-Whelk-O[®]1 column, 5 μm particle size, 15 cm x 3 cm from Regis Technologies on a MultiGram III SFC instrument from Berger Instruments to give:

[0643] **First Eluting Isomers (rt = 1.85 min):** (1*R*,2*S*)-6,7-difluoro-1,2-dimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (only an analytical sample was collected). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 (ddd, *J* = 9.0, 5.5, 2.0 Hz, 1H), 7.51 (ddd, *J* = 10.3, 9.0, 7.0 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 1H), 1.65 (s, 3H), 1.45 (dt, *J* = 6.9, 2.2 Hz, 3H) ppm. ESI-MS *m/z* calc. 320.047, found 321.3 (M+1)⁺; 319.4 (M-1)⁻; Retention time: 0.92 minutes using LC/MS method C.

[0644] **Second Eluting Isomer (rt = 2.38 min):** (1*S*,2*R*)-6,7-Difluoro-1,2-dimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (366.99 g, 26%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 (ddd, *J* = 9.0, 5.5, 2.0 Hz, 1H), 7.50 (ddd, *J* = 10.3, 9.0, 7.0 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 1H), 1.65 (s, 3H), 1.45 (dt, *J* = 6.9, 2.2 Hz, 3H) ppm. ESI-MS *m/z* calc. 320.045, found 321.4 (M+1)⁺; 319.4 (M-1)⁻; Retention time: 0.92 minutes using LC/MS method C.

[0645] **Step 8:**

[0646] A solution of (1*S*,2*R*)-6,7-Difluoro-1,2-dimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (0.89 kg, 2.78 mol) and 20% Pd(OH)₂/C (0.39 kg, 50% wet, Degussa, 0.278 mol) in MeOH (12 L) was stirred under a 40 psi pressure of hydrogen overnight. An increase in the reaction temperature to 37 °C was observed after reacting overnight and the mixture was cooled to 24 °C. The hydrogenation was continued for a total of 48 h. The mixture was filtered through Celite[®], washing with MeOH (20 L) and the filtrates were concentrated *in vacuo*. The residue was dissolved in toluene (4 L) and concentrated *in vacuo*, and this process repeated. The residue was dried under vacuum at 40 °C overnight to give methyl (2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.0 kg at 91% purity, 100%) as a beige solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.20 (br s, 1H), 6.94 (br t, *J* = 7.4 Hz, 1H), 6.79-6.69 (m, 1H), 5.10 (d, *J* = 6.0 Hz, 1H), 4.20 (dd, *J* = 6.1, 8.2 Hz, 1H), 3.43 (s, 3H), 2.94 (p, *J* = 7.7 Hz, 1H), 1.46 (s, 3H), 0.77 (br d, *J* = 6.8 Hz, 3H) ppm.

[0647] **Step 9:**

[0648] K₂CO₃ (2.0 kg, 14.4 mol) and MeI (800 mL, 12.8 mol) were sequentially added to a stirred solution of methyl (2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.0 kg, 2.82 mol) in MeCN (10 L) under nitrogen at ambient temperature. After stirring the reaction mixture overnight, additional MeI (120 mL, 2 mmol) was added and the reaction was stirred overnight. Additional MeI (60 mL, 0.85 mmol) was added and the mixture was stirred for a further 3 days. The reaction mixture was diluted with MTBE (30 L), treated with Celite[®] (1 kg) and filtered through a bed of Celite[®] (1 kg) washing the filtered cake with MTBE (10 L). The mother liquors were filtered a second time through Celite[®] (1 kg) washing the filtered cake with MTBE (4 L) and the filtrate concentrated *in vacuo*. The residue was dissolved in toluene (4 L) and concentrated *in vacuo*, and this process was repeated. The residue was dried under vacuum at 40 °C overnight to give methyl (2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (0.99 kg at 90% purity, 95%) as a brown

solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.14-7.00 (m, 2H), 5.14 (d, $J = 6.0$ Hz, 1H), 4.15 (dd, $J = 6.2$, 8.4 Hz, 1H), 3.88 (d, $J = 1.7$ Hz, 3H), 2.97 (p, $J = 7.8$ Hz, 1H), 1.48 (s, 3H), 0.72 (br d, $J = 6.6$ Hz, 3H) ppm.

[0649] Step 10 and 11:

[0650] NaOMe (65 mL, 25% solution in methanol, 0.28 mol) was added to a stirred solution of methyl (2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (0.98 kg, 2.66 mol) in THF (10 L) at ambient temperature under nitrogen. After 5 h, MeOH (1 L), water (1 L) and LiOH.H₂O (0.168 kg, 4.0 mol) were sequentially added and the mixture was stirred overnight. The reaction mixture was poured into 1M HCl (4.4 L, 4.4 mol) then extracted with MTBE (20 L). The aqueous layer was further extracted with MTBE (2 x 5 L), and the combined organic layers were washed with brine (2 L), dried (Na₂SO₄), filtered, and then treated with activated carbon (50 g, 5% w/w) with stirring for 1 h. The mixture was filtered through Celite®, washing the filtered cake with MTBE (2 x 4 L). The filtrates were concentrated *in vacuo*. The residue was dissolved in toluene (4 L) and concentrated *in vacuo*, then dissolved in MTBE (4 L) and concentrated *in vacuo* again to give (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (1.06 kg at 77.7% purity) as an amber oil, which was used without further purification in the next step.

[0651] Step 12:

[0652] Crude (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (2.09 kg at 77% purity, 4.54 mol) was dissolved in MTBE (25 L) in a 100 L Chemglass reactor then stirred at 84 rpm at ambient temperature. A mixture of (*R*)-1-phenylethylamine (0.704 kg, 5.81 mol) and MTBE (2 L) was added to the reactor, followed by additional MTBE to give a total volume of 30 L in the reactor. After 2 h, additional MTBE (2 L) was added to the reaction. After a total of 3.5 h, the mixture was filtered, washing with MTBE (2 L). The reactor was rinsed with MTBE (4 L), which was used to rinse the solids, which were then compressed and dried on the Büchner funnel for 2 h. The solid product cake was loosened then dried under a stream of nitrogen and under vacuum overnight on the Büchner funnel. The isolated solids were dried in a convection oven at 40 °C for 24 h to give (*R*)-1-phenylethan-1-amine (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.86 kg at 95.7% purity, 74% over 3 steps) as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.34 (br s, 2H), 7.46 - 7.41 (m, 2H), 7.36 - 7.27 (m, 3H), 7.16 - 7.11 (m, 1H), 7.10 - 7.03 (m, 1H), 4.58 (d, $J = 9.9$ Hz, 1H), 4.23 (q, $J = 6.7$ Hz, 1H), 3.99 (dd, $J = 7.8$, 9.8 Hz, 1H), 3.90 (d, $J = 2.0$ Hz, 3H), 2.60 (p, $J = 7.5$ Hz, 1H), 1.50 (s, 3H), 1.40 (d, $J = 6.7$ Hz, 3H), 0.71-0.59 (m, 3H) ppm.

[0653] Step 13:

[0654] To a suspension of (*R*)-1-phenylethan-1-amine (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (10.6 g, 22.3 mmol) in MTBE (250 mL) was added 2 M HCl (200 mL, 400 mmol). The organic layer was separated and

washed with water (200 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to give (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-1**, 8.4 g, 99%) as an oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.96 (ddd, *J* = 7.9, 5.6, 2.0 Hz, 1H), 6.88 (td, *J* = 9.2, 7.3 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.15 (dd, *J* = 10.5, 8.0 Hz, 1H), 4.02 (d, *J* = 2.8 Hz, 3H), 2.74 (p, *J* = 7.6 Hz, 1H), 1.64 (t, *J* = 1.2 Hz, 3H), 0.79 (dq, *J* = 7.4, 2.3 Hz, 3H) ppm.

[0655] The following intermediates were made using the method described in Intermediate 1, except that different alkylating agents were used in Step 9 in place of MeI. The conditions used for the epimerisation hydrolysis Step 10 were those described in Intermediate 2 Step 8:

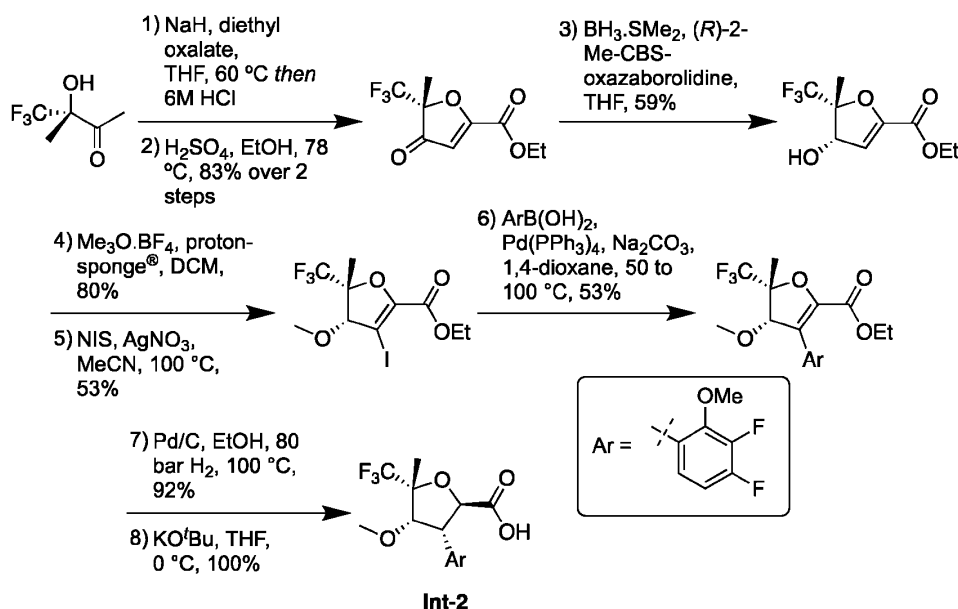
Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(2-Ethoxy-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	368.105	367.4	0.62	C	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 12.96 (s, 1H), 7.24 - 7.04 (m, 2H), 4.97 (d, <i>J</i> = 10.7 Hz, 1H), 4.27 - 4.03 (m, 3H), 2.64 (p, <i>J</i> = 7.4 Hz, 1H), 1.53 (d, <i>J</i> = 1.1 Hz, 3H), 1.34 (t, <i>J</i> = 7.0 Hz, 3H), 0.69 (dt, <i>J</i> = 7.6, 2.4 Hz, 3H) ppm.
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-isopropoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	382.120	381.5	0.66	C	

[0656] The following intermediate was made using the method described in Intermediate 1, except that the conditions used for the alkylation Step 9 were those described in Intermediate 10 Step 7 and the conditions used for the epimerisation hydrolysis Step 10 were those described in Intermediate 2 Step 8:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(2-(Difluoromethoxy)-3,4-difluorophenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	390.070	389.4	0.62	C	

Intermediate 2

(2*R*,3*R*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-2**)



[0657] Step 1 and 2:

[0658] A solution of diethyl oxalate (17.40 mL, 128.1 mmol) and (*R*)-4,4,4-trifluoro-3-hydroxy-3-methylbutan-2-one (20.0 g, 128.1 mmol) in THF (80 mL) was added to a stirred suspension of NaH (10.8 g, 60% dispersion in mineral oil, 270 mmol) in dry THF (140 mL) over 1 h, at such a speed to keep the gas evolution at a steady rate and the internal temperature below 40 °C. After complete addition, the mixture was heated overnight at 60 °C. The reaction mixture was cooled down to ambient temperature and poured into ice/water (400 mL, 20 vol). The measured pH of the solution was 11-12. The mixture was extracted twice with MTBE (5 vol, 100 mL). The resulting aqueous solution was poured into a 6 M HCl (25 vol, 500 mL) solution ensuring that the pH was 1. The mixture was extracted with MTBE (3 x 100 mL, 5 vol). The combined extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give a brown oil, which was used as is in the next step. The oil was solubilized in absolute EtOH (160 mL) and H₂SO₄ (1.4 mL, 26.3 mmol) was added. The reaction mixture was heated to reflux temperature for 3 h. A further amount of H₂SO₄ (5.5 mL, 103 mmol) was added and the heating was continued overnight. The reaction mixture was cooled down to ambient temperature and concentrated *in vacuo* (30 mbar and 35 °C) to give a brown oil. The crude oil was partitioned between NaHCO₃ and DCM. The aqueous phase was further extracted with DCM. The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* (250 mbar, 32 °C) to give ethyl (*R*)-5-methyl-4-oxo-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (30.3 g, 83% over

2 steps) as a brown oil containing 15.5 wt% DCM. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 6.70 (s, 1H), 4.38 (q, $J = 7.1$ Hz, 2H), 1.66 (d, $J = 0.9$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H) ppm.

[0659] Step 3:

[0660] $\text{BH}_3\cdot\text{SMe}_2$ (20 mL, 2 M solution in THF, 40 mmol) was added dropwise over 3 min to a solution of ethyl (*R*)-5-methyl-4-oxo-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (7.92 g, 33.25 mmol) and (*R*)-(+)-2-methyl-CBS-oxazaborolidine (3.3 mL, 1 M solution in toluene, 3.3 mmol) in THF (150 mL). The reaction mixture was stirred at ambient temperature for 2 h. The reaction was quenched by addition of a 1 M HCl solution and diluted with MTBE (150 mL). The layers were separated and the aqueous phase was extracted with MTBE (50 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was passed through a plug of silica (50 g), washing with MTBE (250 mL), and the filtrate purified by flash chromatography (120 g SiO_2 , 0 to 100 % MTBE in hexanes) to give ethyl (4*S*,5*R*)-4-hydroxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (4.7 g, 59%). ^1H NMR (500 MHz, $\text{Chloroform}-d$) δ 6.00 (dd, $J = 2.8$, 0.7 Hz, 1H), 4.85 (d, $J = 2.8$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 1.54 (q, $J = 1.0$ Hz, 3H), 1.35 (t, $J = 7.1$ Hz, 3H) ppm; OH alcohol not observed. ESI-MS m/z calc. 240.061, found 242.8 ($\text{M}+1$) $^+$; Retention time: 0.74 minutes using LC/MS method M.

[0661] Step 4:

[0662] Proton-sponge $^{\text{®}}$ (42 g, 196 mmol) and $\text{Me}_3\text{O}\cdot\text{BF}_4$ (30 g, 203 mmol) were successively added to a solution of ethyl (4*S*,5*R*)-4-hydroxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (16.2 g, 67.45 mmol) in DCM (300 mL). The reaction mixture was stirred in the dark at ambient temperature for 3 days, then passed through a SCX-2 cartridge, washing with MTBE (500 mL). The combined organic layers were washed with 1 M HCl (10 x 50 mL). The combined aqueous extracts were back-extracted with MTBE (2 x 100 mL). The combined organic extracts were washed with brine and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 0 to 50% MTBE in hexanes) gave ethyl (4*S*,5*R*)-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (16.6 g, 80%). ^1H NMR (500 MHz, $\text{Chloroform}-d$) δ 6.06 (t, $J = 2.1$ Hz, 1H), 4.46 (t, $J = 2.1$ Hz, 1H), 4.30 (qd, $J = 7.1$, 1.7 Hz, 2H), 3.43 (d, $J = 1.7$ Hz, 3H), 1.66 - 1.49 (m, 3H), 1.33 (td, $J = 7.1$, 1.7 Hz, 3H) ppm.

[0663] Step 5:

[0664] Silver nitrate (10.9 g, 64.2 mmol) and NIS (15.9 g, 70.7 mmol) were added to a stirred solution of ethyl (4*S*,5*R*)-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (19.6 g, 64.0 mmol) in MeCN (200 mL) under nitrogen. The reaction was heated to 100 $^{\circ}\text{C}$ for 24 h. The reaction mixture was cooled down to ambient temperature and quenched by addition of a saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution (100 mL). The mixture was filtered and the filtrate diluted in MTBE (200 mL). The layers were separated. The aqueous layer was extracted with MTBE (100 mL). The combined organic layers were washed with a saturated NaHCO_3 solution (8 x 100 mL), water (20 mL), brine (20 mL), dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was recrystallised

from EtOAc to give ethyl (4*R*,5*R*)-3-iodo-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (6g), as pale yellow needles. The mother liquors, still containing product, were purified by flash chromatography (220 g SiO₂, 0 to 30% MTBE in hexanes) to give a further 6.8 g of product. A total of 12.8 g (53%) of ethyl (4*R*,5*R*)-3-iodo-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate was obtained. ¹H NMR (500 MHz, Chloroform-*d*) δ 4.42 - 4.27 (m, 3H), 3.64 (s, 3H), 1.63 (d, *J* = 1.0 Hz, 3H), 1.39 (t, *J* = 7.1, 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 379.973, found 381.4 (M+1)⁺; Retention time: 0.93 minutes using LC/MS method M.

[0665] Step 6:

[0666] A mixture of ethyl (4*R*,5*R*)-3-iodo-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (6 g, 15.8 mmol), (3,4-difluoro-2-methoxyphenyl)boronic acid (3.9 g, 20.75 mmol), Pd(PPh₃)₄ (990 mg, 0.857 mmol) and Na₂CO₃ (25 mL, 2 M aqueous solution, 50 mmol) in 1,4-dioxane (150 mL) was heated at 50 °C for 2 h, 70 °C for 2 h and then 100 °C (reflux) for 16 h. The reaction mixture was cooled to ambient temperature, acidified to pH 1 and partitioned between water (150 mL) and EtOAc (300 mL). The layers were separated. The aqueous layer extracted with EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was diluted in EtOH (100 mL) and H₂SO₄ (900 μL, 16.88 mmol) was added. The mixture was heated at reflux for 3 h. Purification by flash chromatography (SiO₂, 0 to 35% EtOAc in heptane) gave ethyl (4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3.3 g, 53%). ESI-MS *m/z* calc. 396.100, found 395.5 (M-1)⁻; Retention time: 1.03 minutes using LC/MS method M.

[0667] Step 7:

[0668] A solution of ethyl (4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (330 mg, 0.83 mmol) in EtOH (15 mL) was cycled through an H-cube[®] fitted with a Pd/C cartridge for 3.5 h. The reaction was carried out at 100 °C and 80 bar of hydrogen with a flow rate of 0.5 mL/min. The resultant solution was concentrated *in vacuo* to give ethyl (2*S*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (304 mg, 92%) as a crystalline solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.25 - 7.22 (m, 1H), 6.85 - 6.78 (m, 1H), 4.79 (d, *J* = 8.0 Hz, 1H), 4.49 (t, *J* = 7.6, 7.6 Hz, 1H), 4.01 - 3.92 (m, 6H), 3.16 (s, 3H), 1.54 (s, 3H), 0.96 (t, *J* = 7.1, 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 398.115, found 399.6 (M+1)⁺; Retention time: 0.99 minutes using LC/MS method M.

[0669] Step 8:

[0670] KO^tBu (3.0 g, 26.7 mmol) was added to a solution of ethyl (2*S*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (3.4 g, 7.6 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min. The solution was acidified to pH 1 by addition of 1 M HCl (50 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and

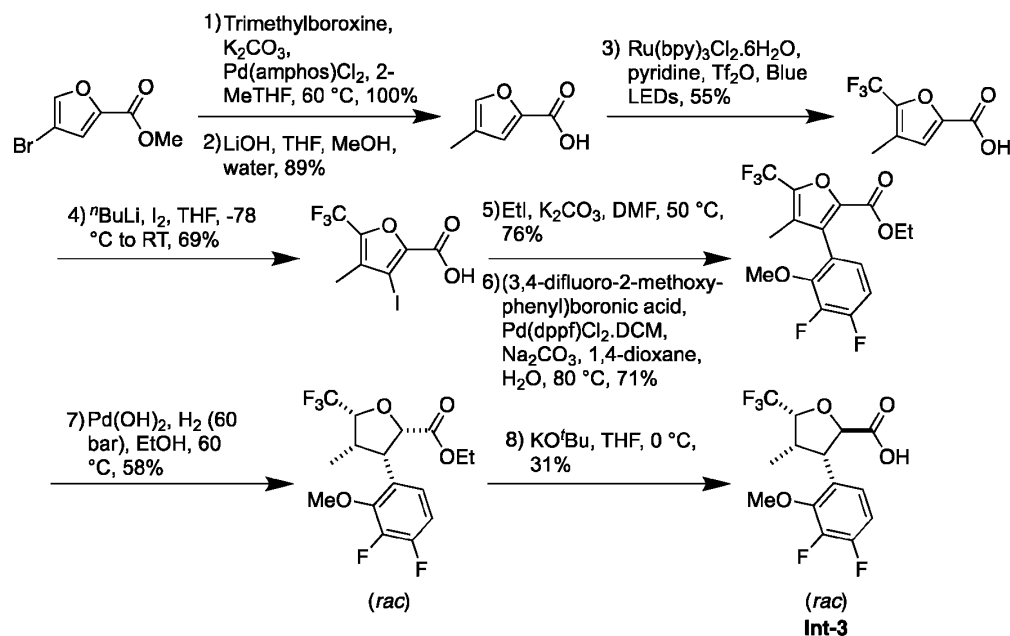
concentrated *in vacuo* to give (2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-2**, 2.81 g, 100%) as a pale yellow oil, which was used in the next step without any further purification. ESI-MS *m/z* calc. 370.084, found 369.7 (M-1)⁺; Retention time: 0.49 minutes using LC/MS method C.

[0671] The following intermediate was made using the method described in Intermediate 2, except that 2-(3,4-difluoro-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was used as the coupling partner in the Suzuki coupling Step 6 in place of (3,4-difluoro-2-methoxyphenyl)boronic acid. The reaction was carried out at 50 °C in the presence of K₃PO₄ as the base and Pd(dppf)Cl₂.DCM as the catalyst:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>R</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methylphenyl)-4-methoxy-5-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	354.089	353.1	2.09	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.29 - 7.16 (m, 1H), 7.05 (q, <i>J</i> = 8.8 Hz, 1H), 5.04 (d, <i>J</i> = 11.1 Hz, 1H), 3.82 (dd, <i>J</i> = 11.1, 4.8 Hz, 1H), 3.76 (d, <i>J</i> = 4.9 Hz, 1H), 2.93 (s, 3H), 2.33 (d, <i>J</i> = 2.4 Hz, 3H), 1.59 (d, <i>J</i> = 1.1 Hz, 3H) ppm; OH acid not observed.

Intermediate 3

rac-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-3**)



[0672] Step 1:

[0673] A solution of trimethylboroxine (25 g of 50 % w/w solution in THF, 99.6 mmol) and K_2CO_3 (21.5 g, 155.6 mmol) in water (40 mL) was added to a solution of methyl 4-bromofuran-2-carboxylate (10 g, 49 mmol) in 2-MeTHF (200 mL) and the reaction mixture degassed for 10 min. $Pd(amphos)Cl_2$ (1.5 g, 2.1 mmol) was added and the reaction mixture was further degassed for 5 min. The mixture was heated at 60 °C for 4 h before cooling down to ambient temperature. The mixture was filtered through a small pad of Celite®, washing the filtered cake with MTBE (200 mL). The layers were separated and the aqueous phase was extracted with MTBE (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and carefully concentrated *in vacuo* (approximately 90 mBar, no heating) to give methyl 4-methylfuran-2-carboxylate (6.836 g, 100%) which was used in the next step without any further purification.

[0674] Step 2:

[0675] $LiOH \cdot H_2O$ (12.3 g, 293 mmol) was added to a stirring solution of methyl 4-methylfuran-2-carboxylate (10 g, 48.8 mmol) in a mixture of THF (40 mL), water (40 mL) and MeOH (10 mL) at ambient temperature. The reaction was stirred for 2 h before MTBE (100 mL) and water (100 mL) were added. The aqueous layer was isolated and treated with a 6 N HCl solution to adjust the pH to about 3-4. The acidic layer was extracted with MTBE (2 x 50 mL). The combined organic extracts

were concentrated *in vacuo* to give 4-methylfuran-2-carboxylic acid (5.5 g, 89%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.92 (s, 1H), 7.65 (s, 1H), 7.07 (s, 1H), 2.00 (s, 3H) ppm.

[0676] Step 3:

[0677] Ru(bpy)₃Cl₂·6H₂O (17 mg, 0.023 mmol), pyridine (288 μL, 3.56 mmol) and triflic anhydride (599 μL, 3.56 mmol) were successively added dropwise over 5 min to a solution of 4-methylfuran-2-carboxylic acid (150 mg, 1.19 mmol) in DCE (25 mL). The mixture was irradiated with blue LEDs for 2 h at ambient temperature stirring at 800 rpm, using a PennPhD Photoreactor m2 (using 450 nm blue LED lights) and an EvoluChemTM PhotoRedOx Box device (using 455 nm blue LED lights) in parallel. This process was repeated in 5 batches and the crude materials were combined for purification. The combined reaction mixtures were washed with 1 M Na₂CO₃ (2 x 80 mL) and the organic layer was discarded. The combined aqueous phases were acidified to pH 2 using 1 M HCl and extracted with MTBE (2 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was redissolved in a small amount of Et₂O and slowly triturated by addition of hexanes. The liquid was decanted to afford 4-methyl-5-(trifluoromethyl)furan-2-carboxylic acid (700 mg at 90% purity, 55%) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.75 (brs, 1H), 7.29 (d, *J* = 1.2 Hz, 1H), 2.19 (q, *J* = 2.0 Hz, 3H) ppm. ESI-MS *m/z* calc. 194.019, found 193.3 (M-1)⁺; Retention time: 0.34 minutes using LC/MS method C.

[0678] Step 4:

[0679] ⁿBuLi (14 mL, 2.5 M solution in hexanes, 35 mmol) was added to a stirred solution of 4-methyl-5-(trifluoromethyl)furan-2-carboxylic acid (2.8 g, 14.0 mmol) in THF (40 mL) at -78 °C. The solution was stirred at -78 °C for 20 min before adding a solution of iodine (3.9 g, 15.4 mmol) in THF (5 mL). The mixture was warmed to ambient temperature, partitioned between MTBE (80 mL) and water (100 mL). The organic layer was discarded. The aqueous layer was acidified to pH 2 with 1 M HCl and extracted with MTBE (2 x 40 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (40 g SiO₂, 0 to 100% MTBE in hexanes) gave 3-iodo-4-methyl-5-(trifluoromethyl)furan-2-carboxylic acid (3.1 g, 69%) as an oil. ESI-MS *m/z* calc. 319.916, found 319.3 (M-1)⁺; Retention time: 0.42 minutes using LC/MS method C.

[0680] Step 5:

[0681] K₂CO₃ (276 mg, 2.00 mmol) and EtI (160 μL, 2.00 mmol) were added to a solution of 3-iodo-4-methyl-5-(trifluoromethyl)furan-2-carboxylic acid (300 mg at 71% purity, 0.666 mmol) in DMF (5 mL). The reaction mixture was heated to 50 °C for 2 h. The mixture was cooled to ambient temperature and partitioned between MTBE (40 mL) and water (80 mL). The aqueous phase was separated and extracted with MTBE (30 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (80 g SiO₂, 0 to 100% EtOAc in petroleum ether) gave ethyl 3-iodo-4-methyl-5-(trifluoromethyl)furan-2-

carboxylate (220 mg at 80% purity, 76%) as an oil. ^1H NMR (500 MHz, Chloroform-*d*) δ 4.42 (dq, J = 20.1, 7.1 Hz, 2H), 2.24 - 2.11 (m, 3H), 1.42 (dt, J = 20.2, 7.1 Hz, 3H) ppm.

[0682] Step 6:

[0683] To a solution of ethyl 3-iodo-4-methyl-5-(trifluoromethyl)furan-2-carboxylate (500 mg at 71% purity, 1.01 mmol) in 1,4-dioxane (2 mL) was added (3,4-difluoro-2-methoxy-phenyl)boronic acid (476 mg, 2.53 mmol), Pd(dppf)Cl₂·DCM (83 mg, 0.10 mmol) and 2 M aqueous Na₂CO₃ (2 mL, 4 mmol). The mixture was heated at 80 °C for 1 h before being cooling down to ambient temperature. The mixture was partitioned between MTBE (30 mL) and water (30 mL). The aqueous layer was separated and extracted with MTBE (10 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100% EtOAc hexanes) gave ethyl 3-(3,4-difluoro-2-methoxy-phenyl)-4-methyl-5-(trifluoromethyl)furan-2-carboxylate (330 mg at 80% purity, 71%) as an oil. ESI-MS m/z calc. 364.073, found 365.4 (M+1)⁺; Retention time: 1.08 minutes using LC/MS method C.

[0684] Step 7:

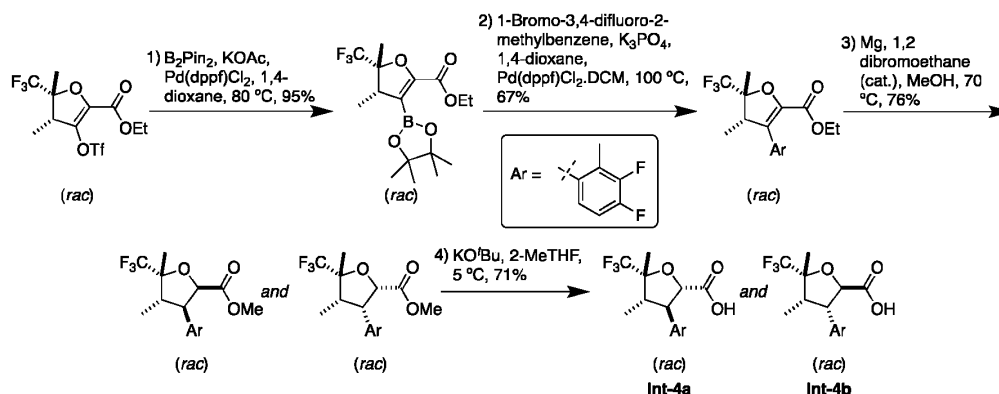
[0685] A solution of ethyl 3-(3,4-difluoro-2-methoxy-phenyl)-4-methyl-5-(trifluoromethyl)furan-2-carboxylate (410 mg at 70% purity, 0.788 mmol) in ethanol (2 mL) was passed through a 70 mm Pd(OH)₂ (90.52 mg, 0.64 mmol) CatCart[®] on an H-Cube[®] at 60 °C and a pressure of hydrogen of 60 bar. The mixture was recirculated for 30 h before being concentrated *in vacuo* to give ethyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (300 mg at 75% purity, 58%), which was used in the next step without further purification in the next step. ESI-MS m/z calc. 368.105, found 369.3 (M+1)⁺; Retention time: 1.01 minutes using LC/MS method C.

[0686] Step 8:

[0687] KO^tBu (822 mg, 7.33 mmol) was added to a stirring solution of ethyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (900 mg at 80% purity, 2.44 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min before being diluted with MTBE (5 mL) and quenched by addition of 1 M HCl. The aqueous layer was separated and extracted with MTBE (5 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4-methyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-3**, 500 mg at 52% purity, 31%) as an oil, which was used without further purification. ESI-MS m/z calc. 340.073, found 341.4 (M+1)⁺; 339.4 (M-1)⁻; Retention time: 0.54 minutes using LC/MS method C.

Intermediate 4

rac-(2*S*,3*R*,4*S*,5*R*)-3-(3,4-Difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-4a**) and *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-4b**)



[0688] Step 1:

[0689] To a 3-neck, 1-L flask flanked with a thermometer and air condenser was added ethyl *rac*-(4*R*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-3-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydrofuran-2-carboxylate (42 g, 108.7 mmol) and 1,4-dioxane (500 mL). The stirred mixture was degassed and flushed with nitrogen. KOAc (32 g, 326 mmol) was added followed by B_2Pin_2 (32 g, 126 mmol). The reaction mixture was evacuated and back filled with nitrogen (x 3). Pd(dppf) Cl_2 (4 g, 5.5 mmol) was added and the mixture was heated to 80 °C for 20 h. The reaction mixture was cooled down to ambient temperature and partitioned between EtOAc (300 mL) and water (100 mL). The mixture was filtered through a pad of Celite[®], washing the filtered cake with EtOAc (5 x 100 mL) until no more product came off. The filtrate phases were separated. The aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic layers were passed through a Whatmann[®] phase separation filter paper. The filtrates were concentrated *in vacuo* to give 47 g of a brown oil. Purification by flash chromatography (Florisil, 100% heptane) gave ethyl *rac*-(4*S*,5*R*)-4,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (47 g, 95%) as a thick viscous yellow oil. ¹H NMR (500 MHz, Chloroform-*d*) δ 4.33 - 4.23 (m, 2H), 3.27 - 3.18 (m, 1H), 1.55 (d, *J* = 1.1 Hz, 3H), 1.32 (s, 12H), 1.28 (d, *J* = 2.3 Hz, 3H), 1.24 (s, 3H) ppm. ESI-MS *m/z* calc. 364.167, found 365.3 (M+1)⁺; Retention time: 1.1 minutes using LC/MS method M.

