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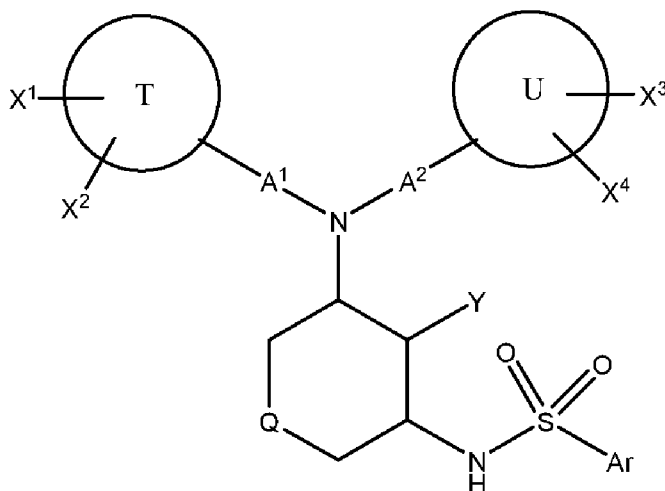
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(54) Title: RING CONSTRAINED DIARYLAMINO SULFONAMIDES AS ANTI-CANCER AGENTS



(57) Abstract: A genus of arylsulfonamide derivatives of ring constrained diarylamino sulfonamide compounds is disclosed. The compounds are of the following genus:. The compounds induce FOXO1 transcription factor translocation to the nucleus by modulating PP2A and, as a consequence, exhibit anti-proliferative effects. They are useful in the treatment of a variety of disorders, including as a therapy in cancer treatment, or used in combination with other drugs to restore sensitivity to chemotherapy where resistance has developed.

RING CONSTRAINED DIARYLAMINO SULFONAMIDES AS ANTI-CANCER AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority of US provisional application 62/216,150, filed September 9, 2015, the entire disclosure of which is hereby incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention relates to the use of chemical modulators of PP2A, comprising ring constrained diarylamino sulfonamides to treat diseases such as cancer, neurodegenerative disease and other disorders.

BACKGROUND

[0003] The FOXO (Forkhead transcription factors, Class O) proteins are a group of transcription factors involved in control of a variety of physiological, metabolic and developmental pathways. They are downstream effectors in a number of signaling pathways including insulin and growth factor signaling; they are also regulated by oxidative stress and nutrient deprivation. Cellular processes affected by FOXO activity include cell cycle control, differentiation, proliferation and apoptosis. Disregulation of FOXO mediated processes has been implicated in a number of pathologies including tumorigenesis, inflammation, diabetes and neurodegenerative conditions amongst others. Activity of FOXO transcription factors are controlled in part by their sub-cellular localization, in particular their localization to the nucleus from the cytosol, and their subsequent transcriptional activation.

[0004] Four FOXO proteins designated FOXO1, FOXO3a, FOXO4 and FOXO6 are present in human cells and their activity is controlled by a variety of mechanisms including stability (proteolytic cleavage), sub-cellular localization and transcriptional activation. Activity of the first three members of the family is controlled by cytosolic-nuclear translocation.

[0005] FOXO1 regulates expression of a number of genes that play critical roles in cell cycle and apoptosis. A pivotal regulatory mechanism of FOXO is reversible phosphorylation, catalyzed by kinases and phosphatases. Phosphorylation of FOXO1 is

associated with 14-3-3 binding and cytosolic localization, whereas dephosphorylated FOXO1 translocates to the nucleus and is transcriptionally active.

[0006] Protein phosphatase 2A is one of the four major serine threonine phosphatases and is implicated in the negative control of cell growth and division. Protein phosphatase 2A holoenzymes are heterotrimeric proteins composed of a structural subunit A, a catalytic subunit C, and a regulatory subunit B. The PP2A heterotrimeric protein phosphatase is a ubiquitous and conserved phosphatase with broad substrate specificity and diverse cellular functions. Among the targets of PP2A are proteins of oncogenic signaling cascades, such as Raf, MEK, and AKT.

[0007] PP2A interacts directly with FOXO1 and dephosphorylates FOXO1. Inhibition of PP2A phosphatases rescues FOXO1-mediated cell death by regulating the level of the pro-apoptotic protein BIM. In addition, PP2A directly regulates FOXO3a subcellular localization and transcriptional activation. Without wishing to be held to any particular theory, it may be that the compounds described herein promote apoptosis by acting on FOXO transcription factors via activation of PP2A.

[0008] Myc proteins (c-myc, Mycn and Mycl) target proliferative and apoptotic pathways vital for progression in cancer and they are overexpressed and deregulated in many human cancers. The control of Myc abundance through protein degradation has attracted considerable interest and Ser-62 phosphorylation by a number of kinases has been shown to stabilize the protein. PP2A is responsible for Ser-62 dephosphorylation which primes the protein for ubiquitylation and degradation, thus PP2A functions as a negative regulator of Myc.

[0009] Prostate cancer is the second leading cause of cancer death in men in America, behind lung cancer. According to the American Cancer Society, approximately 1 man in 36 will die of prostate cancer. Male hormones, specifically testosterone, fuel the growth of prostate cancer. By reducing the amount and activity of testosterone, the growth of advanced prostate cancer is slowed. Endocrine therapy, known as androgen ablation, is the first line of treatment for metastatic prostate cancer. Androgen deprivation therapy for metastatic prostate cancer results in tumor regression and symptomatic improvement in the majority of patients. However, metastatic prostate cancer inevitably progresses despite castrate levels of serum testosterone. Several new therapies have been approved for patients with castration-resistant prostate cancer (CRPC); however, none are curative and tumors

ultimately develop resistance. To combat CRPC new approaches and novel therapies are required.

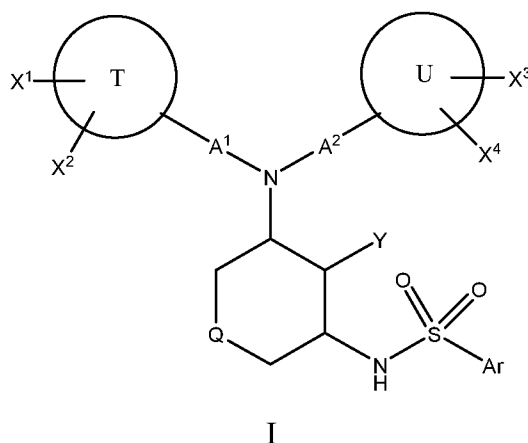
[0010] Breast cancer can affect both men and women. Breast cancer is the most prevalent cancer in women, after skin cancers, with about 1 in every 8 women expected to develop invasive breast cancer at some point. One subset of breast cancer expresses the androgen receptor (AR), which has been implicated as a therapeutic target in that subset. About 10-20% of breast cancers — more than one out of every 10 — are found to be triple-negative. "Triple negative breast cancer" refers to a breast cancer that does not contain estrogen receptors, progesterone receptors, or human epidermal growth factor receptor 2 (HER2). This means that the growth of the cancer is not supported by the hormones estrogen and progesterone, nor by the presence of too many HER2 receptors. Therefore, triple-negative breast cancer does not respond to hormonal therapy (such as tamoxifen or aromatase inhibitors) or therapies that target HER2 receptors, such as Herceptin (chemical name: trastuzumab). While these tumors are often treatable, the chemotherapy is not targeted, and response durations are short. For doctors and researchers, there is intense interest in finding new medications that can treat breast cancer.

[0011] The compounds described herein exhibit anti-proliferative effects and are useful as monotherapy in cancer treatment. Additionally, they can be used in combination with other drugs to restore sensitivity to chemotherapy where resistance has developed.

SUMMARY OF THE INVENTION

[0012] A genus of ring constrained diarylamino sulfonamides derivatives has now been found that induce FOXO1 transcription factor translocation to the nucleus by modulating PP2A. The compounds described herein exhibit anti-proliferative effects, and are useful in the treatment of a variety of disorders, including as a monotherapy in cancer treatment, or used in combination with other drugs to restore sensitivity to chemotherapy where resistance has developed.

[0013] In a first aspect the invention relates to compounds of formula (I):



wherein:

T is a benzene ring or a five- or six-membered heteroaromatic ring;

U is a benzene ring or a five- or six-membered heteroaromatic ring;

X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from hydrogen, halogen, nitro, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkylthio, -NR¹R², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, -SO₂NR¹R², and a heterocyclic ring;

R¹ and R² are independently selected in each instance from the group consisting of hydrogen and (C₁-C₆)alkyl;

A¹ and A² are independently selected in each instance from a direct bond, CH₂, SO₂, and C(=O);

Y is selected from hydrogen and hydroxyl;

Q is selected from -(CH₂)_t-, -O-, S(O)_p-, and -NR^Q-;

p is zero, 1 or 2;

t is zero, 1 or 2;

R^Q is selected from hydrogen, optionally substituted (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl; -SO₂R³; -SO₂N(R³R⁴); -C(=O)R⁵; -C(=O)OR⁵; or -C(=O)N(R³R⁴); wherein said substituents on the (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl are selected from the group consisting of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy;

R³ and R⁴ are independently selected in each instance from hydrogen, (C₁-C₆)alkyl, aryl, and arylalkyl, wherein said aryl or the aryl of the arylalkyl is optionally substituted with hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-

C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, or (C₁-C₄)alkoxy;

R⁵ is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, or optionally substituted aryl, wherein said optional substituents are selected from the group consisting of (C₁-C₃)alkyl, OR¹, NH₂, NHMe, N(Me)₂, and heterocycle; and Ar is an optionally substituted aromatic or heteroaromatic ring.

[0014] In a second aspect, the invention relates to methods and uses of the above-described compounds in medicine, particularly for the treatment of a disease chosen from (a) cancer; (b) diabetes; (c) autoimmune disease; (d) age onset proteotoxic disease; (e) mood disorder; (f) acne vulgaris; (g) solid organ transplant rejection; (h) graft vs. host disease; i) cardiac hypertrophy; j) viral infection; and (k) parasitic infection. These methods include administering to a patient a therapeutically effective amount of a compound described herein.

[0015] In a third aspect, the invention relates to a method for restoring sensitivity to one or more chemotherapeutic agents in the treatment of cancer. The method includes administering an effective amount of a compound described herein.

[0016] In a fourth aspect, the invention relates to a method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of PP2A influenced signaling cascades such as the PI3K-AKT, MAP kinase and mTOR pathways. These methods include administering to a patient a therapeutically effective amount of a compound described herein.

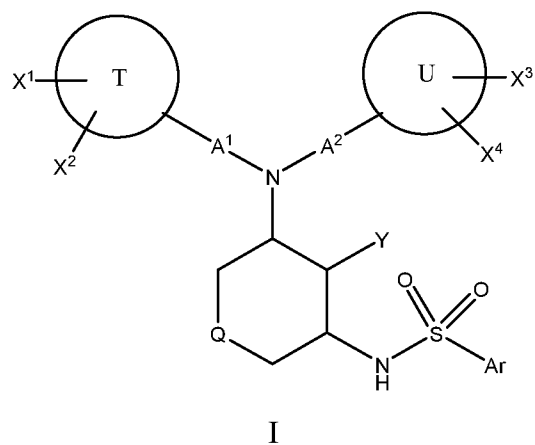
[0017] In a fifth aspect, the invention relates to a method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of a Myc dependent signaling pathway. These methods include administering to a patient a therapeutically effective amount of a compound described herein.

[0018] In a sixth aspect, the invention relates to pharmaceutical compositions comprising the compounds described herein.

DETAILED DESCRIPTION OF THE INVENTION

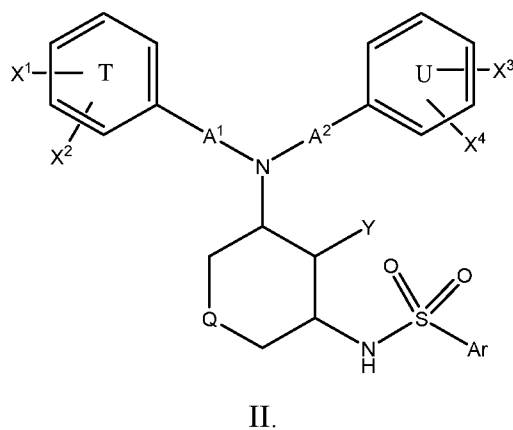
[0019] Substituents are generally defined when introduced and retain that definition throughout the specification and in all independent claims.

[0020] In a composition aspect, the invention relates to compounds of formula (I):

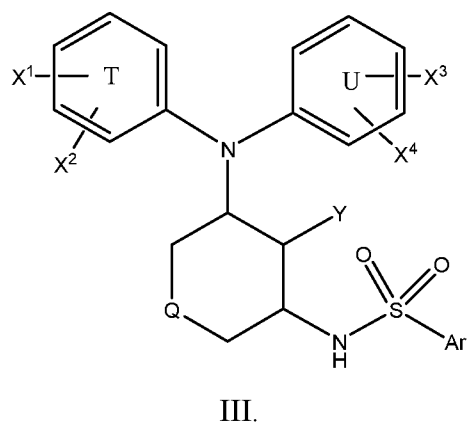


as described above.

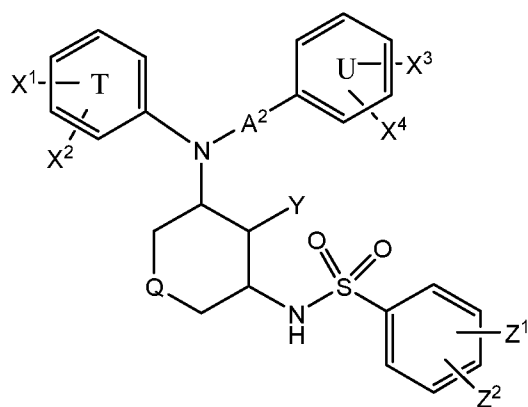
[0021] In some embodiments, the invention relates to compounds of formula (II):



[0022] In some embodiments, the invention relates to compounds of formula III:

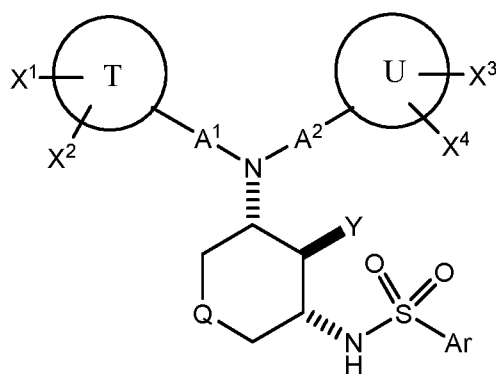


[0023] In some embodiments, the invention relates to compounds of formula IV:



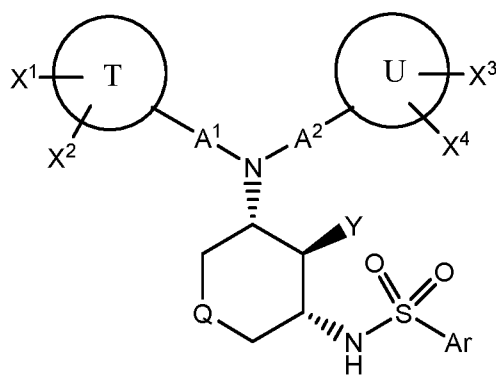
IV.

[0024] In some embodiments, the invention relates to compounds of formula V:

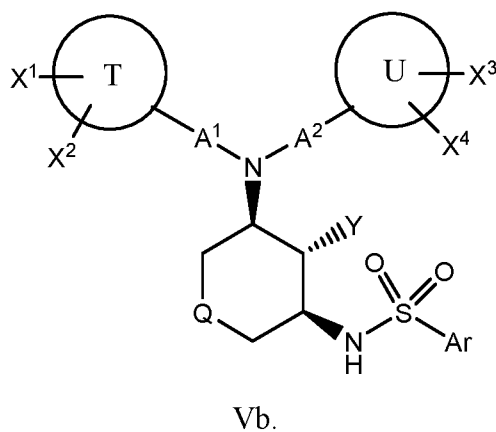


V.

[0025] In some embodiments, the invention relates to compounds of formula Va or Vb:



Va or



[0026] In the embodiments described below, the compound may be of formula I, II, III, IV, V, Va, or Vb, unless otherwise indicated.

[0027] In some embodiments, T is a benzene ring. In other embodiments, T is a five-membered heteroaromatic ring. In still other embodiments, T is a six-membered heteroaromatic ring.

[0028] In some embodiments, U is a benzene ring. In other embodiments, U is a five-membered heteroaromatic ring. In still other embodiments, U is a six-membered heteroaromatic ring.

[0029] In some embodiments, T and U are each independently selected from the group consisting of a benzene ring, furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiadiazole, thiazine, thiazole, thiophene, triazine, and triazole. In some embodiments, T and U are each independently selected from a benzene ring, pyridine, pyrimidine, pyridazine, thiophene, thiazole, oxazole, imidazole, pyrrole, and furan. In some embodiments, one of T and U is a benzene ring, and the other of T and U is selected from a benzene ring, pyridine, pyrimidine, and thiophene. In still other embodiments, T and U are each independently selected from a benzene ring and pyridine. In some embodiments, at least one of T and U is a benzene ring. In other embodiments, T and U are both benzene rings.

[0030] In some embodiments, A¹ is a direct bond. In other embodiments, A¹ is CH₂. In some embodiments, A¹ is SO₂. In still other embodiments, A¹ is C(=O).

[0031] In some embodiments, A² is a direct bond. In other embodiments, A² is CH₂. In some embodiments, A² is SO₂. In still other embodiments, A² is C(=O).

[0032] In some embodiments, at least one of A¹ and A² is a direct bond or CH₂. In other embodiments, both of A¹ and A² are direct bonds.

[0033] In some embodiments, Y is hydroxyl. In other embodiments, Y is hydrogen.

[0034] In some embodiments, R¹ is hydrogen. In other embodiments, R¹ is (C₁-C₆)alkyl. In some embodiments, R² is hydrogen. In other embodiments, R² is (C₁-C₆)alkyl.

[0035] In some embodiments, X¹, X², X³, and X⁴ are independently selected in each instance from hydrogen, halogen, nitro, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkylthio, -NR¹R², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, and -SO₂NR¹R², and a heterocyclic ring. In some embodiments, zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, cyano, and morpholino, and the remainder are hydrogen. In other embodiments, zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen. In yet other embodiments, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the one or two of X¹, X², X³, and X⁴ that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[0036] In some embodiments, Q is a direct bond (when Q is -(CH₂)_t- and t is zero). In other embodiments, Q is -CH₂- (when Q is -(CH₂)_t- and t is one). In still other embodiments, Q is -(CH₂)₂- (when Q is -(CH₂)_t- and t is two). In some embodiments, Q is -O-. In other embodiments, Q is -S- (when Q is -(SO₂)_p- and p is zero). In other embodiments, Q is -S(O)- (when Q is -(SO₂)_p- and p is one). In other embodiments, Q is -S(O)₂- (when Q is -(SO₂)_p- and p is two). In still other embodiments, Q is -NR^Q-.

[0037] In some embodiments, R^Q is hydrogen. In other embodiments, R^Q is optionally substituted (C₁-C₆)alkyl. In still other embodiments, R^Q is optionally substituted (C₃-C₇)cycloalkyl. In yet other embodiments, R^Q is optionally substituted aryl. In further embodiments, R^Q is optionally substituted heteroaryl. In these instances, the optional substituents available for the (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl or heteroaryl may be one or more of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl,

(C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy. In some embodiments, R^Q is (C₁-C₆)alkyl optionally substituted with one or more of hydroxy, fluoro, or (C₃-C₇)cycloalkyl. In other embodiments, R^Q is (C₁-C₃)alkyl optionally substituted with one or more of hydroxy or fluoro. In yet other embodiments, R^Q is (C₃-C₇)cycloalkyl optionally substituted with one or more of hydroxy, methyl, or fluoro. In still other embodiments, R^Q is aryl optionally substituted with one or more of hydroxy, methoxy, halogen, (C₁-C₃)haloalkyl, nitro, amino, or methyl. In further embodiments, R^Q is phenyl optionally substituted with one or more of hydroxy, chloro, fluoro, methoxy, nitro, amino, trifluoromethyl, or methyl. In yet other embodiments, R^Q is heteroaryl optionally substituted with one or more of hydroxy, methoxy, halogen, (C₁-C₃)haloalkyl, nitro, amino, or methyl. In some embodiments, R^Q is a nitrogen-containing heteroaryl optionally substituted with one or two methyl groups. In some embodiments, R^Q is -SO₂R³. In other embodiments, R^Q is -SO₂NR³R⁴. In still other embodiments, R^Q is C(=O)R⁵. In some embodiments, R^Q is -C(=O)OR⁵. In yet other embodiments, R^Q is -C(=O)NR³R⁴.

[0038] In some embodiments, R³ and R⁴ are independently selected in each instance from hydrogen, (C₁-C₆)alkyl, aryl, and arylalkyl. In some embodiments, the aryl or the aryl of the arylalkyl may be optionally substituted with hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, or (C₁-C₄)alkoxy. In some embodiments, R⁴ is selected from hydrogen and methyl. In other embodiments, R³ is selected from hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, aryl, and arylalkyl. In some of these embodiments, the aryl or the aryl of the arylalkyl is optionally substituted with one or more of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy.

[0039] In some embodiments, R⁵ is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, or optionally substituted aryl. In some embodiments, the optional substituents are selected from (C₁-C₃)alkyl, OR¹, NH₂, NHMe, N(Me)₂, and heterocycle. In other embodiments, R⁵ is selected from optionally substituted (C₁-C₄)alkyl or optionally substituted aryl, and the optional substituents are selected from one or more of OH, OMe, NH₂, NHMe, N(Me)₂, or heterocycle.

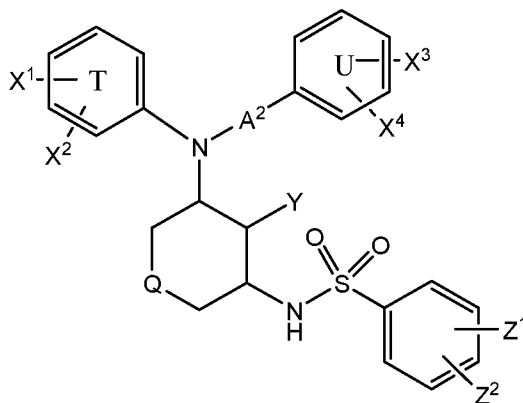
[0040] In some embodiments, R^Q is $-C(=O)R^5$ and R^5 is selected from (C_1-C_4) alkyl, optionally substituted with OR^1 , NH_2 , $NHMe$, $N(Me)_2$, and heterocycle. In other embodiments, R^Q is $-C(=O)OR^5$ and R^5 is selected from the group consisting of phenyl and (C_1-C_4) alkyl, each of which may be substituted with OR^1 ; in some of these embodiments, R^1 is hydrogen, while in other of these embodiments, R^1 is (C_1-C_6) alkyl. In still other embodiments, R^Q is $-SO_2R^3$ and R^3 is selected from hydrogen, (C_1-C_6) alkyl, and aryl. In some of these embodiments, the aryl may be substituted with hydroxy, halogen, cyano, amino, or (C_1-C_4) alkoxy. In yet other embodiments, R^Q is $SO_2NR^3R^4$; R^3 is selected from hydrogen, (C_1-C_3) alkyl, and optionally substituted aryl; and R^4 is hydrogen or methyl. In further embodiments, R^Q is $-C(=O)NR^3R^4$; R^3 is selected from hydrogen, (C_1-C_3) alkyl, and aryl optionally substituted with hydroxy, halogen, cyano, amino, or methoxy; and R^4 is hydrogen or methyl.

[0041] In some embodiments, Ar is an optionally substituted aromatic ring. In other embodiments, Ar is an optionally substituted heteroaromatic ring. In still other embodiments, Ar is phenyl substituted with Z^1 and Z^2 .

[0042] In some embodiments, Z^1 is selected from hydrogen, halogen, nitro, cyano, azide, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-OR^1$, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)NR^1R^2$, $-C(O)OR^1$, $-SR^1$, $-SO_2R^1$, and $-SO_2NR^1R^2$. In some embodiments, Z^2 is selected from hydrogen, halogen, nitro, cyano, azide, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)OR^6$, $-OR^1$, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)NR^1R^2$, $-C(O)OR^1$, $-SR^1$, $-SO_2R^1$, and $-SO_2NR^1R^2$. In other embodiments, Z^1 and Z^2 are independently selected in each instance from hydrogen, halogen, (C_1-C_6) haloalkyl, $-NR^1C(O)OR^6$, (C_1-C_6) alkoxy, and (C_1-C_6) haloalkoxy. In some embodiments, Z^1 is hydrogen and Z^2 is selected from hydrogen, halogen, (C_1-C_6) haloalkyl, $-NR^1C(O)OR^6$, (C_1-C_6) alkoxy, and (C_1-C_6) haloalkoxy. In some embodiments, Z^1 is hydrogen and Z^2 is hydrogen, fluoro, chloro, trifluoromethyl, $NHBoc$, methoxy, or trifluoromethoxy. In other embodiments, Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

[0043] The person of skill will understand that, in some instances, R^1 , R^2 , R^3 , R^4 , and R^5 may not be hydrogen. For instance, when Q is NR^Q , R^Q is $-SO_2R^3$, and R^3 is hydrogen, the resulting moiety will be unstable. The circumstances under which a hydrogen atom would be inappropriate will be clear to the person of skill in the art.

[0044] In some embodiments, A¹ is a direct bond; T, U and Ar are phenyl; and the compound is of formula IV:



IV.

[0045] In some embodiments, Y is OH. In some embodiments, A² is a direct bond. In other embodiments, A² is CH₂. In some embodiments, Q is -(CH₂)_t-. In other embodiments, t is 1. In some embodiments, Q is O. In some embodiments, Q is NR^Q. In these embodiments, R^Q is selected from hydrogen, -C(=O)R⁵, and -C(=O)OR⁵; and R⁵ is selected from hydrogen and optionally substituted (C₁-C₄)alkyl, and the optional substituents are selected from NH₂, NHMe, and N(Me)₂. In some embodiments, zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, cyano, and morpholino, and the remainder are hydrogen. In other embodiments, zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen. In still other embodiments, zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, the one or two of X¹, X², X³, and X⁴ that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen. In some embodiments, Z¹ and Z² are independently selected in each instance from the group consisting of hydrogen, halogen, nitro, cyano, azide, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, -NR¹R², -NR¹C(O)R², -NR¹C(O)OR⁶, -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, and -SO₂NR¹R². In still other embodiments, Z¹ and Z² are independently selected in each instance from hydrogen, halogen, (C₁-C₆)haloalkyl, -NR¹C(O)OR⁶, (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy. In yet other embodiments, Z¹ is hydrogen and Z² is selected from hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, -NR¹C(O)OR⁶, (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy. In other embodiments, Z¹ is hydrogen and Z² is hydrogen, fluoro, chloro, cyano, NHBoc,

methoxy, or trifluoromethoxy. In still other embodiments, Z^1 is hydrogen and Z^2 is trifluoromethoxy. In some embodiments, Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

[0046] In some embodiments, Y is OH; A^2 is a direct bond; Q is selected from CH_2 , O, and NR^Q ; R^Q is selected from hydrogen, $-C(=O)R^5$, and $-C(=O)OR^5$; R^5 is selected from hydrogen and optionally substituted (C_1-C_4) alkyl, wherein said optional substituents are selected from the group consisting of NH_2 , $NHMe$, and $N(Me)_2$; Z^1 is hydrogen; Z^2 is para to the attachment of the phenyl ring to the sulfonyl and is selected from hydrogen, fluoro, chloro, cyano, $NHBoc$, methoxy, or trifluoromethoxy; and zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C_1-C_3) alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro (C_1-C_3) alkyl, and the remainder are hydrogen; wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[0047] In some embodiments of the foregoing subgenera, the relative configurations are such that the amine and the tricycle are both *trans* to the alcohol (Y), as shown above in Formula IV. In this *trans:trans* subgroup, compounds can be either single enantiomers IVa or IVb or a mixture of the two. If a mixture, the mixture will most commonly be racemic, but it need not be. Substantially pure single enantiomers of biologically active compounds such as those described herein often exhibit advantages over their racemic mixture.

[0048] In summary, the invention relates to:

[0049] [1]. A compound of formula I, II, III, IV, V, Va or Vb.

[0050] [2]. A compound according to [1] above wherein T and U are each independently selected from the group consisting of a benzene ring, thiophene, furan, and pyridine.

[0051] [3]. A compound according to any of [1] through [2] above wherein at least one of T and U is a benzene ring.

[0052] [4]. A compound according to any of [1] through [3] above wherein both T and U are benzene rings.

[0053] [5]. A compound according to any of [1] through [4] above wherein at least one of A^1 and A^2 is a direct bond or CH_2 .

[0054] [6]. A compound according to any of [1] through [5] above wherein both of A¹ and A² are direct bonds.

[0055] [7]. A compound according to any of [1] through [6] above wherein Y is hydroxyl.

[0056] [8]. A compound according to any of [1] through [6] above wherein Y is hydrogen.

[0057] [9]. A compound according to any of [1] through [8] above wherein Q is a direct bond.

[0058] [10]. A compound according to any of [1] through [8] above wherein Q is -CH₂-.

[0059] [11]. A compound according to any of [1] through [8] above wherein Q is -(CH₂)₂-.

[0060] [12]. A compound according to any of [1] through [8] above wherein Q is -O-.

[0061] [13]. A compound according to any of [1] through [8] above wherein Q is NR^Q.

[0062] [14]. A compound according to any of [1] through [8] or [13] above wherein Q is NR^Q; R^Q is selected from hydrogen, -C(=O)R⁵, and -C(=O)OR⁵; and R⁵ is selected from hydrogen and optionally substituted (C₁-C₄)alkyl, wherein said optional substituents are selected from the group consisting of NH₂, NHMe, and N(Me)₂.

[0063] [15]. A compound according to any of [1] through [8] above wherein Q is -S(O)_p-.

[0064] [16]. A compound according to any of [1] through [15] above wherein Ar is phenyl substituted with Z¹ and Z²; and Z¹ and Z² are independently selected in each instance from the group consisting of hydrogen, halogen, nitro, cyano, azide, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, -NR¹R², -NR¹C(O)R², -NR¹C(O)OR², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, and -SO₂NR¹R².

[0065] [17]. A compound according to any of [1] through [16] above wherein Ar is phenyl substituted with Z¹ and Z²; and Z¹ and Z² are independently selected in each instance from hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, -NR¹C(O)OR², (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy.

[0066] [18]. A compound according to any of [1] through [17] above wherein Ar is phenyl substituted with Z¹ and Z²; and Z¹ is hydrogen.

[0067] [19]. A compound according to any of [1] through [18] above wherein Ar is phenyl substituted with Z^1 and Z^2 ; Z^1 is hydrogen; and Z^2 is hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, -NR¹C(O)OR², (C₁-C₆)alkoxy, or (C₁-C₆)haloalkoxy.

[0068] [20]. A compound according to any of [1] through [19] above wherein Ar is phenyl substituted with Z^1 and Z^2 ; Z^1 is hydrogen; and Z^2 is hydrogen, fluoro, chloro, cyano, trifluoromethyl, NHBoc, methoxy, or trifluoromethoxy.

[0069] [21]. A compound according to any of [1] through [20] above wherein Z^2 is para to the attachment of the ring to the sulfonyl.

[0070] [22]. A compound according to any of [1] through [21] above, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, cyano, and morpholino, and the remainder are hydrogen.

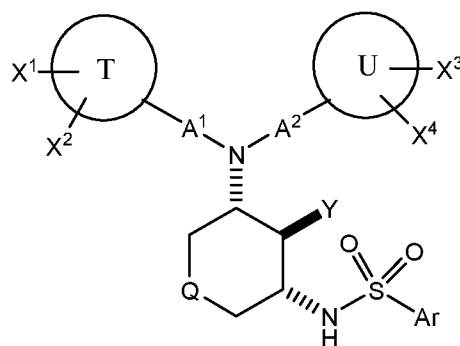
[0071] [23]. A compound according to any of [1] through [22] above, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen.

[0072] [24]. A compound according to any of [1] through [23] above wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

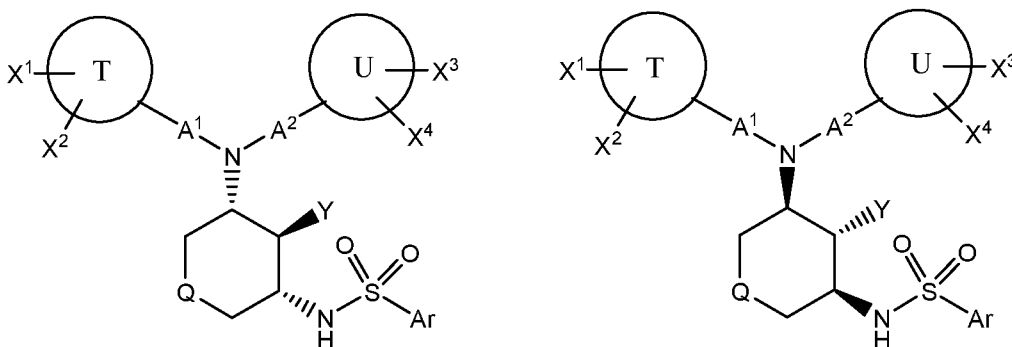
[0073] [25]. A compound according to any of [1] through [7], [10], [12] through [14], and [17] through [24] above wherein Y is hydroxyl; A² is a direct bond; Q is selected from CH₂, O, and NR^Q; R^Q is selected from hydrogen, -C(=O)R⁵, and -C(=O)OR⁵; R⁵ is selected from hydrogen and optionally substituted (C₁-C₄)alkyl, wherein said optional substituents are selected from the group consisting of NH₂, NHMe, and N(Me)₂; Z^1 is hydrogen; Z^2 is para to the attachment of the phenyl ring to the sulfonyl and is selected from hydrogen, fluoro, chloro, cyano, NHBoc, methoxy, or trifluoromethoxy; and zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen; wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[0074] The compounds described herein contain three or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (*R*)- or (*S*)-. The present invention is meant to include all such possible diastereomers as well as their racemic and optically pure forms. Optically active (*R*)- and (*S*)- isomers may be prepared using homo-chiral synthons or homo-chiral reagents, or optically resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended to include both (*E*)- and (*Z*)- geometric isomers. Likewise, all tautomeric forms are intended to be included.

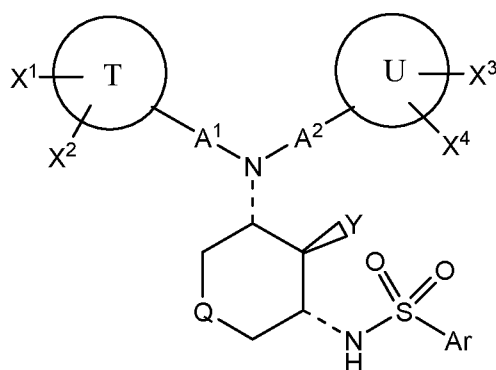
[0075] The graphic representations of racemic, ambiscalemic and scalemic or enantiomerically pure compounds used herein are a modified version of the denotations taken from Maehr J. Chem. Ed. 62, 114-120 (1985): simple lines provide no information about stereochemistry and convey only connectivity; solid and broken wedges are used to denote the absolute configuration of a chiral element; solid and broken bold lines are geometric descriptors indicating the relative configuration shown but not necessarily denoting racemic character; and wedge outlines and dotted or broken lines denote enantiomerically pure compounds of indeterminate absolute configuration. For example, the graphic representation



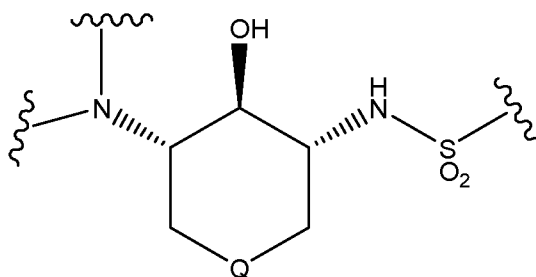
indicates either, or both, of the two *trans:trans* enantiomers:



in any ratio, from pure enantiomers to racemates. The graphic representation:



indicates a single enantiomer of unknown absolute stereochemistry, i.e. it could be either of the two preceding structures, as a substantially pure single enantiomer. And, finally, the representation:



indicates a pure (1*R*,2*R*,6*S*)-2,6-diaminoheterocyclyl-4-ol. For the purpose of the present disclosure, a “pure” or “substantially pure” enantiomer is intended to mean that the enantiomer is at least 95% of the configuration shown and 5% or less of other enantiomers. Similarly, a “pure” or “substantially pure” diastereomer is intended to mean that the diastereomer is at least 95% of the relative configuration shown and 5% or less of other diastereomers. In the text describing the stereochemistry of the examples, the convention of Chemical Abstracts is used. Thus “(1*R*,2*R*,6*S*)-*rel*” indicates that the three chiral centers are in that relative relationship, which would be depicted in a structural diagram by solid bold and dashed lines, whereas “(1*R*,2*R*,6*S*)” without the “*rel*” indicates a single enantiomer of that absolute configuration, which would be depicted in a structural diagram by solid and broken wedges.

[0076] It may be found upon examination that certain species and genera are not patentable to the inventors in this application. In this case, the exclusion of species and genera in applicants' claims are to be considered artifacts of patent prosecution and not reflective of the inventors' concept or description of their invention, which encompasses all members of the genus I that are not in the public's possession.

[0077] As used herein, and as would be understood by the person of skill in the art, the recitation of “a compound” - unless expressly further limited - is intended to include salts of that compound. In a particular embodiment, the term “compound of formula” refers to the compound or a pharmaceutically acceptable salt thereof.

[0078] The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. When the compounds of the present invention are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Suitable pharmaceutically acceptable acid addition salts for the compounds of the present invention include acetic, adipic, alginic, ascorbic, aspartic, benzenesulfonic (besylate), benzoic, boric, butyric, camphoric, camphorsulfonic, carbonic, citric, ethanedisulfonic, ethanesulfonic, ethylenediaminetetraacetic, formic, fumaric, glucoheptonic, gluconic, glutamic, hydrobromic, hydrochloric, hydroiodic, hydroxynaphthoic, isethionic, lactic, lactobionic, laurylsulfonic, maleic, malic, mandelic, methanesulfonic, mucic, naphthylenesulfonic, nitric, oleic, pamoic, pantothenic, phosphoric, pivalic, polygalacturonic, salicylic, stearic, succinic, sulfuric, tannic, tartaric acid, teoclastic, p-toluenesulfonic, and the like. When the compounds contain an acidic side chain, suitable pharmaceutically acceptable base addition salts for the compounds of the present invention include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from lysine, arginine, N,N'-dibenzylethylenediamine, chlorprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium cations and carboxylate, sulfonate and phosphonate anions attached to alkyl having from 1 to 20 carbon atoms.

[0079] Also provided herein is a pharmaceutical composition comprising a compound disclosed above, or a pharmaceutically acceptable salt form thereof, and a pharmaceutically acceptable carrier or diluent.

[0080] While it may be possible for the compounds of formula I to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically carriers thereof and optionally one or more other therapeutic

ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0081] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration. The most suitable route may depend upon the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of formula I or a pharmaceutically acceptable salt thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0082] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0083] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

[0084] Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient. Formulations for parenteral administration also include aqueous and non-aqueous sterile suspensions, which may include suspending agents and thickening agents. The

formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of a sterile liquid carrier, for example saline, phosphate-buffered saline (PBS) or the like, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0085] It will be recognized that the compounds of this invention can exist in radiolabeled form, i.e., the compounds may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine, and chlorine include ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds that contain those radioisotopes and/or other radioisotopes of other atoms are within the scope of this invention. Tritiated, i.e. ^3H , and carbon-14, i.e., ^{14}C , radioisotopes are particularly preferred for their ease in preparation and detectability. Compounds that contain isotopes ^{11}C , ^{13}N , ^{15}O and ^{18}F are well suited for positron emission tomography. Radiolabeled compounds of formula I of this invention and prodrugs thereof can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabeled compounds can be prepared by carrying out the procedures disclosed in the Examples and Schemes by substituting a readily available radiolabeled reagent for a non-radiolabeled reagent.

