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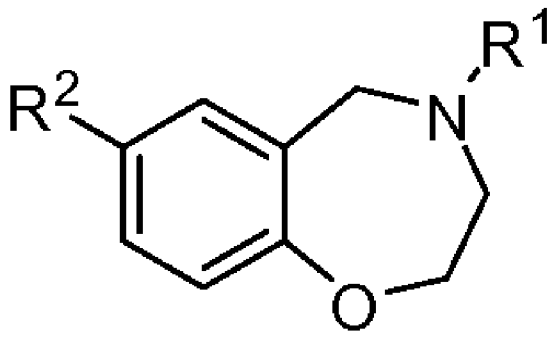
(54) Title: BENZOXAZEPINES AS INHIBITORS OF MTOR AND THEIR USE TO TREAT CANCER



(57) Abstract: The invention is directed to inhibitors of mTOR and pharmaceutically acceptable salts or solvates thereof, as well as methods of using them. The inhibitors are generally of structural formula : wherein the combination of R^1 and R^2 are as defined herein, and pharmaceutically acceptable salts thereof.

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BENZOXAZEPINES AS INHIBITORS OF MTOR AND THEIR USE TO TREAT CANCER

CROSS-REFERENCE TO RELATED APPLCIATIONS

[0001] This application claims the benefit of priority of US provisional application 61/216,888, filed May 22, 2009, the contents of which are incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to the field of protein kinases and inhibitors thereof. In particular, the invention relates to inhibitors of mammalian target of rapamycin (mTOR) signaling pathways, and methods of their use.

Background of the Invention

[0003] The mammalian target of rapamycin, mTOR, is a protein kinase that integrates both extracellular and intracellular signals of cellular growth, proliferation, and survival. Extracellular mitogenic growth factor signaling from cell surface receptors and intracellular pathways that convey hypoxic stress, energy and nutrient status all converge at mTOR. mTOR exists in two distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 is a key mediator of transcription and cell growth (via its substrates p70S6 kinase and 4E-BP1) and promotes cell survival via the serum and glucocorticoid-activated kinase SGK, whereas mTORC2 promotes activation of the pro-survival kinase AKT. Given its central role in cellular growth, proliferation and survival, it is perhaps not surprising that mTOR signaling is frequently dysregulated in cancer and other diseases (Bjornsti and Houghton *Rev Cancer* **2004,** *4(5)*, 335-48; Houghton and Huang *Microbiol Immunol* **2004,** *279,* 339-59; Inoki, Corradetti et al. *Nat Genet* **2005,** *37(1),* 19-24).

[0004] mTOR is a member of the PIKK (PI3K-related Kinase) family of atypical kinases which includes ATM, ATR, and DNAPK, and its catalytic domain is homologous to that of PI3K. Dyregulation of PI3K signaling is a common function of tumor cells. In general, mTOR inhibition may be considered as a strategy in many of the tumor types in which PI3K signaling is implicated such as those discussed below.

[0005] Inhibitors of mTOR may be useful in treating a number of cancers, including the following: breast cancer (Nagata, Lan *et al., Cancer Cell* **2004,** *6(2),* 117-27; Pandolfi

N Engl J Med **2004,** *351(22),* 2337-8; Nahta, Yu *et al. Nat Clin Pract Oncol* **2006,** *3(5),* 269-280); antle cell lymphoma (MCL) (Dal Col, Zancai *et al. Blood* **2008**, *111(10),* 5142-51); renal cell carcinoma (Thomas, Tran *et al. Nat Med* **2006,** *12(1),* 122-7; Atkins, Hidalgo *et al. J Clin Oncol* **2004,** *22(5)*, 909-18; Motzer, Hudes *et al. J Clin Oncol* **2007,** *25(25),* 3958-64); acute myelogenous leukemia (AML) (Sujobert, Bardet *et al.Blood* **2005,** *106(3),* 1063-6; Billottet, Grandage et al. *Oncogene* **2006,** *25(50),* 6648-6659; Tamburini, Elie et al. *Blood* **2007,** *110(3),* 1025-8); chronic myelogenous leukemia (CML) (Skorski, Bellacosa *et al. Embo J* **1997,** *16(20),* 6151-61; Bai, Ouyang *et al. Blood* **2000,** *96(13)*, 4319-27; Hickey and Cotter *Biol Chem* **2006,** *281(5)*, 2441-50); diffuse large B cell lymphoma (DLBCL) (Uddin, Hussain et al. *Blood* **2006,** *108(13)*, 4178-86); several subtypes of sarcoma (Hernando, Charytonowicz et al. *Nat Med* **2007,** *13(6),* 748-53; Wan and Helman *Oncologist* **2007,** *12(8)*, 1007-18); rhabdomyosarcoma (Cao, Yu *et al. Cancer Res* **2008,** *68(19)*, 8039-8048; Wan, Shen et al. *Neoplasia* **2006,** *8(5),* 394-401); ovarian cancer (Shayesteh, Lu et al. *Nat Genet*, **1999,** *21(1)*, 99-102; (Lee, Choi *et al. Gynecol Oncol* **2005**, *97(1)* 26-34); endometrial tumors (Obata, Morland et al. *Cancer Res* **1998,** *58(10),* 2095-7; Lu, Wu *et al. Clin Cancer Res* **2008**, *14(9),* 2543-50); non small cell lung carcinoma (NSCLC) (Tang, He et al. *Lung Cancer* **2006,** *51(2),* 181-91; Marsit, Zheng et al. *Hum Pathol* **2005**, *36(7)*, 768-76); small cell, squamous, large cell and adenocarcinoma (Massion, Taflan et al. *Am J Respir Crit Care Med* **2004,** *170(10)*, 1088-94); lung tumors in general (Kokubo, Gemma *et al. Br J Cancer* **2005,** *92(9)*, 1711-9; Pao, Wang et al. *Pub Library of Science Med* **2005**, *2(1)*, e17); colorectal tumors (Velho, Oliveira et al. *Eur J Cancer* **2005,** *41(11),* 1649-54; Foukas, Claret et al. *Nature,* **2006,** *441(7091),* 366-370), particularly those that display microsatellite instability (Goel, Arnold et al. *Cancer Res* **2004,** *64(9),* 3014-21; Nassif, Lobo et al. *Oncogene* **2004,** *23(2),* 617-28), KRAS-mutated colorectal tumors (Bos *Cancer Res* **1989.** *49(17)*, 4682-9; Fearon *Ann N Y Acad Sci* **1995,** *768,* 101-10); gastric carcinomas (Byun, Cho et al. *Int J Cancer* **2003,** *104(3),* 318-27); hepatocellular tumors (Lee, Soung et al. *Oncogene* **2005,** *24(8)*, 1477-80); liver tumors (Hu, Huang et al. *Cancer* **2003,** *97(8),* 1929-40; Wan, Jiang et al. *Cancer Res Clin Oncol* **2003,** *129(2)*, 100-6); primary melanomas and associated increased tumor thickness (Guldberg, thor Straten et al. *Cancer Res* **1997,** *57(17)*, 3660-3; Tsao, Zhang et al. *Cancer Res* **2000,** *60(7),* 1800-4; Whiteman, Zhou et al. *Int J Cancer***2002,** *99(1),* 63-7; Goel, Lazar et al. *J Invest Dermatol 126(1),* **2006,** 154-60); pancreatic tumors (Asano, Yao et al. *Oncogene* **2004,** *23(53),* 8571-80); prostate

carcinoma (Cairns, Okami et al. *Cancer Res* **1997,** *57(22),* 4997-5000; Gray, Stewart et al. *Br J Cancer* **1998,** *78(10),* 1296-300; Wang, Parsons et al. *Clin Cancer Res* **1998,** *4(3),* 811-5; Whang, Wu et al. *Proc Natl Acad Sci U S A* **1998,** *95(9),* 5246-50; Majumder and Sellers *Oncogene* **2005,** *24(50)* 7465-74; Wang, Garcia et al. *Proc Natl Acad Sci U S A* **2006,** *103(5),* 1480-5; (Lu, Ren et al. *Int J Oncol* **2006,** *28(1),* 245-51; Mulholland, Dedhar et al. *Oncogene 25(3),* **2006,** 329-37; Xin, Teitell et al. *Proc Natl Acad Sci U S A 1***2006,** *03(20)*, 7789-94; Mikhailova, Wang et al. *Adv Exp Med Biol* **2008,** *617,* 397-405; Wang, Mikhailova et al. *Oncogene* **2008,** *27(56),* 7106-7117); thyroid carcinoma, particularly in the anaplastic subtype (Garcia-Rostan, Costa et al. *Cancer Res* **2005,** *65(22),* 10199-207); follicular thyroid carcinoma (Wu, Mambo *et al. J Clin Endocrinol Metab* **2005,** *90(8),* 4688-93); anaplastic large cell lymphoma (ALCL); hamaratomas, angiomyelolipomas, TSC-associated and sporadic lymphangioleiomyomatosis: Cowden's disease (multiple hamaratoma syndrome) (Bissler, McCormack et al. *N Engl J Med* **2008,** *358(2),* 140-151); sclerosing hemangioma (Randa M. S. Amin *Pathology International* **2008,** *58(1),* 38-44); Peutz–Jeghers syndrome (PJS); head and neck cancer (Gupta, McKenna et al. *Clin Cancer Res* **2002,** *8(3),* 885-892); neurofibromatosis (Ferner *Eur J Hum Genet* **2006,** *15(2),* 131-138; Sabatini *Nat Rev Cancer* **2006,** *6(9),* 729-734; Johannessen, Johnson et al. *Current Biology* **2008,** *18(1),* 56-62); macular degeneration; macular edema; myeloid leukemia; systemic lupus; and autoimmune lymphoproliferative syndrome (ALPS).

SUMMARY OF THE INVENTION

[0006] The following only summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below. All references cited in this specification are hereby incorporated by reference in their entirety. In the event of a discrepancy between the express disclosure of this specification and the references incorporated by reference, the express disclosure of this specification shall control.

[0007] In view of the important role of mTOR in biological processes and disease states, the inventors realized that inhibitors of this protein kinase, including dual inhibitors mTORC1 are desirable. Compounds of the Invention are potent and specific inhibitors of mTORC1.

[0008] A first aspect of the invention provides a compound of Table 1, optionally as a pharmaceutically acceptable salt thereof.

[0009] In a second aspect, the invention is directed to a pharmaceutical composition which comprises 1) a compound of Table 1 or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof and 2) a pharmaceutically acceptable carrier, excipient, or diluent.

[0010] In a third aspect of the invention is a method of inhibiting the *in vivo* activity of mTOR, the method comprising administering to a patient an effective mTOR-inhibiting amount of a compound of Table 1 or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof or pharmaceutical composition thereof.

[0011] In a fourth aspect, the Invention provides a method for treating a disease, disorder, or syndrome which method comprises administering to a patient a therapeutically effective amount of a compound of Table 1 or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Table 1 or a single stereoisomer or mixture of isomers thereof, optionally as a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

[0012] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	**Meaning**
br	broad
°C	degrees Celsius
d	doublet
dd	doublet of doublet
dt	doublet of triplet
DCM	dichloromethane
DIEA or DIPEA	*N,N*-di-isopropyl-*N*-ethylamine
DMA	*N,N*-dimethylacetamide

Abbreviation	Meaning
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphano)ferrocene
EI	Electron Impact ionization
g	gram(s)
GC/MS	gas chromatography/mass spectrometry
h or hr	hour(s)
HPLC	high pressure liquid chromatography
L	liter(s)
LC/MS	liquid chromatography/mass spectrometry
M	molar or molarity
m	Multiplet
MeOH	methanol
mg	milligram(s)
MHz	megahertz (frequency)
min	minute(s)
mL	milliliter(s)
µL	microliter(s)
µM	micromolar
µmol	micromole(s)
mM	Millimolar
mmol	millimole(s)
mol	mole(s)
MS	mass spectral analysis
N	normal or normality
nM	nanomolar
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
q	Quartet

Abbreviation	Meaning
rt	Room temperature
s	Singlet
t or tr	Triplet
THF	tetrahydrofuran

[0013] "Administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in combination with one or more other active agents (e.g., surgery, radiation, and chemotherapy, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

[0014] "Yield" for each of the reactions described herein is expressed as a percentage of the theoretical yield.

[0015] "Metabolite" refers to the break-down or end product of a compound or its salt produced by metabolism or biotransformation in the animal or human body; for example, biotransformation to a more polar molecule such as by oxidation, reduction, or hydrolysis, or to a conjugate (see Goodman and Gilman, "The Pharmacological Basis of Therapeutics" 8.sup.th Ed., Pergamon Press, Gilman et al. (eds), 1990 for a discussion of biotransformation). As used herein, the metabolite of a compound of the invention or its salt may be the biologically active form of the compound in the body. In one example, a prodrug may be used such that the biologically active form, a metabolite, is released *in vivo*. In another example, a biologically active metabolite is discovered serendipitously, that is, no prodrug design *per se* was undertaken. An assay for activity of a metabolite of a compound of the present invention is known to one of skill in the art in light of the present disclosure.

[0016] "Patient" for the purposes of the present invention includes humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In a specific embodiment the patient is a mammal, and in a more specific embodiment the patient is human.

[0017] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. It is understood that the pharmaceutically acceptable salts are non-

toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference or S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 both of which are incorporated herein by reference.

[0018] Examples of pharmaceutically acceptable acid addition salts include those formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; as well as organic acids such as acetic acid, trifluoroacetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, 3-(4-hydroxybenzoyl)benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, p-toluenesulfonic acid, and salicylic acid and the like.

[0019] Examples of a pharmaceutically acceptable base addition salts include those formed when an acidic proton present in the parent compound is replaced by a metal ion, such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Specific salts are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include, but are not limited to, salts of primary, secondary, and *tert*iary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, tromethamine, *N*-methylglucamine, polyamine resins, and the like. Exemplary organic bases are isopropylamine, diethylamine, ethanolamine,

trimethylamine, dicyclohexylamine, choline, and caffeine."Platin(s)," and "platin-containing agent(s)" include, for example, cisplatin, carboplatin, and oxaliplatin.

[0020] "Prodrug" refers to compounds that are transformed (typically rapidly) *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. Common examples include, but are not limited to, ester and amide forms of a compound having an active form bearing a carboxylic acid moiety. Examples of pharmaceutically acceptable esters of the compounds of this invention include, but are not limited to, alkyl esters (for example with between about one and about six carbons) the alkyl group is a straight or branched chain. Acceptable esters also include cycloalkyl esters and arylalkyl esters such as, but not limited to benzyl. Examples of pharmaceutically acceptable amides of the compounds of this invention include, but are not limited to, primary amides, and secondary and tertiary alkyl amides (for example with between about one and about six carbons). Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0021] "Therapeutically effective amount" is an amount of a compound of the invention, that when administered to a patient, ameliorates a symptom of the disease. The amount of a compound of the invention which constitutes a "therapeutically effective amount" will vary depending on the compound, the disease state and its severity, the age of the patient to be treated, and the like. The therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their knowledge and to this disclosure.

[0022] "Treating" or "treatment" of a disease, disorder, or syndrome, as used herein, includes (i) preventing the disease, disorder, or syndrome from occurring in a human, i.e. causing the clinical symptoms of the disease, disorder, or syndrome not to develop in an animal that may be exposed to or predisposed to the disease, disorder, or syndrome but does not yet experience or display symptoms of the disease, disorder, or syndrome; (ii) inhibiting the disease, disorder, or syndrome, *i.e.*, arresting its development; and (iii) relieving the disease, disorder, or syndrome, *i.e.*, causing regression of the disease, disorder, or syndrome. As is known in the art, adjustments for systemic versus localized

delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by one of ordinary skill in the art.

Embodiments of the Invention

[0023] Another embodiment provides a pharmaceutical composition which comprises 1) a compound, as a single stereoisomer or mixture of isomers thereof, selected from Table 1, optionally as a pharmaceutically acceptable salt thereof, and 2) a pharmaceutically acceptable carrier, excipient, and/or diluent thereof.

[0024] Another embodiment is a method of treating disease, disorder, or syndrome where the disease is associated with uncontrolled, abnormal, and/or unwanted cellular activities effected directly or indirectly by mTOR which method comprises administering to a human in need thereof a therapeutically effective amount of a Compound selected from Table 1, optionally as a pharmaceutically acceptable salt or pharmaceutical composition thereof. In another embodiment the disease is cancer.

[0025] Embodiment (A): Another embodiment is directed to a method of treating a disease, disorder, or syndrome which method comprises administering to a patient a therapeutically effective amount of a Compound selected from Table 1, optionally as a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a therapeutically effective amount of a Compound selected from Table 1, and a pharmaceutically acceptable carrier, excipient, or diluent. In another embodiment the disease is cancer.

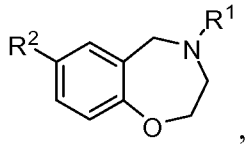
[0026] In another embodiment of any of the embodiments of Embodiment (A), the cancer is breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non small cell lung carcinoma, small cell lung carcinoma, adenocarcinoma, colon cancer, rectal cancer, gastric carcinoma, hepatocellular carcinoma, melanoma, pancreatic cancer, prostate carcinoma, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and neck cancer.

Representative Compounds

[0027] Compounds of the Invention are depicted below. In each instance the embodiment includes both the recited compounds, as well as a single stereoisomer or mixture of stereoisomers thereof, as well as a pharmaceutically acceptable salt thereof.

Compounds of the invention are named according to systematic application of the nomenclature rules agreed upon by the International Union of Pure and Applied Chemistry (IUPAC), International Union of Biochemistry and Molecular Biology (IUBMB), and the Chemical Abstracts Service (CAS). Specifically, names in Table 1 were generated using ACD/Labs naming software 8.00 release, product version 8.08 or later.

[0028] In one embodiment, the invention comprises compounds of structural formula



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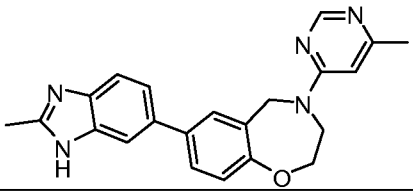
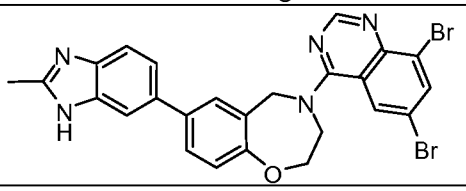
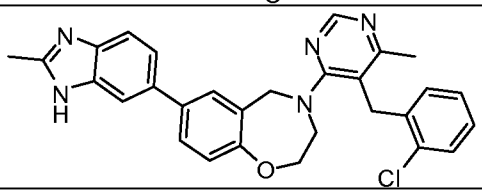
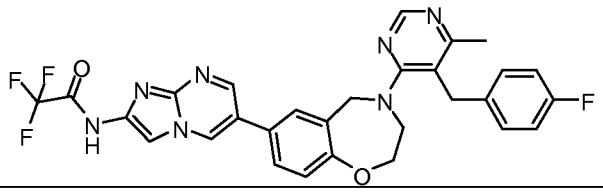
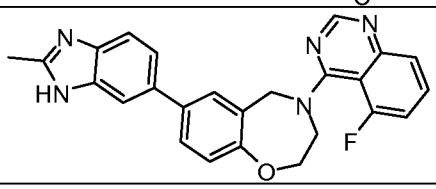
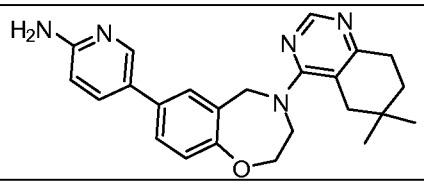
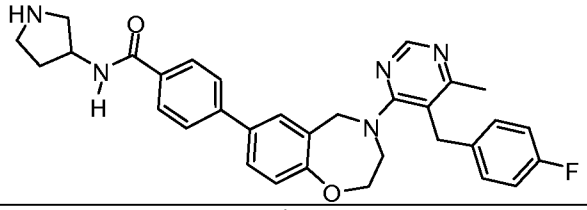
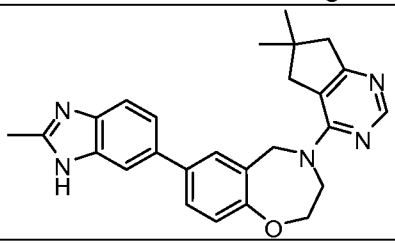
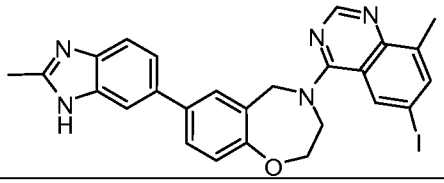
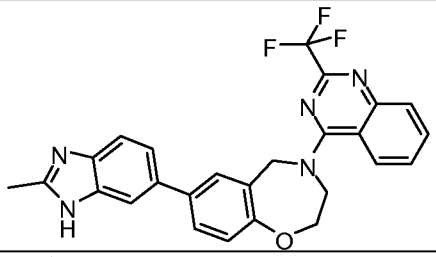
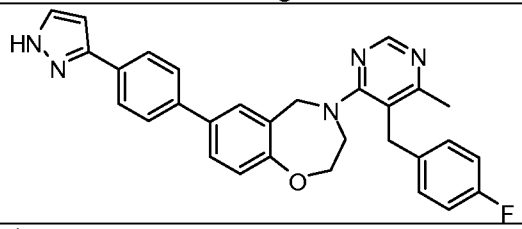
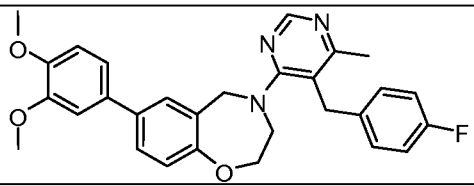
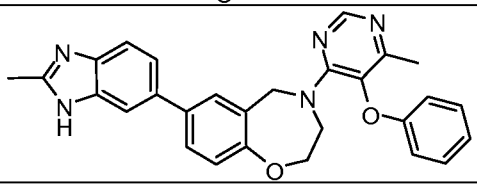
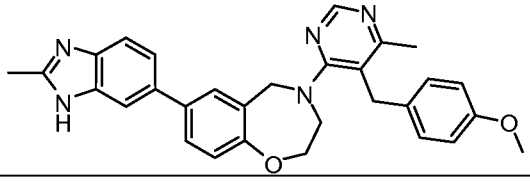
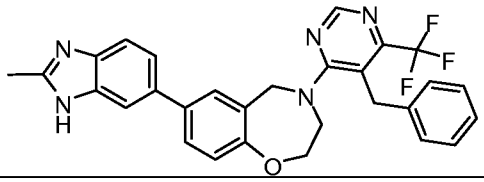
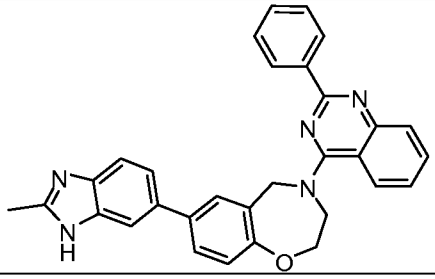
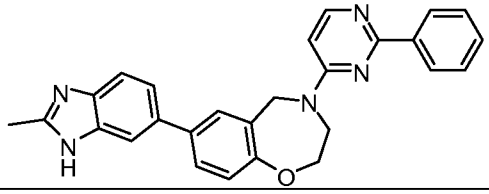
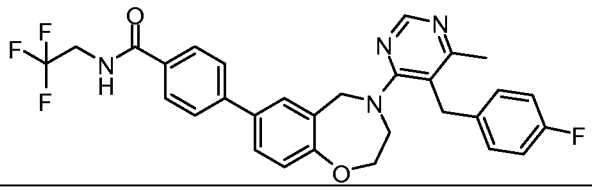
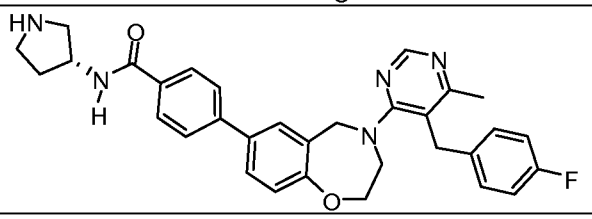
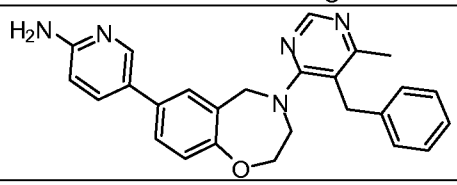
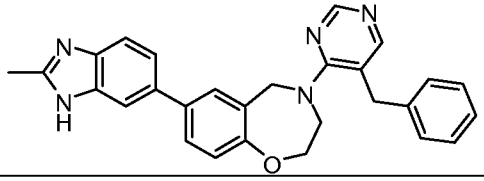
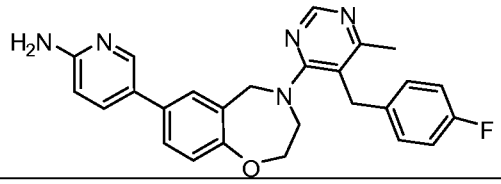
wherein the combination of R^1 and R^2 are as defined in one of the compounds in Table 1, below, and pharmaceutically acceptable salts thereof.