[0690] Step 2:

[0691] A 2 M aqueous K_3PO_4 solution (8 mL, 16 mmol) was added to a solution of *rac*-(4*S*,5*R*)-4,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (3 g, 7.4 mmol), 1-bromo-3,4-difluoro-2-methylbenzene (1.4 g, 6.9 mmol) and Pd(dppf) Cl_2 .CH₂Cl₂ (350 mg, 0.429 mmol) in 1,4-dioxane (60 mL). The mixture was degassed and

placed under a nitrogen atmosphere. The reaction was stirred at 100 °C for 2 h. The mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (3x). The combined organic phases were passed through a Whatmann® phase separation filter paper. The filtrates were concentrated *in vacuo* to give a brown oil. Purification by flash chromatography (24 g SiO₂, 0 to 100% EtOAc in heptane) gave ethyl *rac*-(4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (2.213 g, 67%) as a pale yellow oil. ¹H NMR (500 MHz, Methanol-*d*₄) δ 7.10 (dt, *J* = 10.3, 8.4 Hz, 1H), 6.90 (s, 1H), 4.14 - 4.00 (m, 2H), 3.54 (d, *J* = 8.2 Hz, 1H), 2.19 (d, *J* = 2.7 Hz, 3H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.09 (dq, *J* = 7.5, 2.4 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 364.110, found 365.2 (M+1)⁺; Retention time: 1.08 minutes using LC/MS method C.

[0692] Step 3:

[0693] A pressure tube was loaded with magnesium powder (200 mg, 8.23 mmol) and purged with nitrogen. To the reaction vessel was added a solution of ethyl *rac*-(4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (2.02 g, 5.545 mmol) in MeOH (30 mL). The mixture was degassed and placed under a nitrogen atmosphere. A few drops of 1,2-dibromoethane (5 µL, 0.06 mmol) were added. The reaction mixture was stirred vigorously and heated at 70 °C for 6 h. A further 3 consecutive portions of magnesium powder (200 mg, 8.23 mmol) were added followed by a drop of 1,2-dibromoethane (5 µL, 0.06 mmol). The mixture was stirred at 70 °C for 88 h. The reaction mixture was cooled down to 0 °C prior to opening the pressure vessel. The cooled mixture was added dropwise to an ice cold 1 M solution of HCl. The reaction was stirred at 0 °C for 30 min until all Mg solids dissolved. The mixture was concentrated *in vacuo* to remove the MeOH. The resulting aqueous solution was extracted with EtOAc (x 3). The combined organic extracts were passed through a Whatmann® phase separation filter paper. The filtrate was concentrated *in vacuo* to give a mixture of methyl *rac*-(2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate and methyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.487 g, 76%) as a colourless oil. ESI-MS *m/z* calc. 352.110, found 353.3 (M+1)⁺; Retention times: 0.94, 1.00, 1.01 and 1.04 minutes using LC/MS method C.

[0694] Step 4:

[0695] To a cooled solution of a mixture of methyl *rac*-(2*R*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate and methyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.487 g, 4.221 mmol) in 2-MeTHF (20 mL) was added KO^tBu (1.4 g, 12.5 mmol), causing a ~5 °C increase in temperature. The reaction mixture turned yellow on addition of KO^tBu. The reaction was stirred for 1 h at ambient temperature. The reaction was diluted with EtOAc and 1 N NaOH. The aqueous layer was separated. The organic layer was washed further with 1 M NaOH (x 2). The combined organic layers were passed through a Whatmann® phase separation filter paper. The

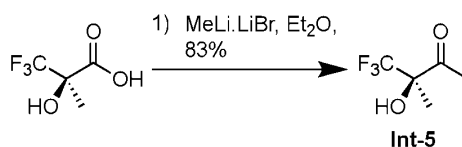
filtrate was concentrated *in vacuo* to give a mixture of 2 major diastereoisomers, *rac*-(2*S*,3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-4a**) and *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-4b**) (1.01 g, 71%) as a colourless oil. ESI-MS *m/z* calc. 338.094, found 337.0 (M-1)⁺; Retention times: 1.20 and 1.27 minutes for the 2 main diastereoisomers using LC/MS method B.

[0696] The following intermediate was made using the method described in Intermediate 4, except that the product of Step 2 was prepared by reaction of ethyl *rac*-(4*R*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-3-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydrofuran-2-carboxylate and different boronic acids using the Suzuki condition of Step 2 with K₂CO₃ as the base:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
<i>rac</i> -(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(2-Methoxy-3-(trifluoromethyl)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	386.095	385.2	0.61	C	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.54 - 7.41 (m, 2H), 7.11 (t, <i>J</i> = 7.8 Hz, 1H), 4.59 (d, <i>J</i> = 10.8 Hz, 1H), 4.11 (q, <i>J</i> = 7.1 Hz, 1H), 3.74 - 3.66 (m, 3H), 2.60 (p, <i>J</i> = 7.8 Hz, 1H), 1.36 (s, 3H), 1.25 - 1.18 (m, 3H) ppm; OH acid not observed.

Intermediate 5

(*R*)-4,4,4-Trifluoro-3-hydroxy-3-methylbutan-2-one (**Int-5**)



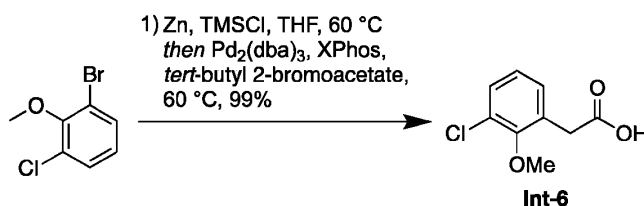
[0697] Step 1:

[0698] A jacketed glass reactor, dried and placed under nitrogen atmosphere, was charged with (*R*)-3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid (1.0 kg, 6.33 mol) and Et₂O (10 L). MeLi.LiBr (3.4 L of 1.5 M in Et₂O, 5.1 mol) was added slowly causing gas evolution and heat formation. The reactor was cooled to maintain a temperature of approximately 16 °C. Additional MeLi.LiBr (6.1 L, 2.2 M solution in Et₂O, 13.4 mol) was added slowly. The mixture was stirred overnight at ambient temperature. The reaction mixture was cooled to 0 °C and poured onto a mixture of water (6 L), ice (2 L) and brine (2 L). The mixture was neutralized by addition of citric acid (1.6 kg, 961 mL, 8.33 mol) and stirred for 30 min. The aqueous phase was separated and extracted with Et₂O (2 x 2.5 L). The combined organic extracts were concentrated *in vacuo* to approximately 2 L. The yellow distillate consisted of 0.8 % w/w product. After further distillation, only 25 g of product was recovered from the distillate. The distillation residue was further concentrated in a distillation

setup with vigreux (30 cm height) at normal pressure. The distillation was continued at reduced pressure (770 mbar) and the pressure was gradually lowered (until 200 mbar) with the collection flask cooled in ice and a cold trap between pump and setup. Mixed fractions were collected until the distillation temperature reached 71 °C. The major fraction (590 g) was then collected until the distillation temperature dropped below 70 °C. The combined mixed fractions were poured in brine and extracted with Et₂O (3 x 75 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in a distillation setup at normal pressure. The product was distilled at reduced pressure (200 mbar) to give the product as a colourless oil (198 g). The collected mixed fractions were redistilled to afford more product (44.25 g). All portions of product were combined (857 g), dried by addition of K₂CO₃ (52 g) and left standing for 6 h. The water level dropped below detectable level and the mixture was filtered over a glass filter to give (*R*)-4,4,4-trifluoro-3-hydroxy-3-methylbutan-2-one (**Int-5**, 815 g, 83%) as a colourless oil (815 g). ¹H NMR (300 MHz, Chloroform-*d*) δ 4.33 (s, 1H), 2.40 (d, *J* = 1.1 Hz, 3H), 1.57 (d, *J* = 1.1 Hz, 3H) ppm. ¹⁹F NMR (282 MHz, Chloroform-*d*) δ -77.96 ppm.

Intermediate 6

2-(3-Chloro-2-methoxyphenyl)acetic acid (**Int-6**)



[0699] Step 1:

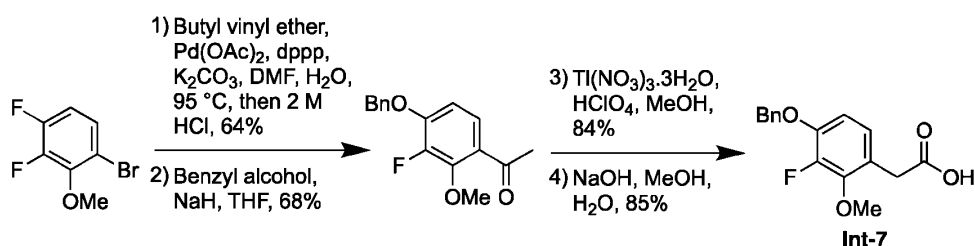
[0700] Chlorotrimethylsilane (1.03 g, 1.2 mL, 9.455 mmol) was added to a slurry of zinc powder (7 g, 107 mmol) in anhydrous THF (100 mL) and the mixture was stirred under argon at 60 °C for 2 h. *tert*-Butyl 2-bromoacetate (17.2 g, 12.9 mL, 88.0 mmol) was slowly added to the reaction mixture. The mixture was stirred at 60 °C for 1 h, giving a clear solution with a small amount of unreacted zinc dust. In a second flask, a solution of 1-bromo-3-chloro-2-methoxybenzene (15 g, 67.7 mmol), XPhos (1.62g, 3.398 mmol) and Pd₂(dba)₃ (1.55 g, 1.69 mmol) in THF (150 mL) was degassed with argon for 10 min before adding the freshly prepared organozincate solution via cannula. The reaction mixture was heated at 60 °C for 2 h, then left to stir at ambient temperature for 16 h. The mixture was quenched by addition of a 10% citric acid solution (60 mL). The mixture was diluted with EtOAc (100 mL). The organic phase was separated, washed with brine (50 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give 2-(3-chloro-2-methoxyphenyl)acetic acid (**Int-6**, 30 g, 99%) as a red solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.31 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.15 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 2H) ppm; OH acid not observed.

[0701] The following intermediate was made using the method described in Intermediate 6, except that 1-bromo-3,4-difluoro-2-methylbenzene was used as the starting material in the Negishi coupling Step 1 in place of 1-bromo-3-chloro-2-methoxybenzene. A subsequent ester hydrolysis step was carried out in the presence of an excess of TFA in DCM as the solvent:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
2-(3,4-Difluoro-2-methylphenyl)acetic acid	186.049		0.74	N	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 6.99-6.90 (m, 2H), 3.64 (s, 2H), 2.24 (d, <i>J</i> = 3.4 Hz, 3H) ppm; OH acid not observed.

Intermediate 7

2-(4-(Benzyloxy)-3-fluoro-2-methoxyphenyl)acetic acid (Int-7)



[0702] Step 1:

[0703] A mixture of 1-bromo-3,4-difluoro-2-methoxybenzene (5 g, 22 mmol), butyl vinyl ether (9 mL, 66.5 mmol), K₂CO₃ (3.74 g, 27.0 mmol), dppp (612.8 mg, 1.486 mmol), and Pd(OAc)₂ (152 mg, 0.677 mmol) in DMF (50 mL) and H₂O (5 mL) was degassed (vacuum nitrogen cycles x 3) and heated to 95 °C overnight. The reaction mixture was cooled down to ambient temperature. 2 M HCl (80 mL, 160 mmol) was added and the mixture was stirred at ambient temperature for 30 min. The mixture was extracted with EtOAc (2 x). The combined organic phases were washed with a saturated NaHCO₃ solution and brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (120 g SiO₂, 0 to 5% EtOAc in hexanes) gave 1-(3,4-difluoro-2-methoxyphenyl)ethan-1-one (2.687 g, 64%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.50 (ddd, *J* = 9.0, 6.1, 2.3 Hz, 1H), 6.92 (td, *J* = 9.0, 6.9 Hz, 1H), 4.08 (d, *J* = 2.7 Hz, 3H), 2.60 (s, 3H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -129.21 (d, *J* = 19.0 Hz), -153.39 (d, *J* = 19.0 Hz) ppm.

[0704] Step 2:

[0705] A solution of benzyl alcohol (2.9 g, 26.8 mmol) in DMF (10 mL) was added to a stirred suspension of NaH (1.05 g, 60 % w/w dispersion in mineral oil, 26.3 mmol) in DMF (40 mL) at ambient temperature. After stirring the mixture for 5 min, 1-(3,4-difluoro-2-methoxyphenyl)ethan-1-one (5 g, 26.9 mmol) was added and the stirring was continued at ambient temperature for 30 min. 2

N HCl (10 mL) and brine (100 mL) were added and the mixture was extracted with EtOAc (100 mL then 50 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 10 to 30% EtOAc in heptane) gave 1-(4-(benzyloxy)-3-fluoro-2-methoxyphenyl)ethan-1-one (5.03 g, 68%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.51 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.44-7.34 (m, 5H), 6.76 (dd, *J* = 8.9, 7.1 Hz, 1H), 5.17 (s, 2H), 4.03 (d, *J* = 2.3 Hz, 3H), 2.58 (s, 3H) ppm. ESI-MS *m/z* calc. 274.101, found 273.0 (M-1)⁻; Retention time: 0.98 minutes using LC/MS method P.

[0706] Step 3:

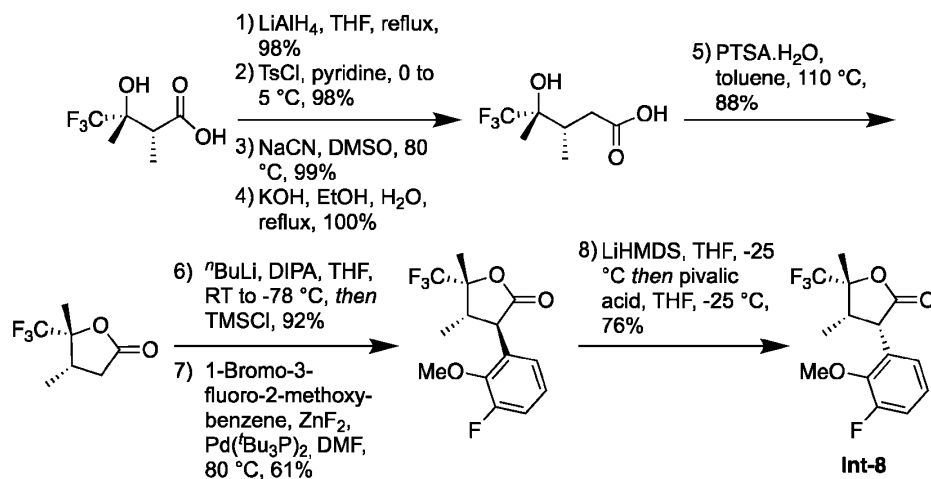
[0707] A solution of 1-(4-(benzyloxy)-3-fluoro-2-methoxyphenyl)ethan-1-one (14.8 g, 54.0 mmol) in methanol (50 mL) was added dropwise to a stirred solution of Ti(NO₃)₃·3H₂O (24 g, 54.0 mmol) and perchloric acid (50 mL, 60 % w/v in water, 299 mmol) in methanol (200 mL). The mixture was stirred at ambient temperature for 4.5 h. The precipitate was filtered and washed with MeOH (2 x 50 mL). The methanolic filtrate was poured into water (1 L) and extracted with DCM (2 x 200 mL). The combined organic extracts were washed with water (100 mL) and brine (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give methyl 2-(4-(benzyloxy)-3-fluoro-2-methoxy-phenyl)acetate (15.25 g, 84%) as a yellow oil, which was used without further purification in the next step. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.44-7.32 (m, 5H), 6.84 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.67 (t, *J* = 8.2 Hz, 1H), 5.11 (s, 2H), 3.93 (d, *J* = 1.8 Hz, 3H), 3.69 (s, 3H), 3.58 (s, 2H) ppm. ESI-MS *m/z* calc. 304.111, found 305.2 (M+1)⁺; Retention time: 2.44 minutes using LC/MS method J.

[0708] Step 4:

[0709] Methyl 2-(4-(benzyloxy)-3-fluoro-2-methoxy-phenyl)acetate (15.2 g, 49.95 mmol) was added to a solution of NaOH (6 g, 150 mmol) in MeOH (30 mL) and water (10 mL). The solution was stood at ambient temperature for 14 h giving an orange solid. The crude product was diluted with a 2 N NaOH solution (200 mL) and extracted with DCM (2 x 30 mL). The aqueous layer was acidified with 6 M HCl (100 mL) and extracted with DCM-ⁱPrOH (9:1, 2 x 150 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give 2-(4-(benzyloxy)-3-fluoro-2-methoxyphenyl)acetic acid (**Int-7**, 13.15 g, 85%) as an orange solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46-7.33 (m, 5H), 6.85 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.69 (t, *J* = 8.0 Hz, 1H), 5.11 (s, 2H), 3.96 (d, *J* = 2.3 Hz, 3H), 3.62 (s, 2H) ppm; OH acid not observed. ESI-MS *m/z* calc. 290.095, found 289.0 (M-1)⁻; Retention time: 2.19 minutes using LC/MS method I.

Intermediate 8

(3*S*,4*S*,5*R*)-3-(3-Fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one
(Int-8)



[0710] Step 1:

[0711] To THF (3 L) under argon was added portionwise LiAlH_4 (200 g, 5.270 mol) over 1 h. The mixture was stirred for 4 h then left to stand overnight at ambient temperature. The mixture was cooled to 0 °C and a solution of (2*R*,3*R*)-4,4,4-trifluoro-3-hydroxy-2,3-dimethylbutanoic acid (326.9 g, 1.756 mol) in THF (1 L) was added over 40 min, keeping the temperature below 22 °C. At the end of the addition, the reaction mixture was heated under reflux for 1.5 h then cooled to 0 °C. A 1:1 mixture of THF and water (1 L) was added dropwise over 1 h keeping the temperature below 20 °C. A 5 M aqueous HCl solution (4 L) was added dropwise over 40 min, while keeping the temperature between 10 and 20 °C. The mixture was extracted with MTBE (2 x 1.5 L). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give (2*S*,3*R*)-4,4,4-trifluoro-2,3-dimethylbutane-1,3-diol (311.2 g, 98%) as a pale yellow oil, which was used without further purification in the next step. ^1H NMR (400 MHz, CHCl_3 -*d*) δ 4.28 (s, 2H), 3.85 (m, 1H), 3.72 (m, 1H), 2.03 (m, 1H), 1.36 (s, 3H), 1.03 (m, 3H) ppm.

[0712] Step 2:

[0713] TsCl (63.4 g, 333 mmol) was added portionwise to a solution of (2*S*,3*R*)-4,4,4-trifluoro-2,3-dimethylbutane-1,3-diol (46 g, 266 mmol) in pyridine (230 mL) at 0 to 5 °C. On complete addition, the mixture was stirred at 0 to 5 °C for 5 h then stored at 10 °C overnight. The mixture was poured onto ice-water (1 L) and extracted with MTBE (2 x 500 mL). The combined organic extracts were washed with a 2 M aqueous HCl (2 x 500 mL) then with a saturated aqueous copper sulphate solution (500 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give (2*S*,3*R*)-4,4,4-trifluoro-3-hydroxy-2,3-dimethylbutyl 4-methylbenzenesulfonate (86.1 g, 98%) as an orange oil, which was

used without further purification in the next step. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.77 (m, 2H), 7.35 (m, 2H), 4.26 (m, 1H), 3.90 (m, 1H), 2.45 (s, 3H), 2.21 - 1.98 (m, 2H), 1.34 (s, 3H), 1.07 (m, 3H) ppm.

[0714] Step 3:

[0715] Sodium cyanide (67.4 g, 1.38 mol) was added to a solution of (2*S*,3*R*)-4,4,4-trifluoro-3-hydroxy-2,3-dimethylbutyl 4-methylbenzenesulfonate (149.7 g, 458.7 mmol) in DMSO (750 mL) and the reaction mixture was heated at 80 °C overnight. On cooling to ambient temperature, water (2.25 L) was added and the mixture was extracted with MTBE (3 x 1 L). The combined organic extracts were washed with brine (1 L), dried (Na_2SO_4), filtered and concentrated *in vacuo* to give (3*S*,4*R*)-5,5,5-trifluoro-4-hydroxy-3,4-dimethylpentanenitrile (85.3 g, 99%) as an orange oil, which was used without further purification in the next step. ^1H NMR (400 MHz, Chloroform-*d*) δ 3.22 (br s, 1H), 2.75 (m, 1H), 2.32 - 2.16 (m, 2H), 1.41 (m, 3H), 1.31 (m, 3H) ppm.

[0716] Step 4:

[0717] Potassium hydroxide (15.6 g, 236 mmol) was added to a solution of (3*S*,4*R*)-5,5,5-trifluoro-4-hydroxy-3,4-dimethylpentanenitrile (11.7 g, 54.9 mmol) in a mixture of EtOH (100 mL) and water (100 mL). The resultant solution was heated under reflux overnight. On cooling to ambient temperature, the ethanol was removed *in vacuo* and the resultant aqueous solution was extracted with MTBE (2 x 100 mL). The aqueous solution was cooled to 5 °C, acidified to pH 1 with concentrated HCl (30 mL) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give (3*S*,4*R*)-5,5,5-trifluoro-4-hydroxy-3,4-dimethylpentanoic acid (11.1 g, 100%) as a yellow solid, which was used without further purification in the next step. ^1H NMR (400 MHz, Chloroform-*d*) δ 2.84 (dd, J = 16.3, 4.0 Hz, 1H), 2.48 - 2.35 (m, 1H), 2.31 - 2.20 (m, 1H), 1.38 (q, J = 1.1 Hz, 3H), 1.13 (dq, J = 7.0, 1.3 Hz, 3H) ppm; OH acid and alcohol not observed.

[0718] Step 5:

[0719] A mixture of (3*S*,4*R*)-5,5,5-trifluoro-4-hydroxy-3,4-dimethylpentanoic acid (5 g, 25 mmol), PTSA monohydrate (4.8 g, 25.2 mmol) and toluene (100 mL) was heated under reflux for 2 h with Dean-Stark apparatus. On cooling to ambient temperature, the reaction mixture was washed with a saturated aqueous NaHCO_3 solution (2 x 100 mL). The aqueous phase was extracted with MTBE (100 mL) and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give (4*S*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (4.3 g, 88%) as a red oil, which was used without further purification in the next step. ^1H NMR (400 MHz, Chloroform-*d*) δ 2.73 - 2.64 (m, 1H), 2.64 - 2.54 (m, 1H), 2.54 - 2.42 (m, 1H), 1.62 (q, J = 1.0 Hz, 3H), 1.29 (dt, J = 6.7, 2.2 Hz, 3H) ppm.

[0720] Step 6:

[0721] "Buli (40 mL, 1.6 M solution in hexanes, 64 mmol) was added over 20 min to a solution of diisopropylamine (7.80 g, 10.8 mL, 77.1 mmol) in THF (45 mL). Upon complete addition, the

mixture was stirred for 5 min before being cooled to -78 °C. A solution of (4*S*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (9.11 g, 48.22 mmol) in THF (27 mL) was added dropwise over 15 min and the mixture was stirred at -78 °C for 20 min. TMSCl (6.25 g, 7.3 mL, 57.5 mmol) was added dropwise over 5 min and the cooling bath was removed. The reaction mixture was warmed to ambient temperature. After 2 h, the mixture was concentrated *in vacuo*. The residue was dissolved in heptane (60 mL) and the resultant suspension was filtered. The filtrate was collected and concentrated *in vacuo* to give (((4*S*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-yl)oxy)trimethylsilane (12.18 g, 92%) as an orange oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 3.53 - 3.51 (m, 1H), 2.83 - 2.76 (m, 1H), 1.35 - 1.34 (m, 3H), 1.02 - 0.98 (m, 3H), 0.10 (s, 9H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -76.1 (s, 3F) ppm.

[0722] Step 7:

[0723] A solution of 1-bromo-3-fluoro-2-methoxybenzene (1.07 g, 5.22 mmol) and (((4*S*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-yl)oxy)trimethylsilane (3.48 g, 8.35 mmol) in DMF (25 mL) was purged with argon for 5 min. Zinc fluoride (270 mg, 2.612 mmol) and Pd(^tBu₃P)₂ (134 mg, 0.262 mmol) were sequentially added and the mixture was heated to 80 °C overnight. The mixture was concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 17% EtOAc in heptane) gave (3*R*,4*S*,5*R*)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (1.07 g, 61%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.12 - 7.05 (m, 1H), 7.01 - 6.95 (m, 1H), 6.91 - 6.86 (m, 1H), 3.93 (d, *J* = 2.6 Hz, 3H), 3.57 (d, *J* = 12.1 Hz, 1H), 2.78 - 2.67 (m, 1H), 1.66 (s, 3H), 1.20 - 1.15 (m, 3H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -76.1 (s, 3F), -129.0 (s, 1F) ppm. ESI-MS *m/z* calc. 306.088, found 307.0 (M+1)⁺; Retention time: 1.04 minutes using LC/MS method P.

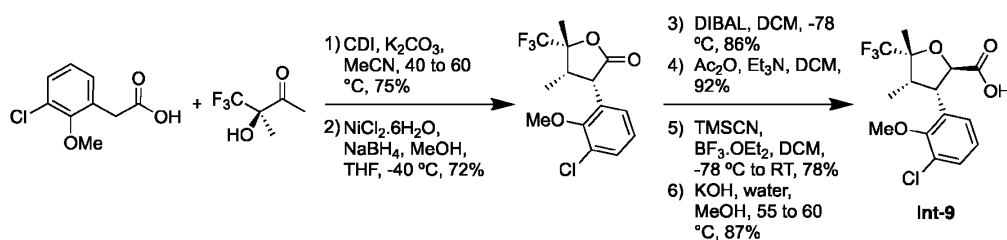
[0724] Step 8:

[0725] A solution of (3*R*,4*S*,5*R*)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (2.4 g, 7.4 mmol) in THF (25 mL) was added dropwise to a stirred solution of LiHMDS (9.93 mL, 1 M solution in THF, 9.93 mmol) under argon at -25 °C. The mixture was warmed to 0 °C and stirred for 1 h, then cooled back down to -25 °C. The solution was added via cannula to a stirred solution of pivalic acid (7.5 g, 73.4 mmol) in THF (50 mL) cooled to -25 °C under argon. The reaction mixture was stirred for 20 min at -25 °C then MTBE (125 mL) was added, keeping the temperature below -15 °C. The mixture was warmed to 0 °C and 1 M HCl (60 mL) was added, keeping the temperature below 5 °C. NaCl (12 g, 205 mmol) was added and the mixture was warmed to ambient temperature. The organic layer was separated and concentrated *in vacuo*. The residue was redissolved in MTBE and washed with aqueous NaHCO₃, 0.5 M HCl and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 25% EtOAc in heptane) gave (3*S*,4*S*,5*R*)-3-(3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (**Int-8**, 1.743 g, 76%) as a colourless oil. ¹H NMR (400

MHz, Chloroform-*d*) δ 7.10 - 6.99 (m, 3H), 4.55 (d, J = 9.2 Hz, 1H), 3.97 (d, J = 2.7 Hz, 3H), 2.90 (dt, J = 16.9, 7.6 Hz, 1H), 1.71 (d, J = 0.9 Hz, 3H), 0.82 - 0.79 (m, 3H) ppm.

Intermediate 9

(2*R*,3*S*,4*S*,5*R*)-3-(3-Chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-9**)



[0726] Step 1:

[0727] 2-(3-Chloro-2-methoxyphenyl)acetic acid (**Int-6**, 8.17 g, 39.3 mmol), dissolved in MeCN (80 mL) at 40 °C, was added over 5 min to a stirred solution of CDI (7.8 g, 48.1 mmol) in MeCN (60 mL) at 40 °C. The reaction mixture was stirred for 30 min. (*R*)-4,4,4-trifluoro-3-hydroxy-3-methylbutan-2-one (**Int-5**, 7.6 g, 48.7 mmol) and K₂CO₃ (7.34 g, 53.1 mmol) were successively added to the reaction mixture, which was stirred at 60 °C for 16 h. The mixture was filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with 2 N HCl (100 mL), with a saturated aqueous NaHCO₃ solution (2 x 30 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give a brown solid (11.5 g). Purification by flash chromatography (300 g SiO₂, 0 to 90 % EtOAc in heptane) gave (*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)furan-2(5*H*)-one (9 g, 75%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46 (dd, J = 7.8, 1.8 Hz, 1H), 7.19 (dd, J = 7.8, 1.8 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 3.67 (s, 3H), 2.05 (s, 3H), 1.75 (d, J = 0.9 Hz, 3H) ppm. ESI-MS m/z calc. 320.043, found 321.0 (M+1)⁺; 318.9 (M-1)⁻; Retention time: 2.74 minutes using LC/MS method J.

[0728] Step 2:

[0729] NiCl₂·6H₂O (2.55 g, 10.7 mmol) was added to a stirred and previously degassed solution of (*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)furan-2(5*H*)-one (3.4 g, 10.4 mmol) in MeOH (100 mL) and THF (30 mL) at -40 °C. NaBH₄ (2 g, 52.9 mmol) was added portionwise over 30 min and the reaction mixture was stirred at -40 °C. Further amounts of NiCl₂ (1 x 1 eq and 1 x 0.5 eq) and NaBH₄ (1 x 5 eq and 1 x 2.5 eq) were added portionwise. Upon reaction completion, the mixture was quenched by addition of a NH₄Cl solution (30 mL). The reaction mixture was warmed up to ambient temperature and stirred under nitrogen for 15 min. The aqueous phase was separated and extracted with DCM (2 x 100 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give (3*S*,4*S*,5*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-

dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (2.93 g, 72%) as a colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.16 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 4.57 (d, *J* = 9.2 Hz, 1H), 3.90 (s, 3H), 2.92 (dd, *J* = 9.4, 7.6 Hz, 1H), 1.72 (d, *J* = 0.9 Hz, 3H), 0.81-0.78 (m, 3H) ppm. ESI-MS *m/z* calc. 322.058, found 323.0 (M+1)⁺; Retention time: 2.79 minutes using LC/MS method I.

[0730] Step 3:

[0731] DIBAL (37 mL, 1 M solution in hexane, 37 mmol) was added dropwise to a stirring solution of (3*S*,4*S*,5*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (6.84 g, 14.84 mmol) in DCM (100 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 1 h. The mixture was quenched by addition of 2 N HCl (30 mL) and diluted with DCM (100 mL). The aqueous layer was separated and extracted with DCM (100 mL). The combined organic extracts were washed with 2 N HCl (30 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *dia*-(2*S*^{*l*},3*S*^{***},4*S*^{***},5*R*^{***})-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-ol (5.9 g, 86%) as a colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.32-7.28 (m, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 5.83 (d, *J* = 5.0 Hz, 1H), 3.87 - 3.85 (m, 1H), 3.86 (s, 3H), 2.92 - 2.81 (m, 1H), 1.64 - 1.63 (m, 3H), 0.80 (td, *J* = 4.8, 2.6 Hz, 3H) ppm; OH alcohol not observed. ESI-MS *m/z* calc. 324.074, found 323.0 (M-1)⁻; Retention time: 2.55 minutes using LC/MS method I.

[0732] Step 4:

[0733] Ac₂O (2.813 g, 2.6 mL, 27.556 mmol) was added to a solution of *dia*-(2*S*^{*l*},3*S*^{***},4*S*^{***},5*R*^{***})-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-ol (5.9 g, 13.6 mmol) and Et₃N (2.8 g, 3.8 mL, 27.3 mmol) in DCM (40 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 14 h. The mixture was quenched by addition of water (30 mL). The mixture was stirred for 30 min at ambient temperature and diluted with DCM (60 mL). The organic phase was separated, washed with 2 N HCl (20 mL), with a saturated aqueous NaHCO₃ solution (2 x 20 mL) and brine (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *dia*-(2*S*^{*l*},3*S*^{***},4*S*^{***},5*R*^{***})-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl acetate (6.15 g, 92%) as a colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.32-7.27 (m, 1H), 7.24 - 7.19 (m, 1H), 7.05 - 7.01 (m, 1H), 6.58 (d, *J* = 3.2 Hz, 1H), 4.07 - 4.02 (m, 1H), 3.83 (s, 3H), 2.96 - 2.85 (m, 1H), 2.08 (s, 3H), 1.62 (d, *J* = 0.9 Hz, 3H), 0.85 - 0.82 (m, 3H) ppm.