[0086] The compounds provided herein can be used for treating cancer in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound of formula I. In some embodiments, the cancer is characterized by dysregulation of the PI3K-AKT-FOXO signaling pathway. For example, the cancer can be selected from the group consisting of: ovarian, pancreatic, renal cell, breast, prostate, lung, hepatocellular carcinoma, glioma, leukemia, lymphoma, colorectal cancers, and sarcomas.

[0087] In some embodiments, the method further comprises administering one or more additional cancer chemotherapeutic agents. In some embodiments, the one or more additional cancer chemotherapeutic agents are EGFR inhibitors.

[0088] In some embodiments, the cancer is chemotherapy resistant cancer. In some embodiments, the method further comprises administering one or more cancer chemotherapeutic agents. In some embodiments, the one or more cancer chemotherapeutic agents are EGFR inhibitors.

[0089] In some embodiments, administration of a compound of formula I can restore sensitivity to one or more chemotherapeutic agents in a patient wherein the patient has developed a resistance to the one or more chemotherapeutic agents. More particularly, cancers that may be treated by the compounds, compositions and methods described herein include, but are not limited to, the following:

cardiac cancers, including, for example sarcoma, e.g., angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma; myxoma; rhabdomyoma; fibroma; lipoma and teratoma;

lung cancers, including, for example, bronchogenic carcinoma, e.g., squamous cell, undifferentiated small cell, undifferentiated large cell, and adenocarcinoma; alveolar and bronchiolar carcinoma; bronchial adenoma; sarcoma; lymphoma; chondromatous hamartoma; and mesothelioma;

gastrointestinal cancer, including, for example, cancers of the esophagus, e.g., squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma; cancers of the stomach, e.g., carcinoma, lymphoma, and leiomyosarcoma; cancers of the pancreas, e.g., ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, and vipoma; cancers of the small bowel, e.g., adenocarcinoma, lymphoma, carcinoid tumors, Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma; cancers of the large bowel, e.g., adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, and leiomyoma;

genitourinary tract cancers, including, for example, cancers of the kidney, e.g., adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, and leukemia; cancers of the bladder and urethra, e.g., squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma; cancers of the prostate, e.g., adenocarcinoma, and sarcoma; cancer of the testis, e.g., seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, and lipoma;

liver cancers, including, for example, hepatoma, e.g., hepatocellular carcinoma; cholangiocarcinoma; hepatoblastoma; angiosarcoma; hepatocellular adenoma; and hemangioma;

bone cancers, including, for example, osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocyoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign

chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors;

nervous system cancers, including, for example, cancers of the skull, e.g., osteoma, hemangioma, granuloma, xanthoma, and osteitis deformans; cancers of the meninges, e.g., meningioma, meningiosarcoma, and gliomatosis; cancers of the brain, e.g., astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, and congenital tumors; and cancers of the spinal cord, e.g., neurofibroma, meningioma, glioma, and sarcoma;

gynecological cancers, including, for example, cancers of the uterus, e.g., endometrial carcinoma; cancers of the cervix, e.g., cervical carcinoma, and pre tumor cervical dysplasia; cancers of the ovaries, e.g., ovarian carcinoma, including serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma, granulosa thecal cell tumors, Sertoli Leydig cell tumors, dysgerminoma, and malignant teratoma; cancers of the vulva, e.g., squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma; cancers of the vagina, e.g., clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma, and embryonal rhabdomyosarcoma; and cancers of the fallopian tubes, e.g., carcinoma;

hematologic cancers, including, for example, cancers of the blood, e.g., acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, and myelodysplastic syndrome, Hodgkin's lymphoma, non Hodgkin's lymphoma (malignant lymphoma) and Waldenström's macroglobulinemia;

skin cancers, including, for example, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and

adrenal gland cancers, including, for example, neuroblastoma.

[0090] Cancers may be solid tumors that may or may not be metastatic. Cancers may also occur, as in leukemia, as a diffuse tissue.

[0091] The compounds described herein can also be administered in combination with existing methods of treating cancers, for example by chemotherapy, irradiation, or surgery. Thus, there is further provided a method of treating cancer comprising administering an

effective amount of a compound according to formula I to a patient, wherein a therapeutically effective amount of one or more additional cancer chemotherapeutic agents are administered to the patient.

[0092] Also provided herein is a method for treating diabetes in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound of formula I.

[0093] Further provided herein is a method for treating an autoimmune disease in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound of formula I. The autoimmune disease can be, for example, inflammatory bowel disease (IBD). Immune responses are constantly and tightly regulated and one important cellular component in maintaining self tolerance (i.e., prevention of autoimmunity) and tolerance of benign commensal gut flora are regulatory T cells (Treg). Treg can be subdivided into multiple phenotypes, but the most common are CD4⁺CD25⁺ T cells that express the transcription factor Foxp3. Foxp3 is a direct transcriptional target of FOXO proteins, particularly FOXO1 and FOXO3. Thus activation of FOXO proteins in naïve T-cells promotes and directs differentiation to maintain a population of Treg cells.

[0094] Acute immune mediated rejection and chronic immune mediated rejection are key obstacles to successful solid organ transplantation. It is believed that these forms of rejection can be prevented/overcome by amplifying Treg number and or function. Similarly, a common and morbid complication of allogeneic hematopoietic cell transplants (Allo-HCT) used to treat various malignant and non-malignant conditions, is graft versus host disease, in which the transplanted immune cells from the donor damage multiple organs in the recipient (most notably skin, gut, and liver). Increasing experimental and clinical data indicate that Tregs can be harnessed to prevent and or treat this disease process.

[0095] Thus compounds of the present invention are useful in treatment of autoimmune and related diseases, by activating FOXO proteins and inducing T cell differentiation to Tregs. Compounds may be administered therapeutically to subjects directly, or alternatively, T cells may be collected from a subject and differentiated *ex vivo* to Tregs as described by Taylor et al. [*Blood* 99, 3493-3499 (2002)].

[0096] Aspects of the invention include methods for treatment of autoimmune disease characterized by deficiency in Treg function comprising administering a therapeutically

useful amount of compound of Formula I. The method can also include extraction of naïve T-cells from a patient, differentiation of T-cells to Tregs *ex vivo* by treatment with a compound of Formula I, optionally supplemented with an HDACi, followed by administration of Tregs to patient with optional separation of compound of Formula I from Tregs prior to their administration. As stated above, autoimmune diseases that can be so treated include IBD, solid organ transplant rejection, and GvHD in allo-HCT

[0097] In some embodiments, the compounds can be administered to a patient to treat an autoimmune disorder, for example, Addison's disease, Amyotrophic Lateral Sclerosis, celiac disease, Crohn's disease, diabetes, eosinophilic fasciitis, Guillain-Barré syndrome (GBS), Graves' disease, Lupus erythematosus, Miller-Fisher syndrome, psoriasis, rheumatoid arthritis, ulcerative colitis, and vasculitis. In some embodiments, the compound provided herein can be used for treating a disease or disorder in a patient wherein the disease or disorder involves excessive or unregulated cellular proliferation, the method comprising administering to the patient a therapeutically effective amount of a compound of formula (I). Also provided herein is a method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of the pi3K-AKT-FOXO signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound of formula I.

[0098] Further provided herein is a method for treating a disease in a patient wherein the disease is characterized by proteotoxicity, including age onset proteotoxicity leading to neurodegeneration, the method comprising administering to the patient a therapeutically effective amount of a compound of formula I. Hyperphosphorylated Tau has been implicated as the pathogenic protein in several neurodegenerative diseases and furthermore PP2A has been shown to be an important phosphatase in reversing aberrant phosphorylation of Tau; see for example Ludovic Martin et al., Tau protein phosphatases in Alzheimer's disease: The leading role of PP2A in Ageing Research Reviews 12 (2013) 39–49; Miguel Medina and Jesus Avila, Further understanding of tau phosphorylation: implications for therapy in Expert Rev. Neurotherapy, 15(1), 115-112 (2015) and Michael Voronkov et al., Phosphoprotein phosphatase 2A: a novel druggable target for Alzheimer's disease in Future Med Chem. 2011 May, 3(7) 821-833. Hyperphosphorylated alpha-Synuclein is a second exemplar of a toxic protein, and again PP2A has been shown to reverse its aberrantly phosphorylated state; see for example Kang-Woo Lee et al., Enhanced Phosphatase Activity Attenuates alpha-Synucleinopathy in a Mouse Model in Neurobiology

of Disease, May 11, 2011, 31(19) 6963-6971. In some embodiments, the disease is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration and Pick's disease.

[0099] The compounds provided herein may further be used in a method for treating a mood disorder in a patient by administering to the patient a therapeutically effective amount of a compound of formula I. In some embodiments, the mood disorder is stress-induced depression.

[00100] Also provided herein is a method for treating acne vulgaris in a patient by administering to the patient a therapeutically effective amount of a compound of formula I.

[00101] Further provided herein is a method for treating cardiac hypertrophy in a patient by administering to the patient a therapeutically effective amount of a compound of formula I. In some embodiments, the cardiac hypertrophy is associated with a disease selected from hypertension, myocardial infarction, and valvular heart disease.

[00102] The compounds provided herein may further be used in a method for treating a viral infection in a patient by administering to the patient a therapeutically effective amount of a compound of formula I. Examples of viruses that may cause viral infections to be treated include, but are not limited to: a polyomavirus, such as John Cunningham Virus (JCV), Simian virus 40 (SV40), or BK Virus (BKV); influenza, Human Immunodeficiency Virus type 1 (HIV-1), Human Papilloma Virus (HPV), adenovirus, Epstein-Barr Virus (EBV), Hepatitis C Virus (HCV), Molluscum contagiosum virus (MCV); Human T-lymphotropic virus type 1 HTLV-1), Herpes Simplex Virus type 1 (HSV-1), cytomegalovirus (CMV), hepatitis B virus, Bovine papillomavirus (BPV-1), human T-cell lymphotropic virus type 1, Japanese encephalitis virus, respiratory syncytial virus (RSV), and West Nile virus.

[00103] Further provided herein is a method for treating a parasitic infection in a patient by administering to the patient a therapeutically effective amount of a compound of formula I. Examples of parasites that may cause parasitic infections to be treated include, but are not limited to, *Plasmodium* and *Theileria*.

[00104] PP2A enzymes are involved in the regulation of cell transcription, cell cycle, and viral transformation. Many viruses, including cytomegalovirus, parainfluenza, DNA tumor viruses, and HIV-1, utilize different approaches to exploit PPA2 in order to modify, control, or inactivate cellular activities of the host [Garcia et al., *Microbes and Infection*, 2, 2000, 401–407]. Therefore, the compounds provided herein may further be used in a method for treating a viral infection in a patient by administering to the patient a therapeutically effective amount of a compound of formula (I). Examples of viruses that may cause viral infections to be treated include, but are not limited to: a polyomavirus, such as John Cunningham Virus (JCV), Simian virus 40 (SV40), or BK Virus (BKV); influenza, Human Immunodeficiency Virus type 1 (HIV-1), Human Papilloma Virus (HPV), adenovirus, Epstein-Barr Virus (EBV), Hepatitis C Virus (HCV), Molluscum contagiosum virus (MCV); Human T-lymphotropic virus type 1 HTLV-1), Herpes Simplex Virus type 1 (HSV-1), cytomegalovirus (CMV), hepatitis B virus, Bovine papillomavirus (BPV-1), human T-cell lymphotropic virus type 1, Japanese encephalitis virus, respiratory syncytial virus (RSV), and West Nile virus.

[00105] Serine/Threonine phosphatases, including PP2A are involved in modulation of synaptic plasticity (D. G. Winder and J. D. Sweatt, *Nature Reviews Neuroscience*, vol 2, July 2001, pages 461 – 474). Persistently decreased PP2A activity is associated with maintenance of Long Term Potentiation (LTP) of synapses, thus treatment PP2A activators such as those described here may reverse synaptic LTP. Psychostimulant drugs of abuse such as cocaine and methamphetamine are associated with deleterious synaptic LTP (L. Mao et al, *Neuron* 67, September 9, 2010 and A. Stipanovich et al, *Nature* vol 453, 2008, pages 879 – 884), which may underlie the pathology of addiction and relapse therefore PP2A activators described here may be useful as treatments for psychostimulant abuse.

[00106] Abnormalities in synaptic structure and signaling are linked to autistic spectrum disorder, see for example, Y Chen et al., CTTNBP2, but not CTTNBP2NL, regulates dendritic spinogenesis and synaptic distribution of the striatin–PP2A complex, *Molecular Biology of the Cell*, 23, November 15, 2012, 4383-4392. PP2A has been shown to be important in normal development of dendritic spines, and treatment with compounds of the present invention may ameliorate or reverse autistic spectrum disorder.

[00107] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which

this disclosure belongs. A comprehensive list of abbreviations utilized by organic chemists (i.e. persons of ordinary skill in the art) appears in the first issue of each volume of the Journal of Organic Chemistry. The list, which is typically presented in a table entitled “Standard List of Abbreviations” is incorporated herein by reference. In the event that there is a plurality of definitions for terms cited herein, those in this section prevail unless otherwise stated.

[00108] As used herein, the terms “comprising” and “including” or grammatical variants thereof are to be taken as specifying the stated features, integers, steps or components but do not preclude the addition of one or more additional features, integers, steps, components or groups thereof. This term encompasses the terms “consisting of” and “consisting essentially of”.

[00109] The phrase “consisting essentially of” or grammatical variants thereof when used herein are to be taken as specifying the stated features, integers, steps or components but do not preclude the addition of one or more additional features, integers, steps, components or groups thereof, but only if the additional features, integers, steps, components or groups thereof do not materially alter the basic and novel characteristics of the claimed composition or method.

[00110] A “patient,” as used herein, includes both humans and other animals, particularly mammals. Thus the methods are applicable to both human therapy and veterinary applications. In some embodiments, the patient is a mammal, for example, a primate. In some embodiments, the patient is a human.

[00111] Treatment can involve administering a compound described herein to a patient diagnosed with a disease, and may involve administering the compound to a patient who does not have active symptoms. Conversely, treatment may involve administering the compositions to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

[00112] The terms “administer”, “administering” or “administration” in reference to a dosage form of the invention refers to the act of introducing the dosage form into the system of subject in need of treatment. When a dosage form of the invention is given in combination with one or more other active agents (in their respective dosage forms),

“administration” and its variants are each understood to include concurrent and/or sequential introduction of the dosage form and the other active agents. Administration of any of the described dosage forms includes parallel administration, co-administration or sequential administration. In some situations, the therapies are administered at approximately the same time, *e.g.*, within about a few seconds to a few hours of one another.

[00113] A “therapeutically effective” amount of the compounds described herein is typically one which is sufficient to achieve the desired effect and may vary according to the nature and severity of the disease condition, and the potency of the compound. It will be appreciated that different concentrations may be employed for prophylaxis than for treatment of an active disease. A therapeutic benefit is achieved with the amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder.

[00114] The term “modulate” with respect to a FOXO transcription factor protein refers to activation of the FOXO transcription factor protein and its biological activities associated with the FOXO pathway. Modulation of FOXO transcription factor proteins includes up-regulation (*i.e.*, agonizing, activation or stimulation). The mode of action of a FOXO modulator can be direct, *e.g.*, through binding to the FOXO transcription factor protein as a ligand. The modulation can also be indirect, *e.g.*, through binding to and/or modifying another molecule which otherwise binds to and activates the FOXO transcription factor protein.

[00115] Throughout this specification the terms and substituents retain their definitions.

[00116] C₁ to C₂₀ hydrocarbon includes alkyl, cycloalkyl, polycycloalkyl, alkenyl, alkynyl, aryl and combinations thereof. Examples include benzyl, phenethyl, cyclohexylmethyl, adamantyl, camphoryl and naphthylethyl. Hydrocarbyl refers to any substituent comprised of hydrogen and carbon as the only elemental constituents. Aliphatic hydrocarbons are hydrocarbons that are not aromatic; they may be saturated or unsaturated, cyclic, linear or branched. Examples of aliphatic hydrocarbons include isopropyl, 2-butenyl, 2-butylnyl, cyclopentyl, norbornyl, etc. Aromatic hydrocarbons include benzene (phenyl), naphthalene (naphthyl), anthracene, etc.

[00117] Unless otherwise specified, alkyl (or alkylene) is intended to include linear or branched saturated hydrocarbon structures and combinations thereof. Alkyl refers to alkyl groups from 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like.

[00118] Cycloalkyl is a subset of hydrocarbon and includes cyclic hydrocarbon groups of from 3 to 8 carbon atoms. Examples of cycloalkyl groups include cy-propyl, cy-butyl, cy-pentyl, norbornyl and the like.

[00119] Unless otherwise specified, the term “carbocycle” is intended to include ring systems in which the ring atoms are all carbon but of any oxidation state. Thus (C₃-C₁₀) carbocycle refers to both non-aromatic and aromatic systems, including such systems as cyclopropane, benzene and cyclohexene; (C₈-C₁₂) carbopolycycle refers to such systems as norbornane, decalin, indane and naphthalene. Carbocycle, if not otherwise limited, refers to monocycles, bicycles and polycycles.

[00120] Heterocycle means an aliphatic or aromatic carbocycle residue in which from one to four carbons is replaced by a heteroatom selected from the group consisting of N, O, and S. The nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. Unless otherwise specified, a heterocycle may be non-aromatic (heteroaliphatic) or aromatic (heteroaryl). Examples of heterocycles include pyrrolidine, pyrazole, pyrrole, indole, quinoline, isoquinoline, tetrahydroisoquinoline, benzofuran, benzodioxan, benzodioxole (commonly referred to as methylenedioxyphenyl, when occurring as a substituent), tetrazole, morpholine, thiazole, pyridine, pyridazine, pyrimidine, thiophene, furan, oxazole, oxazoline, isoxazole, dioxane, tetrahydrofuran and the like. Examples of heterocyclyl residues include piperazinyl, piperidinyl, pyrazolidinyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, tetrahydrofuryl, tetrahydropyranyl, thienyl (also historically called thiophenyl), benzothienyl, thiamorpholinyl, oxadiazolyl, triazolyl and tetrahydroquinolinyl.

[00121] Alkoxy or alkoxyl refers to groups of from 1 to 20 carbon atoms, preferably 1 to 10 carbon atoms, more preferably 1 to 6 carbon atoms of a straight or branched configuration attached to the parent structure through an oxygen. Examples include

methoxy, ethoxy, propoxy, isopropoxy and the like. Lower-alkoxy refers to groups containing one to four carbons. For the purpose of this application, alkoxy and lower alkoxy include methylenedioxy and ethylenedioxy.

[00122] The term "halogen" means fluorine, chlorine, bromine or iodine atoms. In one embodiment, halogen may be a fluorine or chlorine atom.

[00123] Unless otherwise specified, acyl refers to formyl and to groups of 1, 2, 3, 4, 5, 6, 7 and 8 carbon atoms of a straight, branched, cyclic configuration, saturated, unsaturated and aromatic and combinations thereof, attached to the parent structure through a carbonyl functionality. Examples include acetyl, benzoyl, propionyl, isobutyryl and the like. Lower-acyl refers to groups containing one to four carbons. The double bonded oxygen, when referred to as a substituent itself is called "oxo".

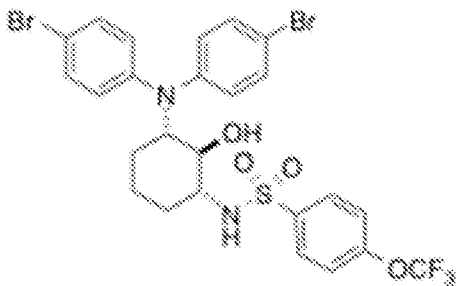
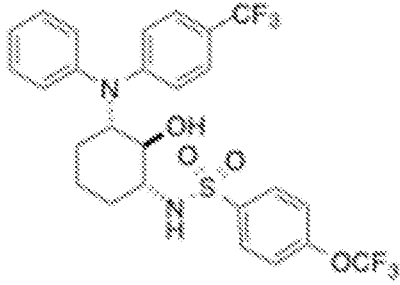
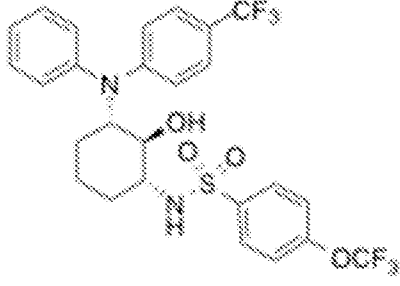
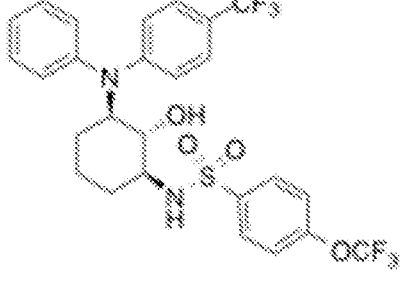
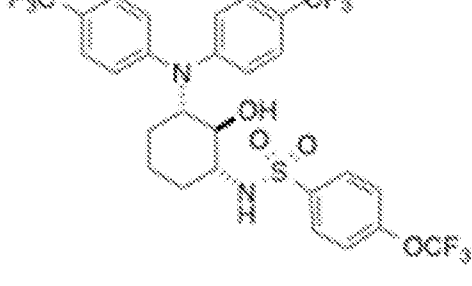
[00124] As used herein, the term "optionally substituted" may be used interchangeably with "unsubstituted or substituted". The term "substituted" refers to the replacement of one or more hydrogen atoms in a specified group with a specified radical. For example, substituted alkyl, aryl, cycloalkyl, heterocyclyl etc. refer to alkyl, aryl, cycloalkyl, or heterocyclyl wherein one or more H atoms in each residue are replaced with halogen, haloalkyl, alkyl, acyl, alkoxyalkyl, hydroxy lower alkyl, carbonyl, phenyl, heteroaryl, benzenesulfonyl, hydroxy, lower alkoxy, haloalkoxy, oxaalkyl, carboxy, alkoxycarbonyl [-C(=O)O-alkyl], alkoxycarbonylamino [HNC(=O)O-alkyl], aminocarbonyl (also known as carboxamido) [-C(=O)NH₂], alkylaminocarbonyl [-C(=O)NH-alkyl], cyano, acetoxy, nitro, amino, alkylamino, dialkylamino, (alkyl)(aryl)aminoalkyl, alkylaminoalkyl (including cycloalkylaminoalkyl), dialkylaminoalkyl, dialkylaminoalkoxy, heterocyclylalkoxy, mercapto, alkylthio, sulfoxide, sulfone, sulfonylamino, alkylsulfinyl, alkylsulfonyl, acylaminoalkyl, acylaminoalkoxy, acylamino, amidino, aryl, benzyl, heterocyclyl, heterocyclylalkyl, phenoxy, benzyloxy, heteroaryloxy, hydroxyimino, alkoxyimino, oxaalkyl, aminosulfonyl, trityl, amidino, guanidino, ureido, benzyloxyphenyl, and benzyloxy. "Oxo" is also included among the substituents referred to in "optionally substituted"; it will be appreciated by persons of skill in the art that, because oxo is a divalent radical, there are circumstances in which it will not be appropriate as a substituent (e.g. on phenyl). In one embodiment, 1, 2, or 3 hydrogen atoms are replaced with a specified radical. In the case of alkyl and cycloalkyl, more than three hydrogen atoms can be replaced by fluorine; indeed, all available hydrogen atoms could be replaced by fluorine.

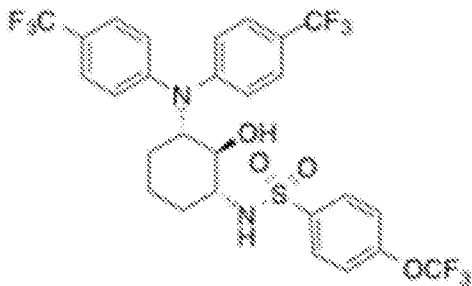
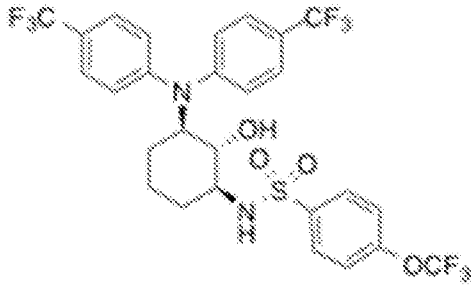
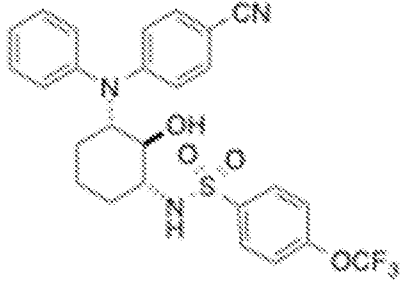
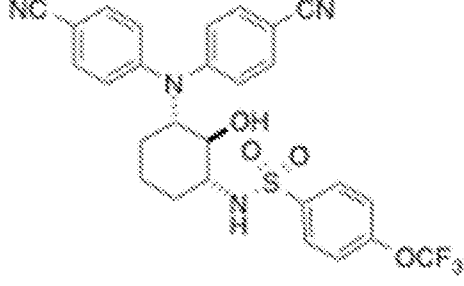
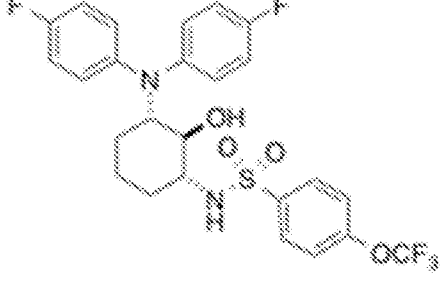
In preferred embodiments, substituents are halogen, haloalkyl, alkyl, acyl, hydroxyalkyl, hydroxy, alkoxy, haloalkoxy, aminocarbonyl oxaalkyl, carboxy, cyano, acetoxy, nitro, amino, alkylamino, dialkylamino, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylsulfonylamino arylsulfonyl, arylsulfonylamino, and benzyloxy.

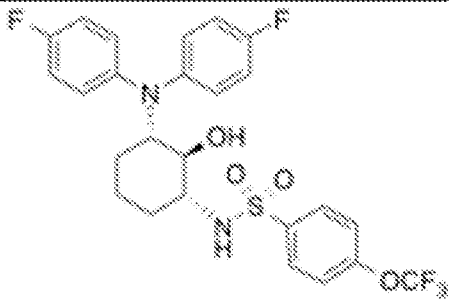
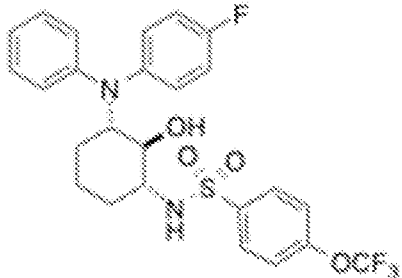
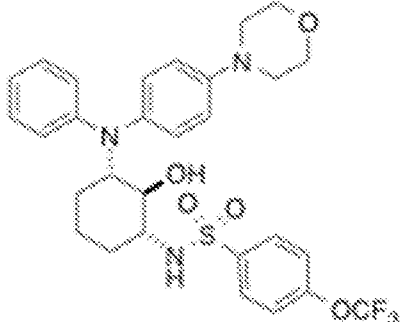
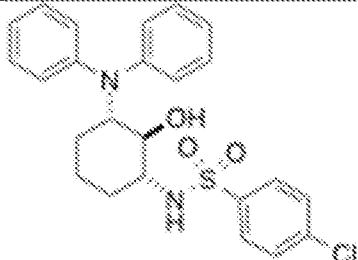
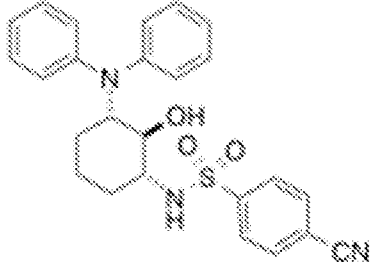
[00125] Substituents Rⁿ are generally defined when introduced and retain that definition throughout the specification and in all independent claims.

Examples

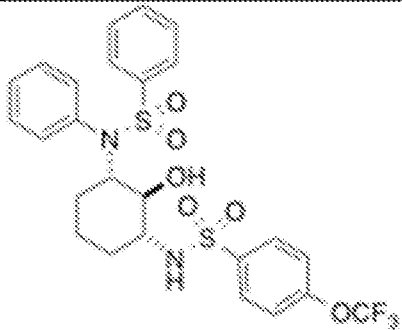
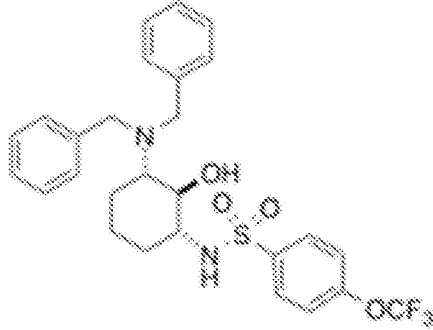
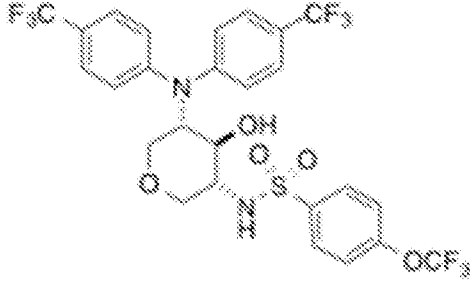
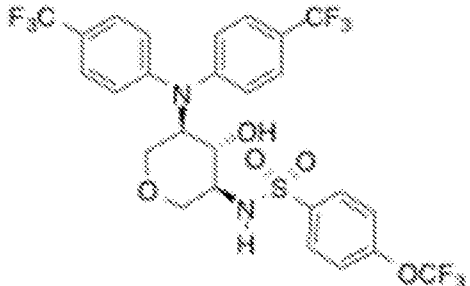
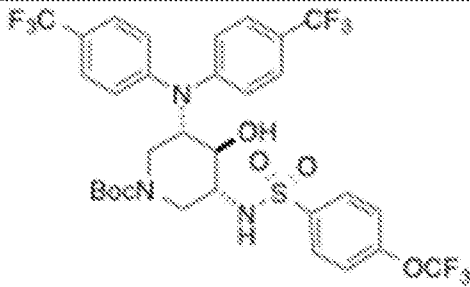
Example No.	Structure
1a	
1b	
1c	
2	

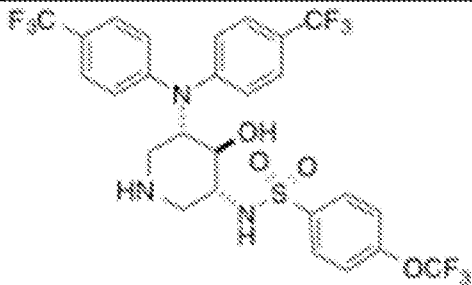
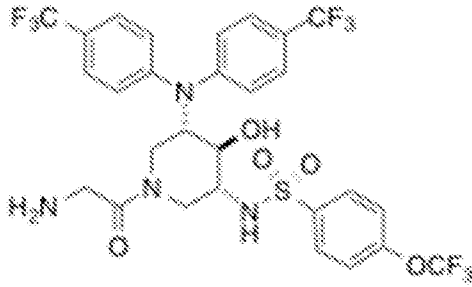
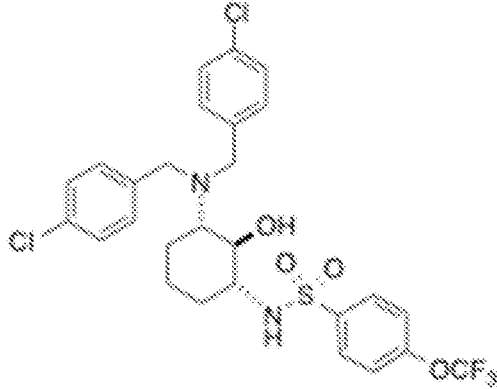
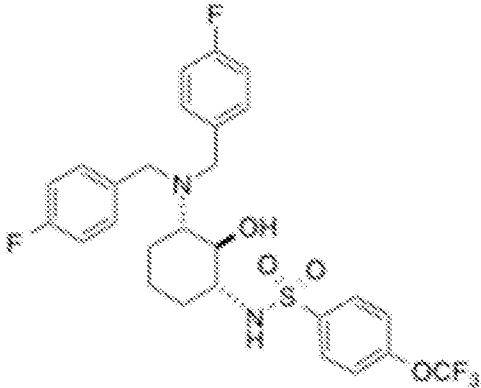
Example No.	Structure
3	
4a	
4b	
4c	
5a	

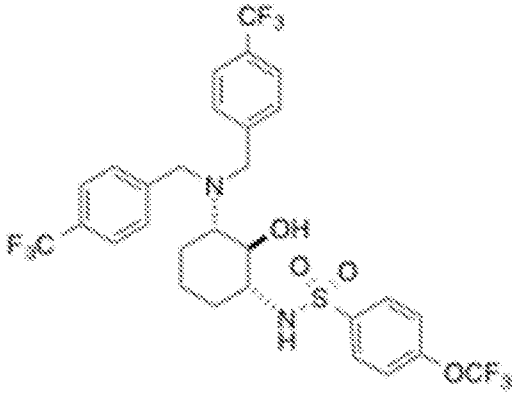
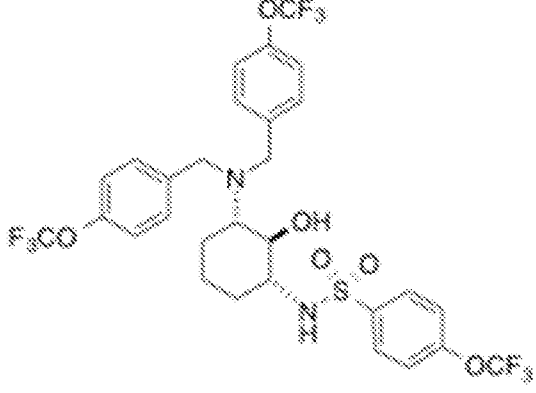
Example No.	Structure
5b	
5c	
6	
7	
8	

Example No.	Structure
8b	
9	
10	
11	
12	

Example No.	Structure
13	 <chem>COc1ccc(cc1)S(=O)(=O)[C@H]2CCCC[C@@H]2CN(Cc3ccccc3)c4ccccc4</chem>
14	 <chem>c1ccc(cc1)S(=O)(=O)[C@H]2CCCC[C@@H]2CN(Cc3ccccc3)c4ccccc4</chem>
15	 <chem>COc1ccc(cc1)S(=O)(=O)[C@H]2CCCC[C@@H]2CN(Cc3ccccc3)c4ccccc4</chem>
16	 <chem>Clc1ccc(cc1)S(=O)(=O)[C@H]2CCCC[C@@H]2CN(Cc3ccccc3)c4ccccc4</chem>
17	 <chem>COc1ccc(cc1)S(=O)(=O)[C@H]2CCCC[C@@H]2CN(Cc3ccccc3)C(=O)c4ccccc4</chem>

Example No.	Structure
18	
19	
20	
20a	
21	

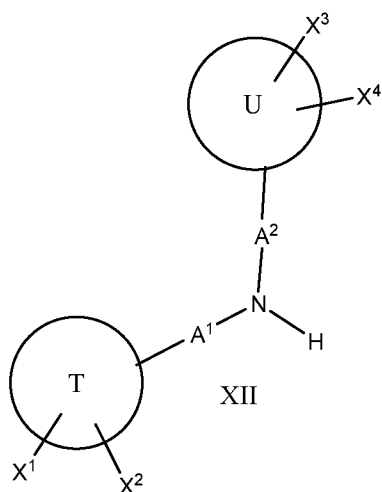
Example No.	Structure
22	
23	
24	
25	

Example No.	Structure
26	
27	

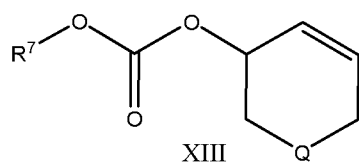
[00126] Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups, can be readily determined by one skilled in the art. Suitable groups for that purpose are discussed in standard textbooks in the field of chemistry, such as *Protective Groups in Organic Synthesis* by T.W.Greene and P.G.M.Wuts [John Wiley & Sons, New York, 1999], in *Protecting Group Chemistry*, 1st Ed., Oxford University Press, 2000; and in *March's Advanced Organic chemistry: Reactions, Mechanisms, and Structure*, 5th Ed., Wiley-Interscience Publication, 2001.

[00127] Many compounds of formula I may be prepared by the schemes shown in U.S. Provisional Application US 62/201,819, which is incorporated herein by reference. In general, compounds of formula I can be prepared by:

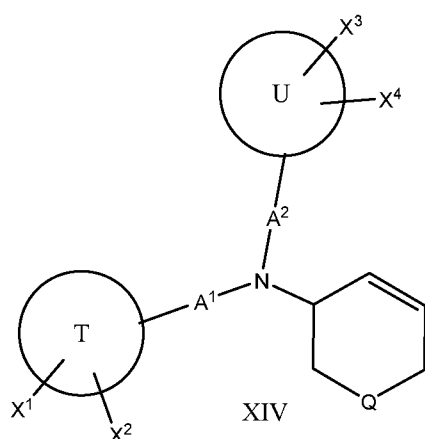
(a) reacting a compound of formula XII



with a compound of formula XIII

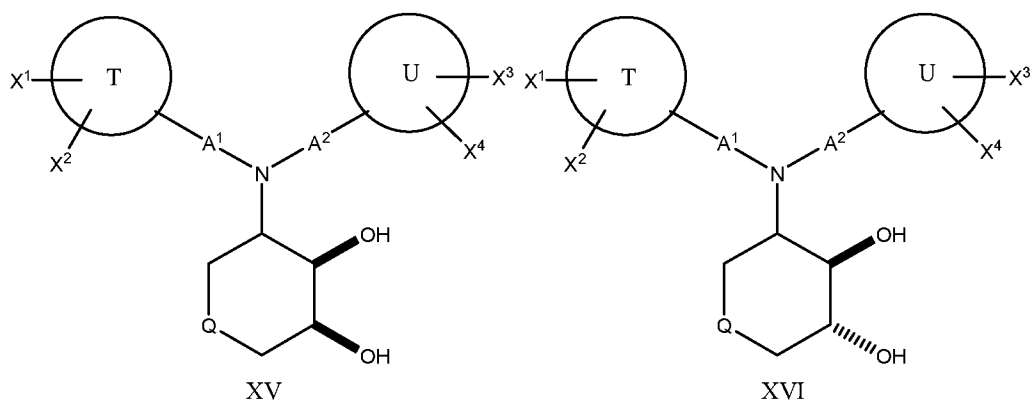


wherein R⁷ is (C₁-C₄)alkyl, in the presence of a palladium catalyst to provide a product of formula XIV



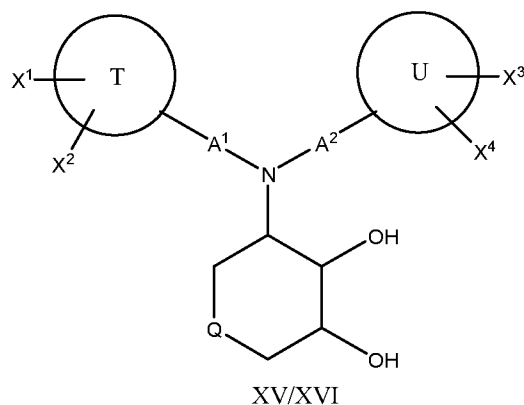
and

oxidizing the product of formula XIV with osmium tetroxide to provide the *cis* diol XV or with *meta* chloroperbenzoic acid followed by hydrolysis of the resulting epoxide to provide the *trans* diol XVI:

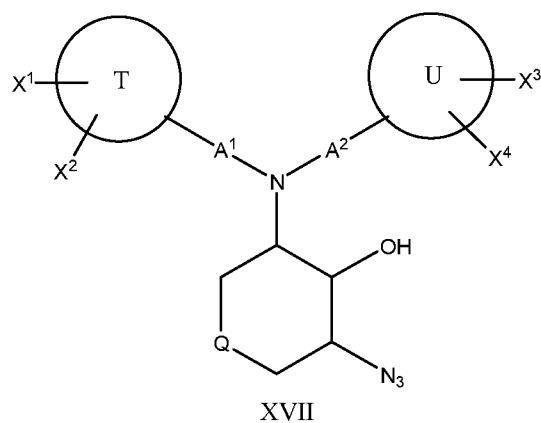


[00128] If a chiral palladium catalyst is used in the initial step to make XIV, the stereochemistry can thus be controlled for all products downstream.

