



(43) International Publication Date
23 June 2016 (23.06.2016)

(10) International Publication Number
WO 2016/100452 A2

- (51) **International Patent Classification:**
A61K 31/506 (2006.01) *C07D 401/12* (2006.01)
- (21) **International Application Number:**
PCT/US2015/066002
- (22) **International Filing Date:**
16 December 2015 (16.12.2015)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/093,037 17 December 2014 (17.12.2014) US
- (71) **Applicant:** CELGENE AVILOMICS RESEARCH, INC. [US/US]; 45 Wiggins Avenue, Bedford, Massachusetts 01730 (US).
- (72) **Inventor:** QIAO, Lixin; 49 Blanchard Street, Andover, Massachusetts 01810 (US).
- (74) **Agents:** BUTEAU, Kristen C. et al.; Choate, Hall & Stewart LLP, Two International Place, Boston, Massachusetts 02110 (US).
- (81) **Designated States** (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

- *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) **Title:** HETEROARYL COMPOUNDS AND USES THEREOF

(57) **Abstract:** The present invention provides compounds which inhibit one or both of ERK1 and ERK2 protein kinase activity, pharmaceutically acceptable compositions thereof, and methods of using the same.



WO 2016/100452 A2

HETEROARYL COMPOUNDS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/093,037, filed December 17, 2014, the contents of which are hereby incorporated herein in their entirety.

FIELD OF THE INVENTION

[0002] The present invention provides various forms and compositions useful as inhibitors of ERK kinases, for example one or both of ERK1 and ERK2 kinases.

BACKGROUND OF THE INVENTION

[0003] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is protein kinases.

[0004] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.).

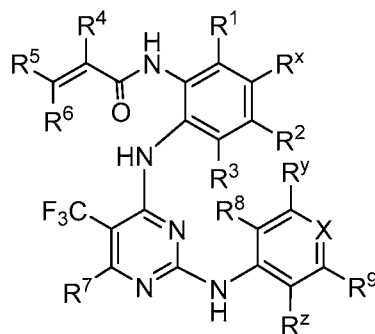
[0005] The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begins with activation of Ras. Activation of Ras leads to the recruitment and activation of Raf, a serine-threonine kinase. Activated Raf then phosphorylates and activates MEK1/2, which then phosphorylates and activates one or both of ERK1 and ERK2. When activated, one or both of ERK1 and ERK2 phosphorylates several downstream targets involved in a multitude of cellular

events including cytoskeletal changes and transcriptional activation. The ERK/MAPK pathway is one of the most important for cell proliferation, and it is believed that the ERK/MAPK pathway is frequently activated in many tumors. Ras genes, which are upstream of one or both of ERK1 and ERK2, are mutated in several cancers including colorectal, melanoma, breast and pancreatic tumors. The high Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased kinase activity. Mutations in BRAF have been identified in melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers.

[0006] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0007] It has now been found that compounds of the present invention, and compositions thereof, are useful as inhibitors of one or both of ERK1 and ERK2 and exhibit desirable characteristics for the same. Such compounds have general Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^y , R^z and X is as defined herein.

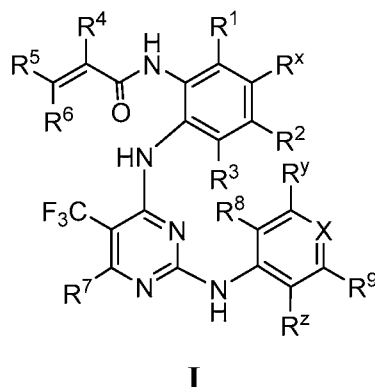
[0008] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with abnormal cellular responses triggered by certain protein kinase-mediated events. Such diseases, disorders, or conditions include those described herein.

[0009] Compounds provided by this invention are also useful for the study of certain kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors. Additional compounds and methods can be found in PCT application publication number WO2014/124230, published August 14, 2014 (“the ‘230 publication,” the entirety of which is hereby incorporated herein by reference). The ‘230 publication describes certain ERK inhibitor compounds which covalently and irreversibly inhibit activity of one or both of ERK1 and ERK2 kinases.

DETAILED DESCRIPTION OF THE INVENTION

1. General Description of Certain Aspects of the Invention

[0010] In certain embodiments, the present invention provides inhibitors of one or both of ERK1 and ERK2 and conjugates thereof. In some embodiments, such compounds include those of the formulae described herein, or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein. Such compounds have the structure of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen or deuterium;

R^x is selected from hydrogen, deuterium, or $-C(H)_j(D)_k$;

j is 0-3;

k is 0-3;

wherein the sum of j and k is 3;

R^y is selected from $R^{y'}$ or $-C(=O)N(H)_r(D)_s$;

$R^{y'}$ is $-\text{OC}(\text{H})_m(\text{D})_n$;

m is 0-3;

n is 0-3;

wherein the sum of m and n is 3;

r is 0-2

s is 0-2

wherein the sum of r and s is 2;

R^z is $-\text{C}(\text{H})_p(\text{D})_q$;

p is 0-3;

q is 0-3;

wherein the sum of p and q is 3; and

X is N or CH;

provided that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^y , or R^z is or contains deuterium.

2. Definitions

[0011] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0012] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in

detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0013] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0014] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

[0015] As used herein, the term “inhibitor” is defined as a compound that binds to and /or inhibits the target protein kinase with measurable affinity. In certain embodiments, an inhibitor has an IC₅₀ and/or binding constant of less than about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, or less than about 10 nM.

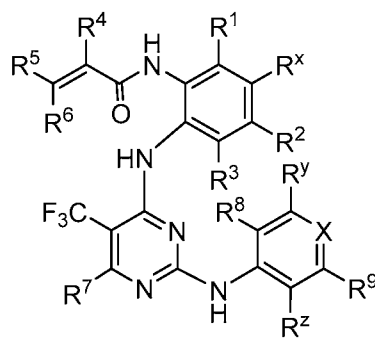
[0016] The term "measurably inhibit", as used herein means a measurable change in one or both of ERK1 and ERK2 protein kinase activity between a sample comprising a provided composition, and one or both of an ERK1 and ERK2 protein kinase and an equivalent sample comprising one or both of ERK1 and ERK2 protein kinase in the absence of a provided composition. Such measurements of protein kinase activity are known to one of ordinary skill in the art and include those methods set forth herein below and/or in the Examples of the '230 publication.

3. Description of Exemplary Compounds

[0017] Deuterium (D or ²H) is a stable, non-radioactive isotope of hydrogen and has an atomic weight of 2.0144. Hydrogen naturally occurs as a mixture of the isotopes ¹H (hydrogen or protium), D (²H or deuterium), and T (³H or tritium). One skilled in the art appreciates that the designation “hydrogen” in hydrogen-containing chemical compounds actually represents a mixture of hydrogen and about 0.015% deuterium.

[0018] Complete deuteration, or 100% deuteration, at any one site can be difficult to achieve in the laboratory. When a deuterium atom is indicated at a given site on any compound described herein, it is understood that a small percentage of hydrogen may still be present. Such compounds are said to be enriched with deuterium. Deuterium-enriched compounds are prepared via synthesis utilizing appropriately enriched starting materials. As used herein, the terms “deuterium-enriched” or “deuterium enrichment” refer to a compound, or a particular site of said compound, which comprises deuterium in an amount that is greater than its natural isotopic abundance (0.015%). Accordingly, in some embodiments, the present invention provides compounds comprising deuterium at a given site, wherein the percentage or level of deuterium incorporation is greater than its natural isotopic abundance.

[0019] According to one aspect, the present invention provides a compound of Formula I:

**I**

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen or deuterium;

R^x is selected from hydrogen, deuterium, or $-C(H)_j(D)_k$;

j is 0-3;

k is 0-3;

wherein the sum of j and k is 3;

R^y is selected from $R^{y'}$ or $-C(=O)N(H)_r(D)_s$;

$R^{y'}$ is $-OC(H)_m(D)_n$;

m is 0-3;

n is 0-3;

wherein the sum of m and n is 3;

r is 0-2

s is 0-2

wherein the sum of r and s is 2;

R^z is $-C(H)_p(D)_q$;

p is 0-3;

q is 0-3;

wherein the sum of p and q is 3; and

X is N or CH;

provided that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^y , or R^z is or contains deuterium.

[0020] As defined above and described herein, each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen or deuterium.

[0021] In some embodiments, R^1 is deuterium.

[0022] In some embodiments, R^1 is deuterium and each of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^1 is deuterium and at least one of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0023] In some embodiments, R^1 is hydrogen.

[0024] In some embodiments, R^1 is hydrogen and each of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^1 is hydrogen and at least one of R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0025] In some embodiments, R^2 is deuterium.

[0026] In some embodiments, R^2 is deuterium and each of R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^2 is deuterium and at least one of R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0027] In some embodiments, R^2 is hydrogen.

[0028] In some embodiments, R^2 is hydrogen and each of R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^2 is hydrogen and at least one of R^1 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0029] In some embodiments, R^3 is deuterium.

[0030] In some embodiments, R^3 is deuterium and each of R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^3 is deuterium and at least one of R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0031] In some embodiments, R^3 is hydrogen.

[0032] In some embodiments, R^3 is hydrogen and each of R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^3 is hydrogen and at least one of R^1 , R^2 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0033] In some embodiments, R^4 is deuterium.

[0034] In some embodiments, R^4 is deuterium and each of R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^4 is deuterium and at least one of R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0035] In some embodiments, R^4 is hydrogen.

[0036] In some embodiments, R^4 is hydrogen and each of R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^4 is hydrogen and at least one of R^1 , R^2 , R^3 , R^5 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0037] In some embodiments, R^5 is deuterium.

[0038] In some embodiments, R^5 is deuterium and each of R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^5 is deuterium and at least one of R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0039] In some embodiments, R^5 is hydrogen.

[0040] In some embodiments, R^5 is hydrogen and each of R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^5 is hydrogen and at least one of R^1 , R^2 , R^3 , R^4 , R^6 , R^7 , R^8 , and R^9 is deuterium.

[0041] In some embodiments, R^6 is deuterium.

[0042] In some embodiments, R^6 is deuterium and each of R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^6 is deuterium and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , and R^9 is deuterium.

[0043] In some embodiments, R^6 is hydrogen.

[0044] In some embodiments, R^6 is hydrogen and each of R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , and R^9 is hydrogen. In some embodiments, R^6 is hydrogen and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^7 , R^8 , and R^9 is deuterium.

[0045] In some embodiments, R^7 is deuterium.

[0046] In some embodiments, R^7 is deuterium and each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 is hydrogen. In some embodiments, R^7 is deuterium and at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^8 , and R^9 is deuterium.

[0047] In some embodiments, R^7 is hydrogen.

[0048] In some embodiments, R^7 is hydrogen and each of $R^1, R^2, R^3, R^4, R^5, R^6, R^8$, and R^9 is hydrogen. In some embodiments, R^7 is hydrogen and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^8$, and R^9 is deuterium.

[0049] In some embodiments, R^8 is deuterium.

[0050] In some embodiments, R^8 is deuterium and each of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^9 is hydrogen. In some embodiments, R^8 is deuterium and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^9 is deuterium.

[0051] In some embodiments, R^8 is hydrogen.

[0052] In some embodiments, R^8 is hydrogen and each of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^9 is hydrogen. In some embodiments, R^8 is hydrogen and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^9 is deuterium.

[0053] In some embodiments, R^9 is deuterium.

[0054] In some embodiments, R^9 is deuterium and each of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^8 is hydrogen. In some embodiments, R^9 is deuterium and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^8 is deuterium.

[0055] In some embodiments, R^9 is hydrogen.

[0056] In some embodiments, R^9 is hydrogen and each of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^8 is hydrogen. In some embodiments, R^9 is hydrogen and at least one of $R^1, R^2, R^3, R^4, R^5, R^6, R^7$, and R^8 is deuterium.

[0057] As defined above and described herein, R^x is selected from hydrogen, deuterium, or $-C(H)_j(D)_k$.

[0058] In some embodiments, R^x is hydrogen.

[0059] In some embodiments, R^x is deuterium.

[0060] In some embodiments, R^x is $-C(H)_j(D)_k$, wherein j is 0-3 and wherein k is 0-3. As defined herein, and as one of skill in the art will appreciate per the rules of valency, the sum of j and k must be 3. Accordingly, if j is 1 then k must be 2, etc. In some embodiments, R^x is $-CH_3$, $-CH_2D$, $-CHD_2$, or $-CD_3$. In certain embodiments, R^x is $-CH_3$ or $-CD_3$.

[0061] In some embodiments, each of R^1, R^2 and R^3 is hydrogen. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$. In some embodiments, one of R^1, R^2 and R^3 is deuterium. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$. In some embodiments,

two of R^1 , R^2 and R^3 are deuterium. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$. In some embodiments, each of R^1 , R^2 and R^3 is deuterium. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$.

[0062] In some embodiments, each of R^4 , R^5 and R^6 is hydrogen. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$. In some embodiments, one of R^4 , R^5 and R^6 is deuterium. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$. In some embodiments, two of R^4 , R^5 and R^6 are deuterium. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$. In some embodiments, each of R^4 , R^5 and R^6 is deuterium. In some such embodiments, R^x is hydrogen, $-CH_3$, or $-CD_3$.

[0063] As defined above and described herein, R^7 is selected from hydrogen or deuterium. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is deuterium.

[0064] As defined above and described herein, R^y is selected from $R^{y'}$ or $-C(=O)N(H)_r(D)_s$.

[0065] In some embodiments, $R^{y'}$ is $-OC(H)_m(D)_n$, wherein m is 0-3 and wherein n is 0-3. As defined herein, and as one of skill in the art will appreciate per the rules of valency, the sum of m and n must be 3. Accordingly, if m is 1 then n must be 2, etc. In some embodiments, $R^{y'}$ is $-OCH_3$, $-OCH_2D$, $-OCHD_2$, or $-OCD_3$. In certain embodiments, $R^{y'}$ is $-OCH_3$ or $-OCD_3$.

[0066] In some embodiments, R^y is $-C(=O)N(H)_r(D)_s$, wherein r is 0-2 and wherein s is 0-2. As defined herein, and as one of skill in the art will appreciate per the rules of valency, the sum of r and s must be 2. In some embodiments, R^y is $-C(=O)NH_2$. In some embodiments, R^y is $-C(=O)NHD$. In some embodiments, R^y is $-C(=O)ND_2$.

[0067] As defined above and described herein, R^z is $-C(H)_p(D)_q$, wherein p is 0-3 and wherein q is 0-3. As defined herein, and as one of skill in the art will appreciate per the rules of valency, the sum of p and q must be 3. Accordingly, if p is 1 then q must be 2, etc. In some embodiments, R^z is $-CH_3$, $-CH_2D$, $-CHD_2$, or $-CD_3$. In certain embodiments, R^z is $-CH_3$.

[0068] As defined above and described herein, X is selected from N or CH. In some embodiments, X is N. In some embodiments, X is CH.

[0069] In some embodiments, each of R^8 and R^9 is hydrogen. In some such embodiments, R^y is $-OCH_3$ or $-OCD_3$ and X is N. In some such embodiments, R^y is $-C(O)NH_2$ and X is CH. In some embodiments, one of R^8 and R^9 is deuterium. In some such embodiments, R^y is $-OCH_3$ or $-OCD_3$ and X is N. In some such embodiments, R^y is $-C(O)NH_2$ and X is CH. In some

embodiments, each of R^8 and R^9 is deuterium. In some such embodiments, R^y is $-OCH_3$ or $-OCD_3$ and X is N. In some such embodiments, R^y is $-C(O)NH_2$ and X is CH.

[0070] In some embodiments, each of R^8 and R^9 is hydrogen. In some such embodiments, R^z is $-CH_3$ and X is N. In some such embodiments, R^z is $-CH_3$ and X is CH. In some embodiments, one of R^8 and R^9 is deuterium. In some such embodiments, R^z is $-CH_3$ and X is N. In some such embodiments, R^z is $-CH_3$ and X is CH. In some embodiments, each of R^8 and R^9 is deuterium. In some such embodiments, R^z is $-CH_3$ and X is N. In some such embodiments, R^z is $-CH_3$ and X is CH.

[0071] In some embodiments, the present invention provides a compound of Formula I, wherein each of R^4 , R^5 , R^6 , R^x , R^y , R^z , and X is as defined above and described herein, and wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth in **Table 1a**, below.

Table 1a.

Entry	R^1	R^2	R^3	R^7	R^8	R^9
<i>i</i>	H	H	H	H	H	H
<i>ii</i>	D	H	H	H	H	H
<i>iii</i>	H	D	H	H	H	H
<i>iv</i>	H	H	D	H	H	H
<i>v</i>	D	D	H	H	H	H
<i>vi</i>	H	D	D	H	H	H
<i>vii</i>	D	H	D	H	H	H
<i>viii</i>	D	D	D	H	H	H
<i>ix</i>	H	H	H	H	D	H
<i>x</i>	D	H	H	H	D	H
<i>xi</i>	H	D	H	H	D	H
<i>xii</i>	H	H	D	H	D	H
<i>xiii</i>	D	D	H	H	D	H
<i>xiv</i>	H	D	D	H	D	H
<i>xv</i>	D	H	D	H	D	H
<i>xvi</i>	D	D	D	H	D	H

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>xvii</i>	H	H	H	H	H	D
<i>xviii</i>	D	H	H	H	H	D
<i>xix</i>	H	D	H	H	H	D
<i>xx</i>	H	H	D	H	H	D
<i>xxi</i>	D	D	H	H	H	D
<i>xxii</i>	H	D	D	H	H	D
<i>xxiii</i>	D	H	D	H	H	D
<i>xxiv</i>	D	D	D	H	H	D
<i>xxv</i>	H	H	H	H	D	D
<i>xxvi</i>	D	H	H	H	D	D
<i>xxvii</i>	H	D	H	H	D	D
<i>xxviii</i>	H	H	D	H	D	D
<i>xxix</i>	D	D	H	H	D	D
<i>xxx</i>	H	D	D	H	D	D
<i>xxxi</i>	D	H	D	H	D	D
<i>xxxii</i>	D	D	D	H	D	D
<i>xxxiii</i>	H	H	H	D	H	H
<i>xxxiv</i>	D	H	H	D	H	H
<i>xxxv</i>	H	D	H	D	H	H
<i>xxxvi</i>	H	H	D	D	H	H
<i>xxxvii</i>	D	D	H	D	H	H
<i>xxxviii</i>	H	D	D	D	H	H
<i>xxxix</i>	D	H	D	D	H	H
<i>xl</i>	D	D	D	D	H	H
<i>xli</i>	H	H	H	D	D	H
<i>xlii</i>	D	H	H	D	D	H
<i>xliii</i>	H	D	H	D	D	H
<i>xliv</i>	H	H	D	D	D	H

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>xlvi</i>	D	D	H	D	D	H
<i>xlvi</i>	H	D	D	D	D	H
<i>xlvi</i>	D	H	D	D	D	H
<i>xlvi</i>	D	D	D	D	D	H
<i>xlvi</i>	H	H	H	D	H	D
<i>l</i>	D	H	H	D	H	D
<i>li</i>	H	D	H	D	H	D
<i>lii</i>	H	H	D	D	H	D
<i>liii</i>	D	D	H	D	H	D
<i>liv</i>	H	D	D	D	H	D
<i>lv</i>	D	H	D	D	H	D
<i>lvi</i>	D	D	D	D	H	D
<i>lvii</i>	H	H	H	D	D	D
<i>lviii</i>	D	H	H	D	D	D
<i>lix</i>	H	D	H	D	D	D
<i>lx</i>	H	H	D	D	D	D
<i>lxi</i>	D	D	H	D	D	D
<i>lxii</i>	H	D	D	D	D	D
<i>lxiii</i>	D	H	D	D	D	D
<i>lxiv</i>	D	D	D	D	D	D

[0072] In some embodiments, the present invention provides a compound of Formula I, wherein each of R¹, R², R³, R⁷, R⁸, R⁹, R^x, R^y, R^z, and X is as defined above and described herein, and wherein each of R⁴, R⁵, and R⁶ is as defined in an entry set forth in **Table 1b**, below.

Table 1b.