[0734] Step 5:

[0735] TMSCN (3.7 g, 5.1 mL, 37.5 mmol) and BF₃·(OEt)₂ (5.41 g, 4.7 mL, 38.1 mmol) were successively added to a stirred solution of *dia*-(2*S*^{*l*},3*S*^{***},4*S*^{***},5*R*^{***})-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl acetate (6.150 g, 12.576 mmol) in DCM (40 mL) under argon at -78 °C. The reaction mixture was stirred at -78 °C for 1 h and at ambient temperature for 14 h. The mixture was poured over a K₂CO₃ solution (100 mL) and extracted with DCM (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in*

vacuo to give *dia*-(2*R'*,3*S'*,4*S'*,5*R'*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carbonitrile (4.99 g, 78%) as an orange oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.37 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.11 - 7.06 (m, 1H), 6.99 - 6.97 (m, 1H), 5.02 (d, *J* = 10.1 Hz, 1H), 4.29 (dd, *J* = 10.1, 8.2 Hz, 1H), 3.93 (s, 3H), 2.86 (m, *J* = 7.8 Hz, 1H), 1.63 (s, 3H), 0.81 - 0.77 (m, 3H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -74.5 (s, 3F) ppm.

[0736] Step 6:

[0737] A stirring mixture of *dia*-(2*R'*,3*S'*,4*S'*,5*R'*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carbonitrile (325 mg, 0.730 mmol) and KOH (140 mg, 2.495 mmol) in a mixture of methanol (5 mL) and water (1 mL) was heated at 55 °C for 14 h. A further amount of KOH (164 mg, 2.92 mmol) was added to the mixture, which was stirred at 60 °C for an additional 8 h. The methanol was removed *in vacuo* and the residue was diluted with water (10 mL). The aqueous residue was extracted with MTBE (5 mL), acidified with 6 N HCl (3 mL) and extracted with MTBE (2 x 10 mL). The initial MTBE extracts were discarded. The remaining combined organic extracts were washed with brine (5 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give (2*R*,3*S*,4*S*,5*R*)-3-(3-chloro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-9**, 265 mg, 87%) as a colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.32 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.16 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 10.5 Hz, 1H), 4.20 (dd, *J* = 10.5, 7.8 Hz, 1H), 3.85 (d, *J* = 5.5 Hz, 3H), 2.76 (td, *J* = 15.2, 7.6 Hz, 1H), 1.62 (s, 3H), 0.76 (td, *J* = 4.8, 2.4 Hz, 3H) ppm; OH acid not observed. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -74.4 (s, 3F) ppm. ESI-MS *m/z* calc. 352.069, found 351.0 (M-1)⁻; Retention time: 2.51 minutes using LC/MS method I.

[0738] The following intermediates were made using the method described in Intermediate 9, except that different aryl acetic acids were used as the starting material in the cyclocondensation Step 1 in place of 2-(3-chloro-2-methoxyphenyl)acetic acid (**Int-6**):

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	338.094	337.0	2.56	I	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.00 - 6.89 (m, 2H), 4.99 (t, <i>J</i> = 10.7 Hz, 1H), 4.00 - 3.91 (m, 1H), 2.71 - 2.55 (m, 1H), 2.23 (d, <i>J</i> = 2.3 Hz, 3H), 1.60 (s, 3H), 0.74 - 0.70 (m, 3H) ppm; OH acid not observed.
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-Fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	336.099	335.0	2.44	I	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.18 - 7.09 (m, 1H), 6.66 - 6.58 (m, 2H), 4.99 - 4.97 (m, 1H), 4.13 (dd, <i>J</i> = 10.5, 7.8 Hz, 1H), 3.81 (s, 3H), 2.80 - 2.72 (m, 1H), 1.61 (s, 3H), 0.70 (td, <i>J</i> = 4.8, 2.3 Hz, 3H) ppm; OH acid not observed.

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(4-Fluoro-2-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	320.104	319.1	2.52	I	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.23 - 7.17 (m, 1H), 6.95 - 6.86 (m, 2H), 5.01 (d, <i>J</i> = 11.0 Hz, 1H), 4.00 (dd, <i>J</i> = 10.5, 7.8 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.29 (s, 3H), 1.62 (s, 3H), 0.73 (d, <i>J</i> = 4.8 Hz, 3H) ppm; OH acid not observed.

[0739] The following intermediate was made using the method described in Intermediate 9, except that the product of Step 2 was prepared using the method described in Intermediate 8:

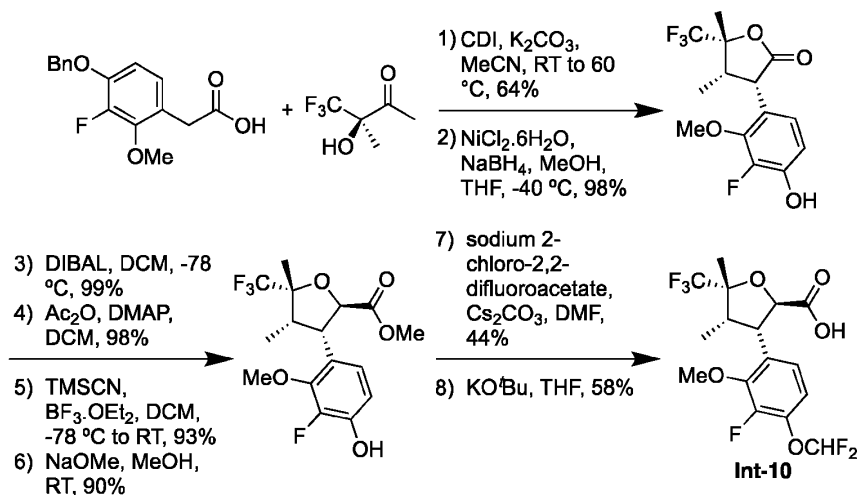
Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3-Fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid	336.099	335.1	1.05	J	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.06 - 6.96 (m, 3H), 4.98 (d, <i>J</i> = 10.5 Hz, 1H), 4.21 - 4.11 (m, 1H), 3.94 (d, <i>J</i> = 2.3 Hz, 3H), 2.78 - 2.70 (m, 1H), 1.62 (d, <i>J</i> = 0.9 Hz, 3H), 0.77 - 0.74 (m, 3H) ppm; OH acid not observed.

[0740] The following intermediate was made using the method described in Intermediate 9, except that the product of Step 2 was prepared using the method described in Intermediate 17. Step 6 was omitted:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M-26	MS r.t.	LC/MS Method	NMR (shifts in ppm)
(2 <i>R</i> ,3 <i>S</i> ,4 <i>S</i> ,5 <i>R</i>)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carbonitrile	335.095	309.1	2.94	R	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 6.99 - 6.73 (m, 2H), 5.01 (d, <i>J</i> = 8.7 Hz, 1H), 4.21 (t, <i>J</i> = 8.5 Hz, 1H), 4.09 - 4.05 (m, 3H), 2.87 - 2.79 (m, 1H), 1.63 - 1.59 (m, 3H), 0.79 (t, <i>J</i> = 3.4 Hz, 3H) ppm.

Intermediate 10

(2*R*,3*S*,4*S*,5*R*)-3-(4-(Difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-10**)



[0741] Step 1:

[0742] CDI (6 g, 37 mmol) was added to a solution of 2-(4-(benzyloxy)-3-fluoro-2-methoxyphenyl)acetic acid (**Int-7**, 9.8 g, 32.1 mmol) in MeCN (100 mL) and the mixture was stirred for 15 min at 40 °C. (*R*)-4,4,4-trifluoro-3-hydroxy-3-methylbutan-2-one (**Int-5**, 6 g, 38.4 mmol) and K₂CO₃ (5.5 g, 39.8 mmol) were added and the stirring was continued at 60 °C for 30 h. The reaction mixture was diluted with water (50 mL) and extracted with MTBE (2 x 100 mL). The organic layer was washed with 2 M HCl (2 x 50 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (120 g SiO₂, 0 to 100% EtOAc in heptane) gave (*R*)-3-(4-(benzyloxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)furan-2(5*H*)-one (9.17 g, 64%) as a yellow solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46 - 7.34 (m, 5H), 6.91 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.80 (dd, *J* = 8.7, 7.8 Hz, 1H), 5.16 (s, 2H), 3.85 (d, *J* = 1.8 Hz, 3H), 2.03 (s, 3H), 1.73 (s, 3H) ppm. ESI-MS *m/z* calc. 410.114, found 411.2 (M+1)⁺; Retention time: 2.97 minutes using LC/MS method J.

[0743] Step 2:

[0744] NiCl₂·6H₂O (1.8 g, 7.6 mmol) was added to a stirred and previously degassed solution of (*R*)-3-(4-(benzyloxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)furan-2(5*H*)-one (3 g, 7.3 mmol) in a mixture of MeOH (300 mL) and THF (60 mL) at -40 °C. NaBH₄ (1.4 g, 37 mmol) was added portionwise and the reaction mixture was stirred until completion. A total of 7 eq of NiCl₂·6H₂O were added. A saturated NH₄Cl solution (100 mL) was added and the mixture partitioned with DCM (100 mL). The organic phase was separated, dried (MgSO₄), filtered, and concentrated *in vacuo* to give a mixture of stereoisomers with (3*S*,4*S*,5*R*)-3-(3-fluoro-4-hydroxy-2-methoxyphenyl)-

4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (2.3 g, 98%) as the main diastereoisomer, which was used in the next step without further purification. ESI-MS *m/z* calc. 322.083, found 321.4 (M-1)⁺; Retention time: 0.79 minutes using LC/MS method C.

[0745] Step 3:

[0746] DIBAL (15 mL, 1 M solution in DCM, 15 mmol) was added dropwise to a stirred solution of (3*S*,4*S*,5*R*)-3-(3-fluoro-4-hydroxy-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (2.3 g, 7.14 mmol) in DCM (40 mL) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C. Upon reaction completion, the mixture was quenched by addition of a 1:1 saturated NH₄Cl solution and Rochelle's salt solution (100 mL, 30 % w/w aqueous). The resulting mixture was vigorously stirred at ambient temperature until a clear phase separation was achieved. The organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to give a mixture of stereoisomers with *dia*-(2*S'*,3*S''*,4*S''*,5*R''*)-3-(3-fluoro-4-hydroxy-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-ol (2.3 g, 99%) as the main diastereoisomer, which was used in the next step without further purification. ESI-MS *m/z* calc. 324.098, found 323.4 (M-1)⁺; Retention time: 0.73 minutes using LC/MS method C.

[0747] Step 4:

[0748] Acetic anhydride (700 μL, 7.42 mmol) was added to a stirred solution of *dia*-(2*S'*,3*S''*,4*S''*,5*R''*)-3-(3-fluoro-4-hydroxy-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-ol (380 mg, 1.17 mmol) and DMAP (210 mg, 1.72 mmol) in DCM (4 mL) at ambient temperature and under a nitrogen atmosphere. The reaction mixture was stirred at ambient temperature. Upon reaction completion, the mixture was quenched by addition of saturated NaHCO₃ solution (30 mL). The mixture was diluted with DCM (20 mL). The aqueous phase was separated and extracted with DCM (10 mL). The combined organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (24g SiO₂, 0 to 100% EtOAc in heptane) gave a mixture of stereoisomers with *dia*-(2*S'*,3*S''*,4*S''*,5*R''*)-3-(4-acetoxy-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl acetate as the main diastereomer (470 mg, 98%) and a mixture of epimers at the C₂ position, which was used in the next step without further purification. ESI-MS *m/z* calc. 408.120, found 407.3 (M-1)⁺; Retention time: 1.01 minutes using LC/MS method C.

[0749] Step 5:

[0750] TMSCN (400 μL, 3.00 mmol) and BF₃·OEt₂ (1 mL, 8.103 mmol) were successively added to a stirred solution of *dia*-(2*S'*,3*S''*,4*S''*,5*R''*)-3-(4-acetoxy-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-yl acetate (470 mg, 1.15 mmol) in DCM (15 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min before being warmed to ambient temperature. Upon completion of the reaction, the mixture was quenched with a saturated NaHCO₃ solution (60 mL). The mixture was extracted with DCM (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give a mixture of stereoisomers with *dia*-

4-((2*S*^l, 3*S*^{*}, 4*S*^{*}, 5*R*^{*})-2-cyano-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-3-yl)-2-fluoro-3-methoxyphenyl acetate (400 mg, 93%) as the main diastereoisomer. ESI-MS *m/z* calc. 375.109, found 374.5 (M-1); Retention time: 1.00 minutes using LC/MS method C.

[0751] Step 6:

[0752] *dia*-4-((2*S*^l, 3*S*^{*}, 4*S*^{*}, 5*R*^{*})-2-Cyano-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-3-yl)-2-fluoro-3-methoxyphenyl acetate was dissolved in MeOH (7 mL). A 0.5 M aqueous NaOMe solution (800 µL, 3.5 mmol) was added and the reaction mixture was stirred under nitrogen at ambient temperature overnight. Upon complete conversion to the corresponding imidate *dia*-2-fluoro-4-((2*S*^l, 3*S*^{*}, 4*S*^{*}, 5*R*^{*})-2-(imino(methoxy)methyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-3-yl)-3-methoxyphenyl acetate (ESI-MS *m/z* calc. 365.125, Retention time: 0.81 minutes; no mass ionisation using LC/MS method C), the mixture was quenched by addition of a saturated citric acid solution. The reaction mixture was stirred at ambient temperature for an additional 4 h. The mixture was extracted with DCM (2 x 30 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give a mixture of stereoisomers with methyl (2*R*,3*S*,4*S*,5*R*)-3-(3-fluoro-4-hydroxy-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (380 mg, 90%) as the main diastereoisomer and containing minor impurities. ESI-MS *m/z* calc. 366.109, found 365.4 (M-1); Retention time: 0.87 minutes using LC/MS method C.

[0753] Step 7:

[0754] Sodium 2-chloro-2,2-difluoroacetate (1.1 g, 7.2 mmol) was added to a mixture of methyl (2*R*,3*S*,4*S*,5*R*)-3-(3-fluoro-4-hydroxy-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (1.01 g, 2.76 mmol) and Cs₂CO₃ (2.7 g, 8.3 mmol) in DMF (10 mL). The reaction mixture was heated to 90 °C. Upon completion of the reaction, the mixture was diluted with DCM (20 mL) and partitioned with water (50 mL). The organic phase was separated, dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification by flash chromatography (12 g SiO₂, 0 to 100% EtOAc in heptane) gave methyl (2*R*,3*S*,4*S*,5*R*)-3-(4-(difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (500 mg, 44%). ESI-MS *m/z* calc. 416.106, Retention time: 0.87 minutes; no mass ionisation using LC/MS method C.

[0755] Step 8:

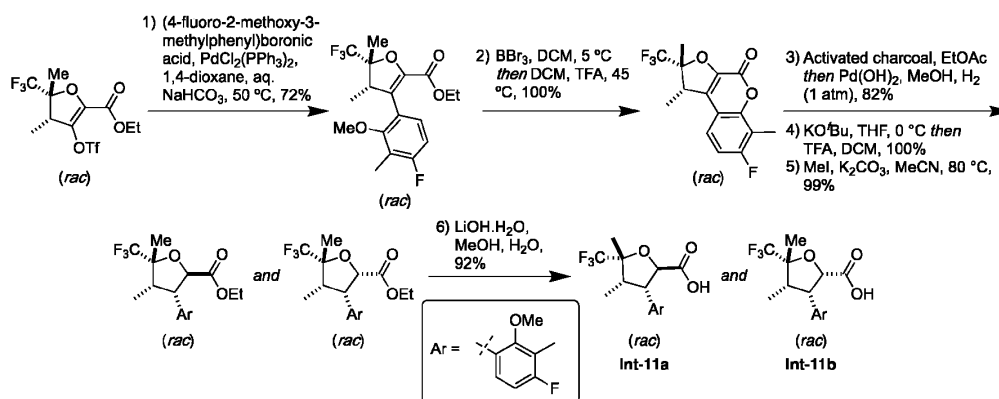
[0756] KO^tBu (200 mg, 1.78 mmol) was added to a stirred solution of methyl (2*R*,3*S*,4*S*,5*R*)-3-(4-(difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (180 mg, 0.432 mmol) in THF (3 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 5 min. The mixture was quenched by addition of a saturated NH₄Cl solution (3 mL) and diluted with DCM (3 mL). The organic phase was separated, washed with DCM (5 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to give (2*R*,3*S*,4*S*,5*R*)-3-(4-(difluoromethoxy)-3-fluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-

carboxylic acid (**Int-10**, 100 mg, 58%), which was used in the next step without further purification.

ESI-MS m/z calc. 402.090, found 401.4 (M-1)⁺; Retention time: 0.6 minutes using LC/MS method C.

Intermediate 11

(2*R*,3*S*,4*S*,5*R*)-3-(4-Fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-11a**) and (2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-11b**)



[0757] Step 1:

[0758] To a 2-L, 3-necked round bottom flask, flanked with a thermometer, was added a mixture of ethyl *rac*-(4*R*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)-3-(((trifluoromethyl)sulfonyl)oxy)-4,5-dihydrofuran-2-carboxylate (39.05 g, 101.1 mmol), (4-fluoro-2-methoxy-3-methylphenyl)boronic acid (**Int-12**, 20.4 g, 110.9 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (1.4 g, 2.0 mmol) in a saturated solution of NaHCO_3 (120 mL) and 1,4-dioxane (400 mL). The orange mixture was heated to 50 °C internally for 20 min. The reaction mixture was cooled to ambient temperature and diluted with EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (4 x 100 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried (MgSO_4), filtered and concentrated *in vacuo* to an approximative volume of 100 mL. Charcoal (10 g) was added and the mixture was stirred for 2 h. The mixture was filtered and the residual cake was washed further with EtOAc. The filtrates were collected and concentrated *in vacuo* to give 50 g of crude product. Purification by flash chromatography (330 g SiO_2 , 0 to 30% EtOAc in heptane) gave ethyl *rac*-(4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (27.348 g, 72%) as a pale yellow oil. ^1H NMR (500 MHz, Chloroform- d) δ 6.98 - 6.88 (m, 1H), 6.81 (t, J = 8.7 Hz, 1H), 4.20 - 4.07 (m, 2H), 3.66 (s, 3H), 3.58 - 3.49 (m, 1H), 2.21 (d, J = 2.1 Hz, 3H), 1.7 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.06 (dq, J = 7.2, 2.3 Hz, 3H) ppm. ESI-MS m/z calc. 376.130, found 377.5 (M+1)⁺; Retention time: 1.09 minutes using LC/MS method C.

[0759] Step 2:

[0760] To a 1-L, 3-necked flask, fitted with a thermometer, was added ethyl *rac*-(4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (27.35 g, 72.67 mmol) followed by DCM (200 mL). The reaction mixture was cooled to 5 °C with an ice bath. Boron tribromide (112 mL, 1 M solution in DCM, 112 mmol) was added via cannula over 30 min, keeping the internal temperature around 5 °C. The reaction mixture was stirred for 1 h. The mixture was quenched by slow addition of water (100 mL) (effervescence observed) and a saturated NaHCO₃ solution (100 mL). The mixture was stirred for 30 min. The aqueous phase was collected and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with a saturated NaHCO₃ solution (5 x 100 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow waxy solid. The waxy solid was re-dissolved in EtOAc (100 mL). Charcoal (15 g) was added and the mixture was stirred at ambient temperature overnight. The mixture was filtered through a pad of Celite®. The filtrates were collected, dried (MgSO₄), filtered and concentrated *in vacuo* to give a ~ 1:1 mixture of *rac*-(1*S*,2*R*)-7-fluoro-1,2,6-trimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one and ethyl *rac*-(4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (27.7 g) as a waxy solid.

[0761] The mixture was dissolved in DCM (200 mL) and TFA (9.8 mL, 127 mmol) was added at ambient temperature under stirring. The reaction mixture was heated at reflux and stirred for 2.5 h. The mixture was cooled to ambient temperature and quenched with a saturated aqueous NaHCO₃ solution (100 mL). The organic phase was separated and washed with a saturated aqueous NaHCO₃ solution (4 x 100 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give a waxy solid. The waxy solid was re-dissolved in EtOAc (200 mL) and activated charcoal (10 g) was added. The mixture was stirred at ambient temperature overnight. The mixture was filtered through a Celite® cartridge, washing with EtOAc (3 x 100 mL). The filtrates were concentrated *in vacuo* to give a waxy solid. Purification by flash chromatography (120 g SiO₂, 50% EtOAc in heptane) gave *rac*-(1*S*,2*R*)-7-fluoro-1,2,6-trimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (24.18 g, 100%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.25 - 7.23 (m, 1H), 7.05 (t, *J* = 8.7 Hz, 1H), 3.65 (q, *J* = 7.4 Hz, 1H), 2.39 (d, *J* = 2.0 Hz, 3H), 1.67 (q, *J* = 1.0 Hz, 3H), 1.58 (t, *J* = 2.2 Hz, 3H) ppm. ESI-MS *m/z* calc. 316.072, found 317.4 (M+1)⁺; 315.4 (M-1)⁻; Retention time: 0.94 minutes using LC/MS method C.

[0762] Step 3:

[0763] *rac*-(1*S*,2*R*)-7-Fluoro-1,2,6-trimethyl-2-(trifluoromethyl)-1,2-dihydro-4*H*-furo[2,3-*c*]chromen-4-one (1.5 g, 3.3 mmol) was dissolved in EtOAc (20 mL) and stirred with activated charcoal (300 mg, 24.98 mmol) for 18 h. The mixture was filtered through a pad of Celite®. The liquors were concentrated *in vacuo* to give a yellow solid. The solid was dissolved in methanol (20 mL) and added to a 100 mL flask containing Pd(OH)₂ (460 mg, 20 % w/w, 0.655 mmol). The resulting mixture was stirred under an atmospheric pressure of hydrogen for 120 h. The mixture was

filtered through a Celite® cartridge washing with MeOH. The filtrates were concentrated *in vacuo* to an approximate volume of 20 mL and added to a flask containing Pd(OH)₂ (230 mg, 20 % w/w, 0.328 mmol). The resulting mixture was stirred under an atmospheric pressure of hydrogen for 12 h. The reaction mixture was filtered through a Celite® cartridge, washing with MeOH. The filtrates were concentrated *in vacuo* to give methyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (939.3 mg, 82%) as an off-white solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.20 (t, *J* = 7.7 Hz, 1H), 6.57 (t, *J* = 8.9 Hz, 1H), 4.88 (d, *J* = 6.1 Hz, 2H), 4.28 (dd, *J* = 8.4, 6.1 Hz, 1H), 3.56 (s, 3H), 2.81 (p, *J* = 7.8 Hz, 1H), 2.14 (d, *J* = 1.6 Hz, 3H), 1.4 (3H), 0.92 (dq, *J* = 7.6, 1.9 Hz, 3H) ppm. ESI-MS *m/z* calc. 350.114, found 349.0 (M-1); Retention time: 0.95 minutes using LC/MS method C.

[0764] Step 4:

[0765] KO^tBu (11.40 g, 101.6 mmol) was added to a stirring solution of methyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (8.896 g, 25.39 mmol) in THF (125 mL) at 0 °C. After 15 min, the mixture was quenched by addition of 1 M HCl (350 mL) and diluted with a saturated brine solution (100 mL) and DCM (100 mL). The aqueous layer was extracted with DCM (3 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was dissolved in DCM (71 mL) and treated with TFA (26.6 g, 18.0 mL, 234 mmol). The reaction mixture was stirred at ambient temperature for 2 h. The mixture was concentrated *in vacuo* and the residue azeotroped with DCM (2 x 50 mL). The residue was partitioned between DCM (100 mL) and water (50 mL). The organic layer was separated and washed with water (3 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo* to give a mixture of *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid and *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (9.753 g, 100%) as a brown oil, which was used without further purification in the next step. ESI-MS *m/z* calc. 336.098, found 335.5 (M-1); Retention time: 0.56 minutes using LC/MS method C.

[0766] Step 5:

[0767] In a vial, K₂CO₃ (6.3 g, 45.6 mmol) and MeI (3.3 mL, 53 mmol) were added to a solution of a mixture of *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid and *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-hydroxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (3.905 g, 11.61 mmol) in MeCN (40 mL). The vial was sealed and heated to 80 °C overnight. The reaction mixture was cooled to ambient temperature and diluted with DCM and water. The aqueous phase was separated and extracted with DCM (3 x). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give a mixture of ethyl *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate and ethyl *rac*-

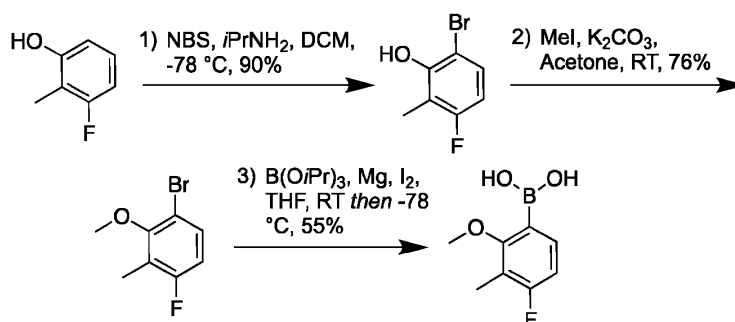
(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (4.2 g, 99%). ESI-MS *m/z* calc. 364.130; Retention time: 1.02 minutes; no mass ionisation using LC/MS method C.

[0768] Step 6:

[0769] LiOH (15 mL, 2 M aqueous solution, 30 mmol) was added to a stirred solution of mixture of ethyl *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate and ethyl *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (4.2 g, 11.5 mmol) in methanol (50 mL) and water (15 mL). The mixture was stirred at ambient temperature for 18 h. The MeOH was removed *in vacuo* and the mixture was acidified with 1 M HCl to pH 1. The mixture was extracted with DCM (2 x 20 mL). The combined organic extracts were dried, by passing the solution through a phase separating cartridge, and concentrated *in vacuo* to give a mixture of *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-11a**, major isomer) and *rac*-(2*S*,3*S*,4*S*,5*R*)-3-(4-fluoro-2-methoxy-3-methylphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-11b**, minor isomer) (377.1 mg, 92%). Major isomer (**Int-11a**): ¹H NMR (500 MHz, Chloroform-*d*) δ 7.06 (dd, *J* = 8.7, 6.2 Hz, 1H), 6.82 (t, *J* = 8.8 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.17 - 4.05 (m, 1H), 3.75 - 3.67 (m, 3H), 2.68 (dt, *J* = 20.9, 7.7 Hz, 1H), 2.27 - 2.19 (m, 3H), 1.63 - 1.55 (m, 3H), 0.79 - 0.69 (m, 3H) ppm. ¹⁹F NMR (471 MHz, Chloroform-*d*) δ -74.56 (d, *J* = 14.1 Hz), -114.41 - -116.05 (m) ppm. ESI-MS *m/z* calc. 350.114, found 349.5 (M-1); Retention time: 0.56 minutes using LC/MS method C.

Intermediate 12

(4-Fluoro-2-methoxy-3-methylphenyl)boronic acid (**Int-12**)



[0770] Step 1:

[0771] To a solution of 3-fluoro-2-methylphenol (50 g, 396 mmol) in DCM (2.5 L) was added isopropylamine (23.5 g, 34.5 mL, 397 mmol) and the reaction mixture was cooled to -78 °C. NBS (70 g, 393 mmol) was added portionwise over 2 h and the mixture was stirred for a further 30 min. The

mixture was warmed to 25 °C. 2 N HCl (500 mL) was added and the mixture was stirred for 15 min. The organic layer was separated and concentrated *in vacuo*, keeping the water bath at 15 °C. Hexane (500 mL) was added to the residue and the mixture was stirred for 10 min. The mixture was filtered and the filtrate was concentrated *in vacuo*, keeping the water bath at 15 °C to give 6-bromo-3-fluoro-2-methylphenol (73 g, 90%) as a light brown oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.24 - 7.21 (m, 1H), 6.55 (t, *J* = 8.8 Hz, 1H), 5.61 (s, 1H), 2.20 (s, 3H) ppm.

[0772] Step 2:

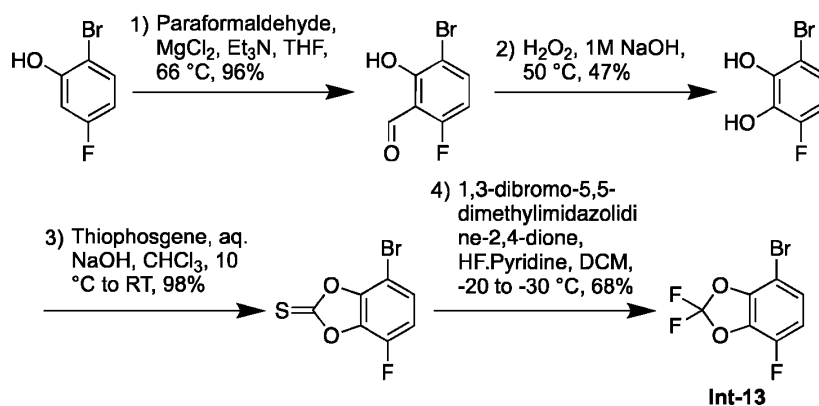
[0773] To a stirred solution of 6-bromo-3-fluoro-2-methylphenol (40 g, 195 mmol) in acetone (400 mL) at ambient temperature was added K₂CO₃ (135 g, 977 mmol). The reaction mixture was stirred at 25 °C for 10 min. MeI (39 g, 17 mL, 275 mmol) was added dropwise over 10 min and the mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered and the solid residues were washed with acetone (50 mL). The filtrate was concentrated *in vacuo* at 15 °C. Hexane (200 mL) was added and the mixture was stirred for 15 min. The solid was collected and washed with hexane (8 mL). The mother liquors were concentrated *in vacuo* at 15 °C. Purification by distillation (520 mm Hg, 192 - 196 °C) gave 1-bromo-4-fluoro-2-methoxy-3-methylbenzene (32.4 g, 76%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.33 - 7.30 (m, 1H), 6.72 (t, *J* = 8.7 Hz, 1H), 3.80 (s, 3H), 2.23 (s, 3H) ppm.

[0774] Step 3:

[0775] Iodine (50 mg, 0.20 mmol) was added at 25 °C to a stirring mixture of Mg turnings (5 g, 206 mmol) in THF (50 mL). The mixture was stirred until the reaction turned into a clear pale yellow colour. 1-Bromo-4-fluoro-2-methoxy-3-methylbenzene (2.5 g, 11.4 mmol) was added dropwise at ambient temperature. When reaction initiation was observed, the remaining solution of 1-bromo-4-fluoro-2-methoxy-3-methylbenzene (22.5 g, 102.7 mmol) in THF (200 mL) was added dropwise. The mixture was stirred for 40 min. The reaction mixture was cooled down to -78 °C and triisopropylborate (64.4 g, 79 mL, 342 mmol) was added dropwise. The reaction mixture was warmed to ambient temperature and stirred for 16 h. The reaction mixture was quenched by addition of a 2 N aqueous HCl solution (25 mL) and stirred for 15 min. The mixture was diluted with water (125 mL) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were separated, washed with water (250 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Hexane (25 mL) was added to the residue at 0 °C and the mixture was stirred for 5 min. The resulting solid was filtered, washed with chilled hexane (10 mL) and dried to give (4-fluoro-2-methoxy-3-methylphenyl)boronic acid (**Int-12**, 11.5 g, 55%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.96 (br s, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 6.88 (t, *J* = 8.7 Hz, 1H), 3.75 (s, 3H), 2.11 (s, 3H) ppm.

Intermediate 13

4-Bromo-2,2,7-trifluorobenzo[d][1,3]dioxole (Int-13)

**[0776] Step 1:**

[0777] Et_3N (23.2 g, 32 mL, 230 mmol) was added to a mixture of paraformaldehyde (20 g, 322 mmol) and MgCl_2 (20 g, 210 mmol) in THF (500 mL) under argon. The reaction mixture was stirred at ambient temperature for 10 min before adding 2-bromo-5-fluorophenol (20 g, 105 mmol). The reaction was heated to reflux for 2 h then allowed to cool to ambient temperature. Et_2O (700 mL) was added and the organic phase washed with a 1 N HCl solution (3 x 400 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 3-bromo-6-fluoro-2-hydroxybenzaldehyde (22 g, 96%), which was used without further purification in the next step.