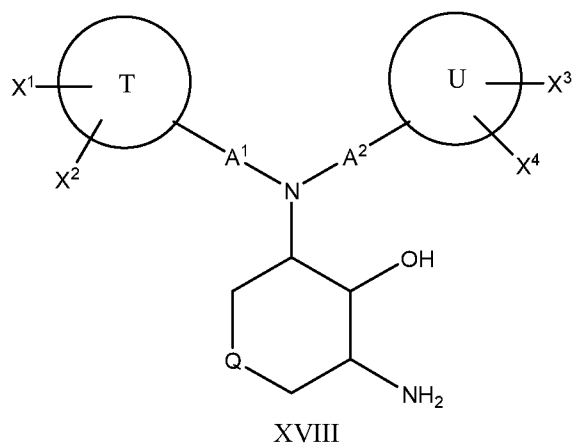
[00129] The diol of formula XV/XVI



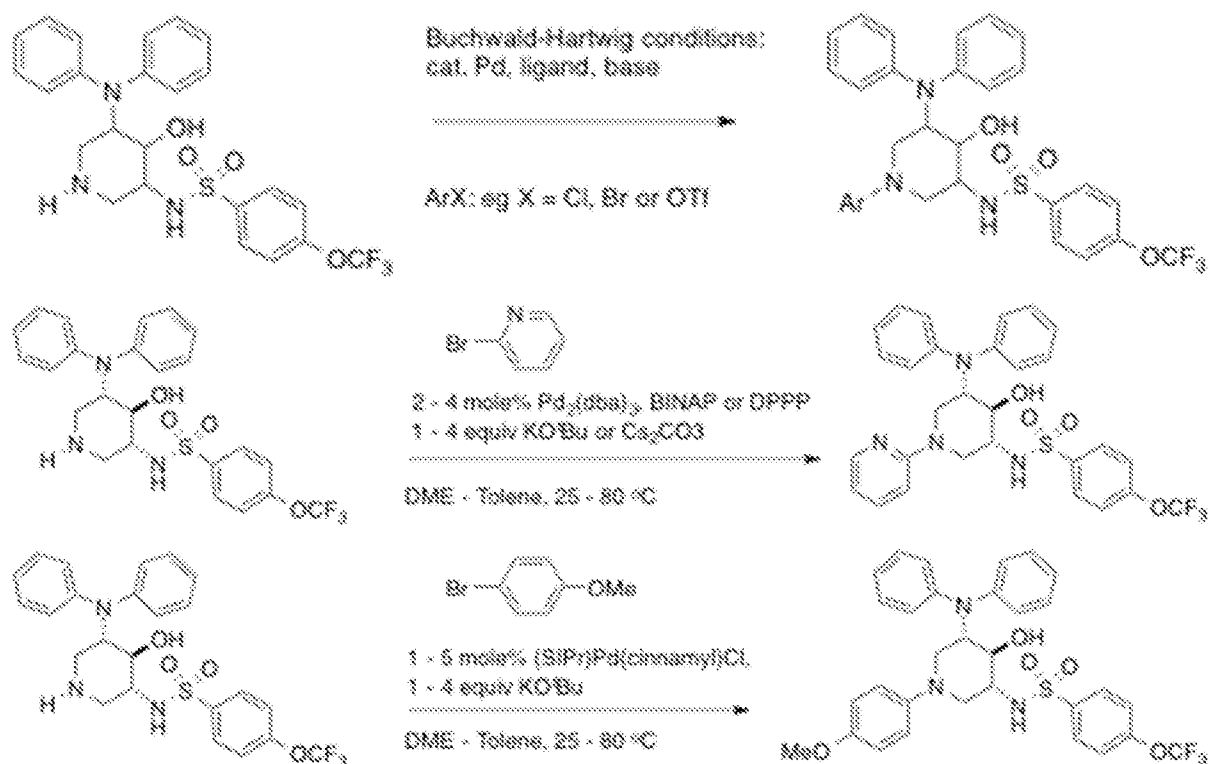
may be reacted with thionyl chloride or a sulfonyl chloride, such as methanesulfonyl chloride, to provide a sulfonylated product; and the sulfonylated product may be reacted with an alkali metal azide to provide a 3-azido-4-hydroxy-5-aminoheterocycle of formula XVII:



The azide may be reduced to provide the corresponding amine XVIII:

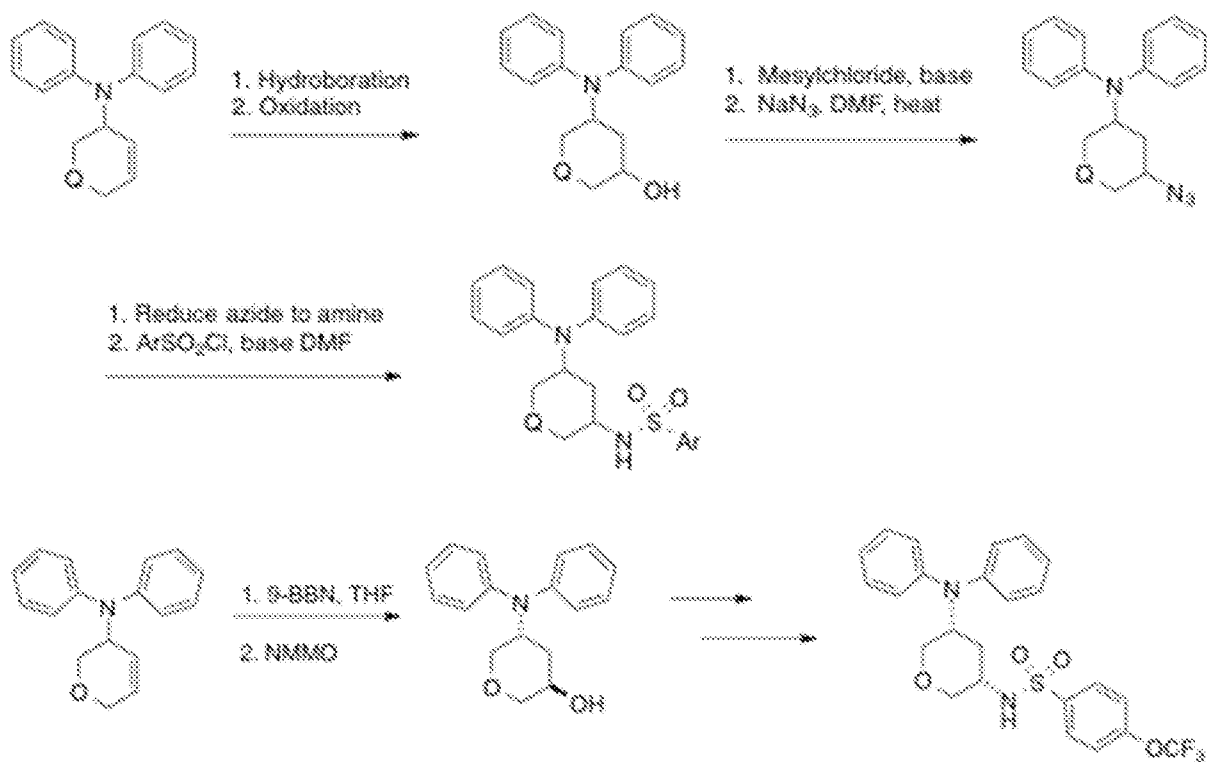


A convenient reducing agent is triphenyl phosphine, but there are many procedures known to persons of skill that may be employed for reducing an azide to an amine. The amine XVIII may be reacted with the appropriate sulfonyl chloride to provide the products described herein in which Y is OH and Q is oxygen. When Q is NR, the compounds may be made in the same fashion as above but with R initially being a protecting group, such as t-Boc or Cbz. The protecting group is then cleaved after synthesis is complete, and the resulting NH condensed with any acylating or alkylating agent needed by procedures well-known in the art. Introduction of aryl or heteroaryl moieties onto the ring nitrogen may be achieved by S_NAr substitution reactions for electron deficient aromatic systems such as 4-nitrophenyl or electrophilic heteroaromatic systems such as 4-pyrimidinyl systems. More generally arylation or heteroarylation of the ring nitrogen may be achieved by palladium mediated N-aryl amination: the Buchwald-Hartwig reaction, see for example N. Marion et al, in "Modified (NHC)Pd(allyl)Cl (NHC) N-Heterocyclic Carbene) Complexes for Room-Temperature Suzuki-Miyaura and Buchwald-Hartwig Reactions" J. Am. Chem. Soc. 2006, 128, 4101 or J. P. Wolfe et al in "Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation. Examples as applied to compounds of the present invention are shown in the scheme below:

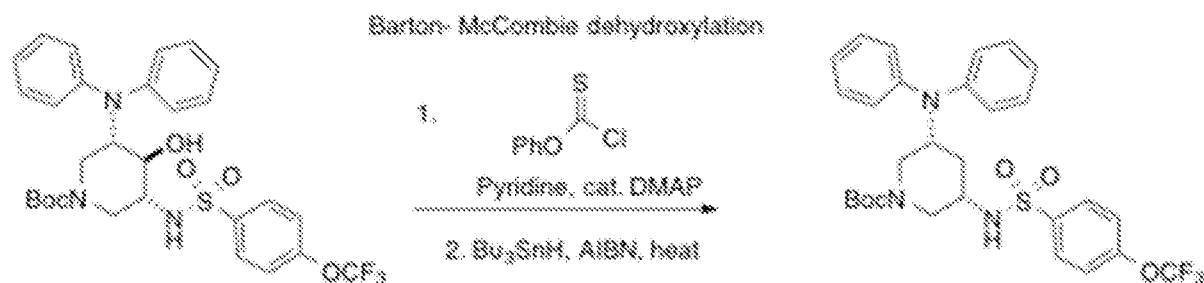


When Q is sulfur, the ring will either start out in the sulfone oxidation state or it will be oxidized to the sulfone when dihydroxylating the allylic olefin.

When compounds in which Y is hydrogen are desired, the olefin XIV may be treated with a sterically hindered hydroborating agent such as 9-BBN or the like, followed by oxidation of the alkyboron to the alcohol with an oxidant such as N-methylmorpholine-N-oxide or aqueous hydrogen peroxide. The alcohol intermediate is converted to leaving group such as the mesylate and displaced with azide. This is carried forward to the target compound by reduction and reaction with the appropriate aryl sulfonyl chloride. This process is illustrated in the scheme below:

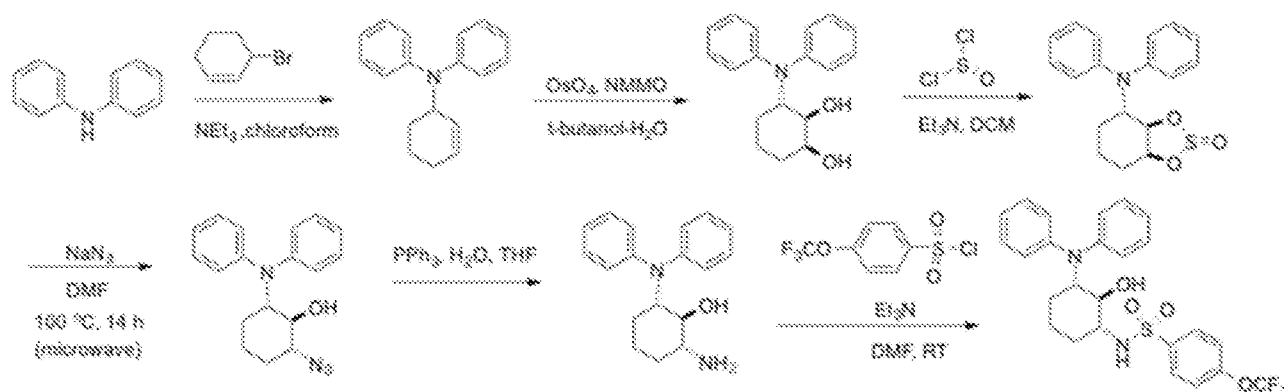


Alternatively compounds in which Y = H may be accessed via radical mediated deoxygenation processes as described in, for example, W. Hartwig in "Modern Methods For The Radical Deoxygenation of Alcohols", Tetrahedron Vol. 39, No. 16, page 2609 (1983). One example of this type of transformation as applied to compounds of the present invention (Barton-McCombie conditions) is shown below:

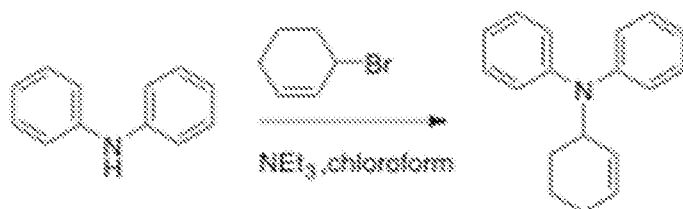


[00130] Exemplary syntheses are presented below:

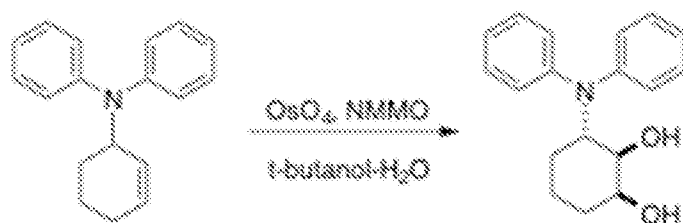
Scheme 1. Synthesis of Example 1a



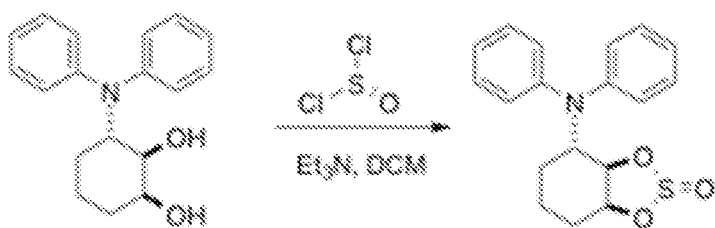
[00131] Experimental



[00132] **N-(cyclohex-2-en-1-yl)-N-phenylaniline.** A solution of diphenylamine (2.00 g, 11.8 mmol) in CHCl_3 (20 mL) at 25 °C was treated with triethylamine (4.92 mL, 35.5 mmol), and 3-bromocyclohexene (1.63 mL, 14.2 mmol). The mixture was warmed to 60 °C and stirred for 14 h. The mixture was then cooled to 25 °C, concentrated in vacuo, and the residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , hexanes) to afford the title compound as a clear oil (1.48 g, 50%). ^1H NMR (600 MHz, CDCl_3) δ 7.25 (4H, t, J = 8.4 Hz), 6.97 (2H, t, J = 7.8 Hz), 6.94 (4H, d, J = 7.8 Hz), 5.88 (1H, d, J = 10.2 Hz), 5.77-5.80 (1H, m), 4.66-4.69 (1H, m), 1.97-2.01 (3H, m), 1.73-1.77 (1H, m), 1.65-1.71 (2H, m); ^{13}C NMR (150 MHz, CDCl_3) δ 147.3, 130.1, 129.5, 129.2, 122.9, 121.7, 55.8, 27.7, 25.0, 22.1; LCMS m/z 250.1584 ($[\text{M} + \text{H}]^+$, $\text{C}_{18}\text{H}_{19}\text{N}$ requires 250.1590).

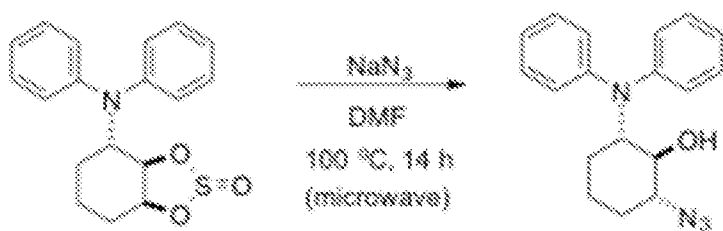


[00133] **rac-(1R,2S,3R)-3-(diphenylamino)cyclohexane-1,2-diol**. A solution of N-(cyclohex-2-en-1-yl)-N-phenylaniline (1.42 g, 5.69 mmol) in t-BuOH-H₂O 5:1 (20.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in t-BuOH, 0.74 mL, 0.0569 mmol) and N-methyl morpholine N-oxide hydrate (0.847 g, 6.26 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (10 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a white solid (1.30 g, 81%). ¹H NMR (600 MHz, CDCl₃) δ 7.30 (4H, t, *J* = 7.8 Hz), 7.06 (2H, t, *J* = 7.8 Hz), 6.97 (4H, d, *J* = 7.8 Hz), 4.32 (1H, ddd, *J* = 10.2, 9.0, 6.6 Hz), 4.17 (1H, d, *J* = 3.0 Hz), 3.37 (1H, dd, *J* = 10.2, 3.0 Hz), 2.96 (1H, s), 2.59 (1H, s), 2.03 (1H, dt, *J* = 12.6, 3.0 Hz), 1.90-1.95 (1H, m), 1.86 (1H, qt, *J* = 13.8, 3.6 Hz), 1.53-1.56 (1H, m), 1.29 (1H, tq, *J* = 14.4, 1.2 Hz), 1.16 (1H, qd, *J* = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 147.1, 129.5, 123.7, 123.0, 73.3, 69.4, 57.6, 29.9, 28.2, 19.4; LCMS *m/z* 284.1835 ([M + H]⁺), C₁₈H₂₁NO₂ requires 284.1645).

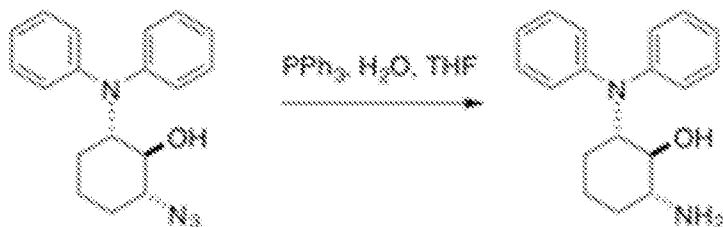


[00134] **rac-(3aS,4R,7aR)-4-(diphenylamino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide**. A solution of rac-(1R,2S,3R)-3-(diphenylamino)cyclohexane-1,2-diol (1.47 g, 5.17 mmol) in CH₂Cl₂ (10.0 mL) at 0 °C was treated dropwise with triethylamine (5.73 mL, 41.3 mmol), and SOCl₂ (1.12 mL, 15.5 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), saturated aqueous sodium chloride (100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (1.26 g, 74%). ¹H NMR (600 MHz, CDCl₃) δ (as a mixture of sulfite diastereomers) 7.31-7.33

(4H, m), 2H[7.06 (t, $J = 7.2$ Hz), 7.04 (t, $J = 7.8$ Hz)], 6.96 (1H, t, $J = 7.2$ Hz), 6.90 (3H, t, $J = 7.8$ Hz), 5.10-5.12 (1H, m), 1H[4.89 (1H, ddd, $J = 13.2, 9.6, 4.2$ Hz), 4.63-4.66 (m), 4.33 (dd, $J = 9.6, 4.8$ Hz),], 4.55 (1H, dd, $J = 9.6, 4.8$ Hz), 3.96 (1H, ddd, $J = 12.6, 9.6, 6.0$ Hz), 2.33-2.38 (1H, m), 2.16-2.21 (1H, m), 3H[1.87-1.92 (qd, $J = 13.2, 3.0$ Hz), 1.70-1.83 (m), 1.62-1.70 (m)], 1H[1.32 (qd, $J = 13.2, 3.0$ Hz), 1.26 (qd, $J = 12.6, 3.0$ Hz)]; LCMS m/z 330.1248 ($[M + H]^+$, $C_{18}H_{19}NO_3S$ requires 330.1158).

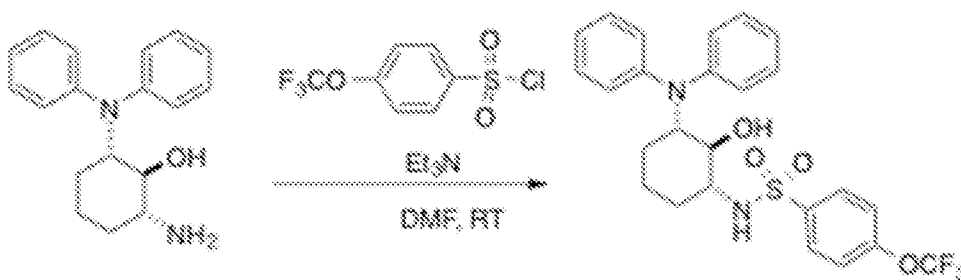


[00135] **rac-(1S,2S,6R)-2-azido-6-(diphenylamino)cyclohexanol**. A solution of rac-(3aS,4R,7aR)-4-(diphenylamino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide (0.927 g, 2.81 mmol) in DMF (5.0 ml) was treated with sodium azide (0.550 g, 8.44 mmol), and heated to 100 °C for 14 h under microwave irradiation. The mixture was diluted with CH_2Cl_2 (200 mL) and this organic layer was washed with saturated aqueous NaCl (3×100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-10% ethyl acetate-hexanes) to afford the title compound as a clear oil (0.877 g, 99%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 (4H, t, $J = 8.4$ Hz), 7.06 (2H, t, $J = 7.2$ Hz), 6.97 (4H, d, $J = 7.8$ Hz), 3.92 (1H, ddd, $J = 12.6, 10.2, 4.2$ Hz), 3.47 (1H, ddd, $J = 12.6, 9.6, 4.8$ Hz), 3.32 (1H, t, $J = 9.0$ Hz), 2.86 (1H, s), 2.02-2.06 (1H, m), 1.96-2.01 (1H, m), 1.82 (1H, doublet of quintets, $J = 13.8, 3.6$ Hz), 1.47 (1H, qt, $J = 13.2, 3.6$ Hz), 1.25 (1H, qt, $J = 12.6, 4.2$ Hz), 1.19 (1H, qd, $J = 13.2, 4.2$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 146.7, 129.6, 123.6, 123.0, 75.4, 66.0, 61.7, 29.9, 28.2, 22.4; LCMS m/z 309.2722 ($[M + H]^+$, $C_{18}H_{20}N_4O$ requires 309.1710).



[00136] **rac-(1R,2S,6R)-2-amino-6-(diphenylamino)cyclohexanol**. A solution of rac-(1S,2S,6R)-2-azido-6-(diphenylamino)cyclohexanol (0.857 g, 2.78 mmol) in THF (5.0 mL)

was cooled to 0 °C, treated with PPh₃ (0.947 g, 3.61 mmol), H₂O (0.25 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as a beige film (0.708 g, 90%). ¹H NMR (600 MHz, CDCl₃) δ 7.28 (4H, t, *J* = 7.8 Hz), 7.03 (2H, t, *J* = 7.2 Hz), 6.96 (4H, d, *J* = 7.8 Hz), 3.89 (1H, ddd, *J* = 13.2, 10.2, 4.2 Hz), 3.06 (1H, t, *J* = 9.0 Hz), 2.77 (1H, ddd, *J* = 12.0, 9.0, 4.2 Hz), 2.23 (2H, br s), 1.99-2.02 (1H, m), 1.81-1.84 (1H, m), 1.73 (1H, doublet of quintets, *J* = 16.8, 3.6 Hz), 1.46 (1H, qt, *J* = 13.2, 3.6 Hz), 1.26 (1H, qd, *J* = 12.6, 3.6 Hz), 1.07 (1H, qd, *J* = 13.2, 4.2 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 147.0, 128.4, 123.6, 122.6, 77.3, 61.7, 56.6, 33.5, 28.7, 23.1; LCMS *m/z* 283.1985 ([M + H]⁺, C₁₈H₂₂N₂O requires 283.1805).



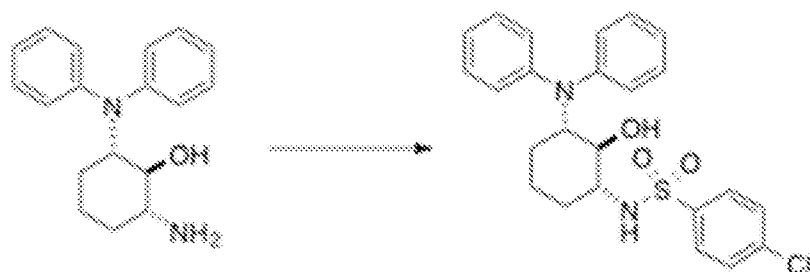
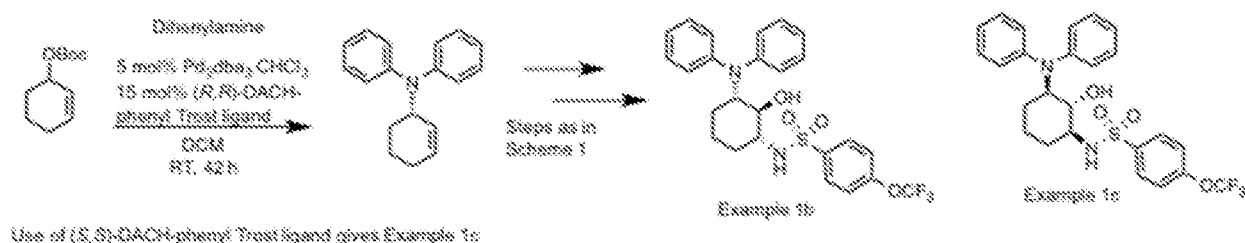
Example 1a

[00137] **rac-N-((1S,2S,3R)-3-(diphenylamino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of rac-(1R,2S,6R)-2-amino-6-(diphenylamino)cyclohexanol (0.100 g, 0.354 mmol) in DMF (1.0 mL) was cooled to 0 °C, treated with Et₃N (22.0 μL, 0.162 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (49.0 μL, 0.354 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.150 g, 84%). ¹H NMR (600 MHz, CDCl₃) δ 7.97 (2H, d, *J* = 9.0 Hz), 7.33 (2H, t, *J* = 8.4 Hz), 7.27 (4H, t, *J* = 7.8 Hz), 7.05 (2H, t, *J* = 7.2 Hz), 6.89 (4H, d, *J* = 7.8 Hz), 5.00

(1H, d, $J = 6.6$ Hz), 3.81 (1H, ddd, $J = 12.6, 9.0, 3.6$ Hz), 3.13-3.19 (2H, m), 2.83 (1H, s), 2.06-2.09 (1H, m), 1.98-2.01 (1H, m), 1.72 (1H, doublet of quintets, $J = 13.8, 3.6$ Hz), 1.38 (1H, qt, $J = 13.2, 3.6$ Hz), 1.26 (1H, qd, $J = 13.2, 4.2$ Hz), 1.07 (1H, qd, $J = 13.2, 4.2$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 152.3, 146.7, 139.0, 129.63, 129.60, 123.7, 123.2, 121.3, 121.0, 100.2, 73.4, 61.9, 59.2, 31.7, 28.1, 22.4; LCMS m/z 507.2088 ($[\text{M} + \text{H}^+]$, $\text{C}_{25}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_4\text{S}$ requires 507.1560).

[00138] **Examples 1b and 1c** may be prepared by chromatographic resolution of 1a. Alternatively asymmetric allylation of diphenylamine gives access to either enantiomer as shown in Scheme 2

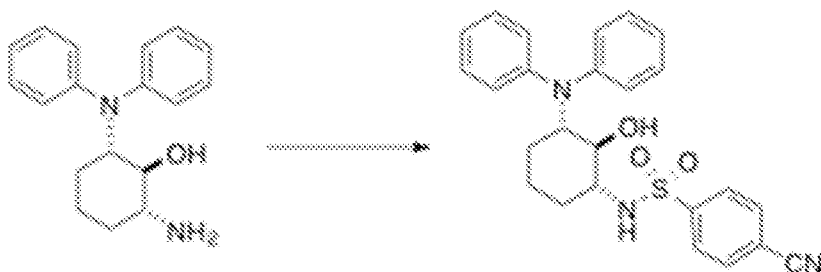
[00139] Scheme 2



Example 11

[00140] **rac-4-chloro-N-((1S,2S,3R)-3-(diphenylamino)-2-hydroxycyclohexyl)benzenesulfonamide**. A solution of rac-(1R,2S,6R)-2-amino-6-(diphenylamino)cyclohexanol (0.100 g, 0.355 mmol) in DMF (1.0 mL) was cooled to 0 °C, treated with Et_3N (50.0 μL , 0.355 mmol), and 4-chlorobenzenesulfonyl chloride (0.075 g, 0.355 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with saturated aqueous NaCl (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl

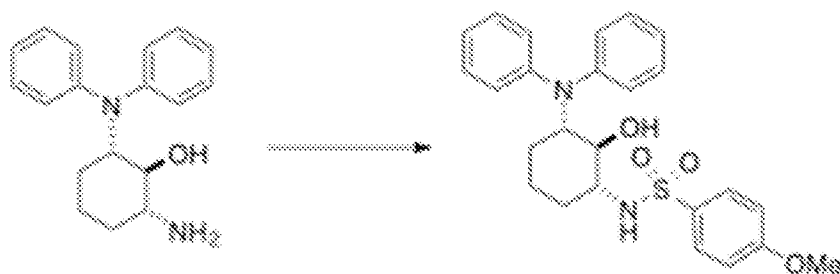
acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.099 g, 84%). ^1H NMR (600 MHz, CDCl_3) δ 7.85 (2H, dd, $J = 8.4, 1.8$ Hz), 7.48 (2H, dd, $J = 8.4, 1.8$ Hz), 7.27 (4H, td, $J = 8.4, 1.8$ Hz), 7.04 (2H, t, $J = 7.2$ Hz), 6.89 (4H, d, $J = 8.4$ Hz), 4.94 (1H, d, $J = 3.6$ Hz), 3.78-3.82 (1H, m), 3.15 (1H, t, $J = 9.0$ Hz), 3.07-3.13 (1H, m), 2.80 (1H, s), 2.05-2.08 (1H, m), 1.97-2.00 (1H, m), 1.70-1.73 (1H, m), 1.31-1.39 (1H, m), 1.16-1.24 (1H, m), 1.08-1.14 (1H, m); ^{13}C NMR (150 MHz, CDCl_3) δ 152.3, 146.7, 139.0, 129.63, 129.60, 123.7, 123.2, 121.3, 121.0, 100.2, 73.4, 61.9, 59.2, 31.7, 28.1, 22.4; LCMS m/z 457.1428 ($[\text{M} + \text{H}^+]$, $\text{C}_{25}\text{H}_{26}\text{ClN}_3\text{O}_3\text{S}$ requires 457.1347).



Example 12

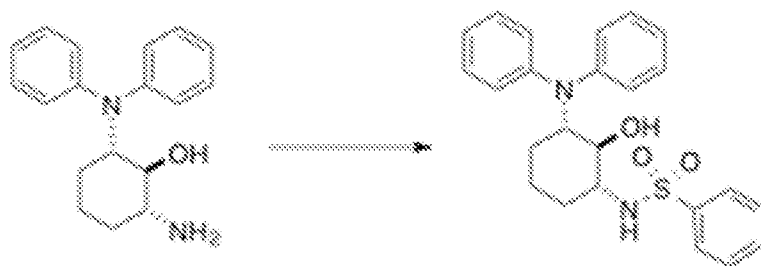
[00141] **rac-4-cyano-N-((1S,2S,3R)-3-(diphenylamino)-2-**

hydroxycyclohexyl)benzenesulfonamide. A solution of rac-(1R,2S,6R)-2-amino-6-(diphenylamino)cyclohexanol (0.060 g, 0.212 mmol) in CH_2Cl_2 (1.0 mL) was cooled to 0 °C, treated with Et_3N (29.4 μL , 0.212 mmol), and 4-cyanobenzenesulfonyl chloride (0.043 g, 0.212 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture purified by flash chromatography (SiO_2 , 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.059 g, 62%). ^1H NMR (600 MHz, CDCl_3) δ 8.02 (2H, d, $J = 8.4$ Hz), 7.77 (2H, d, $J = 8.4$ Hz), 7.26 (4H, t, $J = 7.2$ Hz), 7.04 (2H, t, $J = 7.2$ Hz), 6.88 (4H, d, $J = 7.8$ Hz), 5.20 (1H, d, $J = 4.8$ Hz), 3.79 (1H, ddd, $J = 12.6, 9.0, 3.6$ Hz), 3.15-3.19 (2H, m), 2.93 (1H, s), 1.97-2.02 (2H, m), 1.71 (1H, doublet of quintets, $J = 14.4, 3.0$ Hz), 1.38 (1H, qt, $J = 13.2, 3.6$ Hz), 1.17 (1H, qd, $J = 13.2, 3.6$ Hz), 1.06 (1H, qd, $J = 12.0, 3.6$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 146.7, 145.1, 132.9, 129.6, 128.1, 123.6, 123.2, 117.6, 116.3, 73.9, 61.9, 59.3, 31.9, 27.9, 22.4; LCMS m/z 448.1681 ($[\text{M} + \text{H}^+]$, $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ requires 448.1689).



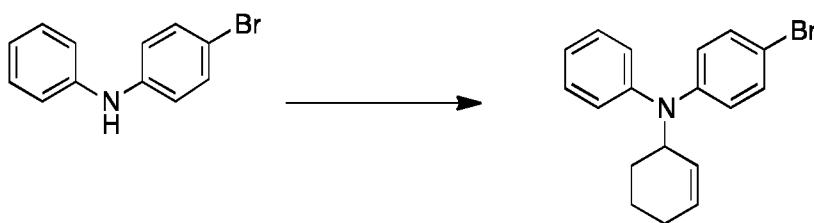
Example 13

[00142] **rac-N-((1S,2S,3R)-3-(diphenylamino)-2-hydroxycyclohexyl)-4-methoxybenzenesulfonamide.** A solution of rac-(1R,2S,6R)-2-amino-6-(diphenylamino)cyclohexanol (0.060 g, 0.212 mmol) in CH₂Cl₂ (1.0 mL) was cooled to 0 °C, treated with Et₃N (29.4 μL, 0.212 mmol), and 4-methoxybenzenesulfonyl chloride (0.044 g, 0.212 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.084 g, 88%). ¹H NMR (600 MHz, CDCl₃) δ 7.83 (2H, d, *J* = 8.4 Hz), 7.27 (4H, t, *J* = 7.8 Hz), 7.03 (2H, t, *J* = 7.2 Hz), 6.98 (2H, d, *J* = 9.0 Hz), 6.89 (4H, d, *J* = 7.2 Hz), 4.83 (1H, d, *J* = 4.8 Hz), 3.88 (3H, s), 3.81 (1H, ddd, *J* = 12.6, 9.6, 3.6 Hz), 3.14 (1H, td, *J* = 9.6, 1.8 Hz), 3.02-3.07 (1H, m), 2.79 (1H, s), 2.01-2.06 (1H, m), 1.96-1.99 (1H, m), 1.69 (1H, doublet of quintets, *J* = 13.8, 3.0 Hz), 1.35 (1H, qt, *J* = 13.8, 3.6 Hz), 1.18 (1H, qd, *J* = 13.2, 3.6 Hz), 1.06 (1H, qd, *J* = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 163.1, 146.7, 131.9, 129.60, 129.53, 123.6, 122.9, 114.4, 74.0, 61.7, 59.1, 55.8, 31.5, 28.2, 22.5; LCMS *m/z* 453.1832 ([*M* + *H*⁺], C₂₅H₂₈N₂O₄S requires 453.1843).



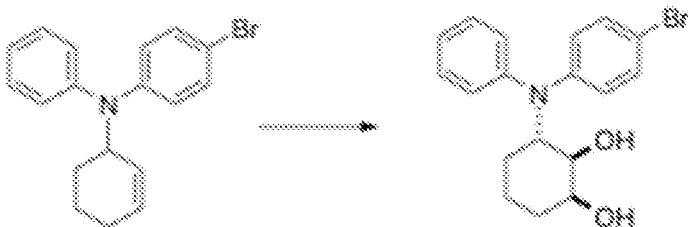
Example 14

[00143] **rac-N-((1S,2S,3R)-3-(diphenylamino)-2-hydroxycyclohexyl)benzenesulfonamide**. A solution of rac-(1R,2S,6R)-2-amino-6-(diphenylamino)cyclohexanol (0.060 g, 0.212 mmol) in CH₂Cl₂ (1.0 mL) was cooled to 0 °C, treated with Et₃N (29.4 μL, 0.212 mmol), and benzenesulfonyl chloride (27.1 μL, 0.212 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.057 g, 64%). ¹H NMR (600 MHz, CDCl₃) δ 7.92 (2H, d, *J* = 8.4 Hz), 7.59 (1H, t, *J* = 7.2 Hz), 7.53 (2H, t, *J* = 7.8 Hz), 7.25-7.28 (4H, m), 7.04 (2H, t, *J* = 7.2 Hz), 6.89 (4H, d, *J* = 8.4 Hz), 4.90 (1H, d, *J* = 4.8 Hz), 3.81 (1H, ddd, *J* = 12.6, 9.6, 3.6 Hz), 3.16 (1H, t, *J* = 9.6 Hz), 3.07-3.12 (1H, m), 2.78 (1H, s), 2.03-2.05 (1H, m), 1.96-1.99 (1H, m), 1.69 (1H, doublet of quintets, *J* = 13.8, 3.0 Hz), 1.35 (1H, qt, *J* = 13.2, 3.6 Hz), 1.18 (1H, qd, *J* = 12.6, 3.6 Hz), 1.09 (1H, qd, *J* = 12.6, 4.2 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 146.7, 140.4, 132.9, 129.6, 127.4, 125.1, 123.6, 123.0, 74.0, 61.8, 59.2, 31.5, 28.2, 22.4; LCMS *m/z* 423.1730 ([*M* + *H*]⁺, C₂₄H₂₆N₂O₃S requires 423.1737).



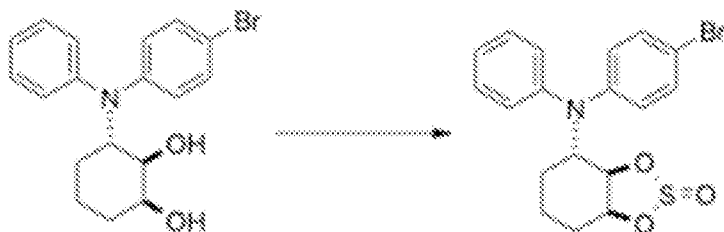
[00144] **4-bromo-N-(cyclohex-2-en-1-yl)-N-phenylaniline**. A solution of 4-bromo-N-phenylaniline (5.00 g, 20.2 mmol) in DMF (5.0 mL) was cooled to 0 °C, treated with sodium hydride (60% wt. suspension in mineral oil, 0.976 g, 24.2 mmol), stirred for 15 minutes, then treated with 3-bromocyclohexene (2.55 mL, 22.2 mmol). The mixture was warmed to 25 °C, stirred for 14 h, then poured over a solution of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The organic layers were combined, washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash

chromatography (SiO₂, 5% ethyl acetate-hexanes) to afford the title compound as a clear oil (8.11 g, 99%). ¹H NMR (600 MHz, CDCl₃) δ 7.31 (4H, m), 7.09 (1H, t, *J* = 7.8 Hz), 7.00 (2H, d, *J* = 7.2 Hz), 6.75 (2H, dt, *J* = 9.0, 2.4 Hz), 5.80-5.85 (2H, m), 4.63 (1H, br s), 1.97-2.00 (3H, m), 1.76-1.80 (1H, m), 1.64-1.72 (3H, m); ¹³C NMR (150 MHz, CDCl₃) δ 146.9, 146.5, 132.1, 130.0, 129.7, 129.5, 125.0, 123.4, 122.5, 113.0, 56.1, 27.7, 25.0, 22.1; LCMS *m/z* 328.0686 ([M + H]⁺, C₁₈H₁₈BrN requires 328.0695).