Entry	R ⁴	R ⁵	R ⁶
<i>i</i>	H	H	H

Entry	R ⁴	R ⁵	R ⁶
<i>ii</i>	D	H	H
<i>iii</i>	H	D	H
<i>iv</i>	H	H	D
<i>v</i>	D	D	H
<i>vi</i>	H	D	D
<i>vii</i>	D	H	D
<i>viii</i>	D	D	D

[0073] In some embodiments, the present invention provides a compound of Formula I, wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹ and X is as defined above and described herein, and wherein each of R^x, R^y or R^{y'}, and R^z, is as defined in an entry set forth in **Table 1c**, below.

Table 1c.

Entry	R ^x	R ^y /R ^{y'}	R ^z
<i>i</i>	H	OCH ₃	CH ₃
<i>ii</i>	D	OCH ₃	CH ₃
<i>iii</i>	CH ₃	OCH ₃	CH ₃
<i>iv</i>	CH ₂ D	OCH ₃	CH ₃
<i>v</i>	CHD ₂	OCH ₃	CH ₃
<i>vi</i>	CD ₃	OCH ₃	CH ₃
<i>vii</i>	H	OCH ₂ D	CH ₃
<i>viii</i>	D	OCH ₂ D	CH ₃
<i>ix</i>	CH ₃	OCH ₂ D	CH ₃
<i>x</i>	CH ₂ D	OCH ₂ D	CH ₃
<i>xi</i>	CHD ₂	OCH ₂ D	CH ₃
<i>xii</i>	CD ₃	OCH ₂ D	CH ₃
<i>xiii</i>	H	OCHD ₂	CH ₃
<i>xiv</i>	D	OCHD ₂	CH ₃
<i>xv</i>	CH ₃	OCHD ₂	CH ₃

Entry	R ^x	R ^y /R ^{y'}	R ^z
<i>xvi</i>	CH ₂ D	OCHD ₂	CH ₃
<i>xvii</i>	CHD ₂	OCHD ₂	CH ₃
<i>xviii</i>	CD ₃	OCHD ₂	CH ₃
<i>xix</i>	H	OCD ₃	CH ₃
<i>xx</i>	D	OCD ₃	CH ₃
<i>xxi</i>	CH ₃	OCD ₃	CH ₃
<i>xxii</i>	CH ₂ D	OCD ₃	CH ₃
<i>xxiii</i>	CHD ₂	OCD ₃	CH ₃
<i>xxiv</i>	CD ₃	OCD ₃	CH ₃
<i>xxv</i>	H	OCH ₃	CH ₂ D
<i>xxvi</i>	D	OCH ₃	CH ₂ D
<i>xxvii</i>	CH ₃	OCH ₃	CH ₂ D
<i>xxviii</i>	CH ₂ D	OCH ₃	CH ₂ D
<i>xxix</i>	CHD ₂	OCH ₃	CH ₂ D
<i>xxx</i>	CD ₃	OCH ₃	CH ₂ D
<i>xxv</i>	H	OCH ₂ D	CH ₂ D
<i>xxvi</i>	D	OCH ₂ D	CH ₂ D
<i>xxvii</i>	CH ₃	OCH ₂ D	CH ₂ D
<i>xxviii</i>	CH ₂ D	OCH ₂ D	CH ₂ D
<i>xxix</i>	CHD ₂	OCH ₂ D	CH ₂ D
<i>xxx</i>	CD ₃	OCH ₂ D	CH ₂ D
<i>xxx</i>	H	OCHD ₂	CH ₂ D
<i>xxxii</i>	D	OCHD ₂	CH ₂ D
<i>xxxiii</i>	CH ₃	OCHD ₂	CH ₂ D
<i>xxxiv</i>	CH ₂ D	OCHD ₂	CH ₂ D
<i>xxxv</i>	CHD ₂	OCHD ₂	CH ₂ D
<i>xxxvi</i>	CD ₃	OCHD ₂	CH ₂ D
<i>xxxvii</i>	H	OCD ₃	CH ₂ D

Entry	R ^x	R ^y /R ^{y'}	R ^z
<i>xxxviii</i>	D	OCD ₃	CH ₂ D
<i>xxxix</i>	CH ₃	OCD ₃	CH ₂ D
<i>xl</i>	CH ₂ D	OCD ₃	CH ₂ D
<i>xli</i>	CHD ₂	OCD ₃	CH ₂ D
<i>xl ii</i>	CD ₃	OCD ₃	CH ₂ D
<i>xl iii</i>	H	OCH ₃	CHD ₂
<i>xl iv</i>	D	OCH ₃	CHD ₂
<i>xl v</i>	CH ₃	OCH ₃	CHD ₂
<i>xl vi</i>	CH ₂ D	OCH ₃	CHD ₂
<i>xl vii</i>	CHD ₂	OCH ₃	CHD ₂
<i>xl viii</i>	CD ₃	OCH ₃	CHD ₂
<i>xl ix</i>	H	OCH ₂ D	CHD ₂
<i>l</i>	D	OCH ₂ D	CHD ₂
<i>li</i>	CH ₃	OCH ₂ D	CHD ₂
<i>li i</i>	CH ₂ D	OCH ₂ D	CHD ₂
<i>li ii</i>	CHD ₂	OCH ₂ D	CHD ₂
<i>li v</i>	CD ₃	OCH ₂ D	CHD ₂
<i>l v</i>	H	OCHD ₂	CHD ₂
<i>l vi</i>	D	OCHD ₂	CHD ₂
<i>l vii</i>	CH ₃	OCHD ₂	CHD ₂
<i>l viii</i>	CH ₂ D	OCHD ₂	CHD ₂
<i>l ix</i>	CHD ₂	OCHD ₂	CHD ₂
<i>l x</i>	CD ₃	OCHD ₂	CHD ₂
<i>l xi</i>	H	OCD ₃	CHD ₂
<i>l xii</i>	D	OCD ₃	CHD ₂
<i>l xiii</i>	CH ₃	OCD ₃	CHD ₂
<i>l x ix</i>	CH ₂ D	OCD ₃	CHD ₂
<i>l x x</i>	CHD ₂	OCD ₃	CHD ₂

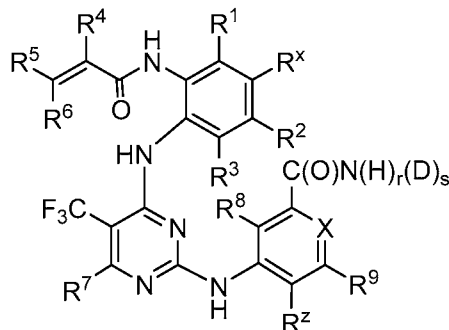
Entry	R ^x	R ^y /R ^{y'}	R ^z
<i>lxxi</i>	CD ₃	OCD ₃	CHD ₂
<i>lxxii</i>	H	OCH ₃	CD ₃
<i>lxxiii</i>	D	OCH ₃	CD ₃
<i>lxxiv</i>	CH ₃	OCH ₃	CD ₃
<i>lxxv</i>	CH ₂ D	OCH ₃	CD ₃
<i>lxxvi</i>	CHD ₂	OCH ₃	CD ₃
<i>lxxvii</i>	CD ₃	OCH ₃	CD ₃
<i>lxxviii</i>	H	OCH ₂ D	CD ₃
<i>lxxix</i>	D	OCH ₂ D	CD ₃
<i>lxxx</i>	CH ₃	OCH ₂ D	CD ₃
<i>lxxxi</i>	CH ₂ D	OCH ₂ D	CD ₃
<i>lxxxii</i>	CHD ₂	OCH ₂ D	CD ₃
<i>lxxxiii</i>	CD ₃	OCH ₂ D	CD ₃
<i>lxxxiv</i>	H	OCHD ₂	CD ₃
<i>lxxxv</i>	D	OCHD ₂	CD ₃
<i>lxxxvi</i>	CH ₃	OCHD ₂	CD ₃
<i>lxxxvii</i>	CH ₂ D	OCHD ₂	CD ₃
<i>lxxxviii</i>	CHD ₂	OCHD ₂	CD ₃
<i>lxxxix</i>	CD ₃	OCHD ₂	CD ₃
<i>xc</i>	H	OCD ₃	CD ₃
<i>xc i</i>	D	OCD ₃	CD ₃
<i>xc ii</i>	CH ₃	OCD ₃	CD ₃
<i>xc iii</i>	CH ₂ D	OCD ₃	CD ₃
<i>xc iv</i>	CHD ₂	OCD ₃	CD ₃
<i>xc v</i>	CD ₃	OCD ₃	CD ₃

[0074] In some embodiments, the present invention provides a compound of Formula I, wherein each of R¹, R², R³, R⁷, R⁸, and R⁹ is as defined in an entry set forth in **Table 1a**, above,

each of R^4 , R^5 , and R^6 is as defined in an entry set forth in **Table 1b**, above, and each of R^x , R^y or $R^{y'}$, and R^z , is as defined in an entry set forth in **Table 1c**, above. In some such instances, X is N. In other such instances, X is C.

Compounds of Formula II

[0075] In some embodiments, the present invention provides a compound of Formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^z , r , s , and X is as defined above and described herein.

[0076] In some embodiments, the present invention provides a compound of Formula **II**, wherein each of R^x , R^4 , R^5 , R^6 , R^z , and X is as defined above and described herein, and wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth in **Table 1a**, above.

[0077] In some embodiments, the present invention provides a compound of Formula **II**, or a pharmaceutically acceptable salt thereof, wherein X is N. In some embodiments, the present invention provides a compound of Formula **II**, or a pharmaceutically acceptable salt thereof, wherein X is CH.

[0078] In some embodiments, the present invention provides a compound of Formula **II**, or a pharmaceutically acceptable salt thereof, wherein R^z is $-CH_3$.

[0079] In some embodiments, the present invention provides a compound of Formula **II**, or a pharmaceutically acceptable salt thereof, wherein one of R^4 , R^5 , and R^6 is hydrogen. In some embodiments, the present invention provides a compound of Formula **II**, or a pharmaceutically acceptable salt thereof, wherein two of R^4 , R^5 , and R^6 are hydrogen. In some embodiments, the present invention provides a compound of Formula **II**, or a pharmaceutically acceptable salt

thereof, wherein each of R^4 , R^5 , and R^6 is hydrogen. In some embodiments, the present invention provides a compound of Formula II, or a pharmaceutically acceptable salt thereof, wherein each of R^4 , R^5 , and R^6 is deuterium.

[0080] In some embodiments, the present invention provides a compound of Formula II, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , R^9 , R^Z and X is as defined above and described herein, and wherein each of R^x , R^4 , R^5 , and R^6 is as defined in an entry set forth in **Table 2**, below.

Table 2.

Entry	R^x	R^4	R^5	R^6
<i>i</i>	H	H	H	H
<i>ii</i>	H	H	H	D
<i>iii</i>	H	H	D	H
<i>iv</i>	H	D	H	H
<i>v</i>	H	H	D	D
<i>vi</i>	H	D	D	H
<i>vii</i>	H	D	H	D
<i>viii</i>	H	D	D	D
<i>ix</i>	CH ₃	H	H	H
<i>x</i>	CH ₃	H	H	D
<i>xi</i>	CH ₃	H	D	H
<i>xii</i>	CH ₃	D	H	H
<i>xiii</i>	CH ₃	H	D	D
<i>xiv</i>	CH ₃	D	D	H
<i>xv</i>	CH ₃	D	H	D
<i>xvi</i>	CH ₃	D	D	D
<i>xvii</i>	CD ₃	H	H	H
<i>xviii</i>	CD ₃	H	H	D
<i>xix</i>	CD ₃	H	D	H
<i>xx</i>	CD ₃	D	H	H
<i>xxi</i>	CD ₃	H	D	D

Entry	R ^x	R ⁴	R ⁵	R ⁶
<i>xxii</i>	CD ₃	D	D	H
<i>xxiii</i>	CD ₃	D	H	D
<i>xxiv</i>	CD ₃	D	D	D

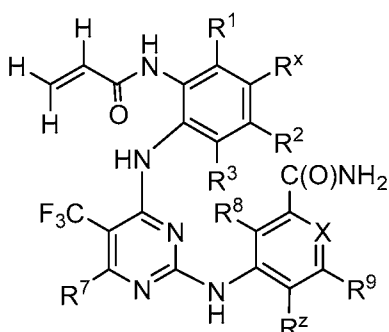
[0081] In some embodiments, the present invention provides a compound of Formula II, wherein each of R^x, R⁴, R⁵, and R⁶ is as defined in Table 2, wherein each of R¹, R², R³, R⁷, R⁸, R⁹ or R^z is or contains hydrogen but not deuterium, and wherein r is 2.

[0082] In some embodiments, the present invention provides a compound of Formula II, wherein each of R^x, R⁴, R⁵, and R⁶ is as defined in Table 2, and wherein one of R¹, R², R³, R⁷, R⁸, R⁹ or R^z is or contains deuterium, or s is 1 or 2.

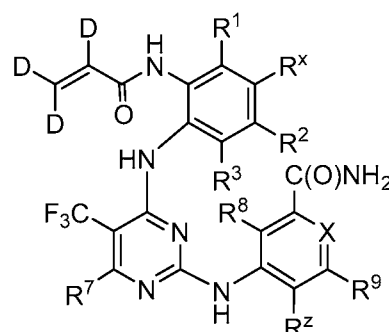
[0083] In some embodiments, the present invention provides a compound of Formula II, wherein each of R^x, R⁴, R⁵, and R⁶ is as defined in Table 2, and wherein R^z is -CH₃.

[0084] In some embodiments, the present invention provides a compound of Formula II, wherein each of R^x, R⁴, R⁵, and R⁶ is as defined in Table 2, and wherein X is N. In some embodiments, the present invention provides a compound of Formula II, wherein each of R^x, R⁴, R⁵, and R⁶ is as defined in Table 2, and wherein X is CH.

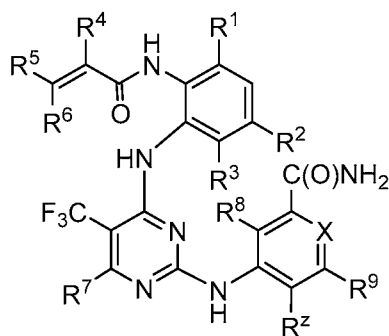
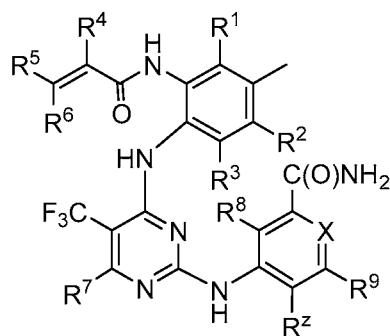
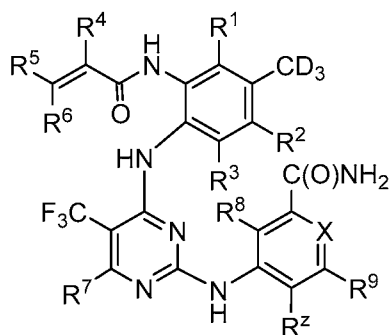
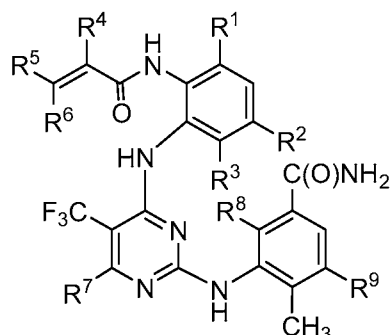
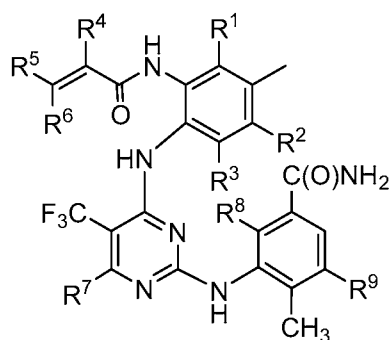
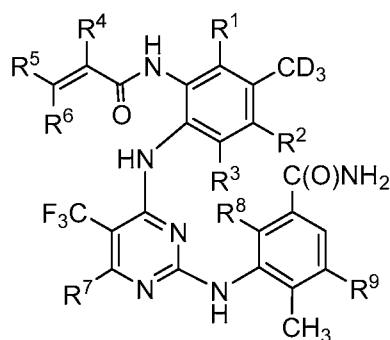
[0085] In some embodiments, the present invention provides a compound of any one of formulae II-a, II-b, II-c, II-d, II-e, II-f, II-g, or II-h:



II-a



II-b

**II-c****II-d****II-e****II-f****II-g****II-h**

or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^z , and X is as defined above and described herein when present.

[0086] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^4 , R^5 , R^6 , R^z and X is as defined above and described herein, and each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth in **Table 1a**, above.

[0087] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein R^z is $-CH_3$.

[0088] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, and wherein X is N. In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein X is CH.

[0089] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is hydrogen.

[0090] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein one of R^4 , R^5 , and R^6 is deuterium. In some such embodiments, R^4 is deuterium. In some such embodiments, R^5 is deuterium. In some such embodiments, R^6 is deuterium.

[0091] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein two of R^4 , R^5 , and R^6 are deuterium. In some such embodiments, R^4 and R^5 are deuterium. In some such embodiments, R^4 and R^6 are deuterium. In some such embodiments, R^5 and R^6 are deuterium.

[0092] In some embodiments, the present invention provides a compound of any one of formulae **II-c**, **II-d**, or **II-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is deuterium.

[0093] In some embodiments, the present invention provides a compound of any one of formulae **II-f**, **II-g**, or **II-h**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is hydrogen.

[0094] In some embodiments, the present invention provides a compound of any one of formulae **II-f**, **II-g**, or **II-h**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein one of R^4 , R^5 , and R^6 is deuterium. In some such embodiments, R^4 is

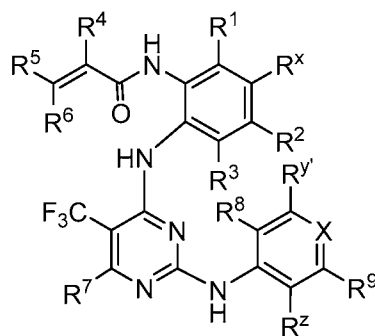
deuterium. In some such embodiments, R⁵ is deuterium. In some such embodiments, R⁶ is deuterium.

[0095] In some embodiments, the present invention provides a compound of any one of formulae **II-f**, **II-g**, or **II-h**, wherein each of R¹, R², R³, R⁷, R⁸, and R⁹ is as defined in **Table 1a**, above, and wherein two of R⁴, R⁵, and R⁶ are deuterium. In some such embodiments, R⁴ and R⁵ are deuterium. In some such embodiments, R⁴ and R⁶ are deuterium. In some such embodiments, R⁵ and R⁶ are deuterium.

[0096] In some embodiments, the present invention provides a compound of any one of formulae **II-f**, **II-g**, or **II-h**, wherein each of R¹, R², R³, R⁷, R⁸, and R⁹ is as defined in **Table 1a**, above, and wherein each of R⁴, R⁵, and R⁶ is deuterium.

Compounds of Formula III

[0097] In some embodiments, the present invention provides a compound of Formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R^x, R^{y'}, R^z, and X, is as defined above and described herein.

[0098] In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein X is N. In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein X is CH.

[0099] In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein R^z is -CH₃.

[0100] In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein one of R^4 , R^5 , and R^6 is hydrogen. In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein two of R^4 , R^5 , and R^6 are hydrogen. In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein each of R^4 , R^5 , and R^6 is hydrogen. In some embodiments, the present invention provides a compound of Formula **III**, or a pharmaceutically acceptable salt thereof, wherein each of R^4 , R^5 , and R^6 is deuterium.

[0101] In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^x , R^4 , R^5 , R^6 , R^z , X , m and n is as defined above and described herein, and wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth in **Table 1a**, above.

[0102] In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth in **Table 1a**, above, each of R^4 , R^5 , and R^6 is as defined in an entry set forth in **Table 1b**, above, and each of R^x , $R^{y'}$, and R^z is as defined in an entry set forth in **Table 1c**, above. In some such embodiments, X is C. In other such embodiments, X is N.

[0103] In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , R^9 , R^z and X is as defined above and described herein, and wherein each of R^x , $R^{y'}$, R^4 , R^5 , and R^6 is as defined in an entry set forth in **Table 3**, below.