[0778] Step 2:

[0779] H_2O_2 (25.5 g, 23 mL, 30 % w/v solution in water, 751 mmol) was added to a solution of 3-bromo-6-fluoro-2-hydroxybenzaldehyde (22 g, 100.5 mmol) in 1 M NaOH (120 mL, 120 mmol), while applying external cooling to keep the temperature below 50°C . The reaction mixture was stirred for 2 h. The reaction was quenched by pouring the mixture in a NaHSO_3 solution (120 mL). The resulting mixture was extracted with EtOAc (500 mL). The organic phase was washed with a saturated NaCl solution (100 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 0 to 5% EtOAc in hexane) gave 3-bromo-6-fluorobenzene-1,2-diol (9.8 g, 47%) as a yellow/orange oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.82 (d, $J = 8.6$ Hz, 1H), 9.65 (s, 1H), 6.94 (dd, $J = 9.0, 5.7$ Hz, 1H), 6.64 (t, $J = 9.6$ Hz, 1H) ppm.

[0780] Step 3:

[0781] A mixture of 3-bromo-6-fluorobenzene-1,2-diol (2.3 g, 11 mmol) and thiophosgene (1.5 g, 1 mL, 13 mmol) in CHCl_3 (15 mL) was cooled to 10°C . NaOH (10 mL, 10 % w/v aqueous solution, 25 mmol) was added dropwise over 30 min under vigorous stirring. The reaction mixture was stirred for 2 h at ambient temperature. The mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL). The organic solution was washed with water (30 mL) and a saturated

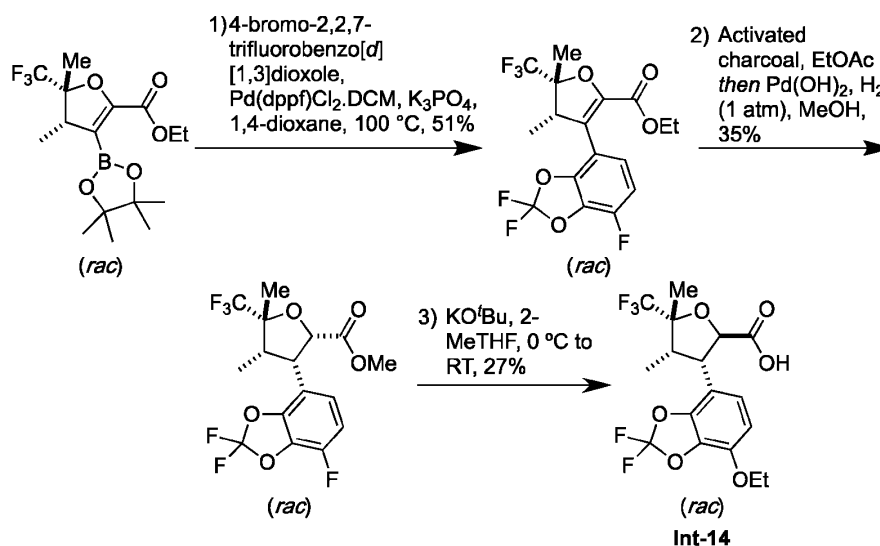
NaCl solution (30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 4-bromo-7-fluorobenzo[d][1,3]dioxole-2-thione (2.7 g, 98%) as an off-white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.66 (dd, $J = 9.2, 4.2$ Hz, 1H), 7.1 (t, $J = 9.6$ Hz, 1H) ppm.

[0782] Step 4:

[0783] Pyridine hydrofluoride (9 mL, 70 % w/v, 63.6 mmol) was added to a solution of 4-bromo-7-fluorobenzo[d][1,3]dioxole-2-thione (3.3 g, 13.3 mmol) in DCM (35 mL) cooled to -30 °C. 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione (4.6 g, 16.1 mmol) was added portionwise over 30 min. The mixture was stirred for 2 h between -20 to -30 °C. The reaction mixture was quenched by pouring the mixture in a 5% NaHSO_3 solution (9 mL). The mixture was stirred for 10 min. The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 100% hexane) gave 4-bromo-2,2,7-trifluorobenzo[d][1,3]dioxole (**Int-13**, 2.3 g, 68%) as a colourless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.16 (dd, $J = 9.2, 4.0$ Hz, 1H), 6.84 (t, $J = 9.2$ Hz, 1H) ppm.

Intermediate 14

rac-(2*R*,3*S*,4*S*,5*R*)-3-(7-Ethoxy-2,2-difluorobenzo[d][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-14**)



[0784] Step 1:

[0785] 2 M K_3PO_4 (8.5 mL, 17 mmol) was added to a solution of ethyl *rac*-(4*S*,5*R*)-4,5-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (**Product of Intermediate 4, Step 1**, 3.00 g, 8.24 mmol), 4-bromo-2,2,7-trifluorobenzo[d][1,3]dioxole (**Intermediate 13**, 2 g, 7.8 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2 \cdot \text{CH}_2\text{Cl}_2$ (400 mg, 0.490 mmol) in 1,4-dioxane (60 mL). The reaction mixture was degassed and flushed with nitrogen (x

3). The mixture was stirred at 100 °C for 2 h. The reaction mixture was cooled to ambient temperature and partitioned between water and EtOAc. The aqueous layer was separated and extracted with EtOAc (x 3). The combined organic extracts were passed through a Whatman® IPS hydrophobic phase separator filter paper. The filtrates were concentrated *in vacuo* to give a brown oil. Purification by flash chromatography (24 g SiO₂, 0 to 70% EtOAc in heptane; then 40 g SiO₂, 0 to 50% EtOAc in heptane) gave ethyl *rac*-(4*S*,5*R*)-4,5-dimethyl-3-(2,2,7-trifluorobenzo[*d*][1,3]dioxol-4-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (2.186 g, 51%) as a pale yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.91 (dd, *J* = 9.0, 4.7 Hz, 1H), 6.84 (t, *J* = 9.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.49 - 3.39 (m, 1H), 1.67 - 1.58 (m, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 412.075, found 413.1 (M+1)⁺; Retention time: 1.12 minutes using LC/MS method C.

[0786] Step 2:

[0787] Ethyl *rac*-(4*S*,5*R*)-4,5-dimethyl-3-(2,2,7-trifluorobenzo[*d*][1,3]dioxol-4-yl)-5-(trifluoromethyl)-4,5-dihydrofuran-2-carboxylate (2.186 g, 5.302 mmol) was dissolved in EtOAc and stirred with activated charcoal overnight at ambient temperature. The mixture was filtered through a pad of Celite®. The filtrate was concentrated *in vacuo* to give a pale yellow oil. The oil was dissolved in MeOH (20 mL) and added to a flask flushed with nitrogen and containing Pd(OH)₂ (1 g, 20 % w/w, 1.424 mmol). The reaction mixture was stirred under an atmospheric pressure of hydrogen for 5 days. The mixture was filtered through a Celite® cartridge and washed with MeOH and water to quench the catalyst. The filtrates were concentrated *in vacuo* to give a pale yellow oil as a mixture of product and starting material. The mixture was dissolved in MeOH (20 mL) and added to a flask flushed with nitrogen and containing Pd(OH)₂ (1g, 20 % w/w, 1.4 mmol). The reaction mixture was stirred under an atmospheric pressure of hydrogen for 48 h. The mixture was filtered through a Celite® cartridge and washed with MeOH and water to quench the catalyst. The filtrates were concentrated *in vacuo* to give a pale yellow oil. Purification by flash chromatography (4 g SiO₂, 0 to 100% EtOAc in heptane) gave methyl *rac*-(2*S*,3*S*,4*S*,5*R*)-4,5-dimethyl-3-(2,2,7-trifluorobenzo[*d*][1,3]dioxol-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (740.5 mg, 35%) as a white solid and methyl (2*S*,3*S*,4*S*,5*R*)-4,5-dimethyl-3-(2,2,7-trifluorobenzo[*d*][1,3]dioxol-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate as the major stereoisomer. ESI-MS *m/z* calc. 400.075, Retention time: 1.10 minutes; no mass ionisation using LC/MS method C.

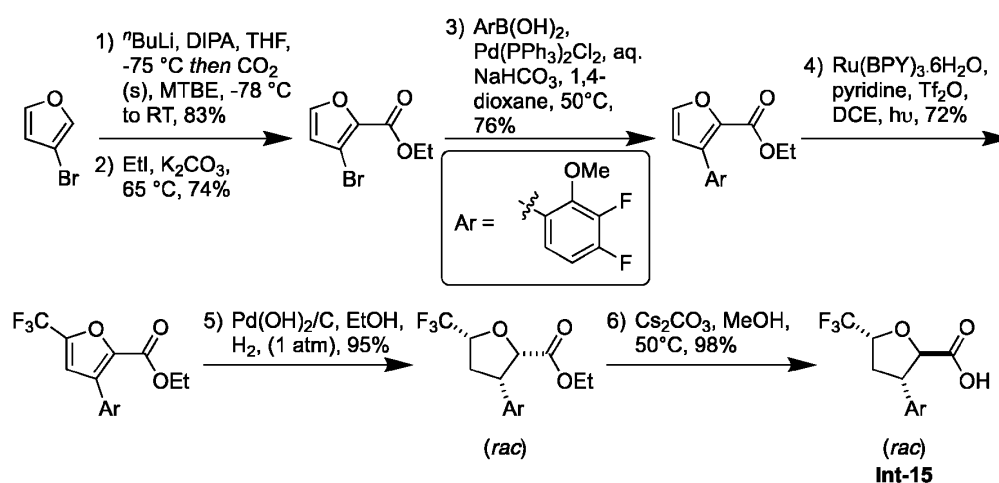
[0788] Step 3:

[0789] KO^tBu (650 mg, 5.79 mmol) was added to an ice-cold and stirred solution of methyl *rac*-(2*S*,3*S*,4*S*,5*R*)-4,5-dimethyl-3-(2,2,7-trifluorobenzo[*d*][1,3]dioxol-4-yl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (740.5 mg, 1.850 mmol) in 2-MeTHF (10 mL). The reaction mixture was stirred for 1 h at ambient temperature. The mixture was partitioned between EtOAc and 1 N NaOH. The organic phase was separated and washed with 1 M NaOH (x 2). The combined organic extracts were passed through a Whatman® IPS hydrophobic phase separator filter

paper. The filtrates were concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (12 g SiO₂, 0 to 100% 3:1 EtOAc:EtOH containing 2% of NH₄OH in water (28 - 30% NH₃ basis) in heptane) gave *rac*-(2*R*,3*S*,4*S*,5*R*)-3-(7-ethoxy-2,2-difluorobenzo[*d*][1,3]dioxol-4-yl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-14**, 517.9 mg, 27%). ESI-MS *m/z* calc. 412.095, found 411.0 (M-1)⁺; Retention time: 0.66 minutes using LC/MS method C.

Intermediate 15

rac-(2*R*,3*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-15**)



[0790] Step 1:

[0791] ^tBuLi (6 mL, 2.5 M solution in hexanes, 15 mmol) was added to a stirred solution of DIPA (2.3 mL, 16.4 mmol) in THF (15 mL) at -78 °C, keeping the temperature below -65 °C. The reaction mixture was stirred at -75 °C for 30 min before a solution of 3-bromofuran (2 g, 13.6 mmol) in THF (10 mL) was added dropwise, again keeping the temperature below -65 °C. The mixture was stirred at -78 °C for 30 min before being added slowly to a pre-cooled (-78 °C) mixture of dry ice (600 mg, 13.6 mmol) and MTBE (25 mL). Further dry ice was added during the addition. The mixture was allowed to warm to ambient temperature over 2 h before being carefully added to water (50 mL). The layers were separated and the aqueous phase was extracted with MTBE (x 2). The aqueous phase was acidified to pH 3 with 1 M HCl and again extracted with MTBE (x 3). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 3-bromofuran-2-carboxylic acid (2.17 g, 83%) as a white solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 1.9 Hz, 1H), 6.66 (d, *J* = 1.8 Hz, 1H) ppm; OH acid not observed.

[0792] Step 2:

[0793] K_2CO_3 (4.7 g, 34 mmol) and EtI (2.7 mL, 34 mmol) were successively added to a solution of 3-bromofuran-2-carboxylic acid (2.17 g, 11.4 mmol) in DMF (25 mL). The reaction mixture was heated to 65 °C for 40 min then cooled to ambient temperature and stirred over the weekend. The reaction mixture was filtered. The filtered cake was washed with EtOAc and the filtrates diluted with water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water (x 5), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO_2 , 0 to 50% EtOAc in heptane) gave ethyl 3-bromofuran-2-carboxylate (1.832 g, 74%) as a white solid. 1H NMR (500 MHz, Chloroform-*d*) δ 7.50 (d, J = 1.9 Hz, 1H), 6.60 (d, J = 1.8 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H) ppm.

[0794] Step 3:

[0795] A mixture of ethyl 3-bromofuran-2-carboxylate (1.55 g, 7.08 mmol), (3,4-difluoro-2-methoxyphenyl)boronic acid (1.45 g, 7.72 mmol), $Pd(PPh_3)Cl_2$ (98 mg, 0.14 mmol) and $NaHCO_3$ (5 mL) in 1,4-dioxane (20 mL) was heated at 50 °C for 1 h before being cooled to ambient temperature and diluted with EtOAc and water. The layers were separated and the aqueous phase was extracted with EtOAc (4 x). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO_2 , 0 to 20% EtOAc in heptane) gave ethyl 3-(3,4-difluoro-2-methoxyphenyl)furan-2-carboxylate (1.511 g, 76%) as a clear oil. 1H NMR (500 MHz, Chloroform-*d*) δ 7.59 (d, J = 1.7 Hz, 1H), 7.07 (ddd, J = 8.8, 5.9, 2.3 Hz, 1H), 6.90 (ddd, J = 9.6, 8.8, 7.3 Hz, 1H), 6.57 (d, J = 1.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.82 (d, J = 2.0 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H) ppm. ESI-MS m/z calc. 282.070, found 283.4 ($M+1$)⁺; Retention time: 0.92 minutes using LC/MS method C.

[0796] Step 4:

[0797] To a solution of ethyl 3-(3,4-difluoro-2-methoxyphenyl)furan-2-carboxylate (200 mg, 0.71 mmol) in DCE (25 mL) was added $Ru(BPY)_3 \cdot 6H_2O$ (11 mg, 0.015 mmol). The reaction mixture was degassed with nitrogen and pyridine (172 μ L, 2.13 mmol) was added followed by Tf_2O (358 μ L, 2.13 mmol) dropwise over 10 min. The mixture was irradiated with blue LEDs (Penn PhD photoreactor M2 and the Blue LED Hepatochem) for 2 h stirring at ambient temperature (100 rpm). This process was repeated 13 times, and the crude mixtures were combined for work-up. The combined mixture was washed with water and brine and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO_2 , 0 to 20% EtOAc in heptane) gave ethyl 3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)furan-2-carboxylate (2.39 g, 72%) as a clear oil that solidified on standing. 1H NMR (500 MHz, Chloroform-*d*) δ 7.07 (ddd, J = 8.8, 5.8, 2.3 Hz, 1H), 6.97 - 6.87 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.88 (d, J = 2.5 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm. ESI-MS m/z calc. 350.058, found 351.4 ($M+1$)⁺; Retention time: 1.05 minutes using LC/MS method C.

[0798] Step 5:

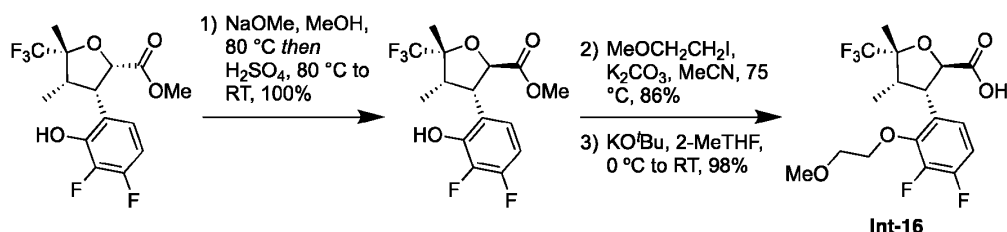
[0799] A solution of ethyl 3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)furan-2-carboxylate (2.29 g, 6.54 mmol) in EtOH (200 mL) was added to Pd(OH)₂/C (920 mg, 20 % w/w, 1.31 mmol) and the mixture was degassed with nitrogen. The mixture was stirred under an atmospheric pressure of hydrogen for 18 h before further Pd(OH)₂ (920 mg, 20 % w/w, 1.31 mmol) was added. The mixture was degassed with nitrogen and stirred under an atmospheric pressure of hydrogen for 18 h. The mixture was filtered through Celite[®], washing the filtered cake with ethanol, and the filtrate was concentrated *in vacuo* to give ethyl *rac*-(2*S*,3*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (3.2 g, 95%). ¹H NMR (500 MHz, Chloroform-*d*) δ 6.91 - 6.75 (m, 2H), 4.88 (d, *J* = 8.8 Hz, 1H), 4.49 (dp, *J* = 11.9, 6.0 Hz, 1H), 4.15 - 4.03 (m, 3H), 3.88 - 3.70 (m, 2H), 2.66 (td, *J* = 12.5, 10.7 Hz, 1H), 2.31 (dt, *J* = 11.9, 5.9 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 354.089, found 355.0 (M+1)⁺; Retention time: 0.98 minutes using LC/MS method C.

[0800] Step 6:

[0801] Cs₂CO₃ (4 g, 12.3 mmol) was added to a stirred solution of ethyl *rac*-(2*S*,3*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (3.2 g, 6.2 mmol) in MeOH (100 mL). The mixture was heated at 50 °C for 16 h before being concentrated *in vacuo*. The residue was partitioned between EtOAc and 1 M HCl. The layers were separated and the organic phase was passed through a phase separator filter and concentrated *in vacuo* to give *rac*-(2*R*,3*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-15**, 1.995 g, 98%) as a yellow oil. ¹H NMR (500 MHz, Chloroform-*d*) δ 6.96 (ddd, *J* = 8.8, 5.5, 2.2 Hz, 1H), 6.88 (td, *J* = 9.1, 7.2 Hz, 1H), 4.70 - 4.59 (m, 2H), 4.00 (d, *J* = 2.7 Hz, 3H), 3.92 - 3.78 (m, 1H), 2.68 - 2.54 (m, 1H), 2.35 - 2.25 (m, 1H) ppm. ESI-MS *m/z* calc. 326.058, found 325.0 (M-1)⁻; Retention time: 0.50 minutes using LC/MS method C.

Intermediate 16

(2*R*,3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-16**)



[0802] Step 1:

[0803] NaOMe (7.8 mL, 25 % w/w solution in methanol, 34 mmol) was added in one portion to a solution of methyl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (**Product of Intermediate 1, Step 8**, 3 g, 8.5 mmol) in MeOH (8 mL) at ambient temperature. The reaction mixture was heated to 80 °C in a sealed vial. Upon reaction completion, the mixture was cooled to ambient temperature, quenched by the dropwise addition of concentrated H₂SO₄ (1.95 mL, 36.6 mmol) and heated to 80 °C for another 15 min. The mixture was partitioned between DCM and water. The organic extracts were separated and concentrated *in vacuo* to give methyl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (2.991 g, 100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.43 (d, *J* = 1.4 Hz, 1H), 7.06 (ddd, *J* = 8.5, 5.8, 2.1 Hz, 1H), 6.84 (ddd, *J* = 10.2, 8.9, 7.6 Hz, 1H), 5.13 (d, *J* = 10.3 Hz, 1H), 4.13 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.63 (s, 3H), 2.76 (p, *J* = 7.5 Hz, 1H), 1.62 - 1.39 (m, 3H), 0.83 - 0.56 (m, 3H) ppm. ESI-MS *m/z* calc. 354.089, found 355.0 (M+1)⁺; 353.1 (M-1)⁻; Retention time: 0.87 minutes using LC/MS method C.

[0804] Step 2:

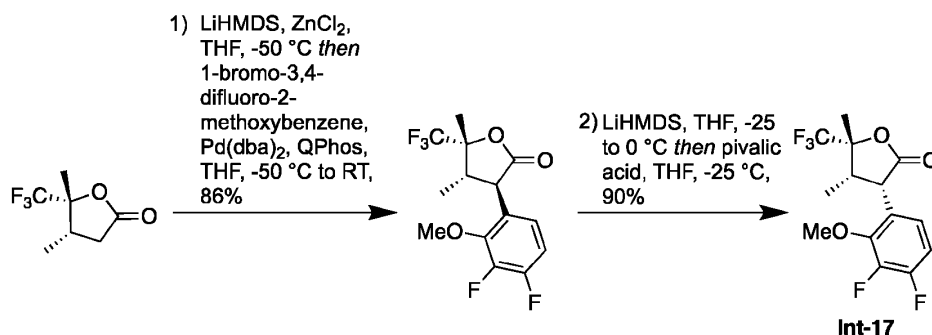
[0805] 1-Iodo-2-methoxyethane (700 mg, 3.76 mmol) and K₂CO₃ (606 mg, 4.39 mmol) were successively added to a stirred solution of methyl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-hydroxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (606 mg, 1.71 mmol) in MeCN (6 mL) at ambient temperature under a nitrogen atmosphere. The vial was sealed and the reaction was heated at 75 °C. After 16 h, the mixture was cooled to ambient temperature. The mixture was partitioned between DCM and water. The organic phase was separated, dried (MgSO₄), filtered, and concentrated *in vacuo* to give methyl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (686 mg, 86%). ¹H NMR (500 MHz, Chloroform-*d*) δ 7.04 - 6.80 (m, 2H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.48 - 4.16 (m, 3H), 3.80 - 3.61 (m, 2H), 3.43 (s, 3H), 2.85 (p, *J* = 7.5 Hz, 1H), 1.65 (q, *J* = 1.2 Hz, 3H), 1.55 (dd, *J* = 12.7, 1.1 Hz, 3H), 0.76 (dq, *J* = 7.4, 2.4 Hz, 3H) ppm. ESI-MS *m/z* calc. 412.131, found 413.1 (M+1)⁺; Retention time: 1.04 minutes using LC/MS method C.

[0806] Step 3:

[0807] KO^tBu (380 μ L, 3.06 mmol) was added to a stirred solution of methyl (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylate (686 mg, 1.46 mmol) in 2-MeTHF (18 mL) cooled down with an ice-bath. The solution was stirred at 0 °C for 30 min. The reaction mixture was quenched by addition of a diluted HCl solution and partitioned between EtOAc and water. The pH of the aqueous layer was adjusted to pH 6. The aqueous phase was extracted with EtOAc (3 x). The combined organic extracts were dried (MgSO₄), filtered, and concentrated *in vacuo* to give (2*R*,3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-(2-methoxyethoxy)phenyl)-4,5-dimethyl-5-(trifluoromethyl)tetrahydrofuran-2-carboxylic acid (**Int-16**, 641 mg, 98%). ESI-MS *m/z* calc. 398.115, found 399.1 (M+1)⁺; 397.1 (M-1)⁻; Retention time: 0.58 minutes using LC/MS method C.

Intermediate 17

(3*S*,4*S*,5*R*)-3-(3,4-Difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (**Int-17**)

**[0808] Step 1:**

[0809] A solution of LiHMDS (3.8 mL, 1 M solution in THF, 3.8 mmol) was added dropwise under nitrogen to a solution of (4*S*,5*R*)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (712 mg, 3.36 mmol) in THF (5 mL) at -50 °C. After stirring the mixture for 1 h at -50 °C, a solution of zinc chloride (15.25 mL, 0.5 M solution in THF, 7.6 mmol) was added dropwise and the reaction mixture was stirred for a further 1 h at -50 °C. A solution of Pd(dba)₂ (25 mg, 0.044 mmol), QPhos (47 mg, 0.066 mmol) and 1-bromo-3,4-difluoro-2-methoxybenzene (500 mg, 2.24 mmol) in THF (10 mL) was added and the reaction mixture was allowed to warm up to ambient temperature overnight. The reaction mixture was cooled down to 0 °C and 20% aqueous NH₄Cl (30 mL) was added (exotherm to 15 °C) followed by MTBE (25 mL). The aqueous layer was separated and extracted with MTBE (25 mL). The combined organic extracts were washed with a 20% aqueous NaCl solution (40 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo* to give crude (3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (1.088 g, 86% with 57.2%

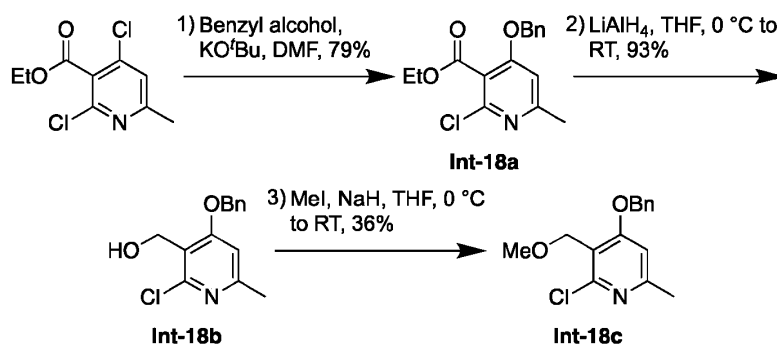
w/w purity by ^{19}F qNMR) as a red oil. Purification of a sample (ca. 200 mg) by reverse phase chromatography (C_{18} column, 5 to 100% methanol in 0.1% aqueous formic acid) gave a residue after partial concentration *in vacuo*. The aqueous residue was saturated with sodium chloride and extracted with MTBE (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give an analytical sample of (3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one as a light red oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 6.91 - 6.80 (m, 2H), 3.98 (d, J = 2.7 Hz, 3H), 3.53 (d, J = 12.0 Hz, 1H), 2.77 - 2.62 (m, 1H), 1.67 (s, 3H), 1.19 - 1.14 (m, 3H) ppm. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -76.10 (s, 3F), -135.14 - -135.71 (m, 1F), -153.19 (dd, J = 19.8, 3.4 Hz, 1F) ppm. ESI-MS m/z calc. 324.079, found 325.1 ($\text{M}+1$) $^+$; Retention time: 2.10 minutes using LC/MS method S.

[0810] Step 2:

[0811] A solution of (3*R*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (50 g, 154 mmol) in THF (250 mL) was added dropwise to LiHMDS (240 mL, 1 M solution in THF, 240 mmol) at -25 °C under argon. The mixture was stirred at -25 °C for 30 min then, the solution was allowed to warm to 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The solution was cooled to -25 °C and added to a solution of pivalic acid (157.50 g, 1.542 mol) in THF (500 mL) at -25 °C under argon. The reaction mixture was stirred at -25 °C for 30 min. MTBE (500 mL) was added portionwise keeping the temperature below -15 °C. A 2 M aqueous HCl solution (750 mL) was added at such a rate to keep the temperature below 0 °C. NaCl (239.7 g, 4.102 mol) was added and the mixture was warmed to ambient temperature. The organic layer was separated and concentrated *in vacuo*. The residue was taken up in heptane (1 L) and concentrated further *in vacuo*. Purification by flash chromatography (SiO_2 , 0 to 25% MTBE in heptane) gave (3*S*,4*S*,5*R*)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-5-(trifluoromethyl)dihydrofuran-2(3*H*)-one (**Int-17**, 59.5 g, 90%) as a colourless oil which contained 24 wt% pivalic acid (based on ^1H NMR). ^1H NMR (400 MHz, Chloroform-*d*) δ 6.88 (m, 2H), 4.49 (m, 1H), 4.02 (d, 3H), 2.88 (m, 1H), 1.70 (m, 3H), 0.80 (m, 3H) ppm.

Intermediate 18

Ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate (**Int-18a**), (4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)methanol (**Int-18b**) and 4-(benzyloxy)-2-chloro-3-(methoxymethyl)-6-methylpyridine (**Int-18c**)



[0812] Step 1:

[0813] KO^tBu (17 g, 151.5 mmol) was added to a stirred solution of ethyl 2,4-dichloro-6-methylnicotinate (30 g, 128 mmol) and benzyl alcohol (15 g, 139 mmol) in DMF (300 mL). The reaction mixture was stirred at ambient temperature for 18 h. The mixture was diluted with water (750 mL) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 20 to 30% EtOAc in hexanes) gave ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate (**Int-18a**, 31 g, 79%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 - 7.35 (m, 5H), 6.68 (s, 1H), 5.15 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 305.082, found 306.4 (M+1)⁺; Retention time: 1.97 minutes using LC/MS method U.

[0814] Step 2:

[0815] A solution of ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate (300 mg, 0.982 mmol) in THF (1.5 mL) was cooled to 0 °C. A solution of LiAlH₄ (980 μL, 1 M solution in THF, 0.98 mmol) was added and the resulting solution was stirred for 4 h at 0 °C before warming the solution to ambient temperature. The mixture was diluted with EtOAc (20 mL). The organic phase was separated, washed with a saturated Rochelle's salt solution and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C₁₈ column, 10 to 99% MeCN in H₂O containing 5 mM HCl) gave (4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)methanol (**Int-18b**, 240 mg, 93%), as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.47 - 7.32 (m, 5H), 6.71 (s, 1H), 5.15 (s, 2H), 4.89 (s, 2H), 2.49 (s, 3H) ppm; OH alcohol not observed. ESI-MS *m/z* calc. 263.071, found 264.1 (M+1)⁺; Retention time: 0.80 minutes using LC/MS method D.

[0816] Step 3:

[0817] A reaction vial equipped with a stir bar was charged with (4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)methanol (90 mg, 0.34 mmol) and THF (1.5 mL). The mixture was cooled to 0 °C and NaH (12.1 mg, 60% dispersion in mineral oil, 0.504 mmol) was added to the stirred solution. The reaction was stirred at ambient temperature for 20 min before being cooled down again to 0 °C. MeI (21 µL, 0.34 mmol) was added dropwise and the reaction mixture was warmed to ambient temperature and stirred for 3 h. The mixture was cooled to 0 °C and carefully quenched by addition of ice-water (2 mL). The THF was removed *in vacuo* and the residue was partitioned between EtOAc (25 mL) and water (25 mL). The aqueous phase was separated and extracted with EtOAc (2 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C₁₈ column, 10 to 99% MeCN in H₂O containing 5 mM HCl) gave 4-(benzyloxy)-2-chloro-3-(methoxymethyl)-6-methylpyridine (**Int-18c**, 34.4 mg, 36%) as a colourless oil. ESI-MS *m/z* calc. 277.087, found 278.1 (M+1)⁺; Retention time: 1.14 minutes using LC/MS method D.

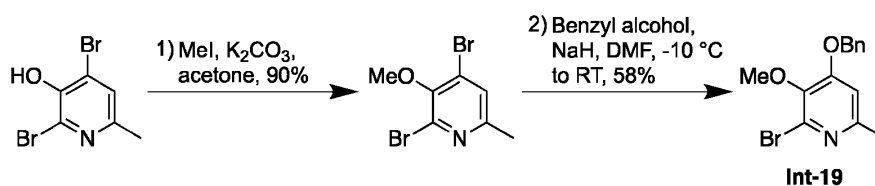
[0818] The following intermediates were made using the method described in Intermediate 18, except that Steps 2 and 3 were omitted. In Step 1, (4-methoxyphenyl)methanol was used in place of benzyl alcohol and different starting materials were used in place of ethyl 2,4-dichloro-6-methylnicotinate. In the case of 2-chloro-4-((4-methoxybenzyl)oxy)-3,6-dimethylpyridine, the reaction was carried over 1 h in DMSO as the solvent:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
2-Chloro-4-((4-methoxybenzyl)oxy)-3,6-dimethylpyridine	277.087	278.4	0.94	C	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.36 - 7.29 (m, 2H), 6.97 - 6.90 (m, 2H), 6.64 (s, 1H), 5.03 (s, 2H), 3.83 (s, 3H), 2.46 (s, 3H), 2.23 (s, 3H) ppm.
Ethyl 6-chloro-4-((4-methoxybenzyl)oxy)-2-methylnicotinate	335.092	336.0	1.99	U	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.41 - 7.30 (m, 2H), 7.28 (s, 1H), 7.00 - 6.91 (m, 2H), 5.21 (s, 2H), 4.28 (q, <i>J</i> = 7.1 Hz, 2H), 3.76 (s, 3H), 2.34 (s, 3H), 1.20 (t, <i>J</i> = 7.1 Hz, 3H) ppm.