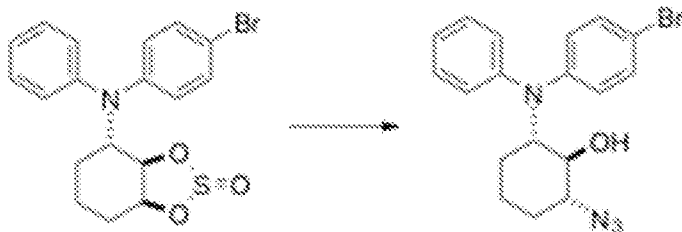
[00145] **rac-(1R,2S,3R)-3-((4-bromophenyl)(phenyl)amino)cyclohexane-1,2-diol.**

A solution of 4-bromo-N-(cyclohex-2-en-1-yl)-N-phenylaniline (8.11 g, 24.7 mmol) in t-BuOH-H₂O 5:1 (30.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in t-BuOH, 3.10 mL, 0.247 mmol) and N-methyl morpholine N-oxide (3.18 g, 27.2 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (20 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a white solid (6.09 g, 68%). ¹H NMR (600 MHz, CDCl₃) δ 7.32-7.35 (4H, m), 7.14 (1H, t, *J* = 7.2 Hz), 7.01 (2H, d, *J* = 8.4 Hz), 6.76 (2H, d, *J* = 8.4 Hz), 4.24 (1H, td, *J* = 13.2, 3.0 Hz), 4.15 (1H, br s), 3.34 (1H, dt, *J* = 10.2, 2.4 Hz), 2.90 (1H, d, *J* = 2.4 Hz), 2.69 (1H, br s), 1.96-2.01 (1H, m), 1.89-1.94 (1H, m), 1.84 (1H, qt, *J* = 14.4, 3.6 Hz), 1.53-1.55 (1H, m), 1.24-1.32 (1H, m), 1.14 (1H, qd, *J* = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 147.2, 145.6, 132.3, 129.8, 125.7, 124.4, 123.2, 114.3, 73.3, 69.5, 57.6, 30.1, 28.2, 19.3; LCMS *m/z* 362.0734 ([M + H]⁺, C₁₈H₂₀BrNO₂ requires 362.0750).



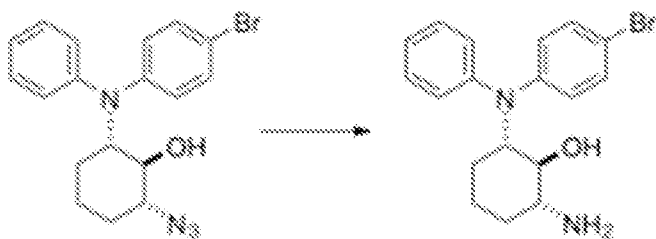
[00146] **rac-(3aS,4R,7aR)-4-((4-**

bromophenyl)(phenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide. A solution of (1R,2S,3R)-3-((4-bromophenyl)(phenyl)amino)cyclohexane-1,2-diol (6.09 g, 16.8 mmol) in CH₂Cl₂ (50.0 mL) at 0 °C was treated dropwise with triethylamine (18.6 mL, 134.5 mmol), and SOCl₂ (3.66 mL, 50.4 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), saturated aqueous sodium chloride (100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes to afford the title compound as an orange solid (5.55 g, 81%). ¹H NMR (600 MHz, CDCl₃) δ (as a mixture of sulfite diastereomers) 7.38-7.42 (2H, m), 7.34 (1H, d, *J* = 9.0 Hz), 7.31 (1H, d, *J* = 9.0 Hz), 7.21 (1H, q, *J* = 7.8 Hz), 7.08 (1H, d, *J* = 7.2 Hz), 7.01 (1H, d, *J* = 7.8 Hz), 6.72 (1H, d, *J* = 9.0 Hz), 6.65 (1H, d, *J* = 9.0 Hz), 1H[5.10-5.12 (m), 4.63-4.65 (m)], 1H[4.83 (ddd, *J* = 13.2, 9.6, 3.6 Hz), 3.92 (ddd, *J* = 13.2, 9.6, 3.6 Hz)], 1H[4.54 (dd, *J* = 9.6, 4.8 Hz), 4.31 (dd, *J* = 10.2, 5.4 Hz)], 2.33-2.39 (1H, m), 2.12-2.17 (1H, m), 1H[1.87 (qt, *J* = 13.2, 3.6 Hz), 1.64 (tt, *J* = 14.4, 4.8 Hz),], 1.70-1.83 (2H, m), 1.22-1.34 (1H, m); LCMS *m/z* 410.0229 ([M + H⁺], C₁₈H₁₈BrNO₃S requires 410.0224).

[00147] **rac-(1S,2S,6R)-2-azido-6-((4-bromophenyl)(phenyl)amino)cyclohexanol**.

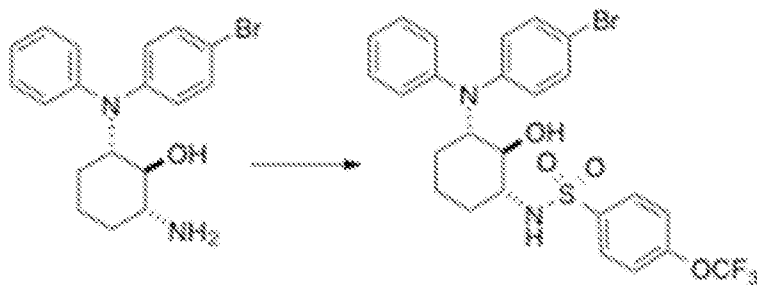
A solution of (3aS,4R,7aR)-4-((4-bromophenyl)(phenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide (5.55 g, 13.6 mmol) in DMF (7.0 mL) was treated with sodium azide (2.65 g, 40.7 mmol), and heated to 110 °C under microwave irradiation for 14 h. The mixture was diluted with CH₂Cl₂ (200 mL) and this organic layer was washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as a white solid (2.80 g, 53%). ¹H NMR (600 MHz, CDCl₃) δ 7.32-7.36 (4H, m), 7.16 (1H, t, *J* = 7.2 Hz), 7.01 (2H, d, *J* = 7.8 Hz), 6.75 (2H, dt, *J* = 10.2,

3.6 Hz), 3.87 (1H, ddd, $J = 12.6, 9.6, 3.6$ Hz), 3.44 (1H, ddd, $J = 12.6, 9.0, 4.8$ Hz), 3.27 (1H, t, $J = 9.6$ Hz), 2.76 (1H, br s), 1.99-2.02 (1H, m), 1.82 (1H, doublet of quintets, $J = 13.8, 3.6$ Hz), 1.46 (1H, qt, $J = 13.8, 3.6$ Hz), 1.21 (1H, sextet of doublets, $J = 13.2, 4.2$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 146.9, 145.1, 132.3, 129.8, 125.8, 124.5, 122.8, 114.1, 75.3, 66.0, 61.5, 29.8, 28.2, 22.3; LCMS m/z 387.0805 ($[\text{M} + \text{H}^+]$, $\text{C}_{18}\text{H}_{19}\text{BrN}_4\text{O}$ requires 387.0815).



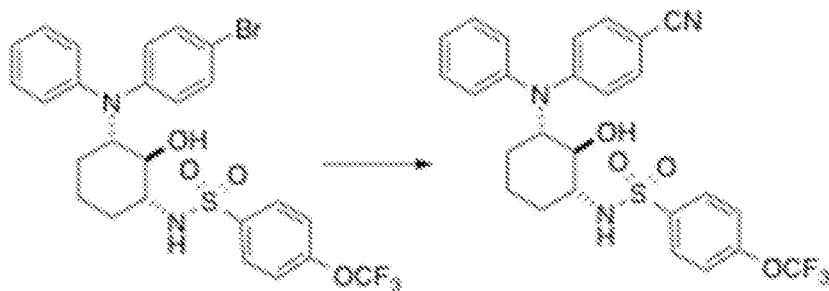
[00148] **rac-(1R,2S,6R)-2-amino-6-((4-bromophenyl)(phenyl)amino)cyclohexanol.**

A solution of (1S,2S,6R)-2-azido-6-((4-bromophenyl)(phenyl)amino)cyclohexanol (2.80 g, 7.24 mmol) in THF (8.0 mL) was cooled to 0 °C, treated with PPh_3 (2.47 g, 9.41 mmol), H_2O (1.0 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% $\text{MeOH}-\text{CH}_2\text{Cl}_2$ to remove triphenylphosphine oxide and 17:2:1 $\text{CH}_2\text{Cl}_2:\text{MeOH}:\text{NH}_4\text{OH}$ to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as beige oil (2.94 g, 99%). ^1H NMR (600 MHz, CDCl_3) δ 7.30-7.33 (4H, m), 7.12 (1H, t, $J = 7.2$ Hz), 7.02 (2H, d, $J = 7.8$ Hz), 6.75 (2H, d, $J = 8.4$ Hz), 3.83 (1H, ddd, $J = 9.6, 8.4, 6.0$ Hz), 3.00 (1H, t, $J = 9.0$ Hz), 2.71 (1H, td, $J = 12.6, 4.2$ Hz), 2.05-2.25 (2H, br m), 1.96-1.99 (1H, m), 1.79-1.82 (1H, m), 1.72 (1H, doublet of quintets, $J = 13.2, 4.2$ Hz), 1.43 (1H, qt, $J = 13.8, 4.2$ Hz), 1.24 (1H, qd, $J = 13.2, 3.6$ Hz), 1.00 (1H, qd, $J = 13.2, 3.6$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 147.2, 145.5, 132.2, 129.7, 125.9, 124.2, 122.8, 113.7, 77.2, 61.8, 56.6, 33.8, 28.8, 23.0; LCMS m/z 361.0901 ($[\text{M} + \text{H}^+]$, $\text{C}_{18}\text{H}_{21}\text{BrN}_2\text{O}$ requires 361.0910).



Example 2

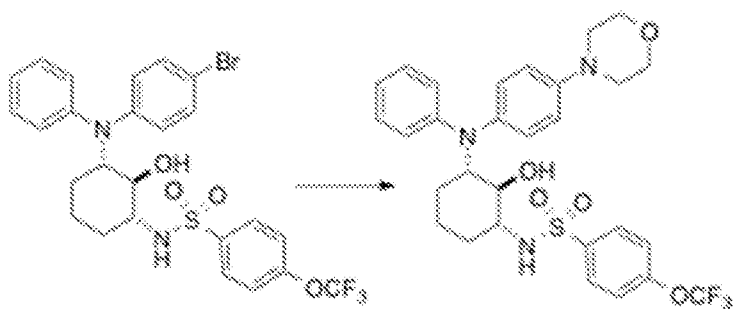
[00149] **rac-N-((1S,2S,3R)-3-((4-bromophenyl)(phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide**. A solution of (1R,2S,6R)-2-amino-6-((4-bromophenyl)(phenyl)amino)cyclohexanol (1.32 g, 3.65 mmol) in CH₂Cl₂ (5.0 mL) was cooled to 0 °C, treated with Et₃N (0.532 mL, 3.84 mmol), and 4-(trifluoromethoxy)benzenesulfonyl chloride (0.652 mL, 3.84 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes) to afford the title compound as a white solid (1.75 g, 82%). mp. 116-117 °C (ethyl acetate-hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.96 (2H, d, *J* = 9.0 Hz), 7.30-7.34 (6H, m), 7.14 (1H, t, *J* = 7.8 Hz), 6.95 (2H, d, *J* = 8.4 Hz), 6.70 (2H, d, *J* = 8.4 Hz), 5.02 (1H, d, *J* = 4.2 Hz), 3.75-3.80 (1H, m), 3.13-3.17 (2H, m), 2.83 (1H, s), 1.94-1.99 (2H, m), 1.71 (1H, doublet of quintets, *J* = 13.8, 3.0 Hz), 1.33 (1H, qt, *J* = 13.8, 3.6 Hz), 1.18 (1H, qd, *J* = 13.2, 4.2 Hz), 1.05-1.11 (1H, m); ¹³C NMR (150 MHz, CDCl₃) δ 152.3, 146.8, 145.1, 138.9, 132.3, 129.8, 129.6, 125.8, 124.6, 123.0, 121.0, 119.6, 114.4, 74.0, 61.8, 59.2, 31.6, 28.1, 22.4; LCMS *m/z* 587.0634 ([M + H]⁺, C₂₅H₂₄BrF₃N₂O₄S requires 587.0645).



Example 6

[00150] **rac-N-((1S,2S,3R)-3-((4-cyanophenyl)(phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide**. A solution of N-

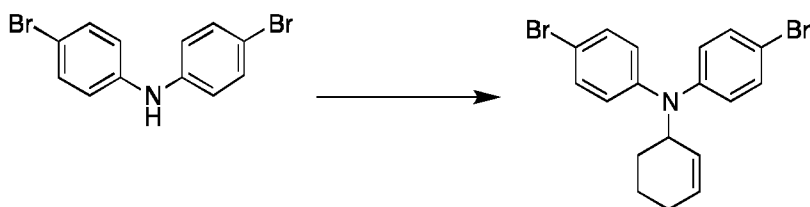
((1S,2S,3R)-3-((4-bromophenyl)(phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.100 g, 0.171 mmol) in NMP (1.0 mL) was treated with copper (I) cyanide (0.0320 g, 0.359 mmol) and heated to 200 °C for 5 h. The mixture was cooled to 25 °C, diluted with CH₂Cl₂ (50 mL) and washed with H₂O ((3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a beige film (0.0747 g, 82%). ¹H NMR (600 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 9.0 Hz), 7.45 (2H, t, *J* = 5.4 Hz), 7.39 (1H, t, *J* = 7.2 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 7.27 (2H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 8.4 Hz), 6.52 (2H, d, *J* = 9.6 Hz), 5.30 (1H, d, *J* = 6.6 Hz), 3.95 (1H, ddd, *J* = 12.6, 9.0, 3.6 Hz), 3.18-3.21 (1H, m), 3.14-3.18 (1H, m), 3.08 (1H, d, *J* = 2.4 Hz), 1.92-1.94 (1H, m), 1.69-1.76 (1H, m), 1.67 (1H, doublet of quintets, *J* = 14.4, 3.0 Hz), 1.32 (1H, qt, *J* = 13.2, 3.6 Hz); 1.18-1.23 (1H, m), 1.04 (1H, qd, *J* = 12.6, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 153.2, 152.4, 140.4, 138.8, 133.4, 131.5, 130.3, 129.5, 128.3, 121.1, 120.5, 119.5, 113.9, 98.8, 74.0, 61.0, 59.2, 31.4, 29.1, 22.4; LCMS *m/z* 532.1513 ([*M* + *H*⁺], C₂₆H₂₄F₃N₃O₄S requires 532.1512).



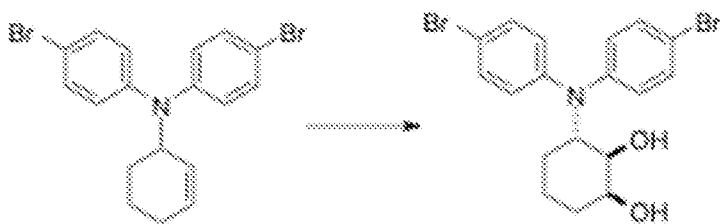
Example 10

[00151] **rac-N-((1S,2S,3R)-2-hydroxy-3-((4-morpholinophenyl)(phenyl)amino)cyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of N-((1S,2S,3R)-3-((4-bromophenyl)(phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.0500 g, 0.0854 mmol) in toluene (1.0 mL) was treated with bis(dibenzylideneacetone)palladium(0) (0.78 mg, 0.854 μmol), Xphos (0.81 mg, 1.71 μmol), potassium tert-butoxide (0.0134 g, 0.120 mmol), and morpholine (11.2 μL, 0.128 mmol). The mixture was degassed with a stream of Ar (g), then heated to 150 °C under microwave irradiation for 0.5 h. The mixture was applied directly to a column and purified by flash chromatography (SiO₂, 0-40% ethyl acetate-hexanes) to afford the title compound as a yellow film (0.0296 g, 58%). ¹H NMR (600 MHz, CDCl₃) δ 7.96 (2H, d, *J* = 9.0 Hz), 7.32 (2H, t, *J* = 8.4 Hz), 7.14 (2H, t, *J* = 7.8 Hz), 7.00 (2H, d, *J* = 9.0 Hz), 6.90

(2H, d, $J = 9.0$ Hz), 6.78 (1H, t, $J = 7.8$ Hz), 6.66 (2H, d, $J = 8.4$ Hz), 5.05 (1H, d, $J = 3.6$ Hz), 3.87 (4H, dd, $J = 9.6, 5.4$ Hz), 3.77 (1H, ddd, $J = 12.6, 9.0, 3.6$ Hz), 3.18 (4H, dd, $J = 9.6, 4.8$ Hz), 3.10-3.14 (1H, m), 2.86 (1H, br s), 2.05-2.08 (1H, m), 1.95-1.98 (1H, m), 1.71 (1H, doublet of quintets, $J = 14.4, 3.0$ Hz), 1.37 (1H, qt, $J = 13.8, 3.6$ Hz); 1.17-1.23 (1H, m), 1.11 (1H, qd, $J = 13.2, 3.6$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 149.9, 149.5, 138.9, 135.2, 130.6, 129.6, 129.2, 126.9, 123.8, 120.9, 119.4, 117.0, 116.4, 73.9, 67.1, 61.7, 59.1, 49.3, 31.7, 27.9, 22.4; LCMS m/z 592.2083 ($[\text{M} + \text{H}^+]$, $\text{C}_{29}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_5\text{S}$ requires 592.2088).

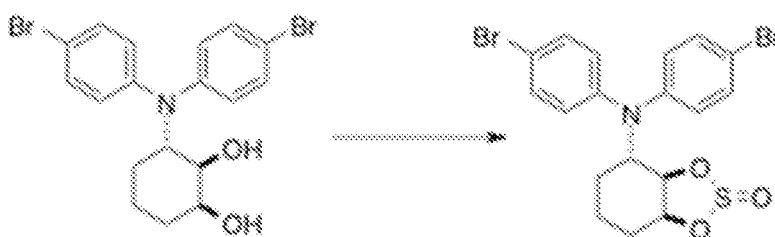


[00152] **4-bromo-N-(4-bromophenyl)-N-(cyclohex-2-en-1-yl)aniline**. A solution of bis(4-bromophenyl)amine (5.00 g, 15.3 mmol) in DMF (30.0 mL) was cooled to 0 °C, treated with sodium hydride (60% wt. suspension in mineral oil, 0.734 g, 18.4 mmol), stirred for 15 minutes, then treated with 3-bromocyclohexene (1.93 mL, 16.8 mmol). The mixture was warmed to 25 °C, stirred for 14 h, then poured over a solution of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 $\times$ 100 mL). The organic layers were combined, washed with saturated aqueous NaCl (3 $\times$ 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 5% ethyl acetate-hexanes) to afford the title compound as a clear oil (6.00 g, 96%). ^1H NMR (600 MHz, CDCl_3) δ 7.35 (4H, d, $J = 9.0$ Hz), 6.79 (4H, d, $J = 8.4$ Hz), 5.76-5.82 (2H, m), 4.58 (1H, br s), 1.92-2.02 (3H, m), 1.73-1.78 (1H, m), 1.57-1.67 (3H, m); ^{13}C NMR (150 MHz, CDCl_3) δ 146.1, 132.3, 130.4, 129.2, 124.6, 114.9, 56.2, 27.6, 25.0, 21.9; LCMS m/z 407.9779 ($[\text{M} + \text{H}^+]$, $\text{C}_{18}\text{H}_{17}\text{Br}_2\text{N}$ requires 407.9781).



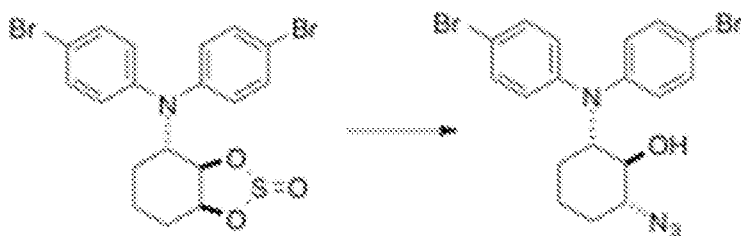
[00153] **rac-(1R,2S,3R)-3-(bis(4-bromophenyl)amino)cyclohexane-1,2-diol**. A solution of 4-bromo-N-(4-bromophenyl)-N-(cyclohex-2-en-1-yl)aniline (6.00 g, 14.7 mmol)

in t-BuOH-H₂O 5:1 (30.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in t-BuOH, 1.84 mL, 0.147 mmol) and N-methyl morpholine N-oxide (1.90 g, 16.2 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (20 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a white solid (5.25 g, 81%). ¹H NMR (600 MHz, CDCl₃) δ 7.39 (4H, t, *J* = 9.0 Hz), 6.83 (4H, d, *J* = 9.0 Hz), 4.22 (1H, td, *J* = 13.2, 3.6 Hz), 4.15 (1H, br s), 3.32 (1H, dt, *J* = 9.6, 3.0 Hz), 2.69 (1H, d, *J* = 3.0 Hz), 2.48 (1H, br s), 1.94 (1H, tt, *J* = 13.2, 3.0 Hz), 1.83 (1H, qt, *J* = 13.8, 3.0 Hz), 1.53-1.56 (1H, m), 1.29 (1H, br t, *J* = 14.4 Hz), 1.14 (1H, qd, *J* = 12.6, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 145.8, 132.6, 125.3, 116.1, 73.2, 69.6, 57.8, 30.1, 28.2, 19.2; LCMS *m/z* 441.9836 ([*M* + *H*⁺], C₁₈H₁₉Br₂NO₂ requires 441.9835).

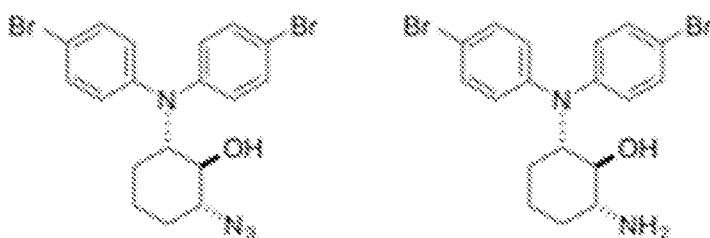


[00154] **rac-(3a*S*,4*R*,7a*R*)-4-(bis(4-**

bromophenyl)amino)hexahydrobenzo[*d*][1,3,2]dioxathiole 2-oxide. A solution of (1*R*,2*S*,3*R*)-3-(bis(4-bromophenyl)amino)cyclohexane-1,2-diol (5.25 g, 11.9 mmol) in CH₂Cl₂ (50.0 mL) at 0 °C was treated dropwise with triethylamine (13.2 mL, 95.3 mmol), and SOCl₂ (2.59 mL, 35.7 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), saturated aqueous sodium chloride (100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as a white solid (5.69 g, 98%). ¹H NMR (600 MHz, CDCl₃) δ (as a mixture of sulfite diastereomers) 7.40 (1H, d, *J* = 9.0 Hz), 6.82 (1H, d, *J* = 9.0 Hz), 4.78 (1H, ddd, *J* = 13.2, 9.6, 3.6 Hz), 4.65-4.67 (1H, m), 4.26 (1H, dd, *J* = 9.6, 4.8 Hz), 2.33-2.36 (1H, m), 2.11-2.14 (1H, m), 1.85 (1H, qt, *J* = 13.2, 3.0 Hz), 1.75-1.77 (1H, m), 1.64 (1H, tt, *J* = 13.2, 4.2 Hz), 1.26 (1H, qd, *J* = 12.6, 3.0 Hz); LCMS *m/z* 487.9349 ([*M* + *H*⁺], C₁₈H₁₇Br₂NO₃S requires 487.9347).

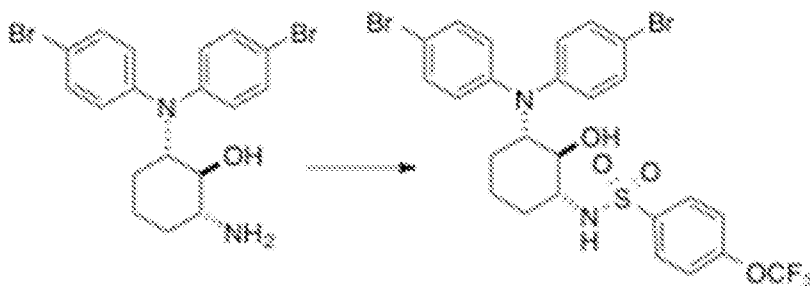


[00155] **rac-(1S,2S,6R)-2-azido-6-(bis(4-bromophenyl)amino)cyclohexanol**. A solution of (3aS,4R,7aR)-4-(bis(4-bromophenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide (5.69 g, 11.7 mmol) in DMF (7.0 mL) was treated with sodium azide (2.284 g, 35.1 mmol), and heated to 110 °C under microwave irradiation for 14 h. The mixture was diluted with CH₂Cl₂ (200 mL) and this organic layer was washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as a beige film (3.70 g, 68%). ¹H NMR (600 MHz, CDCl₃) δ 7.39 (4H, d, *J* = 8.4 Hz), 6.81 (4H, d, *J* = 9.0 Hz), 3.84 (1H, ddd, *J* = 13.2, 10.2, 3.6 Hz), 3.44 (1H, ddd, *J* = 13.2, 9.0, 4.2 Hz), 3.22 (1H, t, *J* = 9.6 Hz), 2.64 (1H, d, *J* = 1.8 Hz), 1.96-2.03 (2H, m), 1.83 (1H, doublet of quintets, *J* = 13.8, 3.6 Hz), 1.45 (1H, qt, *J* = 13.8, 3.0 Hz), 1.17-1.25 (1H, m); ¹³C NMR (150 MHz, CDCl₃) δ 145.4, 132.6, 125.2, 116.1, 75.2, 66.1, 61.4, 29.7, 28.4, 22.3; LCMS *m/z* 466.9906 ([M + H]⁺, C₁₈H₁₈Br₂N₄O requires 466.9900).



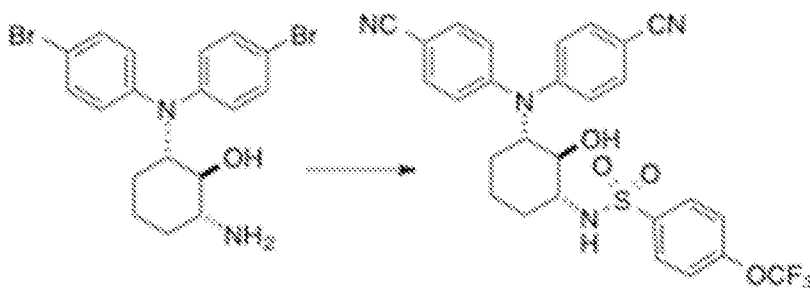
[00156] **rac-(1R,2S,6R)-2-amino-6-(bis(4-bromophenyl)amino)cyclohexanol**. A solution of (1S,2S,6R)-2-azido-6-(bis(4-bromophenyl)amino)cyclohexanol (3.70 g, 7.93 mmol) in THF (8.0 mL) was cooled to 0 °C, treated with PPh₃ (2.71 g, 10.3 mmol), H₂O (1.0 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as beige oil (2.81 g, 81%). ¹H NMR (600 MHz, CDCl₃) δ 7.36

(4H, d, $J = 9.0$ Hz), 6.83 (4H, d, $J = 9.0$ Hz), 3.83 (1H, ddd, $J = 12.6, 9.6, 3.0$ Hz), 2.93 (1H, t, $J = 9.6$ Hz), 2.67 (1H, ddd, $J = 12.0, 9.0, 4.2$ Hz), 1.94-1.96 (1H, m), 1.75-1.83 (1H, m), 1.73 (1H, doublet of quintets, $J = 13.8, 3.0$ Hz), 1.43 (1H, qt, $J = 13.8, 3.6$ Hz), 1.24 (1H, qd, $J = 13.2, 4.2$ Hz), 1.01 (1H, qd, $J = 13.2, 4.2$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 145.7, 132.5, 125.2, 115.6, 76.9, 61.7, 56.6, 34.2, 28.9, 23.0; LCMS m/z 440.9990 ($[\text{M} + \text{H}^+]$, $\text{C}_{18}\text{H}_{20}\text{Br}_2\text{N}_2\text{O}$ requires 440.9995).



Example 3

[00157] **rac-N-((1S,2S,3R)-3-(bis(4-bromophenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide**. A solution of (1R,2S,6R)-2-amino-6-(bis(4-bromophenyl)amino)cyclohexanol (1.30 g, 2.95 mmol) in CH_2Cl_2 (5.0 mL) was cooled to 0 °C, treated with Et_3N (0.430 mL, 3.10 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (0.530 mL, 3.10 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with saturated aqueous NaCl (3 $\times$ 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-35% ethyl acetate-hexanes) to afford the title compound as a white solid (1.51 g, 77%). 151-152 °C (ethyl acetate-hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.95 (2H, d, $J = 9.0$ Hz), 7.36 (4H, d, $J = 8.4$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 6.77 (4H, d, $J = 9.0$ Hz), 5.05 (1H, d, $J = 6.0$ Hz), 3.75 (1H, ddd, $J = 13.2, 9.6, 4.2$ Hz), 3.10-3.20 (2H, m), 2.88 (1H, d, $J = 1.8$ Hz), 1.87-1.94 (2H, m), 1.70 (1H, doublet of quintets, $J = 10.8, 3.0$ Hz), 1.34 (1H, qt, $J = 13.8, 3.0$ Hz), 1.15 (1H, qd, $J = 12.6, 3.6$ Hz), 1.06 (1H, qd, $J = 13.2, 3.6$ Hz); ^{13}C NMR (150 MHz, CDCl_3) δ 152.4, 145.3, 138.9, 132.6, 129.5, 125.2, 121.3, 121.1, 116.1, 74.1, 61.8, 59.2, 31.6, 28.3, 22.4; LCMS m/z 666.9721 ($[\text{M} + \text{H}^+]$, $\text{C}_{25}\text{H}_{23}\text{Br}_2\text{F}_3\text{N}_2\text{O}_4\text{S}$ requires 666.9730).

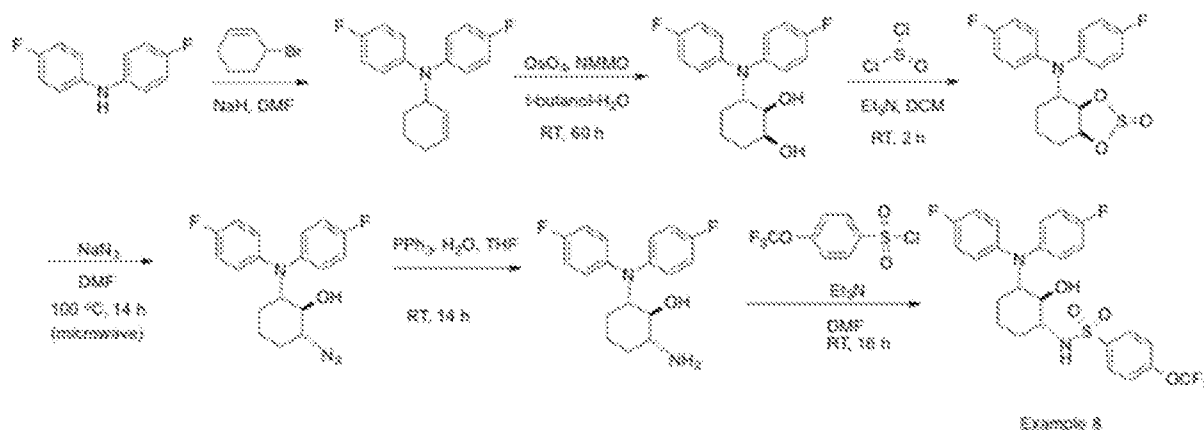


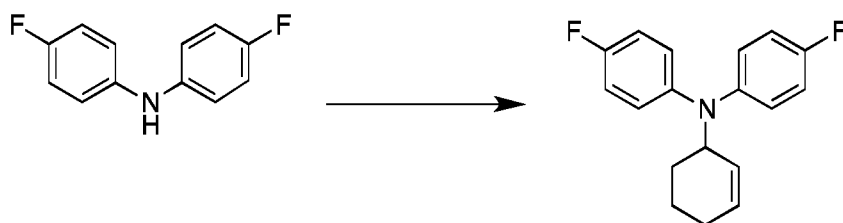
Example 7

[00158] **rac-N-((1*S*,2*S*,3*R*)-3-(bis(4-cyanophenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of *N*-((1*S*,2*S*,3*R*)-3-(bis(4-bromophenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.0500 g, 0.0753 mmol) in NMP (1.0 mL) was treated with copper (I) cyanide (0.0142g, 0.158 mmol) and heated to 200 °C for 5 h. The mixture was cooled to 25 °C, diluted with CH₂Cl₂ (50 mL) and washed with H₂O ((3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a beige film (0.0283 g, 89%). ¹H NMR (600 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 9.0 Hz), 7.57-7.54 (4H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 6.98 (4H, d, *J* = 9.0 Hz), 5.24 (1H, d, *J* = 7.8 Hz), 5.15 (1H, br s), (1H, td, *J* = 12.6, 3.0 Hz), 3.15-3.20 (1H, m), 3.14 (1H, t, *J* = 9.6 Hz), 1.95-1.97 (1H, m), 1.70-1.72 (3H, m), 1.30-1.38 (1H, m), 1.23-1.28 (1H, m), 1.07 (1H, qd, *J* = 12.6, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 152.6, 149.2, 145.2, 138.7, 133.9, 129.4, 128.9, 121.2, 119.3, 118.0, 74.0, 61.6, 59.3, 31.5, 29.2, 22.5; LCMS *m/z* 557.1464 ([*M* + *H*⁺], C₂₇H₂₃F₃N₄O₄S requires 557.1465).

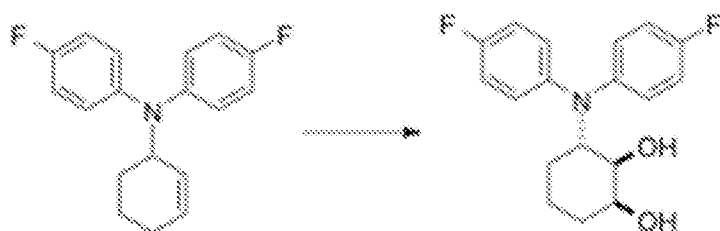
[00159] Synthesis of Example 8

Scheme 3



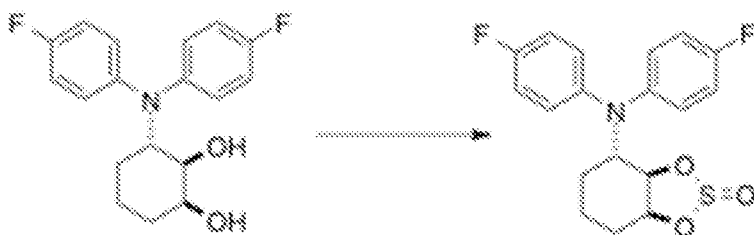


[00160] **N-(cyclohex-2-en-1-yl)-4-fluoro-N-(4-fluorophenyl)aniline.** A solution of bis(4-fluorophenyl)amine (1.40 g, 6.82 mmol) in DMF (5.0 mL) was cooled to 0 °C, treated with sodium hydride (60% wt. suspension in mineral oil, 0.327 g, 8.19 mmol), stirred for 15 minutes, then treated with 3-bromocyclohexene (0.86 mL, 7.50 mmol). The mixture was warmed to 25 °C, stirred for 14 h, then poured over a solution of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The organic layers were combined, washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 5% ethyl acetate-hexanes) to afford the title compound as a clear oil (1.31 g, 67%). ¹H NMR (600 MHz, CDCl₃) δ 6.94-6.97 (4H, m), 6.84-6.86 (4H, m), 5.81 (2H, br s), 4.55-4.57 (1H, m), 1.94-2.01 (3H, m), 1.73-1.78 (1H, m), 1.63-1.70 (1H, m), 1.55-1.62 (2H, m); ¹³C NMR (150 MHz, CDCl₃) δ 158.4 (*J* = 966 Hz), 143.7 (*J* = 12 Hz), 130.2, 129.6, 124.2 (*J* = 36 Hz), 115.9 (*J* = 84 Hz), 56.1, 27.8, 25.1, 22.0; LCMS *m/z* 286.1393 ([*M* + *H*⁺], C₁₈H₁₇F₂N requires 286.1402).

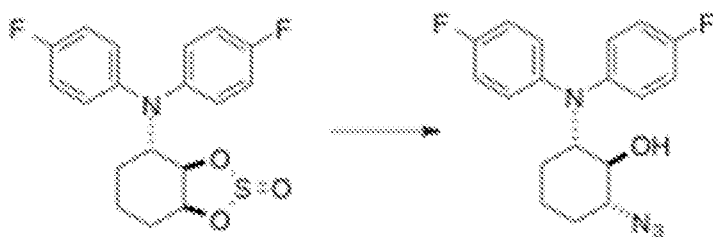


[00161] **rac-(1R,2S,3R)-3-(bis(4-fluorophenyl)amino)cyclohexane-1,2-diol.** A solution of N-(cyclohex-2-en-1-yl)-4-fluoro-N-(4-fluorophenyl)aniline (1.31 g, 4.59 mmol) in t-BuOH-H₂O 5:1 (6.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in t-BuOH, 0.57 mL, 0.0459 mmol) and N-methyl morpholine N-oxide (0.593 g, 5.05 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (5 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a beige film (0.655 g, 45%). ¹H NMR (600 MHz, CDCl₃) δ 6.98 (4H, t, *J* = 7.8 Hz), 6.89-

6.92 (4H, m), 4.15-4.17 (1H, m), 3.30 (1H, dt, $J = 10.2, 1.8$ Hz), 2.94 (1H, d, $J = 1.8$ Hz), 2.60 (1H, br s), 1.96-2.00 (1H, m), 1.90-1.94 (1H, m), 1.85 (1H, qt, $J = 13.2, 3.6$ Hz), 1.53-1.56 (1H, m), 1.25-1.31 (1H, m), 1.11 (1H, qd, $J = 13.2, 3.6$ Hz); LCMS m/z 320.1445 ($[M + H]^+$, $C_{18}H_{19}F_2NO_2$ requires 320.1457).

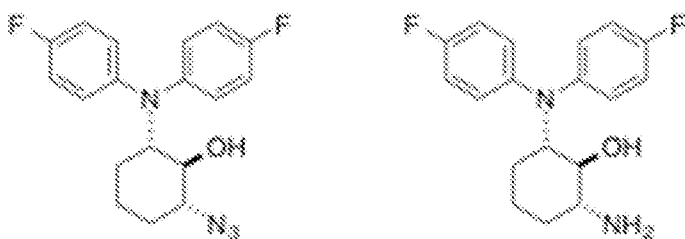


[00162] **rac-(3aS,4R,7aR)-4-(bis(4-fluorophenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide**. A solution of (1R,2S,3R)-3-(bis(4-fluorophenyl)amino)cyclohexane-1,2-diol (0.655 g, 2.05 mmol) in CH_2Cl_2 (10.0 mL) at 0 °C was treated dropwise with triethylamine (2.27 mL, 16.4 mmol), and $SOCl_2$ (0.45 mL, 6.15 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH_2Cl_2 (3×100 mL). The combined organic layers were washed with water (2×100 mL), saturated aqueous sodium chloride (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-10% ethyl acetate-hexanes to afford the title compound as a brown solid (0.689 g, 92%). ^1H NMR (600 MHz, $CDCl_3$) δ (as a mixture of sulfite diastereomers) 6.98-7.02 (4H, m), 6.89 (2H, dd, $J = 8.4, 4.2$ Hz), 6.83 (2H, dd, $J = 9.0, 4.8$ Hz), 1H[5.12 (br s), 4.67 (br s)], 1H[4.76 (ddd, $J = 13.8, 10.2, 4.2$ Hz), 3.84 (ddd, $J = 12.6, 9.6, 3.0$ Hz)], 1H[4.50 (dd, $J = 9.6, 4.8$ Hz), 4.26 (dd, $J = 10.2, 7.2$ Hz)], 2.36 (1H, br t, $J = 15.6$ Hz), 2.11-2.16 (1H, m), 1.62-1.89 (3H, m), 1.20-1.28 (1H, m); LCMS m/z 366.0972 ($[M + H]^+$, $C_{18}H_{17}F_2NO_3S$ requires 366.0970).