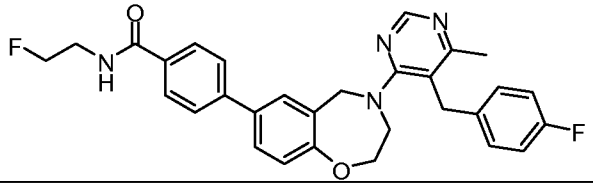
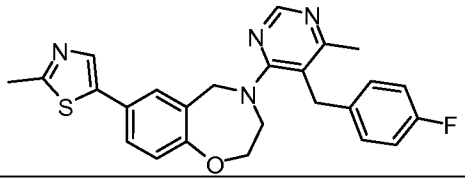
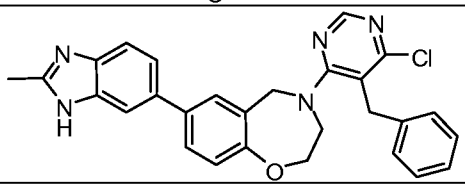
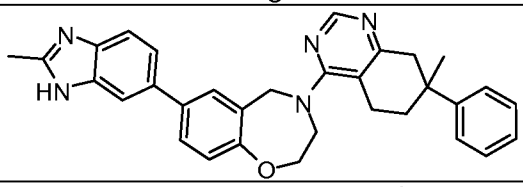
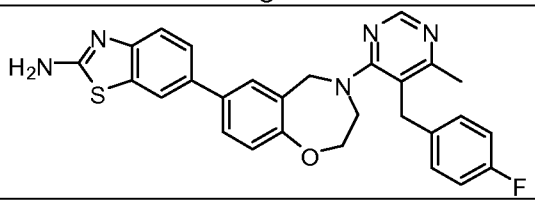
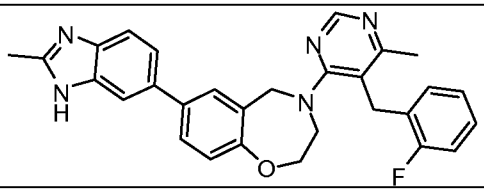
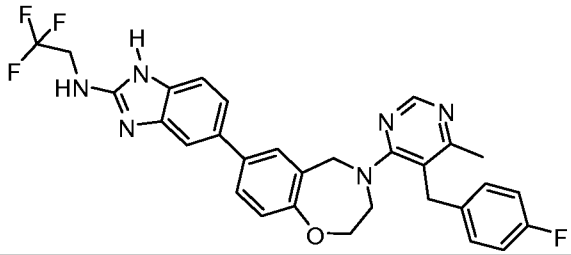
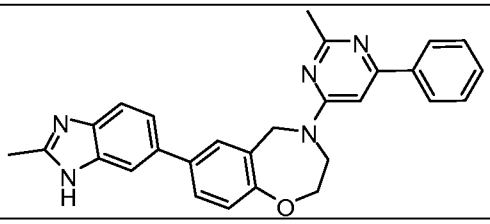
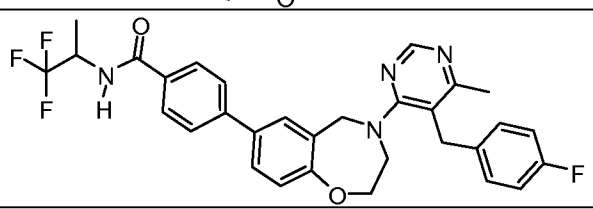
[0029] In another embodiment, the invention comprises a compound in Table 1, and pharmaceutically acceptable salts thereof.

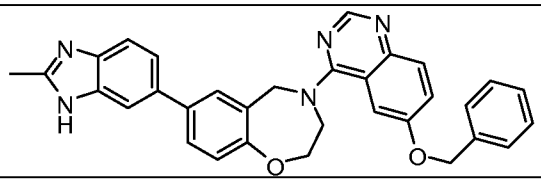
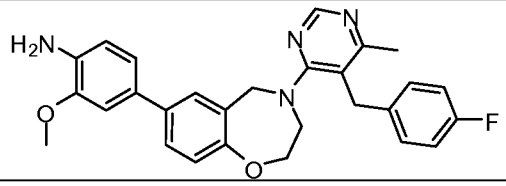
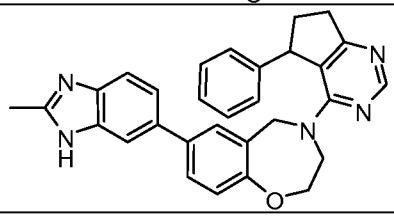
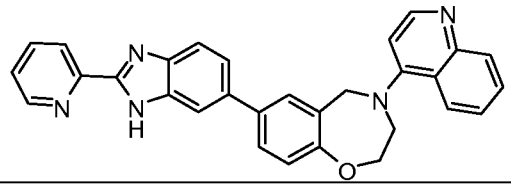
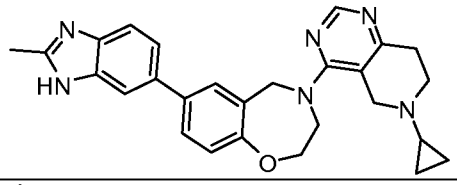
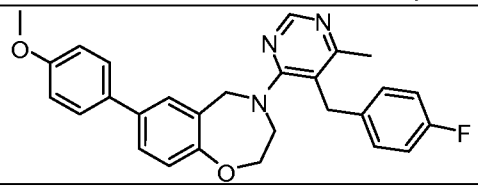
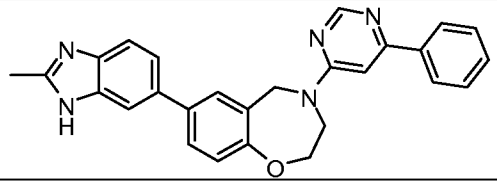
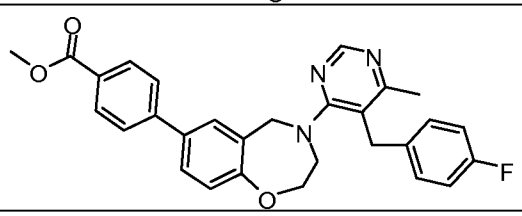
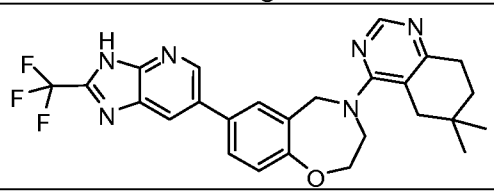
Table 1

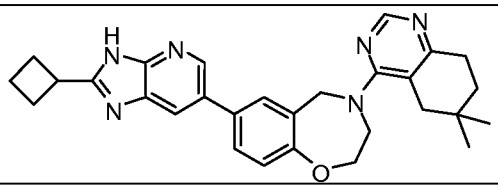
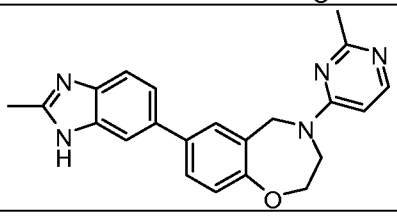
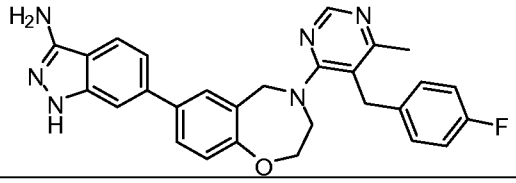
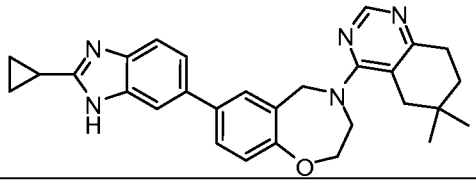
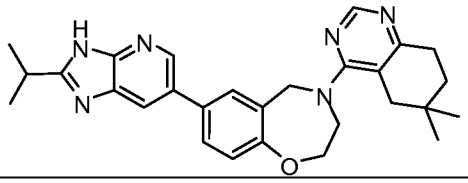
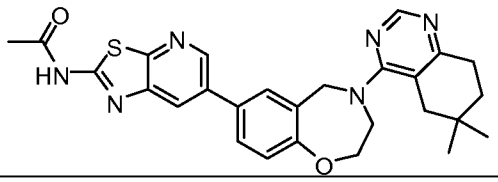
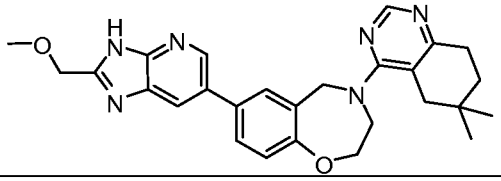
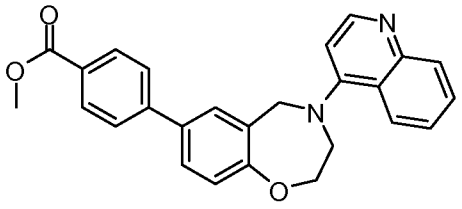
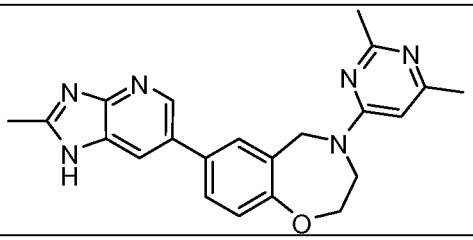
Entry No.	Structure	Name
1		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
2		4-(6,8-dibromoquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
3		4-{5-[(2-chlorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4		2,2,2-trifluoro-*N*-[6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)imidazo[1,2-*a*]pyrimidin-2-yl]acetamide
5		4-(5-fluoroquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

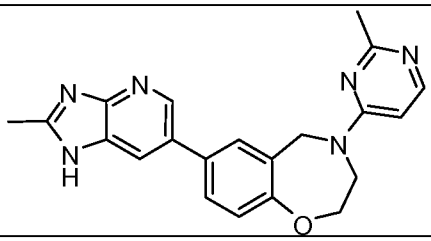
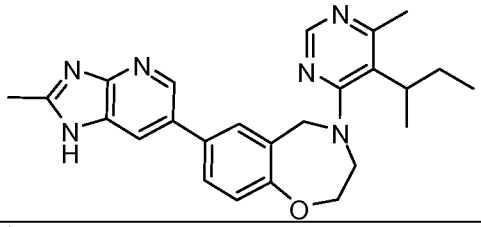
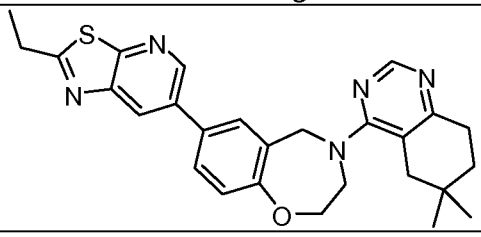
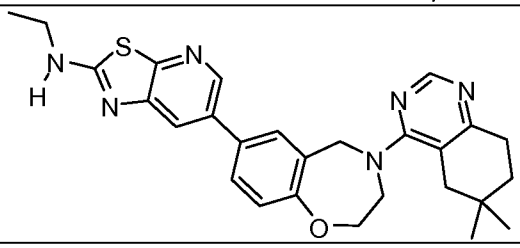
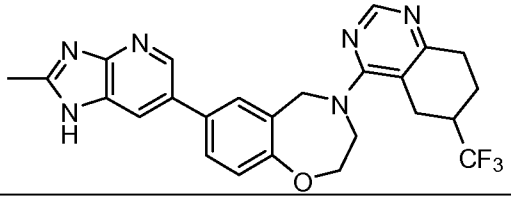
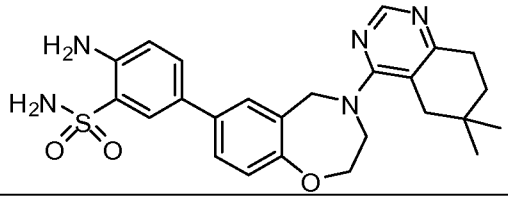
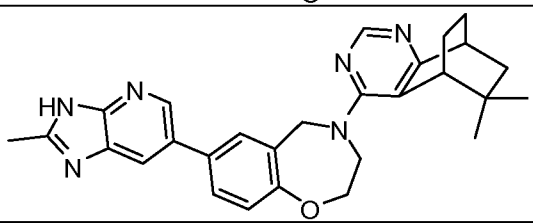
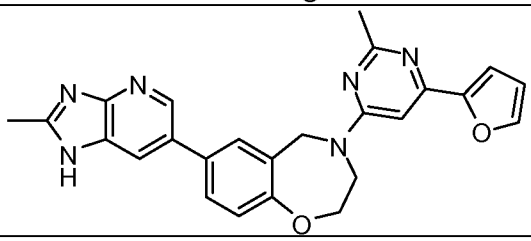
Entry No.	Structure	Name
6		5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-2-amine
7		4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-pyrrolidin-3-ylbenzamide
8		4-(6,6-dimethyl-6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
9		4-(6-iodo-8-methylquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
10		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[2-(trifluoromethyl)quinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
11		4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(1*H*-pyrazol-3-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
12		7-[3,4-bis(methyloxy)phenyl]-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine
13		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[6-methyl-5-(phenyloxy)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine

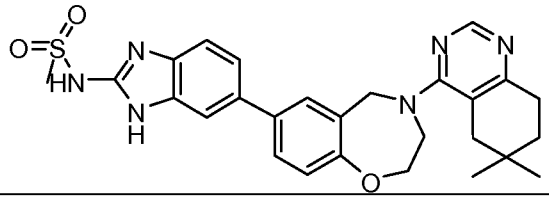
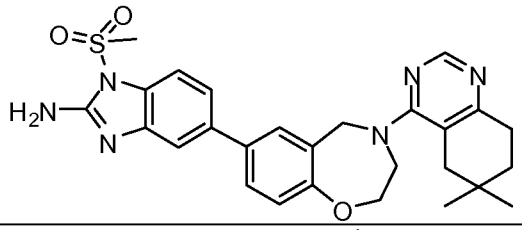
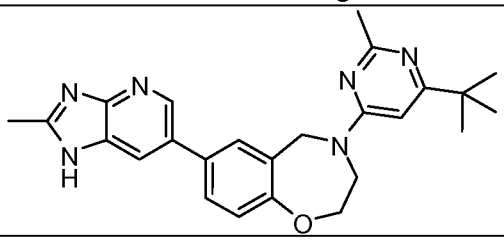
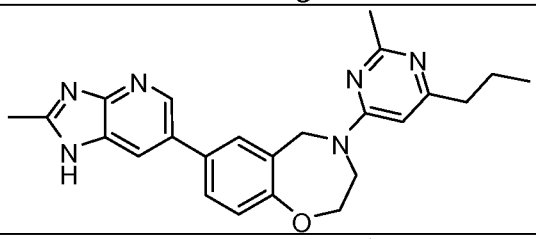
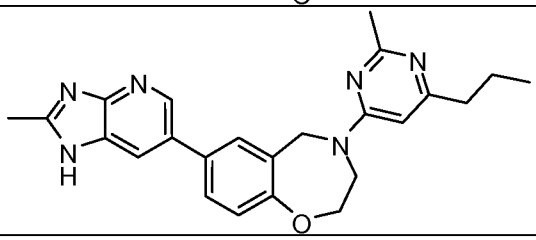
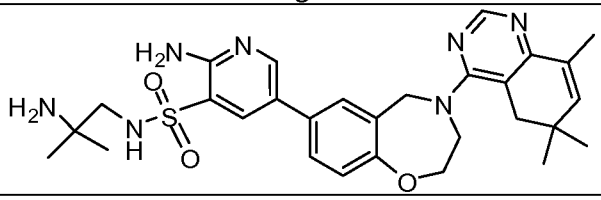
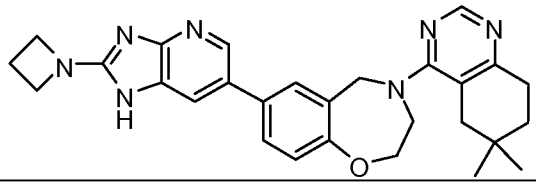
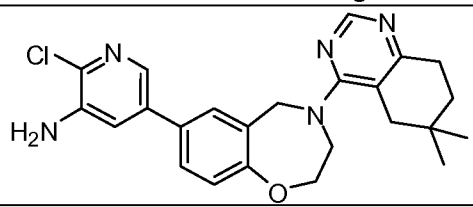
Entry No.	Structure	Name
14		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-methyl-5-{[4-(methyloxy)phenyl]methyl}pyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
15		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[5-(phenylmethyl)-6-(trifluoromethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
16		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-phenylquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
17		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
18		4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoroethyl)benzamide
19		4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-[(3*R*)-pyrrolidin-3-yl]benzamide
20		5-{4-[6-methyl-5-(phenylmethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}pyridin-2-amine
21		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[5-(phenylmethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
22		5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)pyridin-2-amine

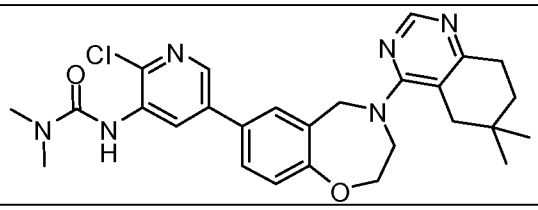
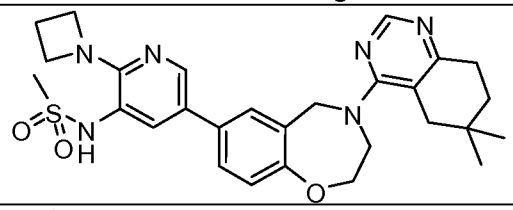
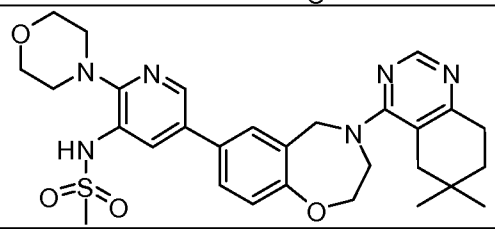
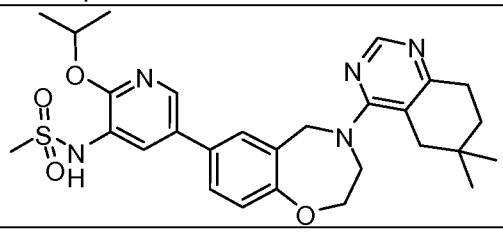
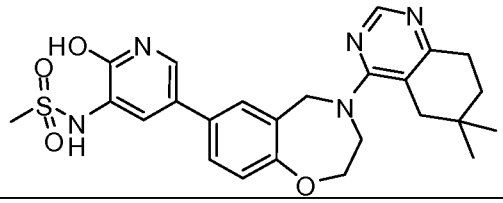
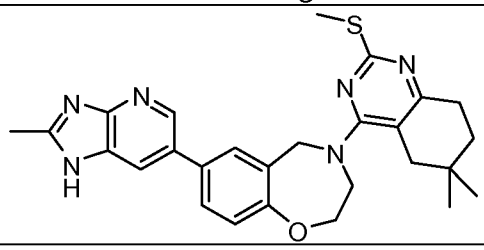
Entry No.	Structure	Name
23		*N*-(2-fluoroethyl)-4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide
24		4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
25		4-[6-chloro-5-(phenylmethyl)pyrimidin-4-yl]-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
26		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(7-methyl-7-phenyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
27		6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-benzothiazol-2-amine
28		4-{5-[(2-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
29		5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoroethyl)-1*H*-benzimidazol-2-amine
30		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-methyl-6-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
31		4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoro-1-methylethyl)benzamide

Entry No.	Structure	Name
32		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-{6-[(phenylmethyl)oxy]quinazolin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine
33		4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-2-(methyloxy)aniline
34		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(5-phenyl-6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
35		7-(2-pyridin-2-yl-1*H*-benzimidazol-6-yl)-4-quinolin-4-yl-2,3,4,5-tetrahydro-1,4-benzoxazepine
36		4-(6-cyclopropyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
37		4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(methyloxy)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
38		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
39		methyl 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate
40		4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine

Entry No.	Structure	Name
41		7-(2-cyclobutyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
42		7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
43		6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1*H*-indazol-3-amine
44		7-(2-cyclopropyl-1*H*-benzimidazol-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
45		4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(1-methylethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
46		*N*-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl][1,3]thiazolo[5,4-*b*]pyridin-2-yl}acetamide
47		4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-{2-[(methyloxy)methyl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine
48		methyl 4-(4-quinolin-4-yl-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate
49		4-(2,6-dimethylpyrimidin-4-yl)-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

Entry No.	Structure	Name
50		7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(2-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
51		7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-methyl-5-(1-methylpropyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
52		4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-(2-ethyl[1,3]thiazolo[5,4-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
53		6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-*N*-ethyl[1,3]thiazolo[5,4-*b*]pyridin-2-amine
54		7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
55		2-amino-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]benzenesulfonamide
56		6,6-dimethyl-4-[7-(2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-yl]-5,6,7,8-tetrahydro-5,8-ethanoquinazoline
57		4-(6-furan-2-yl-2-methylpyrimidin-4-yl)-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

Entry No.	Structure	Name
58		*N*-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1*H*-benzimidazol-2-yl}methanesulfonamide
59		5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1-(methylsulfonyl)-1*H*-benzimidazol-2-amine
60		4-[6-(1,1-dimethylethyl)-2-methylpyrimidin-4-yl]-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
61		7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(2-methyl-6-propylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
62		7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-[2-methyl-6-(1-methylethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
63		2-amino-*N*-(2-amino-2-methylpropyl)-5-[4-(6,6,8-trimethyl-5,6-dihydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-3-sulfonamide
64		7-(2-azetidin-1-yl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
65		2-chloro-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-amine

Entry No.	Structure	Name
66		3-{2-chloro-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-yl}-1,1-dimethylurea
67		*N*-{2-azetidin-1-yl-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-yl}methanesulfonamide
68		*N*-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-morpholin-4-ylpyridin-3-yl}methanesulfonamide
69		*N*-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-[(1-methylethyl)oxy]pyridin-3-yl}methanesulfonamide
70		*N*-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-hydroxypyridin-3-yl}methanesulfonamide
71		4-[6,6-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4-yl]-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

[0030] Useful Intermediates: 4-[6,7-*bis*(methyloxy)quinolin-4-yl]-7-bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine; 4-{4-[6,7-*bis*(methyloxy)quinolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}-2-nitroaniline; 4-{4-[6,7-*bis*(methyloxy)quinolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}benzene-1,2-diamine; *N*-[5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidine-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-thiazol-2-yl]acetamide; 7-bromo-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine; 4-[6,7-

bis(methyloxy)quinazolin-4-yl]-7-bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine; 7-bromo-4-[6-(methyloxy)quinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine.