Table 3.

Entry	R^x	R^4	R^5	R^6	$R^{y'}$
<i>i</i>	H	H	H	H	OCH ₃
<i>ii</i>	H	H	H	D	OCH ₃
<i>iii</i>	H	H	D	H	OCH ₃
<i>iv</i>	H	D	H	H	OCH ₃
<i>v</i>	H	H	D	D	OCH ₃
<i>vi</i>	H	D	D	H	OCH ₃
<i>vii</i>	H	D	H	D	OCH ₃
<i>viii</i>	H	D	D	D	OCH ₃

Entry	R ^x	R ⁴	R ⁵	R ⁶	R ^{y'}
<i>ix</i>	CH ₃	H	H	H	OCH ₃
<i>x</i>	CH ₃	H	H	D	OCH ₃
<i>xi</i>	CH ₃	H	D	H	OCH ₃
<i>xii</i>	CH ₃	D	H	H	OCH ₃
<i>xiii</i>	CH ₃	H	D	D	OCH ₃
<i>xiv</i>	CH ₃	D	D	H	OCH ₃
<i>xv</i>	CH ₃	D	H	D	OCH ₃
<i>xvi</i>	CH ₃	D	D	D	OCH ₃
<i>xvii</i>	CD ₃	H	H	H	OCH ₃
<i>xviii</i>	CD ₃	H	H	D	OCH ₃
<i>xix</i>	CD ₃	H	D	H	OCH ₃
<i>xx</i>	CD ₃	D	H	H	OCH ₃
<i>xxi</i>	CD ₃	H	D	D	OCH ₃
<i>xxii</i>	CD ₃	D	D	H	OCH ₃
<i>xxiii</i>	CD ₃	D	H	D	OCH ₃
<i>xxiv</i>	CD ₃	D	D	D	OCH ₃
<i>xxv</i>	H	H	H	H	OCD ₃
<i>xxvi</i>	H	H	H	D	OCD ₃
<i>xxvii</i>	H	H	D	H	OCD ₃
<i>xxviii</i>	H	D	H	H	OCD ₃
<i>xxix</i>	H	H	D	D	OCD ₃
<i>xxx</i>	H	D	D	H	OCD ₃
<i>xxxi</i>	H	D	H	D	OCD ₃
<i>xxxii</i>	H	D	D	D	OCD ₃
<i>xxxiii</i>	CH ₃	H	H	H	OCD ₃
<i>xxxiv</i>	CH ₃	H	H	D	OCD ₃
<i>xxxv</i>	CH ₃	H	D	H	OCD ₃
<i>xxxvi</i>	CH ₃	D	H	H	OCD ₃

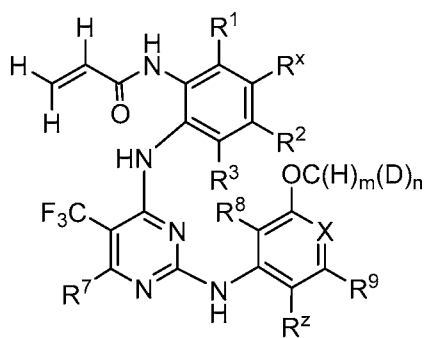
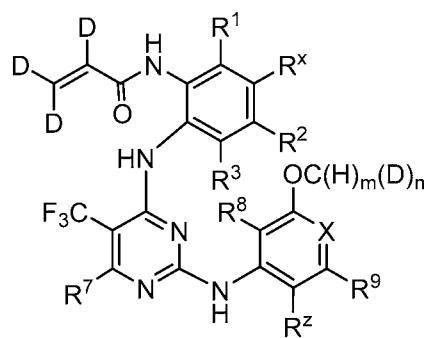
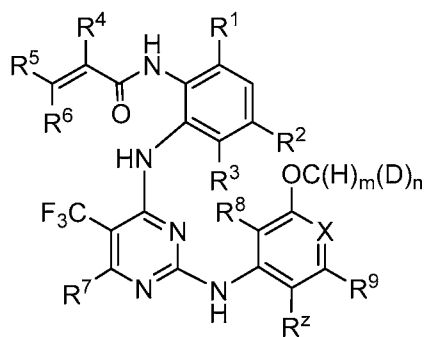
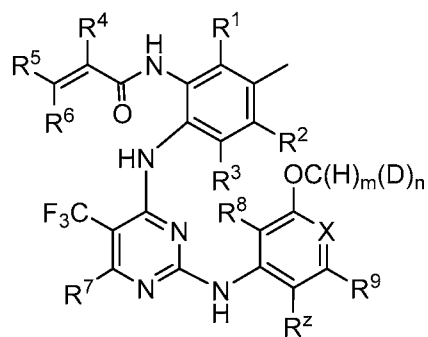
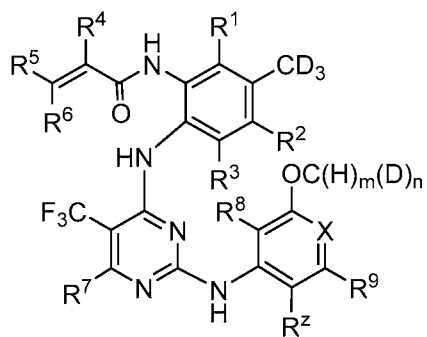
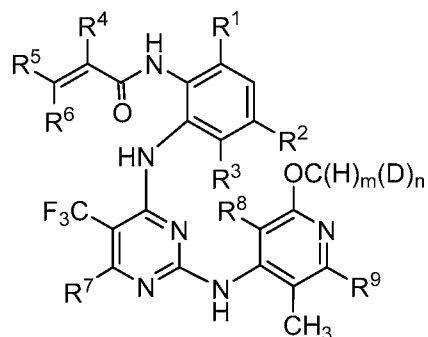
Entry	R ^x	R ⁴	R ⁵	R ⁶	R ^{y'}
<i>xxxvii</i>	CH ₃	H	D	D	OCD ₃
<i>xxxviii</i>	CH ₃	D	D	H	OCD ₃
<i>xxxix</i>	CH ₃	D	H	D	OCD ₃
<i>xl</i>	CH ₃	D	D	D	OCD ₃
<i>xli</i>	CD ₃	H	H	H	OCD ₃
<i>xlvi</i>	CD ₃	H	H	D	OCD ₃
<i>xlvi</i>	CD ₃	H	D	H	OCD ₃
<i>xlvii</i>	CD ₃	D	H	H	OCD ₃
<i>xlviii</i>	CD ₃	H	D	D	OCD ₃
<i>xlviii</i>	CD ₃	D	D	D	OCD ₃

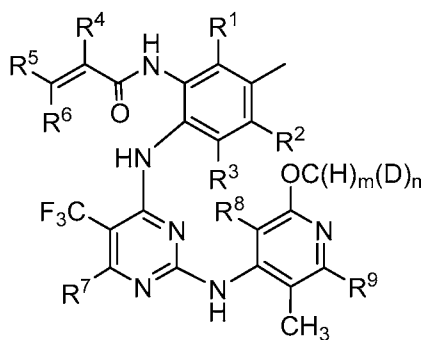
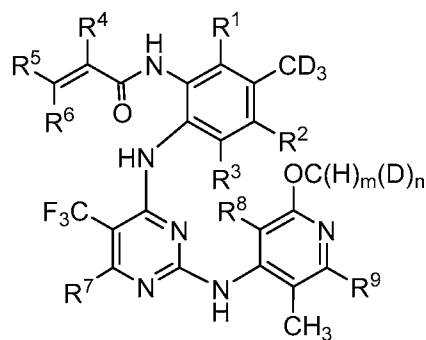
[0104] In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^x, R^{y'}, R⁴, R⁵, and R⁶ is as defined in **Table 3**, and wherein one of R¹, R², R³, R⁷, R⁸, R⁹ or R^z is or contains deuterium.

[0105] In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^x, R^{y'}, R⁴, R⁵, and R⁶ is as defined in **Table 3**, and wherein R^z is -CH₃.

[0106] In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^x, R^{y'}, R⁴, R⁵, and R⁶ is as defined in **Table 3**, and wherein X is N. In some embodiments, the present invention provides a compound of Formula **III**, wherein each of R^x, R^{y'}, R⁴, R⁵, and R⁶ is as defined in **Table 3**, and wherein X is CH.

[0107] In some embodiments, the present invention provides a compound of any one of formulae **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, **III-f**, **III-g**, or **III-h**:

**III-a****III-b****III-c****III-d****III-e****III-f**

**III-g****III-h**

or a pharmaceutically acceptable salt thereof, wherein each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^z , X , m , and n is as defined above and described herein when present.

[0108] In some embodiments, the present invention provides a compound of any of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^4 , R^5 , R^6 , R^z , X , m , and n is as defined above and described herein, and wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth in **Table 1a**, above.

[0109] In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein R^z is $-\text{CH}_3$.

[0110] In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein X is N . In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein X is CH .

[0111] In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is hydrogen.

[0112] In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein one of R^4 , R^5 , and R^6 is deuterium. In some such embodiments, R^4 is

deuterium. In some such embodiments, R^5 is deuterium. In some such embodiments, R^6 is deuterium.

[0113] In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein two of R^4 , R^5 , and R^6 are deuterium. In some such embodiments, R^4 and R^5 are deuterium. In some such embodiments, R^4 and R^6 are deuterium. In some such embodiments, R^5 and R^6 are deuterium.

[0114] In some embodiments, the present invention provides a compound of any one of formulae **III-c**, **III-d**, or **III-e**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is deuterium.

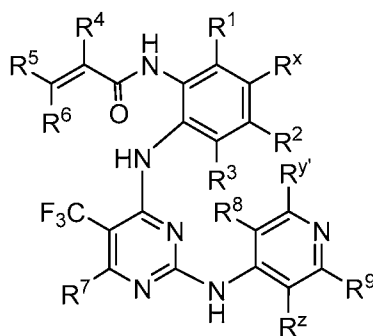
[0115] In some embodiments, the present invention provides a compound of any one of formulae **III-f**, **III-g**, or **III-h**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is hydrogen.

[0116] In some embodiments, the present invention provides a compound of any one of formulae **III-f**, **III-g**, or **III-h**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein one of R^4 , R^5 , and R^6 is deuterium. In some such embodiments, R^4 is deuterium. In some such embodiments, R^5 is deuterium. In some such embodiments, R^6 is deuterium.

[0117] In some embodiments, the present invention provides a compound of any one of formulae **III-f**, **III-g**, or **III-h**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein two of R^4 , R^5 , and R^6 are deuterium. In some such embodiments, R^4 and R^5 are deuterium. In some such embodiments, R^4 and R^6 are deuterium. In some such embodiments, R^5 and R^6 are deuterium.

[0118] In some embodiments, the present invention provides a compound of any one of formulae **III-f**, **III-g**, or **III-h**, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in **Table 1a**, above, and wherein each of R^4 , R^5 , and R^6 is deuterium.

[0119] In some embodiments, the present invention provides a compound of the following formula:



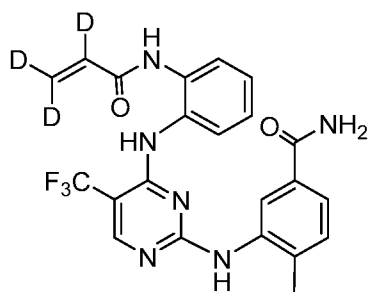
III-i

or a pharmaceutically acceptable salt thereof, wherein each of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R^x, R^y and R^z is as defined above and herein for Formula III.

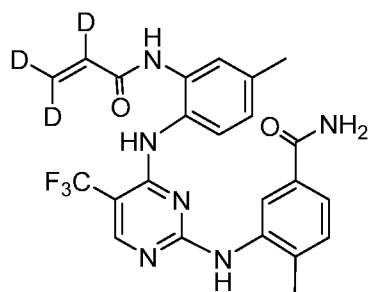
[0120] In certain embodiments, a compound of Formula **III-i** is provided in the form of a salt, e.g., a phosphate salt.

[0121] In some embodiments, the present invention provides a compound of Formula **III-i**, wherein each of R¹, R², R³, R⁷, R⁸, and R⁹ is as defined in an entry set forth in **Table 1a**, above, each of R⁴, R⁵, and R⁶ is as defined in an entry set forth in **Table 1b**, above, and each of R^x, R^y, and R^z is as defined in an entry set forth in **Table 1c**, above. In certain such embodiments, a compound of Formula **III-i** is present in the form of a phosphate salt.

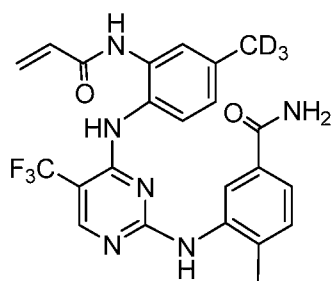
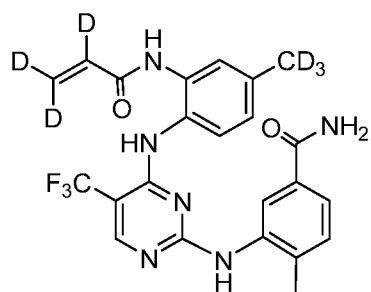
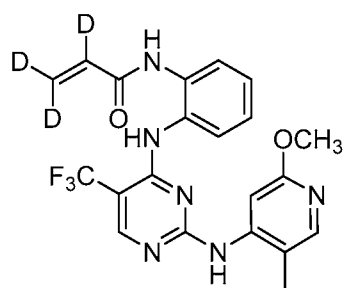
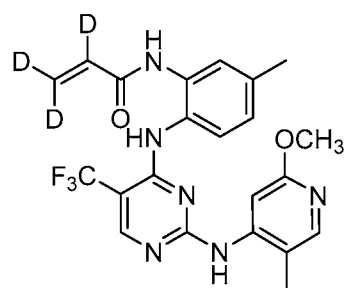
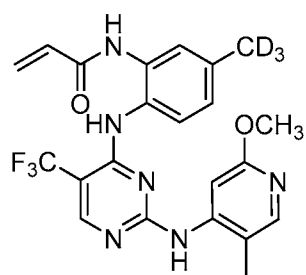
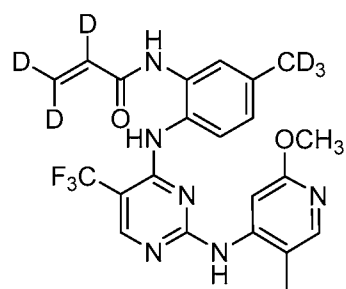
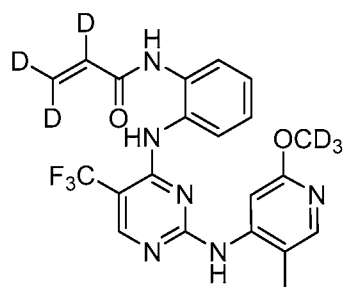
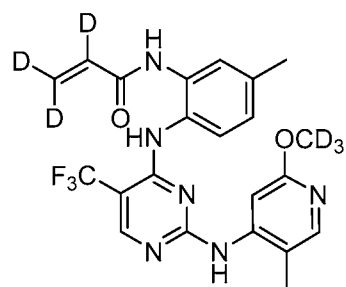
Table 4. Representative Compounds of Formula I

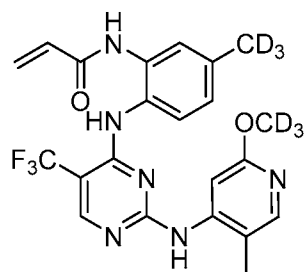
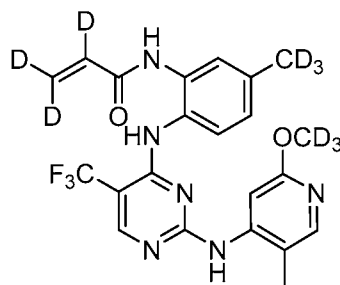
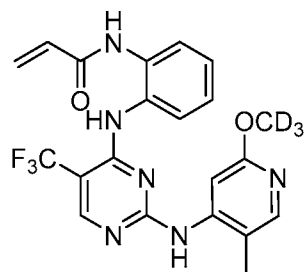
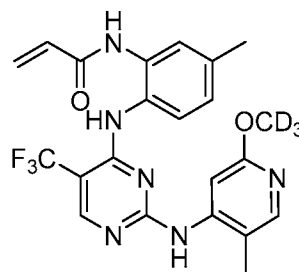


I-1



I-2

**I-3****I-4****I-5****I-6****I-7****I-8****I-9****I-10**

**I-11****I-12****I-13****I-14.**

[0122] In some embodiments, the present invention provides a compound depicted in **Table 4**, above, or a pharmaceutically acceptable salt thereof.

[0123] In some embodiments, the present invention provides compounds comprising one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, or seventeen, or eighteen deuterium atoms.

[0124] In some embodiments, provided compounds comprise deuterium in an amount of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. As used herein in the context of deuterium enrichment, the term “about” means $\pm 2\%$.

[0125] In certain embodiments, the present invention provides any compound described above and herein, or a pharmaceutically acceptable salt thereof.

[0126] In some embodiments, the present invention provides any compound described above and herein in isolated form.

4. Uses of Compounds and Pharmaceutically Acceptable Compositions Thereof

[0127] As described generally above, compounds of Formula **I** of the present invention, and pharmaceutically acceptable salts thereof described herein, are inhibitors of one or both of ERK1 and ERK2. One of ordinary skill in the art will recognize that ERK is one of the key components in the RAS-RAF-MEK-ERK MAPK pathway and that ERK1 and ERK2 are downstream nodes within the MAPK pathway. Without wishing to be bound by theory, because of the downstream location of ERK1 and ERK1 in the MAPK pathway, an ERK inhibitor can treat disease or disorders in which activation of the MAPK pathway at any level (Ras-Raf-Mek-ERK) is known or suspected to play a role, including one or both of ERK1 and ERK2 as well as other nodes in the MAPK pathway upstream from ERK (such as Ras, Raf and Mek). Furthermore, because ERK is a downstream target, ERK inhibitors are believed to be able to overcome, in some instances, drug resistance induced by inhibitors of targets upstream of ERK within the MAPK pathway. For example, small molecule inhibitors of RAF or MEK utilized in the treatment of K-RAS and B-RAF mutant tumors have resulted in such drug resistance. Similarly, drug resistance has been associated with other tumors driven by hyperactivation of the MAPK pathway (such as NF1 mutant tumors). Kinase selectivity was achieved through silencing the selective Cys in a combination of the interactions between the covalent inhibitors of the invention and unique amino acids in the ATP binding pocket. Targeting the selective Cys provides for prolonged pharmacodynamics in silencing ERK activity, as well as potential lower doses in cancer treatment, compared to reversible inhibitors.

[0128] The activity of a compound of Formula **I**, and pharmaceutically acceptable salts thereof, as an inhibitor of one or both of an ERK1 and ERK2 kinase, or a mutant thereof, may be assayed in vitro, in vivo or in a cell line. In vitro assays include assays that determine inhibition of downstream phosphorylation, changes in gene expression, subsequent functional markers and consequences, and/or kinase activity of one or both of activated ERK1 and ERK2 kinase, or a mutant thereof. Alternate in vitro assays quantitate the ability of the test compound to bind to one or both of ERK1 and ERK2. Test compound binding may be measured by radiolabeling the test compound prior to binding, isolating one or both of the compound / ERK1 complex and the compound / ERK2 complex, and determining the amount of radiolabel bound. Alternatively, test

compound binding may be determined by running a competition experiment where test compounds are incubated with one or both of ERK1 and ERK2 kinase bound to known radioligands. Test compound binding may be determined by competition with an ERK covalent probe that is amenable to further functionalization with a detection probe, such as, for example, a fluorophore, biotin conjugate, radiolabel, or any other probe that facilitates its quantification. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of one or both of ERK1 and ERK2, or a mutant thereof, are also set forth below and/or in the Examples of the '230 publication.

[0129] The term "measurably inhibit", as used herein means a measurable change in one or both of ERK1 and ERK2 protein kinase activity between a sample comprising a provided composition, and one or both of an ERK1 and ERK2 protein kinase and an equivalent sample comprising one or both of ERK1 and ERK2 protein kinase in the absence of a provided composition. Such measurements of protein kinase activity are known to one of ordinary skill in the art and include those methods set forth herein below and/or in the Examples of the '230 publication.