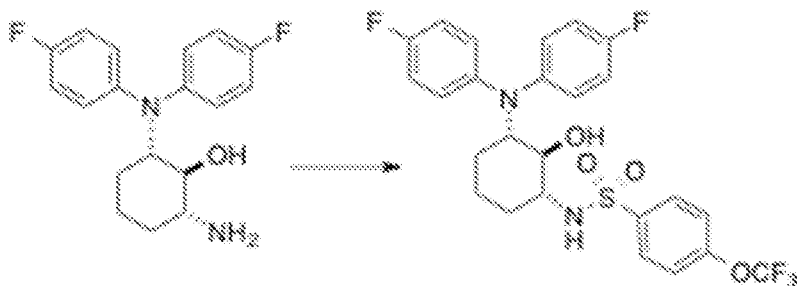
[00163] **rac-(1S,2S,6R)-2-azido-6-(bis(4-fluorophenyl)amino)cyclohexanol**. A solution of (3aS,4R,7aR)-4-(bis(4-

fluorophenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide (0.669 g, 1.83 mmol) in DMF (3.0 ml) was treated with sodium azide (0.358 g, 5.49 mmol), and heated to 110 °C under microwave irradiation for 14 h. The mixture was diluted with CH₂Cl₂ (200 mL) and this organic layer was washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as a beige foam (0.334 g, 53%). ¹H NMR (600 MHz, CDCl₃) δ 6.99 (4H, t, *J* = 9.0 Hz), 6.90 (4H, dd, *J* = 9.0, 4.8 Hz), 3.79 (1H, ddd, *J* = 13.2, 9.6, 3.6 Hz), 3.45 (1H, ddd, *J* = 13.2, 9.0, 4.2 Hz), 3.23 (1H, t, *J* = 9.6 Hz), 2.81 (1H, br s), 1.99-2.02 (2H, m), 1.84 (1H, doublet of quintets, *J* = 13.8, 3.0 Hz), 1.45 (1H, qt, *J* = 13.8, 3.0 Hz), 1.20 (1H, qt, *J* = 13.2, 4.2 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 159.0 (*J* = 972 Hz), 143.0, 125.0 (*J* = 30 Hz), 116.2 (*J* = 90 Hz), 75.3, 66.0, 62.1, 29.8, 28.1, 22.3; LCMS *m/z* 345.1530 ([M + H]⁺, C₁₈H₁₈F₂N₄O requires 345.1521).



[00164] **rac-(1R,2S,6R)-2-amino-6-(bis(4-fluorophenyl)amino)cyclohexanol.** A solution of (1S,2S,6R)-2-azido-6-(bis(4-fluorophenyl)amino)cyclohexanol (0.334 g, 0.970 mmol) in THF (3.0 mL) was cooled to 0 °C, treated with PPh₃ (0.331 g, 1.26 mmol), H₂O (1.0 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as beige oil (0.276 g, 89%). ¹H NMR (600 MHz, CDCl₃) δ 6.94 (4H, d, *J* = 8.4 Hz), 6.89 (4H, dd, *J* = 9.0, 4.8 Hz), 3.75 (1H, ddd, *J* = 13.2, 9.6, 3.6 Hz), 3.13 (3H, m), 2.99 (1H, t, *J* = 9.6 Hz), 2.73 (1H, ddd, *J* = 12.6, 9.0, 3.6 Hz), 2.36 (1H, s), 1.94-1.96 (1H, m), 1.77-1.82 (1H, m), 1.70 (1H, doublet of quintets, *J* = 10.8, 3.0 Hz), 1.40 (1H, qt, *J* = 13.2, 3.0 Hz), 1.19 (1H, qd, *J* = 13.2, 3.6 Hz), 1.00 (1H, qd, *J* = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 158.6 (*J* = 966 Hz), 143.2 (*J* = 12 Hz), 124.7 (*J* = 30 Hz),

116.0 ($J = 90$ Hz), 76.5, 61.9, 56.4, 33.1, 28.6, 22.8; LCMS m/z 319.1636 ($[M + H]^+$, $C_{18}H_{20}F_2N_2O$ requires 319.1616).

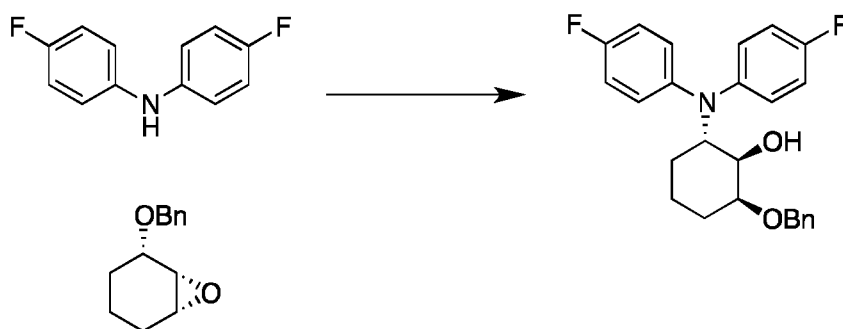
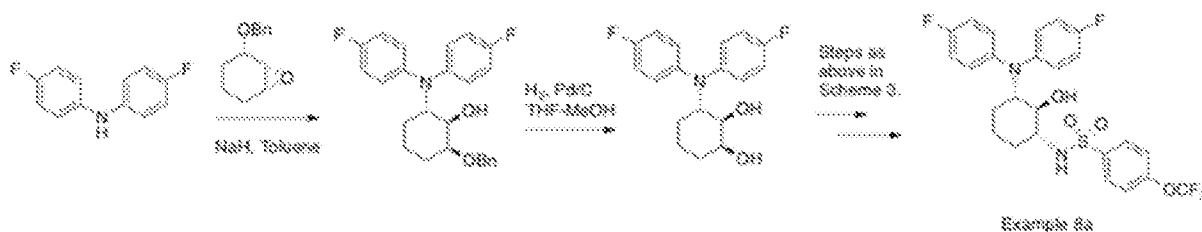


Example 8

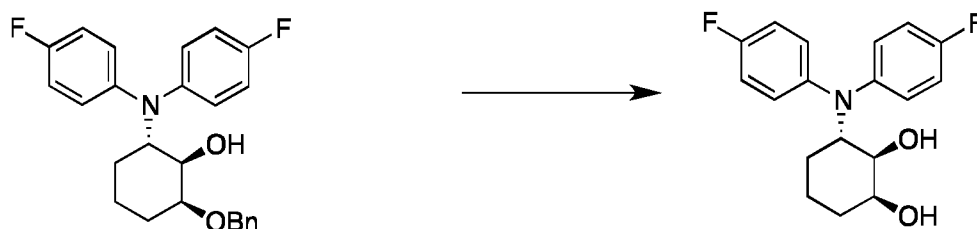
[00165] **rac-N-((1S,2S,3R)-3-(bis(4-fluorophenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide**. A solution of (1*R*,2*S*,6*R*)-2-amino-6-(bis(4-fluorophenyl)amino)cyclohexanol (0.0500 g, 0.157 mmol) in CH_2Cl_2 (5.0 mL) was cooled to 0 °C, treated with Et_3N (22.9 μ L, 0.165 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (28.0 μ L, 0.165 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with saturated aqueous NaCl (3 $\times$ 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-35% ethyl acetate-hexanes) to afford the title compound as a white solid (0.066 g, 78%). mp. 144-145 °C (ethyl acetate-hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ 7.96 (2H, dt, $J = 9.0, 2.4$ Hz), 7.34 (2H, d, $J = 8.4$ Hz), 6.96 (4H, t, $J = 8.4$ Hz), 6.84 (4H, dd, $J = 9.0, 4.8$ Hz), 4.98 (1H, d, $J = 5.4$ Hz), 3.70 (1H, ddd, $J = 13.2, 9.6, 4.2$ Hz), 3.13-3.18 (1H, m), 3.08-3.13 (1H, m), 2.90 (1H, d, $J = 1.8$ Hz), 1.92-2.00 (2H, m), 1.72 (1H, doublet of quintets, $J = 14.4, 3.6$ Hz), 1.36 (1H, qt, $J = 13.2, 3.6$ Hz), 1.12 (1H, sextet of doublets, $J = 13.2, 3.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0 ($J = 966$ Hz), 152.3, 143.0 ($J = 18$ Hz), 138.9, 129.6, 125.0 ($J = 30$ Hz), 121.3, 121.2, 116.3 ($J = 90$ Hz), 74.1, 62.4, 59.2, 33.7, 27.9, 22.4; LCMS m/z 543.1373 ($[M + H]^+$, $C_{25}H_{23}F_5N_2O_4S$ requires 543.1371).

[00166] Chirally enriched examples may be prepared by epoxide opening of known optically pure 2-(benzyloxy)-7-oxabicyclo[4.1.0]heptane with the appropriate diaryl amine, for example:

Scheme 4

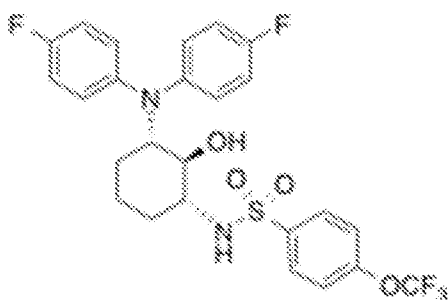


[00167] **(1R,2S,6S)-2-(benzyloxy)-6-(bis(4-fluorophenyl)amino)cyclohexanol**. A solution of bis(4-fluorophenyl)amine (0.500 g, 2.41 mmol) in toluene (8.0 mL) was treated with sodium hydride (60% dispersion in mineral oil (0.193 g, 4.83 mmol) and (1R,2S,6R)-2-(benzyloxy)-7-oxabicyclo[4.1.0]heptane (0.492 g, 2.41 mmol) at 25 °C stirred for 0.5 h. The vessel was then sealed and the mixture heated to 90 °C for 14 h. The vessel was cooled, treated with a solution of saturated ammonium chloride (50 mL), and then extracted with toluene (2 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as a beige oil (0.640 g, 65%). ¹H NMR (600 MHz, CDCl₃) δ 7.39 (4H, d, *J* = 4.2 Hz), 7.33 (1H, sextet, *J* = 4.2 Hz), 6.96 (4H, t, *J* = 9.0 Hz), 6.90 (4H, dd, *J* = 9.0, 6.6 Hz), 4.72 (1H, d, *J* = 11.4 Hz), 4.52 (1H, d, *J* = 12.0 Hz), 4.21 (1H, ddd, *J* = 12.0, 10.2, 3.6 Hz), 3.91 (1H, br s), 3.22-3.25 (1H, m), 2.51 (1H, d, *J* = 9.0 Hz), 2.00-2.06 (2H, m), 1.75 (1H, qt, *J* = 13.2, 3.6 Hz), 1.52-1.56 (1H, m), 1.12-1.20 (2H, m); LCMS *m/z* 410.1946 ([*M* + *H*⁺], C₂₅H₂₅F₂NO₂ requires 410.1926).



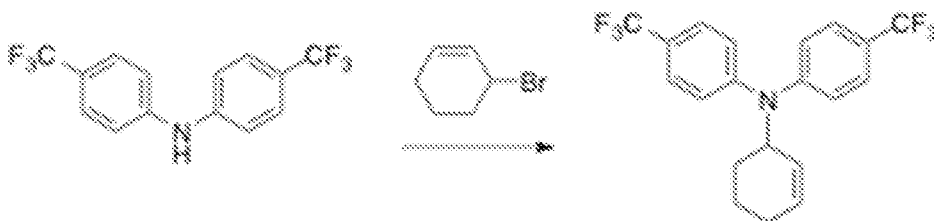
[00168] **(1S,2R,3S)-3-(bis(4-fluorophenyl)amino)cyclohexane-1,2-diol**. A solution of (1R,2S,6S)-2-(benzyloxy)-6-(bis(4-fluorophenyl)amino)cyclohexanol (0.620 g, 1.51 mmol) in THF:MeOH (1:1, 8.0 mL) was treated with 10% Pd/C (0.310 g), placed under an atmosphere of H₂ (g), and stirred for 48 h at 25 °C. The mixture was filtered thru Celite and concentrated in vacuo to afford the title compound as a clear foam (0.385 g, 79%).

Example 8a:



[00169] **Example 8a.** The optically pure diol, **(1S,2R,3S)-3-(bis(4-fluorophenyl)amino)cyclohexane-1,2-diol**, prepared as described above was subjected to the series of conversions shown in Scheme 3 to arrive at optically enriched **Example 8a**, as a white solid which exhibited an $[\alpha]_D = +102$ ($c = 1.0$, CH₂Cl₂).

[00170] **Synthesis of Example 5a**

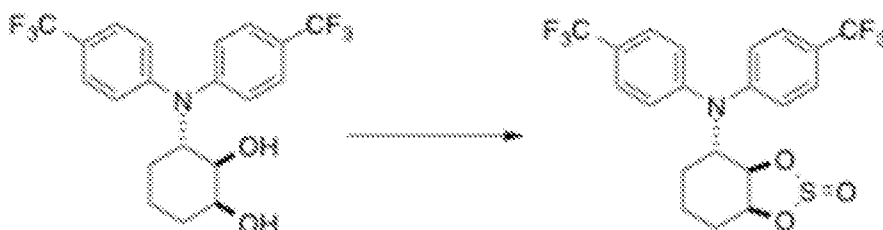


[00171] **N-(cyclohex-2-en-1-yl)-N-(4-(trifluoromethyl)phenyl)-4-(trifluoromethyl)aniline**. A solution of bis(4-(trifluoromethyl)phenyl)amine (1.00 g, 3.28 mmol) in DMF (5.0 mL) was cooled to 0 °C, treated with sodium hydride (60% wt. suspension in mineral oil, 0.170 g, 4.25 mmol), stirred for 15 minutes, then treated with 3-bromocyclohexene (0.46 mL, 3.61 mmol). The mixture was warmed to 25 °C, stirred for 14 h, then poured over a solution of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-5% ethyl acetate-hexanes) to afford the title compound as a white solid (1.34 g, 99%). ¹H NMR (600 MHz,

CDCl₃) δ 7.53 (4H, d, J = 8.4 Hz), 7.02 (4H, d, J = 8.4 Hz), 5.85-5.87 (1H, m), 5.79 (1H, d, J = 10.2 Hz), 1.99-2.03 (3H, m), 1.77-1.82 (1H, m), 1.65-1.72 (2H, m); ¹³C NMR (150 MHz, CDCl₃) δ 149.5, 130.8, 128.9, 126.7 (q, J = 12.0 Hz), 124.3, 124.1, 122.7, 56.8, 27.5, 24.9, 21.9.

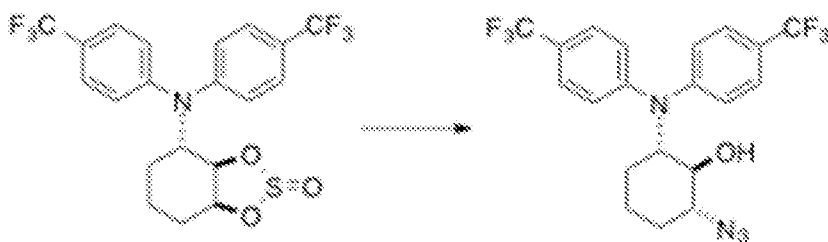


[00172] **rac-(1*R*,2*S*,3*R*)-3-(bis(4-(trifluoromethyl)phenyl)amino)cyclohexane-1,2-diol.** A solution of *N*-(cyclohex-2-en-1-yl)-*N*-(4-(trifluoromethyl)phenyl)-*N*-(4-(trifluoromethyl)phenyl)aniline (1.34 g, 3.48 mmol) in *t*-BuOH-H₂O 5:1 (6.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in *t*-BuOH, 0.44 mL, 0.0348 mmol) and *N*-methyl morpholine *N*-oxide (0.448 g, 3.83 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (5 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a pink solid (1.43 g, 98%). ¹H NMR (600 MHz, CDCl₃) δ 7.57 (4H, d, J = 9.0 Hz), 7.05 (4H, d, J = 8.4 Hz), 4.40 (1H, ddd, J = 12.0, 10.2, 3.6 Hz), 4.16-4.18 (1H, m), 3.36 (1H, dt, J = 10.2, 3.6 Hz), 2.55 (1H, d, J = 4.2 Hz), 2.44 (1H, br s), 1.99-2.04 (1H, doublet of multiplets), 1.92-1.97 (1H, doublet of multiplets), 1.87 (1H, qt, J = 13.2, 3.6 Hz), 1.56-1.60 (1H, doublet of multiplets), 1.33 (1H, triplet of dd, J = 13.8, 4.2, 2.4 Hz), 1.19 (1H, qd, J = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 149.2, 127.0 (q, J = 12.0 Hz), 125.4, 123.6, 123.3, 73.1, 70.0, 57.9, 30.4, 28.9, 19.2; LCMS m/z 418.1239 ([M - H]⁺, C₂₀H₁₉F₆NO₂ requires 418.1242).



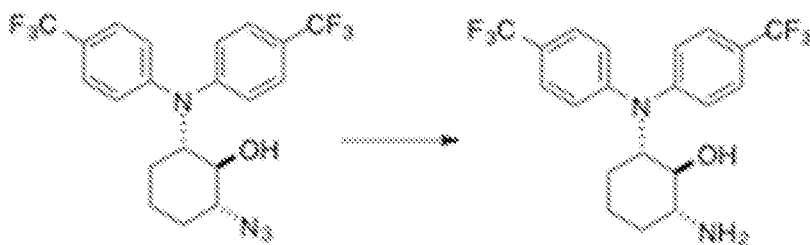
[00173] **rac-(3*aS*,4*R*,7*aR*)-4-(bis(4-(trifluoromethyl)phenyl)amino)hexahydrobenzo[*d*][1,3,2]dioxathiole 2-oxide.** A solution of (1*R*,2*S*,3*R*)-3-(bis(4-(trifluoromethyl)phenyl)amino)cyclohexane-1,2-diol (1.43

g, 3.41 mmol) in CH_2Cl_2 (20.0 mL) at 0 °C was treated dropwise with triethylamine (3.78 mL, 27.3 mmol), and SOCl_2 (0.74 mL, 10.2 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH_2Cl_2 (3×100 mL). The combined organic layers were washed with water (2×100 mL), saturated aqueous sodium chloride (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-10% ethyl acetate-hexanes to afford the title compound as an orange solid (1.14 g, 72%). ^1H NMR (600 MHz, CDCl_3) δ (as a mixture of sulfite diastereomers) 7.57-7.60 (4H, m), 7.04 (2H, d, $J = 9.0$ Hz), 6.96 (2H, d, $J = 9.0$ Hz), 1H[5.14-5.15 (m), 4.69-4.71 (m)], 1H[4.93 (ddd, $J = 13.2, 10.2, 4.2$ Hz), 4.00 (ddd, $J = 13.2, 9.6, 3.6$ Hz)], 1H[4.48 (dd, $J = 10.2, 4.8$ Hz), 4.26 (dd, $J = 9.6, 4.8$ Hz)], 2.36-2.42 (1H, m), 2.13-2.19 (1H, m), 3H[1.87-1.95 (m), 1.76-1.85 (m), 1.65-1.73 (m)], 1.25-1.35 (1H, m); LCMS m/z 464.0741 ($[\text{M} - \text{H}]^+$, $\text{C}_{20}\text{H}_{17}\text{F}_6\text{NO}_3\text{S}$ requires 464.0741).

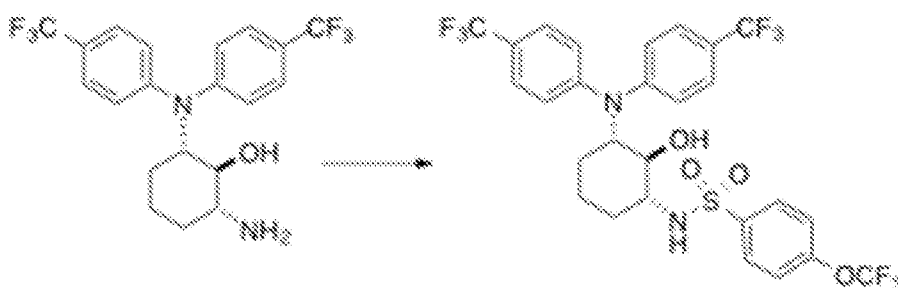


[00174] **rac-(1*S*,2*S*,6*R*)-2-azido-6-(bis(4-**

(trifluoromethyl)phenyl)amino)cyclohexanol. A solution of (3*aS*,4*R*,7*aR*)-4-(bis(4-(trifluoromethyl)phenyl)amino)hexahydrobenzo[*d*][1,3,2]dioxathiole 2-oxide (1.12 g, 2.41 mmol) in DMF (7.0 mL) was treated with sodium azide (0.470 g, 7.22 mmol), and heated to 110 °C under microwave irradiation for 14 h. The mixture was diluted with CH_2Cl_2 (200 mL) and this organic layer was washed with saturated aqueous NaCl (3×100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-10% ethyl acetate-hexanes) to afford the title compound as a beige film (0.783 g, 73%). ^1H NMR (600 MHz, CDCl_3) δ 7.56 (4H, d, $J = 8.4$ Hz), 7.03 (4H, d, $J = 7.8$ Hz), 4.02 (1H, td, $J = 9.6, 3.6$ Hz), 3.47 (1H, ddd, $J = 13.2, 9.6, 4.2$ Hz), 3.23 (1H, t, $J = 9.6$ Hz), 2.53 (1H, br s), 2.03-2.07 (1H, m), 1.86-1.89 (1H, m), 1.46 (1H, qt, $J = 13.8, 3.0$ Hz), 1.21 (1H, sextet of doublets, $J = 13.2, 3.6$ Hz); LCMS m/z 417.1391 ($[\text{M} - \text{N}_2 + \text{H}]^+$, $\text{C}_{20}\text{H}_{18}\text{F}_6\text{N}_4\text{O}$ requires 417.1396).



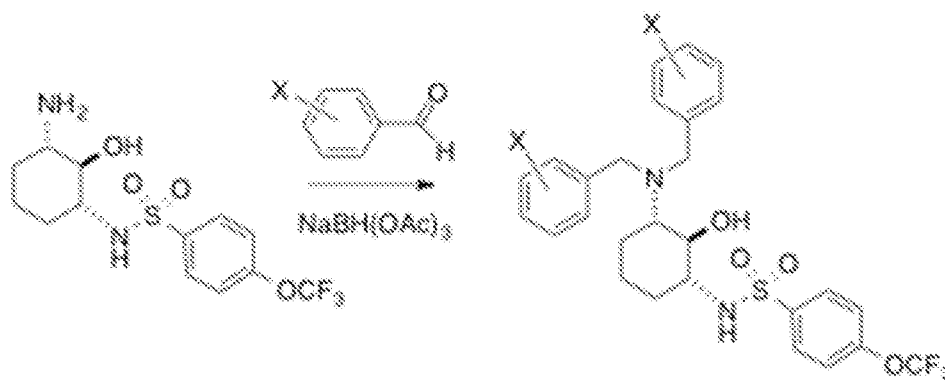
[00175] **rac-(1R,2S,6R)-2-amino-6-(bis(4-(trifluoromethyl)phenyl)amino)cyclohexanol.** A solution of (1S,2S,6R)-2-azido-6-(bis(4-(trifluoromethyl)phenyl)amino)cyclohexanol (0.782 g, 1.76 mmol) in THF (8.0 mL) was cooled to 0 °C, treated with PPh₃ (1.38 g, 5.27 mmol), H₂O (1.0 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as a beige oil (0.635 g, 85%). ¹H NMR (600 MHz, CDCl₃) δ 7.53 (4H, t, *J* = 8.4 Hz), 7.04 (4H, t, *J* = 8.4 Hz), 3.97 (1H, ddd, *J* = 12.6, 9.6, 3.6 Hz), 2.97 (1H, t, *J* = 9.6 Hz), 2.70 (1H, ddd, *J* = 12.0, 9.0, 4.2 Hz), 2.05-2.32 (2H, br m), 1.98-2.01 (1H, m), 1.83-1.86 (1H, m), 1.74 (1H, doublet of quintets, *J* = 13.8, 3.0 Hz), 1.46 (1H, qt, *J* = 13.8, 3.0 Hz), 1.26 (1H, qd, *J* = 12.6, 3.6 Hz), 1.03 (1H, qd, *J* = 13.2, 4.2 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 149.1, 126.8 (q, *J* = 12.0 Hz), 125.4, 123.6, 123.3, 76.5, 61.6, 56.7, 34.3, 29.3, 23.0; LCMS *m/z* 417.1397 ([*M* - H]⁺, C₂₀H₂₀F₆N₂O requires 417.1402).



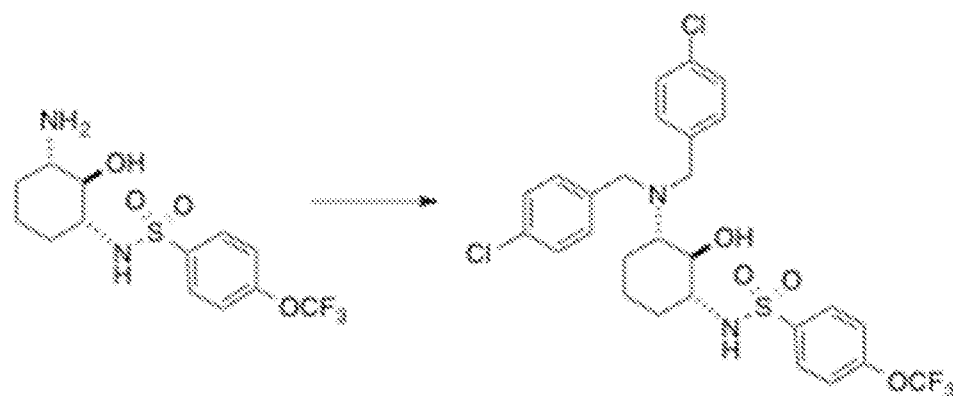
[00176] **Example 5a: rac-N-((1S,2S,3R)-3-(bis(4-(trifluoromethyl)phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of (1R,2S,6R)-2-amino-6-(bis(4-(trifluoromethyl)phenyl)amino)cyclohexanol (0.075 g, 0.179 mmol) in CH₂Cl₂ (2.0 mL) was cooled to 0 °C, treated with Et₃N (27.3 μL, 0.197 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (33.4 μL, 0.197 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated

aqueous NaCl (3×50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-35% ethyl acetate-hexanes) to afford the title compound as a white solid (0.110 g, 96%). mp. 97-98 °C, (white powder, ethyl acetate-hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.96 (2H, d, $J = 9.0$ Hz), 7.53 (4H, d, $J = 8.4$ Hz), 7.35 (2H, d, $J = 9.0$ Hz), 6.99 (4H, d, $J = 7.8$ Hz), 4.92 (1H, d, $J = 6.6$ Hz), 3.94 (1H, ddd, $J = 13.2, 9.6, 4.2$ Hz), 3.18-3.21 (1H, m), 3.17 (1H, t, $J = 9.6$ Hz), 2.89 (1H, br s), 1.97-1.99 (1H, m), 1.81-1.84 (1H, m), 1.72 (1H, doublet of quintets, $J = 14.4, 3.0$ Hz), 1.37 (1H, qt, $J = 13.2, 3.0$ Hz), 1.22 (1H, qd, $J = 13.2, 3.6$ Hz), 1.07 (1H qd, $J = 13.2, 4.2$ Hz); LCMS m/z 643.1304 ($[\text{M} + \text{H}^+]$, $\text{C}_{27}\text{H}_{23}\text{F}_9\text{N}_2\text{O}_4\text{S}$ requires 643.1308).

[00177] Examples where A^1 A^2 are CH_2 (ie bisbenzyl compounds) are prepared by reductive alkylation:



Synthesis of **Example 24**



Example 24

[00178] **Example 24: rac-N-((1S,2S,3R)-3-(bis(4-chlorobenzyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of N-((1S,2S,3R)-3-amino-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.050 g, 0.141 mmol) in CH_2Cl_2 (2.0 mL) was treated with 4-chlorobenzaldehyde (0.046 g, 0.296 mmol), stirred for 15 minutes, treated with sodium triacetoxyborohydride (0.120 g,

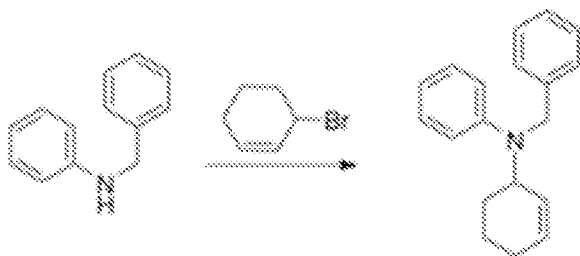
0.564 mmol), and stirred for 14 h. The mixture was diluted with CH₂Cl₂ (20 mL), washed with a solution of saturated aqueous sodium bicarbonate (20 mL), dried Na₂SO₄, concentrated, and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound (0.059 g, 69%) as a clear film. ¹H NMR (600 MHz, CDCl₃) δ 7.91 (2H, dt, *J* = 9.0, 1.8 Hz), 7.31 (1H, d, *J* = 6.0 Hz), 7.28 (1H, d, *J* = 7.8 Hz), 7.26 (4H, d, *J* = 7.8 Hz), 7.13 (4H, d, *J* = 8.4 Hz), 5.22 (1H, br s), 4.67 (1H, s), 3.72 (2H, d, *J* = 13.8 Hz), 3.51 (1H, br s), 3.31 (2H, dt, *J* = 13.2 Hz), 3.27 (1H, t, *J* = 9.6 Hz), 2.84 (1H, td, *J* = 12.6, 4.2 Hz), 2.30 (1H, td, *J* = 12.6, 3.0 Hz), 2.06-2.09 (1H, m), 1.86-1.89 (1H, m), 1.76 (1H, dt, *J* = 13.8, 3.0 Hz), 1.18-1.26 (2H, m), 1.11 (1H, qt, *J* = 13.2, 3.0 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 152.1, 139.1, 137.3, 133.4, 130.3, 129.5, 129.0, 128.5, 120.9, 71.9, 64.762.6, 58.9, 53.2, 31.6, 22.4, 21.9; LCMS *m/z* 603.1096 ([M + H⁺], C₂₇H₂₇Cl₂F₃N₂O₄S requires 603.1093).

[00179] **Example 27: rac-N-((1S,2S,3R)-3-(bis(4-trifluoromethoxybenzyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of N-((1S,2S,3R)-3-amino-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.050 g, 0.141 mmol) in CH₂Cl₂ (2.0 mL) was treated with 4-trifluoromethoxybenzaldehyde (42.3 μL, 0.296 mmol), stirred for 15 minutes, treated with sodium triacetoxyborohydride (0.120 g, 0.564 mmol), and stirred for 14 h. The mixture was diluted with CH₂Cl₂ (20 mL), washed with a solution of saturated aqueous sodium bicarbonate (20 mL), dried Na₂SO₄, concentrated, and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound (0.043 g, 43%) as a clear film. ¹H NMR (600 MHz, CDCl₃) δ 7.91 (2H, dt, *J* = 7.2, 1.8 Hz), 2H[7.40 (d, *J* = 8.4 Hz), 7.27 (d, *J* = 8.4 Hz)], 7.21 (4H, d, *J* = 8.4 Hz), 7.13 (4H, d, *J* = 8.4 Hz), 5.18 (1H, br s), 4.72 (1H, s), 3.76 (2H, d, *J* = 13.8 Hz), 3.51 (1H, br s), 3.38 (2H, d, *J* = 13.2 Hz), 3.30 (1H, t, *J* = 9.6 Hz), 2.82-2.86 (1H, m), 2.32 (1H, td, *J* = 12.6, 3.0 Hz), 2.09-2.11 (1H, m), 1.90-1.92 (1H, m), 1.76-1.80 (1H, m), 1.25 (2H, quintet of d, *J* = 12.6, 3.6 Hz), 1.11-1.18 (1H, m); ¹³C NMR (150 MHz, CDCl₃) δ 152.2, 148.7, 139.0, 137.5, 130.3, 129.5, 128.5, 121.5, 121.2, 120.8, 119.8, 72.0, 64.6, 62.9, 58.9, 53.3, 31.7, 22.4, 22.0; LCMS *m/z* 703.1520 ([M + H⁺], C₂₉H₂₇F₉N₂O₆S requires 703.1519).

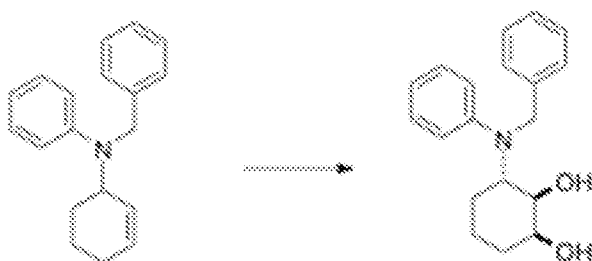
[00180] **Example 26: rac-N-((1S,2S,3R)-3-(bis(4-trifluoromethylbenzyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of N-((1S,2S,3R)-3-amino-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide

(0.050 g, 0.141 mmol) in CH₂Cl₂ (2.0 mL) was treated with 4-trifluoromethylbenzaldehyde (40.4 μL, 0.296 mmol), stirred for 15 minutes, treated with sodium triacetoxyborohydride (0.120 g, 0.564 mmol), and stirred for 14 h. The mixture was diluted with CH₂Cl₂ (20 mL), washed with a solution of saturated aqueous sodium bicarbonate (20 mL), dried Na₂SO₄, concentrated, and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound (0.054 g, 58%) as a clear film. ¹H NMR (600 MHz, CDCl₃) δ 7.91 (2H, dt, *J* = 8.4, 1.8 Hz), 7.61 (1H, d, *J* = 7.8 Hz), 7.54 (3H, d, *J* = 7.8 Hz), 7.48 (1H, d, *J* = 7.8 Hz), 7.33 (3H, d, *J* = 7.8 Hz), 7.27 (2H, d, *J* = 8.4 Hz), 5.22 (1H, d, *J* = 3.0 Hz), 4.78 (1H, s), 3.82 (2H, d, *J* = 13.8 Hz), 3.46-3.49 (1H, m), 3.47 (1H, d, *J* = 13.8 Hz), 3.33 (1H, t, *J* = 9.6 Hz), 2.83-2.87 (1H, m), 2.33 (1H, td, *J* = 12.6, 3.0 Hz), 2.06-2.09 (1H, m), 1.92-1.94 (1H, m), 1.76-1.80 (1H, dt, *J* = 13.2, 3.0 Hz), 1.25 (2H, sextet of d, *J* = 12.6, 3.6 Hz), 1.14 (1H, qt, *J* = 13.2, 3.0 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 152.2, 142.9, 139.0, 130.1, 129.7 (q, *J* = 7.8 Hz), 125.8, 125.7 (d, *J* = 12 Hz), 125.6 (d, *J* = 12 Hz), 123.3, 120.9, 72.1, 64.6, 63.1, 58.8, 53.8, 31.6, 22.4, 22.2; LCMS *m/z* 671.1634 ([M + H]⁺, C₂₉H₂₇F₉N₂O₄S requires 671.1621).

[00181] **Example 25: N-((1S,2S,3R)-3-(bis(4-fluorobenzyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of N-((1S,2S,3R)-3-amino-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.050 g, 0.141 mmol) in CH₂Cl₂ (2.0 mL) was treated with 4-fluorobenzaldehyde (31.8 μL, 0.296 mmol), stirred for 15 minutes, treated with sodium triacetoxyborohydride (0.120 g, 0.564 mmol), and stirred for 14 h. The mixture was diluted with CH₂Cl₂ (20 mL), washed with a solution of saturated aqueous sodium bicarbonate (20 mL), dried Na₂SO₄, concentrated, and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound (0.034 g, 42%) as a clear film. ¹H NMR (600 MHz, CDCl₃) δ 7.91 (2H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 9.0 Hz), 7.15 (4H, dd, *J* = 8.4, 5.4 Hz), 6.99 (4H, t, *J* = 8.4 Hz), 5.11 (1H, br s), 4.67 (1H, s), 3.72 (2H, d, *J* = 13.2 Hz), 3.52 (1H, m), 3.32 (2H, d, *J* = 13.8 Hz), 3.26 (1H, t, *J* = 9.6 Hz), 2.81-2.85 (1H, m), 2.31 (1H, td, *J* = 12.6, 3.0 Hz), 2.08-2.12 (1H, m), 1.87-1.90 (1H, m), 1.77 (1H, dt, *J* = 13.2, 3.0 Hz), 1.19-1.28 (2H, m), 1.13 (1H, qt, *J* = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 163.1, 161.5, 152.1, 139.1, 134.5 (d, *J* = 12 Hz), 130.5 (d, *J* = 7.8 Hz), 129.5, 120.9, 115.6 (d, *J* = 90 Hz), 71.8, 62.5, 58.9, 53.1, 31.6, 22.5, 21.8; LCMS *m/z* 571.1677 ([M + H]⁺, C₂₇H₂₇F₅N₂O₄S requires 571.1684).

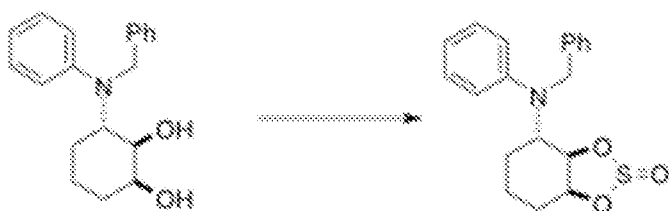


[00182] **N-benzyl-N-(cyclohex-2-en-1-yl)aniline.** A solution of N-benzylaniline (3.00 g, 16.4 mmol) in DMF (20 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil (0.720 g, 18.0 mmol), and 3-bromocyclohexene (2.07 mL, 18.0 mmol). The mixture was warmed to 25 °C and stirred for 14 h. The mixture was partitioned between saturated aqueous NaCl (50 mL), and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of hexanes and purified by flash chromatography (SiO₂, hexanes) to afford the title compound as a clear oil (3.94 g, 91%). ¹H NMR (600 MHz, CDCl₃) δ 7.30-7.32 (4H, m), 7.21-7.25 (1H, m), 7.16-7.20 (2H, m), 6.72 (2H, d, *J* = 8.4 Hz), 6.69 (1H, t, *J* = 7.2 Hz), 5.58-5.90 (1H, m), 5.70 (1H, d, *J* = 10.8 Hz), 4.63-4.67 (1H, m), 4.56 (1H, d, *J* = 17.4 Hz), 4.40 (1H, d, *J* = 17.4 Hz), 2.05-2.09 (3H, m), 1.81-1.86 (1H, m), 1.67-1.74 (1H, m), 1.60 (1H, qt, *J* = 12.6, 3.0 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 149.0, 140.9, 131.5, 129.4, 129.3, 128.6, 126.6, 126.3, 116.6, 113.4, 55.0, 50.7, 27.0, 25.2, 21.8; LCMS *m/z* 264.1744 ([M + H]⁺, C₁₉H₂₁N requires 264.1747).



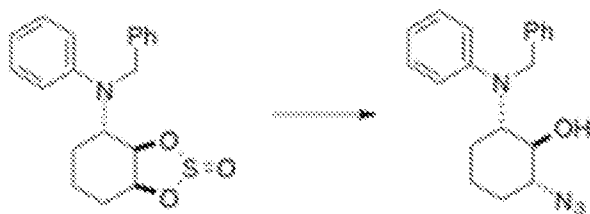
[00183] **rac-(1R,2S,3R)-3-(benzyl(phenyl)amino)cyclohexane-1,2-diol.** A solution of N-benzyl-N-(cyclohex-2-en-1-yl)aniline (3.89 g, 14.8 mmol) in t-BuOH-H₂O 5:1 (20.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in t-BuOH, 1.85 mL, 0.147 mmol) and N-methyl morpholine N-oxide (1.90 g, 16.2 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (10 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a white solid (3.50 g, 80%). ¹H NMR (600

MHz, CDCl₃) δ 7.30-7.33 (4H, m), 7.21-7.25 (3H, m), 6.94 (2H, d, J = 8.4 Hz), 6.82 (1H, t, J = 7.22 Hz), 4.49 (1H, d, J = 16.8 Hz), 4.42 (1H, d, J = 16.8 Hz), 4.20 (1H, d, J = 3.0 Hz), 4.10 (1H, m), 3.60 (1H, dd, J = 10.2, 3.0 Hz), 2.60-2.85 (2H, m), 1.95-1.98 (1H, m), 1.90-1.95 (1H, m), 1.81 (1H, qt, J = 13.8, 3.6 Hz), 1.55-1.58 (1H, m), 1.34-1.43 (2H, m); ¹³C NMR (150 MHz, CDCl₃) δ 149.9, 139.7, 129.3, 128.9, 127.1, 126.9, 119.2, 116.7, 72.7, 69.4, 59.9, 49.4, 30.1, 26.9, 19.4; LCMS m/z 298.1801 ([M + H⁺], C₁₉H₂₃NO₂ requires 298.1802).