General Administration

[0031] In one aspect, the invention provides pharmaceutical compositions comprising an inhibitor of mTOR according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. In certain other specific embodiments, administration is by the oral route. Administration of the compounds of the invention, or their pharmaceutically acceptable salts, in pure form or in an appropriate pharmaceutical composition, can be carried out via any of the accepted modes of administration or agents for serving similar utilities. Thus, administration can be, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically, transdermally, intravaginally, intravesically, intracistemally, or rectally, in the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, suppositories, pills, soft elastic and hard gelatin capsules, powders, solutions, suspensions, or aerosols, or the like, specifically in unit dosage forms suitable for simple administration of precise dosages.

[0032] The compositions will include a conventional pharmaceutical carrier or excipient and a compound of the invention as the/an active agent, and, in addition, may include carriers and adjuvants, etc.

[0033] Adjuvants include preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0034] If desired, a pharmaceutical composition of the invention may also contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, antioxidants, and the like, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylalted hydroxytoluene, etc.

[0035] The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules) and the bioavailability of the drug substance. Recently, pharmaceutical

formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a crosslinked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

[0036] Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

[0037] One specific route of administration is oral, using a convenient daily dosage regimen that can be adjusted according to the degree of severity of the disease-state to be treated.

[0038] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, cellulose derivatives, starch, alignates, gelatin, polyvinylpyrrolidone, sucrose, and gum acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, croscarmellose sodium, complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, magnesium stearate and the like (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc,

calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

[0039] Solid dosage forms as described above can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain pacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[0040] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

[0041] Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

[0042] Compositions for rectal administrations are, for example, suppositories that can be prepared by mixing the compounds of the present invention with for example suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt while in a suitable body cavity and release the active component therein.

[0043] Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed

under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

[0044] Compressed gases may be used to disperse a compound of this invention in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

[0045] Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to about 99% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, and 99% to 1% by weight of a suitable pharmaceutical excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound(s) of the invention, or a pharmaceutically acceptable salt thereof, with the rest being suitable pharmaceutical excipients.

[0046] Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, 18th Ed., (Mack Publishing Company, Easton, Pa., 1990). The composition to be administered will, in any event, contain a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease-state in accordance with the teachings of this invention.

[0047] The compounds of the invention, or their pharmaceutically acceptable salts or solvates, are administered in a therapeutically effective amount which will vary depending upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of the compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular disease-states, and the host undergoing therapy. The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is an example. The specific dosage used, however, can vary. For example, the dosage can depend on a number of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well known to one of ordinary skill in the art.

[0048] If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described above and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically acceptable agent(s) when a combination formulation is inappropriate.

General Synthesis

[0049] Compounds of this invention can be made by the synthetic procedures described below. The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wis.), or Bachem (Torrance, Calif.), or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-17 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989); Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition) and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989). These examples are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these examples can be made and will be suggested to one skilled in the art having referred to this disclosure. The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

[0050] Unless specified to the contrary, the reactions described herein take place at atmospheric pressure and over a temperature range from about -78 °C to about 150 °C, more specifically from about 0 °C. to about 125 °C and more specifically at about room (or ambient) temperature, e.g., about 20 °C. Unless otherwise stated (as in the case of an hydrogenation), all reactions are performed under an atmosphere of nitrogen.

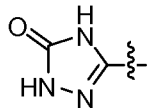
[0051] Prodrugs can be prepared by techniques known to one skilled in the art. These techniques generally modify appropriate functional groups in a given compound. These modified functional groups regenerate original functional groups by routine manipulation or *in vivo*. Amides and esters of the compounds of the present invention may be prepared according to conventional methods. A thorough discussion of prodrugs is provided in T.

Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference for all purposes.

[0052] The compounds of the invention, or their pharmaceutically acceptable salts, may have asymmetric carbon atoms or quaternized nitrogen atoms in their structure. Compounds of the Invention that may be prepared through the syntheses described herein may exist as single stereoisomers, racemates, and as mixtures of enantiomers and diastereomers. The compounds may also exist as geometric isomers. All such single stereoisomers, racemates and mixtures thereof, and geometric isomers are intended to be within the scope of this invention.

[0053] Some of the compounds of the invention contain an active ketone $-C(O)CF_3$ and may exist in part or in whole as the $-C(OH_2)CF_3$ form. Regardless of whether the compound is drawn as the $-C(O)CF_3$ or $-C(OH_2)CF_3$ form, both are included within the scope of the Invention. Although an individual compound may be drawn as the $-C(O)CF_3$ form, one of ordinary skill in the art would understand that the compound may exist in part or in whole as the $-C(OH_2)CF_3$ form and that the ratio of the two forms may vary depending on the compound and the conditions in which it exists.

[0054] Some of the compounds of the invention may exist as tautomers. For example, where a ketone or aldehyde is present, the molecule may exist in the enol form; where an amide is present, the molecule may exist as the imidic acid; and where an enamine is present, the molecule may exist as an imine. All such tautomers are within the scope of the invention. Further, for example, in this application R^1 can be 5-oxo-1*H*-1,2,4-triazol-3-yl, depicted structurally below:



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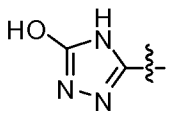
Both 5-oxo-1*H*-1,2,4-triazol-3-yl and the above structure **1** include, and are equivalent to, 3-hydroxy-4*H*-1,2,4-triazol-5-yl and its structure **2**:



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Regardless of which structure or which terminology is used, each tautomer is included within the scope of the Invention.

[0055] The present invention also includes N-oxide derivatives and protected derivatives of compounds of the Invention. For example, when compounds of the Invention contain an oxidizable nitrogen atom, the nitrogen atom can be converted to an N-oxide by methods well known in the art. When compounds of the Invention contain groups such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable "protecting group" or "protective group". A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1991, the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the Invention can be prepared by methods well known in the art.

[0056] Methods for the preparation and/or separation and isolation of single stereoisomers from racemic mixtures or non-racemic mixtures of stereoisomers are well known in the art. For example, optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Enantiomers (R- and S-isomers) may be resolved by methods known to one of ordinary skill in the art, for example by: formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where a desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents or by converting on enantiomer to the other by asymmetric transformation. For a mixture of enantiomers, enriched in a particular enantiomer, the major component enantiomer may be further enriched (with concomitant loss in yield) by recrystallization.

[0057] In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol,

and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

[0058] The chemistry for the preparation of the compounds of this invention is known to those skilled in the art. In fact, there may be more than one process to prepare the compounds of the invention. The following examples illustrate but do not limit the invention. All references cited herein are incorporated by reference in their entirety.

Synthetic Examples

Reagent Preparation 1: 4-chloro-6-(phenylmethoxy)-quinazoline.

[0059] 4-chloro-6-(phenylmethoxy)-quinazoline. Prepared according to the method described in (J. Med. Chem. 2002, 45(17), 3772-3793) using 2-amino-5-benzyloxybenzoic acid methyl ester (J. Org. Chem. 2001, 66(8), 2784-2788). MS (EI) for $C_{15}H_{11}ClN_2O$: 271 (MH^+).

[0060] 4-chloro-6-iodo-8-methylquinazoline. Prepared according to the method described in (J. Med. Chem. 2002, 45(17), 3772-3793) using 2-amino-5-iodo-3-methylbenzoic acid. MS (EI) for $C_9H_6ClIN_2$: 305 (MH^+).

Reagent Preparation 2: 4-chloro-5-[(4-fluorophenyl)methyl]-6-methylpyrimidine

[0061] STEP 1: A solution of methyl 2-[(4-fluorophenyl)methyl]-3-oxobutanoate (90.0 g, 0.41 mol), thiourea (50.0 g, 0.66 mol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (80.0 mL, 0.52 mol) in acetonitrile (250 mL) was heated to reflux and the reaction mixture was stirred for 2 hours. After cooling to room temperature the reaction mixture was concentrated. The resulting viscous oil was dissolved in 2M aqueous sodium hydroxide (400 mL) and washed with ethyl acetate (500 mL). The organic layer was separated and extracted with 2M aqueous sodium hydroxide (2x 100 mL). The aqueous layers were combined and cooled to 0°C then the pH was adjusted to 5 by the slow addition of concentrated hydrochloric acid. The precipitated product was collected by filtration, washed with water and dried in vacuo to give 5-[(4-fluorophenyl)methyl]-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (75 g, 72%). MS (EI) for $C_{12}H_{11}FN_2OS$: 251.1(MH^+).

[0062] STEP 2: To a slurry of 5-[(4-fluorophenyl)methyl]-6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (36.0 g, 0.144 mol) in a mixture of tetrahydrofuran (125 mL) and water (125 mL) at 0 °C was added hydrogen peroxide (30 wt% solution in water, 120 mL, 1.04 mol) in portions and the reaction was stirred for 1 hour while the temperature of the reaction increased to 40 °C. The stirring was continued for an

additional 45 minutes at that time the reaction mixture became a clear, homogeneous solution. The mixture was concentrated and diluted with ethyl acetate (300 mL). The organic layer was separated and washed with saturated aqueous sodium hydrogen sulfite (2x 100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-ol (30 g, 95%). MS (EI) for $C_{12}H_{11}FN_2O$: 219.1(MH^+).

[0063] STEP 3: To a solution of 5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-ol (30.0 g, 0.138 mol) in chloroform (150 mL) was slowly added phosphorus oxychloride (40 mL, 0.429 mol) then the reaction mixture was heated to reflux for 90 minutes. After cooling to room temperature the reaction mixture was concentrated and partitioned between chloroform (300 mL) and saturated aqueous sodium bicarbonate (200 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2x 100 mL). The combined aqueous phase was washed with chloroform (200 mL). The organic phases were combined and washed with brine dried over anhydrous sodium sulfate, filtered and concentrated The resulting crude was purified by gradient flash chromatography (hexane to 20% ethyl acetate in hexane) to give 4-chloro-5-[(4-fluorophenyl)methyl]-6-methylpyrimidine (17.6 g, 54%). MS (EI) for $C_{12}H_{10}ClFN_2$: 237 (MH^+).

[0064] Using analogous techniques and starting with alternative reagents in step 1 the following reagents were prepared. Alternative starting reagents were commercially obtained unless otherwise indicated.

[0065] 4-chloro-6-methyl-5-phenoxy-pyrimidine. Prepared according to reagent preparation 2 by using ethyl 3-oxo-2-phenoxybutanoate in step 1. MS (EI) for $C_{11}H_9ClN_2O$: 221 (MH^+).

[0066] 4-chloro-5-(2-fluorobenzyl)-6-methylpyrimidine. Prepared according to the method of reagent preparation 2 by alkylation of methyl 3-oxobutanoate with 1-(bromomethyl)-2-fluorobenzene to afford methyl 2-[(2-fluorophenyl)methyl]-3-oxobutanoate then proceeding according to step 1. ^1H NMR (400 MHz, $CDCl_3$): 8.79 (1H), 7.28 to 7.12 (m, 1H), 7.14 to 6.97 (m, 2H), 6.82 (dd, 1H), 4.19 (s, 2H), 2.47 (s, 3H), GC-MS for $C_{12}H_{10}ClFN_2$: 236 (M^+).

[0067] 4-chloro-5-(2-chlorobenzyl)-6-methylpyrimidine. Prepared according to reagent preparation 2 by alkylation of methyl 3-oxobutanoate with 2-chlorobenzyl

bromide to afford methyl 2-[(2-chlorophenyl)methyl]-3-oxobutanoate then proceeding according to step 1.

[0068] 4-chloro-5-(4-methoxybenzyl)-6-methylpyrimidine. Prepared according to reagent preparation 2 by alkylation of methyl 3-oxobutanoate with 4-methoxybenzyl bromide to afford methyl 2-[(4-methoxyphenyl)methyl]-3-oxobutanoate then proceeding according to step 1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.76 (s, 1H), 7.02 (d, 2H), 6.83 (d, 2H), 4.13 (s, 2H), 3.78 (s, 3H), 2.51 (s, 3H); MS (EI) for $C_{13}H_{13}ClN_2O$: 249 (MH^+).

[0069] 5-benzyl-4-chloro-6-methylpyrimidine. Prepared according to reagent preparation 2 by using ethyl 2-benzylacetoacetate in step 1. MS (EI) for $C_{12}H_{11}ClN_2$: 219 (MH^+).

[0070] 5-benzyl-4-chloro-6-(trifluoromethyl)pyrimidine. Prepared according to reagent preparation 2 by alkylation of ethyl 4,4,4-trifluoroacetoacetate with benzyl bromide to afford ethyl 2-benzyl-4,4,4-trifluoro-3-oxobutanoate then proceeding according to step 1. MS (EI) for $C_{12}H_8ClF_3N_2$: 272 (M^+).

[0071] 5-*sec*-butyl-4-chloro-6-methylpyrimidine. Prepared according to the method of reagent preparation 2 by alkylation of methyl 3-oxobutanoate with *sec*-butyl iodide to afford methyl 2-acetyl-3-methylpentanoate then proceeding according to step 1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.67 (s, 1H), 3.38 (br s, 1H), 2.62 (s, 3H), 1.92 (br s, 1H), 1.79 (m, 1H), 1.37 (d, 3H), 0.86 (t, 3H).

Reagent Preparation 3: 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinazoline

[0072] STEP 1: To a cooled (0 °C) solution of 4,4-dimethylcyclohexanone (21 g, 0.17 mol) and dimethyl carbonate (45 g, 0.50 mol) in THF (400 mL) was added NaH (60% wt/wt in mineral oil, 17 g, 0.43 mol) portionwise over 30 minutes. The resulting slurry was allowed to stir at ambient temperature for 30 minutes followed by two hours at reflux. The reaction mixture was cooled (0 °C) and MeOH (30 mL) was added dropwise over 20 minutes. The resulting slurry was partitioned between 10% aqueous citric acid and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. Purification by vacuum distillation provided methyl 2-hydroxy-5,5-dimethylcyclohex-1-enecarboxylate (22.5 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (s, 1H), 3.75 (s, 3H), 2.29 (t, 2H), 2.03 (s, 2H), 1.44 (t, 2H), 0.96 (s, 6H); MS (EI) for $C_{10}H_{16}O_3$: 184 (M^+).

[0073] STEP 2: A solution of methyl 2-hydroxy-5,5-dimethylcyclohex-1-enecarboxylate (10.0 g, 54 mmol) and ammonium acetate (10 g, 130 mmol) in ethanol

(50 mL) was heated to reflux for 2 hours. The reaction was concentrated to one third original volume, and then diluted with ethyl acetate (100 mL). The organic solution was washed with water (100 mL) and brine (50 mL) and then dried over anhydrous sodium sulfate. After filtration and concentration, the residue was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:8) to afford methyl 2-amino-5,5-dimethylcyclohex-1-enecarboxylate (7.42 g, 75% yield) as a yellow solid. MS (EI) for $C_{10}H_{17}NO_2$: 184 (MH^+).

[0074] STEP 3: 2-amino-5,5-dimethylcyclohex-1-enecarboxylate (7.42 g, 40 mmol) was dissolved in N,N-dimethylformamide dimethylacetal (50 mL) and heated to 110 °C for 18 hours. The resulting solution was cooled to room temperature and concentrated to provide methyl 2-((dimethylamino)methyleneamino)-5,5-dimethylcyclohex-1-enecarboxylate (9.5 g, 98% yield) as an oil. ^1H NMR (400 MHz, $CDCl_3$): 3.65 (s, 3H), 3.49 (s, 1H), 2.95 (s, 6H), 2.35 (m, 2H), 2.15 (br s, 2H), 1.41 (t, 2H), 0.95 (s, 6H); MS (EI) for $C_{13}H_{22}N_2O_2$: 239 (MH^+).

[0075] STEP 4: A solution of methyl 2-((dimethylamino)methyleneamino)-5,5-dimethylcyclohex-1-enecarboxylate (9.5 g, 40 mol) in 7.0M ammonia in methanol (35 mL) was stirred at 25 °C for 90 minutes then concentrated to an oil. The residue was purified by silica gel column chromatography (ethyl acetate/hexanes, 1:8) to give 6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (6.41 g, 90% yield) as a white solid. ^1H NMR (400 MHz, d_6-DMSO): 7.96 (s, 1H), 2.52 (t, 2H), 2.14 (s, 2H), 1.48 (t, 2H), 0.93 (s, 6H); MS (EI) for $C_{10}H_{14}N_2O$: 179 (MH^+).

[0076] STEP 5: To 6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (6.41 g, 36 mmol) in chloroform (10 mL) added phosphorus oxychloride (10 mL) and refluxed for 2 hours. The mixture was concentrated to an oil, then diluted with ethyl acetate (80 mL) and washed with saturated sodium carbonate (50 mL) and brine (25 mL). The solution was dried over anhydrous sodium sulfate, filtered and concentrated, then the residue purified by silica gel column chromatography (ethyl acetate/hexanes, 1:8) to give 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinazoline (5.3 g, 75% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): 8.72 (s, 1H), 2.52 (t, 2H), 2.14 (s, 2H), 1.48 (t 2H), 0.93 (s, 6H); MS (EI) for $C_{10}H_{13}ClN_2$: 197 (MH^+).

[0077] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 or 2 the following reagents were prepared. Alternative starting materials were available commercially unless otherwise indicated.

[0078] 4-chloro-6-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine. Prepared according to the method of reagent preparation 3; using 4-methyl-2-oxo-cyclopentanecarboxylic acid methyl ester (J. Chem. Soc. Perkin Trans 1 1987, 7, 1485-8) in step1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (s, 1H), 3.20 (m, 2H), 2.70 (m, 3H), 1.22 (d, 3H). GC/MS (EI) for $C_8H_9ClN_2$: 168 (M^+).

[0079] 4-chloro-6-cyclopropyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine. Prepared according to the method of reagent preparation 3 using 1-cyclopropyl-4-oxo-3-piperidinecarboxylic acid methyl ester (*Heterocycles,* **1999,** *50(2),* 867-874) in step1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.78 (s, 1H), 3.79 (s, 2H), 2.98 (m, 4H), 1.88 (m, 1H), 0.60 (m, 2H), 0.54 (m, 2H). MS (EI) for $C_{10}H_{12}ClN_3$: 210 (MH^+).

[0080] 4-chloro-7-methyl-7-phenyl-5,6,7,8-tetrahydroquinazoline. Prepared according to the method of reagent preparation 3 using 4-methyl-2-oxo-4-phenyl cyclohexanecarboxylic acid methyl ester (J. Org. Chem. 1991, 56(21), 6199-205) in step1. MS (EI) for $C_{15}H_{15}ClN_2$: 259 (MH^+).

[0081] 4-chloro-5-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine: Synthesized according to the method of reagent preparation 3 using ethyl 2-oxo-5-phenylcyclopentanecarboxylate in step 1. MS (EI) for $C_{13}H_{11}ClN_2$: 231 (MH^+).

[0082] 4-chloro-6,6,8-trimethyl-5,6-dihydroquinazoline. Synthesized according to the method of reagent preparation 3 using 2,4,4-trimethylcyclohex-2-enone in step 1. MS (EI) for $C_{11}H_{13}ClN_2$: 209 (MH^+).

[0083] 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydro-5,8-ethanoquinazoline. Synthesized according to the method of reagent preparation 3 by using 5,5-dimethyl-bicyclo[2.2.2]octanone (J. Am. Chem. Soc. 2006, 128(25), 8160-8161) in step 1. ^{1}H NMR (400 MHz, d_3-CH3Cl): 8.78 (s, 1H), 2.20 (m, 2H), 1.82 (m, 1H), 1.62 (m, 2H), 1.48 (m, 1H), 1.32 (m, 2H), 0.62 (s, 6H). MS (EI) for $C_{12}H_{15}ClN_2$: 223 (MH^+)

[0084] 4-chloro-6,6,8-trimethyl-5,6-dihydroquinazoline. Synthesized according to the method of reagent preparation 3 using 2,4,4-trimethylcyclohex-2-enone in step 1. MS (EI) for $C_{11}H_{13}ClN_2$: 209 (MH^+).

[0085] 4-chloro-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline. Prepared according to the method of reagent preparation 3; using 4-(trifluoromethyl)cyclohexanone in step 1. GC/MS (EI) for $C_9H_8ClF_3N_2$: 236 (M^+).

Reagent Preparation 4 : 2-amino-*N*-(2-amino-2-methylpropyl)-5-bromopyridine-3-sulfonamide

[0086] To a solution of 2-amino-5-bromopyridine-3-sulfonyl chloride (prepared according to the method in WO2008144463) (0.50 g, 1.84 mmol) and 2-methyl-1,2-propanediamine (0.18 g, 2.00 mmol) in a mixture of tetrahydrofuran (6 mL) and water (0.5 mL) was added potassium carbonate (0.8 g, 6.00 mmol) and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated and partitioned between ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, washed with water (2x 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel gradient chromatography 100% ethyl acetate to 10% of (10% ammonium hydroxide in methanol) in ethyl acetate to give 2-amino-*N*-(2-amino-2-methylpropyl)-5-bromopyridine-3-sulfonamide (0.50 g, 84%). ^{1}H NMR (400 MHz, d_3-chloroform): 8.27 (d, 1H), 8.07 (d, 1H), 7.16 (m, 1H), 5.67 (brs, 2H), 2.72 (s, 2H), 2.37 (brs, 2H), 1.11 (s, 6H). MS (EI) for $C_9H_{15}BrN_4O_2S$: 324 (MH^+)

Reagent Preparation 5: 2-azetidin-1-yl-6-bromo-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1H-imidazo[4,5-*b*]pyridine

[0087] STEP 1: A mixture of 6-bromo-1,3-dihydro-2H-imidazo[4,5-*b*]pyridine-2-one (400 mg, 1.7 mmol, WO 2004035549) and azetidine (450 mg, 7.9 mmol) in ethanol (2 mL) was heated at 100 °C with microwave irradiation for 30 min. Concentration and column chromatography on silica (95:5 dichloromethane/methanol) gave 2-azetidin-1-yl-6-bromo-1H-imidazo[4,5-*b*]pyridine (135 mg, 31% yield) as a yellow solid. MS (EI) for $C_9H_9BrN_4$: 254 (MH^+).

[0088] STEP 2: A suspension of 2-azetidin-1-yl-6-bromo-1H-imidazo[4,5-*b*]pyridine (135 mg 0.53 mmol) in dimethylformamide (5 mL) was cooled to 0°C, sodium hydride (60% dispersion in mineral oil, 22 mg, 0.53 mmol) was added, and the mixture was stirred at 0°C for 30 min. (2-(chloromethoxy)ethyl)trimethylsilane (techn. 90%, 99 mg, 0.53 mmol) was added, and the mixture was stirred for 1 h while warming to room temperature. The resulting mixture was partitioned between water (50 mL) and ethyl acetate (100 mL), the layers were separated, and the organic layer was washed with 5% aqueous lithum chloride (2 x 25 mL), and brine (25 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica (ethyl acetate) to provide the title compound (118 mg, 58% yield) as a pale yellow oil. MS (EI) for $C_{15}H_{23}BrN_4OSi$: 384 (MH^+).

Reagent Preparation 7: N-(5-bromo-2-isopropoxypyridin-3-yl)methanesulfonamide

[0089] STEP 1: A solution of 5-bromo-2-chloro-3-nitropyridine (480 mg, 2.02 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 mL, 10 mmol) in isopropanol (6 mL) was heated to 50 °C for 3.5 h and then cooled to rt. 1 N HCl was added, and the resulting aqueous mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with 1 N HCl, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (gradient, 100% hexanes to 90% hexanes : 10% ethyl acetate) to provide 5-bromo-2-isopropoxy-3-nitropyridine (115.5 mg, 0.442 mmol, 22% yield) as a yellow oil. GC-MS (EI) for $C_8H_9BrN_2O_3$: 260, 262 (Br isotopes, M^+).