[0819] The following intermediate was made using the method described in Intermediate 18, except that the conditions used for Step 1 were those from Intermediate 19 Step 2, using methyl 2-bromo-4-chloronicotinate as the starting material in place of 2,4-dibromo-6-methylpyridin-3-ol:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2-bromo-3-(methoxymethyl)pyridine	307.021	310.0	1.62	D	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.18 (d, <i>J</i> = 5.7 Hz, 1H), 7.42 - 7.33 (m, 5H), 6.83 (d, <i>J</i> = 5.7 Hz, 1H), 5.18 (s, 2H), 4.66 (s, 2H), 3.43 (s, 3H) ppm.

Intermediate 19

4-(Benzyloxy)-2-bromo-3-methoxy-6-methylpyridine (**Int-19**)**[0820] Step 1:**

[0821] In a 2-L round bottomed flask immersed in a water bath, MeI (37.61 g, 16.50 mL, 265 mmol) was slowly added via syringe (no exotherm) to a stirred suspension of 2,4-dibromo-6-methylpyridin-3-ol (50 g, 178 mmol) and K₂CO₃ (36.90 g, 267 mmol) in acetone (1.24 L). The suspension was stirred over the weekend at ambient temperature. The reaction mixture was filtered and the filtered cake was washed with acetone. The brown filtrate was collected and concentrated *in vacuo* at 40 °C. The residue was partitioned between MTBE (400 mL) and water (400 mL) and stirred at ambient temperature. The solid was filtered and rinsed with water (200 mL) to give 2,4-dibromo-3-methoxy-6-methylpyridine (49.72 g, 90%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (s, 1H), 3.82 (s, 3H), 2.41 (s, 3H) ppm. ESI-MS *m/z* calc. 278.889, found 281.8 (M+1)⁺; Retention time: 1.86 minutes using LC/MS method Q.

[0822] Step 2:

[0823] NaH (523 mg, 60% dispersion in mineral oil, 13.1 mmol) was added to a stirred solution of benzyl alcohol (1.35 g, 12.5 mmol) in DMF (24 mL) at -10 °C and the mixture was stirred for 1 h. A solution of 2,4-dibromo-3-methoxy-6-methylpyridine (3.5 g, 12.4 mmol) in DMF (5 mL) was added. The mixture was stirred at -10 °C for 1 h then allowed to warm to ambient temperature over 30 min. The mixture was stirred at ambient temperature for a further 1 h. The mixture was partitioned between water (75 mL) and EtOAc (100 mL) and the layers were separated. The organic phase was washed with water (3 x 75 mL) and brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (120 g SiO₂, 0 to 40% EtOAc in heptane) gave 4-(benzyloxy)-2-bromo-3-methoxy-6-methylpyridine (**Int-19**, 2.25 g, 58%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.42 - 7.33 (m, 5H), 6.69 (s, 1H), 5.14 (s, 2H), 3.85 (s, 3H), 2.43 (s, 3H) ppm. ESI-MS *m/z* calc. 307.021, found 308.0 (M+1)⁺; Retention time: 2.34 minutes using LC/MS method J.

[0824] The following intermediates were made using the method described in Intermediate 19, except that Step 1 was omitted. In Step 2, different starting materials were used in place of 2,4-dibromo-3-methoxy-6-methylpyridine. In the case of 4-(benzyloxy)-6-chloro-2,3-dimethylpyridine, the reaction was carried out at 70 °C overnight. In the case of 2-bromo-3-methoxy-4-((4-methoxybenzyl)oxy)-6-methylpyridine, (4-methoxyphenyl)methanol was used in place of benzyl alcohol and the reaction was carried out at 40 °C in DMA as the solvent. In the case of 4-(benzyloxy)-6-chloro-2-methylpyrimidine, the reaction was carried out at ambient temperature in THF as the solvent:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2-bromo-6-methylpyridine	277.010	280.0	0.63	T	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.47 - 7.39 (m, 4H), 7.39 - 7.34 (m, 1H), 7.13 (d, <i>J</i> = 2.2 Hz, 1H), 6.97 (d, <i>J</i> = 2.1 Hz, 1H), 5.20 (s, 2H), 2.38 (s, 3H) ppm.
4-(Benzyloxy)-6-chloro-2,3-dimethylpyridine	247.076	248.3	2.20	Q	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.45 - 7.33 (m, 5H), 6.72 (s, 1H), 5.08 (s, 2H), 2.46 (s, 3H), 2.15 (s, 3H) ppm.
Ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate	305.082	306.2	1.64	D	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.50 - 7.30 (m, 5H), 6.69 (s, 1H), 5.16 (s, 2H), 4.40 (q, <i>J</i> = 7.1 Hz, 2H), 2.50 (s, 3H), 1.33 (t, <i>J</i> = 7.1 Hz, 3H) ppm.
4-(Benzyloxy)-2-chloro-6-methylpyridine	233.061	234.1	2.01	S	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.46 - 7.34 (m, 5H), 6.76 (d, <i>J</i> = 1.6 Hz, 1H), 6.68 (d, <i>J</i> = 1.6 Hz, 1H), 5.09 (s, 2H), 2.48 (s, 3H) ppm.
Ethyl 4-(benzyloxy)-2-bromonicotinate	335.016	338.0	1.59	D	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.23 (d, <i>J</i> = 5.8 Hz, 1H), 7.49 - 7.30 (m, 5H), 6.86 (d, <i>J</i> = 5.8 Hz, 1H), 5.19 (s, 2H), 4.43 (q, <i>J</i> = 7.1 Hz, 2H), 1.36 (t, <i>J</i> = 7.1 Hz, 3H) ppm.
Ethyl 4-(benzyloxy)-6-chloro-5-fluoronicotinate	309.057	310.0	1.41	D	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 8.47 (s, 1H), 7.52 - 7.43 (m, 2H), 7.42 - 7.32 (m, 3H), 5.42 (s, 2H), 4.34 (q, <i>J</i> = 7.1 Hz, 2H), 1.29 (t, <i>J</i> = 7.1 Hz, 3H) ppm.

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
2-Bromo-3-methoxy-4- ((4-methoxybenzyl)oxy)- 6-methylpyridine	337.031		2.93	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.38 - 7.28 (m, 2H), 6.98 - 6.84 (m, 2H), 6.71 (s, 1H), 5.07 (s, 2H), 3.83 (d, <i>J</i> = 4.1 Hz, 6H), 2.45 (s, 3H) ppm.
4-(Benzyloxy)-6-chloro- 2-methylpyrimidine	234.056	235.1	3.11	E	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.48 - 7.31 (m, 5H), 6.63 (s, 1H), 5.43 (s, 2H), 2.63 (s, 3H) ppm.

[0825] The following intermediate was made using the method described in Intermediate 19, except that, in Step 1, the reaction was carried out at 70 °C using 1-bromo-2-methoxyethane as the alkylating agent and DMF as the solvent:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2-bromo- 3-(2-methoxyethoxy)-6- methylpyridine	351.047	352.1	2.27	J	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.43 - 7.32 (m, 5H), 6.69 (s, 1H), 5.14 (s, 2H), 4.16 (t, <i>J</i> = 4.8 Hz, 2H), 3.72 (t, <i>J</i> = 4.8 Hz, 2H), 3.38 (s, 3H), 2.44 (s, 3H) ppm.

[0826] The following intermediate was made using the method described in Intermediate 19, except that the conditions used in Step 1 were those described in Intermediate 18 Step 3, using 2,4-dichloro-6-methylpyridin-3-amine as the starting material and DMF as the solvent:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2-chloro- <i>N</i> ,6-dimethylpyridin-3- amine	262.087	263.1	0.6	T	

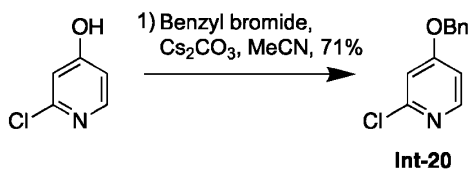
[0827] The following intermediates were made using the method described in Intermediate 19, except that Step 1 was omitted. In Step 2, the reaction was carried out in NMP as the solvent with different starting materials:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-3-chloro- 2-methylpyridine	233.061	234.3	2.93	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.22 (d, <i>J</i> = 5.6 Hz, 1H), 7.45 - 7.33 (m, 5H), 6.75 (d, <i>J</i> = 5.6 Hz, 1H), 5.20 (s, 2H), 2.62 (s, 3H) ppm.

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-5-chloro-2-methylpyridine	233.061	234.3	2.90	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.34 (s, 1H), 7.44 - 7.38 (m, 4H), 7.36 - 7.33 (m, 1H), 6.73 (s, 1H), 5.17 (s, 2H), 2.48 (s, 3H) ppm.
4-(Benzyloxy)-3-fluoro-2-methylpyridine	217.090	218.3	2.73	A	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 8.10 (d, <i>J</i> = 5.5 Hz, 1H), 7.45 - 7.33 (m, 5H), 6.77 (t, <i>J</i> = 5.9 Hz, 1H), 5.17 (s, 2H), 2.49 (d, <i>J</i> = 3.4 Hz, 3H) ppm.
4-(Benzyloxy)-5-bromo-2-methylpyridine	277.010	278.2	0.90	C	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.42 (s, 1H), 7.50 - 7.46 (m, 2H), 7.45 - 7.40 (m, 2H), 7.39 - 7.34 (m, 1H), 7.18 (s, 1H), 5.28 (s, 2H), 2.41 (s, 3H) ppm.
4-(Benzyloxy)-2-methyl-3-(methylthio)pyridine	245.087	247.3	0.84	A	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 8.25 (d, <i>J</i> = 5.7 Hz, 1H), 7.52 - 7.47 (m, 2H), 7.46 - 7.39 (m, 2H), 7.39 - 7.32 (m, 1H), 7.03 (d, <i>J</i> = 5.7 Hz, 1H), 5.26 (s, 2H), 2.60 (s, 3H), 2.28 (s, 3H) ppm.

Intermediate 20

4-(Benzyloxy)-2-chloropyridine (Int-20)

**[0828] Step 1:**

[0829] Cs₂CO₃ (1.89 g, 5.80 mmol) and benzyl bromide (700 μL, 5.89 mmol) were successively added to a solution of 2-chloropyridin-4-ol (500 mg, 3.86 mmol) in MeCN (8 mL), and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was diluted with EtOAc (15 mL) and poured over a saturated aqueous NaHCO₃ solution (20 mL). The aqueous layer was separated and extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 100% EtOAc in heptane) gave 4-(benzyloxy)-2-chloropyridine (**Int-20**, 601 mg, 71%) as a crystalline white solid. ¹H NMR (500 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 5.8 Hz, 1H), 7.44 - 7.35 (m, 5H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.82 (dd, *J* = 5.8, 2.2 Hz, 1H), 5.11 (s, 2H) ppm. ESI-MS *m/z* calc. 219.045, found 220.3 (M+1)⁺; 218.1 (M-1)⁻; Retention time: 2.88 minutes using LC/MS method A.

[0830] The following intermediate was made using the method described in Intermediate 20, except that in Step 1, 3-methoxy-2-methylpyridin-4-ol was used as the starting material in place of 2-chloropyridin-4-ol:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-3-methoxy-2-methylpyridine	229.110	230.3	2.63	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 8.10 (d, <i>J</i> = 5.6 Hz, 1H), 7.44 - 7.38 (m, 4H), 7.36 - 7.33 (m, 1H), 6.75 (d, <i>J</i> = 5.6 Hz, 1H), 5.16 (s, 2H), 3.85 (s, 3H), 2.49 (s, 3H) ppm.

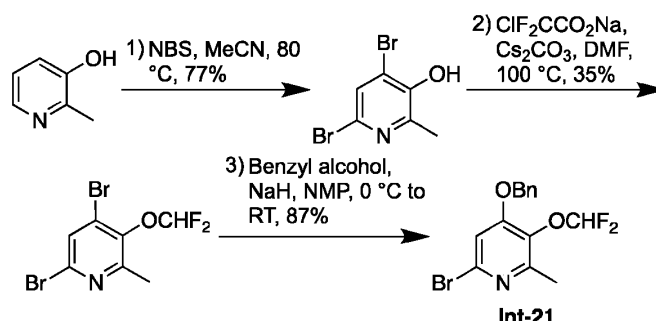
[0831] The following intermediate was made using the method described in Intermediate 20, except that in Step 1, the reaction was carried out at 40 °C using 2,6-dichloropyridin-4-ol as the starting material in place of 2-chloropyridin-4-ol:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2,6-dichloropyridine	253.006	254.2	3.34	A	¹ H NMR (500 MHz, Chloroform- <i>d</i>) δ 7.45 - 7.37 (m, 5H), 6.86 (s, 2H), 5.10 (s, 2H) ppm.

[0832] The following intermediate was made using the method described in Intermediate 20, except that in Step 1, the reaction was carried out using 2-chloro-5-methoxypyridin-4-ol as the starting material, K₂CO₃ as the base and DMF as the solvent:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2-chloro-5-methoxypyridine	249.056	252.0	0.83	C	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.90 (s, 1H), 7.46 - 7.37 (m, 5H), 6.85 (s, 1H), 5.19 (s, 2H), 3.95 (s, 3H) ppm.

Intermediate 21

4-(Benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine (**Int-21**)**[0833] Step 1:**

[0834] A solution of NBS (36.77 g, 206.6 mmol) in MeCN (364 mL) was added dropwise over 1 h to a stirred suspension of 2-methylpyridin-3-ol (11.0 g, 100.8 mmol) in MeCN (165 mL). The mixture was heated at reflux for 2 h, then concentrated *in vacuo*. The residue was dissolved in DCM and filtered. The filtrates were concentrated *in vacuo*. This last step was repeated. Purification by flash chromatography (SiO₂, 0 to 100% EtOAc in hexanes) gave 4,6-dibromo-2-methylpyridin-3-ol (20.83 g, 77%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.99 (s, 1H), 7.70 (s, 1H), 2.40 (s, 3H) ppm. ESI-MS *m/z* calc. 264.874, found 268.1 (M+1)⁺; Retention time: 1.21 minutes using LC/MS method D.

[0835] Step 2:

[0836] Sodium 2-chloro-2,2-difluoroacetate (2.86 g, 18.8 mmol) and Cs₂CO₃ (4.88 g, 15.0 mmol) were successively added to a solution of 4,6-dibromo-2-methylpyridin-3-ol (2.00 g, 7.49 mmol) in DMF (50 mL). The reaction mixture was stirred at 100 °C overnight. The mixture was poured over water (150 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (80 g SiO₂, 0 to 100% EtOAc in heptane) gave 4,6-dibromo-3-(difluoromethoxy)-2-methylpyridine (839 mg, 35%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.61 (d, *J* = 0.7 Hz, 1H), 6.52 (t, *J* = 73.5 Hz, 1H), 2.58 (d, *J* = 0.8 Hz, 3H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -80.64 ppm. ESI-MS *m/z* calc. 314.871, found 318.1 (M+1)⁺; Retention time: 3.03 minutes using LC/MS method A.

[0837] Step 3:

[0838] NaH (75 mg, 60% dispersion in mineral oil, 1.9 mmol) was added to a solution of benzyl alcohol (180 μL, 1.74 mmol) in NMP (6.5 mL) cooled to 0 °C under an atmosphere of nitrogen and the mixture was stirred at this temperature for 45 min. A solution of 4,6-dibromo-3-(difluoromethoxy)-2-methylpyridine (500 mg, 1.58 mmol) in NMP (1.5 mL) was then added at 0 °C. The mixture was warmed to ambient temperature and stirred overnight. The reaction was quenched by addition of a saturated NH₄Cl solution (2 mL) and water (25 mL) was added. The mixture was

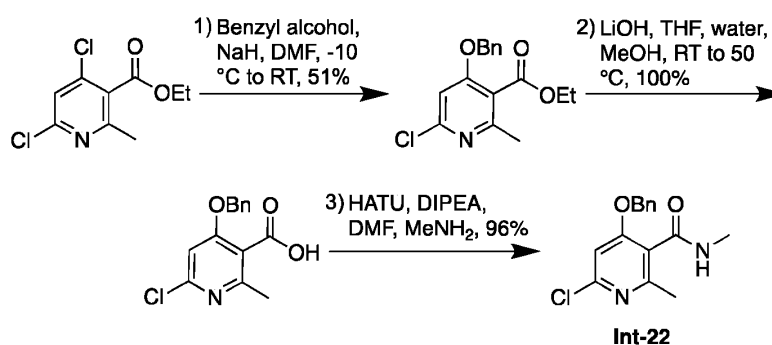
partitioned with EtOAc (25 mL) and the layers were separated. The organic phase was washed with water (25 mL) and a saturated brine solution (25 mL), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (24 g SiO₂, 0 to 100% EtOAc in heptane) gave 4-(benzyloxy)-6-bromo-3-(difluoromethoxy)-2-methylpyridine (**Int-21**, 472 mg, 87%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46 - 7.36 (m, 5H), 7.00 (s, 1H), 6.54 (t, *J* = 75.2 Hz, 1H), 5.14 (s, 2H), 2.50 (s, 3H) ppm. ¹⁹F NMR (376 MHz, Chloroform-*d*) δ -81.41 ppm. ESI-MS *m/z* calc. 343.002, found 344.3 (M+1)⁺; 342.2 (M-1)⁻; Retention time: 3.37 minutes using LC/MS method A.

[0839] The following intermediate was made using the method described in Intermediate 21, except that in Step 1, 6-methylpyridin-3-ol was used as the starting material in place of 2-methylpyridin-3-ol. In Step 3, (4-methoxyphenyl)methanol was used in place of benzyl alcohol:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
2-Bromo-3-(difluoromethoxy)-4-((4-methoxybenzyl)oxy)-6-methylpyridine	373.013		0.94	C	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ 7.44 - 7.38 (m, 2H), 7.31 (s, 1H), 7.08 (t, <i>J</i> = 73.3 Hz, 1H), 6.99 - 6.95 (m, 2H), 5.17 (s, 2H), 3.77 (s, 3H), 2.43 (s, 3H) ppm.

Intermediate 22

4-(Benzyloxy)-6-chloro-*N*,2-dimethylnicotinamide (**Int-22**)



[0840] Step 1:

[0841] Benzyl alcohol (1.3 mL, 12.6 mmol) was added dropwise over 5 min to a stirred suspension of NaH (513 mg, 60% dispersion in mineral oil, 12.8 mmol) in DMF (9 mL) at 5 °C. The mixture was stirred for 30 min at ambient temperature. A solution of ethyl 4,6-dichloro-2-methylnicotinate (3 g, 12.8 mmol) in DMF (1 mL) was added and the reaction mixture was stirred for 2 h. The reaction was quenched by slow addition of water. The mixture was extracted with EtOAc. The organic layer was dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C₁₈ column, 1 to 99% MeCN in water containing HCl modifier) gave ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate (2.0 g, 51%) as a white solid. ¹H NMR (400 MHz,

Chloroform-*d*) δ 7.50 - 7.30 (m, 5H), 6.69 (s, 1H), 5.16 (s, 2H), 4.40 (q, $J = 7.1$ Hz, 2H), 2.50 (s, 3H), 1.33 (t, $J = 7.1$ Hz, 3H) ppm. ESI-MS m/z calc. 305.082, found 306.2 (M+1)⁺; Retention time: 1.64 minutes using LC/MS method D.

[0842] Step 2:

[0843] A solution of LiOH.H₂O (700 mg, 16.7 mmol) in water (10 mL) was added to a stirred solution of ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate (1 g, 3.2 mmol) in a mixture of THF (10 mL) and methanol (10 mL). The reaction mixture was stirred at ambient temperature for 19 h followed by 2 h at 50 °C. Another portion of LiOH.H₂O (700 mg, 16.7 mmol) was added at ambient temperature and the mixture was stirred at 50 °C for 4 days. The mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was dissolved in water (20 mL) and acidified to pH ~3 - 4 by addition of an aqueous 1 M HCl solution. The precipitate was collected by filtration and rinsed with water (50 mL). The solid was dried under high vacuum to give 4-(benzyloxy)-6-chloro-2-methylnicotinic acid (1 g, 100%) as a white solid, which was used without further purification in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.49 (br s, 1H), 7.44 - 7.32 (m, 5H), 7.23 (s, 1H), 5.29 (s, 2H), 2.37 (s, 3H) ppm. ESI-MS m/z calc. 277.051, found 278.2 (M+1)⁺; Retention time: 1.77 minutes using LC/MS method E.

[0844] Step 3:

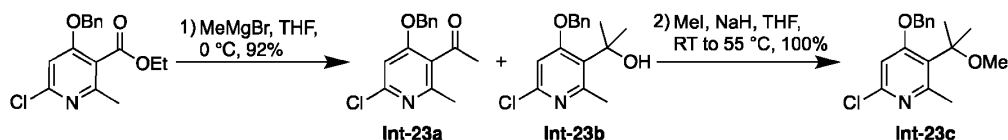
[0845] HATU (246.8 mg, 0.649 mmol), DIPEA (115 μ L, 0.660 mmol) and methanamine (126 mg, 1.62 mmol) were successively added to a 5-mL vial containing a solution of 4-(benzyloxy)-6-chloro-2-methylnicotinic acid (180 mg, 0.648 mmol) in DMF (1 mL). The reaction mixture was stirred for 30 min. The mixture was diluted with EtOAc, washed with a saturated NH₄Cl solution and brine. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0% to 100% EtOAc in hexanes) gave 4-(benzyloxy)-6-chloro-*N*,2-dimethylnicotinamide (**Int-22**, 180.2 mg, 96%) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 (q, $J = 4.6$ Hz, 1H), 7.40 (d, $J = 5.4$ Hz, 4H), 7.37 - 7.32 (m, 1H), 7.15 (s, 1H), 5.25 (s, 2H), 2.74 (d, $J = 4.7$ Hz, 3H), 2.30 (s, 3H) ppm. ESI-MS m/z calc. 290.082, found 291.1 (M+1)⁺; Retention time: 0.79 minutes using LC/MS method D.

[0846] The following intermediate was made using the method described in Intermediate 22, except that in Step 3, dimethylamine was used as the coupling agent in place of methanamine:

Intermediate Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-6-chloro- <i>N</i> ,2-trimethylnicotinamide	304.098	305.0	1.67	Q	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.45 - 7.32 (m, 5H), 7.21 (s, 1H), 5.29 (s, 2H), 2.97 (s, 3H), 2.76 (s, 3H), 2.26 (s, 3H) ppm.

Intermediate 23

1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethan-1-one (**Int-23a**), 2-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)propan-2-ol (**Int-23b**) and 4-(benzyloxy)-6-chloro-3-(2-methoxypropan-2-yl)-2-methylpyridine (**Int-23c**)



[0847] Step 1:

[0848] A solution of MeMgBr (760 μ L, 3 M solution in Et₂O, 2.3 mmol) was added under a nitrogen atmosphere to a stirred solution of ethyl 4-(benzyloxy)-6-chloro-2-methylnicotinate (**Product of Intermediate 22, Step 1**; 200 mg, 0.654 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h. The reaction was quenched by addition of a saturated NH₄Cl solution. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and water, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (C₁₈ column, 10 to 99% MeCN in H₂O containing 5 mM HCl) gave 1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethan-1-one (**Int-23a**, 51 mg, 28%) (ESI-MS *m/z* calc. 275.071, found 276.1 (M+1)⁺; Retention time: 1.18 minutes using LC/MS method D) and 2-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)propan-2-ol (**Int-23b**, 122.2 mg, 64%) (ESI-MS *m/z* calc. 291.103, found 292.14 (M+1)⁺; Retention time: 1.05 minutes using LC/MS method D) as a white solid.

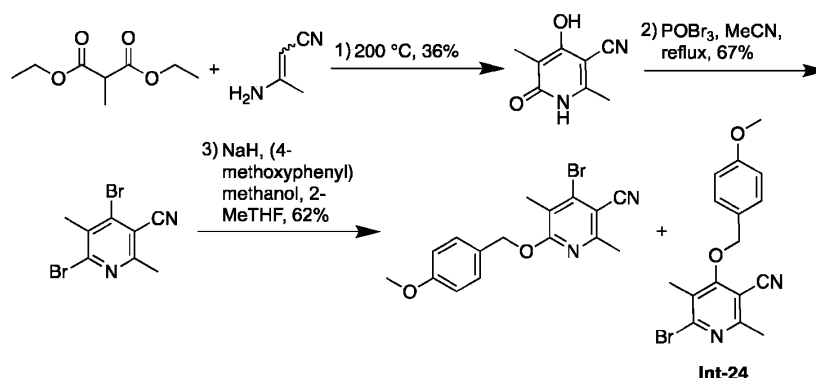
[0849] Step 2:

[0850] NaH (41.2 mg, 60% dispersion in mineral oil, 1.03 mmol) was added to a suspension of 2-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)propan-2-ol (**Int-23b**, 98.6 mg, 0.338 mmol) in THF (1 mL). The reaction mixture was stirred at ambient temperature for 5 min. MeI (65 μ L, 1.04 mmol) was added and the reaction was stirred at 55 °C for 5 h. The mixture was diluted with EtOAc and the layers were separated. The organic phase was washed with NH₄Cl and brine, dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (30 to 99% MeCN in H₂O containing 5 mM HCl) gave 4-(benzyloxy)-6-chloro-3-(2-methoxypropan-2-yl)-2-methylpyridine (**Int-23c**, 102.8 mg, 100%) as an off-white solid. ESI-MS *m/z* calc. 305.118, found 306.1 (M+1)⁺; Retention time: 1.35 minutes using LC/MS method D.

[0851] The following intermediate was made using the method described in Intermediate 23, except that ethyl 4-(benzyloxy)-2-chloro-6-methylnicotinate was used as the starting material in Step 1 and Step 2 was omitted:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
2-(4-(Benzyloxy)-2-chloro-6-methylpyridin-3-yl)propan-2-ol	291.103	292.2	0.51	T	¹ H NMR (400 MHz, Methanol- <i>d</i> ₄) δ 7.50 - 7.33 (m, 5H), 7.01 (s, 1H), 5.22 (s, 2H), 2.40 (s, 3H), 1.66 (s, 6H) ppm; OH alcohol not observed.

Intermediate 24

6-Bromo-4-((4-methoxybenzyl)oxy)-2,5-dimethylnicotinonitrile (**Int-24**)**[0852] Step 1:**

[0853] Diethyl 2-methylmalonate (10.3 g, 59.1 mmol) and 3-aminocrotononitrile (1.8 g, 21.9 mmol) were combined in a sealed tube and heated at 200 °C for 2 h and 45 min. The reaction mixture was cooled to ambient temperature and treated with MTBE, which caused a precipitate to crash out of solution. The solid was filtered and dried to give 4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (1.3 g, 36%). ESI-MS *m/z* calc. 164.059, found 165.2 (M+1)⁺; Retention time: 0.93 minutes using LC/MS method W.

[0854] Step 2:

[0855] POBr₃ (5 g, 17.4 mmol) was added to a stirring mixture of 4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carbonitrile (1.3 g, 7.9 mmol) in MeCN (15 mL) and the reaction mixture was stirred at reflux under nitrogen for 4 h and 45 min. The mixture was concentrated *in vacuo* and partitioned between EtOAc and a saturated NaHCO₃ solution. The mixture was filtered to give a first crop of product (250 mg). The organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo* to give a second crop of product. The 2 crops were combined to give 4,6-dibromo-2,5-dimethylnicotinonitrile (1.538 g, 67%). ESI-MS *m/z* calc. 287.890, found 290.8 (M+1)⁺; Retention time: 0.88 minutes using LC/MS method C.

[0856] Step 3:

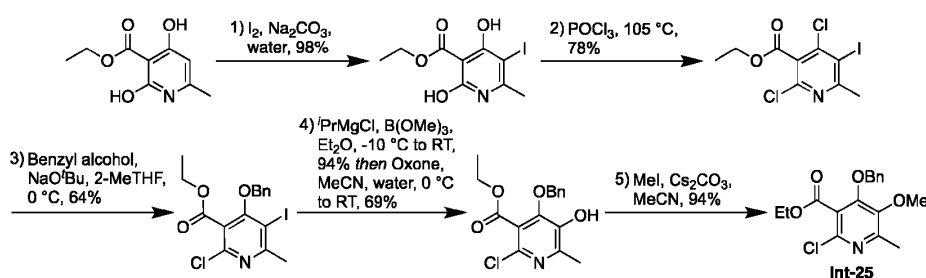
[0857] NaH (446 mg, 60% dispersion in mineral oil, 11.2 mmol) and 4,6-dibromo-2,5-dimethylnicotinonitrile (1.488 g, 5.130 mmol) were successively added to a stirring solution of (4-methoxyphenyl)methanol (724 mg, 5.24 mmol) in 2-MeTHF (30 mL). The reaction mixture was stirred at ambient temperature under nitrogen for 4.5 h. The mixture was diluted with EtOAc and washed with a saturated NaHCO₃ solution. The organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 5% EtOAc in heptane) gave 4-bromo-6-((4-methoxybenzyl)oxy)-2,5-dimethylnicotinonitrile (520.3 mg, 29%) (ESI-MS *m/z* calc. 346.032, found 224.8 (M+1)⁺; Retention time: 1.00 minutes using LC/MS method C) and 6-bromo-4-((4-methoxybenzyl)oxy)-2,5-dimethylnicotinonitrile (**Int-24**, 585.1 mg, 33%) (ESI-MS *m/z* calc. 346.032, found 120.9 (M+1)⁺; Retention time: 1.11 minutes using LC/MS method C).

[0858] The following intermediate was made using the method described in Intermediate 24, except that Step 1 was omitted. Step 2 was carried out at 70 °C in toluene as the solvent using 5,6-dimethylpyrimidine-2,4(1*H*,3*H*)-dione as the starting material in place of 4-hydroxy-2,5-dimethyl-6-oxo-1,6-dihydropyridine-3-carbonitrile. In Step 3, benzyl alcohol was used in place of (4-methoxyphenyl)methanol and the reaction was carried out at 0 to 80 °C:

Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-2-bromo-5,6-dimethylpyrimidine	292.021	293.4	0.98	C	¹ H NMR (400 MHz, Chloroform- <i>d</i>) δ 7.41 - 7.24 (m, 5H), 5.34 (s, 2H), 2.34 (d, <i>J</i> = 0.6 Hz, 3H), 2.05 - 2.00 (m, 3H) ppm.

Intermediate 25

Ethyl 4-(benzyloxy)-2-chloro-5-methoxy-6-methylnicotinate (**Int-25**)

**[0859] Step 1:**

[0860] In a 1-L round-bottomed flask, I₂ (27.2 g, 107.2 mmol) was added to a stirring mixture of ethyl 2,4-dihydroxy-6-methylnicotinate (20.75 g, 105.2 mmol) and Na₂CO₃ (34.05 g, 321.3 mmol) in H₂O (350 mL). The reaction mixture was stirred at ambient temperature for 17 h. The mixture was treated with a concentrated HCl solution (75 mL). The precipitate was filtered and washed with water (300 mL), a saturated Na₂S₂O₃ solution (300 mL), water (300 mL), and MeCN (100 mL) to give ethyl

2,4-dihydroxy-5-iodo-6-methylnicotinate (33.262 g, 98%) as an off-white solid. ^1H NMR (400 MHz, DMSO- d_6) δ 14.27 - 13.65 (br s, 1H), 12.11 - 11.66 (br s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm. ESI-MS m/z calc. 322.965, found 324.1 (M+1) $^+$; Retention time: 1.47 minutes using LC/MS method Q.

[0861] Step 2:

[0862] A solution of ethyl 2,4-dihydroxy-5-iodo-6-methylnicotinate (9.11 g, 28.2 mmol) in POCl₃ (50 mL, 536 mmol) was heated to 105 °C for 28 h. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (100 mL). The aqueous layer was separated and extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 10% EtOAc in heptane) gave ethyl 2,4-dichloro-5-iodo-6-methylnicotinate (7.870 g, 78%). ^1H NMR (500 MHz, DMSO- d_6) δ 4.42 (q, J = 7.1 Hz, 2H), 2.77 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm. ESI-MS m/z calc. 358.898, found 360.1 (M+1) $^+$; Retention time: 1.00 minutes using LC/MS method C.