[00184] **rac-(3aS,4R,7aR)-4-**

(benzyl(phenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide. A solution of rac-(1R,2S,3R)-3-(benzyl(phenyl)amino)cyclohexane-1,2-diol (3.50 g, 11.8 mmol) in CH₂Cl₂ (20.0 mL) at 0 °C was treated dropwise with triethylamine (13.1 mL, 94.2 mmol), and SOCl₂ (2.56 mL, 35.3 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), saturated aqueous sodium chloride (100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as an orange solid (3.94 g, 97%). ¹H NMR (600 MHz, CDCl₃) δ (as a mixture of sulfite diastereomers) 7.37-7.39 (2H, m), 7.32 (2H, t, J = 7.2 Hz), 7.24 (1H, t, J = 6.6 Hz), 7.16-7.21 (2H, m), 3H[6.89 (d, J = 8.4 Hz), 6.72-6.78 (m)], 5.17-5.19 (1H, br m), 1H[4.77 (dd, J = 9.0, 4.8 Hz), 4.49-4.53 (m)], 4.53 (1H, d, J = 16.8 Hz), 4.46 (1H, d, J = 16.8 Hz), 3.82 (1H, ddd, J = 13.2, 9.6, 4.2 Hz), 2.37-2.41 (1H, m), 1.92-1.97 (1H, m), 1.82-1.89 (1H, m), 1.73-1.79 (1H, m), 1.67 (1H, qt, J = 13.2, 3.6 Hz), 1.46 (1H, qd, J = 13.2, 3.0 Hz); LCMS m/z 344.1318 ([M + H⁺], C₁₉H₂₁NO₃S requires 344.1315).

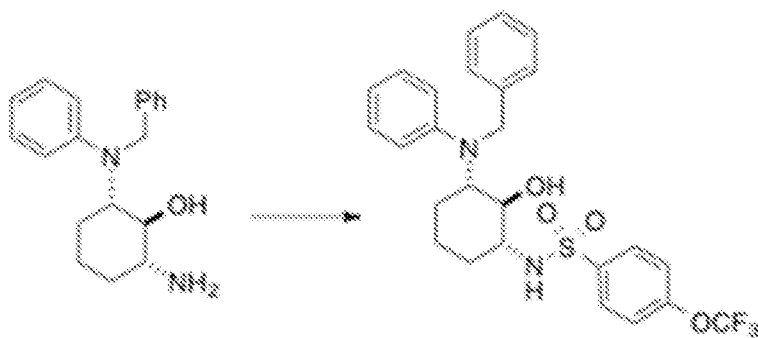


[00185] **rac-(1S,2S,6R)-2-azido-6-(benzyl(phenyl)amino)cyclohexanol**. A solution of rac-(3aS,7aR)-4-(benzyl(phenyl)amino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide (3.84 g, 11.2 mmol) in DMF (5.0 ml) was treated with sodium azide (2.18 g, 33.5 mmol), and heated to 110 °C for 14 h under microwave irradiation. The mixture was diluted with CH₂Cl₂ (200 mL) and this organic layer was washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound as a beige oil (1.94 g, 54%). ¹H NMR (600 MHz, CDCl₃) δ 7.29-7.33 (4H, m), 7.21-7.25 (3H, m), 6.95 (2H, d, *J* = 7.8 Hz), 6.95 (1H, t, *J* = 7.2 Hz), 4.44 (2H, q, *J* = 16.2 Hz), 3.62-3.65 (1H, m), 3.56 (1H, t, *J* = 9.6 Hz), 3.43 (1H, ddd, *J* = 12.6, 9.0, 4.8 Hz), 2.87 (1H, br s), 2.00-2.02 (1H, m), 1.91-1.93 (1H, m), 1.82-1.84 (1H, m), 1.40 (2H, q, *J* = 9.0 Hz), 1.27-1.32 (1H, m); ¹³C NMR (150 MHz, CDCl₃) δ 146.7, 129.6, 123.6, 123.0, 75.4, 66.0, 61.7, 29.9, 28.2, 22.4; LCMS *m/z* 323.1870 [*M* + H⁺], C₁₉H₂₂N₄O requires 323.1866).



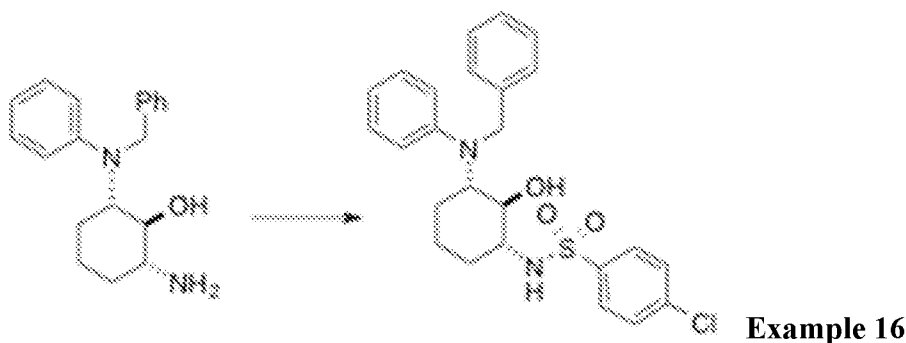
[00186] **rac-(1R,2S,6R)-2-amino-6-(benzyl(phenyl)amino)cyclohexanol**. A solution of rac-(1S,2S,6R)-2-azido-6-(benzyl(phenyl)amino)cyclohexanol (1.94 g, 6.02 mmol) in THF (10.0 mL) was cooled to 0 °C, treated with PPh₃ (2.05 g, 7.83 mmol), H₂O (0.5 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as a beige film (1.14 g, 64%). ¹H NMR (600 MHz, CDCl₃) δ 7.29-7.31 (4H, m), 7.18-7.24 (3H, m), 6.90 (2H, d, *J* = 7.8 Hz), 6.78 (1H, t, *J* = 7.2 Hz),

4.50 (1H, d, $J = 16.8$ Hz), 4.42 (1H, d, $J = 16.8$ Hz), 3.36 (1H, ddd, $J = 13.2, 11.4, 3.6$ Hz), 3.30 (1H, t, $J = 9.0$ Hz), 2.75 (1H, ddd, $J = 11.4, 8.4, 4.2$ Hz), 2.18 (3H, br s), 1.88-1.91 (1H, m), 1.86-1.88 (1H, m), 1.73-1.76 (1H, m), 1.37-1.46 (2H, m), 1.16 (1H, qd, $J = 13.2, 3.6$ Hz), ^{13}C NMR (150 MHz, CDCl_3) δ 149.9, 139.8, 129.3, 128.9, 127.1, 126.9, 118.8, 116.3, 64.3, 56.1, 49.3, 33.4, 31.8, 27.3, 23.0; LCMS m/z 297.1963 ($[\text{M} + \text{H}^+]$, $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}$ requires 297.1961).

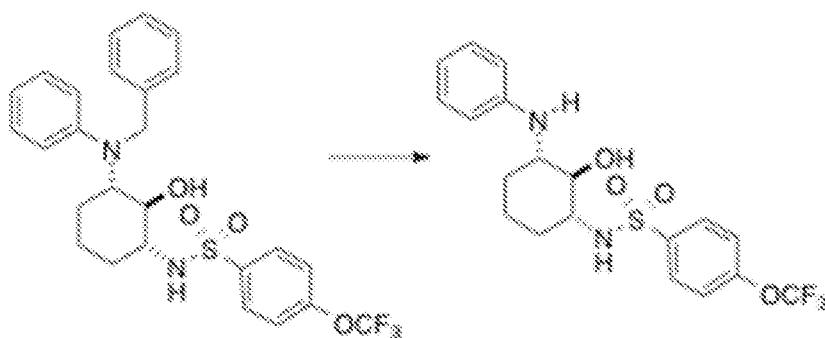


Example 15

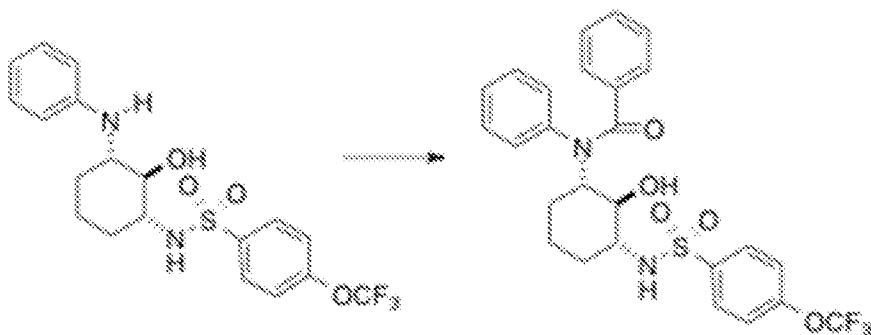
[00187] **rac-N-((1S,2S,3R)-3-(benzyl(phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of rac-(1R,2S,6R)-2-amino-6-(benzyl(phenyl)amino)cyclohexanol (0.184 g, 0.621 mmol) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C, treated with Et_3N (90.0 μL , 0.652 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (111.0 μL , 0.652 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with saturated aqueous NaCl (3 $\times$ 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.129 g, 40%). ^1H NMR (600 MHz, CDCl_3) δ 7.94 (2H, d, $J = 9.0$ Hz), 7.33 (2H, d, $J = 9.0$ Hz), 7.30 (2H, d, $J = 7.8$ Hz), 7.23-7.26 (3H, m), 7.20 (2H, t, $J = 8.4$ Hz), 6.86 (2H, d, $J = 8.4$ Hz), 6.83 (1H, t, $J = 7.2$ Hz), 5.00 (1H, d, $J = 4.2$ Hz), 4.40 (2H, d, $J = 4.8$ Hz), 3.51 (1H, ddd, $J = 13.2, 9.6, 3.6$ Hz), 3.36 (1H, t, $J = 9.6$ Hz), 3.02-3.05 (1H, m), 2.67 (1H, s), 2.18-2.20 (1H, m), 1.86-1.89 (1H, m), 1.74-1.77 (1H, m), 1.39 (1H, qd, $J = 12.6, 3.6$ Hz), 1.22-1.34 (m); ^{13}C NMR (150 MHz, CDCl_3) δ 152.3, 149.5, 139.4, 138.8, 132.8, 129.6, 129.4, 129.1, 127.4, 126.9, 121.0, 119.9, 117.2, 73.5, 64.8, 58.9, 49.7, 31.6, 26.3, 22.4; LCMS m/z 521.1728 ($[\text{M} + \text{H}^+]$, $\text{C}_{26}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_4\text{S}$ requires 521.1716).



[00188] **rac-N-((1S,2S,3R)-3-(benzyl(phenyl)amino)-2-hydroxycyclohexyl)-4-chlorobenzenesulfonamide.** A solution of rac-(1R,2S,6R)-2-amino-6-(benzyl(phenyl)amino)cyclohexanol (0.184 g, 0.621 mmol) in CH₂Cl₂ (2.0 mL) was cooled to 0 °C, treated with Et₃N (90.0 μL, 0.652 mmol), and 4-chlorobenzenesulfonyl chloride (0.066 g, 0.652 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.167 g, 57%). ¹H NMR (600 MHz, CDCl₃) δ 7.82 (2H, d, *J* = 8.4 Hz), 7.47 (2H, d, *J* = 8.4 Hz), 7.30 (2H, t, *J* = 7.2 Hz), 7.22-7.27 (3H, m), 7.20 (2H, t, *J* = 8.4 Hz), 6.86 (2H, d, *J* = 8.4 Hz), 6.81 (1H, t, *J* = 7.8 Hz), 5.02 (1H, d, *J* = 4.2 Hz), 4.40 (2H, d, *J* = 7.2 Hz), 3.51 (1H, ddd, *J* = 13.2, 9.6, 3.6 Hz), 3.36 (1H, t, *J* = 9.0 Hz), 2.97-3.02 (1H, m), 2.66 (1H, s), 2.16-2.18 (1H, m), 1.84-1.89 (1H, m), 1.72-1.76 (1H, m), 1.38 (1H, qd, *J* = 12.6, 3.6 Hz), 1.21-1.32 (2H, m); ¹³C NMR (150 MHz, CDCl₃) δ 149.5, 139.4, 139.2, 138.9, 129.5, 129.4, 129.1, 129.0, 127.4, 126.9, 119.8, 117.0, 73.5, 64.7, 58.8, 49.7, 31.5, 26.3, 22.4; LCMS *m/z* 471.1505 ([*M* + *H*⁺], C₂₅H₂₇ClN₂O₃S requires 471.1504).

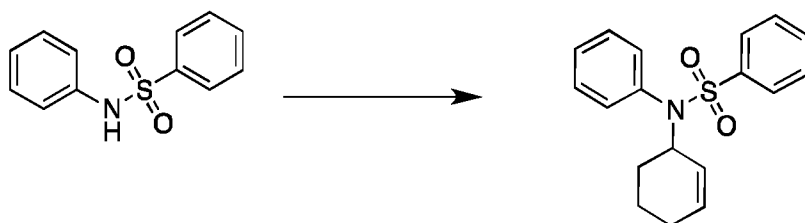


[00189] **rac-N-((1S,2S,3R)-2-hydroxy-3-(phenylamino)cyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide**. A solution of N-((1S,2S,3R)-3-(benzyl(phenyl)amino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (1.71 g, 3.28 mmol) in methanol (5.0 mL) was treated with Pd(OH)₂ (0.85 g), placed under an atmosphere of H₂(g) and stirred for 14 h at 25 °C. The mixture was filtered through Celite and concentrated to dryness to afford the title compound as beige oil (1.31 g, 93%). ¹H NMR (600 MHz, CDCl₃) δ 8.00 (4H, t, *J* = 7.8 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 7.31 (1H, d, *J* = 8.4 Hz), 7.16 (2H, t, *J* = 7.2 Hz), 6.75 (1H, t, *J* = 7.2 Hz), 6.65 (2H, d, *J* = 7.8 Hz), 3.55-3.65 (1H, m), 3.28 (1H, t, *J* = 9.0 Hz), 3.12-3.19 (1H, m), 3.08-3.12 (1H, m), 2.78-2.88 (1H, m), 2.06-2.10 (1H, m), 1.94-1.99 (1H, m), 1.77-1.81 (1H, m), 1.65-1.73 (1H, m), 1.60-1.64 (1H, m), 1.10-1.32 (2H, m); ¹³C NMR (150 MHz, CDCl₃) δ 152.2, 147.6, 139.1, 129.5, 129.3, 121.3, 121.0, 118.8, 114.6, 76.6, 58.7, 58.4, 31.8, 31.1, 22.2; LCMS *m/z* 431.1244 ([*M* + H⁺], C₁₉H₂₁F₃N₂O₄S requires 431.1247).

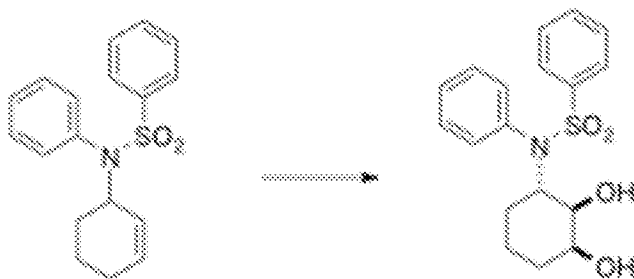
**Example 17**

[00190] **Example 17: rac-N-((1R,2S,3S)-2-hydroxy-3-(4-(trifluoromethoxy)phenylsulfonyl)cyclohexyl)-N-phenylbenzamide**. A solution of N-((1S,2S,3R)-2-hydroxy-3-(phenylamino)cyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide (0.078 g, 0.181 mmol) in CH₂Cl₂ (1.0 mL) was cooled to 0 °C, treated with triethylamine (75.0 μL, 0.544 mmol), benzoyl chloride (21.0 μL, 0.181 g), allowed to warm to 25 °C and stirred for 3 h. The mixture was concentrated, and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes) to afford the title compound as a clear film (0.034 g, 35%). ¹H NMR (600 MHz, CDCl₃) δ 7.71 (2H, br d, *J* = 8.4 Hz), 7.65 (2H, br d, *J* = 6.6 Hz), 7.48-7.53 (1H, m), 7.27-7.33 (2H, m), 7.02-7.07 (2H, m), 6.90 (2H, br d, *J* = 7.2 Hz), 6.57-6.61 (1H, m), 6.55 (2H, br d, *J* = 7.2 Hz), 5.55 (1H, br s), 4.87 (1H, t, *J* = 9.0 Hz), 3.49-3.62 (3H, m), 2.20 (2H, br d, *J* = 12.0 Hz), 1.77-1.82 (1H, m), 1.38-1.57 (2H, m), 1.24-1.30 (1H, m); ¹³C NMR (150 MHz, CDCl₃) δ 152.2,

147.6, 139.1, 129.5, 129.3, 121.3, 121.0, 118.8, 114.6, 76.6, 58.7, 58.4, 31.8, 31.1, 22.2;
LCMS m/z 535.1510 ($[M + H]^+$, $C_{26}H_{25}F_3N_2O_5S$ requires 535.1509).

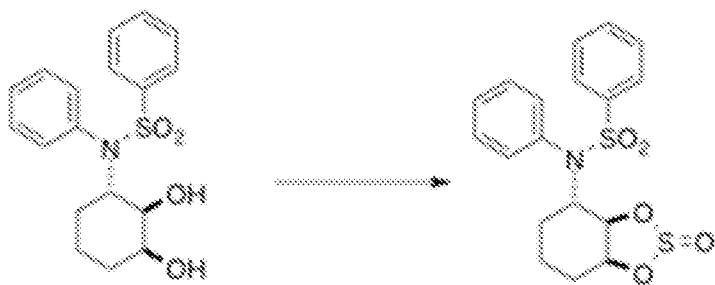


[00191] **rac-N-(cyclohex-2-en-1-yl)-N-phenylbenzenesulfonamide.** A solution of N-phenylbenzenesulfonamide (2.00 g, 8.57 mmol) in DMF (5.0 mL) was cooled to 0 °C, treated with sodium hydride (60% wt. suspension in mineral oil, 0.412 g, 10.29 mmol), stirred for 15 minutes, then treated with 3-bromocyclohexene (1.20 mL, 9.43 mmol). The mixture was warmed to 25 °C, stirred for 14 h, then poured over a solution of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined, washed with saturated aqueous NaCl (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 10% ethyl acetate-hexanes) to afford the title compound as a clear oil (2.59 g, 96%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (1H, d, $J = 7.8$ Hz), 7.57 (1H, t, $J = 7.8$ Hz), 7.48 (2H, t, $J = 7.8$ Hz), 7.29-7.35 (3H, m), 7.07 (1H, d, $J = 7.8$ Hz), 5.65-5.68 (1H, m), 5.51 (1H, d, $J = 10.2$ Hz), 4.98-5.02 (1H, m), 1.92-1.95 (1H, m), 1.80-1.84 (1H, m), 1.69-1.75 (1H, m), 1.52-1.60 (2H, m), 1.41 (1H, qt, $J = 12.6, 3.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 136.3, 132.5, 132.2, 131.5, 129.1, 128.9, 128.7, 128.3, 127.5, 56.7, 29.1, 24.3, 21.4; LCMS m/z 314.1216 ($[M + H]^+$, $C_{18}H_{19}NO_2S$ requires 314.1209).



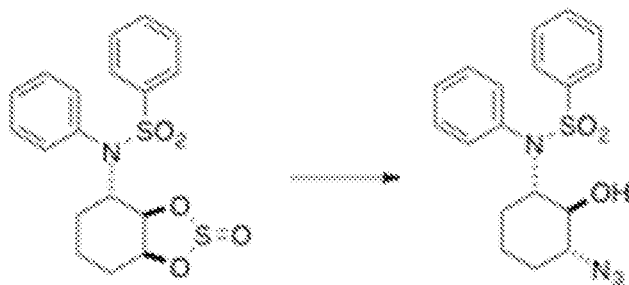
[00192] **rac-N-((1R,2S,3R)-2,3-dihydroxycyclohexyl)-N-phenylbenzenesulfonamide.** A solution of rac-N-(cyclohex-2-en-1-yl)-N-phenylbenzenesulfonamide (2.57 g, 8.20 mmol) in t-BuOH- H_2O 5:1 (6.0 mL) at 25 °C was treated with OsO_4 (2.5 wt.% solution in t-BuOH, 1.03 mL, 0.082 mmol) and N-methyl

morpholine N-oxide (1.06 g, 9.02 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (5 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a white solid (2.35 g, 82%). ¹H NMR (600 MHz, CDCl₃) δ 7.82 (2H, d, *J* = 9.0 Hz), 7.60 (1H, t, *J* = 7.8 Hz), 7.51 (2H, d, *J* = 7.8 Hz), 7.35-7.41 (3H, m), 7.15 (2H, d, *J* = 7.2 Hz), 4.39 (1H, ddd, *J* = 12.0, 10.2, 3.6 Hz), 4.11 (1H, br s), 3.26 (1H, d, *J* = 5.4 Hz), 3.19 (1H, ddd, *J* = 7.8, 4.8, 3.0 Hz), 1.82-1.87 (1H, m), 1.73 (1H, qt, *J* = 13.8, 3.6 Hz), 1.62-1.65 (1H, m), 1.37-1.43 (1H, m), 1.16 (1H, tt, *J* = 13.8, 2.4 Hz), 1.02 (1H, qd, *J* = 13.2, 4.2 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 141.0, 134.9, 132.9, 132.4, 129.3 (2C), 129.2, 127.6, 72.1, 70.0, 59.6, 30.5, 30.0, 19.1; LCMS *m/z* 348.1262 ([M + H⁺], C₁₈H₂₁NO₄S requires 348.1264).

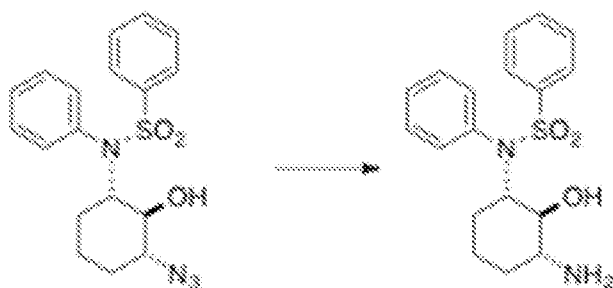


[00193] **rac-N-((3aS,4R,7aR)-2-oxidohexahydrobenzo[d][1,3,2]dioxathiol-4-yl)-N-phenylbenzenesulfonamide**. A solution of rac-N-((1R,2S,3R)-2,3-dihydroxycyclohexyl)-N-phenylbenzenesulfonamide (2.35 g, 6.76 mmol) in CH₂Cl₂ (10.0 mL) at 0 °C was treated dropwise with triethylamine (7.50 mL, 54.11 mmol), and SOCl₂ (1.47 mL, 20.3 mmol). The mixture was warmed to 25 °C, stirred for 2 h, poured over a solution of saturated aqueous sodium chloride (100 mL), and then extracted CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), saturated aqueous sodium chloride (100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-20% ethyl acetate-hexanes to afford the title compound as an orange solid (3.11 g, 99%). ¹H NMR (600 MHz, CDCl₃) δ (as a mixture of sulfite diastereomers) 2H[7.77 (d, *J* = 7.8 Hz), 7.73 (d, *J* = 8.4 Hz)], 1H[7.58 (td, *J* = 8.4, 1.2 Hz), 7.55 (td, *J* = 8.4, 1.2 Hz)], 2H[7.48 (t, *J* = 7.8 Hz), 7.45 (t, *J* = 7.8 Hz)], 7.33-7.42 (3H, m), 2H[7.11 (d, *J* = 7.8 Hz), 7.09 (d, *J* = 7.8 Hz)], 1H[5.01-5.03 (m), 4.58-4.60 (m)], 1H[4.90 (ddd, *J* = 13.2, 10.2, 4.2 Hz), 4.10-4.15 (m)], 1H[4.31 (dd, *J* = 9.6, 4.8 Hz), 4.13 (dd, *J* = 10.2, 5.4 Hz)], 2H[2.21-2.31 (m), 2.04-2.07 (m)], 2H[1.88 (qt, *J*

= 13.8, 4.2 Hz), 1.65-1.71 (m)], 1H[1.65-1.70 (m), 1.54-1.61 (m)], 1H[1.45 (qd, J = 12.6, 3.0 Hz), 1.21-1.28 (m)].

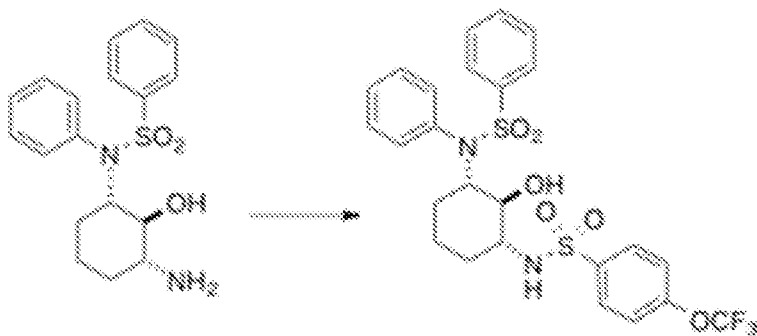


[00194] **rac-N-((1R,2R,3S)-3-amino-2-hydroxycyclohexyl)-N-phenylbenzenesulfonamide**. A solution of rac-N-((3aS,4R,7aR)-2-oxidohexahydrobenzo[d][1,3,2]dioxathiol-4-yl)-N-phenylbenzenesulfonamide (1.43 g, 5.37 mmol) in DMF (8.0 mL) was treated with sodium azide (1.05 g, 16.1 mmol), and heated to 110 °C under microwave irradiation for 14 h. The mixture was diluted with CH₂Cl₂ (200 mL) and this organic layer was washed with saturated aqueous NaCl (3 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-20% ethyl acetate-hexanes) to afford the title compound as a white solid (1.43 g, 71%). ¹H NMR (600 MHz, CDCl₃) δ 7.75 (2H, d, J = 7.2 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.45 (2H, t, J = 7.8 Hz), 7.37 (1H, d, J = 7.2 Hz), 7.33 (2H, t, J = 7.2 Hz), 7.12 (2H, d, J = 7.8 Hz), 4.17 (1H, ddd, J = 12.0, 10.2, 3.6 Hz), 3.38 (1H, ddd, J = 12.6, 9.6, 4.8 Hz), 2.65-2.85 (1H, br m), 1.88-1.91 (1H, m), 1.78-1.81 (1H, m), 1.68-1.72 (1H, m), 1.38 (1H, t, J = 6.6, 3.0 Hz), 1.14 (1H, qd, J = 12.6, 3.6 Hz), 1.03 (1H, qd, J = 13.2, 3.6 Hz); LCMS m/z 373.1332 ([M + H]⁺, C₁₈H₂₀N₄O₃S requires 373.1329).



[00195] **rac-N-((1R,2R,3S)-3-amino-2-hydroxycyclohexyl)-N-phenylbenzenesulfonamide**. A solution of rac-N-((1R,2R,3S)-3-amino-2-hydroxycyclohexyl)-N-phenylbenzenesulfonamide (1.41 g, 3.78 mmol) in THF (10.0 mL) was cooled to 0 °C, treated with PPh₃ (1.29 g, 4.92 mmol), H₂O (1.0 mL), and stirred for 14

h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as a white solid (0.459 g, 35%). ¹H NMR (600 MHz, CDCl₃) δ 7.76 (2H, d, *J* = 7.2 Hz), 7.54 (1H, t, *J* = 7.2 Hz), 7.44 (2H, t, *J* = 8.4 Hz), 7.33-7.36 (1H, m), 7.31 (2H, d, *J* = 6.6 Hz), 7.14 (2H, d, *J* = 7.2 Hz), 4.13 (2H, ddd, *J* = 13.2, 9.6, 3.6 Hz), 2.78 (1H, t, *J* = 9.6 Hz), 2.66-2.70 (1H, m), 2.40-2.58 (4H, br s), 1.73-1.81 (2H, m), 1.61-1.64 (1H, m), 1.39 (2H, qt, *J* = 13.2, 3.6 Hz), 1.16 (2H, qd, *J* = 13.2, 3.6 Hz); ¹³C NMR (150 MHz, CDCl₃) 141.1, 134.8, 132.9, 132.7, 132.6, 129.1, 128.9, 127.8, 75.8, 74.5, 63.0, 56.6, 31.0, 22.8; LCMS *m/z* 347.1422 ([*M* + H]⁺, C₁₈H₂₂N₂O₃S requires 347.1424).

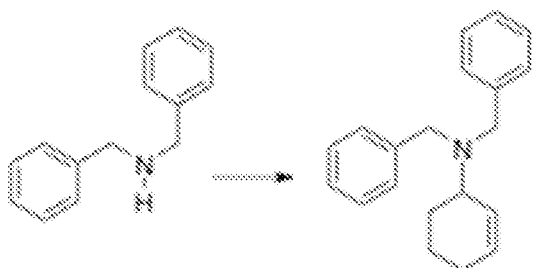
**Example 18**

[00196] **rac-N-((1R,2R,3S)-2-hydroxy-3-(4-**

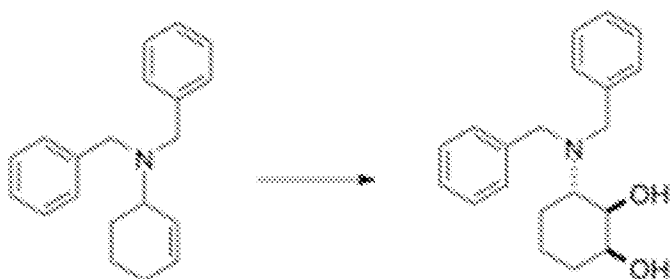
(trifluoromethoxy)phenylsulfonamido)cyclohexyl)-N-phenylbenzenesulfonamide. A

solution of rac-N-((1R,2R,3S)-3-amino-2-hydroxycyclohexyl)-N-phenylbenzenesulfonamide (0.0500 g, 0.144 mmol) in CH₂Cl₂ (1.0 mL) was cooled to 0 °C, treated with Et₃N (21.0 μL, 0.151 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (25.6 μL, 0.151 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL) and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes). The pure fractions were combined, concentrated, and the residue was dissolved in a minimal amount of ethyl acetate and precipitated with the addition of hexanes to afford the title compound as a white solid (0.0585 g, 71%). mp. 78-79 °C (ethyl acetate-hexanes); ¹H NMR (600 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 9.0 Hz), 7.72 (2H, d, *J* = 8.4 Hz), 7.57 (1H, t, *J* = 7.2 Hz), 7.46 (2H, t, *J* =

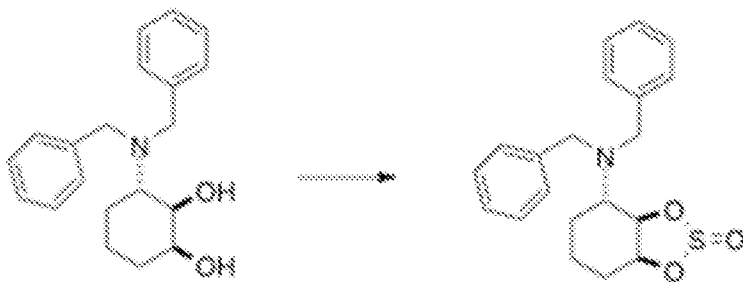
7.8 Hz), 7.32-7.40 (5H, m), 7.08 (2H, d, $J = 7.2$ Hz), 4.90 (1H, d, $J = 4.8$ Hz), 4.06 (1H, d, $J = 12.6, 10.2, 4.2$ Hz), 3.02-3.07 (1H, m), 2.93 (1H, td, $J = 10.2, 4.8$ Hz), 2.78 (1H, d, $J = 5.4$ Hz), 1.91-1.93 (1H, m), 1.72-1.75 (1H, m), 1.60-1.63 (1H, m), 1.29 (1H, qt, $J = 13.2, 3.0$ Hz), 1.09 (1H, qd, $J = 13.2, 3.0$ Hz), 0.98 (1H, qd, $J = 13.2, 4.2$ Hz); LCMS m/z 571.1190 ($[M + H]^+$, $C_{25}H_{25}F_3N_2O_6S_2$ requires 571.1179).



[00197] **N,N-dibenzylcyclohex-2-enamine**. A solution of dibenzylamine (5.00 g, 25.3 mmol) in DMF (20.0 mL) was cooled to 0 °C, treated with sodium hydride (60% wt. suspension in mineral oil, 1.06 g, 26.6 mmol), stirred for 15 minutes, then treated with 3-bromocyclohexene (2.91 mL, 25.3 mmol). The mixture was warmed to 25 °C, stirred for 14 h, then poured over a solution of saturated aqueous ammonium chloride (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The organic layers were combined, washed with saturated aqueous NaCl (3×100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-10% ethyl acetate-hexanes) to afford the title compound as a clear oil (4.97 g, 71%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (4H, d, $J = 7.8$ Hz), 7.30 (4H, t, $J = 7.8$ Hz), 7.21 (2H, d, $J = 7.2$ Hz), 5.82-5.83 (1H, m), 5.75 (1H, d, $J = 10.2$ Hz), 3.74 (2H, d, $J = 13.8$ Hz), 3.54 (2H, d, $J = 13.8$ Hz), 3.33-3.36 (1H, m), 1.97-2.01 (1H, m), 1.93-1.97 (1H, m), 1.88-1.93 (1H, m), 1.77-1.82 (1H, m), 1.51-1.58 (1H, m), 1.42-1.50 (1H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.1, 131.1, 130.3, 128.7, 128.3, 126.8, 54.7, 54.0, 25.6, 23.4, 22.1; LCMS m/z 278.1904 ($[M + H]^+$, $C_{20}H_{23}N$ requires 278.1903).

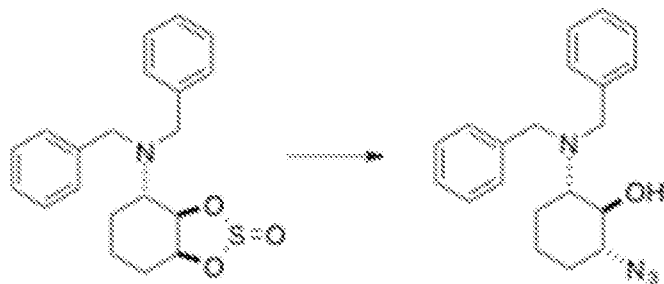


[00198] **rac-(1R,2S,3R)-3-(dibenzylamino)cyclohexane-1,2-diol**. A solution of N,N-dibenzylcyclohex-2-enamine. (3.40 g, 12.26 mmol) in t-BuOH-H₂O 5:1 (12.0 mL) at 25 °C was treated with OsO₄ (2.5 wt.% solution in t-BuOH, 1.53 mL, 0.122 mmol) and N-methylmorpholine N-oxide hydrate (1.82 g, 13.48 mmol). The mixture was stirred for 14 h at 25 °C, treated with a saturated aqueous solution of sodium hydrosulfite (5 mL) and stirred for an additional 1 h. The mixture was concentrated in vacuo and the residue was taken up in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes) to afford the title compound as a white solid (2.04 g, 53%). ¹H NMR (600 MHz, CDCl₃) δ 7.26-7.29 (4H, m), 7.20 (6H, m), 4.08 (1H, q, *J* = 2.4 Hz), 3.78 (2H, d, *J* = 13.8 Hz), 3.70 (1H, s), 3.46 (1H, dd, *J* = 10.2, 3.0 Hz), 3.34 (2H, d, *J* = 13.2 Hz), 2.85 (1H, ddd, *J* = 12.6, 10.8, 3.6 Hz), 2.20 (1H, d, *J* = 2.4 Hz), 1.93 (1H, doublet of quintets, *J* = 12.0, 3.0 Hz), 1.85 (2H, doublet of quintets, *J* = 14.4, 3.0 Hz), 1.53-1.60 (2H, m), 1.28-1.34 (1H, m), 1.20 (1H, qd, *J* = 12.0, 5.4 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 139.5, 129.2, 128.7, 127.4, 71.0, 68.5, 57.6, 53.8, 29.7, 22.2, 19.7; LCMS *m/z* 312.1959 ([M + H⁺], C₂₀H₂₅NO₂ requires 312.1958).

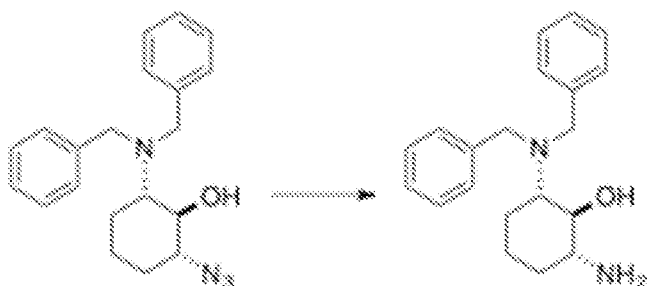


[00199] **rac-(3aS,4R,7aR)-4-(dibenzylamino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide**. A solution of rac-(1R,2S,3R)-3-(dibenzylamino)cyclohexane-1,2-diol (3.40 g, 10.9 mmol) in CH₂Cl₂ (10.0 mL) was cooled to 0 °C, treated with triethylamine (12.1 mL, 87.3 mmol) and then treated dropwise with thionyl chloride (2.38 mL, 32.8 mmol). The mixture was warmed to 25 °C, stirred for 2 h, and then poured over H₂O (200 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 100 mL) and then the combined organic layers were washed with H₂O (2 × 100 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-10% ethyl acetate-hexanes) to afford the title compound, a mixture of sulfite diastereoisomers, as an orange solid (4.51 g, 99%). ¹H NMR (600 MHz, CDCl₃) δ (as a mixture of diastereomers) 7.43 (2H, d, *J* = 7.2 Hz), 7.39 (2H, d, *J* = 7.2 Hz), 7.31-7.33 (2H, m), 2.28-7.30 (2H, m), 7.21-7.25 (2H, m), 1H[5.09-5.11 (m), 4.64-4.66 (m)], 1H[4.81 (dd,

$J = 9.6, 4.8 \text{ Hz}$), 4.50 (dd, $J = 9.6, 5.4 \text{ Hz}$), 3.85 (1H, d, $J = 14.4 \text{ Hz}$), 3.83 (1H, d, $J = 13.8 \text{ Hz}$), 3.71 (1H, d, $J = 14.4 \text{ Hz}$), 3.59 (1H, d, $J = 13.8 \text{ Hz}$), 1H[3.53 (ddd, $J = 12.6, 9.6, 4.2 \text{ Hz}$), 2.61 (ddd, $J = 12.6, 9.6, 3.6 \text{ Hz}$)], 2.24-2.29 (1H, m), 1.89-1.95 (1H, m), 1H[1.74-1.81 (m), 1.38 (qt, $J = 10.2, 3.6 \text{ Hz}$)], 1.60-1.67 (2H, m), 1.19-1.29 (1H, m); LCMS m/z 358.1465 ($[M + H]^+$, $C_{20}H_{23}NO_3S$ requires 357.1471).