[0130] As described above, in some embodiments, a compound of Formula I, and pharmaceutically acceptable salts thereof, is an inhibitor of one or both of ERK1 and ERK2 protein kinases, and ERK1 and ERK2 are downstream targets within the MAPK pathway. Without wishing to be bound by any particular theory, such compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder in which activation of the MAPK pathway at any level (Ras-Raf-Mek-ERK) is known or suspected to play a role. Such disease, condition, or disorder may be referred to herein as associated with the MAPK pathway or alternatively as associated with one or both of ERK1 and ERK2. Such diseases, conditions, or disorders may also be referred to herein as an "ERK1- or ERK2-mediated disease, condition, or disorder."

[0131] In some embodiments, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation of the MAPK pathway (at any level in Ras-Raf-Mek-ERK), including one or both of ERK1 and ERK2 protein kinases, is implicated in said disease, condition, or disorder, wherein said method comprises administering to a patient in need thereof a compound of the present invention.

[0132] In some embodiments, the present invention relates to a method of inhibiting one or both of ERK1 and ERK2 protein kinase activity in a patient comprising the step of administering to said patient a composition comprising a compound of the present invention.

[0133] In other embodiments, the present invention provides a method for treating a disease, condition, or disorder mediated by one or both of ERK1 and ERK2 kinase, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound of the present invention.

[0134] In certain embodiments, the present invention provides a method for overcoming drug resistance to Raf or MEK inhibitors, comprising the step of administering to a patient an inhibitor compound of one or both of ERK1 and ERK2, such as a compound of the present invention. In certain embodiments, the mechanism of drug resistance is through mutation of a target protein or reactivation of the MAPK pathway.

[0135] As used herein, the term “resistance” may refer to changes in a wild-type nucleic acid sequence coding a target protein, and/or to the amino acid sequence of the target protein and/or to the amino acid sequence of another protein, which changes, decreases or abolishes the inhibitory effect of the inhibitor on the target protein. The term “resistance” may also refer to overexpression or silencing of a protein differing from a target protein that can reactivate the MAPK pathway or other survival pathways.

[0136] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment is administered after one or more symptoms have developed. In other embodiments, treatment is administered in the absence of symptoms. For example, treatment is administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment is also continued after symptoms have resolved, for example to prevent, delay or lessen the severity of their recurrence.

[0137] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof a composition comprising a compound of the present invention.

[0138] General diseases, conditions, or disorders treated by a compound of the present invention include cancer, an autoimmune disorder, a neurodegenerative or neurological disorder, liver disease, a cardiac disorder, schizophrenia, or a bone-related disorder.

[0139] In some embodiments, the present invention relates to a method of treating or lessening the severity of a disease, condition, or disorder selected from cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases, wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention.

[0140] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention. In some embodiments, the cancer is recurring. In certain embodiments, the cancer is refractory. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is locally advanced.

[0141] In certain embodiments, the cancer is a RAF inhibitor-resistant cancer. In some such embodiments, the RAF inhibitor-resistant cancer is a BRAF inhibitor-resistant cancer.

[0142] In certain embodiments, the cancer is a MEK inhibitor-resistant cancer.

[0143] In certain embodiments, the cancer is a MAPK pathway-mediated cancer.

[0144] In some embodiments, the cancer is a BRAF-mutated cancer. In certain embodiments, the BRAF-mutated cancer is a BRAF^{V600}-mutated cancer, such as BRAF^{V600E}, BRAF^{V600K}, BRAF^{V600R}, and BRAF^{V600D}.

[0145] In some embodiments, the cancer is a RAS-mutated cancer. In certain embodiments, the RAS-mutated involves codons 12, 13, or 61. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, KRAS^{G12C/D/V}, KRAS^{G13C/D}, or KRAS^{Q61L/H/R}. In certain embodiments, the RAS-mutated cancer is an NRAS-mutated cancer, including, but not limited to, NRAS^{Q61R}, NRAS^{Q61K}, NRAS^{Q61L}, or NRAS^{Q61H}. In certain embodiments, the RAS-mutated cancer is an HRAS-mutated cancer, including, but not limited to, HRAS^{G12V}, HRAS^{Q61R}, and HRAS^{G12S}.

[0146] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is selected from multiple myeloma, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung, bone, colon, thyroid, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma (including uveal melanoma) sarcoma, bladder carcinoma, liver carcinoma (e.g., hepatocellular carcinoma (HCC)) and biliary passage carcinoma), kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colorectal carcinoma, large intestine, rectum, brain and central nervous system, endometrial, multiple myeloma (MM), prostate, AML, and leukemia. In some such embodiments, the cancer is relapsed. In some embodiments, the cancer is refractory. In some embodiments, the cancer is locally advanced. In some embodiments, the cancer is metastatic.

[0147] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is selected from carcinoma, lymphoma, blastoma, sarcoma, and leukemia. In some embodiments, a sarcoma is a soft tissue sarcoma. In some embodiments, a lymphoma is non-Hodgkin's lymphoma. In some embodiments, a lymphoma is large cell immunoblastic lymphoma. In some embodiments, the cancer is selected from adenocarcinoma; adenoma; adrenocortical cancer; bladder cancer; bone cancer; brain cancer; breast cancer; cancer of the buccal cavity; cervical cancer; colon cancer; colorectal cancer; endometrial or uterine carcinoma; epidermoid carcinoma; oesophageal cancer; eye cancer; follicular carcinoma; gallbladder cancer; prostate, AML, multiple myeloma (MM), gastrointestinal cancer, such as, for example, gastrointestinal stromal tumor; cancer of the genitourinary tract; glioblastoma; hairy cell carcinoma; various types of head and neck cancer; hepatic carcinoma; hepatocellular cancer; Hodgkin's disease; keratoacanthoma; kidney cancer; large cell carcinoma; cancer of the large intestine; laryngeal cancer; liver cancer; lung cancer, such as, for example, adenocarcinoma of the lung, anaplastic carcinoma of the lung, papillary

lung adenocarcinoma, small-cell lung cancer, squamous carcinoma of the lung, non-small cell lung cancer; melanoma and nonmelanoma skin cancer; lymphoid disorders; myeloproliferative disorders, such as, for example, polycythemia vera, essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), hypereosinophilic syndrome, systematic mast cell disease, atypical CML, AML, or juvenile myelomonocytic leukemia; plasmacytoma; multiple myeloma; neuroblastoma; ovarian cancer; papillary carcinoma; pancreatic cancer; cancer of the peritoneum; prostate cancer, including benign prostatic hyperplasia; rectal cancer; salivary gland carcinoma; sarcoma; seminoma; squamous cell cancer; small cell carcinoma; cancer of the small intestine; stomach cancer; testicular cancer; thyroid cancer; undifferentiated carcinoma; and vulval cancer. In some such embodiments, the cancer is relapsed. In some embodiments, the cancer is refractory. In some embodiments, the cancer is locally advanced. In some embodiments, the cancer is metastatic.

[0148] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is selected from melanoma, pancreatic cancer, thyroid cancer, colorectal cancer, lung cancer (e.g., non-small cell lung cancer), breast cancer, endometrial cancer, prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), multiple myeloma (MM), and leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia. In certain embodiments, a leukemia is acute lymphoblastic leukemia.

[0149] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is selected from melanoma, colorectal cancer, lung cancer, or pancreatic.

[0150] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is melanoma. In certain embodiments, the melanoma is uveal melanoma. In some embodiments, the melanoma is a

melanoma of the skin. In certain embodiments, the melanoma is locally advanced. In some embodiments, the melanoma is metastatic. In some embodiments, the melanoma is recurring. In some embodiments, the melanoma is BRAF^{v600}-mutated melanoma. In certain embodiments, the melanoma is a RAS-mutated melanoma. In some embodiments, the melanoma is NRAS-mutated melanoma. In certain embodiments, the melanoma is wild type for KRAS, NRAS or BRAF. In certain embodiments, the melanoma is a BRAF inhibitor-resistant melanoma. In certain embodiments, the cancer is a VemR (i.e., Vemurfenib-resistant) BRAF-mutated melanoma. In some embodiments, the melanoma is relapsed. In some embodiments, the melanoma is refractory.

[0151] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is colorectal cancer. In certain embodiments, the colorectal cancer is locally advanced. In certain embodiments, the colorectal cancer is metastatic. In certain embodiments, the colorectal cancer is a BRAF-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a BRAF^{v600}-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a RAS-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a KRAS-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a NRAS-mutated colorectal cancer. In some embodiments, the colorectal cancer is relapsed. In some embodiments, the colorectal cancer is refractory.

[0152] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is pancreatic cancer. In certain embodiments, the pancreatic cancer is locally advanced. In certain embodiments, the pancreatic cancer is metastatic. In certain embodiments, the pancreatic cancer is a pancreatic ductal adenocarcinoma (PDAC). In certain embodiments, the pancreatic cancer is a RAS-mutated pancreatic cancer. In certain embodiments, the pancreatic cancer is a KRAS-mutated pancreatic cancer. In certain embodiments, the pancreatic cancer is KRAS-mutated pancreatic cancer, including, but not limited to, KRAS^{G12C/D/V}, KRAS^{G13C/D}, or KRAS^{Q61L/H/R}. In some

embodiments, the pancreatic cancer is relapsed. In some embodiments, the pancreatic cancer is refractory.

[0153] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is a papillary thyroid cancer. In certain embodiments, the papillary thyroid cancer is locally advanced. In some embodiments, the papillary thyroid cancer is metastatic. In some embodiments, the papillary thyroid cancer is recurring. In some embodiments, the papillary thyroid cancer is BRAF-mutated papillary thyroid cancer. In some embodiments, the papillary thyroid cancer is BRAF^{v600}-mutated papillary thyroid cancer. In some embodiments, the papillary thyroid cancer is relapsed. In some embodiments, the papillary thyroid cancer is refractory.

[0154] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is lung cancer. In certain embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In certain embodiments, the lung cancer is locally advanced. In certain embodiments, the lung cancer is metastatic. In certain embodiments, the lung cancer is a RAS-mutated lung cancer. In certain embodiments, the lung cancer is KRAS-mutated lung cancer. In certain embodiments, the lung cancer is a KRAS-mutated lung cancer, including, but not limited to, KRAS^{G12C/D/V}, KRAS^{G13C/D}, or KRAS^{Q61L/H/R}. In some embodiments, the lung cancer is relapsed. In some embodiments, the lung cancer is refractory.

[0155] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is a leukemia. In some embodiments, a leukemia is a chronic leukemia. In certain embodiments, a leukemia is chronic myeloid leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia (AML). In certain embodiments, a leukemia is acute monocytic leukemia (AMoL, or AML-M5). In certain embodiments, a leukemia is acute lymphoblastic leukemia (ALL). In certain embodiments, a leukemia is acute T cell leukemia. In certain embodiments, a leukemia is myelomonoblastic leukemia. In certain

embodiments, a leukemia is human B cell precursor leukemia. In certain embodiments, a leukemia has a Flt3 mutation or rearrangement. In some embodiments, the leukemia is relapsed. In some embodiments, the leukemia is refractory.

[0156] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is a CNS cancer, for instance CNS tumors. In certain embodiments, a CNS tumor is a glioblastoma or glioblastoma multiforme (GBM). In some embodiments, the present invention relates to a method of treating stomach (gastric) and esophageal tumors and cancers.

[0157] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is multiple myeloma (MM). In certain embodiments, the multiple myeloma is locally advanced. In certain embodiments, the multiple myeloma is metastatic. In certain embodiments, the multiple myeloma is a RAS-mutated multiple myeloma. In certain embodiments, the multiple myeloma is KRAS-mutated multiple myeloma. In certain embodiments, the multiple myeloma is a KRAS-mutated multiple myeloma, including, but not limited to, KRAS^{G12C/D/V}, KRAS^{G13C/D}, or KRAS^{Q61L/H/R}. In some embodiments, the multiple myeloma is relapsed. In some embodiments, the multiple myeloma is refractory.

[0158] In some embodiments, the present invention relates to a method of treating a cancer, wherein the method comprises administering to a patient in need thereof a composition comprising a compound of the present invention, wherein the cancer is hepatocellular carcinoma (HCC). In certain embodiments, the HCC is locally advanced. In certain embodiments, the HCC is metastatic. In certain embodiments, the HCC is a RAS-mutated HCC. In certain embodiments, the HCC is KRAS-mutated HCC. In certain embodiments, the HCC is a KRAS-mutated HCC, including, but not limited to, KRAS^{G12C/D/V}, KRAS^{G13C/D}, or KRAS^{Q61L/H/R}. In some embodiments, the hepatocellular carcinoma is relapsed. In some embodiments, the hepatocellular carcinoma is refractory.

[0159] In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition

comprising a compound of the present invention, wherein the cancer is selected from breast, colorectal, endometrial, hematological, leukemia (e.g., AML), liver, lung, melanoma, ovarian, pancreatic, prostate, or thyroid.

5. Pharmaceutically Acceptable Compositions

[0160] The compounds and compositions, according to the method of the present invention, are administered using any amount and any route of administration effective for treating or lessening the severity of a disorder provided above. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[0161] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention are administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25

mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0162] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0163] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0164] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0165] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively,

delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0166] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0167] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0168] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other

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

[0169] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0170] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0171] According to one embodiment, the invention relates to a method of inhibiting protein kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[0172] According to another embodiment, the invention relates to a method of inhibiting one or both of ERK 1 and ERK2 kinase, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound. In certain embodiments, the invention relates to a method of irreversibly inhibiting one or both of ERK1 and ERK2 kinase, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[0173] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0174] Inhibition of one or both of ERK1 and ERK2, or a mutant thereof, activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0175] Another embodiment of the present invention relates to a method of inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[0176] According to another embodiment, the invention relates to a method of inhibiting one or both of ERK1 and ERK2 kinase, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of irreversibly inhibiting one or both of ERK1 and ERK2 kinase, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 166 of ERK2. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 183 of

ERK1 and Cys 166 of ERK2. In other embodiments, the present invention provides a method for treating a disease, disorder, or condition mediated by one or both of ERK1 and ERK2 kinase, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[0177] All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

[0178] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

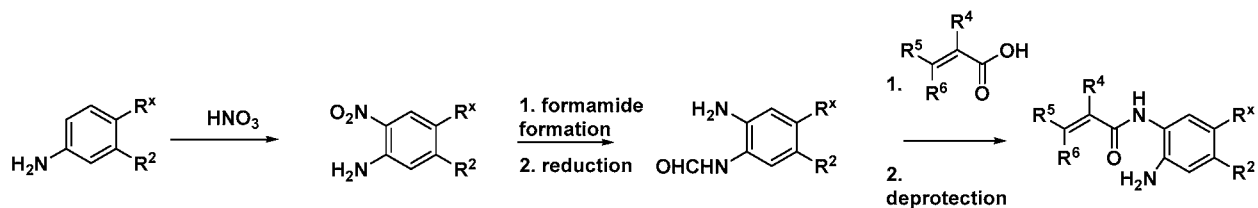
EXEMPLIFICATION

[0179] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

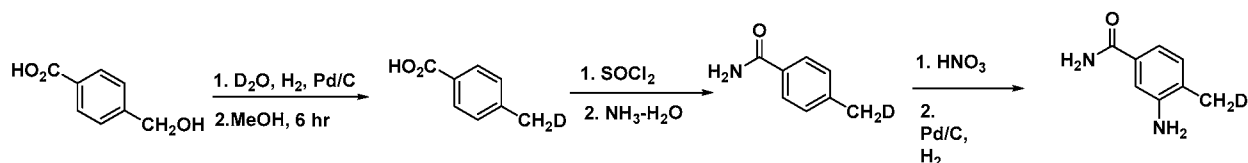
Example 1. General reaction sequence for compounds of Formula I-a

[0180] Deuterium-labeled ERK inhibitors were made via Method B described in PCT application publication number WO2014/124230, published August 14, 2014, optionally using deuterium-labeled intermediates. Exemplary such methods are described further below.

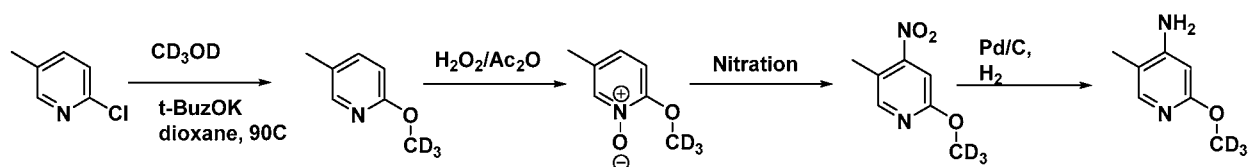
[0181] Exemplary method for preparing optionally deuterated acrylamide-containing intermediates, e.g., **E-2**, below:



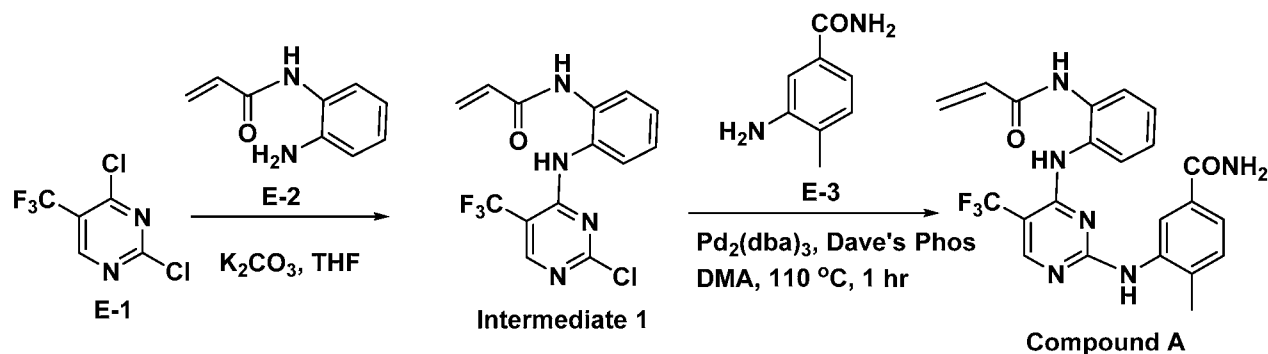
[0182] Exemplary method for preparing optionally deuterated amide-containing intermediates, e.g., **E-3**, below:



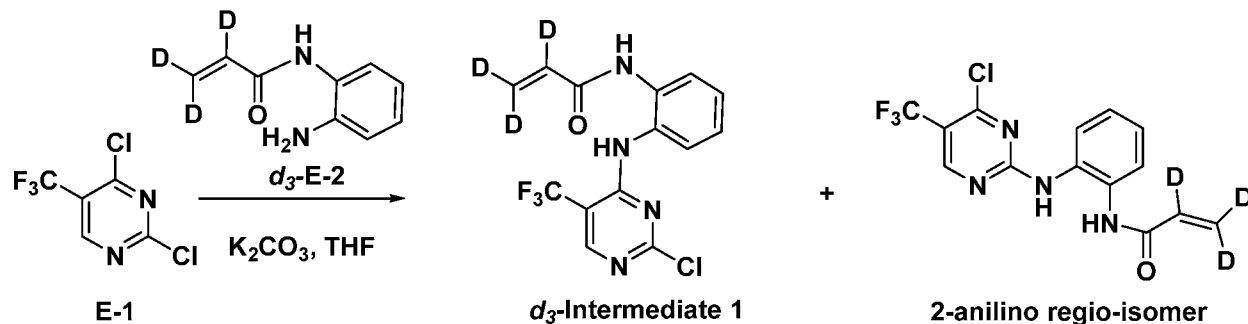
[0183] Exemplary method for preparing optionally deuterated methoxy-containing intermediates:



[0184] First, ortho-acrylamide aniline **E-2** was introduced at the C-4 position of pyrimidine **E-1**, followed by a Pd-mediated coupling reaction with coupling partner **E-3**, which coupled to the C-2 position of pyrimidine ring **E-1**. General reaction sequences are described below.