[0090] STEP 2:To a solution of 5-bromo-2-isopropoxy-3-nitropyridine (125 mg, 0.48 mmol) in acetic acid (2.5 mL) at 60 °C was added iron powder (268 mg, 4.8 mmol), and the mixture was stirred for 25 min. After cooling to rt, ethyl acetate was added, and the solids were removed by filtration through celite. The organic filtrate was washed with water followed by saturated aqueous sodium bicarbonate. The organic extracts were then dried over magnesium sulfate, filtered, and concentrated in vacuo to provide 5-bromo-2-isopropoxypyridin-3-amine (102 mg, 0.441 mmol, 92% yield) as a yellow film. MS (EI) for $C_7H_9BrN_2O$: 231, 233 (Br isotopes, MH^+).

[0091] STEP 3: A solution of 5-bromo-2-isopropoxypyridin-3-amine (118 mg, 0.51 mmol) and diisopropylethylamine (195 uL, 1.12 mmol) in dichloromethane (2 mL) was cooled to 0 °C and methanesulfonyl chloride (79 uL, 1.02 mmol) was added. The mixture was allowed to warm to rt over 15 h, and was then diluted with dichloromethane. The organic mixture was washed with 10% aqueous citric acid followed by water. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in dioxane (2 mL), and then sodium hydroxide (50%, 108 uL, 0.38 mmol) was added. After stirring for 1.25 h at rt, the mixture was heated to 60 °C and further sodium hydroxide (50%, 108 uL) was added. After stirring 20 min, the mixture was cooled to rt. The mixture was diluted with ethyl acetate and then was washed with 10% aqueous citric acid followed by water. The organic phase was dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (gradient 100% hexanes to 70% hexanes : 30% ethyl acetate) to provide N-(5-bromo-2-isopropoxypyridin-3-yl)methanesulfonamide (99.7 mg, 0.322 mmol, 63% yield) as a waxy solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H), 7.88 (d, 1H), 6.72 (br

s, 1H), 5.41- 5.29 (m, 1H), 3.03 (s, 3H), 1.36 (d, 6H); MS (EI) for $C_9H_{13}BrN_2O_3S$: 307, 309 (Br isotopes, M-H).

[0092] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[0093] N-(2-(benzyloxy)-5-bromopyridin-3-yl)methanesulfonamide Prepared according to the methods described in reagent preparation 7 using benzyl alcohol in step 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1H), 7.91 (d, 1H), 7.44-7.34 (m, 5H), 6.71 (br s, 1H), 5.40 (s, 2H), 2.99 (s, 3H); MS (EI) for $C_{13}H_{13}BrN_2O_3S$: 357, 359 (Br isotopes, MH^+).

[0094] N-(2-(azetidin-1-yl)-5-bromopyridin-3-yl)methanesulfonamide Prepared according to the methods described in reagent preparation 7 using azetidine in step 1. MS (EI) for $C_9H_{12}BrN_3O_2S$: 306, 308 (Br isotopes, MH^+).

[0095] N-(5-bromo-2-morpholinopyridin-3-yl)methanesulfonamide Prepared according to the methods described in reagent preparation 7 using morpholine in step 1. MS (EI) for $C_{10}H_{14}BrN_3O_3S$: 336, 338 (Br isotopes, MH^+).

Reagent Preparation 8: tert-Butyl 3-(bis(tert-butoxycarbonyl)amino)-6-bromo-1H-indazole-1-carboxylate

[0096] To a cooled (0 °C) solution of 6-bromo-1H-indazol-3-amine (0.30 g, 1.4 mmol), DIPEA (2.5 mL, 14 mmol) and di tert-butyl dicarbonate (1.5 g, 7.0 mmol) in THF (15 mL) was added DMAP (0.09 g, 0.70 mmol). The reaction mixture was then stirred at ambient temperature for three hours. The resulting solution was diluted with ethyl acetate (75 mL) and washed with saturated aqueous ammonium chloride (2 x 50 mL). The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography provided tert-butyl 3-(bis(tert-butoxycarbonyl)amino)-6-bromo-1H-indazole-1-carboxylate (0.57 g, 80%) as a waxy solid. MS (ES) for $C_{22}H_{30}BrN_3O_6$: 512 (MH^+).

Reagent Preparation 9: isobutyl 5-bromo-2-(2,2,2-trifluoroethylamino)-1H-benzo[d]imidazole-1-carboxylate

[0097] Step 1: Trifluoroethylamine hydrochloride salt (275 mg, 2.03 mmol) was suspended in THF (3 mL) followed by addition of DIPEA (1.7 mL, 10.2 mmol) and the resulting solution was cooled to 0°C. Thiophosgene (156 uL, 2.03 mmol) was added to the solution by syringe and the mixture was allowed to stir 15 min. at 0°C followed by

addition of 4-bromobenzene-1,2-diamine (380 mg, 2.03 mmol). The mixture was allowed to warm to room temperature and stirred an additional 30 min. then concentrated. The residue was taken into ethyl acetate and washed twice with 10% aqueous citric acid then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was then taken into THF (10 mL) followed by addition of solid mercury (II) oxide (500 mg, 2.3 mmol) and the mixture was brought to reflux for 12 h. On cooling to room temperature the solution was filtered through a bed of celite and the filtrate concentrated to give 5-bromo-N-(2,2,2-trifluoroethyl)-1H-benzo[d]imidazol-2-amine that was used without further purification. MS (EI) for $C_9H_7BrF_3N_3$: 294, 296 (MH^+, Br isotope pattern).

[0098] Step 2: 5-Bromo-N-(2,2,2-trifluoroethyl)-1H-benzo[d]imidazol-2-amine as obtained above was taken into THF (15 mL) followed by addition of DIPEA (0.5 mL, 2.9 mmol) and isobutyl chloroformate (0.3 mL, 2.3 mmol) and the resulting mixture was allowed to stir at room temperature for one hour. The solution was then concentrated and taken into ethyl acetate then washed twice with 10% aqueous citric acid then brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue thus obtained was purified by silica gel chromatography using 3.5:1 hexanes:ethyl acetate as eluent to give isobutyl 5-bromo-2-(2,2,2-trifluoroethylamino)-1H-benzo[d]imidazole-1-carboxylate as a colorless crystalline solid MS (EI) for $C_{14}H_{15}BrF_3N_3O_3$: 394, 396 (MH^+, Br isotope pattern).

Reagent Preparation 10: 5-bromo-2-ethylbenzo[d]thiazole

[0099] Step 1: 5-Bromo-2-chloropyridin-3-amine (55.3 mg, 0.27 mmol) was taken into dichloromethane (1 mL) followed by addition of DIPEA (50 uL, 0.29 mmol) and propionyl chloride (25 uL) and the mixture was stirred at room temperature for 30 min. at which point additional DIPEA (50 uL) and propionyl chloride (20 uL) were added. After one hour the mixture was concentrated and the residue was partitioned with ethyl acetate and 10% aqueous citric acid. The organic phase was separated and washed twice with saturated aqueous sodium bicarbonate then dried over sodium sulfate, filtered and concentrated to give N-(5-bromo-2-chloropyridin-3-yl)propionamide (84 mg) as a tan solid. MS (EI) for $C_8H_8BrClN_2O$: 265, 263 (MH^+, Br, Cl isotope pattern).

[00100] Step 2: N-(5-bromo-2-chloropyridin-3-yl)propionamide (29.7 mg, 0.11 mmol), phosphorous pentasulfide (66 mg, 0.15 mmol) and sodium carbonate (16 mg) were taken into THF (2 mL) and the mixture was stirred for 12h. at room temperature.

Additional phosphorous pentasulfide (88 mg) and sodium carbonate (20 mg) were then added and stirring was continued 12 h. Aqueous sodium hydroxide (2M, 1 mL) was then added to the reaction mixture and stirred 2 h. at room temperature then partitioned with ethyl ether and water. The organic phase was dried over magnesium sulfate, filtered and concentrated then the residue purified by silica gel chromatography using ethyl ether:hexanes 1:3 as eluent to give 5-bromo-2-ethylbenzo[d]thiazole (17 mg, 64%) as a colorless crystalline solid. MS (EI) for $C_8H_7BrN_2S$: 245, 243 (MH^+, Br isotope pattern).

Reagent Preparation 11: 6-bromo-N-ethylthiazolo[5,4-*b*]pyridin-2-amine

[00101] Step 1: 5-Bromo-2-chloropyridin-3-amine (27 mg, 0.13 mmol) was taken into dimethylacetamide (1 mL) followed by addition of ethyl isothiocyanate (100 uL) and the mixture was heated to 90°C over 24 h at which point an additional aliquot of ethyl isothiocyanate (100 uL) was added and the mixture was heated at 120°C an additional 24 h. On cooling to room temperature the mixture was diluted with ethyl acetate and the organic solution was washed with water (4x) then dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography using hexanes:ethyl acetate 2:1 as eluent to give 6-bromo-N-ethylthiazolo[5,4-*b*]pyridin-2-amine (19.5 mg, 58 %). MS (EI) for $C_8H_8BrN_3S$: 260, 258 (MH^+, Br, isotope pattern).

Reagent Preparation 12: 4-chloro-6,6-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazoline

[00102] STEP 1: To a freshly prepared solution of sodium metal (0.72 g, 30.0 mmol) in dry ethanol (50 mL) was added thiourea (1.60 g, 21.0 mmol) and methyl 5,5-dimethyl-2-oxocyclohexanecarboxylate (3.00 g, 16.0 mmol), and the mixture was refluxed for 17 h. The reaction was concentrated, water (40 mL) was added and the pH was adjusted to 6. The precipitate was collected by filtration, washed with water then dried to afford 2-mercapto-6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-ol (2.83 g, 84% yield) as a off-white solid. MS (EI) for $C_{10}H_{14}N_2OS$: 211 (MH^+).

[00103] STEP 2: A mixture of 2-mercapto-6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-ol (2.82 g, 13.4 mmol), potassium carbonate (9.27 g, 67.0 mmol), and iodomethane (1.90 g, 13.4 mmol) in dimethylformamide (30 mL) was stirred at room temperature for 23 h. Ethyl acetate (300 mL) was added, and the organic layer was washed with water (100 mL), 5% aqueous lithum chloride (2 x 100 mL), and brine (100 mL), dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica (0-50% ethyl acetate in hexanes) to give 6,6-dimethyl-2-

(methylthio)-5,6,7,8-tetrahydroquinazolin-4-ol (0.33 g, 11% yield) as a colorless solid. MS (EI) for $C_{11}H_{16}N_2OS$: 225 (MH^+).

[00104] STEP 3: A solution of 6,6-dimethyl-2-(methylthio)-5,6,7,8-tetrahydro-quinazolin-4-ol (0.33 g, 1.47 mmol) in phosphorus oxychloride (10 mL) was stirred at 60 °C for 2 h. The mixture was concentrated, ethyl acetate (10 mL) and saturated sodium bicarbonate (10 mL) were added, and the biphasic mixture was stirred for 45 min. More ethyl acetate (50 mL) was added and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL), dried over sodium sulfate, filtered and concentrated to provide the title compound (0.33 g, 92% yield) as a yellow solid. MS (EI) for $C_{11}H_{15}ClN_2S$: 243 (MH^+).

Reagent Preparation 13: 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate

[00105] STEP 1: Commercially-available 5-bromo-2-hydroxybenzaldehyde (4.0 g, 10 mmol) and 2-aminoethanol were combined in THF/MeOH (100 mL, 10:1) and sodium borohydride (0.76 g, 2.0 mmol) was added with stirring. The resulting reaction mixture was stirred at 40 °C for 4 h, concentrated on a rotary evaporator then diluted with EtOAc (50 mL) and saturated $NaHCO_3$ (30 mL). To this suspension was added di-*tert*-butyl dicarbonate (2.83 g, 13 mmol). The mixture was stirred at rt overnight. The organic layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated on a rotary evaporator. Hexane was subsequently added to the crude reaction product which resulted in the formation of a white solid. This slurry was filtered to obtain *tert*-butyl-5-bromo-2-hydroxybenzyl(2-hydroxyethyl)carbamate (6.8 g, 98 %) as a white solid. MS (EI) for $C_{14}H_{20}BrNO_4$, found 346 (MH^+).

[00106] STEP 2: *tert*-Butyl-5-bromo-2-hydroxybenzyl(2-hydroxyethyl)carbamate (3.46 g, 10 mmol) and triphenylphosphine (3.96 g, 15 mmol) were combined in DCM (100 mL) and diisopropyl azodicarboxylate (3.03 g, 15 mmol) was added. The resulting reaction mixture was stirred at rt for 12 h. The reaction mixture was washed with water, dried, filtered, and concentrated on a rotary evaporator. The resulting crude product was purified via silica gel chromatography eluting with 8:2 hexane/ethyl acetate to give the desired product (1.74 g, 53 %) as a white solid. MS (EI) for $C_{14}H_{18}BrNO_3$, found 328 (MH^+).

Reagent Preparation 14: isobutyl 6-bromo-2-methyl-1*H*-imidazo[4,5-*b*]pyridine-1-carboxylate

[00107] STEP 1: To a solution of 6-bromo-2-methyl-1*H*-imidazo[4,5-*b*]pyridine (3.40 g, 16.0 mmol) and diisopropylethylamine (6.5 mL, 65 mmol) in *N,N*-dimethylformamide (20 mL) cooled in an ice bath was added dropwise isobutyl chloroformate (2.51 mL, 19.2 mmol) and the mixture was warmed to room temperature. After 1 hour the reaction was diluted with ethyl acetate (80 mL) and washed with water (60 mL), 10% aqueous citric acid (40 mL) and brine (20 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to a slurry. The residue was triturated diethyl ether (100 mL) and the solid isolated by filtration to give isobutyl 6-bromo-2-methyl-1*H*-imidazo[4,5-*b*]pyridine-1-carboxylate (2.3 g, 46% yield). MS (EI) for $C_{12}H_{14}BrN_3O_2$: 313 (MH^+).

Example 1

7-(2-methyl-1H-benzimidazol-6-yl)-4-(6-methyl-5-{[4-(methyloxy)phenyl]methyl}pyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00108] STEP 1: To 5-bromo-2-methylbenzimidazole (38 g, 180 mmol) in THF (400 mL) was added di-*tert*-butyl dicarbonate (39 g, 189 mmol). The reaction mixture was stirred at room temperature for 24 h and then concentrated. Ethyl acetate (400 mL) was added to the residue, and the solution was washed with 10% aqueous citric acid (2 x 100 mL), water (100 mL), and brine (100 mL), dried over sodium sulfate, and concentrated. Column chromatography on silica (gradient 20-30% ethyl acetate in hexane) provided 1,1-dimethylethyl 6-bromo-2-methyl-1*H*-benzimidazole-1-carboxylate (27 g, 48% yield) as a beige solid. MS (EI) for $C_{13}H_{15}BrN_2O_2$: 312 (MH^+).

[00109] STEP 2: A solution of 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (30.0 g, 91.4 mmol) and triisopropyl borate (22.4 g, 119 mmol) in THF (300 mL) was cooled to -78 °C, and a 2.5 M solution of n-butyllithium in hexanes (47.6 mL, 119 mmol) was added dropwise over 40 min at this temperature. The reaction mixture was stirred at -78 °C for an additional 30 min, then quenched by dropwise addition of 2 N hydrochloric acid (80 ml), and allowed to warm up to room temperature. Ethyl acetate (100 mL) and water (100 mL) were added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. Hexane (200 mL) was added to the residue and the mixture was stirred overnight. The precipitate was filtered, washed several times with hexane, and dried to

give (4-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (23.4g, 87%) as a colorless solid. MS (EI) for $C_{14}H_{20}BNO_5$: 294 (MH^+).

[00110] STEP 3: A suspension of 1,1-dimethylethyl 6-bromo-2-methyl-1*H*-benzimidazole-1-carboxylate (11.3 g, 36 mmol), (4-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (example 5, step 1)(11.7 g, 40 mmol), dichloro[1,1-*bis*(diphenylphosphino]ferrocenepalladium (II) dichloromethane adduct (3.0 g, 10 mol %) in dioxane (115 mL) and water (28.5 mL) was degassed with nitrogen, and then diisopropylethylamine (18.6 g, 144 mmol) was added. The reaction mixture was stirred at 90 °C for 220 min, cooled to room temperature, and concentrated. Column chromatography on silica of the residue (gradient 25-30% ethyl acetate in hexane) afforded 1,1-dimethylethyl 7-(1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-methyl-1*H*-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (13.2 g, 76% yield) as an amorphous solid. MS (EI) for $C_{27}H_{33}N_3O_5$: 480(MH^+).

[00111] STEP 4: A solution of 1,1-dimethylethyl 7-(1-{[(1,1-dimethylethyl)oxy]carbonyl}-2-methyl-1*H*-benzimidazol-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (13.1 g, 27 mmol) in a mixture of methanol (20 mL) and 4 N hydrogen chloride in dioxane (30 mL) was refluxed for 15 min. After cooling to room temperature ethyl ether (100 mL) was added, and the reaction mixture was concentrated. Another portion of ethyl ether (100 mL) was added, the precipitate was filtered off, washed several times with ethyl ether, and dried to give 7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine dihydrochloride (8.9 g, 93% yield) as a light beige solid. ^{1}HNMR (400 MHz, CD_3OD): 7.93(s, 1H), 7.86-7.67(m, 4H), 7.28(s, 1H), 4.54(s, 2H), 4.33-4.23(m, 2H), 3.65-3.54(m, 2H), 2.91(s, 3H); MS (EI) for $C_{17}H_{17}N_3O$: 280 (MH^+).

[00112] STEP 5: STEP 5: A suspension of 7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine dihydrochloride (132 mg, 0.47 mmol), 4-chloro-5-(4-methoxybenzyl)-6-methylpyrimidine (107 mg, 0.43 mmol, reagent preparation 2), and potassium carbonate (178 mg, 1.29 mmol) in dimethylformamide (3 mL) was heated at 120 °C with microwave irradiation for 3 h. Direct purification of the resulting mixture by preparative reverse phase HPLC (0.1% aqueous ammonium acetate-acetonitrile mobile phase) followed by lyophillization of product fractions and trituration with ethyl ether provided the title compound (79 mg, 42% yield) as off-white solid. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.46 (s, 1H), 7.50 (br s, 2H), 7.41 (dd, 1H), 7.21 (dd, 1H), 6.98 (m, 3H),

6.78 (d, 2H), 6.68 (s, 1H), 4.51 (s, 2H), 4.30 (m, 2H), 3.92 (s, 2H), 3.90 (m, 2H), 3.64 (s, 3H), 2.60 (s, 3H), 2.21 (s, 3H); MS (EI) for $C_{30}H_{29}N_5O_2$: 492 (MH^+).

[00113] Using analogous synthetic techniques and substituting with alternative starting reagents in step 5 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00114] 4-(6,6-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using 4-chloro-6,6-dimethyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (reagent preparation 2) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 12.26 (br s, 1H), 8.30 (s, 1H), 7.65 (d, 2H), 7.54 (d, 1H), 7.46 (dd, 1H), 7.34 (t, 1H), 7.00 (d, 1H), 4.58 (s, 2H), 4.22 (m, 2H), 4.09 (m, 2H), 2.51 (s, 3H), 2.50 (s, 4H), 1.10 (s, 6H). MS (EI) for $C_{25}H_{27}N_5O$: 426 (MH^+).

[00115] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(5-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using 4-chloro-5-phenyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (reagent preparation 3) in step 5. MS (EI) for $C_{30}H_{27}N_5O$: 474 (MH^+).

[00116] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine: Prepared according to the the method of example 1 by using 4-chloro-6-phenylpyrimidine in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 12.24 (d, 1H), 8.58 (s, 1H), 8.16 (m, 3H), 7.76 (br s, 1H), 7.61-7.34 (m, 7H), 7.03 (d, 1H), 5.01 (br s, 2H), 4.25 (br s, 2H), 4.18 (br s, 2H), 3.34 (s, 3H); MS (EI) for $C_{27}H_{23}N_5O$: 434 (MH^+).

[00117] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-{6-[(phenylmethyl)oxy]quinazolin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using 4-chloro-6-(phenylmethoxy)-quinazoline (reagent preparation 1) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 12.18 (s, 1H), 8.46 (s, 1H), 7.82 (d, 1H), 7.78 (s, 0.5H), 7.76 (s, 1H), 7.58-7.50 (m, 2.5H), 7.44 (m, 0.5H), 7.38 (d, 1H), 7.34 (m, 0.5H), 7.25 (br s, 1H), 7.18 (t, 1H), 7.10-7.02 (m, 3H), 6.96 (br s, 2H), 5.03 (s, 2H), 4.88 (d, 2H), 4.48 (m, 2H), 4.43 (m, 2H), 2.48 (s, 3H). MS (EI) for $C_{32}H_{28}N_5O_2$: 514 (MH^+).

[00118] 4-{5-[(2-chlorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-chloro-5-(2-chlorobenzyl)-6-methylpyrimidine (reagent preparation 2) in step 5. ^{1}H NMR (400 MHz, $CDCl_3$): 8.63 (s, 1H), 7.42 (d, 2H), 7.29-

7.15 (m, 5H), 7.05 (d, 1H), 6.94 (m, 1H), 6.58 (m, 1H), 4.40 (s, 2H), 4.28 (m, 2H), 3.94 (s, 2H), 3.86 (m, 2H), 2.69 (s, 3H), 2.23 (s, 3H); MS (EI) for $C_{29}H_{26}ClN_5O$: 496 (MH^+).

[00119] 4-(6-cyclopropyl-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using 4-chloro-6-cyclopropyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (reagent preparation 3) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.66 (s, 1H), 7.91 (s, 1H), 7.78 (d, 1H), 7.70 (m, 1H), 7.63 (d, 1H), 7.48 (d, 1H), 7.12 (d, 1H), 4.93 (s, 2H), 4.40 (br s, 2H), 4.22 (br s, 2H), 4.11 (s, 2H), 3.32 (t, 2H), 2.87 (s, 3), 3.14 (t, 2H), 2.88(s, 3H), 2.32 (m, 1H), 0.70 (m, 2H), 0.58 (m, 2H); MS (EI) for $C_{27}H_{28}N_6O$: 453 (MH^+).

[00120] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(7-methyl-7-phenyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 1 using 4-chloro-7-methyl-7-phenyl-5,6,7,8-tetrahydroquinazoline (reagent preparation 3) in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.65 (s, 1H), 7.90 (s, 1H), 7.84 (d, 1H), 7.72 (d, 1H), 7.59 (m, 2H), 7.38 (d, 2H), 7.27 (t, 2H), 7.08 (m, 2H), 5.04 (q, 2H), 4.41 (s, 2H), 4.13 (br s, 2H), 4.02 (br s, 2H), 3.18 (d, 1H), 2.92 (d, 1H), 2.81 (s, 3H), 1.98 (m, 2H), 1.34 (s, 3H); MS (EI) for $C_{32}H_{31}N_5O$: 502 (MH^+).

[00121] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[5-(phenylmethyl)-6-(trifluoromethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 5-benzyl-4-chloro-6-(trifluoromethyl)pyrimidine (synthesized according to reagent preparation 2) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.64 (s, 1H), 7.53 (m, 2H), 7.43 (dd, 1H), 7.33 (dd, 1H), 7.20 (m, 3H), 7.04 (m, 1H), 6.96 (m, 3H), 4.67 (s, 2H), 4.21 (m, 4H), 3.93 (m, 2H), 2.60 (s, 3H); MS (EI) for $C_{29}H_{24}F_3N_5O$: 516 (MH^+).