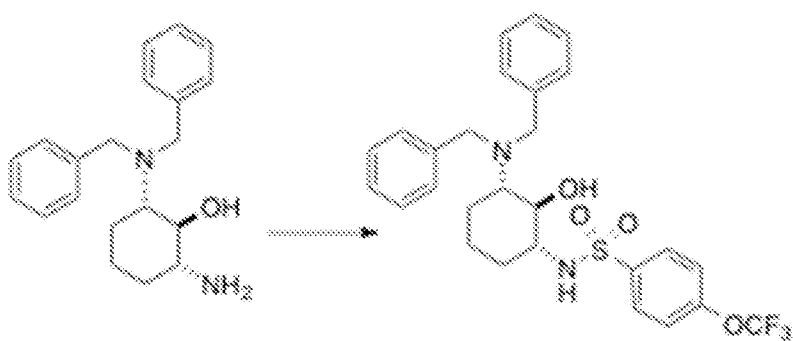


[00200] **rac-(1S,2S,6R)-2-azido-6-(dibenzylamino)cyclohexanol**. A solution of rac-(3aS,7aR)-4-(dibenzylamino)hexahydrobenzo[d][1,3,2]dioxathiole 2-oxide (4.51 g, 12.6 mmol) in DMF (5.0 mL) was treated with NaN_3 (2.46 g, 37.9 mmol) and heated to 100 °C for 14 h under microwave irradiation. The mixture was cooled to 25 °C, poured over a solution of saturated aqueous NaCl (100 mL), and extracted with CH_2Cl_2 ($3 \times 100 \text{ mL}$). The combined organic layers were washed with H_2O ($3 \times 100 \text{ mL}$), saturated aqueous NaCl (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was suspended in a minimal amount of CH_2Cl_2 and purified by flash chromatography (SiO_2 , 0-10% ethyl acetate-hexanes) to afford the title compound as a clear oil (0.549 g, 13%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.23-7.26 (4H, m), 7.16-7.20 (6H, m), 3.77 (2H, d, $J = 13.2 \text{ Hz}$), 3.39 (1H, t, $J = 9.6 \text{ Hz}$), 3.27 (2H, d, $J = 13.2 \text{ Hz}$), 3.08 (1H, ddd, $J = 12.6, 10.8, 4.2 \text{ Hz}$), 2.35 (1H, ddd, $J = 13.2, 11.4, 3.0 \text{ Hz}$), 1.87-1.89 (1H, m), 1.80-1.83 (1H, m), 1.75-1.78 (1H, m), 1.10-1.23 (3H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.0, 129.2, 128.8, 127.6, 73.4, 65.4, 62.3, 53.8, 30.0, 22.6, 21.5; LCMS m/z 337.2017 ($[M + H]^+$, $C_{20}H_{24}N_4O$ requires 337.2023).



[00201] **rac-(1R,2S,6R)-2-amino-6-(dibenzylamino)cyclohexanol**. A solution of rac-(1S,2S,6R)-2-azido-6-(dibenzylamino)cyclohexanol (0.549 g, 1.63 mmol) in THF (5.0 mL)

was cooled to 0 °C, treated with PPh₃ (0.642 g, 2.45 mmol), H₂O (0.25 mL), and stirred for 14 h at 25 °C. The solution was concentrated to dryness, dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-50% ethyl acetate-hexanes to remove nonpolar impurities followed by 3% MeOH-CH₂Cl₂ to remove triphenylphosphine oxide and 17:2:1 CH₂Cl₂:MeOH:NH₄OH to elute the product). The combined fractions of pure product were concentrated, dried azeotropically with toluene to afford the title compound as a beige film (0.410 g, 81%). ¹H NMR (600 MHz, CDCl₃) δ 7.24 (4H, d, *J* = 7.8 Hz), 7.15-7.20 (6H, m), 3.77 (2H, d, *J* = 12.0 Hz), 3.27 (2H, d, *J* = 12.6 Hz), 3.12 (1H, t, *J* = 9.6 Hz), 2.40 (1H, br s), 2.31 (1H, br s), 1.86 (1H, br s), 1.69 (2H, d, *J* = 10.2 Hz), 1.00-1.22 (3H, m); ¹³C NMR (150 MHz, CDCl₃) δ 139.4, 129.1, 128.7, 127.4, 75.6, 62.1, 55.9, 53.8, 32.9, 23.0, 21.9; LCMS *m/z* 311.2114 ([M + H]⁺, C₂₀H₂₆N₂O requires 311.2118).

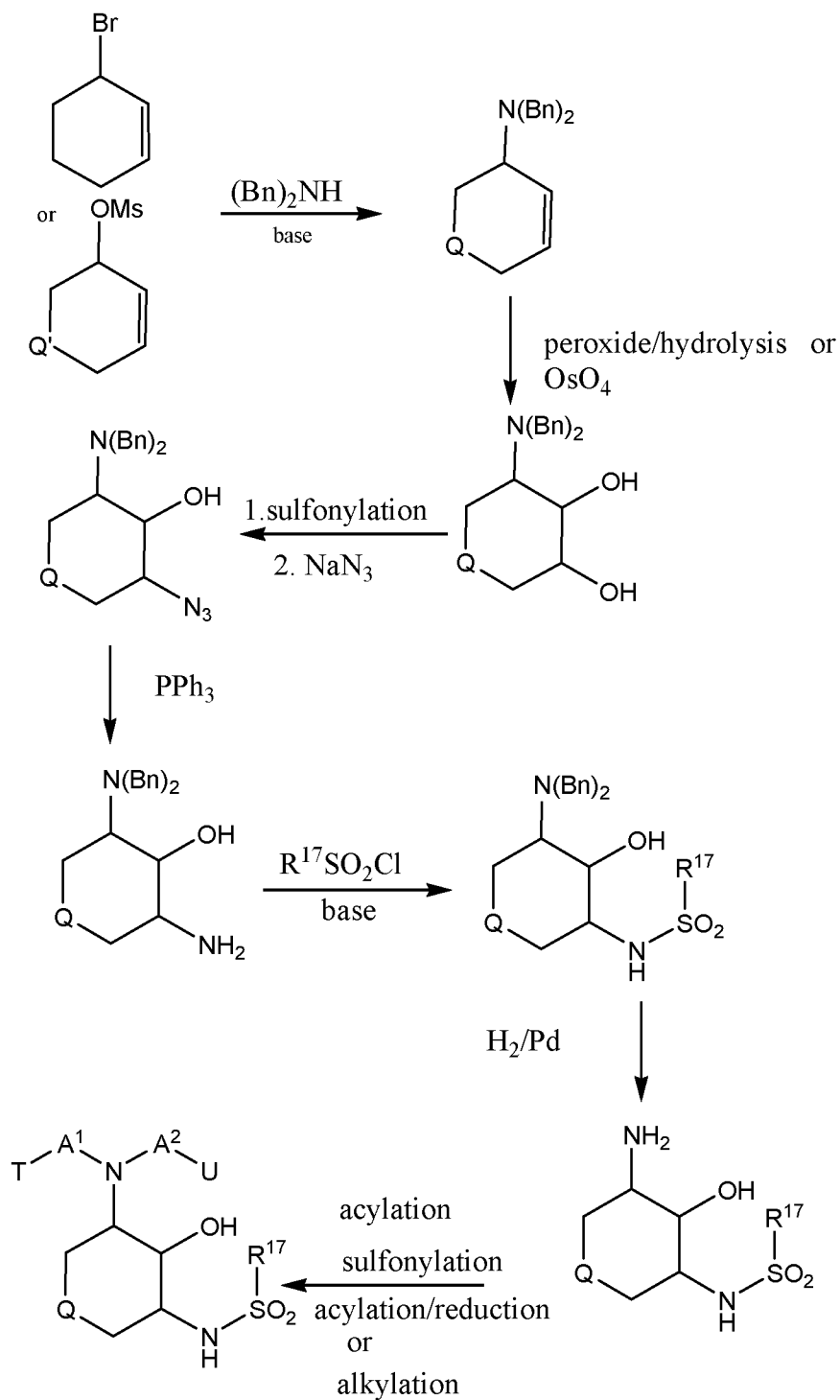


Example 19

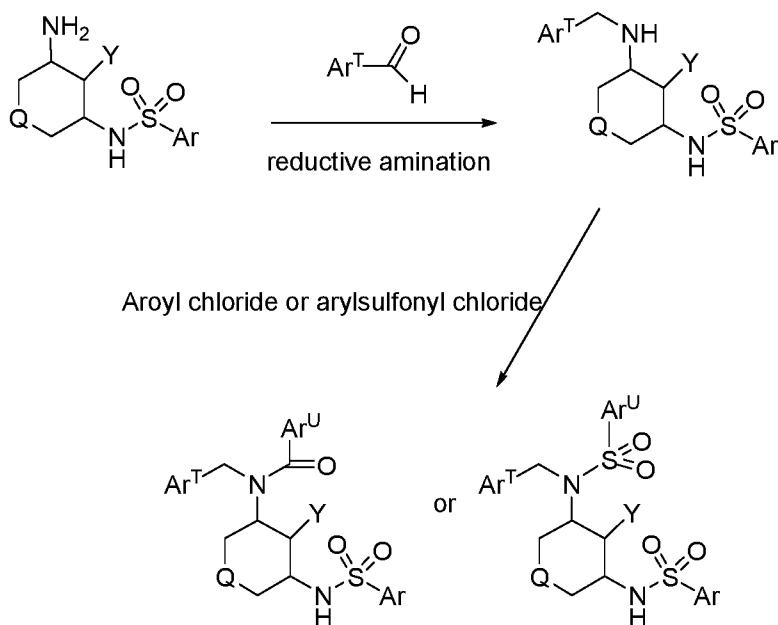
[00202] **rac-N-((1S,2S,3R)-3-(dibenzylamino)-2-hydroxycyclohexyl)-4-(trifluoromethoxy)benzenesulfonamide.** A solution of rac-(1R,2S,6R)-2-amino-6-(dibenzylamino)cyclohexanol (0.200 g, 0.644 mmol) in DMF (2.0 mL) was cooled to 0 °C, treated with Et₃N (89.0 μL, 0.644 mmol), and 4-trifluoromethoxybenzenesulfonyl chloride (109.0 μL, 0.644 mmol). The mixture was warmed to 25 °C, and stirred for 2 h. The mixture was partitioned between saturated aqueous NaCl (50 mL), and CH₂Cl₂ (100 mL). The organic layer was washed with saturated aqueous NaCl (3 × 50 mL), dried (Na₂SO₄), and concentrated in vacuo. The residue was dissolved in a minimal amount of CH₂Cl₂ and purified by flash chromatography (SiO₂, 0-35% ethyl acetate-hexanes) to afford the title compound as a yellow solid (0.322 g, 93%). ¹H NMR (600 MHz, CDCl₃) δ 7.83 (2H, d, *J* = 9.0 Hz), 7.16-7.24 (8H, m), 7.12 (4H, d, *J* = 7.12 Hz), 4.90 (1H, d, *J* = 3.6 Hz), 3.71 (2H, d, *J* = 13.2 Hz), 3.56 (1H, br s), 3.27 (2H, d, *J* = 13.8 Hz), 3.17 (1H, t, *J* = 9.6 Hz), 2.69-2.74 (1H, m), 2.26 (1H, m), 2.04-2.06 (1H, m), 1.81-1.84 (1H, m), 1.69 (1H, doublet of quintets, *J* = 10.8, 3.0 Hz), 1.10-1.22 (2H, m), 1.01-1.09 (1H, m); ¹³C NMR (150 MHz, CDCl₃) δ

152.1, 139.1, 139.0, 129.6, 129.0, 128.8, 127.6, 120.9, 119.6, 71.8, 62.5, 59.0, 53.8, 31.7, 22.5, 21.8; LCMS m/z 535.1863 ($[M + H]^+$, $C_{27}H_{29}F_3N_2O_4S$ requires 535.1873).

[00203] An alternative synthesis follows the route:

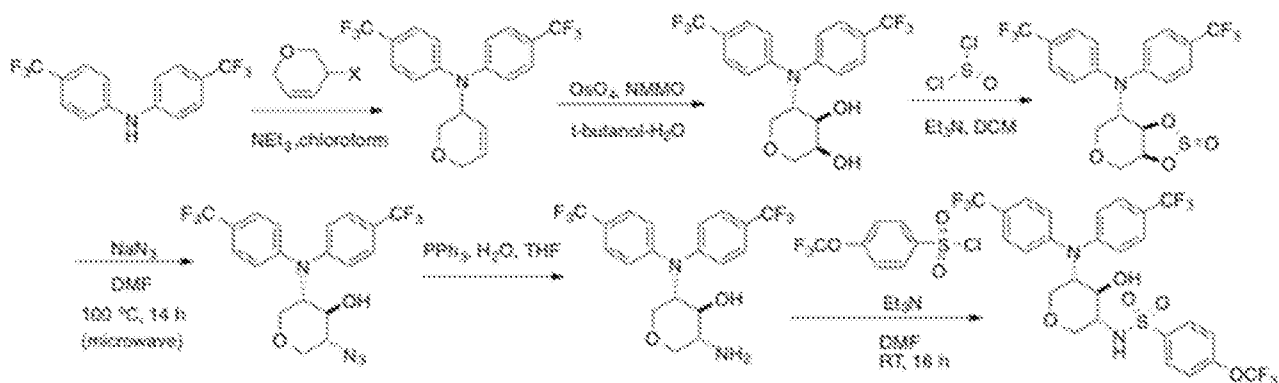


For example:



[00204] Examples in which the central ring constraint of Formula III is a heterocycle such as tetrahydropyran may be prepared as shown in Scheme 5.

Scheme 5

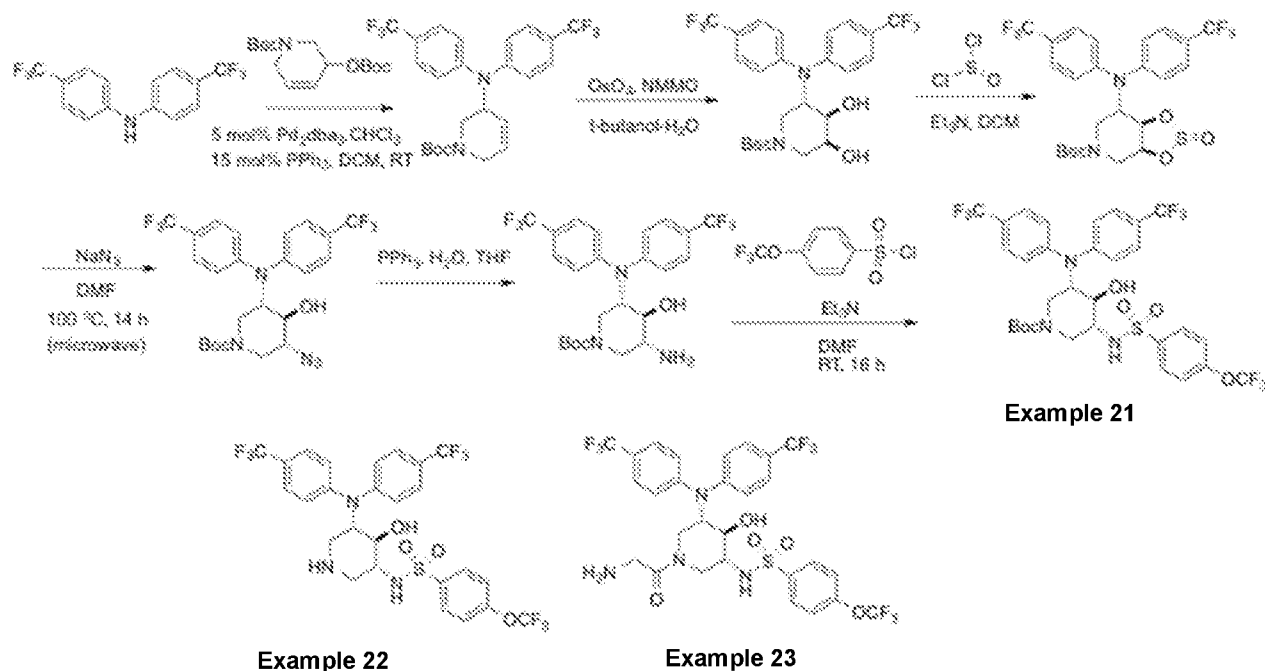


Example 20

[00205] Steps in the synthesis are analogous to Scheme 1, except that the alkylating reagent in the first step is either 3-bromo-3,6-dihydro-2*H*-pyran (X = Br) or 3-chloro-3,6-dihydro-2*H*-pyran (X = Cl)

[00206] Examples in which the central ring constraint of Formula III is piperidiny or N-substituted piperidiny may be prepared as shown in Scheme 6.

Scheme 6



[00207] To a solution of *tert*-butyl 5-hydroxy-5,6-dihydropyridine-1(2*H*)-carboxylate (10.0 g, 50.1 mmol) in THF (160 mL) was added *n*-butyllithium (2.5 M in hexanes, 19.8 mL, 2.50 mmol) at -78 °C. The resulting solution was warmed to 0 °C and stirred for 5 min prior to addition of di-*tert*-butyl dicarbonate (12.0 g, 55.1 mmol) in THF (80.0 mL). The reaction was warmed to RT, stirred for 16 h. The reaction was then quenched with water, extracted with ethyl acetate, washed with brine, concentrated, and the residue purified by flash chromatography (SiO₂, 0%-3% ethyl acetate-hexanes) to afford slightly crude *tert*-butyl 5-((*tert*-butoxycarbonyl)oxy)-5,6-dihydropyridine-1(2*H*)-carboxylate (15.3 g) as a colorless oil which was taken to the next step without further purification. This material serves as the alkylating agent in the first step of Scheme 6.

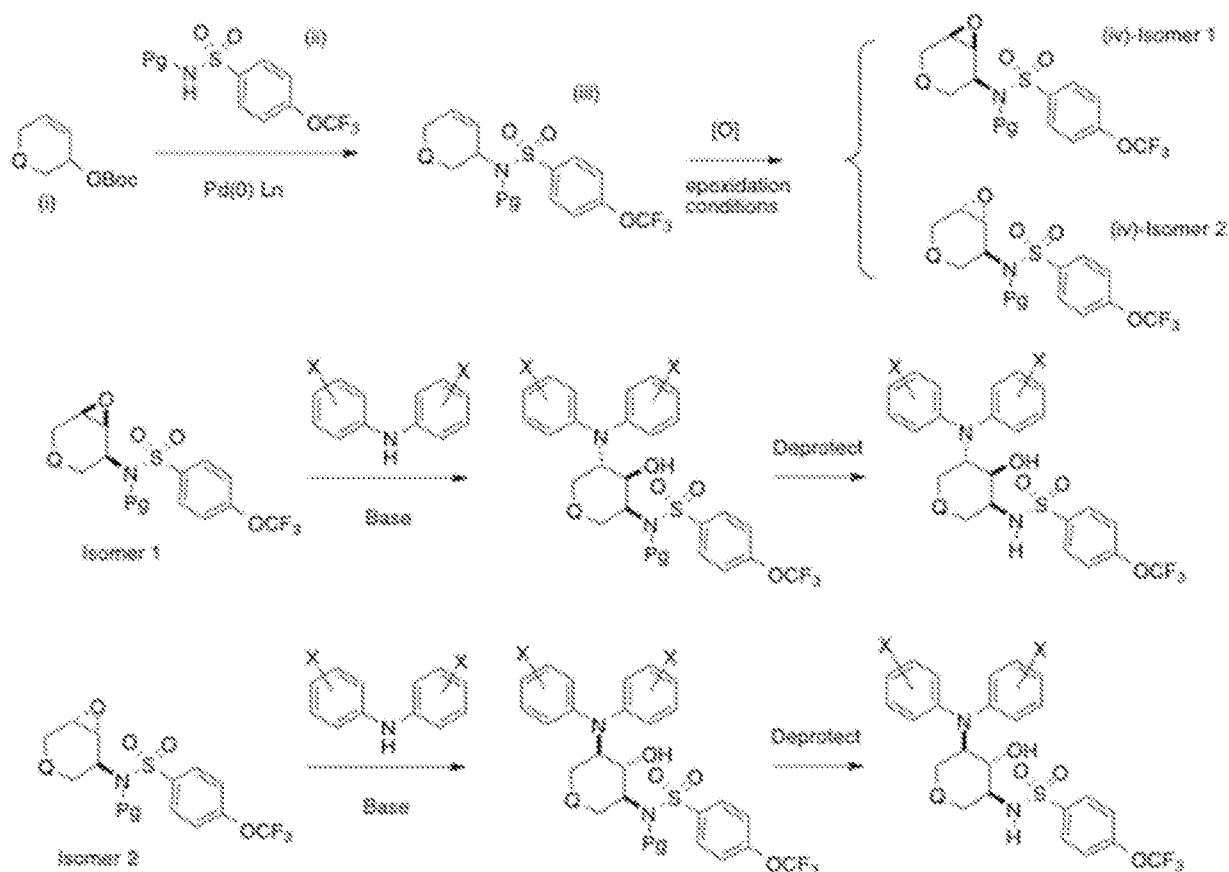
[00208] A Pd mediated alkylation may be carried out as follows: a 350 mL glass[®] pressure vessel was charged with Pd₂.dba₃, CHCl₃ (1.11 g, 1.07 mmol, 5 mol%), and triphenylphosphine (0.841 g, 3.21 mmol, 15 mol%). The vessel is sealed, evacuated and backfilled with argon three times. Dry degassed dichloromethane (60.0 mL) is added, and the mixture is stirred at room temperature for 60 min. Racemic *tert*-butyl cyclohex-2-en-1-yl carbonate (15.3 g, 51.1 mmol) is added followed by bis(4-(trifluoromethyl)phenyl)amine (21.4 mmol) in dry degassed dichloromethane. The reaction mixture is sealed and stirred at room temperature for one to ten days. At this point, the reaction mixture is evaporated onto silica gel and subjected to column chromatography on silica gel eluting with ethyl acetate-hexane to afford *tert*-butyl 3-(bis(4-(trifluoromethyl)phenyl)amino)-3,6-dihydropyridine-

1(2*H*)-carboxylate which is taken to the next step without purification. Use of chiral bisphosphine ligands such as DACH-phenyl Trost ligand will yield enantiomerically enriched material.

[00209] *Tert*-butyl 3-(bis(4-(trifluoromethyl)phenyl)amino)-3,6-dihydropyridine-1(2*H*)-carboxylate obtained in the above process (or by other routes) is carried forward using the steps shown in Scheme 6, using conditions analogous to those described for Scheme 1. Boc-protected Example 21 may be deprotected using trifluoroacetic acid in methylenechloride to give Example 22, which is then further elaborated to give Example 23 or related compounds.

[00210] Alternate Epoxidation Route

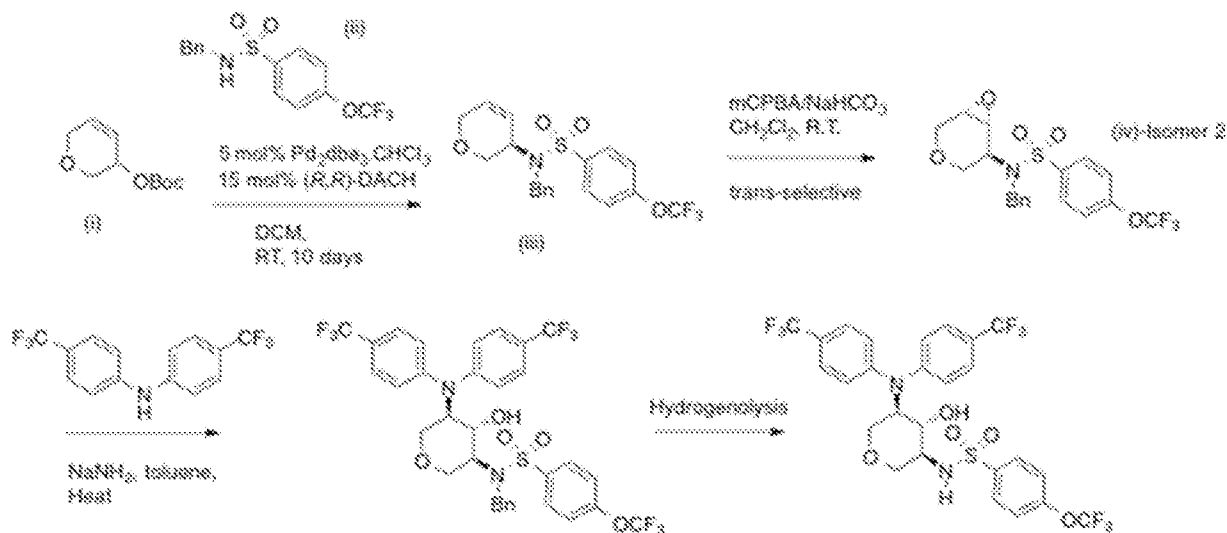
Scheme 7



[00211] An alternative route to compounds of the present invention is outlined in Scheme 7 in which a cyclic or heterocyclic allylic carbonate is first reacted with a protected aryl sulfonamide in the presence of a palladium catalyst. This may be carried out with control of the newly formed chiral center by using a chiral ligand such as the Trost-DACH bisphosphine. Thus reagents of type (i) are reacted with an optionally protected

arylsulfonamide(ii), for example 4-trifluoromethoxybenzene sulfonamide in the presence of a chiral palladium catalyst to give enantiomerically enriched allylarylsulfonamides of type (iii). Protecting groups, Pg, include but are not limited to, benzyl(Bn) and substituted benzyl groups or alkoxycarbonyl groups such as Boc or Cbz. The protected allylic sulfonamides (iii) may be epoxidized in a non-diastereoselective fashion to give a diastereomeric mixture of epoxides, (iv), which are separated by chromatographic techniques; or alternatively stereoselective epoxidation will give access to one diastereoisomer preferentially. Epoxidation reagents include peroxy acids such as mCPBA, dioxiranes such as dimethyldioxirane, oxaziridines such as 3-phenyl-2-tosyl-1,2-oxaziridine or hydroperoxides such as *t*-butylhydroperoxide with transition metal ion catalysis. Either isomer of compound (iv) is converted to PP2A activators of the present invention by treatment with an optionally substituted diaryl amine in the presence of a base such as sodium amide, sodium hydride or potassium *t*-butoxide in an aprotic solvent. Protecting groups are removed by, for example hydrogenolysis where Pg = benzyl, or other condition appropriate for the original choice of protecting groups. Alternatively the diastereomeric mixture of (iv) may be carried forward and isomers separated at the penultimate benzyl protected stage or the final deprotected products.

[00212] A specific example of this process is shown in **Scheme 8**:



[00213] **Synthesis of (R)-N-benzyl-N-(3,6-dihydro-2H-pyran-3-yl)-4-(trifluoromethoxy)benzenesulfonamide (iii):**

N-benzyl-4-(trifluoromethoxy)benzenesulfonamide (0.200 g, 0.603 mmol) was reacted with *tert*-butyl (3,6-dihydro-2H-pyran-3-yl) carbonate (0.289 g, 1.45 mmol) in presence of

(*R,R*)-DACH for 10 days to afford (*R*)-*N*-benzyl-*N*-(3,6-dihydro-2*H*-pyran-3-yl)-4-(trifluoromethoxy)benzenesulfonamide (0.228 g, 92%). ¹H NMR (600 MHz, MeOD) δ 7.89 (2H, d, *J* = 8.4 Hz), 7.43 (2H, d, *J* = 8.4 Hz), 7.32 (2H, d, *J* = 7.2 Hz), 7.26-7.20 (3H, m), 5.93 (1H, d, *J* = 10.2 Hz), 5.41 (1H, d, *J* = 10.2 Hz), 4.66-4.63 (1H, m), 4.48-4.44 (2H, m), 3.98-3.91 (2H, m), 3.70 (1H, dd, *J* = 12.0, 4.2 Hz), 3.55 (1H, dd, *J* = 12.0, 3.6 Hz); ¹³C NMR (150 MHz, MeOD) δ 152.0, 140.0, 138.6, 132.0, 129.3, 127.9, 127.0, 123.0, 121.2, 119.6, 68.1, 64.5, 51.6, 48.3; HPLC analysis: (CHIRALPAK IA-3, 70:30 hexanes-EtOH-diethylamine, 1.0 mL/min, UV: 254 nm), t_R = 2.72 min (minor), 5.10 min (major); HPLC analysis: >94% ee Material produced in this fashion exhibited [α]²⁵_D = -93.0° (c = 1.0, CH₃OH); HRMS *m/z* 414.0989 ([M + H]⁺, C₁₉H₁₉F₃NO₄S requires 414.0988).

[00214] **Conversion to PP2A Activator, *N*-((3*S*,4*S*,5*R*)-5-(bis(4-(trifluoromethyl)phenyl)amino)-4-hydroxytetrahydro-2*H*-pyran-3-yl)-4-(trifluoromethoxy)benzenesulfonamide.**

Trans-stereoselective epoxidation of intermediate (iii) is carried out using conditions reported in O'Brein et al, Organic Letters, vol. 5, Pages 4955-4957, 2003, to give epoxide intermediate, (iv)-isomer 2. Epoxide opening is carried out with bis(4-(trifluoromethyl)phenyl)amine in the presence of a base such as NaNH₂ in toluene with heating for 50 – 100°C for between 1 and 24 hours. Deprotection of the benzyl group is carried out by hydrogenolysis with a catalyst such as palladium on carbon or palladium hydroxide on carbon, to give the product *N*-((3*S*,4*S*,5*R*)-5-(bis(4-(trifluoromethyl)phenyl)amino)-4-hydroxytetrahydro-2*H*-pyran-3-yl)-4-(trifluoromethoxy)benzenesulfonamide.

Cell viability assays (IC₅₀ determination)

[00215] Cell viability assays were performed according to Denizot, F. and R. Lang, Journal of Immunological Methods, 1986. 89(22): p. 271 - 277. H1650 lung cancer cells were plated at 150,000 cells per well in a 12 well plate. Twenty-four hours after plating, cells were treated as described with increasing concentrations of drug and control. Forty-eight hours after drug treatment, cells were treated with 100 μL of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and incubated for 2 hours at 37 °C. The MTT solution was subsequently replaced with 300 μL of n-propyl alcohol and re-aliquoted to a 96 well plate. Spectrophotometric analysis of each solution was performed using a 96 well plate reader at 600 nm in triplicate. Results are shown in Table 1:

[00216] Table1. Cell Viability Data

Example No.	H1650 GI50
1a	15 uM
2	10 uM
3	5 uM
5a	10 uM
6	10 uM
7	15 uM
8	10 uM
8a	5 uM
10	20 uM
11	15 uM
12	20 uM

Example No.	H1650 GI50
13	30 uM
14	25 uM
15	10 uM
16	15 uM
17	20 uM
18	20 uM
19	15 uM
24	10 uM
25	15 uM
26	45% @ 40 uM
27	52% @ 40 uM

Colony Formation Assay

[00217] Protocol for clonogenic assay follows Sangodkar et al., J Clin Invest 2012;122:2637-51.

[00218] Cell culture and staining: For both A549luc and H1650 cells, 500 cells are seeded into each well of a 6-well plate and allowed to attach for 24 hours before drug treatment. The following day, cells are treated with either the appropriate dose of drug or an equivalent volume of DMSO (two replicates are treated for each condition). For each condition, depleted media is replaced with fresh media containing the equivalent drug dose four days after initial treatment. Cells are harvested either 7 (A549luc) or 8 (H1650) days after initial treatment. Briefly, medium is aspirated from each well and the cells are washed twice with ice-cold PBS, then plates are allowed to dry at room temperature for 4 hours. Cells are fixed for one hour in a fixing solution consisting of 10% methanol and 10% glacial acetic acid in distilled water, then stained overnight in 1% (w/v) crystal violet dissolved in methanol. The next day, staining solution is aspirated from the wells and plates are washed gently with distilled water to remove excess stain before colony counting. Colonies are imaged on a ChemiDoc XRS+ (Bio-Rad) and images are exported as 8-bit TIFF files. Colonies are counted using the Colony Counter plugin in ImageJ, with colony size defined as between 4 and 400 square pixels, and minimum circularity set at 0.6. Duplicate wells are averaged to obtain a single value for each condition. Results (number

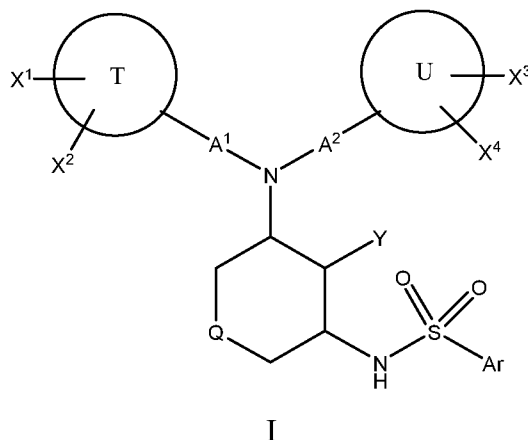
of colonies) for A549luc cells and results (number of colonies) for H1650 cells may be analyzed separately.

In vivo cancer model

[00219] To assess the *in vivo* effects of the compounds, subcutaneous xenograft of lung cancer cell line H441 is generated. Cells (5×10^6) are injected into the right flank of 6- to 8-week-old male BALB/c *nu/nu* mice (Charles River, Wilmington, MA). Tumor volume is assessed twice a week by caliper measurement. Mice are randomized to treatment groups based on initial tumor volume average of 100mm^3 per group. Mice are dosed by oral gavage with, for example, 15 mg/kg QD, 15 mg/kg BID, 50 mg/kg QD, or 50 mg/kg BID. Mouse tumors are measured twice a week for the duration of the study. Mouse body weights are recorded weekly and percentage of mice body weights during treatment is calculated as: weight at each time point/initial weight $\times 100$. Animals are observed for signs of toxicity (mucous diarrhea, abdominal stiffness and weight loss). Mice undergo treatment for 30 days and are sacrificed 2 hours after the last dose. Tumors are then excised and cut for both formalin-fixation and snap frozen in liquid nitrogen.

[00220] Various embodiments of the invention can be described in the text below:

[1]. A compound of formula I:



wherein:

T is a benzene ring or a five- or six-membered heteroaromatic ring;

U is a benzene ring or a five- or six-membered heteroaromatic ring;

X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from hydrogen, halogen, nitro, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkylthio, -NR¹R², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, -SO₂NR¹R², and a heterocyclic ring;

R^1 and R^2 are independently selected in each instance from the group consisting of hydrogen and (C₁-C₆)alkyl;

A^1 and A^2 are independently selected in each instance from a direct bond, CH₂, SO₂, and C(=O);

Y is selected from hydrogen and hydroxyl;

Q is selected from -(CH₂)_t-, -O-, S(O)_p-, and -NR^Q-;

p is zero, 1 or 2;

t is zero, 1 or 2;

R^Q is selected from hydrogen, optionally substituted (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl; -SO₂R³; -SO₂N(R³R⁴); -C(=O)R⁵; -C(=O)OR⁵; or -C(=O)N(R³R⁴); wherein said substituents on the (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl are selected from the group consisting of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy;

R^3 and R^4 are independently selected in each instance from hydrogen, (C₁-C₆)alkyl, aryl, and arylalkyl, wherein said aryl or the aryl of the arylalkyl is optionally substituted with hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, or (C₁-C₄)alkoxy;

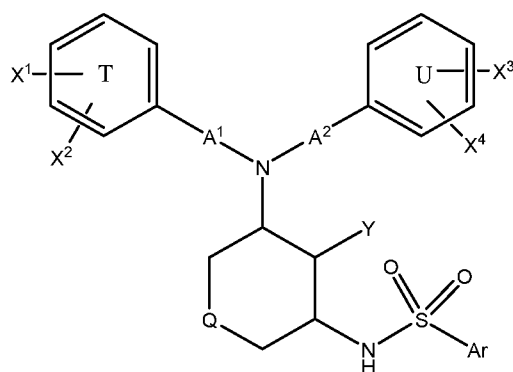
R^5 is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, or optionally substituted aryl, wherein said optional substituents are selected from the group consisting of (C₁-C₃)alkyl, OR¹, NH₂, NHMe, N(Me)₂, and heterocycle; and

Ar is an optionally substituted aromatic or heteroaromatic ring.

[2]. A compound of [1] above, or according to other embodiments of the invention, wherein T and U are each independently selected from the group consisting of a benzene ring and pyridine.

[3]. A compound of [2] above, or according to other embodiments of the invention, wherein at least one of T and U is a benzene ring.

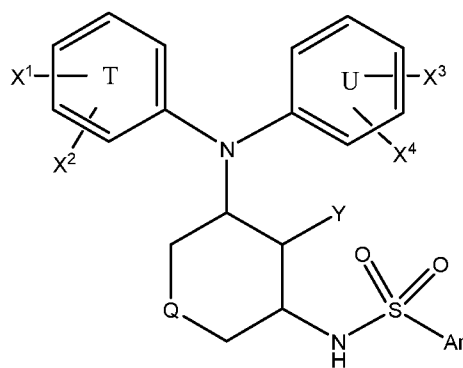
[4]. A compound of [3] above, or according to other embodiments of the invention, of formula II:



II.

[5]. A compound of [1] above, or according to other embodiments of the invention, wherein at least one of A^1 and A^2 is a direct bond or CH_2 .

[6]. A compound of [5] above, or according to other embodiments of the invention, of formula III, wherein both of A^1 and A^2 are direct bonds:



III.

[7]. A compound of [1] above, or according to other embodiments of the invention, wherein Y is hydroxyl.

[8]. A compound of [1] above, or according to other embodiments of the invention, wherein Y is hydrogen.

[9]. A compound of [1] above, or according to other embodiments of the invention, wherein Q is $-(CH_2)_t$.

[10]. A compound of [9] above, or according to other embodiments of the invention, wherein t is 1.

[11]. A compound of [9] above, or according to other embodiments of the invention, wherein t is 2.

[12]. A compound of [9] above, or according to other embodiments of the invention, wherein t is 0.

[13]. A compound of [1] above, or according to other embodiments of the invention, wherein Q is -O-.

[14]. A compound of [1] above, or according to other embodiments of the invention, wherein Q is -NR^Q-.

[15]. A compound of [14] above, or according to other embodiments of the invention, wherein R^Q is hydrogen; (C₁-C₆)alkyl optionally substituted with one or more of hydroxy, fluoro, or (C₃-C₇)cycloalkyl; (C₃-C₇)cycloalkyl optionally substituted with one or more of hydroxy, methyl, or fluoro; aryl optionally substituted with one or more of hydroxy, methoxy, halogen, (C₁-C₃)haloalkyl, nitro, amino, or methyl; heteroaryl optionally substituted with one or more of hydroxy, methoxy, halogen, (C₁-C₃)haloalkyl, nitro, amino, or methyl; -SO₂R³; -SO₂NR³R⁴; -C(=O)R⁵; -C(=O)OR⁵; or -C(=O)NR³R⁴;

R³ is selected in each instance from hydrogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, aryl, and arylalkyl, wherein said aryl or the aryl of the arylalkyl is optionally substituted with one or more of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy;

R⁴ is selected in each instance from hydrogen and methyl;

R⁵ is selected from optionally substituted (C₁-C₄)alkyl or optionally substituted aryl, wherein said optional substituents are selected from one or more of OH, OMe, NH₂, NHMe, N(Me)₂, and heterocycle.

[16]. A compound of [15] above, or according to other embodiments of the invention, wherein R^Q is selected from hydrogen; (C₁-C₃)alkyl optionally substituted with one or more of hydroxy or fluoro; (C₃-C₇)cycloalkyl optionally substituted with one or more of hydroxy, methyl, or fluoro; phenyl optionally substituted with one or more of hydroxy, chloro, fluoro, methoxy, nitro, amino, trifluoromethyl, or methyl; or a nitrogen-containing heteroaryl optionally substituted with one or two methyl groups.

[17]. A compound of [14] above, or according to other embodiments of the invention, wherein R^Q is -C(=O)R⁵.

[18]. A compound of [17] above, or according to other embodiments of the invention, wherein R^5 is selected from (C₁-C₄)alkyl, optionally substituted with OR¹, NH₂, NHMe, N(Me)₂, and heterocycle.

[19]. A compound of [14] above, or according to other embodiments of the invention, wherein R^Q is -C(=O)OR⁵.

[20]. A compound of [19] above, or according to other embodiments of the invention, wherein R^5 is selected from the group consisting of phenyl and (C₁-C₄)alkyl, each of which may be substituted with OR¹.

[21]. A compound of [14] above, or according to other embodiments of the invention, wherein R^Q is -SO₂R³.

[22]. A compound of [21] above, or according to other embodiments of the invention, wherein wherein R^3 is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, and aryl; wherein said aryl is optionally substituted with hydroxy, halogen, cyano, amino, or (C₁-C₄)alkoxy.