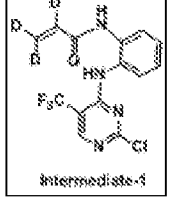
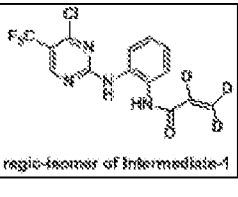
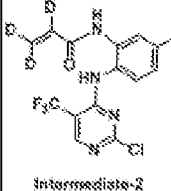
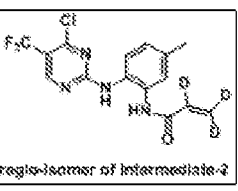
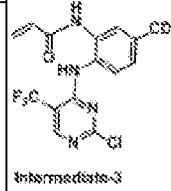
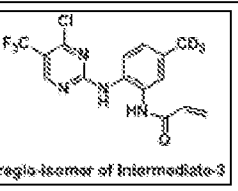
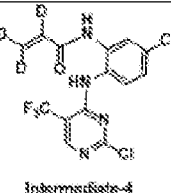
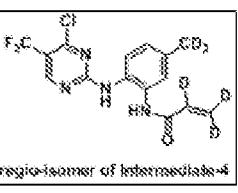
[0185] Proton Nuclear Magnetic Resonance (^1H NMR) spectra were obtained on a Joel model AMX 400 MHz NMR spectrometer. LC-MS was recorded on the Agilent Technology LC-1200 system, and quadrupole MS model-6120.

General method to prepare deuterated Intermediate 1.

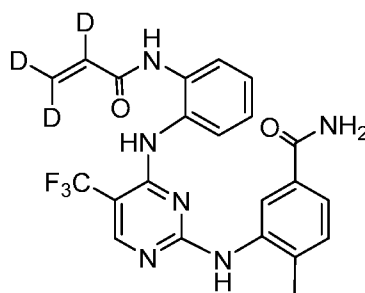
[0186] At 0 °C, to a stirring solution of N-(2-aminophenyl)- d_3 -acrylamide d_3 -**E-2** (165 mg 1.0 mmol) and potassium carbonate (42 mg, 3.0 mmol) in 5 mL of anhydrous tetrahydrofuran, was added 2,4-dichloro-5-(trifluoromethyl)pyrimidine **E-1** (240 mg, 1.1 mmol) in 1 mL of THF. The resulting mixture was stirred at rt for 1 hr, followed by solvent removal under reduced pressure. The residue was subject to aqueous work up and extracted with ethyl acetate. The combined organic layer was concentrated, and the regioisomers were separated using reversed phase HPLC, giving desired **Intermediate 1** (i.e., N-(2-((2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)- d_3 -acrylamide) (80 mg, early retention time on LC-MS) and 2-anilino regio-isomer (75 mg, late retention time on LC-MS).

[0187] Employing this synthetic method, the following deuterium-labeled key intermediates were prepared. Analytical data were recorded in **Table 5**, below.

Table 5

Desired Intermediate	HNMR (CDCl ₃ , MHz), ppm, desired	retention time	MS (ES+)	Regio-isomer	HNMR (CDCl ₃ , MHz), ppm, regio isomer	retention time	MS (ES+)
 Intermediate-1	8.56 (br s, 1H, NH), 8.38 (s, 1H), 7.74 (dd, 1H, J = 8.4 Hz), 7.50 (br s, 1H, NH), 7.38 (t, 1H, J = 7.6 Hz), 7.28 (d, 1H, J = 8.0 Hz), 7.18 (d, 1H, J = 7.6 Hz).	2.20	346.0	 regio-isomer of Intermediate-1	8.51 (s, 1H), 7.70 (br d, 1H), 7.45-7.58 (m, 2H), 7.30 (t, 2H, J = 8.4 Hz).	2.41	345.8
 Intermediate-2	8.50 (br s, 1H, NH), 8.36 (s, 1H), 7.58 (d, 1H, J = 8.0 Hz), 7.46 (br s, 1H), 7.18 (d, 1H, J = 8.0 Hz), 6.95 (s, 1H), 2.34 (s, 3H, Me).	2.40	359.9	 regio-isomer of Intermediate-2	8.50 (s, 1H), 7.50 (br s, 2H), 7.33 (br s, 1H), 7.12 (d, 1H, J = 8.4 Hz), 2.36 (s, 3H, Me).	2.59	359.9
 Intermediate-3	8.46 (br s, 1H, NH), 8.36 (s, 1H), 7.58 (d, 1H, J = 8.4 Hz), 7.45 (br s, 1H), 7.18 (d, 1H, J = 8.0 Hz), 6.98 (s, 1H), 6.50 (d, 1H, J = 16.4 Hz), 6.28 (dd, 1H, J = 10.4, 16.4 Hz), 5.84 (d, 1H, J = 10.4 Hz).	2.41	359.9	 regio-isomer of Intermediate-3	8.49 (s, 1H), 7.55 (br s, 2H), 7.32 (br s, 1H), 7.11 (d, 1H, J = 7.6 Hz), 6.46 (d, 1H, J = 16.8 Hz), 6.24 (dd, 1H, J = 10.4, 16.4 Hz), 5.82 (d, 1H, J = 10.4 Hz).	2.55	359.9
 Intermediate-4	8.48 (br s, 1H, NH), 8.37 (s, 1H), 7.58 (d, 1H, J = 8.0 Hz), 7.47 (br s, 1H, NH), 7.16 (dd, 1H, J = 2.0, 8.0 Hz), 6.95 (d, 1H, J = 1.6 Hz).	2.40	362.9	 regio-isomer of Intermediate-4	8.49 (s, 1H), 7.70 (br d, 1H), 7.51 (br s, 2H), 7.32 (br s, 1H), 7.11 (d, 1H, J = 8.4 Hz).	2.56	362.9

Example 2. Synthesis of I-1

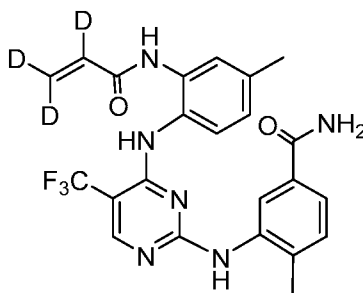


I-1

[0188] 3-((4-((2-*d*₃-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methyl benzamide. To a solution of 3-amino-4-methylbenzamide (10 mg, 65 μmol),

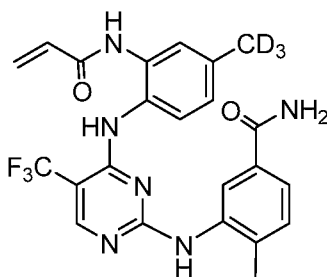
Intermediate 1 (17 mg, 50 μ mol), and Na_2CO_3 (22 mg, 0.20 mmol) in 1 mL of degassed N,N-dimethylacetamide, was added tris-dibenzylamino dipalladium (5.0 mg) and DavePhos (7.5 mg). The mixture was degassed and purged again with argon, then heated at 110 $^\circ\text{C}$ for 1h. LC-MS confirmed the completion of the reaction. The reaction mixture was purified by MS-tiggered prep-HPLC, giving 5.0 mg of final product. ^1H NMR (400 MHz, d_6 -acetone) δ ppm: 9.53 (br s, 1H, NH), 8.25 (s, 1H); 8.18 (s, 1H), 8.05 (s, 1H), 7.70 (d, 1H, $J = 6.8$ Hz), 7.62 (d, 1H, $J = 8.0$ Hz), 7.40 (br s, 1H, NH), 7.24 (m, 2H), 7.11 (m, 2H), 6.60 (br s, 1H, NH), 2.18 (s, 3H, Me). MS: m/z 460.1 (ES^+ , $\text{M}+\text{H}$).

Example 3. Synthesis of I-2

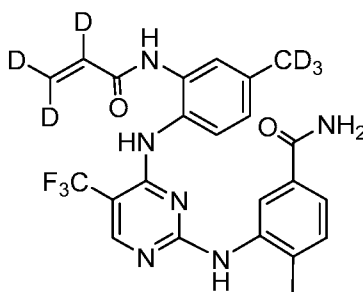


I-2

[0189] 3-((4-((2- d_3 -acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methylbenzamide. Compound I-2 was prepared in a manner similar to Example 1, substituting Intermediate 2 for Intermediate 1, with Intermediate 2 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-methylphenyl)- d_3 -acrylamide for N-(2-aminophenyl)- d_3 -acrylamide. ^1H NMR (400 MHz, d_6 -acetone) δ ppm: 9.45 (br s, 1H, NH), 8.24 (s, 1H); 8.11 (s, 1H), 8.05 (s, 1H), 7.62 (d, 1H, $J = 8.0$ Hz), 7.52 (d, 1H, $J = 8.0$ Hz), 7.35 (br s, 1H, NH), 7.24 (d, 1H, $J = 8.4$ Hz), 7.05 (s, 1H), 6.95 (s, 1H, $J = 8.0$ Hz), 6.60 (br s, 1H, NH), 2.30 (s, 3H, Me), 2.05 (s, 3H, Me). MS: m/z 474.2 (ES^+ , $\text{M}+\text{H}$).

Example 4. Synthesis of I-3**I-3**

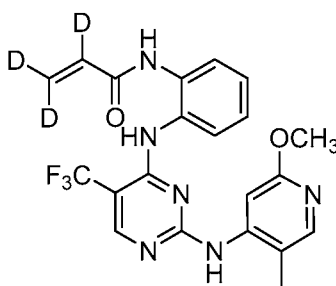
[0190] 3-((4-((2-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-*d*₃-methylbenzamide. Compound I-3 was prepared in a manner similar to Example 1, substituting Intermediate 3 for Intermediate 1, with Intermediate 3 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-*d*₃-methylphenyl)acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.45 (br s, 1H, NH), 8.24 (s, 1H); 8.11 (s, 1H), 8.05 (s, 1H), 7.62 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.35 (br s, 1H, NH), 7.24 (d, 1H, J = 7.6 Hz), 7.05 (s, 1H), 6.95 (s, 1H, J = 8.0 Hz), 6.60 (br s, 1H, NH), 6.47 (dd, 1H, J = 9.6, 16.4 Hz), 6.40 (d, 1H, J = 16.4 Hz), 5.76 (dd, 1H, J = 2.0, 12.0 Hz), 2.30 (s, 3H, Me). MS: m/z 474.2 (ES⁺, M+H).

Example 5. Synthesis of I-4**I-4**

[0191] 3-((4-((2-*d*₃-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-*d*₃-methylbenzamide. Compound I-4 was prepared in a manner similar to Example 1, substituting Intermediate 4 for Intermediate 1, with Intermediate 4 being made in a manner

similar to Intermediate 1 but substituting N-(2-amino-5-*d*₃-methylphenyl)-*d*₃-acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.45 (br s, 1H, NH), 8.23 (s, 1H); 8.11 (s, 1H), 8.04 (s, 1H), 7.62 (d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.35 (br s, 1H, NH), 7.24 (d, 1H, J = 7.6 Hz), 7.05 (s, 1H), 6.95 (s, 1H, J = 8.0 Hz), 6.60 (br s, 1H, NH), 2.28 (s, 3H, Me). MS: m/z 477.2 (ES⁺, M+H).

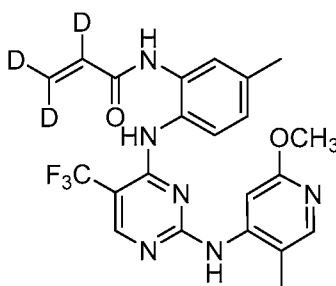
Example 6. Synthesis of I-5



I-5

[0192] **N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-*d*₃-acrylamide.** Compound **I-5** was prepared in a manner similar to **Example 1**, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.61 (br s, 1H, NH), 8.57 (br s, 1H, NH), 8.37 (s, 1H); 7.81 (s, 1H), 7.75 (d, 1H, J = 8.4 Hz), 7.43~7.24 (m, 4H), 3.80 (s, 3H, OMe), 2.22 (s, 3H, Me). MS: m/z 448.2 (ES⁺, M+H).

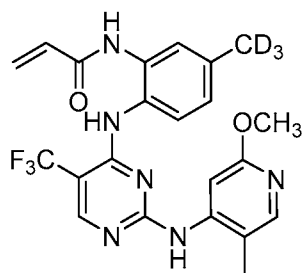
Example 7. Synthesis of I-6



I-6

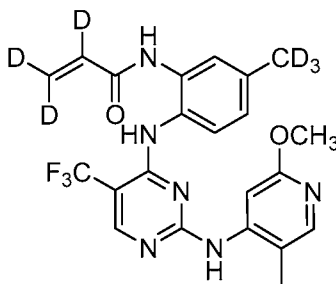
[0193] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)-*d*₃-acrylamide. Compound I-6 was prepared in a manner similar to Example 1, substituting Intermediate 2 for Intermediate 1, with Intermediate 2 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-methylphenyl)-*d*₃-acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.58 (br s, 1H, NH), 8.49 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.70 (br s, 1H, NH), 7.56 (d, 1H, J = 8.4 Hz), 7.40 (s, 1H), 7.19 (br d, 2H), 3.80 (s, 3H, OMe), 2.37 (s, 3H, Me), 2.21 (s, 3H, Me). MS: *m/z* 462.3(ES⁺, M+H).

Example 8. Synthesis of I-7

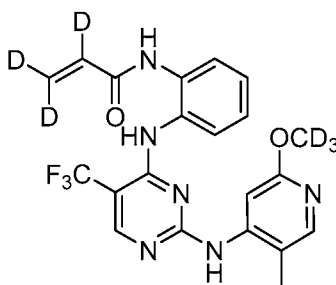


I-7

[0194] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-*d*₃-methylphenyl)acrylamide. Compound I-7 was prepared in a manner similar to Example 1, substituting Intermediate 3 for Intermediate 1, with Intermediate 3 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-*d*₃-methylphenyl)acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.62 (br s, 1H, NH), 8.50 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.70 (br s, 1H, NH), 7.56 (d, 1H, J = 8.4 Hz), 7.41 (s, 1H), 7.20 (br d, 2H), 6.50 (dd, 1H, J = 9.6, 17.2 Hz), 6.40 (dd, 1H, J = 1.6, 16.4 Hz), 5.76 (dd, 1H, J = 2.4, 10.4 Hz), 3.80 (s, 3H, OMe), 2.21 (s, 3H, Me). MS: *m/z* 462.2 (ES⁺, M+H).

Example 9. Synthesis of I-8**I-8**

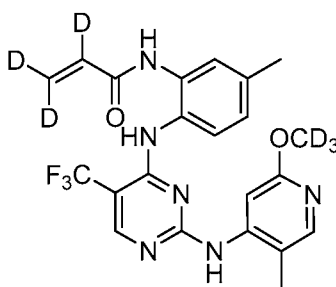
[0195] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-*d*₃-methylphenyl)-*d*₃-acrylamide. Compound I-8 was prepared in a manner similar to Example 1, substituting Intermediate 4 for Intermediate 1, with Intermediate 4 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-*d*₃-methylphenyl)-*d*₃-acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.53 (br s, 1H, NH), 8.50 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.69 (br s, 1H, NH), 7.57 (d, 1H, J = 8.0 Hz), 7.41 (s, 1H), 7.19 (br d, 2H), 3.80 (s, 3H, OMe), 2.21 (s, 3H, Me). MS: m/z 465.4 (ES⁺, M+H).

Example 10. Synthesis of I-9**I-9**

[0196] N-(2-((2-((2-*d*₃-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-*d*₃-acrylamide. Compound I-9 was prepared in a manner similar to Example 1, substituting 2-*d*₃-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.61 (br s, 1H, NH), 8.57 (br s, 1H, NH), 8.37 (s, 1H); 7.81

(s, 1H), 7.75 (d, 1H, J = 8.4 Hz), 7.43~ 7.24 (m, 4H), 2.22 (s, 3H, Me). MS: m/z 451.2 (ES⁺, M+H).

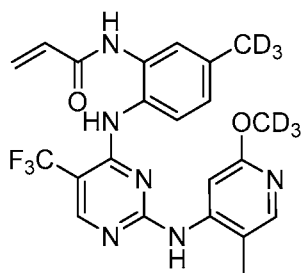
Example 11. Synthesis of I-10



I-10

[0197] N-(2-((2-((2-*d*₃-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)-*d*₃-acrylamide. Compound I-10 was prepared in a manner similar to Example 1, substituting Intermediate 2 for Intermediate 1, with Intermediate 2 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-methylphenyl)-*d*₃-acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-*d*₃-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.53 (br s, 1H, NH), 8.49 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.69 (br s, 1H, NH), 7.56 (d, 1H, J = 8.4 Hz), 7.40 (s, 1H), 7.19 (br d, 2H), 2.37 (s, 3H, Me), 2.21 (s, 3H, Me). MS: m/z 465.2 (ES⁺, M+H).

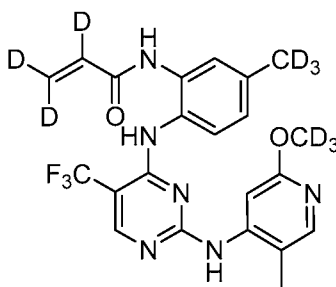
Example 12. Synthesis of I-11



I-11

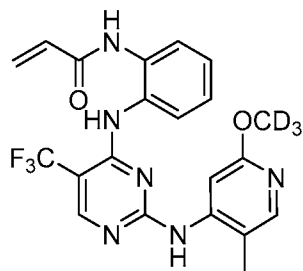
[0198] N-(2-((2-((2-*d*₃-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-*d*₃-methylphenyl)acrylamide. Compound I-11 was prepared in a manner similar to Example 1, substituting Intermediate 3 for Intermediate 1, with Intermediate 3 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-*d*₃-methylphenyl)acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-*d*₃-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.55 (br s, 1H, NH), 8.50 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.70 (br s, 1H, NH), 7.56 (d, 1H, J = 8.4 Hz), 7.41 (s, 1H), 7.20 (br d, 2H), 6.50 (dd, 1H, J = 9.6, 17.2 Hz), 6.40 (dd, 1H, J = 1.6, 16.4 Hz), 5.76 (dd, 1H, J = 2.4, 10.4 Hz), 2.21 (s, 3H, Me). MS: m/z 465.2 (ES⁺, M+H).

Example 13. Synthesis of I-12

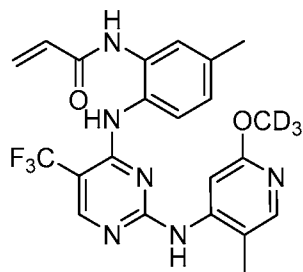


I-12

[0199] N-(2-((2-((2-*d*₃-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-*d*₃-methylphenyl)-*d*₃-acrylamide. Compound I-12 was prepared in a manner similar to Example 1, substituting Intermediate 4 for Intermediate 1, with Intermediate 4 being made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-*d*₃-methylphenyl)-*d*₃-acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-*d*₃-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.55 (br s, 1H, NH), 8.49 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.69 (br s, 1H, NH), 7.57 (d, 1H, J = 7.6 Hz), 7.40 (s, 1H), 7.19 (br d, 2H), 2.21 (s, 3H, Me). MS: m/z 468.2 (ES⁺, M+H).

Example 14. Synthesis of I-13**I-13**

[0200] N-(2-((2-((2-*d*₃-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound I-13 was prepared in a manner similar to Example 1, substituting Intermediate 1 with an intermediate made in a manner similar to Intermediate 1 but substituting N-(2-aminophenyl)acrylamide for N-(2-aminophenyl)-*d*₃-acrylamide, and substituting 2-*d*₃-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.63 (br s, 1H, NH), 8.57 (br s, 1H, NH), 8.37 (s, 1H); 7.81 (s, 1H), 7.75 (d, 1H, J = 8.4 Hz), 7.45~7.28(m, 4H), 6.50 (dd, 1H, J = 10.0, 17.2Hz), 6.40 (dd, 1H, J = 2.0, 16.4Hz), 5.76 (dd, 1H, J = 1.6, 9.6Hz), , 2.22 (s, 3H, Me). MS: m/z 448.1 (ES⁺, M+H).