[00122] 4-(6-iodo-8-methylquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-chloro-6-iodo-8-methylquinazoline (reagent preparation 1) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 12.24 (br. s, 1H), 8.64 (d, 1H), 8.06 (m, 1H), 7.99 (d, 1H), 7.76 (m, 2H), 7.55 (m, 2H), 7.48 (m, 1H), 7.05 (m, 1H), 5.00 (m, 2H), 4.49 (m, 2H), 4.12 (m, 2H), 2.56 (s, 3H); MS (EI) for $C_{26}H_{22}IN_5O$: 548 (MH^+).

[00123] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[6-methyl-5-(phenyloxy)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the

method of example 1 by using 4-chloro-6-methyl-5-phenoxy-pyrimidine (reagent preparation 2) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.29 (s, 1H), 7.61 (s, 1H), 7.56 (d, 1H), 7.52 (d, 1H), 7.38 (m, 2H), 7.29 (m, 2H), 7.03 (m, 1H), 6.97 (d, 1H), 6.79 (d, 2H), 4.89 (s, 2H), 4.20 (m, 2H), 4.10 (m, 2H), 2.59 (s, 3H), 2.13 (s, 3H), 1.98 (s, 3H); MS (EI) for $C_{286}H_{259}N_5O_2$: 464 (MH^+).

[00124] 4-[6-chloro-5-(phenylmethyl)pyrimidin-4-yl]-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 5-benzyl-4,6-dichloropyrimidine (Bioorganic & Medicinal Chemistry 2007, 15(4), 1586-1605) in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.37 (s, 1H), 7.50 (m, 2H), 7.43 (d, 1H), 7.25 (m, 4H), 7.09 (m, 2H), 6.98 (d, 1H), 6.80 (s, 1H), 4.63 (s, 2H), 4.27 (m, 2H), 4.11 (s, 2H), 3.96 (m, 2H), 2.60 (s, 3H); MS (EI) for $C_{28}H_{24}ClN_5O$: 482 (MH^+).

[00125] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-phenylquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine: Prepared as the dihydrochloride salt according to the method of example 1 using 4-chloro-2-phenylquinazoline in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.37-8.29 (br d, 3H), 8.23-8.11 (m, 2H), 8.06-8.00 (m, 2H), 7.92-7.84 (m, 2H), 7.72 (br t, 1H), 7.65-7.53 (m, 2H), 7.46-7.35 (m, 2H), 6.98 (d, 1H), 5.54 (br s, 2H), 4.68 (br s, 2H), 4.59 (br s, 2H), 2.86 (s, 3H); MS (EI) for $C_{31}H_{25}N_5O$: 484 (MH^+).

[00126] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[2-(trifluoromethyl)quinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine: Prepared as the dihydrochloride salt according to the method of example 1 using 4-chloro-2-(trifluoromethyl)quinazoline in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.21 (d, 1H), 7.97-7.78 (m, 6H), 7.72-7.65 (m, 1H), 7.58 (dd, 1H), 7.03 (d, 1H), 5.22 (s, 2H), 4.59-4.50 (m, 2H), 4.44-4.32 (m, 2H), 2.83 (s, 3H); MS (EI) for $C_{26}H_{20}F_3N_5O$: 476 (MH^+).

[00127] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-methyl-6-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine: Prepared according to the method of example 1 by using 4-chloro-2-methyl-6-phenylpyrimidine in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.22 (br s, 1H), 8.00-7.91 (m, 3H), 7.87-7.73 (m, 2H), 7.69-7.35 (m, 5H), 7.14 (d, 1H), 5.23 (s, 2H), 4.48-4.30 (m, 4H), 2.83 (s, 3H), 2.72-2.57 (m, 3H); MS (EI) for $C_{28}H_{25}N_5O$: 448 (MH^+).

[00128] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine: Prepared as the dihydrochloride salt according to the method of example 1 using 4-chloro-2-phenylpyrimidine in step 5. ^{1}H NMR (400 MHz,

d_6-DMSO): 8.49-8.27 (m, 3H), 8.18-8.02 (m, 1H), 7.97 (s, 1H), 7.90-7.57 (m, 6H), 7.46-7.16 (m, 1H), 7.11 (d, 1H), 5.22 (d, 2H), 4.61-4.21 (m, 4H), 2.84 (s, 3H); MS (EI) for $C_{27}H_{23}N_5O$: 434 (MH^+).

[00129] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[5-(phenylmethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 5-benzyl-4-chloropyrimidine (reagent preparation 2) in step 5. ^{1}H NMR (400 MHz, DMSO-d_6): 8.64 (s, 1H), 7.53 (m, 2H), 7.43 (dd, 1H), 7.33 (dd, 1H), 7.20 (m, 3H), 7.04 (m, 1H), 6.96 (m, 3H), 4.67 (s, 2H), 4.21 (m, 4H), 3.93 (m, 2H), 2.60 (s, 3H); MS (EI) for $C_{29}H_{24}F_3N_5O$: 516 (MH^+).

[00130] 4-(6,8-dibromoquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the trifluoroacetate salt according to the method of example 1 by using 6,8-dibromo-4-chloroquinazoline in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.47 (s, 1H), 8.21 (s, 1H), 8.17 (s, 1H), 7.86 (s, 1H), 7.81 (d, 1H), 7.71-7.64 (m, 2H), 7.58 (d, 1H), 7.04 (d, 1H), 5.04 (s, 2H), 4.44 (t, 2H), 4.23 (t, 2H), 2.79 (s, 3H); MS (EI) for $C_{25}H_{19}BrN_5O$: 566 (MH^+).

[00131] 7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the acetate salt according to the method of example 1 by using 4-chloro-6-methylpyrimidine in step 5. ^{1}H NMR (400 MHz, methanol-d_4): 8.36 (s, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 7.53 (d, 1H), 7.48-7.43 (m, 2H), 7.05 (d, 1H), 4.80 (s, 2H), 4.25-4.14 (m, 4H), 2.59 (s, 3H), 2.31 (s, 3H); MS (EI) for $C_{22}H_{21}N_5O$: 372 (MH^+).

[00132] 4-(5-fluoroquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-chloro-5-fluoroquinazoline in step 5. ^{1}H NMR (400 MHz, Methanol-D_4): 8.39, (s, 1H), 7.82- 7.76 (m, 1H), 7.63 to 7.50 (m, 4H), 7.44 to 7.39 (m, 2H), 7.29 (dd, 1H), 6.97 (d, 1H), 5.09 (s, 2H), 4.32 (m, 2H), 4.11 (m, 2H), 2.58 (s, 3H), MS (EI) for $C_{25}H_{20}FN_5O$: 426(MH^+).

[00133] 4-{5-[(2-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 by using 4-chloro-5-(2-fluorobenzyl)pyrimidine (reagent preparation 2) in step 5. ^{1}H NMR (400 Methanol-D_4): 8.49 (s, 1H), 7.53 to 7.41 (m, 3H), 7.30 to 7.23 (m, 2H), 7.14 (t, 1H), 7.00 (dd, 2H), 6.87 (t, 1H), 6.65 (br, 1H), 4.48 (s, 2H),

4.30 (m, 2H), 3.96 (s, 2H), 3.90 (m, 2H), 2.60 (s, 3H), 2.21 (s, 3H), MS (EI) for $C_{29}H_{26}FN_5O$: 480 (MH^+).

[00134] 7-(2-methyl-1H-benzimidazol-6-yl)-4-(2-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 1 using 4-chloro-2-methylpyrimidine in step 5. ^1H NMR (400 MHz, dmso-d_6): δ 12.03 (brs, 1H), 8.01 (d, 1H), 7.87 (brs, 1H), 7.75 (s, 1H), 7.50 (m, 3H), 7.01 (d, 1H), 6.78 (brs, 1H), 4.87 (brs, 2H), 4.24 (brs, 4H), 2.48 (s, 3H), 1.98 (s, 3H); MS(EI) for $C_{22}H_{21}N_5O$: 372.2 (MH^+).

Example 2

Methyl 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate

[00135] STEP 1: A suspension of {4-[(methyloxy)carbonyl]phenyl}boronic acid (0.36 g, 2.0 mmol), 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (reagent preparation 13) (0.66 g, 2.0 mmol), [1,1'-*bis*(diphenylphosphino)ferrocene]dichloropalladium(II) (70.0 mg, 0.10 mmol), and tripotassium phosphate (1.30 g, 12.0 mmol) in dioxane (20 mL) was refluxed for 3 h, and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (80 mL), the organic layer was washed with brine (40 mL), dried over sodium sulfate then filtered and concentrated. Column chromatography on silica (ethyl acetate:hexanes 1:4) gave 1,1-dimethylethyl 7-{4-[(methyloxy)carbonyl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (0.47 g, 60% yield). ^1H NMR (400MHZ, DMSO-D_6): 8.11 (m, 2H), 7.63-7.52 (m, 2H), 7.43 (m, 2H), 7.10 (t, 1H), 4.57-4.43 (br, 2H), 4.08 (m, 2H), 3.82 (m, 2H), 1.40 (s, 9H); MS (EI) for $C_{22}H_{25}NO_5$: 469 (MH^+).

[00136] STEP 2: To a solution of 1,1-dimethylethyl 7-{4-[(methyloxy)carbonyl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (1.90 g, 4.96 mmol) in dry methanol (10 mL) was added drop wise 4 N hydrogen chloride in dioxane (10 mL) at room temperature. The reaction mixture was warmed to 55 °C for 60 min, at which time it was cooled to room temperature. The precipitated product was isolated by filtration, washed with diethyl ether, and dried to yield methyl 4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate hydrochloride (1.53 g, 97% yield) as a white solid.

[00137] STEP 3: A mixture of methyl 4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate hydrochloride (0.20 g, 0.64 mmol), 4-chloro-3-[(4-fluorophenyl)methyl]-2-

methylpyridine (0.15 g, 0.64 mmol) (reagent preparation 2) and potassium carbonate (0.26 g, 1.90 mmol) in dimethylformamide (5.0 mL) was stirred at 140 °C for 16 hours. The reaction mixture was cooled to room temperature and diluted with water (25 mL). The aqueous layer was extracted with ethyl acetate (2x 100 mL). The combined organic layer was washed with water (2x 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated. The resulting crude was purified by silica gel column chromatography (hexanes-ethyl acetate 1:1) to give methyl 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate (0.30 g, 94%). ^{1}H NMR (400 MHz, d_6-DMSO): 8.48 (s, 1H), 8.01 (d, 2H), 7.62 (d, 2H), 7.56 (dd, 1H), 7.11 (m, 4H), 7.02 (d, 1H), 6.92 (d, 1H), 4.52 (s, 2H), 4.32 (m, 2H), 3.95 (s, 2H), 3.92 (s, 3H), 3.76 (m, 2H), 2.13 (s, 3H); MS (EI) for $C_{29}H_{26}FN_3O_3$: 485 (MH^+).

[00138] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 and 3 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00139] 5-{4-[6-methyl-5-(phenylmethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}pyridin-2-amine. Prepared according to the method of example 2 by using (4-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid and 5-bromopyridin-2-amine in step 1 and 4-chloro-3-[(phenyl)methyl]-2-methylpyridine (reagent preparation 2) in step 3. ^{1}H NMR (400 DMSO-D_6): 8.39 (1H), 7.82 (s, 1H), 7.42 (dd, 1H), 7.27 to 7.17 (m, 4H), 7.02 (d, 2H), 6.88 (d, 1H), 6.56 (d, 1H), 6.45 (br, 1H), 4.38 (s, 2H), 4.16 (m, 2H), 3.91 (s, 2H), 3.58 (s, 2H), 3.89 (m, 2H), 2.12 (3H), MS (EI) for $C_{26}H_{25}N_5O$: 424 (MH^+).

[00140] 5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-2-amine. Prepared according to the method of example 1 by using (4-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid and 5-bromopyridin-2-amine in step 1 and 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinazoline (reagent preparation 3) in step 3. ^{1}H NMR (400 MHz, Methano-D_4): 8.33 (s, 1H), 8.12(br, 1H), 7.73 (dd, 1H), 7.45 (br, 1H), 7.36 (dd, 1H0, 7.01 (d, 1H), 6.67 (d, 1H), 4.67 (dd, 2H), 4.33 (m, 2H), 3.94 (m, 2H), 2.79 (t, 2H), 2.48 (s, 2H), 1.68 (t, 2H), 0.90 (s, 6H), MS (EI) for $C_{24}H_{27}N_5O$: 402 (MH^+).

Example 3: 7-[3,4-bis(methyloxy)phenyl]-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00141] STEP 1: 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (reagent preparation 13) (500 mg, 1.52 mmol) and 3,4-dimethoxyphenylboronic acid (305 mg, 1.68 mmol) were taken into a mixture of 1,2-dimethoxyethane (4 mL) and water (0.4 mL) followed by addition of potassium carbonate (842 mg, 6.1 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (112 mg, 0.15 mmol) then heated in a microwave reactor at 70C for 1 h. On cooling to room temperature the mixture was partitioned with ethyl acetate and water. The aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by silica chromatography using hexanes:ethyl acetate (85:15) as eluent to afford 1,1-dimethylethyl 7-[3,4-bis(methyloxy)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (508 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): 7.50 (br s, 0.5H), 7.42-7.37 (br d, 1.5H), 7.13-7.06 (m, 3H), 6.96-6.91 (m, 1H), 4.57-4.47 (br d, 2H), 4.09-4.06 (br m, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.85-3.81 (br m, 2H).

[00142] STEP 2: 1,1-dimethylethyl 7-[3,4-bis(methyloxy)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (508 mg, 1.32 mmol) was dissolved in methanol (5 mL) followed by addition of 4M hydrogen chloride in dioxane (1.2 mL). The resulting solution was heated to reflux then allowed to slowly cool to room temperature over 1 h. The mixture was concentrated and the resulting white solid was collected by filtration to give 7-[3,4-bis-(methyloxy)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride salt (287 mg, 66% yield). ^{1}H NMR (400 MHz, CD_3OD): 7.65 (d, 1H), 7.61 (dd, 1H), 7.19-7.10 (m, 3H), 7.03-6.97 (m, 1H), 4.46 (s, 2H), 4.30-4.26 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.63-3.60 (m, 2H).

[00143] STEP 3: To a mixture of 7-[3,4-bis-(methyloxy)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride salt (150 mg, 0.47 mmol) and 4-chloro-5-(4-fluorobenzyl)-6-methylpyrimidine (reagent preparation 2) (100 mg, 0.42 mmol) in 1-methyl-2-pyrrolidinone (3 mL) was added DIPEA (0.3 mL, 1.69 mmol.) then heated at 120C for 4 h in a microwave reactor. On cooling to room temperature the mixture was partitioned with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by preparative reverse phase HPLC to give 7-[3,4-bis(methyloxy)phenyl]-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine

(74.9 mg). ^{1}H NMR (400 MHz, d_6-DMSO): 8.78 (s, 1H), 7.48 (dd, 1H), 7.23-7.14 (m, 5H), 7.10 (br s, 1H), 7.09-7.02 (m, 2H), 6.95 (d, 1H), 4.89 (s, 2H), 4.32 (br tr, 2H), 4.00 (s, 2H), 3.99 (br tr, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.25 (s, 3H). MS (EI) $C_{29}H_{28}FN_3O_3$: 487 (MH^+).

[00144] Using analogous synthetic techniques and substituting with alternative starting reagents in step 1 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00145] 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(methyloxy)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine: Prepared according to the method of example 4 by using 4-methoxyphenylboronic acid in step 1. ^{1}H NMR (400 MHz, d_6-DMSO): 8.77 (s, 1H), 7.74 (d, 2H), 7.43 (dd, 1H), 7.24-7.15 (m, 4H), 7.11 (br s, 1H), 7.02 (d, 2H), 6.96 (d, 1H), 4.84 (s, 2H), 4.31 (br s, 2H), 4.04 (s, 2H), 3.98 (br s, 2H), 3.91 (s, 3H), 2.24 (s, 3H). MS (EI) $C_{28}H_{26}FN_3O_2$: 457 (MH^+).

EXAMPLE 4: 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(1H-pyrazol-3-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine:

[00146] STEP 1: To a slurry of 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (reagent preparation 13) (5.0 g, 17 mmol) in methanol (50 mL) was added anhydrous hydrogen chloride (20 mL, 4N in dioxane, 80 mmol) and the mixture was heated (50 °C). After 1.5 h the reaction mixture was concentrated to 10 mL and diluted with ethyl ether (100 mL). The resulting precipitate was collected by filtration and washed with ethyl ether (2 x 30 mL) affording 7-bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (3.7 g, 83% yield) as a crystalline white solid. MS (EI) for $C_9H_{10}BrNO$: 229 (MH^+).

[00147] STEP 2: To a solution of 7-bromo-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride (1.0 g, 3.8 mmol) and DIPEA (3.3 mL, 19 mmol) in NMP (15 mL) was added 4-chloro-5-(4-fluorobenzyl)-6-methylpyrimidine (reagent preparation 2) (0.90 g, 3.8 mmol). The resulting mixture was heated (120 °C) for 20 h and then purified by column chromatography on silica (0-30% EtOAc/hexanes) to afford 7-bromo-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine (1.3 g, 79% yield) as an orange solid. MS (EI) for $C_{21}H_{19}BrFN_3O$: 429 (MH^+).

[00148] STEP 3: To a slurry of 4-(1H-pyrazol-3-yl)phenylboronic acid (0.11 g, 0.60 mmol), 7-bromo-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine (0.26 g, 0.60 mmol) and potassium carbonate (0.46 g, 3.0

mmol) in DMA (4.5 mL) and water (0.5 mL) was added dichloro[1,1-bis(diphenylphosphino]ferrocenepalladium (II) dichloromethane adduct (0.04 g, 0.05 mmol). The resulting mixture was heated (99 °C) for 24 h and then partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous layer was washed with ethyl acetate (2 x 10 mL) and the combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The resulting residue was purified by preparative reverse phase HPLC to provide 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(1H-pyrazol-3-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine (0.013 g, 5% yield) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-D_6): δ 8.50 (s, 1H), 7.79-7.92 (m, 3H), 7.46-7.58 (m, 3H), 7.11-7.17 (m, 4H), 7.02 (d, 1H), 6.87-6.93 (m, 1H), 6.77 (s, 1H), 4.50 (s, 2H), 4.25-4.43 (m, 2H), 3.99 (s, 2H), 3.74-3.82 (m, 2H), 2.16 (s; 3H); MS (EI) for $C_{23}H_{26}N_4O_2$: 492 (MH^+).

[00149] Using analogous synthetic techniques and substituting with alternative starting reagents in steps 2 or 3 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00150] Methyl 4-(4-quinolin-4-yl-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate. Synthesized according to the method of example 4 using 4-chloroquinoline in step 2 and 4-methoxycarbonylphenylboronic acid in step 3. ^{1}H NMR (400 MHz, DMSO-d_6); δ 8.06 (d, 1H), 8.08-7.80 (m, 7H), 7.72-7.64 (m, 2H), 7.54-7.45 (m, 1H), 7.13 (d, 1H), 6.99 (d, 1H), 4.70 (s, 2H), 4.45-4.38 (m, 2H), 3.92-3.80 (m, 5H); MS (EI) for $C_{26}H_{22}N_2O_3$: 411.0 (MH^+).

Example 5: 4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-(2-ethyl[1,3]thiazolo[5,4-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00151] STEP 1: A solution of 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (reagent preparation 13) (30.0 g, 91.4 mmol) and triisopropyl borate (22.4 g, 119 mmol) in THF (300 mL) was cooled to -78 °C, and a 2.5M solution of n-butyllithium in hexanes (47.6 mL, 119 mmol) was added dropwise over 40 min at this temperature. The reaction mixture was stirred at -78 °C for an additional 30 min, then quenched by dropwise addition of 2N hydrochloric acid (80 ml), and allowed to warm up to room temperature. Ethyl acetate (100 mL) and water (100 mL) were added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. Hexane (200 mL) was added to the residue and

the mixture was stirred overnight. The precipitate was filtered, washed several times with hexane, and dried to give (4-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (23.4g, 87%) as a colorless solid. MS (EI) for $C_{14}H_{20}BNO_5$: 294 (MH^+).

[00152] STEP 2: (4-{[(1,1-dimethylethyl)oxycarbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (1.07 g, 3.64 mmol) was dissolved into 4M hydrogen chloride in dioxane and the resulting solution was allowed to stir at room temperature for 1.3 h. The heterogeneous mixture was then diluted with ethyl ether (100 mL) and the solid collected by filtration to give 2,3,4,5-tetrahydro-1,4-benzoxazepin-7-ylboronic acid hydrochloride salt (791 mg, 95%). ^1H NMR (400 MHz, D_2O): 7.79 (dd, 1H), 7.74 (d, 1H), 7.21 (d, 1H), 4.47 (s, 2H), 4.36 (m, 2H), 3.69 (m, 2H).

[00153] Step 3: To a slurry of 2,3,4,5-tetrahydro-1,4-benzoxazepin-7-ylboronic acid hydrochloride salt (5.7 g, 25 mmol) (example 8, step 1) and 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinazoline (reagent preparation 3) (3.0 g, 15 mmol) in dioxane (75 mL) and H_2O (75 mL) was added DIPEA (17 mL, 100 mmol) and the resulting mixture was heated (90 °C). After 72 hours the solution was concentrated and partitioned between 2M aqueous sodium hydroxide and ethyl ether. The aqueous layer was neutralized and extracted with chloroform. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. Trituration with ethyl ether provided [4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]boronic acid (4.2 g, 80% yield) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 8.68 (s, 1H), 7.77 (s, 1H), 7.64 (dd, 1H), 6.86 (dd, 1H), 5.04 (s, 2H), 4.46 (m, 2H), 4.18 (m, 2H), 2.80 (t, 2H), 2.52 (s, 2H), 1.58 (t, 2H), 0.86 (s, 6H); MS (ES) for $C_{19}H_{24}BN_3O_3$: 354 (MH^+).

[00154] Step 4: 5-bromo-2-ethylbenzo[d]thiazole (reagent preparation 10) (17 mg, 0.07 mmol) and [4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]boronic acid (25.9 mg, 0.07 mmol) were taken into dioxane (0.5 mL) and water (0.1 mL) followed by addition of diisopropylethylamine (0.05 mL, 0.28 mmol.) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (3.7 mg). The mixture was heated at 95 °C in a sealed vessel for 18 h then cooled to room temperature. The mixture was diluted with ethyl acetate and dried over sodium sulfate then filtered through a plug of silica gel using ethyl acetate as eluent. The filtrate was concentrated and the residue purified by preparative reverse phase HPLC to afford 4-(6,6-dimethyl-

5,6,7,8-tetrahydroquinazolin-4-yl)-7-(2-ethyl[1,3]thiazolo[5,4-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine as a amorphous solid after lyophillization of the combined pure fractions. ^{1}H NMR (400MHZ, CD_3OD): 8.75 (d, 1H), 8.37 (d, 1H), 8.34 (s, 1H), 7.65 (d, 1H), 7.54 (dd, 1H), 7.09 (d, 1H), 4.73 (s, 2H), 4.38 (m, 2H), 3.96 (m, 2H), 3.19 (q, 2H), 2.77 (tr, 2H), 2.47 (s, 2H), 1.66 (tr, 2H), 1.47 (tr, 3H), 0.89 (s, 6H); MS (EI) for $C_{27}H_{29}N_5SO$: 472 (MH^+).