[0863] Step 3:

[0864] A solution of benzyl alcohol (188.5 g, 1.743 mol) and sodium *tert*-butoxide (175 g, 1.82 mol) in 2-MeTHF (2.75 L) was added at -5 to 0 °C, over 80 min to a solution of ethyl 2,4-dichloro-5-iodo-6-methylnicotinate (570 g, 1.58 mol) in 2-MeTHF (5 L). The reaction mixture was stirred for 1 h at 0 °C before being quenched by addition of a mixture containing 50% brine, 40% water and a 10% aqueous KHCO₃ solution (3 L). The aqueous phase was separated and extracted with 2-MeTHF (1 L). The combined organic phases were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The resulting orange oil was dissolved in DCM (500 mL), filtered through a plug of silica (350 g), rinsing the silica with DCM (4 L). The filtrate was concentrated *in vacuo* and solubilized in heptane (5.5 L). Seeds of ethyl 4-(benzyloxy)-2-chloro-5-iodo-6-methylnicotinate (10 g, 22.3 mmol) were added and the mixture was stirred at 20 °C for 30 min, then cooled to -15 °C in 5 h, stirred at -15 °C for 16 h and cooled to -20 °C for 4 h. The solid was filtered and dried *in vacuo* to give ethyl 4-(benzyloxy)-2-chloro-5-iodo-6-methylnicotinate (466 g, 64%) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 7.51 - 7.37 (m, 5H), 5.09 (s, 2H), 4.35 (q, J = 7.1 Hz, 2H), 2.70 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H) ppm. ESI-MS m/z calc. 430.979, found 432.0 (M+1) $^+$; Retention time: 3.40 minutes using LC/MS method E.

[0865] Step 4:

[0866] $^i\text{PrMgCl}$ (544 mL, 2 M solution in Et₂O, 1.09 mol) was added to a stirred solution of ethyl 4-(benzyloxy)-2-chloro-5-iodo-6-methylnicotinate (414 g, 906 mmol) in Et₂O (5 L) at -11 to -5 °C over 40 min. The reaction mixture was stirred at -10 °C for 10 min. Trimethyl borate (188 g, 1.81 mol) was added at -10 °C over 10 min. The reaction was warmed to ambient temperature and stirred for 1 h. The mixture was quenched by addition of a mixture of NH₄Cl (2 M aqueous solution, 1.5 L) and brine (1.5 L). The organic phase was separated, dried (Na₂SO₄), filtered and concentrated *in*

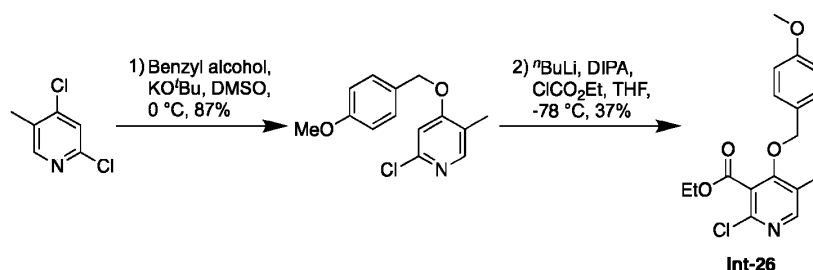
vacuo to give 4-(benzyloxy)-6-chloro-5-(ethoxycarbonyl)-2-methylpyridin-3-yl)boronic acid (395 g, 94%) as a light yellow solid.

[0867] The crude boronic acid was suspended in MeCN (4 L) and a solution of Oxone® (418 g, 680 mmol) in water (2 L) was added at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 16 h. Additional Oxone® (60 g, 97.6 mmol) was added and the reaction was stirred at ambient temperature for 20 h. The mixture was filtered and the solid rinsed with MeCN (2 x 250 mL). The solid was partitioned between brine (1 L) and EtOAc (2 L). The organic phase was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo* to around 1 kg. Heptane (3 L) was added and the mixture was concentrated to around 1.5 kg, cooled to ambient temperature and filtered. The solid was dissolved in MTBE (4 L) and washed with 1 M NaOH (2 x 1 L). The combined aqueous extracts were acidified to pH 2 by addition of 3 N HCl and extracted with EtOAc (2 x 1 L). The organic extracts were combined, dried (Na₂SO₄), filtered and concentrated *in vacuo* to around 750 g. Heptane (1.5 L) was added and the mixture was concentrated to around 1.5 kg inducing crystallization of the product. Heptane (1.5 L) was added and the mixture was concentrated to around 1.5 kg. The solid was filtered, rinsed with heptane (200 mL) and dried *in vacuo* to give ethyl 4-(benzyloxy)-2-chloro-5-hydroxy-6-methylnicotinate (209 g, 69%) as a yellowish solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.87 (s, 1H), 7.42 - 7.31 (m, 5H), 5.16 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 321.077, found 322.1 (M+1)⁺; Retention time: 3.00 minutes using LC/MS method E.

[0868] Step 5:

[0869] Cs₂CO₃ (125 g, 383.7 mmol) and MeI (43 g, 18.9 mL, 303 mmol) were successively added to a solution of ethyl 4-(benzyloxy)-2-chloro-5-hydroxy-6-methylnicotinate (83 g, 255 mmol) in MeCN (415 mL) at ambient temperature. The reaction mixture was stirred for 1 h at ambient temperature, then filtered. The cake was rinsed with MeCN (2 x 100 mL) and the filtrates were concentrated *in vacuo*. The residue was solubilized in DCM (100 mL), filtered on a plug of silica (75 g), rinsing the filtered cake with DCM (1.5 L). The filtrates were concentrated *in vacuo* to give ethyl 4-(benzyloxy)-2-chloro-5-methoxy-6-methylnicotinate (**Int-25**, 81.4 g, 94%) as a yellowish oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48 - 7.28 (m, 5H), 5.24 (s, 2H), 4.26 (q, *J* = 7.3 Hz, 2H), 3.82 (s, 3H), 2.42 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 335.092, found 336.1 (M+1)⁺; Retention time: 3.09 minutes using LC/MS method E.

Intermediate 26

Ethyl 2-chloro-4-((4-methoxybenzyl)oxy)-5-methylnicotinate (**Int-26**)**[0870] Step 1:**

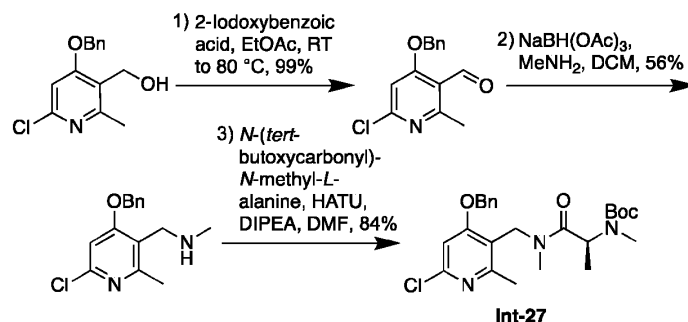
[0871] KO^tBu (22 g, 196 mmol) was added portionwise at 0 °C to a solution of (4-methoxyphenyl)methanol (25.6 g, 23 mL, 185 mmol) in DMSO (300 mL) and the mixture was stirred for 30 min at 0 °C. A solution of 2,4-dichloro-5-methylpyridine (25 g, 154 mmol) in DMSO (100 mL) was added and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was quenched by addition of ice-cold water (1 L) and extracted with EtOAc (2 x 1 L). The combined organic extracts were washed with water (2 x 1 L) and brine (1 L), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 5 to 10% EtOAc in hexanes) gave 2-chloro-4-((4-methoxybenzyl)oxy)-5-methylpyridine (35.22 g, 87%) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.06 (s, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.18 (s, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 5.17 (s, 2H), 3.76 (s, 3H), 2.08 (s, 3H) ppm. ESI-MS *m/z* calc. 263.071, found 264.0 (M+1)⁺; Retention time: 3.94 minutes using LC/MS method Y.

[0872] Step 2:

[0873] ^tBuLi (50 mL, 2 M solution in hexanes, 100 mmol) was added to a stirred solution of DIPA (10.8 g, 15 mL, 107 mmol) in THF (100 mL) at -78 °C and the reaction mixture was stirred at 0 °C for 30 min. The mixture was cooled back down to -78 °C. A solution of 2-chloro-4-((4-methoxybenzyl)oxy)-5-methylpyridine (10 g, 37.9 mmol) in THF (30 mL) was added and the mixture was stirred for 1 h at -78 °C. A solution of ethyl chloroformate (11.4 g, 10 mL, 105 mmol) in THF (30 mL) was added and the mixture was stirred for 1 h at -78 °C. The reaction mixture was quenched by addition of a saturated NH₄Cl solution (200 mL) and extracted with EtOAc (2 x 250 mL). The combined organic extracts were washed with brine (200 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 5 to 7% EtOAc in hexanes) gave ethyl 2-chloro-4-((4-methoxybenzyl)oxy)-5-methylnicotinate (**Int-27**, 4.88 g, 37%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (s, 1H), 7.38 - 7.30 (m, 2H), 7.00 - 6.92 (m, 2H), 5.01 (s, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 2.22 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 335.092, found 336.4 (M+1)⁺; Retention time: 5.90 minutes using LC/MS method Z.

Intermediate 27

tert-Butyl (S)-(1-(((4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methyl)(methyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (**Int-27**)



[0874] Step 1:

[0875] 2-Iodoxybenzoic acid (2.3 g, 8.2 mmol) was added to a solution of (4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methanol (prepared in 2 chemical steps using the conditions described in Intermediate 19 Step 2 starting from ethyl 4,6-dichloro-2-methylnicotinate as a first step, followed by the conditions described in Intermediate 18 Step 2 as a second step) (722 mg, 2.54 mmol) in EtOAc (18 mL) at ambient temperature and the reaction mixture was stirred at 80 °C for 3 h. The mixture was filtered through a pad of Celite[®], rinsing the filtered cake with EtOAc (100 mL). The mother liquors were collected, washed with a NaHCO₃ aqueous solution (2 x 80 mL) and brine (80 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 4-(benzyloxy)-6-chloro-2-methylnicotinaldehyde (739 mg, 99%) as a light yellow solid, which was used without further purification in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.45 (s, 1H), 7.53 - 7.48 (m, 2H), 7.46 - 7.35 (m, 4H), 5.38 (s, 2H), 2.60 (s, 3H) ppm. ESI-MS *m/z* calc. 261.056, found 262.2 (M+1)⁺; Retention time: 2.06 minutes using LC/MS method S.

[0876] Step 2:

[0877] A solution of methylamine (4.92 g, 6.51 mL, 33 % w/w solution in ethanol, 52.3 mmol) and STAB (1.1 g, 5.19 mmol) were successively added to a stirred solution of 4-(benzyloxy)-6-chloro-2-methylnicotinaldehyde (715 mg, 2.44 mmol) in DCM (8 mL) at ambient temperature and the reaction mixture was stirred at ambient temperature overnight. The mixture was diluted with water (50 mL), brine (50 mL) and DCM (70 mL). The aqueous layer was separated and extracted with DCM (70 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (50 g C₁₈ column, 2 to 100% MeCN in water containing 0.1% formic acid). The residue, obtained after concentration of the volatiles *in vacuo*, was partitioned between a saturated NaHCO₃ (150 mL) and EtOAc (200 mL). The organic layer was separated, dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)-*N*-methylethylmethanamine (377 mg, 56%) as a yellow oil. ¹H NMR (400 MHz,

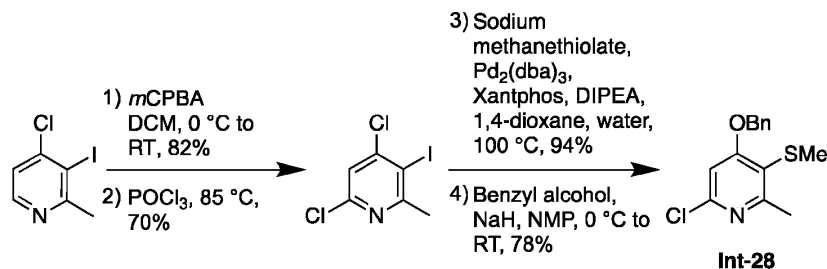
DMSO-*d*₆) δ 7.48 - 7.39 (m, 4H), 7.38 - 7.32 (m, 1H), 7.08 (s, 1H), 5.22 (s, 2H), 3.63 (s, 2H), 2.45 (s, 3H), 2.23 (s, 3H) ppm; NH amine not observed. ESI-MS *m/z* calc. 276.103, found 277.2 (M+1)⁺; Retention time: 1.44 minutes using LC/MS method S.

[0878] Step 3:

[0879] HATU (563 mg, 1.48 mmol) was added to a solution of 1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)-*N*-methylmethanamine (375 mg, 1.35 mmol), DIPEA (334 mg, 0.45 mL, 2.58 mmol) and *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-alanine (300 mg, 1.48 mmol) in DMF (3.5 mL) at ambient temperature and the mixture was stirred for 1.5 h. Purification by reverse phase chromatography (50 g C₁₈ column, 0 to 100% MeCN in water containing 0.1% formic acid). The residue, obtained after concentration of the volatiles *in vacuo*, was partitioned between a saturated NaHCO₃ (30 mL) and EtOAc (50 mL). The aqueous layer was separated, extracted with EtOAc (50 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *tert*-butyl (S)-((1-((4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methyl)(methyl)amino)-1-oxopropan-2-yl)(methyl)carbamate (**Int-28**, 527 mg, 84%) as a light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48 - 7.33 (m, 5H), 7.12 (s, 1H), 5.25 (s, 2H), 4.97 - 4.77 (m, 1H), 4.75 - 4.37 (m, 2H), 2.75 - 2.62 (m, 6H), 2.40 (s, 3H), 1.38 (s, 9H), 1.11 (br s, 3H) ppm. ESI-MS *m/z* calc. 461.208, found 462.4 (M+1)⁺; Retention time: 2.18 minutes using LC/MS method S.

Intermediate 28

4-(Benzyloxy)-6-chloro-2-methyl-3-(methylthio)pyridine (**Int-28**)



[0880] Step 1:

[0881] *m*CPBA (23.4 g, 70 - 75 % w/w in water, 101.7 mmol) was added portionwise to a solution of 4-chloro-3-iodo-2-methylpyridine (17.2 g, 67.9 mmol) in DCM (250 mL) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred overnight. The mixture was diluted with DCM (250 mL) and washed with water (250 mL). The aqueous layer was separated and extracted with DCM (200 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was triturated from MeOH (2 x 30 mL), filtered and dried to give 4-chloro-3-iodo-2-methylpyridine 1-oxide (15 g, 82%) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 6.9 Hz, 1H), 2.90 (s, 3H) ppm. ESI-MS *m/z* calc. 268.910, found 269.8 (M+1)⁺; Retention time: 0.52 minutes using LC/MS method P.

[0882] Step 2:

[0883] A solution of 4-chloro-3-iodo-2-methylpyridine 1-oxide (1.75 g, 6.49 mmol) in POCl₃ (16.5 g, 10 mL, 107 mmol) was heated at 85 °C for 5 h. On cooling, the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and water (20 mL). The aqueous layer was separated and extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 4,6-dichloro-3-iodo-2-methylpyridine (2.5 g, 70%) as a brown solid. ESI-MS *m/z* calc. 286.877, found 287.7 (M+1)⁺; Retention time: 1.10 minutes using LC/MS method N.

[0884] Step 3:

[0885] A mixture of 4,6-dichloro-3-iodo-2-methylpyridine (212 mg, 0.708 mmol), sodium methanethiolate (50 mg, 0.70 mmol), Pd₂(dba)₃ (16 mg, 0.018 mmol), Xantphos (20 mg, 0.035 mmol) and DIPEA (183 mg, 247 µL, 1.42 mmol) in a mixture of 1,4-dioxane (2 mL) and water (0.2 mL) was stirred under microwave irradiation at 100 °C for 1 h. The mixture was partitioned between EtOAc and water. The aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 20% EtOAc in heptane) gave 4,6-dichloro-2-methyl-3-(methylthio)pyridine (186 mg, 94%) as a pale yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.30 (s, 1H), 2.78 (s, 3H), 2.34 (s, 3H) ppm. ESI-MS *m/z* calc. 206.968, found 207.9 (M+1)⁺; Retention time: 0.61 minutes using LC/MS method N.

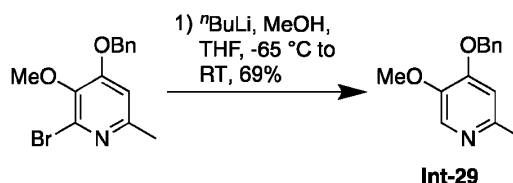
[0886] Step 4:

[0887] Benzyl alcohol (160 µL, 1.55 mmol) was added dropwise to a stirred suspension of NaH (88 mg, 60% dispersion in mineral oil, 2.2 mmol) in NMP (3.0 mL) at 0 °C and the reaction mixture stirred at ambient temperature for 15 min. A solution of 4,6-dichloro-2-methyl-3-(methylthio)pyridine (305 mg, 1.47 mmol) in NMP (3.0 mL) was added at 0 °C. The mixture was warmed to ambient temperature and stirred for a further 1 h. The mixture was quenched by addition of a saturated NH₄Cl solution (5 mL) and poured over water (50 mL). The mixture was diluted with EtOAc (50 mL). The aqueous layer was separated and extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (40 g SiO₂, 0 to 30% EtOAc in heptane) gave 4-(benzyloxy)-6-chloro-2-methyl-3-(methylthio)pyridine (**Int-28**, 319 mg, 78%) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.47 - 7.35 (m, 5H), 6.76 (s, 1H), 5.18 (s, 2H), 2.69 (s, 3H), 2.30 (s, 3H) ppm. ESI-MS *m/z* calc. 279.048, found 280.4 (M+1)⁺; Retention time: 3.43 minutes using LC/MS method A.

[0888] The following intermediate was made using the method described in Intermediate 29, except that Step 1 and Step 3 were omitted. In Step 2, the reaction was carried out at 105 °C using ethyl 4-hydroxy-5,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carboxylate as the starting material. In Step 4, the reaction was carried out in DMF as the solvent in place of NMP:

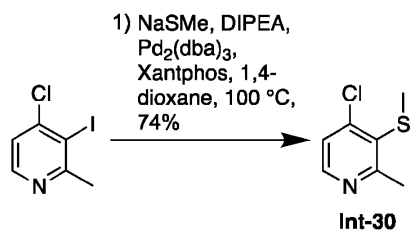
Intermediate Name	LC/MS (<i>m/z</i> calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
Ethyl 4-(benzyloxy)-2-chloro-5,6-dimethylnicotinate	319.098	320.3	0.71	T	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.44 - 7.37 (m, 5H), 4.99 (s, 2H), 4.31 (q, <i>J</i> = 7.1 Hz, 2H), 2.45 (s, 3H), 2.17 (s, 3H), 1.24 (t, <i>J</i> = 7.1 Hz, 3H) ppm.

Intermediate 29

4-(Benzyloxy)-5-methoxy-2-methylpyridine (**Int-29**)**[0889] Step 1:**

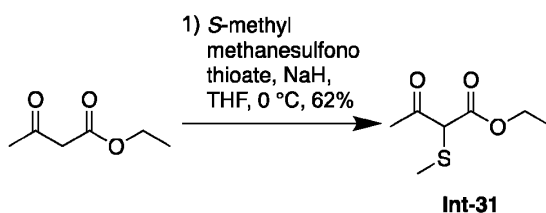
[0890] In a 3-necked-flask, ⁿBuLi (4.3 mL, 1.6 M solution in hexanes, 6.9 mmol) was added dropwise to a solution of 4-(benzyloxy)-2-bromo-3-methoxy-6-methylpyridine (**Int-19**, 1.754 g, 5.692 mmol) in THF (15 mL) at -65 °C, keeping the temperature below -55 °C. The reaction mixture was stirred for 20 min at -65 °C. MeOH (500 μL, 12.3 mmol) was added dropwise and the reaction was stirred at -65 °C for 20 min. The mixture was warmed to ambient temperature, quenched by addition of a saturated NH₄Cl solution and diluted with EtOAc. The aqueous phase was separated and extracted with EtOAc (x 3). The combined organic extracts were washed with brine, dried and filtered using a Whatman[®] IPS hydrophobic phase separator filter paper and concentrated *in vacuo* to give 4-(benzyloxy)-5-methoxy-2-methylpyridine (**Int-29**, 1.018 g, 69%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46 - 7.39 (m, 2H), 7.33 - 7.21 (m, 3H), 6.88 (d, *J* = 7.8 Hz, 1H), 6.58 (dd, *J* = 7.8, 0.7 Hz, 1H), 5.40 (s, 2H), 3.75 (s, 3H), 2.31 (d, *J* = 0.7 Hz, 3H) ppm. ESI-MS *m/z* calc. 229.110, found 230.6 (M+1)⁺; Retention time: 0.95 minutes using LC/MS method C.

Intermediate 30

4-Chloro-2-methyl-3-(methylthio)pyridine (**Int-30**)**[0891] Step 1:**

[0892] 1,4-Dioxane (60 mL) was added to a vial containing 4-chloro-3-iodo-2-methylpyridine (3.8 g, 15 mmol), Xantphos (460 mg, 0.795 mmol) and Pd₂(dba)₃ (380 mg, 0.415 mmol) and the mixture was purged with nitrogen gas. DIPEA (5 mL, 28.7 mmol) and sodium NaSMe (5 mL, 21 % w/v in water, 15 mmol) were successively added and the reaction mixture was heated to 100 °C for 1 h. The mixture was partitioned between EtOAc (150 mL) and NH₄Cl (100 mL). The organic phase was separated and washed with water (2 x 100 mL) and brine (200 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (80 g SiO₂, 0 to 100% EtOAc in heptane) gave 4-chloro-2-methyl-3-(methylthio)pyridine (**Int-30**, 2.1 g, 74%) as a colourless oil. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.35 (d, *J* = 5.2 Hz, 1H), 7.47 (d, *J* = 5.2 Hz, 1H), 2.74 (s, 3H), 2.36 (s, 3H) ppm. ESI-MS *m/z* calc. 173.007, found 173.7 (M+1)⁺; Retention time: 0.73 minutes using LC/MS method C.

Intermediate 31

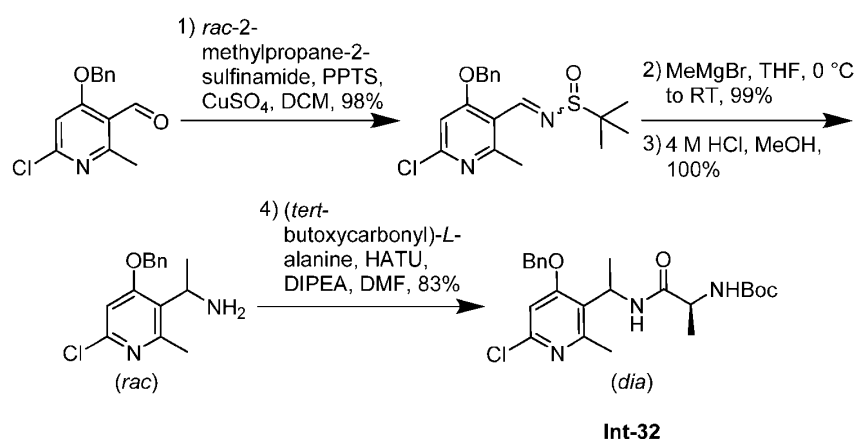
Ethyl *rac*-2-(methylthio)-3-oxobutanoate (**Int-31**)**[0893] Step 1:**

[0894] NaH (350 mg, 60% dispersion in mineral oil, 8.75 mmol) was added to a solution of ethyl 3-oxobutanoate (1 mL, 7.8 mmol) in THF (15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. *S*-Methyl methanesulfonylthioate (900 μL, 9.54 mmol) was added and the reaction mixture was stirred at 0 °C for 2.5 h. The mixture was quenched by addition of a NH₄Cl solution (5 mL) and partitioned between EtOAc (50 mL) and water (50 mL). The aqueous phase was separated and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (24 g SiO₂, 0 to 25 % EtOAc in heptane)

gave ethyl *rac*-2-(methylthio)-3-oxobutanoate (**Int-31**, 900 mg, 62%) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.63 (d, *J* = 0.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.28 (d, *J* = 0.4 Hz, 3H), 2.09 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 176.051, found 177.0 (M+1)⁺; Retention time: 0.63 minutes using LC/MS method C.

Intermediate 32

tert-Butyl *dia*-((*S*^{*})-1-(((*S*^d)-1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethyl)amino)-1-oxopropan-2-yl)carbamate (**Int-32**)



[0895] Step 1:

[0896] *rac*-2-Methylpropane-2-sulfinamide (460 mg, 3.80 mmol), copper sulfate (1.2 g, 7.5 mmol) and PPTS (65 mg, 0.26 mmol) were added to a solution of 4-(benzyloxy)-6-chloro-2-methylnicotinaldehyde (Product of Intermediate 27 Step 1, 650 mg, 2.357 mmol) in DCM (20 mL) and the reaction mixture was stirred at ambient temperature for 16 h. The mixture was filtered on a pad of Celite®, rinsing the filtered cake with DCM (150 mL). The filtrate was concentrated *in vacuo*. Purification by flash chromatography (40 g SiO₂, 0 to 20 % EtOAc in heptane) gave *N*-((4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (840 mg, 98%) as a mixture of *E*- and *Z*-stereoisomers and as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 9.10 (s, 1H), 7.45 - 7.33 (m, 5H), 6.87 (s, 1H), 5.23 (s, 2H), 2.79 (s, 3H), 1.25 (s, 9H) ppm. ESI-MS *m/z* calc. 364.101, found 365.2 (M+1)⁺; Retention time: 2.23 minutes using LC/MS method S.

[0897] Step 2:

[0898] MeMgBr (0.22 mL, 3 M solution in Et₂O, 0.66 mmol) was added to a solution of *N*-((4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (115 mg, 0.315 mmol) in THF (2 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 1 h. The mixture was partitioned between a saturated aqueous NH₄Cl solution (20 mL) and EtOAc (20 mL). The aqueous layer was separated and extracted with EtOAc (20 mL). The combined organic

extracts were washed with water (10 mL) and brine (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *rac-N*-(1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (120 mg, 99%) as a light brown oil and, as a mixture of isomers. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.47 - 7.38 (m, 5H), 6.83 (s, 1H), 5.18 - 5.06 (m, 2H), 4.89 - 4.57 (m, 1H), 2.58 (s, 0.9H), 2.56 (s, 2.1H), 1.64 - 1.58 (m, 3H), 1.05 (s, 2.7H), 1.02 (s, 6.3H) ppm. ESI-MS *m/z* calc. 380.133, found 381.2 (M+1)⁺; Retention time: 2.02 minutes using LC/MS method S.

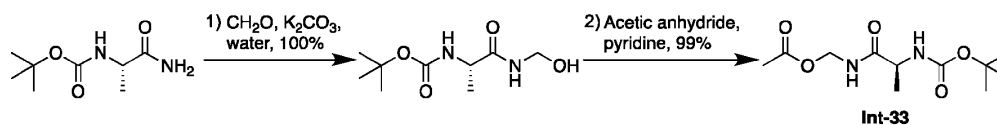
[0899] Step 3:

[0900] 4 M HCl (2.2 mL, 4 M solution in 1,4-dioxane, 8.8 mmol) was added dropwise to a solution of *rac-N*-(1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethyl)-2-methylpropane-2-sulfonamide (1 g, 2.26 mmol) in MeOH (15 mL). The reaction mixture was stirred at ambient temperature for 1 h. The mixture was quenched by addition of a 1 M NaOH aqueous solution (20 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *rac*-1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethan-1-amine (Hydrochloride salt) (790 mg, 100%) as a tan oil, which was used without further purification in the next step. ESI-MS *m/z* calc. 276.103, found 277.2 (M+1)⁺; Retention time: 1.52 minutes using LC/MS method S.

[0901] Step 4:

[0902] HATU (785 mg, 2.07 mmol) was added to a stirred solution of *rac*-1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethan-1-amine (Hydrochloride salt) (690 mg, 2.11 mmol), (*tert*-butoxycarbonyl)-*L*-alanine (400 mg, 2.11 mmol) and DIPEA (814 mg, 6.3 mmol) in DMF (7 mL) at 0 °C and the reaction mixture was stirred at ambient temperature for 1 h. After purification by reverse phase chromatography (150 g C₁₈ column, 5 to 100% MeCN in water containing 0.1% formic acid), the residue was partitioned between a saturated aqueous NaHCO₃ solution (70 mL) and DCM (150 mL). The aqueous phase was separated and extracted with DCM (2 x 150 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give *tert*-butyl *dia*-((*S*^{*})-1-(((*S'*)-1-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)ethyl)amino)-1-oxopropan-2-yl)carbamate (**Int-32**, 827 mg, 83%) as a brown solid and, as a mixture of diastereoisomers. ESI-MS *m/z* calc. 447.193, found 448.2 (M+1)⁺; Retention time: 3.15 minutes using LC/MS method E.

Intermediate 33

(S)-(2-((*tert*-Butoxycarbonyl)amino)propanamido)methyl acetate (**Int-33**)**[0903] Step 1:**

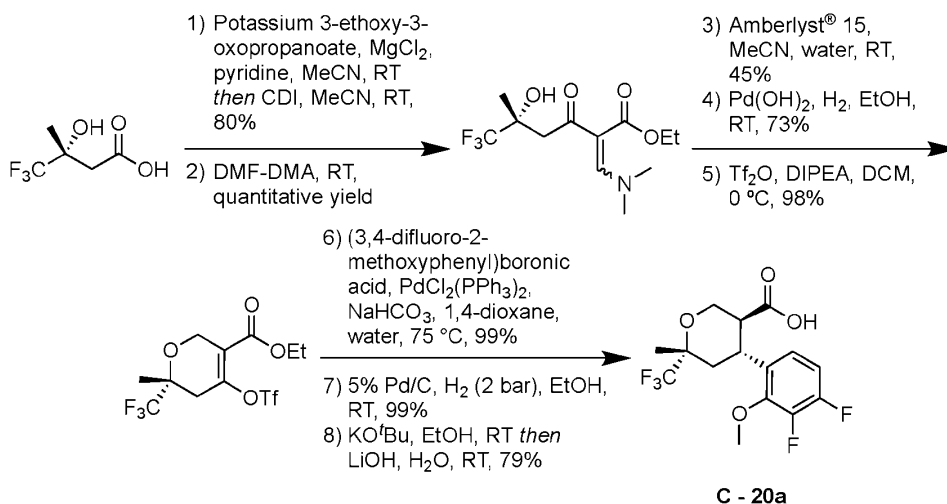
[0904] Formaldehyde (14.8 mL, 37 % w/w in water, 199 mmol) was added to a stirring suspension of *tert*-butyl (S)-(1-amino-1-oxopropan-2-yl)carbamate (25 g, 133 mmol) and K₂CO₃ (918 mg, 6.64 mmol) in water (100 mL) and the mixture was stirred at ambient temperature for 19 h. The solution was saturated with NaCl and extracted with EtOAc (1 x 250 mL, then 2 x 200 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to give *tert*-butyl (S)-(1-((hydroxymethyl)amino)-1-oxopropan-2-yl)carbamate (30.6 g, 100%) as a colourless glassy solid, which was used without further purification in the next step. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (t, *J* = 6.4 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.54 (t, *J* = 6.8 Hz, 1H), 4.60 - 4.37 (m, 2H), 3.93 (p, *J* = 7.3 Hz, 1H), 1.37 (s, 9H), 1.16 (dd, *J* = 7.1, 3.5 Hz, 3H) ppm.

[0905] Step 2:

[0906] *tert*-Butyl (S)-(1-((hydroxymethyl)amino)-1-oxopropan-2-yl)carbamate (50 g, 229 mmol) was added to a stirring solution of acetic anhydride (100 mL, 1.06 mol) and pyridine (150 mL) at ambient temperature, causing a 22 °C exotherm. The reaction mixture was stirred at ambient temperature overnight. Toluene (500 mL) was added to the mixture, which was concentrated *in vacuo* at 45 °C. The residue was co-evaporated with toluene (2 x 500 mL). The residue was recrystallized from toluene (100 mL, 1.68 vol) and heptane (170 mL, 2.85 vol) at 50 °C. The solid was filtered, rinsed with a 20% toluene in heptane solution, then with heptane, dried under house vacuum with a nitrogen bleed at ambient temperature overnight to give (S)-(2-((*tert*-butoxycarbonyl)amino)propanamido)methyl acetate (**Int-33**, 59.1 g, 99%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.78 (t, *J* = 7.0 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 5.18 - 4.97 (m, 2H), 4.04 - 3.74 (m, 1H), 1.99 (s, 3H), 1.37 (s, 9H), 1.16 (d, *J* = 7.2 Hz, 3H) ppm.