Example 15. Synthesis of I-14**I-14**

[0201] N-(2-((2-((2-*d*₃-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound I-14 was prepared in a manner similar to Example 1, substituting Intermediate 1 with an intermediate made in a manner similar to Intermediate 1 but substituting N-(2-amino-5-methylphenyl) acrylamide for N-(2-aminophenyl)-

*d*₃-acrylamide, and substituting 2-*d*₃-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. ¹H NMR (400 MHz, *d*₆-acetone) δ ppm: 9.55 (br s, 1H, NH), 8.49 (br s, 1H, NH), 8.34 (s, 1H); 7.80 (s, 1H), 7.69 (br s, 1H, NH), 7.56 (d, 1H, J = 8.4 Hz), 7.40 (s, 1H), 7.19 (br d, 2H), 6.50 (dd, 1H, J = 9.6, 17.2 Hz), 6.40 (dd, 1H, J = 2.0, 16.4 Hz), 5.76 (dd, 1H, J = 2.4, 9.6 Hz), 2.38 (s, 3H, Me), 2.21 (s, 3H, Me). MS: m/z 462.2 (ES⁺, M+H).

Example 16. In Vitro Assays

Protein Mass Modification Assay

[0202] Compounds of the invention were assayed in a mass spectrometric assay to measure their ability to covalently modify ERK1 protein. The procedure for this assay is as follows. Intact ERK1 protein (Eurofins 14-439M, Lot#2052233-D) was incubated for 60 min. at room temperature with a 10-fold excess of test compound to protein. 4 μL aliquots of the resulting mixture were diluted with 15 μL of 0.2% TFA prior to micro C4 ZipTipping directly onto the MALDI target using sinapinic acid as the desorption matrix (10 mg/ml in 0.1% TFA:Acetonitrile 50:50, v/v). The centroid mass of the target protein in the control sample was compared with the centroid mass of the target protein incubated with compound. A shift in the centroid mass of the treated protein compared to the untreated protein was divided by the molecular weight of the compound. This number corresponds to the percentage of modified protein (a measure of the proportion of total target protein covalently bound to the test compound) after one hour incubation. Results from this assay are reported in **Table A** under the column “**ERK1 Mass Mod**”

Omnia Assay Protocol for Potency Assessment against MEK1 activated ERK1:

[0203] The protocol below describes continuous-read kinase assays to measure potency of compounds against activated ERK1 enzyme. The mechanics of the assay platform are best described by the vendor (Invitrogen, Carlsbad, CA) on their website at the following URL: invitrogen.com/site/us/en/home.html.

[0204] Briefly, a 1.25X stock of ERK1 enzyme (14-439-K) from Millipore (Billerica, MA), 5X ATP (AS001A) and ST17-Sox conjugated peptide substrate (KNZ1171C) were prepared in 1X kinase reaction buffer consisting of 20 mM Tris, pH 7.5, 5 mM MgCl₂, 1 mM EGTA, 5 mM

β -glycerophosphate, 5% glycerol (10X stock, KB001A) and 0.2 mM DTT. 10 μ L of ATP/ST17-sox peptide substrate mix was combined with 0.5 μ L volume of 100% DMSO and serially diluted compounds were prepared in 100% DMSO in a Corning (#3574) 384-well, white, non-binding surface microtiter plate (Corning, NY). Kinase reactions were started with the addition of 40 μ L of ERK1 solution and monitored every 71 seconds for 30-240 minutes at $\lambda_{\text{ex}}360/\lambda_{\text{em}}485$ in a Synergy plate reader from BioTek (Winooski, VT). At the conclusion of each assay, progress curves from each well were examined for linear reaction kinetics and fit statistics (R^2 , 95% confidence interval, absolute sum of squares). Initial velocity (0 minutes to ~30+ minutes) from each reaction was determined from the slope of a plot of relative fluorescence units vs time (minutes or seconds) and then plotted against inhibitor concentration to estimate AppIC_{50} from log[Inhibitor] vs Response, Variable Slope model in GraphPad Prism from GraphPad Software (San Diego, CA).

[Reagent] used in optimized protocol:

[ERK1] = 4 nM, [ATP] = 50 μ M, [ST17-Sox] = 10 μ M (ATP appK_M 48 μ M)

[0205] The results of this assay show the degree of inhibition of ERK activity, which is a direct measurement of inhibition of ERK activity. Results from this assay are reported in **Table A** under the column “**ERK1 Omnia WT ATP KM IC₅₀**.”

pRSK MSD Assay

Detection of total and phosphor-RSK by MSD ELISA (A375)

[0206] The protocol below describes an assay to measure the kinase activity of ERK1/2 to phosphorylate a substrate, p90RSK, in the presence or absence of a test compound.

Cell Treatment

[0207] A375 cells were grown in DMEM/10% FBS. Twenty four hours prior to the assay, 50,000 cells per well were plated in a 96 well flat bottom plate. Once cells attached to the plate, the medium was replaced with 100 μ L of DMEM/0.1% FBS. Cells were cultured overnight in an incubator at 37 °C.

Compound dilution

[0208] Compound stock solutions of 10 mM in DMSO were prepared. 1000x dilutions were then prepared in DMSO. 1 μ L of DMSO solution was then transferred to 1 ml DMEM/0.1% FBS in a deep well plate. Cell plate media was discarded, followed by addition of 100 μ L of the compound-containing media. The preparation was incubated at 37 °C for 2 hrs.

[0209] Cell lysates were prepared as described below.

pRSK or total RSK MSD Assay

DAY 1

[0210] MSD plates: Blank MSD plates were coated with 30 μ L capture antibody (BD 610226) at a final concentration of 1 μ g/mL in PBS. Both pRSK and total RSK MSD assays used the same capture antibody at the same concentration. Antibody stock concentration was 250 μ g/mL. Once antibody solution was added to the MSD plate, the sides were tapped to be certain it was coated completely (visual inspection). It was then covered and placed at 4 °C overnight on a level surface.

DAY 2

[0211] Block MSD Plate: The coating antibody was removed and the plate was washed on a plate washer in MSD wash buffer. The last bit of wash solution was tapped out and 150 μ L/well of 3% BSA in MSD wash buffer was added in. The preparation was placed on a shaker at room temperature for at least an hour.

[0212] Add samples: Media was removed from compound-treated cells and replaced with 55 μ L/well MSD cell lysis buffer containing protease and phosphatase I & II inhibitors. The preparation was incubated on a shaker in a cold room for 30-45 min. The blocked MSD plate was washed on a plate washer, tapping out the last bit of wash solution, followed by addition of 50 μ L (of the 55 μ L) cell lysate in a well-well transfer. The preparation was covered and incubated on a shaker at room temp for 2 hours. The lysate was removed, washed on a plate washer 3 times, and the last bit of wash buffer was tapped out and replaced with 25 μ L/well detection antibody (described below).

Detection antibody:

[0213] For pRSK detection, a pRSK antibody stock of 21 µg/mL was prepared as follows: 1 µg/mL pRSK Ser380 antibody (Cell Signaling Technology, Cat. # 9335) + 1:750 anti-rabbit SulfoTag (Mesoscale Discovery, Cat. # R32AB-1) in 1% BSA in MSD wash buffer.

[0214] For total RSK detection, a total RSK antibody stock of 200 µg/mL was prepared as follows: 1 µg/mL total RSK (Santa Cruz sc-231G) antibody + 1:750 anti-goat SulfoTag (from MSD, R32AG-1) in 1% BSA in MSD wash buffer.

[0215] The plate was incubated for 1 hr at room temperature on a shaker, followed by three washings. The last bit of wash buffer was tapped out. 150 µL/well 1X MSD Read buffer was added and the plate was then analyzed. Curve fitting analysis was done with variable slope in Graph Pad software to generate EC₅₀ based on DMSO control (untreated) being 100% pRSK signal and maximum inhibition with a reference compound provided by the manufacturer as a positive control. Results from this assay, showing EC₅₀ (i.e., the concentration at which a test compound inhibits phosphorylation of RSK by 50%) are reported in **Table A** under the column “**ERK1/ERK2 PRSK MSD A375 EC₅₀**.”

Detection of total and phospho-RSK by MSD ELISA (HCT116)

[0216] The protocol below describes an assay to measure the kinase activity of ERK1/2 to phosphorylate a substrate, p90RSK, in the presence or absence of a test compound.

Cell Treatment

[0217] HCT116 cells were grown in RPMI/10%FBS. Prior to the assay, 50,000 cells per well were plated in a 96 well flat bottom plate. Cells were cultured overnight in an incubator at 37 °C.

Compound dilution

[0218] Compound stocks were 10 mM in DMSO. A 1000x dilution was made in DMSO. 1 µL of the DMSO solution was transferred to 1 ml RPMI/10%FBS in a deep well plate. Media in the cell plate was discarded, and 100 µL of the compound-containing media was added. The preparation was incubated at 37 °C for 2 hrs.

Preparation of cell lysates are described below.

pRSK or total RSK MSD Assay

DAY 1

[0219] MSD plates: Blank MSD plates were coated with 30 μ L capture antibody (BD 610226) at a final concentration of 1 μ g/mL in PBS. Both pRSK and total RSK MSD assays used the same capture antibody at the same concentration. Antibody stock concentration was 250 μ g/mL. Once antibody solution was added to MSD plate, the sides were tapped to be certain it was coated completely (visual inspection). It was then covered and placed at 4 °C overnight on a level surface.

DAY 2

[0220] Block MSD Plate: The coating antibody was removed and the plate was washed on a plate washer in MSD wash buffer. The last bit of wash solution was tapped out and 150 μ L/well 3% BSA (MSD Blocker A) in MSD wash buffer was added. The preparation was placed on a shaker at room temperature for at least an hour.

[0221] Add samples: Media was removed from compound-treated cells and replaced with 55 μ L/well MSD cell lysis buffer containing protease and phosphatase I & II inhibitors. The preparations was incubate on a shaker in a cold room for 30-45 min. The blocked MSD plate was washed on a plate washer, and the last bit of wash solution was tapped out. Next was added 50 μ L (of the 55 μ L) cell lysate in a well-well transfer. The preparation was covered and incubated on shaker at room temp for 2 hours. The lysate was then removed and washed on plate washer 3 times. The last bit of wash buffer was then tapped out and replaced with 25 μ L/well detection antibody (described below).

Detection antibody:

[0222] For pRSK detection, a pRSK antibody stock of 21 μ g/mL was prepared as follows: 1 μ g/mL pRSK Ser380 antibody (Cell Signaling Technology, Cat. # 9335) + 1:750 anti-rabbit SulfoTag (from MSD, R32AB-1) in 1% BSA in MSD wash buffer.

[0223] For total RSK detection, a total RSK antibody stock of 200 μ g/mL was prepared as follows: 1 μ g/mL total RSK (Santa Cruz sc-231G) antibody + 1:750 anti-goat SulfoTag (from MSD, R32AG-1) in 1% BSA in MSD wash buffer.

[0224] The plate was incubated for 1 hr at room temperature on a shaker, followed by three washes. The last bit of wash buffer was tapped out. Next, 150 μ L/well 1X MSD Read buffer

was added and the plate was analyzed by the MSD reader. Curve fitting analysis was done with variable slope in Graph Pad software to generate EC₅₀ based on DMSO control (untreated) being 100% pRSK signal and maximum inhibition with a reference compound provided by the manufacturer as a positive control. Results from this assay, showing EC₅₀ (i.e., the concentration at which a test compound inhibits phosphorylation of RSK by 50%) are reported in **Table A** under the column “**ERK1/ERK2 PRSK MSD HCT116 EC₅₀.**”

[0225] Table A shows data for selected compounds in various assays. Compound numbers in Table A correspond to Compound numbers in **Table 4**, above. Compounds having an activity designated as “A” provided an EC₅₀/IC₅₀ ≤100 nM; compounds having an activity designated as “B” provided an EC₅₀/IC₅₀ of 101-500 nM; compounds having an activity designated as “C” provided an EC₅₀/IC₅₀ of 501-999 nM; compounds having an activity designated as "D" provided an EC₅₀/IC₅₀ of ≥1000 nM.

[0226] Compounds having an activity designated as “E” provided a mass modification of ≥70%; compounds having an activity designated as “F” provided a mass modification of 31 – 69%; compounds having an activity designated as “G” provided a mass modification ≤30 %.

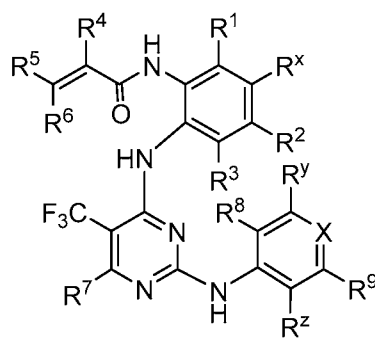
Table A.

Compound	ERK1 Mass Mod	ERK1 Omnia WT ATP KM IC₅₀	ERK1/ERK2 PRSK MSD A375 EC₅₀	ERK1/ERK2 PRSK MSD HCT116 EC₅₀
I-1	E	B	B	A
I-2	E	B	B	A
I-3	E	C	C	B
I-4	E	B	B	A
I-5	E	A	A	A
I-6	E	A	A	B
I-7	E	A	B	A
I-8	E	A	A	B
I-9	E	A	A	A
I-10	E	A	A	A
I-11	E	A	A	A
I-12	E	A	A	B
I-13	E	A	A	A
I-14	E	B	B	B

CLAIMS

We claim:

1. A compound of Formula I:

**I**

or a pharmaceutically acceptable salt thereof, wherein:

each of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen or deuterium;

R^x is selected from hydrogen, deuterium, or $-C(H)_j(D)_k$;

j is 0-3;

k is 0-3;

wherein the sum of j and k is 3;

R^y is selected from $R^{y'}$ or $-C(=O)N(H)_r(D)_s$;

$R^{y'}$ is $-OC(H)_m(D)_n$;

m is 0-3;

n is 0-3;

wherein the sum of m and n is 3;

r is 0-2

s is 0-2

wherein the sum of r and s is 2;

R^z is $-C(H)_p(D)_q$;

p is 0-3;

q is 0-3;

wherein the sum of p and q is 3; and

X is N or CH;

provided that at least one of R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^x , R^y , or R^z is or contains deuterium.

2. The compound according to claim 1, wherein each of R^1 , R^2 and R^3 is hydrogen.
3. The compound according to claim 1, wherein one of R^1 , R^2 and R^3 is deuterium.
4. The compound according to claim 1, wherein two of R^1 , R^2 and R^3 are deuterium.
5. The compound according to claim 1, wherein two of R^1 , R^2 and R^3 are deuterium.
6. The compound according to claim 1, wherein each of R^1 , R^2 and R^3 is deuterium.
7. The compound according to any of claims 1-6, wherein R^x is hydrogen.
8. The compound according to any of claims 1-6, wherein R^x is deuterium.
9. The compound according to any of claims 1-6, wherein R^x is $-C(H)_j(D)_k$.
10. The compound according to any of claims 1-6, wherein R^x is $-CH_3$ or $-CD_3$.
11. The compound according to any of claims 1-6, wherein R^x is $-CH_3$.
12. The compound according to any of claims 1-6, wherein R^x is $-CD_3$.
13. The compound according to any of claims 1-12, wherein each of R^4 , R^5 and R^6 is hydrogen.

14. The compound according to any of claims 1-12, wherein one of R^4 , R^5 and R^6 is deuterium.
15. The compound according to any of claims 1-12, wherein two of R^4 , R^5 and R^6 are deuterium.
16. The compound according to any of claims 1-12, wherein each of R^4 , R^5 and R^6 is deuterium.
17. The compound according to any of claims 1-16, wherein R^7 is hydrogen.
18. The compound according to any of claims 1-16, wherein R^7 is deuterium.
19. The compound according to any of claims 1-18, wherein R^y is $-C(=O)NH_2$.
20. The compound according to any of claims 1-18, wherein R^y is $-R^{y'}$.
21. The compound according to claim 20, wherein $R^{y'}$ is $-OCH_3$ or $-OCD_3$.
22. The compound according to claim 21, wherein $R^{y'}$ is $-OCH_3$.
23. The compound according to claim 21, wherein $R^{y'}$ is $-OCD_3$.
24. The compound according to any of claims 1-23, wherein X is N.
25. The compound according to any of claims 1-23, wherein X is CH.
26. The compound according to any of claims 1-25, wherein each of R^8 and R^9 is hydrogen.
27. The compound according to any of claims 1-25, wherein one of R^8 and R^9 is deuterium.

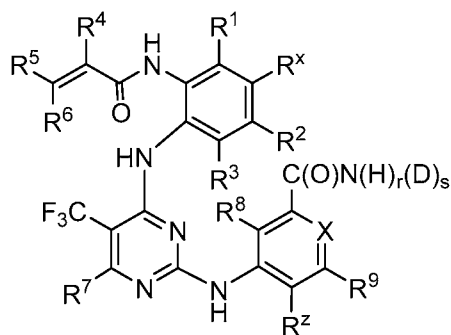
28. The compound according to any of claims 1-25, wherein each of R^8 and R^9 is deuterium.
29. The compound according to any of claims 1-28, wherein R^z is $-CH_3$.
30. The compound according to any of claims 1-29, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 are as defined in one of the following entries:

Entry	R^1	R^2	R^3	R^7	R^8	R^9
<i>i</i>	H	H	H	H	H	H
<i>ii</i>	D	H	H	H	H	H
<i>iii</i>	H	D	H	H	H	H
<i>iv</i>	H	H	D	H	H	H
<i>v</i>	D	D	H	H	H	H
<i>vi</i>	H	D	D	H	H	H
<i>vii</i>	D	H	D	H	H	H
<i>viii</i>	D	D	D	H	H	H
<i>ix</i>	H	H	H	H	D	H
<i>x</i>	D	H	H	H	D	H
<i>xi</i>	H	D	H	H	D	H
<i>xii</i>	H	H	D	H	D	H
<i>xiii</i>	D	D	H	H	D	H
<i>xiv</i>	H	D	D	H	D	H
<i>xv</i>	D	H	D	H	D	H
<i>xvi</i>	D	D	D	H	D	H
<i>xvii</i>	H	H	H	H	H	D
<i>xviii</i>	D	H	H	H	H	D
<i>xix</i>	H	D	H	H	H	D
<i>xx</i>	H	H	D	H	H	D
<i>xxi</i>	D	D	H	H	H	D

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>xxii</i>	H	D	D	H	H	D
<i>xxiii</i>	D	H	D	H	H	D
<i>xxiv</i>	D	D	D	H	H	D
<i>xxv</i>	H	H	H	H	D	D
<i>xxvi</i>	D	H	H	H	D	D
<i>xxvii</i>	H	D	H	H	D	D
<i>xxviii</i>	H	H	D	H	D	D
<i>xxix</i>	D	D	H	H	D	D
<i>xxx</i>	H	D	D	H	D	D
<i>xxxi</i>	D	H	D	H	D	D
<i>xxxii</i>	D	D	D	H	D	D
<i>xxxiii</i>	H	H	H	D	H	H
<i>xxxiv</i>	D	H	H	D	H	H
<i>xxxv</i>	H	D	H	D	H	H
<i>xxxvi</i>	H	H	D	D	H	H
<i>xxxvii</i>	D	D	H	D	H	H
<i>xxxviii</i>	H	D	D	D	H	H
<i>xxxix</i>	D	H	D	D	H	H
<i>xl</i>	D	D	D	D	H	H
<i>xli</i>	H	H	H	D	D	H
<i>xlvi</i>	D	H	H	D	D	H
<i>xlvi</i>	H	D	H	D	D	H
<i>xlvi</i>	H	H	D	D	D	H
<i>xlvi</i>	D	D	H	D	D	H
<i>xlvi</i>	H	D	D	D	D	H
<i>xlvi</i>	D	H	D	D	D	H
<i>xlvi</i>	D	D	D	D	D	H
<i>xlvi</i>	H	H	H	D	H	D

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>l</i>	D	H	H	D	H	D
<i>li</i>	H	D	H	D	H	D
<i>lii</i>	H	H	D	D	H	D
<i>liii</i>	D	D	H	D	H	D
<i>liv</i>	H	D	D	D	H	D
<i>lv</i>	D	H	D	D	H	D
<i>lvi</i>	D	D	D	D	H	D
<i>lvii</i>	H	H	H	D	D	D
<i>lviii</i>	D	H	H	D	D	D
<i>lix</i>	H	D	H	D	D	D
<i>lx</i>	H	H	D	D	D	D
<i>lxi</i>	D	D	H	D	D	D
<i>lxii</i>	H	D	D	D	D	D
<i>lxiii</i>	D	H	D	D	D	D
<i>lxiv</i>	D	D	D	D	D	D

31. The compound according to claim 1, of Formula **II**:



II

or a pharmaceutically acceptable salt thereof.