[23]. A compound of [14] above, or according to other embodiments of the invention, wherein R^Q is SO₂NR³R⁴.

[24]. A compound of [23] above, or according to other embodiments of the invention, wherein R^3 is selected from the group consisting of hydrogen, (C₁-C₃)alkyl, and optionally substituted aryl; and R^4 is hydrogen or methyl.

[25]. A compound of [14] above, or according to other embodiments of the invention, wherein R^Q is -C(=O)NR³R⁴.

[26]. A compound of [25] above, or according to other embodiments of the invention, wherein R^3 is selected from the group consisting of hydrogen, (C₁-C₃)alkyl, and aryl optionally substituted with hydroxy, halogen, cyano, amino, or methoxy; and R^4 is hydrogen or methyl.

[27]. A compound of [1] above, or according to other embodiments of the invention, wherein Q is -S(O)_p-.

[28]. A compound of [27] above, or according to other embodiments of the invention, wherein p is 2.

[29]. A compound of [27] above, or according to other embodiments of the invention, wherein p is 1.

[30]. A compound of [27] above, or according to other embodiments of the invention, wherein p is 0.

[31]. A compound of [1] above, or according to other embodiments of the invention, wherein Ar is phenyl substituted with Z^1 and Z^2 ; and

Z^1 and Z^2 are independently selected in each instance from the group consisting of hydrogen, halogen, nitro, cyano, azide, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, -NR¹R², -NR¹C(O)R², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, and -SO₂NR¹R².

[32]. A compound of [31] above, or according to other embodiments of the invention, wherein Z^1 and Z^2 are independently selected in each instance from hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy.

[33]. A compound of [32] above, or according to other embodiments of the invention, wherein Z^1 is hydrogen and Z^2 is selected from hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy.

[34]. A compound of [33] above, or according to other embodiments of the invention, wherein Z^2 is hydrogen, fluoro, chloro, cyano, trifluoromethyl, methoxy, or trifluoromethoxy.

[35]. A compound of [34] above, or according to other embodiments of the invention, wherein Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

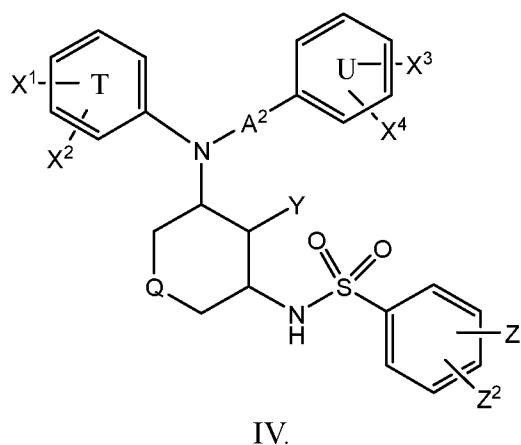
[36]. A compound of [1] above, or according to other embodiments of the invention, wherein zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, cyano, and morpholino, and the remainder are hydrogen.

[37]. A compound of [36] above, or according to other embodiments of the invention, wherein zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance

from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen.

[38]. A compound of [36] above, or according to other embodiments of the invention, wherein the one or two of X¹, X², X³, and X⁴ that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[39]. A compound of [1] above, or according to other embodiments of the invention, of formula IV:



[40]. A compound of [39] above, or according to other embodiments of the invention, wherein Y is hydroxyl.

[41]. A compound of [39] above, or according to other embodiments of the invention, wherein A² is a direct bond or CH₂.

[42]. A compound of [41] above, or according to other embodiments of the invention, wherein A² is a direct bond.

[43]. A compound of [39] above, or according to other embodiments of the invention, wherein Q is selected from CH₂, O, and NR^Q; R^Q is selected from hydrogen, -C(=O)R⁵, and -C(=O)OR⁵; and R⁵ is selected from hydrogen and optionally substituted (C₁-C₄)alkyl, wherein said optional substituents are selected from the group consisting of NH₂, NHMe, and N(Me)₂.

[44]. A compound of [39] above, or according to other embodiments of the invention, wherein Z¹ is hydrogen and Z² is selected from hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy.

[45]. A compound of [44] above, or according to other embodiments of the invention, wherein Z^2 is hydrogen, fluoro, chloro, cyano, methoxy, or trifluoromethoxy.

[46]. A compound of [45] above, or according to other embodiments of the invention, wherein Z^2 is trifluoromethoxy.

[47]. A compound of [44] above, or according to other embodiments of the invention, wherein Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

[48]. A compound of [39] above, or according to other embodiments of the invention, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, cyano, and morpholino, and the remainder are hydrogen.

[49]. A compound of [48] above, or according to other embodiments of the invention, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen.

[50]. A compound of [48] above, or according to other embodiments of the invention, wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[51]. A compound of [39] above, or according to other embodiments of the invention, wherein:

Y is hydroxyl;

A^2 is a direct bond;

Q is selected from CH₂, O, and NR^Q;

R^Q is selected from hydrogen, -C(=O)R⁵, and -C(=O)OR⁵;

R⁵ is selected from hydrogen and optionally substituted (C₁-C₄)alkyl, wherein said optional substituents are selected from the group consisting of NH₂, NHMe, and N(Me)₂;

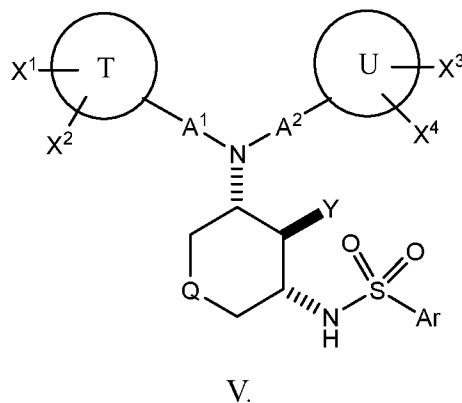
Z^1 is hydrogen;

Z^2 is para to the attachment of the phenyl ring to the sulfonyl and is selected from hydrogen, fluoro, chloro, cyano, methoxy, or trifluoromethoxy; and

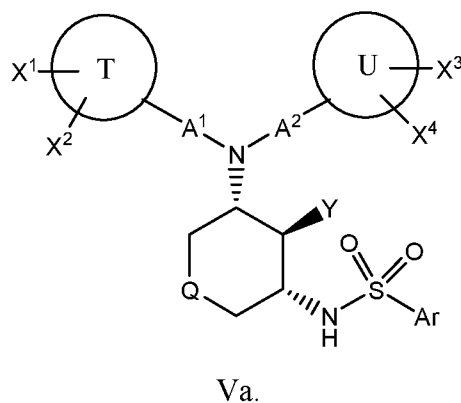
zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen; wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not

hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

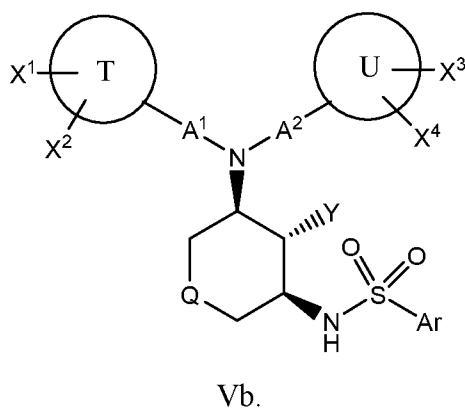
[52]. A compound of [1] above, or according to other embodiments of the invention, wherein the relative stereochemistry is of formula V:



[53]. A compound of [52] above, or according to other embodiments of the invention, of formula Va:



[54]. A compound of [52] above, or according to other embodiments of the invention, of formula Vb:



[55]. A method for treating a disease in a patient chosen from:

- (a) cancer
- (b) diabetes
- (c) autoimmune disease
- (d) age onset proteotoxic disease
- (e) mood disorder
- (f) acne vulgaris
- (g) solid organ transplant rejection
- (h) graft vs. host disease
- (i) cardiac hypertrophy
- (j) viral infection and
- (k) parasitic infection;

the method comprising administering to the patient a therapeutically effective amount of a compound of any of [1] to [54] above, or according to other embodiments of the invention.

[56]. The method of [55] above, or according to other embodiments of the invention, wherein said cancer is selected from the group consisting of: ovarian, pancreatic, renal cell, breast, prostate, lung, hepatocellular carcinoma, glioma, leukemia, lymphoma, colorectal cancers, and sarcomas.

[57]. The method of [55] above, or according to other embodiments of the invention, for treating cancer, wherein said cancer is chemotherapy resistant cancer.

[58]. The method of [57] above, or according to other embodiments of the invention, wherein the method further comprises administering one or more additional cancer chemotherapeutic agents.

[59]. The method of [55] above, or according to other embodiments of the invention, for treating an age onset proteotoxic disease, wherein said disease is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.

[60]. The method of [55] above, or according to other embodiments of the invention, for treating a viral infection.

[61]. The method of [60] above, or according to other embodiments of the invention, wherein said viral infection is caused by a virus selected from the group consisting of influenza, HIV-1, HPV, adenovirus, BKV, EBV, JCV, HCV, MCV, polyomavirus, SV40,

HTLV-1, HSV-1, CMV, hepatitis B, BPV-1, human T-cell lymphotropic virus type 1, Japanese encephalitis virus, RSV, and West Nile virus.

[62]. The method of [55] above, or according to other embodiments of the invention, for treating a parasitic infection.

[63]. The method of [62] above, or according to other embodiments of the invention, wherein said parasitic infection is caused by a parasite selected from the group consisting of *Plasmodium* and *Theileria*.

[64]. A method for restoring sensitivity to one or more chemotherapeutic agents in the treatment of cancer, the method comprising administering an effective amount of a compound of any of [1] to [54] above, or according to other embodiments of the invention.

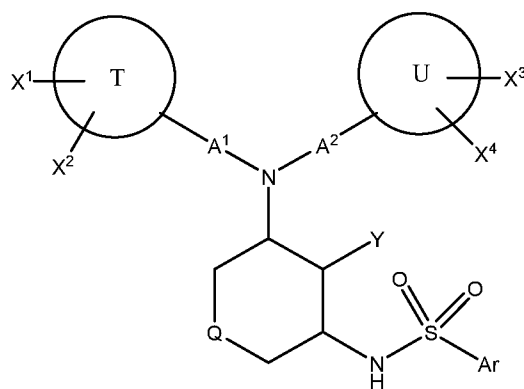
[65]. A method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of the PI3K-AKT-FOXO signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound of any of [1] to [54] above, or according to other embodiments of the invention.

[66]. A method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of a Myc dependent signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound of any of [1] to [54] above, or according to other embodiments of the invention.

[67]. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of [1] to [54] above, or according to other embodiments of the invention.

[00221] Various embodiments of the invention can be described in the text below:

[101]. A compound of formula I:



I

wherein:

T is a benzene ring, thiophene, furan, or pyridine;

U is a benzene ring, thiophene, furan, or pyridine;

X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from hydrogen, halogen, nitro, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkylthio, -NR¹R², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, -SO₂NR¹R², and a heterocyclic ring;

R¹ and R² are independently selected in each instance from the group consisting of hydrogen and (C₁-C₆)alkyl;

A¹ and A² are independently selected in each instance from a direct bond, CH₂, SO₂, and C(=O);

Y is selected from hydrogen and hydroxyl;

Q is selected from -(CH₂)_t-, -O-, S(O)_p-, and -NR^Q-;

p is zero, 1 or 2;

t is zero, 1 or 2;

R^Q is selected from hydrogen, optionally substituted (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl; -SO₂R³; -SO₂N(R³R⁴); -C(=O)R⁵; -C(=O)OR⁵; or -C(=O)N(R³R⁴); wherein said substituents on the (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl are selected from the group consisting of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy;

R³ and R⁴ are independently selected in each instance from hydrogen, (C₁-C₆)alkyl, aryl, and arylalkyl, wherein said aryl or the aryl of the arylalkyl is optionally substituted with hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, or (C₁-C₄)alkoxy;

R⁵ is selected from hydrogen, optionally substituted (C₁-C₄)alkyl, or optionally substituted aryl, wherein said optional substituents are selected from the group consisting of (C₁-C₃)alkyl, OR¹, NH₂, NHMe, N(Me)₂, and heterocycle; and

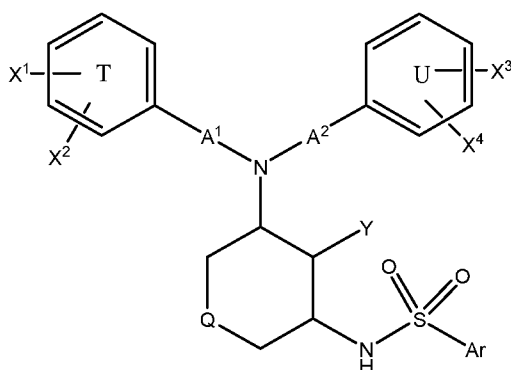
Ar is an optionally substituted aromatic or heteroaromatic ring,

with the proviso that, when A¹ and A² are both CH₂, Y is hydroxyl, Q is -(CH₂)_t-, and Ar is 4-trifluoromethoxyphenyl, then T and U may not both be phenyl substituted at the para position by methoxy or cyano.

[102]. A compound of [101] above, or according to other embodiments of the invention, wherein T and U are each independently selected from the group consisting of a benzene ring and pyridine.

[103]. A compound of [102] above, or according to other embodiments of the invention, wherein at least one of T and U is a benzene ring.

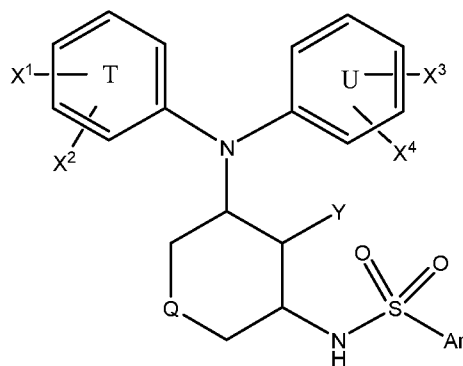
[104]. A compound of [103] above, or according to other embodiments of the invention, of formula II:



II.

[105]. A compound of [101] above, or according to other embodiments of the invention, wherein at least one of A¹ and A² is a direct bond or CH₂.

[106]. A compound of [105] above, or according to other embodiments of the invention, of formula III, wherein both of A¹ and A² are direct bonds:



III.

[107]. A compound of [101] above, or according to other embodiments of the invention, wherein Y is hydroxyl.

[108]. A compound of [101] above, or according to other embodiments of the invention, wherein Y is hydrogen.

[109]. A compound of [101] above, or according to other embodiments of the invention, wherein Q is $-(CH_2)_t-$.

[110]. A compound of [109] above, or according to other embodiments of the invention, wherein t is 1.

[111]. A compound of [109] above, or according to other embodiments of the invention, wherein t is 2.

[112]. A compound of [109] above, or according to other embodiments of the invention, wherein t is 0.

[113]. A compound of [101] above, or according to other embodiments of the invention, wherein Q is $-O-$.

[114]. A compound of [101] above, or according to other embodiments of the invention, wherein Q is $-NR^Q-$.

[115]. A compound of [114] above, or according to other embodiments of the invention, wherein R^Q is hydrogen; (C_1-C_6) alkyl optionally substituted with one or more of hydroxy, fluoro, or (C_3-C_7) cycloalkyl; (C_3-C_7) cycloalkyl optionally substituted with one or more of hydroxy, methyl, or fluoro; aryl optionally substituted with one or more of hydroxy, methoxy, halogen, (C_1-C_3) haloalkyl, nitro, amino, or methyl; heteroaryl optionally substituted with one or more of hydroxy, methoxy, halogen, (C_1-C_3) haloalkyl, nitro, amino, or methyl; $-SO_2R^3$; $-SO_2NR^3R^4$; $-C(=O)R^5$; $-C(=O)OR^5$; or $-C(=O)NR^3R^4$;

R^3 is selected in each instance from hydrogen, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, aryl, and arylalkyl, wherein said aryl or the aryl of the arylalkyl is optionally substituted with one or more of hydroxy, halogen, cyano, nitro, amino, (C_1-C_4) alkylamino, (C_1-C_4) dialkylamino, (C_1-C_4) acylamino, (C_1-C_4) alkylsulfonyl, (C_1-C_4) alkylthio, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, and (C_1-C_4) alkoxy;

R^4 is selected in each instance from hydrogen and methyl;

R^5 is selected from optionally substituted (C_1-C_4) alkyl or optionally substituted aryl, wherein said optional substituents are selected from one or more of OH, OMe, NH_2 , NHMe, $N(Me)_2$, and heterocycle.

[116]. A compound of [115] above, or according to other embodiments of the invention, wherein R^Q is selected from hydrogen; (C_1-C_3) alkyl optionally substituted with

one or more of hydroxy or fluoro; (C₃-C₇)cycloalkyl optionally substituted with one or more of hydroxy, methyl, or fluoro; phenyl optionally substituted with one or more of hydroxy, chloro, fluoro, methoxy, nitro, amino, trifluoromethyl, or methyl; or a nitrogen-containing heteroaryl optionally substituted with one or two methyl groups.

[117]. A compound of [114] above, or according to other embodiments of the invention, wherein R^Q is -C(=O)R⁵.

[118]. A compound of [117] above, or according to other embodiments of the invention, wherein R⁵ is selected from (C₁-C₄)alkyl, optionally substituted with OR¹, NH₂, NHMe, N(Me)₂, and heterocycle.

[119]. A compound of [114] above, or according to other embodiments of the invention, wherein R^Q is -C(=O)OR⁵.

[120]. A compound of [119] above, or according to other embodiments of the invention, wherein R⁵ is selected from the group consisting of phenyl and (C₁-C₄)alkyl, each of which may be substituted with OR¹.

[121]. A compound of [114] above, or according to other embodiments of the invention, wherein R^Q is -SO₂R³.

[122]. A compound of [121] above, or according to other embodiments of the invention, wherein R³ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, and aryl; wherein said aryl is optionally substituted with hydroxy, halogen, cyano, amino, or (C₁-C₄)alkoxy.

[123]. A compound of [114] above, or according to other embodiments of the invention, wherein R^Q is SO₂NR³R⁴.

[124]. A compound of [123] above, or according to other embodiments of the invention, wherein R³ is selected from the group consisting of hydrogen, (C₁-C₃)alkyl, and optionally substituted aryl; and R⁴ is hydrogen or methyl.

[125]. A compound of [114] above, or according to other embodiments of the invention, wherein R^Q is -C(=O)NR³R⁴.

[126]. A compound of [125] above, or according to other embodiments of the invention, wherein R^3 is selected from the group consisting of hydrogen, (C_1-C_3) alkyl, and aryl optionally substituted with hydroxy, halogen, cyano, amino, or methoxy; and R^4 is hydrogen or methyl.

[127]. A compound of [101] above, or according to other embodiments of the invention, wherein Q is $-S(O)_p-$.

[128]. A compound of [127] above, or according to other embodiments of the invention, wherein p is 2.

[129]. A compound of [127] above, or according to other embodiments of the invention, wherein p is 1.

[130]. A compound of [127] above, or according to other embodiments of the invention, wherein p is 0.

[131]. A compound of [101] above, or according to other embodiments of the invention, wherein Ar is phenyl substituted with Z^1 and Z^2 ; and

Z^1 and Z^2 are independently selected in each instance from the group consisting of hydrogen, halogen, nitro, cyano, azide, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)OR^2$, $-OR^1$, $-C(O)R^1$, $-OC(O)R^1$, $-C(O)NR^1R^2$, $-C(O)OR^1$, $-SR^1$, $-SO_2R^1$, and $-SO_2NR^1R^2$.

[132]. A compound of [131] above, or according to other embodiments of the invention, wherein Z^1 and Z^2 are independently selected in each instance from hydrogen, halogen, (C_1-C_6) haloalkyl, cyano, $-NR^1C(O)OR^6$, (C_1-C_6) alkoxy, and (C_1-C_6) haloalkoxy.

[133]. A compound of [132] above, or according to other embodiments of the invention, wherein Z^1 is hydrogen and Z^2 is selected from hydrogen, halogen, (C_1-C_6) haloalkyl, cyano, $-NR^1C(O)OR^6$, (C_1-C_6) alkoxy, and (C_1-C_6) haloalkoxy.

[134]. A compound of [133] above, or according to other embodiments of the invention, wherein Z^2 is hydrogen, fluoro, chloro, cyano, trifluoromethyl, NHBoc, methoxy, or trifluoromethoxy.

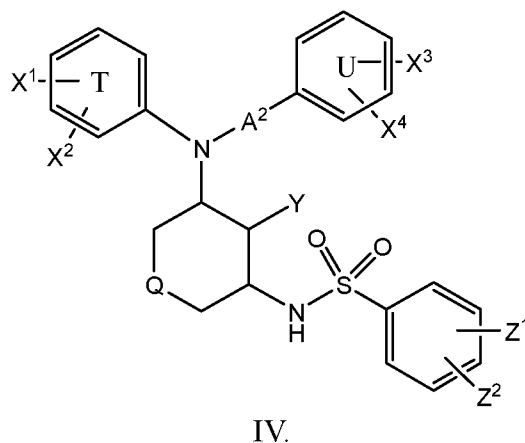
[135]. A compound of [134] above, or according to other embodiments of the invention, wherein Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

[136]. A compound of [101] above, or according to other embodiments of the invention, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from halogen, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, cyano, and morpholino, and the remainder are hydrogen.

[137]. A compound of [136] above, or according to other embodiments of the invention, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C_1-C_3) alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro (C_1-C_3) alkyl, and the remainder are hydrogen.

[138]. A compound of [136] above, or according to other embodiments of the invention, wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[139]. A compound of [101] above, or according to other embodiments of the invention, of formula IV:



[140]. A compound of [139] above, or according to other embodiments of the invention, wherein Y is hydroxyl.

[141]. A compound of [139] above, or according to other embodiments of the invention, wherein A^2 is a direct bond or CH_2 .

[142]. A compound of [141] above, or according to other embodiments of the invention, wherein A^2 is a direct bond.

[143]. A compound of [139] above, or according to other embodiments of the invention, wherein Q is selected from CH_2 , O, and NR^Q ; R^Q is selected from hydrogen, $-C(=O)R^5$, and $-C(=O)OR^5$; and R^5 is selected from hydrogen and optionally substituted $(C_1-$

C₄)alkyl, wherein said optional substituents are selected from the group consisting of NH₂, NHMe, and N(Me)₂.

[144]. A compound of [139] above, or according to other embodiments of the invention, wherein Z¹ is hydrogen and Z² is selected from hydrogen, halogen, (C₁-C₆)haloalkyl, cyano, -NR¹C(O)OR⁶, (C₁-C₆)alkoxy, and (C₁-C₆)haloalkoxy.

[145]. A compound of [144] above, or according to other embodiments of the invention, wherein Z² is hydrogen, fluoro, chloro, cyano, NHBoc, methoxy, or trifluoromethoxy.

[146]. A compound of [145] above, or according to other embodiments of the invention, wherein Z² is trifluoromethoxy.

[147]. A compound of [144] above, or according to other embodiments of the invention, wherein Z² is para to the attachment of the phenyl ring to the sulfonyl.

[148]. A compound of [139] above, or according to other embodiments of the invention, wherein zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from halogen, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, cyano, and morpholino, and the remainder are hydrogen.

[149]. A compound of [148] above, or according to other embodiments of the invention, wherein zero, one or two of X¹, X², X³, and X⁴ are independently selected in each instance from (C₁-C₃)alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro(C₁-C₃)alkyl, and the remainder are hydrogen.

[150]. A compound of [148] above, or according to other embodiments of the invention, wherein the one or two of X¹, X², X³, and X⁴ that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

[151]. A compound of [139] above, or according to other embodiments of the invention, wherein:

Y is hydroxyl;

A² is a direct bond;

Q is selected from CH₂, O, and NR^Q;

R^Q is selected from hydrogen, -C(=O)R⁵, and -C(=O)OR⁵;

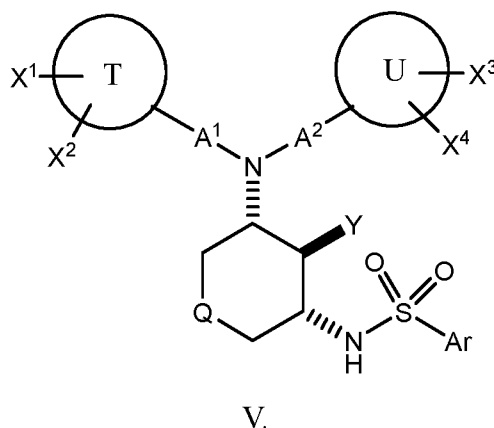
R^5 is selected from hydrogen and optionally substituted (C_1-C_4) alkyl, wherein said optional substituents are selected from the group consisting of NH_2 , $NHMe$, and $N(Me)_2$;

Z^1 is hydrogen;

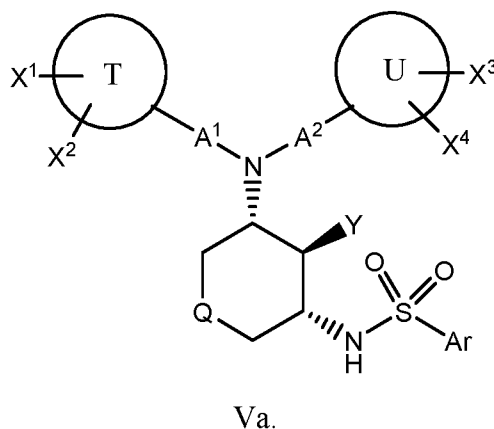
Z^2 is para to the attachment of the phenyl ring to the sulfonyl and is selected from hydrogen, fluoro, chloro, cyano, $NHBoc$, methoxy, or trifluoromethoxy; and

zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C_1-C_3) alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro (C_1-C_3) alkyl, and the remainder are hydrogen; wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

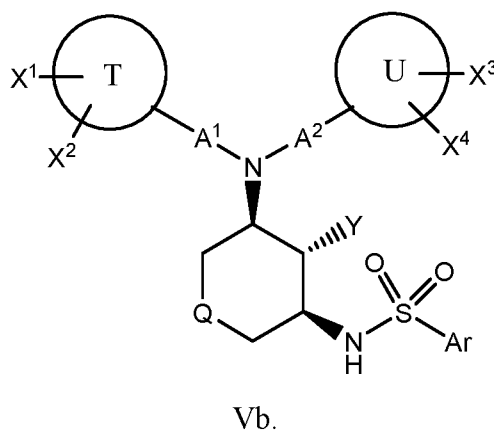
[152]. A compound of [101] above, or according to other embodiments of the invention, wherein the relative stereochemistry is of formula V:



[153]. A compound of [152] above, or according to other embodiments of the invention, of formula Va:



[154]. A compound of [152] above, or according to other embodiments of the invention, of formula Vb:



[155]. A method for treating a disease in a patient chosen from:

- (a) cancer
- (b) diabetes
- (c) autoimmune disease
- (d) age onset proteotoxic disease
- (e) mood disorder
- (f) acne vulgaris
- (g) solid organ transplant rejection
- (h) graft vs. host disease
- (i) cardiac hypertrophy
- (j) viral infection and
- (k) parasitic infection;

the method comprising administering to the patient a therapeutically effective amount of a compound of any of [101] to [154] above, or according to other embodiments of the invention.

[156]. The method of [155] above, or according to other embodiments of the invention, wherein said cancer is selected from the group consisting of: ovarian, pancreatic, renal cell, breast, prostate, lung, hepatocellular carcinoma, glioma, leukemia, lymphoma, colorectal cancers, and sarcomas.

[157]. The method of [155] above, or according to other embodiments of the invention, for treating cancer, wherein said cancer is chemotherapy resistant cancer.

[158]. The method of [157] above, or according to other embodiments of the invention, wherein the method further comprises administering one or more additional cancer chemotherapeutic agents.

[159]. The method of [155] above, or according to other embodiments of the invention, for treating an age onset proteotoxic disease, wherein said disease is selected from the group consisting of: Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis.

[160]. The method of [155] above, or according to other embodiments of the invention, for treating a viral infection.

[161]. The method of [160] above, or according to other embodiments of the invention, wherein said viral infection is caused by a virus selected from the group consisting of influenza, HIV-1, HPV, adenovirus, BKV, EBV, JCV, HCV, MCV, polyomavirus, SV40, HTLV-1, HSV-1, CMV, hepatitis B, BPV-1, human T-cell lymphotropic virus type 1, Japanese encephalitis virus, RSV, and West Nile virus.

[162]. The method of [155] above, or according to other embodiments of the invention, for treating a parasitic infection.

[163]. The method of [162] above, or according to other embodiments of the invention, wherein said parasitic infection is caused by a parasite selected from the group consisting of *Plasmodium* and *Theileria*.

[164]. A method for restoring sensitivity to one or more chemotherapeutic agents in the treatment of cancer, the method comprising administering an effective amount of a compound of any of [101] to [154] above, or according to other embodiments of the invention.

[165]. A method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of the PI3K-AKT-FOXO signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound of any of [101] to [154] above, or according to other embodiments of the invention.

[166]. A method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of a Myc dependent signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound of any of [101] to [154] above, or according to other embodiments of the invention.

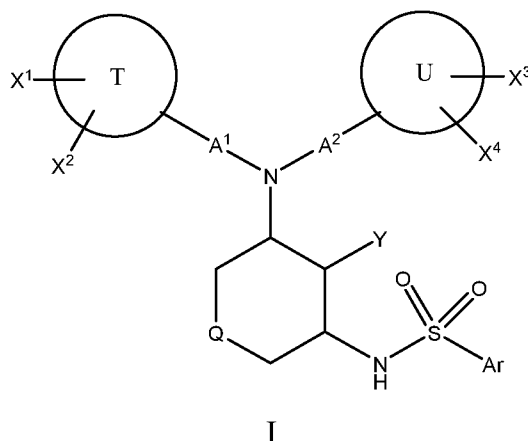
[167]. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of [101] to [154] above, or according to other embodiments of the invention.

[00222] While typical embodiments have been set forth for the purpose of illustration, the foregoing descriptions and examples should not be deemed to be a limitation on the scope of the invention. Accordingly, various modifications, adaptations, and alternatives may occur to one skilled in the art without departing from the spirit and scope of the present invention.

CLAIMS

We claim:

1. A compound of formula I:



wherein:

T is a benzene ring, thiophene, furan, or pyridine;

U is a benzene ring, thiophene, furan, or pyridine;

X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from hydrogen, halogen, nitro, cyano, (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkylthio, -NR¹R², -OR¹, -C(O)R¹, -OC(O)R¹, -C(O)NR¹R², -C(O)OR¹, -SR¹, -SO₂R¹, -SO₂NR¹R², and a heterocyclic ring;

R¹ and R² are independently selected in each instance from the group consisting of hydrogen and (C₁-C₆)alkyl;

A¹ and A² are independently selected in each instance from a direct bond, CH₂, SO₂, and C(=O);

Y is selected from hydrogen and hydroxyl;

Q is selected from -(CH₂)_t-, -O-, S(O)_p-, and -NR^Q-;

p is zero, 1 or 2;

t is zero, 1 or 2;

R^Q is selected from hydrogen, optionally substituted (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl; -SO₂R³; -SO₂N(R³R⁴); -C(=O)R⁵; -C(=O)OR⁵; or -C(=O)N(R³R⁴); wherein said substituents on the (C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, aryl, or heteroaryl are selected from the group consisting of hydroxy, halogen, cyano, nitro, amino, (C₁-C₄)alkylamino, (C₁-C₄)dialkylamino, (C₁-C₄)acylamino, (C₁-C₄)alkylsulfonyl, (C₁-C₄)alkylthio, (C₁-C₄)alkyl, (C₃-C₇)cycloalkyl, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, and (C₁-C₄)alkoxy;

R^3 and R^4 are independently selected in each instance from hydrogen, (C_1-C_6) alkyl, aryl, and arylalkyl, wherein said aryl or the aryl of the arylalkyl is optionally substituted with hydroxy, halogen, cyano, nitro, amino, (C_1-C_4) alkylamino, (C_1-C_4) dialkylamino, (C_1-C_4) acylamino, (C_1-C_4) alkylsulfonyl, (C_1-C_4) alkylthio, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, or (C_1-C_4) alkoxy;

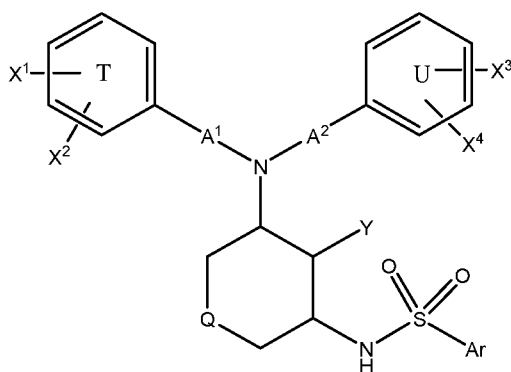
R^5 is selected from hydrogen, optionally substituted (C_1-C_4) alkyl, or optionally substituted aryl, wherein said optional substituents are selected from the group consisting of (C_1-C_3) alkyl, OR^1 , NH_2 , $NHMe$, $N(Me)_2$, and heterocycle; and

Ar is an optionally substituted aromatic or heteroaromatic ring,

with the proviso that, when A^1 and A^2 are both CH_2 , Y is hydroxyl, Q is $-(CH_2)_t-$, and Ar is 4-trifluoromethoxyphenyl, then T and U may not both be phenyl substituted at the para position by methoxy or cyano.

2. A compound according to claim 1 wherein at least one of T and U is a benzene ring.

3. A compound according to claim 2 of formula II:



II.

4. A compound according to any one of claims 1-3 wherein at least one of A^1 and A^2 is a direct bond or CH_2 .

5. A compound according to any one of the above claims wherein Y is hydroxyl.

6. A compound according to any one of the above claims wherein Q is $-(CH_2)_t-$.

7. A compound according to any one of the above claims, wherein Ar is phenyl substituted with Z^1 and Z^2 ; and

Z^1 and Z^2 are independently selected in each instance from the group consisting of hydrogen, halogen, nitro, cyano, azide, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy,

$-\text{NR}^1\text{R}^2$, $-\text{NR}^1\text{C}(\text{O})\text{R}^2$, $-\text{NR}^1\text{C}(\text{O})\text{OR}^2$, $-\text{OR}^1$, $-\text{C}(\text{O})\text{R}^1$, $-\text{OC}(\text{O})\text{R}^1$, $-\text{C}(\text{O})\text{NR}^1\text{R}^2$, $-\text{C}(\text{O})\text{OR}^1$, $-\text{SR}^1$, $-\text{SO}_2\text{R}^1$, and $-\text{SO}_2\text{NR}^1\text{R}^2$.

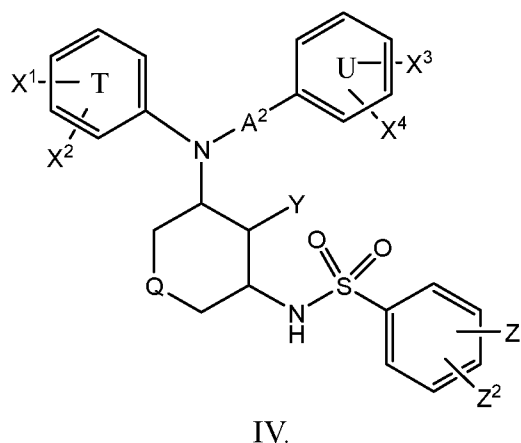
8. A compound according to claim 7 wherein Z^1 is hydrogen and Z^2 is selected from hydrogen, halogen, $(\text{C}_1\text{-C}_6)\text{haloalkyl}$, cyano, $-\text{NR}^1\text{C}(\text{O})\text{OR}^6$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, and $(\text{C}_1\text{-C}_6)\text{haloalkoxy}$.

9. A compound according to claim 8 wherein Z^2 is hydrogen, fluoro, chloro, cyano, trifluoromethyl, NHBoc, methoxy, or trifluoromethoxy.

10. A compound according to any one of the above claims wherein Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

11. A compound according to any one of the above claims, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from halogen, $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_1\text{-C}_6)\text{haloalkyl}$, cyano, and morpholino, and the remainder are hydrogen.

12. A compound according to claim 1 of formula IV:



13. A compound according to claim 12 wherein Y is hydroxyl.

14. A compound according to claim 12 wherein Q is selected from CH_2 , O, and NR^Q ; R^Q is selected from hydrogen, $-\text{C}(=\text{O})\text{R}^5$, and $-\text{C}(=\text{O})\text{OR}^5$; and R^5 is selected from hydrogen and optionally substituted $(\text{C}_1\text{-C}_4)\text{alkyl}$, wherein said optional substituents are selected from the group consisting of NH_2 , NHMe , and $\text{N}(\text{Me})_2$.

15. A compound according to claim 12 wherein Z^2 is hydrogen, fluoro, chloro, cyano, NHBoc, methoxy, or trifluoromethoxy.

16. A compound according to claim 15 wherein Z^2 is para to the attachment of the phenyl ring to the sulfonyl.

17. A compound according to claim 12, wherein zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from halogen, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, cyano, and morpholino, and the remainder are hydrogen.

18. A compound according to claim 12, wherein:

Y is hydroxyl;

A^2 is a direct bond;

Q is selected from CH_2 , O, and NR^Q ;

R^Q is selected from hydrogen, $-C(=O)R^5$, and $-C(=O)OR^5$;

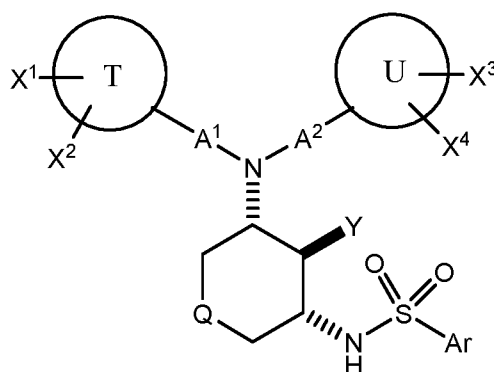
R^5 is selected from hydrogen and optionally substituted (C_1-C_4) alkyl, wherein said optional substituents are selected from the group consisting of NH_2 , $NHMe$, and $N(Me)_2$;

Z^1 is hydrogen;

Z^2 is para to the attachment of the phenyl ring to the sulfonyl and is selected from hydrogen, fluoro, chloro, cyano, $NHBoc$, methoxy, or trifluoromethoxy; and

zero, one or two of X^1 , X^2 , X^3 , and X^4 are independently selected in each instance from (C_1-C_3) alkyl, chloro, fluoro, bromo, cyano, morpholino, and fluoro (C_1-C_3) alkyl, and the remainder are hydrogen; wherein the one or two of X^1 , X^2 , X^3 , and X^4 that are not hydrogen are in the para position relative to the attachment of ring T and/or ring U to the nitrogen.

19. A compound according to any one of the above claims wherein the relative stereochemistry is of formula V:



V.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any one of claims 1-19.

21. A method for treating a disease in a patient chosen from:

- (a) cancer
- (b) diabetes
- (c) autoimmune disease
- (d) age onset proteotoxic disease
- (e) mood disorder
- (f) acne vulgaris
- (g) solid organ transplant rejection
- (h) graft vs. host disease
- (i) cardiac hypertrophy
- (j) viral infection and
- (k) parasitic infection;

the method comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-19.

22. A method for restoring sensitivity to one or more chemotherapeutic agents in the treatment of cancer, the method comprising administering an effective amount of a compound according to any one of claims 1-19.

23. A method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of the PI3K-AKT-FOXO signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-19.

24. A method for treating a disease or disorder in a patient where the disease or disorder involves the dysregulation of a Myc dependent signaling pathway, the method comprising administering to the patient a therapeutically effective amount of a compound according to any one of claims 1-19.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/050692

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D309/14 C07C311/29 C07D211/56 A61K31/18 A61K31/351
A61K31/445 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/025882 A2 (MT SINAI SCHOOL OF MEDICINE [US]; OHLMEYER MICHAEL [US]; NARLA GOUTHAM) 21 February 2013 (2013-02-21) paragraph [0002] paragraph [0006] paragraph [0016] page 109; example 73 claim 1 -----	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

18 October 2016

Date of mailing of the international search report

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Koch, Kristian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/050692

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