Intermediate 34

(3*S*,4*R*,6*R*)-4-(3,4-Difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylic acid (**Int-34**)

**[0907] Step 1:**

[0908] CDI (30 g, 185 mmol) was added to a solution of (*R*)-4,4,4-trifluoro-3-hydroxy-3-methylbutanoic acid (25 g, 145 mmol) in THF (150 mL) and the reaction mixture was stirred for 5 h under an argon atmosphere. In a separate flask, MgCl_2 (17 g, 179 mmol) was added to a suspension of potassium 3-ethoxy-3-oxopropanoate (30 g, 176 mmol) in MeCN (150 mL) and the mixture was stirred for 20 min. Pyridine (27.4 g, 28 mL, 346 mmol) was added and the white suspension was stirred for 4 h. The above prepared activated acid solution was added to the magnesium salt suspension and the mixture was stirred overnight. The mixture was quenched by addition of a 10% aqueous citric acid solution (300 mL) and concentrated *in vacuo* to remove the acetonitrile. The aqueous residue was extracted with EtOAc (800 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in EtOAc (800 mL), washed with a saturated aqueous NaHCO_3 solution (300 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 10 to 20% EtOAc in hexane) gave ethyl (*R*)-6,6,6-trifluoro-5-hydroxy-5-methyl-3-oxohexanoate (28 g, 80%). ^1H NMR (400 MHz, Chloroform-*d*) δ 4.43 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.55 - 3.46 (m, 2H), 3.09 (d, J = 16.9 Hz, 1H), 2.74 (d, J = 16.9 Hz, 1H), 1.42 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H) ppm.

[0909] Step 2:

[0910] A mixture of ethyl (*R*)-6,6,6-trifluoro-5-hydroxy-5-methyl-3-oxohexanoate (30.1 g, 124.3 mmol) and *N,N*-dimethylformamide dimethyl acetal (17.9 g, 20 mL, 151 mmol) was stirred for 1 h. The reaction mixture was diluted with toluene (50 mL) and concentrated *in vacuo*. The residue was co-evaporated with toluene (2 x 50 mL) to give ethyl (*R*)-2-(dimethylaminomethylene)-6,6,6-

trifluoro-5-hydroxy-5-methyl-3-oxohexanoate (39.21 g, 106%) as a mixture of *E*- and *Z*-stereoisomers, which was used without further purification in the next step.

[0911] Step 3:

[0912] To a stirring solution of ethyl (*R*)-2-(dimethylaminomethylene)-6,6,6-trifluoro-5-hydroxy-5-methyl-3-oxohexanoate (22.92 g, 77.10 mmol) in a mixture of MeCN (800 mL) and water (200 mL) was added Amberlyst® 15 (28 g, washed with 1:1 MeCN/water). The mixture was stirred at ambient temperature for 17 h. Additional washed Amberlyst® 15 (12 g) was added and the mixture stirred for 3 h. The mixture was filtered and concentrated *in vacuo*. Purification through a plug of silica (700 mL SiO₂, 10 % EtOAc in heptane (1L), 20 % EtOAc in heptane (6 L), and 30 % EtOAc in heptane (2L)) gave two fractions. The first fraction (7.9 g) was repurified by flash chromatography (SiO₂ 330 g, EtOAc in heptane) to provide 1.43 g of desired compound. This material was combined with the second fraction to afford ethyl (*R*)-2-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-carboxylate (9.66 g, 45%). ¹H NMR (300 MHz, Chloroform-*d*) δ 8.19 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.00 (d, *J* = 16.2 Hz, 1H), 2.63 (d, *J* = 16.2 Hz, 1H), 1.60 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm.

[0913] Step 4:

[0914] In a round-bottomed flask, nitrogen was bubbled through a solution of ethyl (*R*)-2-methyl-4-oxo-2-(trifluoromethyl)-3,4-dihydro-2*H*-pyran-5-carboxylate (17.92 g, 41.92 mmol) in EtOH (40 mL) for 5 min. In a separate three-necked flask, nitrogen was bubbled through a suspension of Pd(OH)₂ (1.47 g, 20 % w/w, 2.09 mmol) in EtOH (130 mL) for 10 min. The solution of ethyl (2*R*)-2-methyl-4-oxo-2-(trifluoromethyl)-3*H*-pyran-5-carboxylate in EtOH was added to the suspension of Pd(OH)₂ in EtOH. Nitrogen was passed through the mixture for 5 min and the mixture was stirred under an atmospheric pressure of hydrogen for 18 h at 20 °C. The suspension was carefully filtered over a pad of Celite®, rinsing the filtered cake with EtOH. The filtrate was concentrated *in vacuo*. Purification by flash chromatography (SiO₂ 330 g, EtOAc in heptane) gave ethyl (*R*)-4-hydroxy-6-methyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-carboxylate (7.75 g, 73%). ¹H NMR (300 MHz, Chloroform-*d*) δ 11.86 (s, 1H), 4.46 (ddt, *J* = 14.5, 1.8, 0.9 Hz, 1H), 4.37 - 4.13 (m, 3H), 2.71 (d, *J* = 17.8 Hz, 1H), 2.21 (d, *J* = 16.5 Hz, 1H), 1.43 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm. ¹⁹F NMR (282 MHz, Chloroform-*d*) δ -83.01 ppm.

[0915] Step 5:

[0916] To a stirring solution of ethyl (*R*)-4-hydroxy-6-methyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-carboxylate (41 g, 161 mmol) in DCM (400 mL) at 0 °C was added DIPEA (70 mL, 409 mmol) followed by the dropwise addition of Tf₂O (31 mL, 180 mmol) over 15 min. The mixture was stirred at 0 °C for 1 h, then diluted with water (100 mL). The organic layer was separated and washed with a 10% aqueous citric acid solution and water, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 70% DCM in hexanes) gave ethyl (*R*)-6-methyl-6-(trifluoromethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydro-2*H*-pyran-3-carboxylate (61 g,

98%). ¹H NMR (400 MHz, Chloroform-*d*) δ 4.72 - 4.62 (m, 1H), 4.49 (dt, *J* = 17.0, 3.0 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.84 (dt, *J* = 17.9, 3.2 Hz, 1H), 2.32 (dt, *J* = 17.9, 2.2 Hz, 1H), 1.47 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ESI-MS *m/z* calc. 386.026, found 387.2 (M+1)⁺; Retention time: 1.97 minutes using method D.

[0917] Step 6:

[0918] Ethyl (*R*)-6-methyl-6-(trifluoromethyl)-4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydro-2*H*-pyran-3-carboxylate (30 g, 77.7 mmol) and (3,4-difluoro-2-methoxyphenyl)boronic acid (17.52 g, 93.22 mmol) were dissolved in 1,4-dioxane (300 mL), followed by addition of a saturated aqueous NaHCO₃ solution (84 mL). Nitrogen was bubbled through the mixture for 15 min. PdCl₂(PPh₃)₂ (3.28 g, 4.67 mmol) was added and the mixture was heated at 75 °C for 30 min. A mixture of 20% EtOAc in hexanes (150 mL) and water (150 mL) were added and the mixture was filtered to removed insoluble solids. The phases were separated and the organic phase was dried (MgSO₄), filtered and concentrated *in vacuo* to give a red oil (32.6 g). DCM (50 mL) was added to the crude material, then hexanes (450 mL) was added and stirred at ambient temperature overnight. The resulting precipitate was removed by filtration and rinsed with 10% DCM in hexanes, then the filtrate was concentrated to give a red oil (31.5 g). Purification by flash chromatography (SiO₂, 10 to 75% DCM in hexanes) gave ethyl (*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-carboxylate (29.20 g, 99%) was obtained as an almost colourless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 6.92 - 6.80 (m, 1H), 6.76 - 6.66 (m, 1H), 4.67 (d, *J* = 17.1 Hz, 1H), 4.50 (dt, *J* = 17.1, 3.0 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.92 (d, *J* = 2.1 Hz, 3H), 2.90 - 2.57 (m, 1H), 2.41 - 2.12 (m, 1H), 1.49 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 380.105, found 381.5 (M+1)⁺; Retention time: 2.90 minutes using LC/MS method AD

[0919] Step 7 and 8:

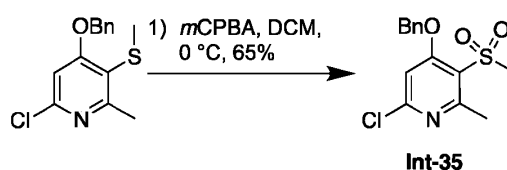
[0920] Under a nitrogen atmosphere, 5% Pd/C (60.4 g, 50% wet, Johnson Matthey A503032-5, 14.19 mmol) was added to a solution of ethyl (*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)-5,6-dihydro-2*H*-pyran-3-carboxylate (77.1 g, 202.7 mmol) in EtOH (771 mL) and the reaction mixture was stirred under a pressure of 2 bar of hydrogen gas for 30 h. The mixture was filtered through a pad of Celite[®] and the filtrates were concentrated *in vacuo* to give ethyl (3*R*,4*R*,6*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylate (76.9 g, 99%) as the major syn diastereomer and as a colourless oil.

[0921] KO^tBu (38.7 g, 344.9 mmol) was added to a stirred solution of ethyl (3*R*,4*R*,6*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylate (76.9 g, 201.1 mmol) in EtOH (463 mL) cooled to 0 °C and the reaction mixture was stirred at ambient temperature for 3 days. A solution of LiOH.H₂O (25.6 g, 610.1 mmol) in water (463 mL) was added and the mixture was stirred at ambient temperature for 24 h. The majority of the EtOH was removed *in vacuo* and the mixture was diluted MTBE (600 mL). The mixture was quenched by addition of HCl (609 mL, 2 M aqueous solution, 1.22 mol) while keeping the temperature between 8 and 22 °C. The

organic phase was separated, washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by recrystallisation from MTBE and heptane gave (3*S*,4*R*,6*R*)-4-(3,4-difluoro-2-methoxyphenyl)-6-methyl-6-(trifluoromethyl)tetrahydro-2*H*-pyran-3-carboxylic acid (**Intermediate 33**, 56.4 g, 79%). ^1H NMR (400 MHz, Chloroform-*d*) δ 10.55 (s, 1H), 6.96 - 6.73 (m, 2H), 4.16 (dd, J = 11.8, 4.7 Hz, 1H), 3.96 (d, J = 2.3 Hz, 3H), 3.90 - 3.76 (m, 1H), 3.66 - 3.49 (m, 1H), 3.13 - 2.95 (m, 1H), 1.87 (t, J = 13.2 Hz, 1H), 1.70 (dd, J = 13.4, 4.0 Hz, 1H), 1.54 (s, 3H) ppm. ESI-MS m/z calc. 354.089, found 355.4 ($\text{M}+1$)⁺; Retention time: 2.39 minutes using LC/MS method AD.

Intermediate 35

4-Benzyloxy-6-chloro-2-methyl-3-methylsulfonyl-pyridine (**Int-35**)

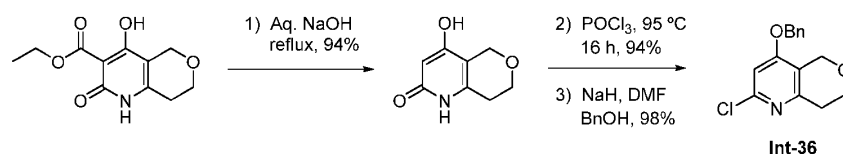


[0922] Step 1:

[0923] To a solution of 4-(benzyloxy)-6-chloro-2-methyl-3-(methylthio)pyridine (101 mg, 0.307 mmol) in DCM (10 mL) at 0 °C was added *m*CPBA (90 mg, 75 % w/w solution in water, 0.39 mmol). The mixture was stirred at this temperature for 1 h. Additional *m*CPBA (70 mg, 75 % w/w solution in water, 0.30 mmol) was added and the stirring continued for 3 h at 0 °C. The mixture was diluted with DCM (25 mL) and washed with a saturated aqueous NaHCO_3 solution (2 x 25 mL), water and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 4-(benzyloxy)-6-chloro-2-methyl-3-(methylsulfonyl)pyridine (92 mg, 65%). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.53 - 7.37 (m, 5H), 6.94 (s, 1H), 5.26 (s, 2H), 3.17 (s, 3H), 2.85 (s, 3H). ESI-MS m/z calc. 311.038, found 312.0 ($\text{M}+1$)⁺; Retention time: 0.58 minutes using LC/MS method AA.

Intermediate 36

4-Benzyloxy-2-chloro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (**Int-36**)



[0924] Step 1:

[0925] A solution of ethyl 4-hydroxy-2-oxo-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridine-3-carboxylate (1.97 g, 7.61 mmol) in 2 M aqueous NaOH (20 mL, 40 mmol) was refluxed for 2 h. The mixture was cooled to 5 °C and acidified using a concentrated aqueous HCl solution. The resulting solid was collected by filtration, washed with cold water and dried to provide 4-hydroxy-1,5,7,8-

tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one (1.22 g, 94%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.89 (br s, 1H), 5.41 (s, 1H), 4.46-4.24 (m, 2H), 3.75 (t, *J* = 5.7 Hz, 2H), 2.42 (t, *J* = 5.5 Hz, 2H) ppm; exchangeable proton not observed. ESI-MS *m/z* calc. 167.058, found 168.0 (M+1)⁺; Retention time: 0.37 minutes using LC/MS method N.

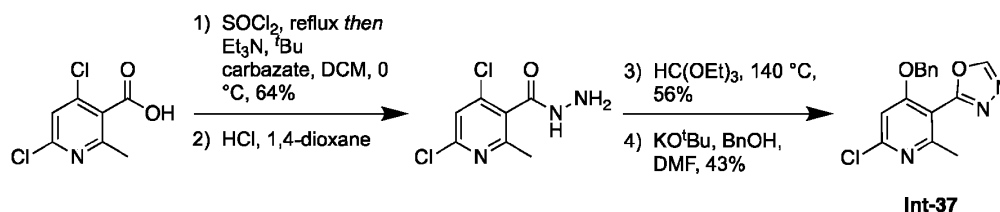
[0926] Step 2:

[0927] A suspension of 4-hydroxy-1,5,7,8-tetrahydro-2*H*-pyrano[4,3-*b*]pyridin-2-one (1.2 g, 7.03 mmol) and POCl₃ (82 g, 50 mL, 54 mmol) was heated at 95 °C for 16 h. The mixture was cooled and concentrated under reduced pressure. The residue was diluted with water (150 mL) and EtOAc (100 mL), cooled to 5 °C, then solid Na₂CO₃ (25 g) added portionwise. The mixture was stirred for 30 min then extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated to provide 2,4-dichloro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (1.4 g, 94%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.21 (s, 1H), 4.73 (s, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 2.99 - 2.96 (m, 2H) ppm. ESI-MS *m/z* calc. 202.990, found 204.0 (M+1)⁺; Retention time: 0.83 minutes using LC/MS method N.

[0928] Step 3:

[0929] A suspension of sodium hydride (231 mg, 60 % w/w dispersion in mineral oil, 5.78 mmol) in DMF (20 mL) at 0 °C under argon was treated with benzyl alcohol (630 mg, 0.6 mL, 5.8 mmol) and stirred for 40 min. A solution of 2,4-dichloro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (1.02 g, 4.81 mmol) in DMF (5 mL) was added and the mixture stirred at 0 °C for 30 min, then allowed to warm to ambient temperature over 3 h. The mixture was diluted with a saturated aqueous NH₄Cl solution (40 mL) and extracted with EtOAc (2 x 50 mL). The combined extracts were washed with water (2 x 50 mL) and brine (40 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 10 to 35% EtOAc in heptanes) provided 4-benzyl-2-chloro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (1.3 g, 98%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 - 7.35 (m, 5H), 6.72 (s, 1H), 5.10 (s, 2H), 4.70 (s, 2H), 3.99 (t, *J* = 5.7 Hz, 2H), 2.92 (t, *J* = 5.5 Hz, 2H) ppm. ESI-MS *m/z* calc. 275.071, found 276.4 (M+1)⁺; Retention time: 0.46 minutes using LC/MS method AA.

Intermediate 37

2-(4-(Benzyloxy)-6-chloro-2-methylpyridin-3-yl)-1,3,4-oxadiazole (**Int-37**)**[0930] Step 1:**

[0931] A mixture of 4,6-dichloro-2-methylnicotinic acid (7.0 g, 34 mmol) and SOCl_2 (24.5 g, 15 mL, 206 mmol) was refluxed for 2 h. The mixture was concentrated *in vacuo*, dissolved in benzene and concentrated *in vacuo* to provide 9 g of the corresponding acid chloride. The product was dissolved in DCM (40 mL) and added slowly to a mixture of *tert*-butyl carbazate (4.5 g, 34 mmol) and TEA (10.9 g, 15 mL, 108 mmol) in DCM (80 mL) at 0 °C. The mixture was stirred for 2 h, diluted with water (60 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with an aqueous NaHCO_3 solution (100 mL) and brine (100 mL), dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 16 to 20% EtOAc in hexanes) provided *tert*-butyl 2-(4,6-dichloro-2-methylnicotinoyl)hydrazine-1-carboxylate (7.0 g, 64%). ESI-MS *m/z* calc. 319.049, found 320.1 ($\text{M}+1$)⁺; Retention time: 2.93 minutes using LC/MS method Y.

[0932] Step 2:

[0933] A mixture of *tert*-butyl 2-(4,6-dichloro-2-methylnicotinoyl)hydrazine-1-carboxylate (7.0 g, 22 mmol) and HCl (120 mL, 4 M solution in 1,4-dioxane, 480 mmol) was stirred at ambient temperature for 3 h. The mixture was evaporated to dryness to provide 4,6-dichloro-2-methylnicotinohydrazide (5 g, 98%). ESI-MS *m/z* calc. 218.997, found 220.1 ($\text{M}+1$)⁺; Retention time: 1.27 minutes using LC/MS method U.

[0934] Step 3:

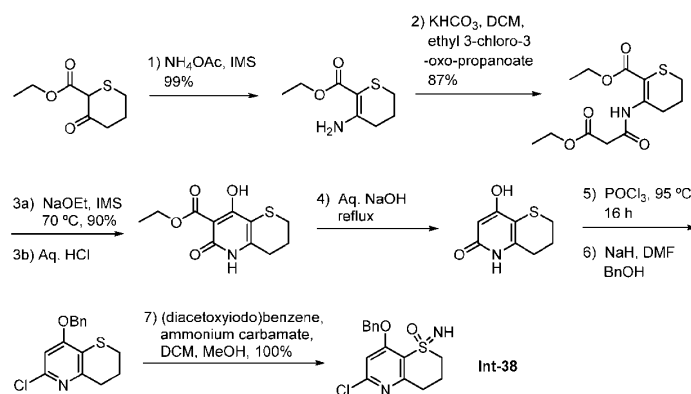
[0935] A mixture of 4,6-dichloro-2-methylnicotinohydrazide (5.0 g, 22.7 mmol) and triethyl orthoformate (22.3 g, 25 mL, 150 mmol) was heated at 140 °C for 16 h. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 10 to 15% EtOAc in hexanes) provided 2-(4,6-dichloro-2-methylpyridin-3-yl)-1,3,4-oxadiazole (3.0 g, 56%). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.60 (s, 1H), 7.99 (s, 1H), 2.43 (s, 3H) ppm. ESI-MS *m/z* calc. 228.981, found 230.1 ($\text{M}+1$)⁺; Retention time: 1.67 minutes using LC/MS method X.

[0936] Step 4:

[0937] 2-(4,6-Dichloro-2-methylpyridin-3-yl)-1,3,4-oxadiazole (3.0 g, 13 mmol) was treated via the method described in Intermediate 36 Step 3, except that KO^tBu was used in place of sodium hydride, to provide 2-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)-1,3,4-oxadiazole (1.7 g, 43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.48 (s, 1H), 7.44 - 7.28 (m, 6H), 5.34 (s, 2H), 2.37 (s, 3H) ppm. ESI-MS *m/z* calc. 301.062, found 302.3 (M+1)⁺; Retention time: 2.80 minutes using LC/MS method AF.

Intermediate 38

rac-8-(Benzyloxy)-6-chloro-1-imino-1,2,3,4-tetrahydro-1λ⁴-thiopyrano[3,2-*b*]pyridine 1-oxide (**Int-38**)

**[0938] Step 1:**

[0939] A mixture of ethyl *rac*-3-oxotetrahydro-2H-thiopyran-2-carboxylate (23.35 g, 117.8 mmol) and ammonium acetate (45.4 g, 589 mmol) in IMS (468 mL) was heated at reflux for 2 h. The mixture was cooled and concentrated *in vacuo*. The residue was dissolved in EtOAc (250 mL), washed with water (2 x 150 mL) and brine (150 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo* to provide ethyl 5-amino-3,4-dihydro-2H-thiopyran-6-carboxylate (24.23 g, 99%). ¹H NMR (400 MHz, Chloroform-*d*) δ 6.33 (br s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.77 - 2.74 (m, 2H), 2.33 (t, *J* = 6.4 Hz, 2H), 2.06 - 1.99 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm. ESI-MS *m/z* calc. 187.067, found 188.0 (M+1)⁺; Retention time: 0.69 minutes using LC/MS method P.

[0940] Step 2:

[0941] A solution of ethyl 5-amino-3,4-dihydro-2H-thiopyran-6-carboxylate (127 mg, 0.582 mmol) in DCM (2 mL) at 0 °C was stirred with KHCO₃ (300 mg, 3.0 mmol) for 5 min then treated dropwise with a solution of ethyl 3-chloro-3-oxopropanoate (130 mg, 0.863 mmol) in DCM (0.5 mL). The mixture was stirred at ambient temperature for 2 h. The solids were removed by filtration and the filtrate concentrated *in vacuo* to provide ethyl 5-(3-ethoxy-3-oxopropanamido)-3,4-dihydro-2H-thiopyran-6-carboxylate (190 mg, 87%). ¹H NMR (400 MHz, Chloroform-*d*) δ 11.66 (br s, 1H), 4.30 -

4.22 (m, 4H), 3.40 (s, 2H), 3.09 (t, 2H, $J = 6.4$ Hz), 2.83 - 2.80 (m, 2H), 2.10 - 2.04 (m, 2H), 1.37 - 1.30 (m, 6H) ppm.

[0942] Step 3:

[0943] A solution of ethyl 5-(3-ethoxy-3-oxopropanamido)-3,4-dihydro-2H-thiopyran-6-carboxylate (2.59 g, 4.77 mmol) in IMS (26 mL) at 0 °C was treated portionwise with NaOEt (2.34 g, 34.4 mmol) and heated at 70 °C for 1 h. The mixture was cooled and the pH of the reaction was adjusted to pH 4 by addition of a 2 N aqueous HCl solution. The resulting solid was collected by filtration, washed with water (2 x 20 mL) and dried to provide ethyl 6,8-dihydroxy-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine-7-carboxylate (1.25 g, 90%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.62 (s, 1H), 11.44 (s, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.91 - 2.88 (m, 2H), 2.59 (t, $J = 6.5$ Hz, 2H), 2.03 - 1.97 (m, 2H), 1.27 (t, $J = 6.9$ Hz, 3H) ppm. ESI-MS m/z calc. 255.057, found 256.1 (M+1)⁺; Retention time: 0.64 minutes using LC/MS method N.

[0944] Steps 4 to 6:

[0945] Ethyl 6,8-dihydroxy-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine-7-carboxylate was treated using the methods described in Intermediate 36, Steps 1-3 to provide 8-benzyloxy-6-chloro-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.46 - 7.43 (m, 4H), 7.41 - 7.35 (m, 1H), 6.69 (s, 1H), 5.19 (s, 2H), 3.03 - 3.00 (m, 2H), 2.97 (t, $J = 6.3$ Hz, 2H), 2.26 - 2.20 (m, 2H) ppm. ESI-MS m/z calc. 291.049, found 292.0 (M+1)⁺; Retention time: 0.58 minutes using LC/MS method AA.

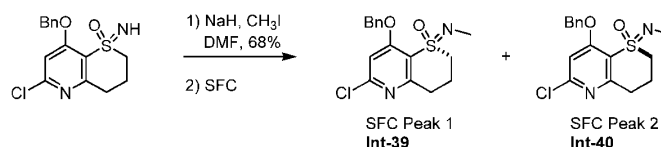
[0946] Step 7:

[0947] A solution of 8-benzyloxy-6-chloro-3,4-dihydro-2H-thiopyrano[3,2-*b*]pyridine (130 mg, 0.444 mmol) in DCM (5 mL) and MeOH (5 mL) was treated with (diacetoxyiodo)benzene (180 mg, 0.559 mmol) and ammonium carbamate (40 mg, 0.51 mmol) and heated at 40 °C for 2 h. Additional amounts of (diacetoxyiodo)benzene (180 mg, 0.559 mmol) and ammonium carbamate (40 mg, 0.51 mmol) were added and the heating was continued for 2 h. The mixture was cooled and concentrated *in vacuo*. The residue was swirled with Et₂O (5 mL) to give a pale brown solid. The solvent was decanted off and the solid triturated with additional Et₂O (5 mL). The resulting solid was dried to provide *rac*-8-(benzyloxy)-6-chloro-1-imino-1,2,3,4-tetrahydro-1λ⁴-thiopyrano[3,2-*b*]pyridine 1-oxide (170 mg, 100%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.50 - 7.30 (m, 5H), 7.27 (s, 1H), 5.42 (s, 2H), 4.07 (br s, 1H), 3.48 - 3.30 (m, 2H), 2.95 (t, $J = 6.2$ Hz, 2H), 2.19 (t, $J = 5.7$ Hz, 2H) ppm. ESI-MS m/z calc. 322.054, found 323.0 (M+1)⁺; Retention time: 0.69 minutes using LC/MS method P.

Intermediate 39 and Intermediate 40

rel-(*R*)-8-(benzyloxy)-6-chloro-1-(methylimino)-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide (**Int-39**, SFC Peak 1) and

rel-(*S*)-8-(benzyloxy)-6-chloro-1-(methylimino)-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide (**Int-40**, SFC Peak 2)

**[0948] Step 1:**

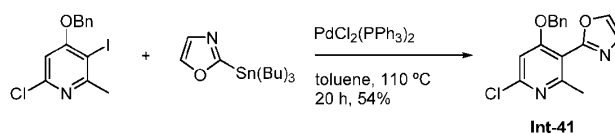
[0949] To a solution of *rac*-8-(benzyloxy)-6-chloro-1-imino-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide (340 mg, 1.05 mmol) in DMF (10 mL) at 0 °C under nitrogen was added sodium hydride (85 mg, 60 % w/w dispersion in mineral oil, 2.1 mmol) and the reaction mixture was stirred for 15 min. MeI (350 μ L, 5.62 mmol) was added and the mixture was stirred at ambient temperature for 3 h. The mixture was diluted with saturated aqueous NH_4Cl and water and the aqueous layer was separated and extracted with EtOAc (2 x). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 20 to 100% EtOAc in hexanes) provided *rac*-8-(benzyloxy)-6-chloro-1-(methylimino)-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide (242 mg, 68%). ESI-MS *m/z* calc. 336.070, found 337.0 ($\text{M}+1$)⁺; Retention time: 0.98 minutes using LC/MS method D.

[0950] Step 2:

[0951] The enantiomers of *rac*-8-(benzyloxy)-6-chloro-1-(methylimino)-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide were separated by chiral SFC using a ChiralPak[®] IC column, 5 μ m particle size, 25 cm x 21.2 mm from Daicel Corporation to give:

[0952] First Eluting Isomer (rt = 5.38 minutes): *rel*-(*R*)-8-(benzyloxy)-6-chloro-1-(methylimino)-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide (**Int-39**, 94.2 mg, 53%). ESI-MS *m/z* calc. 336.070, found 337.1 ($\text{M}+1$)⁺; Retention time: 0.99 minutes using LC/MS method D.

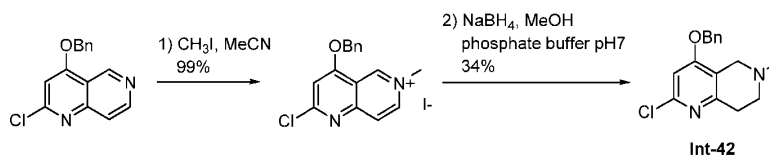
[0953] Second Eluting Isomer (rt = 6.35 minutes): *rel*-(*S*)-8-(benzyloxy)-6-chloro-1-(methylimino)-1,2,3,4-tetrahydro-1 λ^4 -thiopyrano[3,2-*b*]pyridine 1-oxide (**Int-40**, 98.3 mg, 55%). ESI-MS *m/z* calc. 336.070, found 337.1 ($\text{M}+1$)⁺; Retention time: 1.00 minutes using LC/MS method D.

Intermediate 412-(4-(Benzyloxy)-6-chloro-2-methylpyridin-3-yl)oxazole (**Int-41**)**[0954] Step 1:**

[0955] A mixture of 4-benzyloxy-6-chloro-3-iodo-2-methylpyridine (63 mg, 0.18 mmol), 2-(tributylstannyl)oxazole (80 mg, 0.22 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (19 mg, 0.027 mmol) in toluene (2 mL) was degassed for 5 min. The reaction vial was sealed and the mixture was stirred under a nitrogen atmosphere at 110 °C for 20 h. The mixture was cooled, diluted with EtOAc and washed with a saturated aqueous NH_4Cl solution and brine. The organic layer was separated, dried (MgSO_4), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2 , 0 to 70% EtOAc in hexanes) provided 2-(4-(benzyloxy)-6-chloro-2-methylpyridin-3-yl)oxazole (28.6 mg, 54%). ^1H NMR (400 MHz, Methanol- d_4) δ 8.09 (d, J = 0.9 Hz, 1H), 7.38 (d, J = 0.9 Hz, 1H), 7.37 - 7.27 (m, 5H), 7.20 (s, 1H), 5.23 (s, 2H), 2.35 (s, 3H) ppm. ESI-MS m/z calc. 300.067, found 301.2 ($\text{M}+1$)⁺; Retention time: 2.28 minutes using LC/MS method Q.

[0956] The following intermediate was made using the method described in Intermediate 41, except that 2-methyl-5-(tributylstannyl)-2H-tetrazole was used as the coupling partner in place of 2-(tributylstannyl)oxazole, and the reaction was carried out in the presence of catalytic CuI (0.14 eq):

Intermediate Name	LC/MS (m/z calc.)	Found M+1	MS r.t.	LC/MS Method	NMR (shifts in ppm)
4-(Benzyloxy)-6-chloro-2-methyl-3-(2-methyl-2H-tetrazol-5-yl)pyridine	315.089	316.2	1.99	Q	^1H NMR (400 MHz, DMSO- d_6) δ 7.40 - 7.25 (m, 6H), 5.29 (s, 2H), 4.46 (s, 3H), 2.23 (s, 3H) ppm.

Intermediate 424-(Benzyloxy)-2-chloro-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (**Int-42**)**[0957] Step 1:**

[0958] A solution of 4-benzyloxy-2-chloro-1,6-naphthyridine (100 mg, 0.366 mmol) in MeCN (1 mL) was treated with MeI (105 mg, 46 μL , 0.74 mmol) and the mixture was stirred for 4 h. Additional MeI (105 mg, 46 μL , 0.74 mmol) was added and the stirring was continued for 18 h. The mixture concentrated *in vacuo* to afford 4-benzyloxy-2-chloro-6-methyl-1,6-naphthyridin-6-ium iodide (160 mg, 99%) as a yellow solid. ^1H NMR (400MHz, DMSO- d_6) δ 9.95 (s, 1H), 8.94 (d, J = 7.1 Hz, 1H),

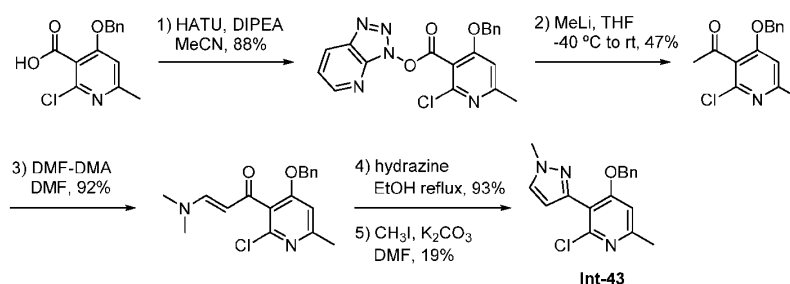
8.43 (d, $J = 7.2$ Hz, 1H), 7.83 (s, 1H), 7.65 - 7.59 (m, 2H), 7.53 - 7.40 (m, 3H), 5.63 (s, 2H), 4.48 (s, 3H) ppm. ESI-MS m/z calc. 411.984, found 285.1 (M-126); Retention time: 1.66 minutes using LC/MS method S.