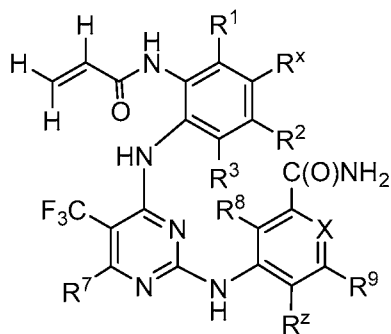
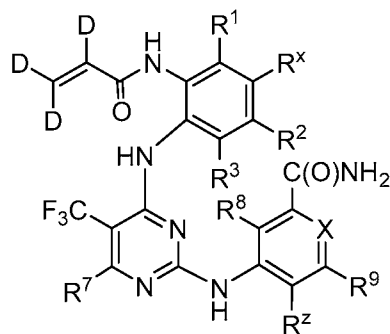
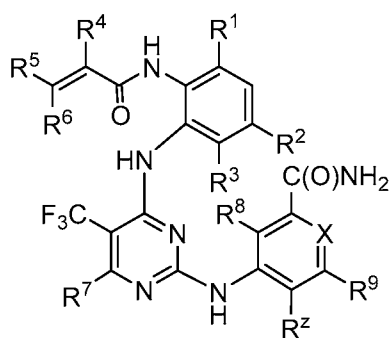
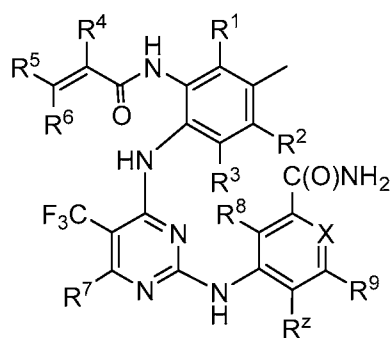
32. The compound according to claim 31, wherein each of R⁴, R⁵, and R⁶ is hydrogen.

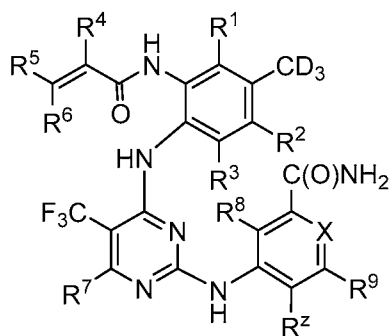
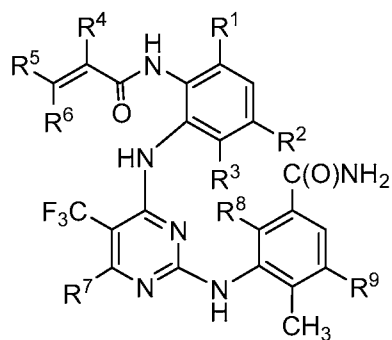
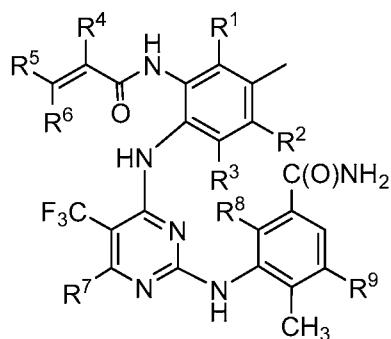
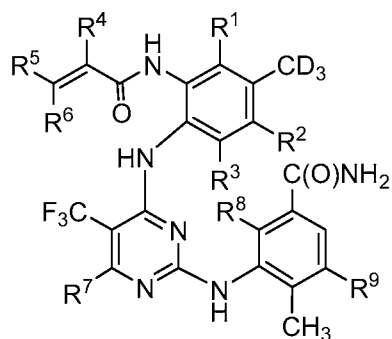
33. The compound according to claim 31, wherein each of R^4 , R^5 , and R^6 is deuterium.

34. The compound according to any of claim 31, wherein each of R^x , R^4 , R^5 , and R^6 is as defined in one of the following entries:

Entry	R^x	R^4	R^5	R^6
<i>i</i>	H	H	H	H
<i>ii</i>	H	H	H	D
<i>iii</i>	H	H	D	H
<i>iv</i>	H	D	H	H
<i>v</i>	H	H	D	D
<i>vi</i>	H	D	D	H
<i>vii</i>	H	D	H	D
<i>viii</i>	H	D	D	D
<i>ix</i>	CH ₃	H	H	H
<i>x</i>	CH ₃	H	H	D
<i>xi</i>	CH ₃	H	D	H
<i>xii</i>	CH ₃	D	H	H
<i>xiii</i>	CH ₃	H	D	D
<i>xiv</i>	CH ₃	D	D	H
<i>xv</i>	CH ₃	D	H	D
<i>xvi</i>	CH ₃	D	D	D
<i>xvii</i>	CD ₃	H	H	H
<i>xviii</i>	CD ₃	H	H	D
<i>xix</i>	CD ₃	H	D	H
<i>xx</i>	CD ₃	D	H	H
<i>xxi</i>	CD ₃	H	D	D
<i>xxii</i>	CD ₃	D	D	H
<i>xxiii</i>	CD ₃	D	H	D
<i>xxiv</i>	CD ₃	D	D	D

35. The compound according to any of claims 31-34, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , R^9 or R^z is or contains hydrogen.
36. The compound according to any of claims 31-34, wherein one of R^1 , R^2 , R^3 , R^7 , R^8 , R^9 or R^z is or contains deuterium.
37. The compound according to any of claims 31-36, wherein R^z is $-\text{CH}_3$.
38. The compound according to any of claims 31-37, wherein X is CH.
39. The compound according to any of claims 31-38, of any one of formulae **II-a**, **II-b**, **II-c**, **II-d**, **II-e**, **II-f**, **II-g**, or **II-h**:

**II-a****II-b****II-c****II-d**

**II-e****II-f****II-g****II-h**

or a pharmaceutically acceptable salt thereof.

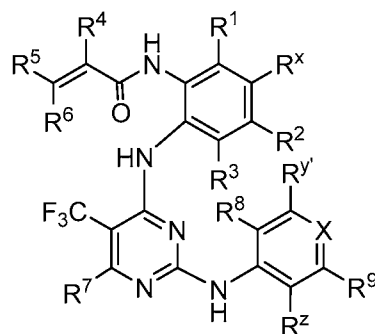
40. The compound according to any of claims 31-39, wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 are as defined in one of the following entries:

Entry	R^1	R^2	R^3	R^7	R^8	R^9
<i>i</i>	H	H	H	H	H	H
<i>ii</i>	D	H	H	H	H	H
<i>iii</i>	H	D	H	H	H	H
<i>iv</i>	H	H	D	H	H	H
<i>v</i>	D	D	H	H	H	H
<i>vi</i>	H	D	D	H	H	H
<i>vii</i>	D	H	D	H	H	H
<i>viii</i>	D	D	D	H	H	H
<i>ix</i>	H	H	H	H	D	H

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>x</i>	D	H	H	H	D	H
<i>xi</i>	H	D	H	H	D	H
<i>xii</i>	H	H	D	H	D	H
<i>xiii</i>	D	D	H	H	D	H
<i>xiv</i>	H	D	D	H	D	H
<i>xv</i>	D	H	D	H	D	H
<i>xvi</i>	D	D	D	H	D	H
<i>xvii</i>	H	H	H	H	H	D
<i>xviii</i>	D	H	H	H	H	D
<i>xix</i>	H	D	H	H	H	D
<i>xx</i>	H	H	D	H	H	D
<i>xxi</i>	D	D	H	H	H	D
<i>xxii</i>	H	D	D	H	H	D
<i>xxiii</i>	D	H	D	H	H	D
<i>xxiv</i>	D	D	D	H	H	D
<i>xxv</i>	H	H	H	H	D	D
<i>xxvi</i>	D	H	H	H	D	D
<i>xxvii</i>	H	D	H	H	D	D
<i>xxviii</i>	H	H	D	H	D	D
<i>xxix</i>	D	D	H	H	D	D
<i>xxx</i>	H	D	D	H	D	D
<i>xxxi</i>	D	H	D	H	D	D
<i>xxxii</i>	D	D	D	H	D	D
<i>xxxiii</i>	H	H	H	D	H	H
<i>xxxiv</i>	D	H	H	D	H	H
<i>xxxv</i>	H	D	H	D	H	H
<i>xxxvi</i>	H	H	D	D	H	H
<i>xxxvii</i>	D	D	H	D	H	H

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>xxxviii</i>	H	D	D	D	H	H
<i>xxxix</i>	D	H	D	D	H	H
<i>xl</i>	D	D	D	D	H	H
<i>xli</i>	H	H	H	D	D	H
<i>xl ii</i>	D	H	H	D	D	H
<i>xl iii</i>	H	D	H	D	D	H
<i>xl iv</i>	H	H	D	D	D	H
<i>xl v</i>	D	D	H	D	D	H
<i>xl vi</i>	H	D	D	D	D	H
<i>xl vii</i>	D	H	D	D	D	H
<i>xl viii</i>	D	D	D	D	D	H
<i>xl ix</i>	H	H	H	D	H	D
<i>l</i>	D	H	H	D	H	D
<i>li</i>	H	D	H	D	H	D
<i>li i</i>	H	H	D	D	H	D
<i>li ii</i>	D	D	H	D	H	D
<i>li v</i>	H	D	D	D	H	D
<i>li v</i>	D	H	D	D	H	D
<i>li vi</i>	D	D	D	D	H	D
<i>li vii</i>	H	H	H	D	D	D
<i>li viii</i>	D	H	H	D	D	D
<i>li x</i>	H	D	H	D	D	D
<i>li x</i>	H	H	D	D	D	D
<i>li xi</i>	D	D	H	D	D	D
<i>li xii</i>	H	D	D	D	D	D
<i>li xiii</i>	D	H	D	D	D	D
<i>li xiv</i>	D	D	D	D	D	D

41. The compound according to claim 1, of Formula **III**:



III

or a pharmaceutically acceptable salt thereof.

42. The compound according to claim 41, wherein each of R^4 , R^5 , and R^6 is hydrogen.

43. The compound according to claim 41, wherein each of R^4 , R^5 , and R^6 is deuterium.

44. The compound according to claim 41, wherein each of R^x , $R^{y'}$, R^4 , R^5 , and R^6 is as defined in an entry set forth below:

Entry	R^x	R^1	R^5	R^6	$R^{y'}$
<i>i</i>	H	H	H	H	OCH ₃
<i>ii</i>	H	H	H	D	OCH ₃
<i>iii</i>	H	H	D	H	OCH ₃
<i>iv</i>	H	D	H	H	OCH ₃
<i>v</i>	H	H	D	D	OCH ₃
<i>vi</i>	H	D	D	H	OCH ₃
<i>vii</i>	H	D	H	D	OCH ₃
<i>viii</i>	H	D	D	D	OCH ₃
<i>ix</i>	CH ₃	H	H	H	OCH ₃
<i>x</i>	CH ₃	H	H	D	OCH ₃
<i>xi</i>	CH ₃	H	D	H	OCH ₃

Entry	R ^x	R ⁴	R ⁵	R ⁶	R ^{y'}
<i>xii</i>	CH ₃	D	H	H	OCH ₃
<i>xiii</i>	CH ₃	H	D	D	OCH ₃
<i>xiv</i>	CH ₃	D	D	H	OCH ₃
<i>xv</i>	CH ₃	D	H	D	OCH ₃
<i>xvi</i>	CH ₃	D	D	D	OCH ₃
<i>xvii</i>	CD ₃	H	H	H	OCH ₃
<i>xviii</i>	CD ₃	H	H	D	OCH ₃
<i>xix</i>	CD ₃	H	D	H	OCH ₃
<i>xx</i>	CD ₃	D	H	H	OCH ₃
<i>xxi</i>	CD ₃	H	D	D	OCH ₃
<i>xxii</i>	CD ₃	D	D	H	OCH ₃
<i>xxiii</i>	CD ₃	D	H	D	OCH ₃
<i>xxiv</i>	CD ₃	D	D	D	OCH ₃
<i>xxv</i>	H	H	H	H	OCD ₃
<i>xxvi</i>	H	H	H	D	OCD ₃
<i>xxvii</i>	H	H	D	H	OCD ₃
<i>xxviii</i>	H	D	H	H	OCD ₃
<i>xxix</i>	H	H	D	D	OCD ₃
<i>xxx</i>	H	D	D	H	OCD ₃
<i>xxxi</i>	H	D	H	D	OCD ₃
<i>xxxii</i>	H	D	D	D	OCD ₃
<i>xxxiii</i>	CH ₃	H	H	H	OCD ₃
<i>xxxiv</i>	CH ₃	H	H	D	OCD ₃
<i>xxxv</i>	CH ₃	H	D	H	OCD ₃
<i>xxxvi</i>	CH ₃	D	H	H	OCD ₃
<i>xxxvii</i>	CH ₃	H	D	D	OCD ₃
<i>xxxviii</i>	CH ₃	D	D	H	OCD ₃
<i>xxxix</i>	CH ₃	D	H	D	OCD ₃

Entry	R ^x	R ⁴	R ⁵	R ⁶	R ^{y'}
<i>xl</i>	CH ₃	D	D	D	OCD ₃
<i>xli</i>	CD ₃	H	H	H	OCD ₃
<i>xlii</i>	CD ₃	H	H	D	OCD ₃
<i>xliii</i>	CD ₃	H	D	H	OCD ₃
<i>xliv</i>	CD ₃	D	H	H	OCD ₃
<i>xlv</i>	CD ₃	H	D	D	OCD ₃
<i>xlvi</i>	CD ₃	D	D	H	OCD ₃
<i>xlvii</i>	CD ₃	D	H	D	OCD ₃
<i>xlviii</i>	CD ₃	D	D	D	OCD ₃

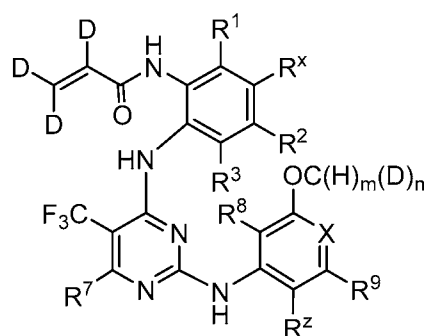
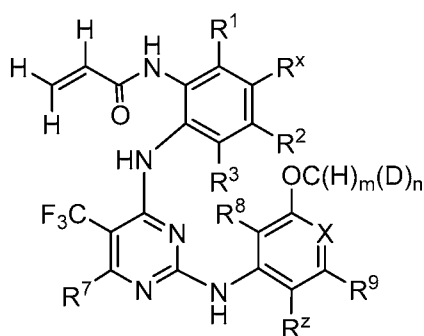
45. The compound according to any of claims 41-44, wherein each of R¹, R², R³, R⁷, R⁸, R⁹ or R^z is or contains hydrogen.

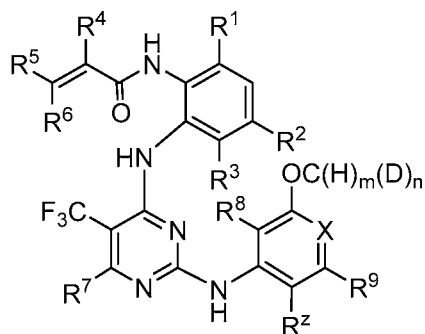
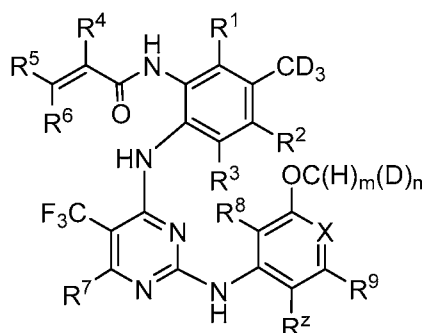
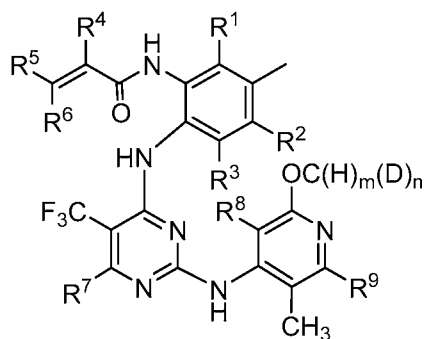
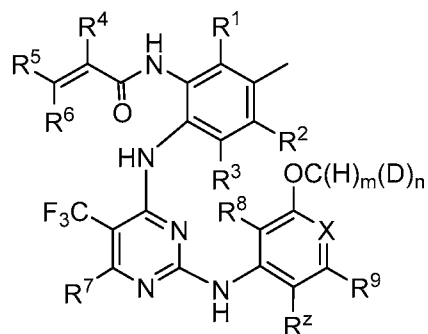
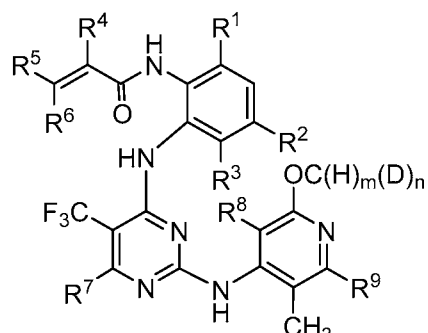
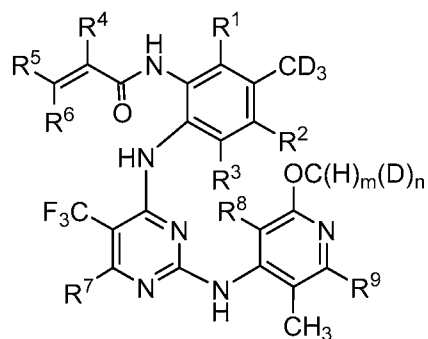
46. The compound according to any of claims 41-44, wherein one of R¹, R², R³, R⁷, R⁸, R⁹ or R^z is or contains deuterium.

47. The compound according to any one of claims 41-46, wherein R^z is -CH₃.

48. The compound according to any one of claims 41-47, wherein X is N.

49. The compound according to any one of claims 41-48, of any one of formulae **III-a**, **III-b**, **III-c**, **III-d**, **III-e**, **III-f**, **III-g**, or **III-h**:



III-a**III-c****III-e****III-g****III-b****III-d****III-f****III-h**

or a pharmaceutically acceptable salt thereof.