[00155] Using analogous synthetic techniques and substituting with alternative starting reagents in steps 3 or 4 and conducting protecting group removal as required according to literature techniques appropriate for a given protecting group (see, for example: Greene and Wuts, Protective Groups in Organic Synthetic, Wiley-Interscience) the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00156] 4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(1-methylethyl)-3H-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 5 using 5-bromo-N-ethylbenzo[d]thiazol-2-amine in step 4. ^{1}H NMR (400MHZ, CD_3OD): 8.34 (s, 1H), 8.31 (d, 1H), 7.83 (d, 1H), 7.57 (d, 1H), 7.48 (dd, 1H), 7.07 (d, 1H), 4.71 (s, 2H), 4.36 (br, 2H), 3.96 (br, 2H), 3.51 (q, 2H), 2.78 (br, 2H), 2.47 (s, 2H), 1.66 (br, 2H), 1.30 (tr, 3H), 0.88 (s, 6H). MS (EI) for $C_{27}H_{30}N_6SO$: 488 (MH^+).

[00157] 5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoroethyl)-1*H*-benzimidazol-2-amine. Synthesized according to the method of example 5 using 4-chloro-5-(4-fluorobenzyl)-6-methylpyrimidine (reagent preparation 2) in step 3 and 5-bromo-N-(2,2,2-trifluoroethyl)-1H-benzo[d]imidazol-2-amine (reagent preparation 9) in step 4. ^{1}H NMR (400MHZ, DMSO-d_6): 11.05 (s, 1H), 8.50 (s, 1H), 7.44-7.34 (m, 3H), 7.26-7.19 (m, 1H), 7.12 (d, 4H), 7.02-6.95 (m, 2H), 6.86 (d, 1H), 4.47 (s, 2H), 4.25 (br s, 2H), 4.19 (m, 2H), 4.01 (br s, 2H), 2.17 (s, 3H); MS (EI) for $C_{30}H_{26}F_4N_6O$: 564 (MH^+).

[00158] 2-amino-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]benzenesulfonamide. Prepared according to the method of example 5 by using 2-amino-5-bromobenzenesulfonamide in step 4. ^{1}H NMR (400 MHz, methanol-d_4): 8.34 (s, 1H), 7.90 (d, 1H), 7.54 (dd, 1H), 7.45 (d, 1H), 7.39 (dd, 1H), 7.01 (d, 1H), 6.90 (d, 1H), 4.69 (s, 2H), 4.32 (m, 2H), 3.95 (m, 2H), 2.79 (t, 2H), 2.49 (s, 2H), 1.69 (t, 2H), 0.91 (s, 6H); MS (EI) for $C_{25}H_{29}N_5O_3S$: 480 (MH^+).

[00159] 7-(2-azetidin-1-yl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as the trifluoroacetate salt according to the method of example 5 by using 2-azetidin-1-yl-6-bromo-1-({[2-(trimethylsilyl)ethyl]oxy}methyl)-1*H*-imidazo[4,5-*b*]pyridine (reagent preparation 5) in step 4 followed by SEM deprotection. ^{1}H NMR (400 MHz, methanol-d_4): 8.50 (s, 1H), 8.30 (s, 1H), 7.93 (m, 1H), 7.69 (m, 1H), 7.53 (m, 1H), 7.08 (d, 1H), 5.14 (s, 2H), 4.47 (m, 2H), 4.43 (m, 4H), 4.30 (m, 2H), 2.85 (t, 2H), 2.64 (m, 2H), 2.59 (s, 2H), 1.93 (s, 3H), 1.70 (t, 2H), 0.94 (s, 6H); MS (EI) for $C_{28}H_{31}N_7O$: 482 (MH^+).

[00160] 6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-benzothiazol-2-amine. Prepared according to the method of example 5 by using 4-chloro-5-(4-fluorobenzyl)-6-methylpyrimidine (reagent preparation 2) in step 3 and N-(6-bromobenzo[d]thiazol-2-yl)acetamide (Journal of the Indian Chemical Society 1958, 35, 807-10) in step 4 followed by acetate group deprotection. ^{1}H NMR (400 MHz, DMSO-d_6): 8.49 (s, 1H), 7.67 (s, 1H), 7.54 (s, 2H), 7.44 (dd, 1H), 7.35 (d, 1H), 7.28 (dd, 1H), 7.11 (d, 4H), 6.97 (d, 1H), 6.79 (s, 1H), 4.44 (s, 2H), 4.26 (m, 2H), 3.96 (s, 2H), 3.75 (m, 2H), 2.13 (s, 3H); MS (EI) for $C_{28}H_{24}FN_5OS$: 498 (MH^+).

[00161] 2,2,2-trifluoro-N-[6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)imidazo[1,2-*a*]pyrimidin-2-yl]acetamide. Synthesized according to the method of example 5 using 4-chloro-5-(4-fluorobenzyl)-6-methylpyrimidine (reagent preparation 2) in step 3 and N-(6-bromoimidazo[1,2-*a*]pyrimidin-2-yl)-2,2,2-trifluoroacetamide (Synthesis 1999, 12, 2124-2130) in step 4. ^{1}H NMR (400 DMSO-D_6): 9.16 (br, 1H), 8.72 (br, 1H), 8.49 (s, 1H), 8.21 (s, 1H), 7.55 (dd, 1H), 7.11 to 7.05 (m, 5H), 7.02 (br, 1H), 4.55 (s, 2H), 4.30 (m, 2H), 3.96 (s, 2H), 3.77 (m, 2H), 2.17 (s, 3H), MS (EI) for $C_{29}H_{23}F_4N_7O_2$: 588 (MH^+).

[00162] N-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl][1,3]thiazolo[5,4-*b*]pyridin-2-yl}acetamide. Prepared according to the method of example 5 by using *N*-(6-bromo[1,3]thiazolo[5,4-*b*]pyridin-2-yl)acetamide synthesized according to the method of Journal of Heterocyclic Chemistry (200), 40(2), 621-628 in step 4. MS (EI) for $C_{27}H_{28}N_6O_2S$ 501 (MH^+).

[00163] 2-amino-N-(2-amino-2-methylpropyl)-5-[4-(6,6,8-trimethyl-5,6-dihydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-3-sulfonamide. Prepared as the acetate salt according to the method of example 5 by 4-chloro-6,6,8-trimethyl-5,6-dihydroquinazoline (reagent preparation 3) in step 3 and 2-

amino-*N*-(2-amino-2-methylpropyl)-5-bromopyridine-3-sulfonamide (reagent preparation 4) in step 4. ^{1}H NMR (400 MHz, d_6-DMSO): 8.49 (d, 1H), 8.47 (s, 1H), 8.04 (d, 1H), 7.55 (d, 1H), 7.44 (dd, 1H), 7.02 (d, 1H), 6.74 (brs, 2H), 5.98 (d, 1H), 4.60 (brs, 2H), 4.31 (m, 2H), 3.82 (m, 2H), 2.69 (s, 2H), 2.62 (s, 2H), 1.97 (d, 3H), 0.95 (s, 6H), 0.92 (s, 6H). MS (EI) for $C_{29}H_{37}N_7O_3S$ 564 (MH^+).

[00164] 2-chloro-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-amine. Prepared according to the method of example 5 by using 5-bromo-2-chloropyridin-3-amine in step 4. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 7.86 (d, 1H), 7.59 (d, 1H), 7.42 (dd, 1H), 7.33 (d, 1H), 7.04 (d, 1H), 5.65 (s, 2H), 4.64 (s, 2H), 4.38-4.29 (m, 2H), 3.88-3.80 (m, 2H), 2.71 (t, 2H), 2.41 (s, 2H), 1.59 (t, 2H), 0.84 (s, 6H); MS (EI) for $C_{24}H_{26}ClN_5O$: 436 (MH^+).

[00165] 3-{2-chloro-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-yl}-1,1-dimethylurea. Prepared according to the method of example 5 by using 5-bromo-2-chloropyridin-3-amine in step 4 followed by treatment dimethylcarbamoyl chloride according to the general method described in WO87/00840. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.61 (br s, 1H), 8.45 (d, 1H), 8.30 (d, 1H), 8.07 (s, 1H), 7.75 (d, 1H), 7.56 (dd, 1H), 7.04 (d, 1H), 4.99 (s, 2H), 4.49-4.42 (m, 2H), 4.15-4.07 (m, 2H), 2.98 (s, 6H), 2.75 (s, 1H), 2.51 (s, 2H), 1.58 (t, 2H), 0.86 (s, 6H); MS (EI) for $C_{27}H_{31}ClN_6O_2$: 507 (MH^+).

[00166] N-{2-azetidin-1-yl-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-yl}methanesulfonamide. Prepared according to the method of example 5 by using N-(2-(azetidin-1-yl)-5-bromopyridin-3-yl)methanesulfonamide (reagent preparation 7) in step 4. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.20 (br s, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 7.39 (dd, 1H), 7.00 (d, 1H), 4.62 (s, 2H), 4.34-4.25 (m, 2H), 4.12 (t, 4H), 3.87-3.79 (m, 2H), 3.01 (br s, 3H), 2.71 (t, 2H), 2.44 (s, 2H), 2.26-2.20 (m, 2H), 1.60 (t, 2H), 0.85 (s, 6H); MS (EI) for $C_{28}H_{34}N_6O_3S$: 535 (MH^+).

[00167] N-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-morpholin-4-ylpyridin-3-yl}methanesulfonamide. Prepared according to the method of example 5 by using N-(5-bromo-2-morpholinopyridin-3-yl)methanesulfonamide (reagent preparation 7) in step 4. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.03 (br s, 1H), 8.40 (s, 1H), 8.36 (s, 1H), 7.78 (d, 1H), 7.60 (d, 1H), 7.46 (dd, 1H), 7.04 (d, 1H), 4.64 (s, 2H), 4.36-4.29 (m, 2H), 3.88-3.81 (m, 2H), 3.80-3.71 (m, 4H), 3.26-

3.19 (m, 4H), 3.17 (s, 3H), 2.71 (t, 2H), 2.44 (s, 2H), 1.59 (t, 2H), 0.85 (s, 6H); MS (EI) for $C_{29}H_{36}N_6O_4S$: 565 (MH^+).

[00168] N-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-[(1-methylethyl)oxy]pyridin-3-yl}methanesulfonamide. Prepared according to the method of example 5 by using N-(5-bromo-2-isopropoxypyridin-3-yl)methanesulfonamide (reagent preparation 7) in step 4. ^{1}H NMR (400 MHz, DMSO-d6) δ 9.19 (br s, 1H), 8.36 (s, 1H), 8.25 (d, 1H), 7.80 (d, 1H), 7.58 (d, 1H), 7.45 (dd, 1H), 7.03 (d, 1H), 5.38-5.27 (m, 1H), 4.63 (s, 2H), 4.36-4.28 (m, 2H), 3.87-3.78 (m, 2H), 3.05 (s, 3H), 2.71 (t, 2H), 2.44 (s, 2H), 1.60 (t, 2H), 1.34 (d, 6H), 0.85 (s, 6H); MS (EI) for $C_{28}H_{35}N_5O_4S$: 538 (MH^+).

[00169] N-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-hydroxypyridin-3-yl}methanesulfonamide. Prepared according to the method of example 5 by using N-(2-(benzyloxy)-5-bromopyridin-3-yl)methanesulfonamide (reagent preparation 7) in step 4 followed by benzyl deprotection. ^{1}H NMR (400 MHz, DMSO-d6) δ 12.23 (br s, 1H), 8.87 (br s, 1H), 8.35 (s, 1H), 7.65 (d, 1H), 7.51-7.43 (m, 2H), 7.35 (dd, 1H), 6.99 (d, 1H), 4.61 (s, 2H), 4.33-4.26 (m, 2H), 3.87-3.79 (m, 2H), 3.11 (s, 3H), 2.71 (t, 2H), 2.42 (s, 2H), 1.60 (t, 2H), 0.85 (s, 6H); MS (EI) for $C_{25}H_{29}N_5O_4S$: 496 (MH^+).

[00170] 6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-indazol-3-amine. Prepared according to example 5 using tert-butyl 3-(bis(tert-butoxycarbonyl)amino)-6-bromo-1H-indazole-1-carboxylate (reagent preparation 8) in step 4 followed by BOC deprotection. ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.45 (s, 1H), 8.49 (s, 1H), 7.73 (d, 1H), 7.48 (dd, 1H), 7.26 (s, 1H), 7.12 (d, 4H), 7.01 (d, 1H), 6.97 (dd, 1H), 6.92 (d, 1H), 5.39 (s, 2H), 4.49 (s, 2H), 4.28 (t, 2H), 3.99 (s, 2H), 3.77 (t, 2H), 2.16 (s, 3H); MS (ES) for $C_{28}H_{25}FN_6O$: 481.2 (MH^+).

Example 6: 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-2-(methyloxy)aniline

[00171] STEP 1: 1,1-Dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (reagent preparation 13) (5.0 g, 20.1 mmol), bis(pinacolato)diboron (5.6 g, 22.1 mmol), potassium acetate (5.9 g, 60.2 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (440 mg, 0.62 mmol) were heated in DMSO (5 mL) solution at 80°C for 1.5 h. The mixture was then cooled to room temperature and diluted with an excess of ethyl acetate and filtered through a bed of

celite. The filtrate was partitioned with 1M aqueous hydrochloric acid and the organic phase washed with brine and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated and the residue purified by silica chromatography using 4:1 hexanes:ethyl acetate as eluent to give tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzoxazepine-4(5H)-carboxylate (7.6g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (s, 0.4H), 7.67 (s, 1H), 7.65 (s, 0.6H), 7.04-6.98 (m, 1H), 4.54 (s, 0.7H), 4.43 (s, 1.3H), 4.09-4.01 (m, 2H), 3.79 (dd, 2H), 1.40 (br s, 9H), 1.26 (s, 12H). MS (EI) for $C_{20}H_{30}BNO_5$: 376 (MH^+).

[00172] STEP 2: tert-Butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydrobenzoxazepine-4(5H)-carboxylate (500 mg, 2.33 mmol), 4-bromo-2-methoxyaniline (296 mg, 1.47 mmol), potassium carbonate (737 mg, 5.34 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (97.5 mg, 0.13 mmol) were heated at 110°C in DME (7 mL) and water (1 mL) over 48 h. The mixture was then cooled to room temperature and diluted with an excess of ethyl acetate and filtered through a bed of celite. The filtrate was partitioned with water and the organic phase washed with brine and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated and the residue purified by silica chromatography using 85:15 hexanes:ethyl acetate as eluent to give 1,1-dimethylethyl 7-[4-amino-3-(methyloxy)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (198 mg, 40%). MS (EI) $C_{21}H_{26}N_2O_4$: 371 (MH^+).

[00173] STEP 3: 1,1-dimethylethyl 7-[4-amino-3-(methyloxy)phenyl]-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (198 mg, 0.53 mmol) was taken into methanol (5 mL) and 4M hydrogen chloride in dioxane (2.5 mL) and the mixture was heated to reflux then cooled to room temperature. The mixture was then concentrated and dried in vacuo to give 2-(methyloxy)-4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)aniline hydrochloride salt (150 mg, 100%). MS (EI) $C_{16}H_{18}N_2O_2$: 271 (MH^+).

[00174] STEP 4: 2-(methyloxy)-4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)aniline hydrochloride salt (150 mg, 0.55 mmol), 4-chloro-5-(4-fluorobenzyl)-6-methylpyrimidine (reagent preparation 2) (119 mg, 0.5 mmol) in 1-methyl-2-pyrrolidinone (3 mL) was added DIPEA (0.35 mL, 2.01 mmol.) then heated at 120°C for 5 h in a microwave reactor. On cooling to room temperature the mixture was partitioned with ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate then filtered and

concentrated. The residue was purified by preparative reverse phase HPLC to give 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-2-(methyloxy)aniline (7.1 mg). ^{1}H NMR (400 MHz, d_6-DMSO): 8.49 (s, 1H), 7.37 (d, 1H), 7.10 (s, 2H), 7.08 (s, 2H), 6.97 (d, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 6.76 (d, 1H), 6.67 (d, 1H), 4.84 (s, 2H), 4.45 (s, 2H), 4.24 (br s, 2H), 3.98 (s, 2H), 3.82 (s, 3H), 3.75 (br s, 2H), 3.14 (s, 3H).

EXAMPLE 7: 7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00175] STEP 1: A mixture of isobutyl 6-bromo-2-methyl-1H-imidazo[4,5-*b*]pyridine-1-carboxylate (2.2 g, 7.1 mmol) (reagent preparation 14), (4-{[(1,1-dimethylethyl)-oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (2.7 g, 9.2 mmol, example 5, step 1), potassium acetate (2.8 g, 28.3 mmol), and dichloro[1,1-bis(diphenyl-phosphino]ferrocenepalladium (II) dichloromethane adduct (0.78g, 1.1 mmol) in dioxane (50 ml) was stirred at 95 °C under nitrogen for 29h. The mixture was cooled to room temperature, filtered through celite, and the filter cake was washed with ethyl acetate (100 ml). The filtrate was concentrated and purified by column chromatography on silica (0-100% ethyl acetate in hexanes) to give 1,1-dimethylethyl 7-(2-methyl-1-{[(2-methylpropyl) oxy]carbonyl}-1H-imidazo[4,5-*b*]pyridine-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)carboxylate (1.1g, 33% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 8.74 (d, 1H), 8.39 (s, 1H), 7.47 (d, 1H), 7.43 (s, 1H), 7.14 (d, 1H), 4.50 (s, 2H), 4.34 (d, 2H), 4.12 (m, 2H), 3.88 (m, 2H), 2.96 (s, 3H), 2.22 (m, 1H), 1.42 (s, 9H), 1.21 (d, 6H); MS (EI) for $C_{26}H_{32}N_4O_5$: 481 (MH^+).

[00176] STEP 2: A mixture of 1,1-dimethylethyl 7-(2-methyl-1-{[(2-methylpropyl)-oxy]carbonyl}-1H-imidazo[4,5-*b*]pyridine-6-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)carboxylate (1.1 g, 2.3 mmol) in methanol (6 ml) and 4N hydrochloric acid in dioxane (12 ml) was stirred at room temperature for 1 h and then concentrated. The resulting solid was triturated with ethyl acetate to afford the hydrochloride salt of 2-methylpropyl 2-methyl-6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-*b*]pyridine-1-carboxylate (0.92 g, 91% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): 9.78 (s, 1H), 8.79 (d, 1H), 8.42 (d, 1H), 7.88 (d, 1H), 7.70 (dd, 1H), 7.24 (d, 1H), 4.42 (brs, 2H), 4.32 (d, 2H), 4.27 (brs, 2H), 3.50 (brs, 2H), 2.82 (s, 3H), 2.19 (m, 1H), 1.06 (d, 6H); MS (EI) for $C_{21}H_{24}N_4O_3$: 381 (MH^+).

[00177] STEP 3: To a solution of 2-methylpropyl 2-methyl-6-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1H-imidazo[4,5-*b*]pyridine-1-carboxylate (0.065 g, 0.14 mmol) and DIPEA (0.2 mL, 1.1 mmol) in NMP (1 mL) was added 4-chloro-6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazoline (reagent preparation 3) (0.037 g, 0.16 mmol) and the resulting mixture was was heated (120 °C) for twelve hours. Methanol (1 mL) and potassium carbonate (0.020 g, 0.14 mmol) were then added and the resulting slurry was heated (50 °C) for 1 hour. The reaction mixture was adjusted to neutral pH by addition of aqueous acetic acid and the solution obtained was purified by preparative reverse phase HPLC. Combined pure fractions were acidified by addition of aqueous hydrochloric acid and subsequent lyophilization provided the 7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine hydrochloride salt (0.055 g, 71% yield) as a white powder. ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (d, 1H), 8.60 (s, 1H), 8.39 (d, 1H), 7.77 (d, 1H), 7.63 (dd, 1H), 7.12 (d, 1H), 5.24 (d, 1H), 5.18 (d, 1H), 4.69 (m, 1H), 4.61 (m, 1H), 4.42 (d, 1H), 4.07 (d, 1H), 3.09 (m, 2H), 2.90 (s, 3H), 2.88 (m, 2H), 2.46 (m, 1H), 2.23 (s, 1H), 1.89 (m, 1H): MS (ES) for $C_{25}H_{23}F_3N_6O$: 481 (MH^+).

[00178] Using analogous synthetic techniques and substituting with alternative starting reagents in step 3 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00179] 4-(2,6-dimethylpyrimidin-4-yl)-7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the method of example 7 by using 4-chloro-2,6-dimethylpyrimidine in step 3. ^{1}H NMR (400 MHz, methanol-d_4): 8.52 (d, 1H), 8.05 (d, 1H), 7.77 (d, 1H), 7.48 (d, 1H), 7.48 (dd, 1H), 7.09 (d, 1H), 6.62 (br s, H), 4.28-4.14 (m, 4H), 2.64 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 1.94 (s, 3H); MS (EI) for $C_{22}H_{22}N_6O$: 387 (MH^+).

[00180] 7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-methyl-5-(1-methylpropyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 7 by using 4-chloro-6-methylpyrimidine in step 3. ^{1}H NMR (400 MHz, methanol-d_4): 8.52 (s, 1H), 8.06 (s, 1H), 8.01 (d, 1H), 7.76 (d, 1H), 7.49 (dd, 1H), 7.10 (d, 1H), 6.74 (d, H), 4.24 (br. s, 2H), 4.19 (m, 2H), 2.64 (s, 3H), 2.42 (s, 3H); MS (EI) for $C_{21}H_{20}N_6O$: 373 (MH^+).

[00181] 7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-methyl-5-(1-methylpropyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according

to the method of example 7 by using 5-sec-butyl-4-chloro-6-methylpyrimidine (reagent preparation 2) in step 3. ^{1}H NMR (400 MHz, methanol-d_4): 8.51 (s, 1H), 8.38 (s, 1H), 8.04 (s, 1H), 7.53 (m, 2H), 7.11 (d, 1H), 4.66 (d, 1H), 4.45 (m, 2H), 4.26 (m, 1H), 3.87 (m, 1H), 3.72 (m, 1H), 3.09 (m, 1H), 2.64 (s, 3H), 2.51 (s, 3H), 1.63 (m, 2H), 1.50 (d, 3H), 0.63 (t, 3H); MS (EI) for $C_{25}H_{28}N_6O$: 429 (MH^+).

[00182] 4-[6,6-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4-yl]-7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 7 by using 4-chloro-6,6-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazoline (reagent preparation 12) in step 3. ^{1}H NMR (400 MHz, methanol-d_4): 8.52 (s, 1H), 8.05 (s, 1H), 7.59 (d, 1H), 7.48 (dd, 1H), 7.06 (d, 1H), 4.78 (s, 2H), 4.37 m, 2H), 3.99 (m, 2H), 2.68 (t, 2H), 2.64 (s, 3H), 2.45 (s, 2H), 2.32 (s, 3H), 1.63 (t, 2H), 0.92 (s, 6H); MS (EI) for $C_{27}H_{30}N_6OS$: 487 (MH^+).

[00183] 4-[6-(1,1-dimethylethyl)-2-methylpyrimidin-4-yl]-7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the method of example 7 by using 4-chloro-6-(1,1-dimethylethyl)-2-methylpyrimidine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.56 (s, 1H), 8.06 (s, 1H), 7.92 (s, 1H), 7.56 (d, 1H), 7.04 (d, 1H), 6.70 (brs, 1H), 4.83 (s, 2H), 4.11 (brs, 4H), 2.48 (s, 3H), 2.33 (s, 3H), 1.20 (s, 9H). MS (EI) for $C_{25}H_{28}N_6O$ 429 (MH^+).

[00184] 7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-(2-methyl-6-propylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the method of example 7 by using 4-chloro-2-methyl-6-propylpyrimidine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.54 (s, 1H), 8.04 (s, 1H), 7.98 (s, 1H), 7.51 (d, 1H), 7.03 (d, 1H), 6.72 (brs, 1H), 4.81 (s, 2H), 4.18 (s, 4H), 2.54 (s, 3H), 2.42 (m, 2H), 2.30 (s, 3H), 1.58 (m, 2H), 0.79 (t, 3H). MS (EI) for $C_{24}H_{26}N_6O$ 415 (MH^+).