[0959] Step 2:

[0960] A solution of 4-benzyloxy-2-chloro-6-methyl-1,6-naphthyridin-6-ium iodide (193 mg, 0.529 mmol) in methanol (6.3 mL) and phosphate buffer (4.2 mL, 0.5 M aqueous solution at pH 7) was treated with NaBH₄ (28 mg, 0.74 mmol) and stirred for 1.5 h. The methanol was removed *in vacuo* and the residue was partitioned between MTBE (20 mL) and water (20 mL). The aqueous phase was separated and extracted with MTBE (2 x 20 mL). The combined extracts were washed with a saturated aqueous Na₂S₂O₃ solution (20 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 10% methanol in DCM) provided 4-(benzyloxy)-2-chloro-6-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (54 mg, 34%). ESI-MS m/z calc. 288.103, found 289.2 (M+1)⁺; Retention time: 1.46 minutes using LC/MS method S.

Intermediate 43

4-(Benzyloxy)-2-chloro-6-methyl-3-(1-methyl-1H-pyrazol-3-yl)pyridine (**Int-43**)



[0961] Step 1:

[0962] A mixture of 4-(benzyloxy)-2-chloro-6-methylnicotinic acid (500 mg, 1.35 mmol) and HATU (720 mg, 1.89 mmol) in MeCN (4 mL) was treated with DIPEA (455 mg, 3.52 mmol) and stirred for 16 h under inert atmosphere. The mixture was partitioned between EtOAc and water. The layer aqueous was separated and extracted with EtOAc (2 x). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was stirred with EtOAc (25 mL) for 30 min and the resulting solid was collected by filtration to provide 3H-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 4-(benzyloxy)-2-chloro-6-methylnicotinate (623 mg, 88%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 (d, $J = 3.9$ Hz, 1H), 8.77 (d, $J = 7.8$ Hz, 1H), 7.70 (dd, $J = 8.4$ Hz, 4.3 Hz, 1H), 7.60 - 7.54 (m, 3H), 7.46 - 7.36 (m, 3H), 5.50 (s, 2H), 2.57 (s, 3H) ppm. ESI-MS m/z calc. 395.079, found 394.1 (M-1)⁺; Retention time: 1.05 minutes using LC/MS method AC.

[0963] Step 2:

[0964] MeLi (1.2 mL, 1.6 M solution in THF, 1.9 mmol) was added dropwise over a period of 5 min to a stirring solution of 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yl 4-(benzyloxy)-2-chloro-6-methylnicotinate (330 mg, 0.628 mmol) in THF (6 mL) at -40 °C and the mixture was stirred for 30 min at -40 °C. The reaction was diluted with a saturated aqueous NH₄Cl solution (10 mL) and water (5 mL). The aqueous phase was separated and extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 0 to 50% EtOAc in heptane) provided 1-(4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)ethan-1-one (136 mg, 47%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.34 - 7.24 (m, 5H), 6.62 (s, 1H), 5.05 (s, 2H), 2.43 (s, 3H), 2.40 (s, 3H) ppm. ESI-MS *m/z* calc. 275.071, found 276.0 (M+1)⁺; Retention time: 0.95 minutes using LC/MS method N.

[0965] Step 3:

[0966] A stirring solution of 1-(4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)ethan-1-one (1.3 g, 4.5 mmol) in DMF (30 mL) was treated with DMF-DMA (1.11 g, 1.24 mL, 9.33 mmol) and heated at 80 °C for 3 h. The mixture was diluted with water (300 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to provide (*E*)-1-(4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)-3-(dimethylamino)prop-2-en-1-one (1.7 g, 92%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.43 (d, *J* = 4.8 Hz, 1H), 7.39 - 7.33 (m, 4H), 7.11 (s, 1H), 5.28 - 5.21 (m, 3H), 5.12 (d, *J* = 12.9 Hz, 1H), 3.03 (s, 3H), 2.80 (s, 3H), 2.41 (s, 3H) ppm. ESI-MS *m/z* calc. 330.114, found 331.1 (M+1)⁺; Retention time: 0.70 minutes using LC/MS method N.

[0967] Step 4:

[0968] A stirring solution of (*E*)-1-(4-(benzyloxy)-2-chloro-6-methylpyridin-3-yl)-3-(dimethylamino)prop-2-en-1-one (130 mg, 0.304 mmol) in EtOH (2 mL) was treated with hydrazine monohydrate (51 mg, 0.05 mL, 1.0 mmol) at ambient temperature and the mixture was heated to reflux for 3 h. The mixture was concentrated *in vacuo*. Purification by flash chromatography (SiO₂, 40 to 80% EtOAc in heptane) gave 4-benzyloxy-2-chloro-6-methyl-3-(1*H*-pyrazol-3-yl)pyridine (90 mg, 93%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.63 (d, *J* = 2.0 Hz, 1H), 7.33 - 7.23 (m, 5H), 6.73 (s, 1H), 6.61 (d, *J* = 1.6 Hz, 1H), 5.09 (s, 2H), 2.53 (s, 3H) ppm; NH pyrazole not observed. ESI-MS *m/z* calc. 299.083, found 300.1 (M+1)⁺; Retention time: 0.80 minutes using LC/MS method N.

[0969] Step 5:

[0970] A mixture of 4-benzyloxy-2-chloro-6-methyl-3-(1*H*-pyrazol-3-yl)pyridine (90 mg, 0.28 mmol) and K₂CO₃ (118 mg, 0.854 mmol) in DMF (1 mL) was treated with MeI (125 mg, 55 μL, 0.88 mmol) and stirred at ambient temperature for 16 h. The mixture was partitioned between EtOAc and water and the layers were separated. The aqueous phase was extracted with EtOAc (2 x). The combined organics layers were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by reverse phase chromatography (C₁₈ column, 5 to 80% MeCN in H₂O containing 0.1% NH₄OH) gave:

[0971] **First Eluting Isomer:** 4-(benzyloxy)-2-chloro-6-methyl-3-(1-methyl-1*H*-pyrazol-3-yl)pyridine (**Int-43**, 18 mg, 19%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 1.9 Hz, 1H), 7.29 - 7.23 (m, 3H), 7.14 - 7.12 (m, 2H), 6.70 (s, 1H), 6.22 (d, *J* = 1.9 Hz, 1H), 5.06 (s, 2H), 3.60 (s, 3H), 2.47 (s, 3H) ppm. ESI-MS *m/z* calc. 313.098, found 314.1 (M+1)⁺; Retention time: 0.89 minutes using LC/MS method N.

[0972] **Second Eluting Isomer:** 4-(benzyloxy)-2-chloro-6-methyl-3-(1-methyl-1*H*-pyrazol-5-yl)pyridine (4 mg, 4%). ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 2.2 Hz, 1H), 7.28 - 7.19 (m, 5H), 6.63 (s, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 5.05 (s, 2H), 3.90 (s, 3H), 2.42 (s, 3H) ppm. ESI-MS *m/z* calc. 313.098, found 314.1 (M+1)⁺; Retention time: 0.86 minutes using LC/MS method N.

E-VIPR Assay Detecting and Measuring Na_v Inhibition Properties

[0973] Sodium ion channels are voltage-dependent proteins that can be activated by inducing membrane voltage changes by applying electric fields. The electrical stimulation instrument and methods of use, referred to as E-VIPR, are described in International Publication No. WO 2002/008748 A3 and C.-J. Huang et al. *Characterization of voltage-gated sodium channel blockers by electrical stimulation and fluorescence detection of membrane potential*, 24 Nature Biotech. 439-46 (2006), both of which are incorporated by reference in their entirety. The instrument comprises a microtiter plate handler, an optical system for exciting the coumarin dye while simultaneously recording the coumarin and oxonol emissions, a waveform generator, a current- or voltage-controlled amplifier, and parallel electrode pairs that are inserted into assay plate wells. Under integrated computer control, this instrument passes user-programmed electrical stimulus protocols to cells within the wells of the microtiter plate.

[0974] 16-20 hours prior to running the assay on E-VIPR, HEK cells expressing a truncated form of human Na_v 1.8 with full channel activity were seeded into microtiter 384-well plates, pre-coated with matrigel, at a density of 25,000 cells per well. 2.5-5% KIR2.1 BacMam virus was added to the final cell suspension before seeding into cell plates. HEK cells were grown in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% FBS (Fetal Bovine Serum, qualified; Sigma #F4135), 1% NEAA (Non-Essential Amino Acids, Gibco #11140), 1% HEPES (Gibco #15630), 1% Pen-Strep (Penicillin-Streptomycin; Gibco #15140) and 5 μ g/ml Blasticidin (Gibco #R210-01). Cells were expanded in 5-layer CellSTACK culture chambers or cell culture flasks with vented caps, with 90-95% humidity and 5% CO₂.

[0975] Reagents and Stock Solutions:

[0976] 100 mg/mL Pluronic F-127 (Sigma #P2443), in dry DMSO

[0977] Compound Plates: Corning 384-well Polypropylene Round Bottom #3656

[0978] Cell Plates: 384-well tissue culture treated plates (Greiner #781091-2B)

[0979] 2.5-5% KIR 2.1 Bacmam virus (produced in-house), prepared as described in Section 3.3 of J. A. Fornwald et al., *Gene Expression in Mammalian Cells Using BacMam, a Modified*

Baculovirus System, 1350 Methods in Molecular Biology 95-116 (2016), the entire contents of which are incorporated by reference. The concentration used can be dependent on viral titer of each batch.

[0980] 5 mM DiSBAC₆(3), a voltage sensitive oxonol acceptor (CAS number 169211-44-3; 5-[3-(1,3-dihexylhexahydro-4,6-dioxo-2-thioxo-5-pyrimidinyl)-2-propen-1-ylidene]-1,3-dihexyldihydro-2-thioxo-4,6(1H,5H)-pyrimidinedione), in dry DMSO. The preparation of DiSBAC₆(3) is analogous to that of DiSBAC₄(3) as described in *Voltage Sensing by Fluorescence Resonance Energy Transfer in Single Cells*, Gonzalez, J.E. and Tsien, R.Y. (1995) *Biophys. J.* 69, 1272-1280.

[0981] 5 mM CC2-DMPE, a commercially available membrane-bound coumarin phospholipid FRET donor (ThermoFisher Scientific catalog number K1017, CAS number 393782-57-5; tetradecanoic acid, 1,1'-[(1R)-1-[8-(6-chloro-7-hydroxy-2-oxo-2H-1-benzopyran-3-yl)-3-hydroxy-3-oxido-8-oxo-2,4-dioxo-7-aza-3-phosphaoct-1-yl]-1,2-ethanediyl] ester) was prepared in dry DMSO. See also, *Improved indicators of cell membrane potential that use fluorescence resonance energy transfer*, Gonzalez, J.E. and Tsien, R.Y. (1997) *Chem. Biol.* 4, 269-277.

[0982] Voltage Assay Background Suppression Compound (VABSC-1) is prepared in H₂O (89-363 mM, range used to maintain solubility)

[0983] Human Serum (HS, Millipore #S1P1-01KL, or Sigma SLBR5469V and SLBR5470V as a 50%/50% mixture, for 25% assay final concentration)

[0984] Bath 1 Buffer:

Sodium Chloride 160 mM (9.35 g/L), Potassium Chloride, 4.5 mM (0.335 g/L), Glucose 10 mM (1.8 g/L), Magnesium Chloride (Anhydrous) 1 mM (0.095 g/L), Calcium Chloride 2 mM (0.222 g/L), HEPES 10 mM (2.38 g/L) in water.

[0985] Na/TMA Cl Bath 1 Buffer:

Sodium Chloride 96 mM (5.61 g/L), Potassium Chloride 4.5 mM (0.335 g/L), Tetramethylammonium (TMA)-Cl 64 mM (7.01 g/L), Glucose 10 mM (1.8 g/L), Magnesium Chloride (Anhydrous) 1 mM (0.095 g/L), Calcium Chloride 2 mM (0.222 g/L) HEPES 10 mM (2.38 g/L) in water.

[0986] Hexyl Dye Solution (2X concentration):

Bath 1 Buffer containing 0.5% β -cyclodextrin (made fresh prior to each use, Sigma #C4767), 8 μ M CC2-DMPE and 2 μ M DiSBAC₆(3). The solution was made by adding 10% Pluronic F127 stock equal to combined volumes of CC2-DMPE and DiSBAC₆(3). The order of preparation was first mix Pluronic and CC2-DMPE, then add DiSBAC₆(3), then while vortexing add Bath 1/ β -Cyclodextrin.

[0987] Compound Loading Buffer (2X concentration): Na/TMA Cl Bath1 Buffer containing HS (omitted in experiments run in the absence of human serum (HS))50%, VABSC-1 1 mM, BSA 0.2 mg/ml (in Bath-1), KCl 9 mM, DMSO 0.625%.

[0988] Assay Protocol:

[0989] 1) To reach the final concentration in each well, 375 nL of each compound was pre-spotted (in neat DMSO) into polypropylene compound plates at 240x desired final concentration from an intermediate stock concentration of either 6 mM in an 16-point dose response, 3-fold dilution, resulting in a top dose of 25 μ M final concentration in the cell plate, or 0.075 mM in an 11-point dose response, 3-fold dilution, resulting in a top dose of 300 nM final concentration in the cell plate. Vehicle control (neat DMSO), and positive control (an established $\text{Na}_v1.8$ inhibitor, 25 μ M final in assay in DMSO) were added manually to the outermost columns of each plate respectively. The compound plate was backfilled with 45 μ L per well of Compound Loading Buffer resulting in a 240-fold dilution of compound following a 1:1 transfer of compound into the cell plate (see Step 6). Final DMSO concentration for all wells in the assay was 0.625% (0.75% DMSO was supplemented to the Compound Loading Buffer for a final DMSO concentration of 0.625%). This assay dilution protocol was adjusted to enable a higher dose range to be tested in the presence of HS or if the final assay volume was altered.

[0990] 2) Hexyl Dye Solution was prepared.

[0991] 3) Cell plates were prepared. On the day of the assay, the media was aspirated, and the cells were washed three times with 80 μ L of Bath-1 buffer, maintaining 25 μ L residual volume in each well.

[0992] 4) 25 μ L per well of Hexyl Dye Solution was dispensed into the cell plates. The cells were incubated for 20 minutes at room temperature or ambient conditions in darkness.

[0993] 5) 45 μ L per well of Compound Loading Buffer was dispensed into compound plates.

[0994] 6) The cell plates were washed three times with 80 μ L per well of Bath-1 Buffer, leaving 25 μ L of residual volume. Then 25 μ L per well from compound plate was transferred to each cell plate. The mixture was incubated for 30 minutes at room temperature/ambient conditions.

[0995] 7) The cell plate containing compound was read on E-VIPR using the current-controlled amplifier to deliver stimulation wave pulses using a symmetrical biphasic waveform. The user-programmed electrical stimulus protocols were 1.25-4 Amps and 4 millisecond pulse width (dependent on electrode composition) were delivered at 10 Hz for 10 seconds. A pre-stimulus recording was performed for each well for 0.5 seconds to obtain the un-stimulated intensities baseline. The stimulatory waveform was followed by 0.5 seconds of post-stimulation recording to examine the relaxation to the resting state. All E-VIPR responses were measured at 200 Hz acquisition rate.

[0996] Data Analysis:

[0997] Data were analyzed and reported as normalized ratios of emission intensities measured in the 460 nm and 580 nm channels. The response as a function of time was reported as the ratios obtained using the following formula:

$$(\text{intensity}_{460\text{ nm}})$$

$$R(t) = \frac{\text{intensity}_{580\text{ nm}}}{\text{intensity}_{580\text{ nm}}}$$

[0998] The data were normalized by calculating the initial (R_i) and final (R_f) ratios. These were the average ratio values during part or all of the pre-stimulation period and during sample points during the stimulation period. The fluorescence ratio (R_f/R_i) was then calculated and reported as a function of time.

[0999] Control responses were obtained by performing assays in the presence of the positive control, and in the absence of pharmacological agents (DMSO vehicle negative control). Responses to the negative (N) and positive (P) controls were calculated as above. The compound antagonist % activity A was then defined as:

$$A = \frac{X - N}{P - N} \times 100$$

where X is the maximum amplitude of the ratio response or number of action potential peaks, at the beginning of the pulse train in the presence of test compound. Using this analysis protocol, dose response curves were plotted and IC_{50} values were generated for various compounds of the present invention.

[1000] Compounds having a measured IC_{50} value less than $0.01\text{ }\mu\text{M}$ in the E-VIPR Assay described above include: 1-4, 6-8, 10-12, 14, 17-22, 25, 26, 28, 30-35, 37, 39, 47-52, 54-56, 58, 61-63, 65, 67-78, 80, 84-87, 91-106, 108-117, 119, 121-123, 125, 127-130, 132, 133, 135-156, 158, 159, 161-164, 167, 168, 171-179, 181, 182, 184-186, 188-190, 192, 193, 195-200, 202-204, 209-213, 215, 217-219, 223-229, and 232-235.

[1001] Compounds having a measured IC_{50} value less than $0.1\text{ }\mu\text{M}$ and greater than or equal to $0.01\text{ }\mu\text{M}$ in the E-VIPR Assay described above include: 5, 9, 13, 16, 27, 40, 41, 57, 66, 79, 81, 83, 89, 90, 107, 120, 124, 126, 131, 134, 157, 160, 165, 166, 170, 183, 187, 201, 205-208, 214, 216, 220-222, 230, and 231.

[1002] Compounds having a measured IC_{50} value less than $1\text{ }\mu\text{M}$ and greater than or equal to $0.1\text{ }\mu\text{M}$ in the E-VIPR Assay described above include: 15, 23, 24, 29, 36, 43, 53, 59, 60, 118, 169, 180, and 191.

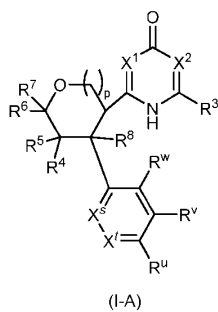
[1003] Compounds having a measured IC_{50} value greater than or equal to $1\text{ }\mu\text{M}$ in the E-VIPR Assay described above include: 38, 42, 44-46, 64, 82, 88, and 194.

[1004] Many modifications and variations of the embodiments described herein may be made without departing from the scope, as is apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only.

CLAIMS

What is claimed is:

1. A compound of formula (I-A):



or a pharmaceutically acceptable salt thereof, wherein:

X¹ is C-R¹ or N:

X^2 is $\mathbb{C}$ - $\mathbb{R}^2$ or $\mathbb{N}$:

X^s is C-R^s or N;

 X^t is C- R^t or N:

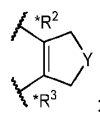
R^1 is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-(CH_2)_mO_n(CH_2)_oOCH_3$, $-(CH_2)_mR^a$, $-C(O)(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^bR^cNR^gC(O)CR^hR^iR^j$, $-NR^bC(O)CR^hR^gR^j$, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy;

R^2 and R^3 are defined as follows:

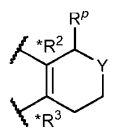
(i) R² is H, OH, halo, CN, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, - (CH₂)_mR^a, -C(O)OR^b, -C(O)R^b, -C(O)NR^bR^c, -NR^bR^c, -CR^dR^eR^f, -CR^bR^cNR^gC(O)CR^hRⁱ, -O(CH₂)_mR^a, -CR^bR^cOR^g, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)OR^g, -CR^bR^c(CH₂)_mO(CH₂)_oCR^gR^hR^a, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)NR^gR^h, -CR^bR^c(CH₂)_mO(CH₂)_oR^d, -CR^bR^cC(R^d)(R^e)(R^f), -CR^bR^cNR^gR^h, -CH₂C(O)NR^bR^c, -C(O)O_n(CH₂)_mR^a, -NR^b(CH₂)_mOR^c, -NR^b(CH₂)_mRⁿ, -(CH₂)_mNR^bC(O)Rⁿ, -NR^bCR^gR^h, -(CH₂)_mNR^bC(O)R^c, -SR^b, -S(=O)₂Rⁱ, -N=S(=O)(R^j)(R^m), -S(=O)(=NR^b)(Rⁱ), C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -CH₂OH, -C(O)OR^b, -NR^bR^c, and -C(O)NR^bR^c; and

R^3 is H, OH, halo, CN, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, $-(CH_2)_mOCH_3$, or $-(CH_2)_mR^a$.

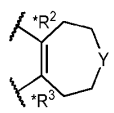
(ii) R² and R³, together with the carbon atoms to which they are attached, form a ring of formula:



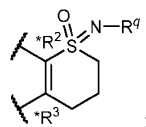
(iii) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(iv) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



(v) R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



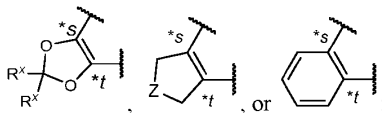
Y is O or NR^o ;

R^4 and R^5 are each independently H, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_1\text{-C}_6$ alkoxy;

R^6 and R^7 are each independently H, OH, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_3\text{-C}_6$ cycloalkyl, or $\text{C}_1\text{-C}_6$ alkoxy, or R^6 and R^7 , together with the carbon atom to which they are attached, form a $\text{C}_3\text{-C}_6$ cycloalkyl;

R^8 is H or CH_3 ;

R^s and R^t are each independently H, OH, halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{NR}^b\text{R}^c$, $-\text{NO}_2$, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_m\text{R}^a$, or $-\text{O}(\text{CH}_2)_m\text{OCH}_3$, or R^s and R^t , together with the atoms to which they are attached, form a ring of formula:



Z is O or CH_2 ;

R^u , R^v , and R^w are each independently H, OH, halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ haloalkoxy, $-\text{NR}^b\text{R}^c$, $-\text{NO}_2$, $-\text{SO}_3\text{H}$, $-(\text{CH}_2)_m\text{R}^a$, or $-\text{O}(\text{CH}_2)_m\text{OCH}_3$;

each R^x is independently H, halo, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl;

R^a is OH, halo, C₁-C₆ alkoxy, or $-NR^bR^c$;

R^b , R^c , R^g , R^h , R^i , and R^k are each independently H or C₁-C₆ alkyl, or R^b and R^c , together with the nitrogen atom to which they are attached, form a 3-6 membered heterocyclyl;

R^d , R^e , and R^f are each independently H, OH, halo, C₁-C₆ alkyl, or C₁-C₆ alkoxy;

R^j is H, C₁-C₆ alkyl, $-NR^bR^c$, or $-N(CH_3)_3^+$;

R^l and R^m are each independently C₁-C₆ alkyl;

R^n is C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl wherein said C₃-C₆ cycloalkyl or 4-6 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents selected from C₁-C₆ alkyl and halo;

R^o is H, C₁-C₆ alkyl, or $-C(O)O(C_1-C_6 \text{ alkyl})$;

R^p is H, C₁-C₆ alkyl, $-C(O)NR^bR^c$, or oxo;

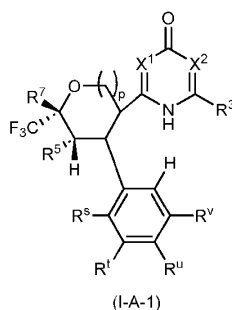
R^q is H or C₁-C₆ alkyl;

m and o are each independently 0, 1, 2, or 3;

n is 0 or 1; and

p is 0 or 1.

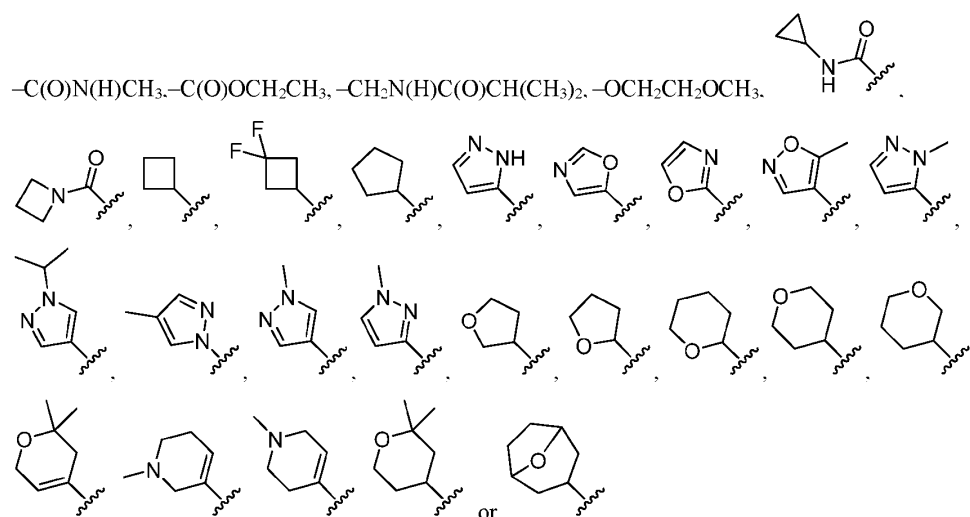
2. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein p is 0.
3. The compound of claim 1, or pharmaceutically acceptable salt thereof, wherein p is 1.
4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula (I-A-1):



5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein X^1 is N.
6. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein X^1 is C- R^1 and R^1 is H, halo, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, $-(CH_2)_mO_n(CH_2)_oOCH_3$, $-(CH_2)_mR^a$, $-C(O)(CH_2)_mR^a$, $-C(O)OR^b$, $-C(O)R^b$, $-C(O)NR^bR^c$, $-NR^bR^c$, $-CR^dR^eR^f$, $-CR^hR^cNR^gC(O)CR^hR^j$, $-(CH_2)_mNR^bC(O)R^a$, C₃-C₆ cycloalkyl, 5-6 membered

heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, and C₁-C₆ haloalkoxy,

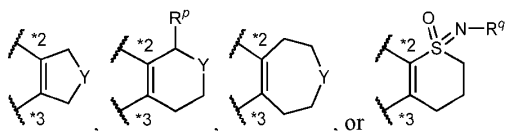
optionally wherein R¹ is H, Br, Cl, F, CN, -CH₃, -CH₂OH, -OCH₃, -OCHF₂, -CH(CH₃)₂, -CH₂OCH₃, -N(CH₃)₂, -C(O)OH, -C(O)CH₃, -C(O)OCH₃, -C(O)CH₂CH₂CH₂OH, -C(O)N(CH₃)₂,



7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein X² is C-R² and R² is H, halo, CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, -CR^dR^eR^f, -CR^bR^cOR^g, -(CH₂)_mR^a, -C(O)R^b, -NR^bR^c, -O(CH₂)_mR^a, -C(O)NR^bR^c, -C(O)OR^b, -C(O)O_n(CH₂)_mR^a, -CH₂C(O)NR^bR^c, -CR^bR^cNR^gR^h, -NR^b(CH₂)_mOR^c, -NR^bCR^cR^gR^h, -(CH₂)_mNR^bC(O)R^c, -(CH₂)_mNR^bC(O)Rⁿ, -CR^bR^c(CH₂)_mO(CH₂)_oCR^gR^hR^a, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)NR^gR^h, -CR^bR^c(CH₂)_mO(CH₂)_oC(O)OR^g, -CR^bR^c(CH₂)_mO(CH₂)_oR^d, -CR^bR^cC(R^d)(R^e)(R^f), -CR^bR^cNR^gC(O)CR^bR^c, -N=S(=O)(Rⁱ)(R^m), -SR^b, -S(=O)(=NR^b)(Rⁱ), -S(=O)₂Rⁱ, C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl, wherein said C₃-C₆ cycloalkyl, 5-6 membered heteroaryl, or 4-10 membered heterocyclyl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, -CH₂OH, -C(O)NR^bR^c.

8. The compound of any of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R³ is H, C₁-C₆ alkyl, or -(CH₂)_mOCH₃.

9. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein X^2 is CR^2 , and R^2 and R^3 , together with the carbon atoms to which they are attached, form a ring of formula:



10. The compound of any one of claims 1 to 4 and 6 to 14, or a pharmaceutically acceptable salt thereof, wherein R^4 is H and R^8 is H.

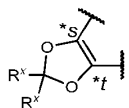
11. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^5 is H, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.

12. The compound of any one of claim 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 are each independently H, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, or C_3 - C_6 cycloalkyl, or R^6 and R^7 , together with the carbon atom to which they are attached, form a C_3 - C_6 cycloalkyl.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein X^5 is $C-R^s$, and R^s is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, or $-O(CH_2)_mOCH_3$.

14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, wherein X^t is $C-R^t$, and R^t is H, halo, or C_1 - C_6 haloalkyl.

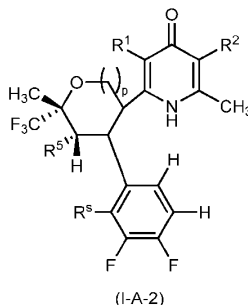
15. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein X^s is $C-R^s$, X^t is $C-R^t$, and R^s and R^t , together with the carbon atoms to which they are attached, form a ring of formula:



16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R^9 is H, halo, C_1 - C_6 alkoxy, or C_1 - C_6 haloalkoxy.

17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, wherein R^9 is H or $-NR^bR^c$.

18. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula (I-A-2):



19. The compound of any one of claims 1 to 3 and 18, or a pharmaceutically acceptable salt thereof, wherein R^1 is H or 5-6 membered heteroaryl, wherein said 5-6 membered heteroaryl may be unsubstituted or may be substituted with 1-4 substituents independently selected from halo and C_1 - C_6 alkyl.

20. The compound of any one of claims 1 to 3, 18, and 19, or a pharmaceutically acceptable salt thereof, wherein R^2 is H, $-CR^bR^cNR^dR^e$, $-S(=O)(=NR^f)(R^g)$, or 5-6 membered heteroaryl, wherein said 5-6 membered heteroaryl may be unsubstituted or may be substituted with 1-4 substituents independently selected from OH, CN, halo, oxo, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy, $-CH_2OH$, and $-C(O)NR^hR^i$.

21. The compound of any one of claims 1 to 3 and 18 to 20, or a pharmaceutically acceptable salt thereof, wherein R^5 is H, C_1 - C_6 alkyl, or C_1 - C_6 alkoxy.

22. The compound of any one of claims 1 to 3 and 18 to 21, or a pharmaceutically acceptable salt thereof, wherein R^5 is C_1 - C_6 alkyl or C_1 - C_6 alkoxy.

23. A compound selected from Table A or Table C, or a pharmaceutically acceptable salt thereof.

24. A compound selected from Table B or Table C, or a pharmaceutically acceptable salt thereof.

25. The compound of any one of claims 1 to 24 in non-salt form.

26. A pharmaceutical composition comprising the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, or the compound of claim 25, and one or more pharmaceutically acceptable carriers or vehicles.

27. A method of inhibiting a voltage-gated sodium channel in a subject comprising administering to the subject the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, the compound of claim 25, or the pharmaceutical composition of claim 26, optionally wherein the voltage-gated sodium channel is Nav1.8.

28. A method of treating or lessening the severity in a subject of chronic pain, gut pain, neuropathic pain, musculoskeletal pain, acute pain, inflammatory pain, cancer pain, idiopathic pain, postsurgical pain, visceral pain, multiple sclerosis, Charcot-Marie-Tooth syndrome, incontinence, pathological cough, or cardiac arrhythmia comprising administering to the subject an effective amount of the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, the compound of claim 25, or the pharmaceutical composition of claim 26, optionally wherein:

(i) the method comprises treating or lessening the severity in the subject of neuropathic pain, optionally wherein the neuropathic pain comprises post-herpetic neuralgia, small-fiber neuropathy, idiopathic small-fiber neuropathy, diabetic neuropathy, or diabetic peripheral neuropathy; or

(ii) the method comprises treating or lessening the severity in the subject of musculoskeletal pain, optionally wherein the musculoskeletal pain comprises osteoarthritis pain; or

(iii) the method comprises treating or lessening the severity in the subject of acute pain, optionally wherein the acute pain comprises acute post-operative pain; or

(iv) the method comprises treating or lessening the severity in the subject of postsurgical pain, optionally wherein the postsurgical pain comprises bunionectomy pain, abdominoplasty pain, or herniorrhaphy pain; or

(v) the method comprises treating or lessening the severity in the subject of visceral pain.

29. The method of claim 27 or 28, wherein said subject is treated with one or more additional therapeutic agents administered concurrently with, prior to, or subsequent to treatment with the compound, pharmaceutically acceptable salt, or pharmaceutical composition.

30. Use of the compound of any one of claims 1 to 24, or a pharmaceutically acceptable salt thereof, the compound of claim 25, or the pharmaceutical composition of claim 26, as a medicament.