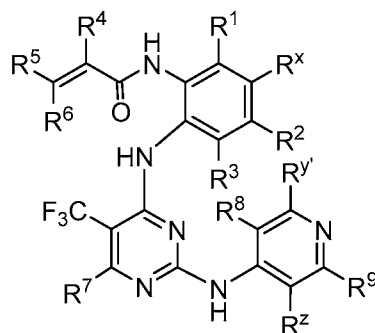
50. The compound according to any one of claims 41-49 wherein each of R^1 , R^2 , R^3 , R^7 , R^8 , and R^9 is as defined in an entry set forth below:

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>i</i>	H	H	H	H	H	H
<i>ii</i>	D	H	H	H	H	H
<i>iii</i>	H	D	H	H	H	H
<i>iv</i>	H	H	D	H	H	H
<i>v</i>	D	D	H	H	H	H
<i>vi</i>	H	D	D	H	H	H
<i>vii</i>	D	H	D	H	H	H
<i>viii</i>	D	D	D	H	H	H
<i>ix</i>	H	H	H	H	D	H
<i>x</i>	D	H	H	H	D	H
<i>xi</i>	H	D	H	H	D	H
<i>xii</i>	H	H	D	H	D	H
<i>xiii</i>	D	D	H	H	D	H
<i>xiv</i>	H	D	D	H	D	H
<i>xv</i>	D	H	D	H	D	H
<i>xvi</i>	D	D	D	H	D	H
<i>xvii</i>	H	H	H	H	H	D
<i>xviii</i>	D	H	H	H	H	D
<i>xix</i>	H	D	H	H	H	D
<i>xx</i>	H	H	D	H	H	D
<i>xxi</i>	D	D	H	H	H	D
<i>xxii</i>	H	D	D	H	H	D
<i>xxiii</i>	D	H	D	H	H	D
<i>xxiv</i>	D	D	D	H	H	D
<i>xxv</i>	H	H	H	H	D	D
<i>xxvi</i>	D	H	H	H	D	D
<i>xxvii</i>	H	D	H	H	D	D
<i>xxviii</i>	H	H	D	H	D	D

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>xxix</i>	D	D	H	H	D	D
<i>xxx</i>	H	D	D	H	D	D
<i>xxxi</i>	D	H	D	H	D	D
<i>xxxii</i>	D	D	D	H	D	D
<i>xxxiii</i>	H	H	H	D	H	H
<i>xxxiv</i>	D	H	H	D	H	H
<i>xxxv</i>	H	D	H	D	H	H
<i>xxxvi</i>	H	H	D	D	H	H
<i>xxxvii</i>	D	D	H	D	H	H
<i>xxxviii</i>	H	D	D	D	H	H
<i>xxxix</i>	D	H	D	D	H	H
<i>xl</i>	D	D	D	D	H	H
<i>xli</i>	H	H	H	D	D	H
<i>xl ii</i>	D	H	H	D	D	H
<i>xl iii</i>	H	D	H	D	D	H
<i>xl iv</i>	H	H	D	D	D	H
<i>xl v</i>	D	D	H	D	D	H
<i>xl vi</i>	H	D	D	D	D	H
<i>xl vii</i>	D	H	D	D	D	H
<i>xl viii</i>	D	D	D	D	D	H
<i>xl ix</i>	H	H	H	D	H	D
<i>l</i>	D	H	H	D	H	D
<i>li</i>	H	D	H	D	H	D
<i>lii</i>	H	H	D	D	H	D
<i>liii</i>	D	D	H	D	H	D
<i>liv</i>	H	D	D	D	H	D
<i>lv</i>	D	H	D	D	H	D
<i>lvi</i>	D	D	D	D	H	D

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>lvii</i>	H	H	H	D	D	D
<i>lviii</i>	D	H	H	D	D	D
<i>lix</i>	H	D	H	D	D	D
<i>lx</i>	H	H	D	D	D	D
<i>lxi</i>	D	D	H	D	D	D
<i>lxii</i>	H	D	D	D	D	D
<i>lxiii</i>	D	H	D	D	D	D
<i>lxiv</i>	D	D	D	D	D	D

51. The compound according to claim 41 of the following formula:



III-i

or a pharmaceutically acceptable salt thereof.

52. The compound of claim 51, wherein the compound is in the form of a phosphate salt.

53. The compound of either of claim 51 or 52, wherein each of R¹, R², R³, R⁷, R⁸, and R⁹ is as defined in an entry set forth below:

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>i</i>	H	H	H	H	H	H
<i>ii</i>	D	H	H	H	H	H
<i>iii</i>	H	D	H	H	H	H
<i>iv</i>	H	H	D	H	H	H

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>v</i>	D	D	H	H	H	H
<i>vi</i>	H	D	D	H	H	H
<i>vii</i>	D	H	D	H	H	H
<i>viii</i>	D	D	D	H	H	H
<i>ix</i>	H	H	H	H	D	H
<i>x</i>	D	H	H	H	D	H
<i>xi</i>	H	D	H	H	D	H
<i>xii</i>	H	H	D	H	D	H
<i>xiii</i>	D	D	H	H	D	H
<i>xiv</i>	H	D	D	H	D	H
<i>xv</i>	D	H	D	H	D	H
<i>xvi</i>	D	D	D	H	D	H
<i>xvii</i>	H	H	H	H	H	D
<i>xviii</i>	D	H	H	H	H	D
<i>xix</i>	H	D	H	H	H	D
<i>xx</i>	H	H	D	H	H	D
<i>xxi</i>	D	D	H	H	H	D
<i>xxii</i>	H	D	D	H	H	D
<i>xxiii</i>	D	H	D	H	H	D
<i>xxiv</i>	D	D	D	H	H	D
<i>xxv</i>	H	H	H	H	D	D
<i>xxvi</i>	D	H	H	H	D	D
<i>xxvii</i>	H	D	H	H	D	D
<i>xxviii</i>	H	H	D	H	D	D
<i>xxix</i>	D	D	H	H	D	D
<i>xxx</i>	H	D	D	H	D	D
<i>xxxi</i>	D	H	D	H	D	D
<i>xxxii</i>	D	D	D	H	D	D

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>xxxiii</i>	H	H	H	D	H	H
<i>xxxiv</i>	D	H	H	D	H	H
<i>xxxv</i>	H	D	H	D	H	H
<i>xxxvi</i>	H	H	D	D	H	H
<i>xxxvii</i>	D	D	H	D	H	H
<i>xxxviii</i>	H	D	D	D	H	H
<i>xxxix</i>	D	H	D	D	H	H
<i>xl</i>	D	D	D	D	H	H
<i>xli</i>	H	H	H	D	D	H
<i>xl ii</i>	D	H	H	D	D	H
<i>xl iii</i>	H	D	H	D	D	H
<i>xl iv</i>	H	H	D	D	D	H
<i>xl v</i>	D	D	H	D	D	H
<i>xl vi</i>	H	D	D	D	D	H
<i>xl vii</i>	D	H	D	D	D	H
<i>xl viii</i>	D	D	D	D	D	H
<i>xl ix</i>	H	H	H	D	H	D
<i>l</i>	D	H	H	D	H	D
<i>li</i>	H	D	H	D	H	D
<i>li i</i>	H	H	D	D	H	D
<i>li ii</i>	D	D	H	D	H	D
<i>li v</i>	H	D	D	D	H	D
<i>li v</i>	D	H	D	D	H	D
<i>li vi</i>	D	D	D	D	H	D
<i>li vii</i>	H	H	H	D	D	D
<i>li viii</i>	D	H	H	D	D	D
<i>li x</i>	H	D	H	D	D	D
<i>li x</i>	H	H	D	D	D	D

Entry	R ¹	R ²	R ³	R ⁷	R ⁸	R ⁹
<i>lxi</i>	D	D	H	D	D	D
<i>lxii</i>	H	D	D	D	D	D
<i>lxiii</i>	D	H	D	D	D	D
<i>lxiv</i>	D	D	D	D	D	D

54. The compound of any one of claims 51-53, wherein each of R⁴, R⁵, and R⁶ is as defined in an entry set forth below:

Entry	R ⁴	R ⁵	R ⁶
<i>i</i>	H	H	H
<i>ii</i>	D	H	H
<i>iii</i>	H	D	H
<i>iv</i>	H	H	D
<i>v</i>	D	D	H
<i>vi</i>	H	D	D
<i>vii</i>	D	H	D
<i>viii</i>	D	D	D

55. The compound of any one of claims 51-54, wherein each of R^x, R^y, and R^z is as defined in an entry set forth below:

Entry	R ^x	R ^y	R ^z
<i>i</i>	H	OCH ₃	CH ₃
<i>ii</i>	D	OCH ₃	CH ₃
<i>iii</i>	CH ₃	OCH ₃	CH ₃
<i>iv</i>	CH ₂ D	OCH ₃	CH ₃
<i>v</i>	CHD ₂	OCH ₃	CH ₃
<i>vi</i>	CD ₃	OCH ₃	CH ₃
<i>vii</i>	H	OCH ₂ D	CH ₃

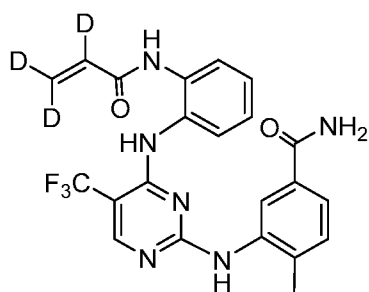
Entry	R ^x	R ^{y'}	R ^z
<i>viii</i>	D	OCH ₂ D	CH ₃
<i>ix</i>	CH ₃	OCH ₂ D	CH ₃
<i>x</i>	CH ₂ D	OCH ₂ D	CH ₃
<i>xi</i>	CHD ₂	OCH ₂ D	CH ₃
<i>xii</i>	CD ₃	OCH ₂ D	CH ₃
<i>xiii</i>	H	OCHD ₂	CH ₃
<i>xiv</i>	D	OCHD ₂	CH ₃
<i>xv</i>	CH ₃	OCHD ₂	CH ₃
<i>xvi</i>	CH ₂ D	OCHD ₂	CH ₃
<i>xvii</i>	CHD ₂	OCHD ₂	CH ₃
<i>xviii</i>	CD ₃	OCHD ₂	CH ₃
<i>xix</i>	H	OCD ₃	CH ₃
<i>xx</i>	D	OCD ₃	CH ₃
<i>xxi</i>	CH ₃	OCD ₃	CH ₃
<i>xxii</i>	CH ₂ D	OCD ₃	CH ₃
<i>xxiii</i>	CHD ₂	OCD ₃	CH ₃
<i>xxiv</i>	CD ₃	OCD ₃	CH ₃
<i>xxv</i>	H	OCH ₃	CH ₂ D
<i>xxvi</i>	D	OCH ₃	CH ₂ D
<i>xxvii</i>	CH ₃	OCH ₃	CH ₂ D
<i>xxviii</i>	CH ₂ D	OCH ₃	CH ₂ D
<i>xxix</i>	CHD ₂	OCH ₃	CH ₂ D
<i>xxx</i>	CD ₃	OCH ₃	CH ₂ D
<i>xxv</i>	H	OCH ₂ D	CH ₂ D
<i>xxvi</i>	D	OCH ₂ D	CH ₂ D
<i>xxvii</i>	CH ₃	OCH ₂ D	CH ₂ D
<i>xxviii</i>	CH ₂ D	OCH ₂ D	CH ₂ D
<i>xxix</i>	CHD ₂	OCH ₂ D	CH ₂ D

Entry	R ^x	R ^{y'}	R ^z
<i>xxx</i>	CD ₃	OCH ₂ D	CH ₂ D
<i>xxxi</i>	H	OCHD ₂	CH ₂ D
<i>xxxii</i>	D	OCHD ₂	CH ₂ D
<i>xxxiii</i>	CH ₃	OCHD ₂	CH ₂ D
<i>xxxiv</i>	CH ₂ D	OCHD ₂	CH ₂ D
<i>xxxv</i>	CHD ₂	OCHD ₂	CH ₂ D
<i>xxxvi</i>	CD ₃	OCHD ₂	CH ₂ D
<i>xxxvii</i>	H	OCD ₃	CH ₂ D
<i>xxxviii</i>	D	OCD ₃	CH ₂ D
<i>xxxix</i>	CH ₃	OCD ₃	CH ₂ D
<i>xl</i>	CH ₂ D	OCD ₃	CH ₂ D
<i>xli</i>	CHD ₂	OCD ₃	CH ₂ D
<i>xl ii</i>	CD ₃	OCD ₃	CH ₂ D
<i>xl iii</i>	H	OCH ₃	CHD ₂
<i>xl iv</i>	D	OCH ₃	CHD ₂
<i>xl v</i>	CH ₃	OCH ₃	CHD ₂
<i>xl vi</i>	CH ₂ D	OCH ₃	CHD ₂
<i>xl vii</i>	CHD ₂	OCH ₃	CHD ₂
<i>xl viii</i>	CD ₃	OCH ₃	CHD ₂
<i>xl ix</i>	H	OCH ₂ D	CHD ₂
<i>l</i>	D	OCH ₂ D	CHD ₂
<i>li</i>	CH ₃	OCH ₂ D	CHD ₂
<i>lii</i>	CH ₂ D	OCH ₂ D	CHD ₂
<i>liii</i>	CHD ₂	OCH ₂ D	CHD ₂
<i>liv</i>	CD ₃	OCH ₂ D	CHD ₂
<i>lv</i>	H	OCHD ₂	CHD ₂
<i>lvi</i>	D	OCHD ₂	CHD ₂
<i>lvii</i>	CH ₃	OCHD ₂	CHD ₂

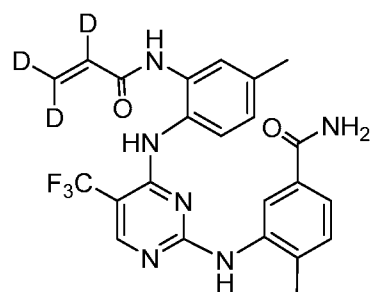
Entry	R ^x	R ^{y'}	R ^z
<i>lviii</i>	CH ₂ D	OCHD ₂	CHD ₂
<i>lix</i>	CHD ₂	OCHD ₂	CHD ₂
<i>lx</i>	CD ₃	OCHD ₂	CHD ₂
<i>lxi</i>	H	OCD ₃	CHD ₂
<i>lxii</i>	D	OCD ₃	CHD ₂
<i>lxiii</i>	CH ₃	OCD ₃	CHD ₂
<i>lxix</i>	CH ₂ D	OCD ₃	CHD ₂
<i>lxx</i>	CHD ₂	OCD ₃	CHD ₂
<i>lxxi</i>	CD ₃	OCD ₃	CHD ₂
<i>lxxii</i>	H	OCH ₃	CD ₃
<i>lxxiii</i>	D	OCH ₃	CD ₃
<i>lxxiv</i>	CH ₃	OCH ₃	CD ₃
<i>lxxv</i>	CH ₂ D	OCH ₃	CD ₃
<i>lxxvi</i>	CHD ₂	OCH ₃	CD ₃
<i>lxxvii</i>	CD ₃	OCH ₃	CD ₃
<i>lxxviii</i>	H	OCH ₂ D	CD ₃
<i>lxxix</i>	D	OCH ₂ D	CD ₃
<i>lxxx</i>	CH ₃	OCH ₂ D	CD ₃
<i>lxxxi</i>	CH ₂ D	OCH ₂ D	CD ₃
<i>lxxxii</i>	CHD ₂	OCH ₂ D	CD ₃
<i>lxxxiii</i>	CD ₃	OCH ₂ D	CD ₃
<i>lxxxiv</i>	H	OCHD ₂	CD ₃
<i>lxxxv</i>	D	OCHD ₂	CD ₃
<i>lxxxvi</i>	CH ₃	OCHD ₂	CD ₃
<i>lxxxvii</i>	CH ₂ D	OCHD ₂	CD ₃
<i>lxxxviii</i>	CHD ₂	OCHD ₂	CD ₃
<i>lxxxix</i>	CD ₃	OCHD ₂	CD ₃
<i>xc</i>	H	OCD ₃	CD ₃

Entry	R ^x	R ^{y'}	R ^z
<i>xc</i> i	D	OCD ₃	CD ₃
<i>xc</i> ii	CH ₃	OCD ₃	CD ₃
<i>xc</i> iii	CH ₂ D	OCD ₃	CD ₃
<i>xc</i> iv	CHD ₂	OCD ₃	CD ₃
<i>xc</i> v	CD ₃	OCD ₃	CD ₃

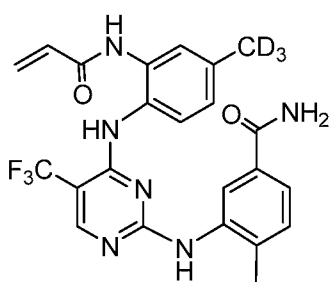
56. The compound of claim 1, selected from any one of the following structures:



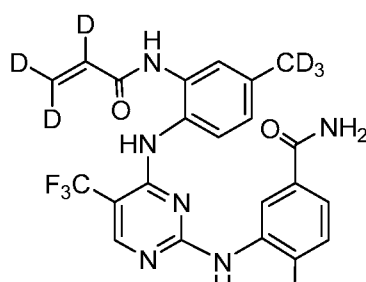
I-1



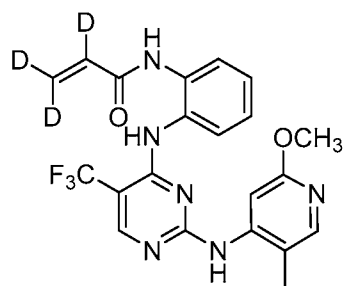
I-2



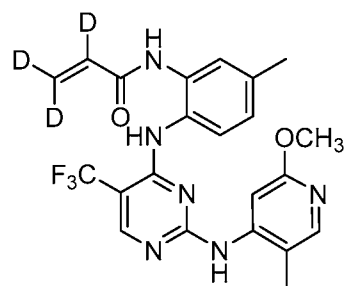
I-3



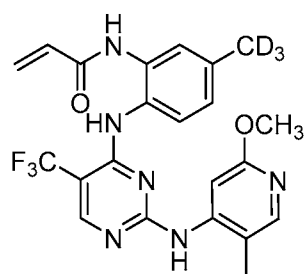
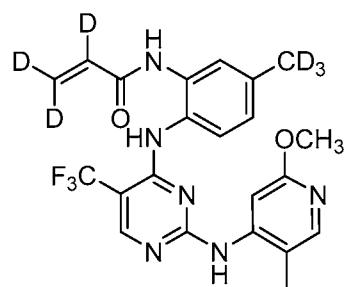
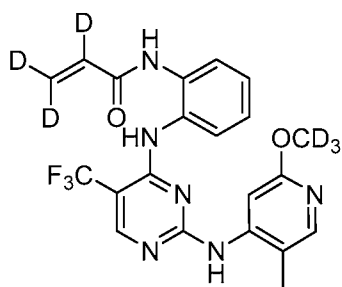
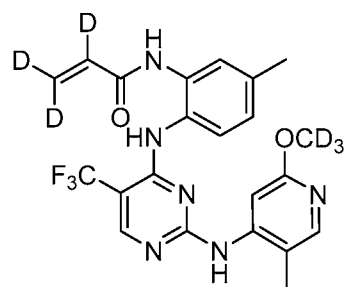
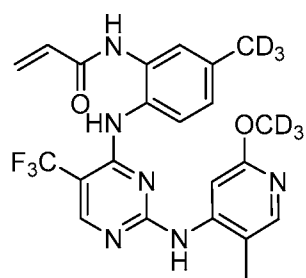
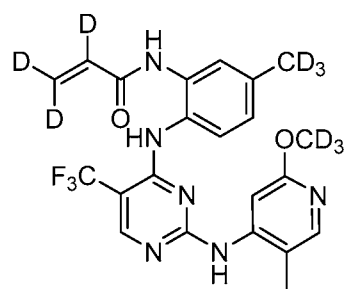
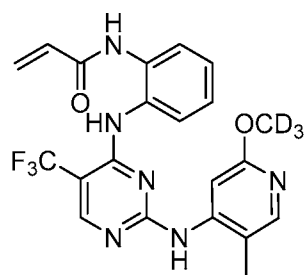
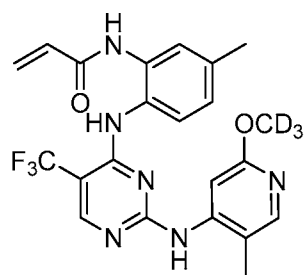
I-4



I-5



I-6

**I-7****I-8****I-9****I-10****I-11****I-12****I-13****I-14.**

57. A composition comprising a compound according to any one of claims 1-56 and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

58. The composition according to claim 57, in combination with an additional therapeutic agent.

59. The composition according to claim 58, wherein the additional therapeutic agent is a chemotherapeutic agent.

60. A method for inhibiting one or both of ERK1 and ERK2 protein kinase, or a mutant thereof, activity in a patient or in a biological sample comprising the step of administering to said patient or contacting said biological sample with a compound according to any one of claims 1-56.

61. The method according to claim 60, wherein the one or both of ERK1 and ERK2 protein kinase, or a mutant thereof, activity is inhibited irreversibly.

62. A method for treating a disorder mediated by one or both of ERK1 and ERK2 protein kinase activity in a patient in need thereof, comprising the step of administering to said patient a compound according to any one of claims 1-56 or a composition according to claim 50.

63. The method according to claim 62, wherein the disorder is selected from cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases.

64. The method according to claim 63, wherein the disorder is a cancer selected from multiple myeloma, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung, bone, colon, thyroid, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma (including uveal melanoma) sarcoma, bladder carcinoma, liver carcinoma (e.g., hepatocellular carcinoma (HCC)) and biliary passage carcinoma), kidney

carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colorectal carcinoma, large intestine, rectum, brain and central nervous system, endometrial, multiple myeloma (MM), prostate, AML, and leukemia.