[00185] 7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-4-[2-methyl-6-(1-methylethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the method of example 7 by using 4-chloro-2-methyl-6-(1-methylethyl)pyrimidine in step 3. ^{1}H NMR (400 MHz, d_6-DMSO): 8.58 (s, 1H), 8.03 (brs, 1H), 7.96 (brs, 1H), 7.56 (dd, 1H), 7.02 (d, 1H), 6.64 (brs, 1H), 4.82 (s, 2H), 4.14 (brs, 4H), 2.74 (m, 1H), 2.48 (s, 3H), 2.32 (s, 3H), 1.08 (d, 6H). MS (EI) for $C_{24}H_{26}N_6O$ 415 (MH^+).

[00186] 6,6-dimethyl-4-[7-(2-methyl-3H-imidazo[4,5-*b*]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5H)-yl]-5,6,7,8-tetrahydro-5,8-ethanoquinazoline. Prepared according to

the method of example 7 by using 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydro-5,8-ethanoquinazoline (reagent preparation 3) in step 3. ^{1}H NMR (400 MHz, d_4-MeOH): 8.18 (s, 1H), 8.03 (s, 1H), 7.74 (s, 1H), 7.23 (s, 1H), 7.18 (dd, 1H), 6.74 (d, 1H), 4.70 (d, 1H), 4.43 (d, 1H), 4.10 (m, 1H), 4.09 (m, 1H), 3.87 (m, 1H), 3.55 (m, 1H), 2.67 (s, 1H), 2.57 (s, 1H), 2.31 (s, 3H), 1.90 (m, 1H), 1.58 (s, 6H), 1.49 (m, 1H), 1.19 (m, 3H), 0/84 (m, 1H). MS (EI) for $C_{28}H_{30}N_6O$ 467 (MH^+).

[00187] 4-(6-furan-2-yl-2-methylpyrimidin-4-yl)-7-(2-methyl-1H-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. The hydrochloride salt was prepared according to the method of example 7 using 4-chloro-6-(furan-2-yl)-2-methylpyrimidine in step 3. ^{1}H NMR (400 MHz, D_2O) δ 8.18 (s, 1H), 7.84 (s, 1H), 7.65 – 7.55 (m, 1H), 7.54 – 7.26 (m, 1H), 7.23 – 7.12 (m, 1H), 7.08 – 6.91 (m, 1H), 6.83 – 6.67 (m, 2H), 6.58 – 6.40 (m, 1H), 4.71 (d, 2H), 4.15 (d, 2H), 3.98 (d, 2H), 2.62 (s, 3H), 2.34 (d, 3H); MS (ES) for $C_{25}H_{22}N_6O_2$: 427.2 (MH^+).

Example 8: 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00188] STEP 1: A solution of 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (example 6, step 1) (3.0 g, 8.00 mmol) in dichloromethane (90 mL) and trifluoroacetic acid (10 mL) was heated to reflux for 1 h, and then cooled to room temperature. The reaction mixture was concentrated and the residue was azeotroped with toluene (100 mL) to give 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine trifluoroacetate salt (2.9 g, quantitative yield). MS (EI) for $C_{15}H_{22}BNO_3$: 276 (MH^+).

[00189] STEP 2: A mixture of 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1,4-benzoxazepine trifluoroacetate salt (2.9 g, 8.00 mmol, 4-chloro-5-[(4-fluorophenyl)methyl]-6-methylpyrimidine (reagent preparation 2) (1.9 g, 8.00 mmol) and N,N-diisopropylethylamine (7.0 mL, 40.0 mmol) in N-methyl-2-pyrrolidone (10 mL) was reacted in a microwave apparatus (250 W) for 2 h at 150 °C. After cooling to room temperature the reaction mixture was partitioned between ethyl acetate (500 mL) and brine (100 mL). The organic layer was separated, washed with brine (100 mL), dried over sodium sulfate then filtered and concentrated. Column chromatography of the residue on silica (gradient 20 to 40% ethyl acetate in hexane) gave 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (1.6 g, 42% yield). ^{1}H NMR

(400 MHz, DMSO-D_6): 8.58 (s, 1H), 7.62 (dd, 1H), 7.08 (m, 4H), 7.02 (d, 1H), 6.96 (d, 1H), 4.36 (s, 2H), 4.30 (m, 2H), 3.92 (s, 2H), 3.84 (m, 2H), 2.26 (s, 3H), 1.36 (s, 12H); MS (EI) for $C_{27}H_{31}BFN_3O_3$: 476 (MH^+).

[00190] STEP 3: To a solution of 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (46 mg, 0.096 mmol) and 5-bromo-2-methyl-1,3-thiazole (17 mg, 0.096 mmol) in dioxane (5 mL) was added potassium carbonate (66 mg, 0.48 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) dichloromethane adduct (8 mg, 0.0096 mmol). The reaction mixture was stirred at 100 °C for 20 h, and then cooled to room temperature. The reaction mixture was concentrated, and then partitioned between ethyl acetate (100 mL) and water (50 mL). The layers were separated and the organic layer was washed with brine, dried over magnesium sulfate then filtered and concentrated. The residue was taken up in a minimum of acetonitrile and purified by preparative reverse phase HPLC to afford 4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine (18 mg) as a white powder. ^{1}H NMR (400 MHz, DMSO-D_6): 8.47 (s, 1H), 7.77 (s, 1H), 7.41 (dd, 1H), 7.19-7.05 (m, 4H), 6.96 (d, 1H), 6.83 (d, 1H), 4.47 (s, 2H), 4.27 (t, 2H), 3.93 (s, 2H), 3.74 (t, 2H), 2.67 (s, 3H), 2.14 (s, 3H); MS (EI) for $C_{25}H_{23}FN_4OS$: 446 (M^+).

[00191] Using analogous synthetic techniques and substituting with alternative starting reagents in step 3 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00192] 5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)pyridin-2-amine. Synthesized according to the method of example 8 using 2-amino-5-bromopyridine in step 3. ^{1}H NMR (400 MHz, DMSO-d_6): 8.71 (s, 1H), 8.16 (s, 2H), 8.13 (s, 1H), 7.48 (dd, 1H), 7.17 (d, 4H), 7.03 (dd, 1H), 4.82 (s, 2H), 4.31-4.33 (m, 2H), 4.01 (s, 2H), 3.93-3.96 (m, 2H), 2.24 (s, 3H); MS (EI) for $C_{26}H_{24}FN_5O$: 442 (MH^+).

Example 9: N-(2-fluoroethyl)-4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide

[00193] STEP 1: A suspension of {4-[(methyloxy)carbonyl]phenyl}boronic acid (0.36 g, 2.0 mmol), 1,1-dimethylethyl 7-bromo-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (reagent preparation 13) (0.66 g, 2.0 mmol), [1,1'-

Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (70.0 mg, 0.10 mmol), and tripotassium phosphate (1.30 g, 12.0 mmol) in dioxane (20 mL) was refluxed for 3 h, and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (50 mL) and water (80 mL), the organic layer was washed with brine (40 mL), dried over sodium sulfate then filtered and concentrated. Column chromatography on silica (ethyl acetate:hexanes 1:4) gave 1,1-dimethylethyl 7-{4-[(methyloxy)carbonyl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (0.47 g, 60% yield). ^{1}H NMR (400MHZ, DMSO-D_6): 8.11 (m, 2H), 7.63-7.52 (m, 2H), 7.43 (m, 2H), 7.10 (t, 1H), 4.57-4.43 (br, 2H), 4.08 (m, 2H), 3.82 (m, 2H), 1.40 (s, 9H); MS (EI) for $C_{22}H_{25}NO_5$: 469 (MH^+).

[00194] STEP 2: To a solution of 1,1-dimethylethyl 7-{4-[(methyloxy)carbonyl]phenyl}-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (1.90 g, 4.96 mmol) in dry methanol (10 mL) was added drop wise 4N hydrogen chloride in dioxane (10 mL) at room temperature. The reaction mixture was warmed to 55 °C for 60 min, at which time it was cooled to room temperature. The precipitated product was isolated by filtration, washed with diethyl ether, and dried to yield methyl 4-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate hydrochloride (1.53 g, 97% yield) as a white solid.

[00195] STEP 3: A suspension of -(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate hydrochloride (1.30 g, 4.14 mmol), 4-chloro-5-[(4-fluorophenyl)methyl]-6-methylpyrimidine (reagent preparation 2) (0.98 g, 4.14 mmol), and potassium carbonate (1.71 g, 12.4 mmol) in DMF (20 mL) was heated to 130 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (40 mL), and then washed with water (50 mL) and brine (20 mL). The organic layer was dried over sodium sulfate then filtered and concentrated. Column chromatography on silica (gradient 10 to 20% ethyl acetate in hexane) followed by recrystallization from 1:1 ethyl acetate and ether (40 mL) provided methyl 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate (1.05 g, 50% yield) as a white solid. ^{1}H NMR (400MHZ, DMSO-D_6): 8.48 (s, 1H), 8.01 (d, 2H), 7.62 (d, 2H), 7.56 (dd, 1H), 7.11 (d, 4H), 7.02 (d, 1H), 6.91 (d, 1H), 4.52 (s, 2H), 4.32 (m, 2H), 3.95 (s, 2H), 3.90 (s, 3H), 3.76 (m, 2H), 2.13 (s, 3H); MS (EI) for $C_{29}H_{26}FN_3O_3$: 484 (MH^+).

[00196] STEP 4: To a solution of methyl 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate (1.0 g, 2.0

mmol) in 1:1 methanol and THF (10 mL) was added drop wise 2N aqueous potassium hydroxide (8 mL). The reaction mixture was stirred at room temperature for 18 h and then refluxed for 90 min. The mixture was cooled by adding ice, and the pH adjusted to 6 with 2N aqueous hydrochloric acid. The precipitate was filtered, washed with water, azeotroped with toluene (20 mL), and dried to afford 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoic acid (0.97 g, 100% yield).

[00197] STEP 5: To a solution of 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoic acid (0.50 g, 1.07 mmol) and DMF (20 μL) in chloroform (15 mL) was added drop wise oxalyl chloride (0.35 mL, 4.0 mmol). The reaction mixture was refluxed for 15 min, and then concentrated to give 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoyl chloride as an oil.

[00198] STEP 6: STEP 6: To a solution of 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoyl chloride (0.06g, 0.12 mmol) and 2-fluoroethanamine hydrochloride (0.05 g, 0.50 mmol) in tetrahydrofuran (8 mL) at 0°C was added triethylamine (0.25 mL, 2.00 mmol) and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated and the residue was partitioned between water (10 mL) and ethyl acetate (30 mL). The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate (10 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting residue was purified by gradient flash chromatography (10% to 100% ethyl acetate in hexane). The fractions were collected and the resulting solution was treated with 4N hydrogen chloride in 1,4-dioxane (0.5 mL) then concentrated and dried to give N-(2-fluoroethyl)-4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide hydrochloride (42.6 mg, 63%). ^{1}H NMR (400 MHz, d_6-DMSO); 8.81 (m, 2H), 7.97 (d, 2H), 7.67 (d, 1H), 7.22 (m, 4H), 7.02 (d, 1H), 4.96 (s, 2H), 4.64 (t, 1H), 4.57 (t, 1H), 4.37 (br s, 2H), 4.05 (s, 2H), 3.98 (br s, 2H), 3.60 (br m, 2H), 2.25 (s, 3H); MS (EI) for $C_{30}H_{28}FN_4O_2$: 515 (MH^+).

[00199] Using analogous synthetic techniques and substituting with alternative starting reagents in step 6 and conducting protecting group removal as required according to literature techniques appropriate for a given protecting group (see, for example: Greene

and Wuts, Protective Groups in Organic Synthetic, Wiley-Interscience) the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00200] 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-N-(2,2,2-trifluoro-1-methylethyl)benzamide. Synthesized according to the method of example 9 using 2,2,2-trifluoro-1-methylethylamine in step 6. ^{1}H NMR (400 MHz, d_6-DMSO): 8.89 (d, 1H), 8.77 (s, 1H), 7.96 (d, 2H), 7.67 (d, 2H), 7.56 (d, 1H), 7.25 (br s, 1H), 7.16 (m, 4H), 6.98 (d, 2H), 4.89 (m, 3H), 4.33 (br s, 2H), 4.02 (s, 2H), 3.98 (br s, 2H), 2.24 (s, 3H), 1.36 (d, 3H); MS (EI) for $C_{31}H_{26}F_4N_4O_2$: 565 (MH^+).

[00201] 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-N-(2,2,2-trifluoroethyl)benzamide. Synthesized according to the method of example 9 using 2,2,2-trifluoroethylamine in step 6. ^{1}H NMR (400 MHz, d_6-DMSO): 9.18 (t, 1H), 8.80 (s, 1H), 8.02 (d, 2H), 7.71 (d, 2H), 7.60 (d, 1H), 7.19 (m,4H), 7.01 (d, 1H), 4.96 (s, 2H), 4.37 (br s, 2H), 4.14 (m, 2H), 4.05 (s, 2H), 4.01 (br s, 2H), 2.25 (s, 3H); MS (EI) for $C_{30}H_{26}F_4N_4O_2$: 551 (MH^+).

[00202] 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-N-pyrrolidin-3-ylbenzamide. Synthesized according to the method of example 9 using racemic N1-BOC-pyrrolidin-3-ylamine in step 6 followed by BOC group deprotection. ^{1}H NMR (400 MHz, d_6-DMSO): 9.46 (br s, 1H), 9.25 (br s, 1H), 8.04 (d, 2H), 7.68 (d, 2H), 7.57 (d, 1H), 7.38 (s, 1H), 7.21 (m 5H), 7.11 (s, 1H), 7.03 (d, 1H), 4.92 (s, 2H), 4.37 (br s, 2H), 4.08 (s, 2H), 4.02 (br s, 2H), 3.68 (m, 1H), 3.23 (m, 1H), 2.28 (s, 3H), 2.22 (m, 1H), 2.04 (m, 1H); MS (EI) for $C_{32}H_{32}FN_5O_2$: 538 (MH^+).

[00203] 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-N-[(3R)-pyrrolidin-3-yl]benzamide. Synthesized according to the method of example 9 using (3R)-N1-BOC-pyrrolidin-3-ylamine in step 6 followed by BOC group deprotection. ^{1}H NMR (400 MHz, d_6-DMSO): 9.42 (br s, 1H), 9.19 (br s, 1H), 8.01 (d, 2H), 7.66 (d, 2H), 7.57 (d, 1H), 7.33 (s, 1H), 7.21 (m, 4H), 7.07 (s, 1H), 7.00 (d, 1H), 4.93 (s, 2H), 4.60 (m, 1H), 4.35 (br s, 2H), 4.04 (s, 2H), 3.99 (br s, 2H), 3.68 (br m, 1H), 2.26 (s, 3H), 2.22 (q, 1H), 2.04 (m, 1H); MS (EI) for $C_{32}H_{32}FN_5O_2$: 538 (MH^+).

Example 10: 4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-{2-[(methyloxy)methyl]-3H-imidazo[4,5-*b*]pyridin-6-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine

[00204] STEP 1: A suspension of 5-bromo-3-nitropyridin-2-amine (4.84 g, 22.2 mmol) , (4-{[(1,1-dimethylethyl)oxy]carbonyl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)boronic acid (6.51 g, 22.2 mmol) (example 5, step 1), dichloro[1,1-bis(diphenyl)-phosphino]ferrocenepalladium (II) dichloromethane adduct (1.60 g, 10 mol %) in dioxane (75 mL) and water (15 mL) was degassed with nitrogen, and then cesium carbonate (14.46 g, 44.4 mmol) was added. The reaction mixture was stirred at 90 °C overnight. The mixture was cooled to room temperature, water (150 ml) was added and stirred for 30 min to give a precipitate. The product 1,1-dimethylethyl -7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5H)-carboxylate (8.1 g, 94% yield) was collected by filtration, dried under vacuum. MS (EI) for $C_{19}H_{22}N_4O_5$: 387.1(MH^+).

[00205] STEP 2: A mixture of 1,1-dimethylethyl 7-(6-amino-5-nitropyridin-3-yl)-2,3-dihydro-1,4-benzoxazepine-4(5*H*)-carboxylate (3.5 g, 9.1 mmol) in methanol (75 mL) and 4N hydrogen chloride in dioxane (11 mL) was stirred at 50 °C for 1.5 h and then concentrated. The resulting residue was triturated with a 10% methanol in diethyl ether solution (50 mL) to provide 3-nitro-5-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)pyridin-2-amine dihydrochloride (3.1 g, 95%) as a red solid. ^{1}H NMR (400 MHz, d_6-DMSO) δ 9.76 (bs, 2H), 8.80 (d, 1H), 8.60 (s, 1H), 7.90 (s, 1H), 7.73 (dd, 1H), 7.16 (d, 1H), 4.39 (bs, 2H), 4.25 (bs, 2H), 3.48 (bs, 2H); MS (EI) for $C_{14}H_{14}N_4O_3$: 287 (MH^+).

[00206] STEP 3: A solution of 3-nitro-5-(2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)pyridin-2-amine dihydrochloride (540 mg, 1.50 mmol), 4-chloro-6,6-dimethyl-5,6,7,8-tetrahydroquinazoline (270 mg, 1.37 mmol, reagent preparation 3), and diisopropylethylamine (970 mg, 7.49 mmol) in N-methylpyrrolidinone (3 mL) was stirred at 120 °C for 18 h. After cooling to room temperature ethyl acetate (100 mL) was added, the formed precipitate was filtered off, the organic filtrate was washed with saturated sodium bicarbonate (50 mL), water (2 x 50 mL), and brine (50 mL), dried over sodium sulfate, filtered and concentrated to afford crude 5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-3-nitropyridine-2-amine (0.5 g) as a brown solid which was used in the next step without further purification. MS (EI) for $C_{24}H_{26}N_6O_3$: 447 (MH^+).

[00207] STEP 4: A mixture of 5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-3-nitropyridine-2-amine (0.5 g, 1.37 mmol) and palladium on carbon (0.5 g, 50% water) in methanol (50 mL) was hydrogenated in a Parr apparatus at 40 psi for 90 min. The mixture was filtered through celite and concentrated. Column chromatography of the residue on silica (dichloromethane/methanol 9:1) provided 5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-2,3-diamine (174 mg, 30% yield over 2 steps) as a brown solid. MS (EI) for $C_{24}H_{28}N_6O$: 417 (MH^+).

[00208] STEP 5: To a solution of 5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-2,3-diamine (32 mg, 0.08 mmol) and (methyloxy)acetyl chloride (4 μL, 0.08 mmol) in tetrahydrofuran (2 mL) at 0°C was added triethylamine (12 μL, 0.08 mmol) and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, the residue was dissolved in acetic acid (1.0 mL) and heated to reflux for 1 hour. After cooling it to room temperature it was concentrated, dissolved in methanol and purified by reverse phase preparative HPLC (0.1% aqueous ammonium acetate-acetonitrile) to give 4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-{2-[(methyloxy)methyl]-3H-imidazo[4,5-*b*]pyridin-6-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine as acetate salt (4.4 mg, 12%). ^{1}H NMR (400 MHz, d_4-MeOH): 8.50 (s, 1H), 8.25 (s, 1H), 8.02 (s, 1H), 7.52 (d, 1H), 7.41 (dd, 1H), 7.01 (d, 1H), 4.67 (s, 2H), 4.65 (s, 2H), 4.28 (t, 2H), 3.87 (t, 2H), 3.41 (s, 3H), 2.70 (t, 2H), 2.40 (s, 2H), 1.59 (t, 2H), 0.80 (s, 6H). MS (EI) for $C_{27}H_{30}N_6O_2$: 471 (MH^+).

[00209] Using analogous synthetic techniques and substituting with alternative starting reagents in step 3 or 5 the following compounds of the invention were prepared. Alternative starting materials were obtained commercially unless otherwise indicated.

[00210] 7-(2-pyridin-2-yl-1*H*-benzimidazol-6-yl)-4-quinolin-4-yl-2,3,4,5-tetrahydro-1,4-benzoxazepine. Synthesized according to the method of example 10 using picolinic acid in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.78 (d, 1H), 8.69 (d, 1H), 8.37 (dd, 2H), 7.97 (br m, 5H), 7.65 (br m, 2H), 7.60 (br m, 3H), 7.02 (m, 2H), 5.30 (s, 2H), 4.62 (br s, 2H) 4.41 (br s, 2H); MS (EI) for $C_{30}H_{23}N_5O$: 470 (MH^+).

[00211] 7-(2-cyclopropyl-1H-benzimidazol-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as hydrochloride salt according to the method of example 10 by using cyclopropanecarbonyl

chloride in step 5. ^{1}H NMR (400 MHz, d_6-DMSO): 8.54 (s, 1H), 7.72 (dd, 2H), 7.59 (m, 2H), 7.52 (dd, 1H), 7.02 (d, 1H), 4.89 (brs, 2H), 4.40 (brs, 2H), 4.02 (brs, 2H), 2.76 (t, 2H), 2.50 (s, 2H), 1.59 (m, 3H), 1.24 (m, 4H), 0.82 (s, 6H). MS (EI) for $C_{29}H_{31}N_5O$: 466 (MH^+).

[00212] 4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(1-methylethyl)-3H-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the method of example 10 by using 1,1,1-trimethoxy-2-methylpropane in step 5. ^{1}H NMR (400 MHz, d_4-MeOH): 8.53 (s, 1H), 8.34 (s, 1H), 8.07 (s, 1H), 7.59 (s, 1H), 7.51 (dd, 1H), 7.10 (d, 1H), 4.73 (s, 2H), 4.57 (t, 2H), 3.97 (t, 2H), 3.20 (m, 1H), 2.80 (t, 2H), 2.48 (s, 2H), 1.68 (t, 2H), 1.46 (d, 6H), 0.88 (s, 6H). MS (EI) for $C_{28}H_{32}N_6O$: 469 (MH^+).

[00213] 4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(trifluoromethyl)-3H-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared as acetate salt according to the method of example 10 by using trifluoroacetic acid in step 5. ^{1}H NMR (400 MHz, d_4-MeOH): 8.67 (s, 1H), 8.36 (s, 1H), 8.23 (s, 1H), 7.68 (s, 1H), 7.59 (dd, 1H), 7.10 (d, 1H), 4.61 (s, 2H), 4.35 (t, 2H), 3.97 (t, 2H), 2.76 (t, 2H), 2.51 (s, 2H), 1.70 (t, 2H), 0.90 (s, 6H). MS (EI) for $C_{26}H_{25}F_3N_6O$: 495 (MH^+).

[00214] 7-(2-cyclobutyl-3H-imidazo[4,5-*b*]pyridin-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine. Prepared according to the method of example 10 by using cyclobutanecarbonyl chloride in step 5. ^{1}H NMR (400 MHz, d_4-MeOH): 8.52 (s, 1H), 8.36 (s, 1H), 8.07 (s, 1H), 7.59 (d, 1H), 7.48 (dd, 1H), 7.08 (d, 1H), 4.72 (s, 2H), 4.36 (t, 2H), 3.96 (t, 2H), 3.82 (m, 1H), 2.79 (t, 2H), 2.52 (m, 3H), 2.48 (s, 2H), 2.17 (m, 2H), 2.02 (m, 1H), 1.66 (t, 2H), 0.89 (s, 6H). MS (EI) for $C_{29}H_{32}N_6O$: 481 (MH^+).

Example 11

N-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl}methanesulfonamide.

[00215] STEP 1: A solution of 4-bromo-2-nitroaniline (0.19 g, 0.88 mmol), [4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]boronic acid (0.31 g, 0.88 mmol) and cesium carbonate (1.50 g, 4.5 mmol) in a mixture of tetrahydrofuran (20 mL) and water (5 mL) was degassed with nitrogen for 30 minutes and then dichloro[1,1-bis(diphenyl)phosphino]ferrocenepalladium (II) (0.06 g, 0.09 mmol) was added. The reaction mixture was stirred at 90 °C for 1 hour. It was cooled to

room temperature and partitioned between water (50 ml) and ethyl acetate (120 mL). The organic layer was separated, washed with water (50 mL) and brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude was purified by silica gel gradient chromatography (ethyl acetate to 10% methanol in ethyl acetate) to give 4-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-nitroaniline (0.36 g, 92%). MS (EI) for $C_{25}H_{27}N_5O_3$: 446.1(MH^+).

[00216] STEP 2: A solution of 4-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-nitroaniline (0. 36 g, 0.80 mmol) in a mixture of tetrahydrofuran (80 mL) and methanol (20 mL) in the presence of 5% palladium on carbon (50% water) was hydrogenated at atmospheric pressure for 16 hours. The mixture was filtered through a pad of Celite and concentrated. Silica gel gradient chromatography (ethyl acetate to 10% (10% ammonium hydroxide in methanol) in ethyl acetate) provided 4-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]benzene-1,2-diamine (0.32 g, 96%) as a brown oil. ^1H NMR (400 MHz, d_6-DMSO): 8.38 (s, 1H), 7.40 (s, 1H), 7.28 (d, 1H), 6.92 (d, 1H), 6.80 (s, 1H), 6.67 (d, 1H), 6.54 (d, 1H), 4.63 (brs, 2H), 4.58 (s, 2H), 4.25 (t, 2H), 3.81 (t, 2H), 3.15 (brs, 2H), 2.70 (t, 2H), 2.45 (s, 2H), 1.59 (t, 2H), 0.86 (s, 6H). MS (EI) for $C_{25}H_{29}N_5O$: 416 (MH^+).

[00217] STEP 3: To a solution of 4-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]benzene-1,2-diamine (0.16 g, 0.38 mmol) in acetic acid (10 mL) was added N,N'-bis(methoxycarbonyl)-S-methylisothiourea (0.30 g, 0.70 mmol) and the reaction mixture was stirred at 80 °C for 2 hours. After cooling to room temperature it was concentrated and partitioned between ethyl acetate (100 mL) and water (20 mL). The organic layer was separated, washed with water (2x 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The resulting crude was purified by silica gel gradient chromatography (ethyl acetate to 10% methanol in ethyl acetate) to give methyl {6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1*H*-benzimidazol-2-yl}carbamate (0.11 g, 58%). ^1H NMR (400 MHz, d_6-DMSO): 8.71 (s, 1H), 7.61 (s, 1H), 7.58–7.44 (m, 3H), 6.99 (d, 1H), 5.10 (s, 2H), 4.43 (m, 2H), 4.18 (m, 2H), 3.81 (s, 3H), 2.78 (t, 2H), 2.56 (s, 2H), 1.57 (t, 2H), 0.86 (s, 6H); MS (EI) for $C_{28}H_{30}N_6O_3$: 499 (MH^+).

[00218] STEP 4: A solution of methyl {6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1*H*-benzimidazol-

2-yl}carbamate (0.10 g, 0.20 mmol) and 2M aqueous sodium hydroxide (8.0 mL, 16.0 mmol) in methanol (10 mL) was heated to reflux for 4 hours. After cooling to room temperature it was concentrated and partitioned between ethyl acetate (100 mL) and brine (10 mL). The organic layer was separated washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give 6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1*H*-benzimidazol-2-amine (80 mg, 89%). ^{1}H NMR (400 MHz, d_6-DMSO): 8.70 (s, 1H), 8.56 (s, 2H), 7.68 (m, 1H), 7.58 (s, 1H), 7.51–7.47 (m, 2H), 7.01 (d, 1H), 5.08 (br s, 2H), 4.47 (m, 2H), 4.19 (m, 2H), 2.79 (t, 2H), 2.54 (s, 2H), 1.73 (s, 3H), 1.58 (t, 2H), 0.84 (s, 6H); MS (EI) for $C_{26}H_{28}N_6O$: 441 (MH^+).

[00219] STEP 5: To a solution of 6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1*H*-benzimidazol-2-amin (50 mg, 0.11 mmol) and diisopropylethylamine (40 μL, 0.22 mmol) in dimethylformamide (0.5mL) was added methanesulfonyl chloride (9 μL, 0.11 mmol) at 0°C and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated, dissolved in methanol and purified by reverse phase preparative HPLC (0.1% aqueous ammonium acetate-acetonitrile) to give N-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1H-benzimidazol-2-yl}methanesulfonamide (6 mg, 10%). ^{1}H NMR (400 MHz, d_4-MeOH): 8.26 (s, 1H), 7.74 (s, 1H), 7.45-7.34 (m, 3H), 7.21 (d, 1H), 6.93 (d, 1H), 4.61 (s, 2H), 4.26 (t, 2H), 3.86 (t, 2H), 3.28 (s, 3H), 2.71 (t, 2H), 2.42 (s, 2H), 1.56 (t, 2H), 0.81 (s, 6H). MS (EI) for $C_{27}H_{30}N_6O_3S$: 519 (MH^+) and 5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1-(methylsulfonyl)-1H-benzimidazol-2-amine. (9.5 mg, 17%) as a mixture of N1,N3 isomers. MS (EI) for $C_{27}H_{30}N_6O_3S$: 519 (MH^+).

Biological Examples

[00220] Compounds of this invention have been tested using the assay described in Biological Example 1 and have been determined to be mTORc1 inhibitors. As such compounds of Formula I are useful for treating diseases, particularly cancer in which mTOR activity contributes to the pathology and/or symptomatology of the disease. Suitable *in vitro* assays for measuring mTORc1 and mTORc2 activity and the inhibition thereof by compounds, as well as cell-based assays for measurement of *in vitro* efficacy in treatment of cancer, are known in the art and examples are described below. Suitable *in*

vivo models for cancer are known to those of ordinary skill in the art and examples are disclosed in below. Following the examples disclosed herein, as well as that disclosed in the art, a person of ordinary skill in the art can determine the mTOR-inhibitory activity of a compound of this invention.

Biological Example 1

mTOR/GbL/Raptor (mTORC1) ELISA Assay

[00221] The measurement of mTORC1 enzyme activity was performed in an ELISA assay format following the phosphorylation of 4E-BP1 protein. All experiments were performed in the 384-well format. Generally, 0.5 μL DMSO containing varying concentrations of the test compound was mixed with 15 μL enzyme solution. Kinase reactions were initiated with the addition of 15 μL of substrates-containing solution. The assay conditions were as follows; 0.2 nM mTORC1, 10 μM ATP and 50 nM NHis-tagged 4E-BP1 in 20 mM Hepes, pH 7.2, 1 mM DTT, 50 mM NaCl, 10 mM $MnCl_2$, 0.02 mg/mL BSA, 0.01% CHAPS, 50 mM β-glycerophosphate. Following an incubation of 120 minutes at ambient temperature, 20 μL of the reaction volume was transferred to a Ni-Chelate-coated 384-well plate. The binding step of the 4E-BP1 protein proceeded for 60 minutes, followed by washing 4 times each with 50 μL of Tris-buffered saline solution (TBS). Anti-phospho-4E-BP1 rabbit-IgG (20 μL, 1:5000) in 5% BSA-TBST (0.2% Tween-20 in TBS) was added and further incubated for 60 minutes. Incubation with a secondary HRP-tagged anti-IgG was similarly performed after washing off the primary antibody (4 washes of 50 μL). Following the final wash step with TBST, 20 μL of SuperSignal ELISA Femto (Pierce Biotechnology) was added and the luminescence measured using an EnVision plate reader.

[00222] All Compounds in Table 1 were tested in the above assay. In one embodiment the Compound of the Invention has an mTOR-inhibitory activity of about 0.40 μM or less. In another embodiment the Compound of the Invention has an mTOR-inhibitory activity of about 0.10 μM or less. In another embodiment the Compound of the Invention has an mTOR-inhibitory activity of about 0.20 μM or less. In another embodiment the Compound of the Invention has an mTOR-inhibitory activity of about 0.05 μM or less. In another embodiment the Compound of the Invention has an mTOR-inhibitory activity of about 0.02 μM or less. In another embodiment the Compound of the Invention has an mTOR-inhibitory activity of about 0.01 μM or less.

[00223] As numbered in Table 1, Compounds 15-29, 42-47, 51, 53-56, 63, 64, and 71 have an IC_{50} in this assay of less than or equal to 20 nM. As numbered in Table 1, Compounds 7-14, 41, 58-60, 65 have an IC_{50} in this assay of greater than 20 nM but less than or equal to 50 nM. As numbered in Table 1, Compounds 1-6, 40, 57, 61-62, 67-70 have an IC_{50} in this assay of greater than 50 nM but less than or equal to 100 nM. As numbered in Table 1, Compounds 30-39, 48-50, 52, and 66 have an IC_{50} in this assay of greater than 100 nM but less than or equal to 690 nM.

Biological Example 2

Immune-Complex mTORC2 Kinase (mTORC2 IP-Kinase) Assay

[00224] HeLa (ATCC) cells are grown in suspension culture and lysed in ice-cold lysis buffer containing 40 mM HEPES pH 7.5, 120 mM NaCl, 1 mM EDTA, 10 mM sodium pyrophosphate, 10 mM β-glycerophosphate, 10 mM NaF, 10 mM NaN_3, one tablet of protease inhibitors (Complete-Mini, EDTA-free, Roche), 0.3% cholamidopropyldimethylammoniopropanesulfonate (CHAPS), 1 mM AEBSF, 0.5 mM benzamidine HCl, 20 μg/mL heparin, and 1.5 mM Na_3VO_4. The mTORC2 complex is immunoprecipitated with anti-RICTOR antibody for 2 h. The immune complexes are immobilized on Protein A sepharose (GE Healthcare, 17-5280-01), washed sequentially 3 times with wash buffer (40 mM HEPES pH 7.5, 120 mM NaCl, 10 mM β-glycerophosphate, 0.3% CHAPS, 1 mM AEBSF, 20 μg/mL heparin, 1.5 mM Na_3VO_4, and Complete-Mini, EDTA-free) and resuspended in kinase buffer (40 mM HEPES, pH 7.5, 120 mM NaCl, 0.3% CHAPS, 20 μg/mL heparin, 4 mM $MgCl_2$, 4 mM $MnCl_2$, 10% Glycerol, and 10 mM DTT). The immune complexes (equivalent to 1×10^7 cells) are pre-incubated at 37 °C with a test compound or 0.6% DMSO for 5 min, and then subjected to a kinase reaction for 8 min in a final volume of 33 μL (including 5 μL bed volume) containing kinase buffer, 50 μM ATP, and 0.75 μg full length dephosphorylated AKT1. Kinase reactions are terminated by addition of 11 μL 4× SDS sample buffer containing 20% β-mercaptoethanol and resolved in a 10% Tris Glycine gels. The gels are transferred onto PVDF membrane at 50 V for 20 h at 4 °C. The membranes are blocked in 5% non-fat milk in TBST for 1 h and incubated overnight at 4 °C with 1/1000 dilution of rabbit anti-pAKT (S473) (Cell Signaling Technology, 4060) in 3% BSA/TBST. The membranes are washed 3 times in TBST and incubated for 1 h with a 1/10000 dilution of secondary goat anti-rabbit HRP antibody (Cell Signaling Technology, 2125) in 5% non-

fat milk/TBST. The signal is detected using Amersham ECL-plus. The scanned data are analyzed using ImageQuant software. IC_{50} for the test compound is determined relative to DMSO treated sample using XLfit4 software.

Biological Example 3

pS6 (S240/244) ELISA Assay

[00225] MCF-7 cells (ATCC) cells were seeded at 24000 cells per well in 96-well plates (Corning, 3904) in DMEM (Cellgro) containing 10% FBS (Cellgro), 1% NEAA (Cellgro) and 1% penicillin-streptomycin (Cellgro). Cells were incubated at 37°C, 5% CO2 for 48 h, and the growth medium was replaced with serum-free DMEM or in medium containing 0.4% BSA. Serial dilutions of the test compound in 0.3% DMSO (vehicle) were added to the cells and incubated for 3h. To fix the cells, medium was removed and 100μL/well of 4% formaldehyde (Sigma Aldrich, F8775) in TBS (20 mM Tris, 500 mM NaCl) was added to each well at RT for 30 min. Cells were washed 4 times with 200μL TBS containing 0.1% Triton X-100 (Sigma, catalog # T9284). Plates were blocked with 100μL Odyssey blocking buffer (Li-Cor Biosciences, 927-40000) for 1h at RT. Anti-pS6 (S240/244) antibody (Cell Signaling Technology, 2215) and anti-total-S6 antibody (R&D systems, MAB5436) were diluted 1:400 in Odyssey blocking buffer, and 50μL of the antibody solution containing both antibodies was added to one plate to detect pS6 and total S6. After incubation overnight at 4°C, plates were washed 4 times with 200μL TBS containing 0.1% Tween20 (Bio-Rad, catalog # 170-6351) (TBST). Goat anti-rabbit and Goat anti-mouse secondary antibody (Li-Cor Biosciences, catalog # 926-32221 and 926-32210) conjugated to IRDye were diluted 1:400 in Odyssey blocking buffer containing 0.1% Tween20. 50μL of antibody solution containing both antibodies was added to each well and incubated for 1h at RT. Plates were washed 3 times with 200μL TBST and 2 times with 200μL TBS. Fluorescence was read on an Odyssey plate reader. IC50 values were determined based on the ratio of pS6 to total S6 signal for compound treated wells, normalized to the DMSO-treated control wells.

[00226] In one embodiment, the Compound of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of 1.5 μM or less. In another embodiment, the Compound of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of 1.0 μM or less. In another embodiment, the Compound of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of 0.5 μM or less. In one embodiment, the Compound of the Invention tested in this assay in MCF-7 cells had an inhibitory

activity of 0.25 μM or less. In one embodiment, the Compound of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of 0.2 μM or less. In one embodiment, the Compound of the Invention tested in this assay in MCF-7 cells had an inhibitory activity of 0.1 μM or less.

Biological Example 4-10

Pharmacodynamic xenograft tumor models

[00227] Female and male athymic nude mice (NCr) 5-8 weeks of age and weighing approximately 20-25 g are used in the following models. Prior to initiation of a study, the animals are allowed to acclimate for a minimum of 48 h. During these studies, animals are provided food and water ad libitum and housed in a room conditioned at 70-75°F and 60% relative humidity. A 12 h light and 12 h dark cycle is maintained with automatic timers. All animals are examined daily for compound-induced or tumor-related deaths.

MCF-7 Breast adenocarcinoma model

[00228] MCF7 human mammary adenocarcinoma cells are cultured in vitro in DMEM (Cellgro) supplemented with 10% Fetal Bovine Serum (Cellgro), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization, and 5 x 10^6 cells in 100 μL of a solution made of 50% cold Hanks balanced salt solution with 50% growth factor reduced matrigel (Becton Dickinson) implanted subcutaneously into the hindflank of female nude mice. A transponder is implanted into each mouse for identification and data tracking, and animals are monitored daily for clinical symptoms and survival.

[00229] Tumors are established in female athymic nude mice and staged when the average tumor weight reached 100-200 mg. A Compound of the Invention is orally administered as a solution/fine suspension in water (with 1:1 molar ratio of 1 N HCL) once-daily (qd) or twice-daily (bid) at 10, 25, 50 and 100 mg/kg for 14 days. During the dosing period of 14-19 days, tumor weights are determined twice-weekly and body weights are recorded daily.

Colo-205 colon model

[00230] Colo-205 human colorectal carcinoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization, and 3x10^6 cells (passage 10-15, >95% viability) in 0.1 mL ice-cold Hank's balanced salt solution are implanted

intradermally in the hind-flank of 5-8 week old female athymic nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival.

[00231] Tumors are established in female athymic nude mice and staged when the average tumor weight reached 100-200 mg. A Compound of the Invention is orally administered as a solution/fine suspension in water (with 1:1 molar ratio of 1 N HCL) once-daily (qd) or twice-daily (bid) at 10, 25, 50 and 100 mg/kg for 14 days. During the dosing period of 14 days, tumor weights are determined twice-weekly and body weights are recorded daily.

PC-3 prostate adenocarcinoma model

[00232] PC-3 human prostate adenocarcinoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 20% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization and $3x10^6$ cells (passage 10-14, >95% viability) in 0.1 mL of ice-cold Hank's balanced salt solution are implanted subcutaneously into the hindflank of 5-8 week old male nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival.

[00233] Tumors are established in male athymic nude mice and staged when the average tumor weight reached 100-200 mg. A Compound of the Invention is orally administered as a solution/fine suspension in water (with 1:1 molar ratio of 1 N HCl) once-daily (qd) or twice-daily (bid) at 10, 25, 50, or 100-mg/kg for 19 days. During the dosing period of 14-19 days, tumor weights are determined twice-weekly and body weights are recorded daily.

U-87 MG human glioblastoma model

[00234] U-87 MG human glioblastoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization and $2x10^6$ cells (passage 5, 96% viability) in 0.1 mL of ice-cold Hank's balanced salt solution are implanted intradermally into the hindflank of 5-8 week old female nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

A549 human lung carcinoma model

[00235] A549 human lung carcinoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization and $10x10^6$ cells (passage 12, 99% viability) in 0.1 mL of ice-cold Hank's balanced salt solution are implanted intradermally into the hindflank of 5-8 week old female nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

A2058 human melanoma model

[00236] A2058 human melanoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization and $3x10^6$ cells (passage 3, 95% viability) in 0.1 mL ice-cold Hank's balanced salt solution are implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

WM-266-4 human melanoma model

[00237] WM-266-4 human melanoma cells are cultured in vitro in DMEM (Mediatech) supplemented with 10% Fetal Bovine Serum (Hyclone), Penicillin-Streptomycin and non-essential amino acids at 37 °C in a humidified, 5% CO_2 atmosphere. On day 0, cells are harvested by trypsinization and $3x10^6$ cells (passage 5, 99% viability) in 0.1 mL ice-cold Hank's balanced salt solution are implanted intradermally in the hind-flank of 5-8 week old female athymic nude mice. A transponder is implanted in each mouse for identification, and animals are monitored daily for clinical symptoms and survival. Body weights are recorded daily.

[00238] Tumor weight (TW) in the above models is determined by measuring perpendicular diameters with a caliper, using the following formula:

tumor weight (mg) = [tumor volume = length (mm) x width^2 (mm^2)]/2

These data were recorded and plotted on a tumor weight vs. days post-implantation line graph and presented graphically as an indication of tumor growth rates. Percent inhibition of tumor growth (TGI) is determined with the following formula:

$$\left[1-\left(\frac{(X_f - X_0)}{(Y_f - X_0)}\right)\right]*100$$

where X_0 = average TW of all tumors on group day

X_f = TW of treated group on Day f

Y_f = TW of vehicle control group on Day f

If tumors regress below their starting sizes, then the percent tumor regression is determined with the following formula:

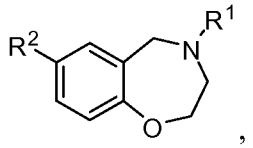
$$\left(\frac{X_0 - X_f}{X_0}\right)*100$$

Tumor size is calculated individually for each tumor to obtain a mean ± SEM value for each experimental group. Statistical significance is determined using the 2-tailed Student's t-test (significance defined as $P<0.05$).

[00239] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. The invention has been described with reference to various specific embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled. All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

What is claimed is:

1. A compound of structural formula



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wherein the combination of R^1 and R^2 are as defined in one of the following compounds:

Name
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(6,8-dibromoquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-{5-[(2-chlorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
2,2,2-trifluoro-*N*-[6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)imidazo[1,2-*a*]pyrimidin-2-yl]acetamide
4-(5-fluoroquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-2-amine
4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-pyrrolidin-3-ylbenzamide
4-(6,6-dimethyl-6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(6-iodo-8-methylquinazolin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[2-(trifluoromethyl)quinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(1*H*-pyrazol-3-yl)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-[3,4-bis(methyloxy)phenyl]-4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[6-methyl-5-(phenyloxy)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-methyl-5-{[4-(methyloxy)phenyl]methyl}pyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[5-(phenylmethyl)-6-(trifluoromethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-phenylquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoroethyl)benzamide
4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-[(3*R*)-pyrrolidin-3-yl]benzamide
5-{4-[6-methyl-5-(phenylmethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl}pyridin-2-amine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-[5-(phenylmethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)pyridin-2-amine
N-(2-fluoroethyl)-4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzamide
4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1,3-thiazol-5-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-[6-chloro-5-(phenylmethyl)pyrimidin-4-yl]-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

Name
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(7-methyl-7-phenyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1,3-benzothiazol-2-amine
4-{5-[(2-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
5-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoroethyl)-1*H*-benzimidazol-2-amine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-methyl-6-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-*N*-(2,2,2-trifluoro-1-methylethyl)benzamide
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-{6-[(phenylmethyl)oxy]quinazolin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-2-(methyloxy)aniline
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(5-phenyl-6,7-dihydro-5*H*-cyclopenta[d]pyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-pyridin-2-yl-1*H*-benzimidazol-6-yl)-4-quinolin-4-yl-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(6-cyclopropyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-yl)-7-(2-methyl-1*H*-benzimidazol-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-7-[4-(methyloxy)phenyl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(6-phenylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
methyl 4-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate
4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(trifluoromethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-cyclobutyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-benzimidazol-6-yl)-4-(2-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
6-(4-{5-[(4-fluorophenyl)methyl]-6-methylpyrimidin-4-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)-1*H*-indazol-3-amine
7-(2-cyclopropyl-1*H*-benzimidazol-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-[2-(1-methylethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
N-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl][1,3]thiazolo[5,4-*b*]pyridin-2-yl}acetamide
4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-{2-[(methyloxy)methyl]-3*H*-imidazo[4,5-*b*]pyridin-6-yl}-2,3,4,5-tetrahydro-1,4-benzoxazepine
methyl 4-(4-quinolin-4-yl-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl)benzoate
4-(2,6-dimethylpyrimidin-4-yl)-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(2-methylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-methyl-5-(1-methylpropyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-7-(2-ethyl[1,3]thiazolo[5,4-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-*N*-ethyl[1,3]thiazolo[5,4-*b*]pyridin-2-amine
7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-[6-(trifluoromethyl)-5,6,7,8-tetrahydroquinazolin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
2-amino-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]benzenesulfonamide
6,6-dimethyl-4-[7-(2-methyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3-dihydro-1,4-benzoxazepin-4(5*H*)-

Name
yl]-5,6,7,8-tetrahydro-5,8-ethanoquinazoline
4-(6-furan-2-yl-2-methylpyrimidin-4-yl)-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
N-{6-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1*H*-benzimidazol-2-yl}methanesulfonamide
5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-1-(methylsulfonyl)-1*H*-benzimidazol-2-amine
4-[6-(1,1-dimethylethyl)-2-methylpyrimidin-4-yl]-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(2-methyl-6-propylpyrimidin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-[2-methyl-6-(1-methylethyl)pyrimidin-4-yl]-2,3,4,5-tetrahydro-1,4-benzoxazepine
2-amino-*N*-(2-amino-2-methylpropyl)-5-[4-(6,6,8-trimethyl-5,6-dihydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridine-3-sulfonamide
7-(2-azetidin-1-yl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine
2-chloro-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-amine
3-{2-chloro-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-yl}-1,1-dimethylurea
N-{2-azetidin-1-yl-5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]pyridin-3-yl}methanesulfonamide
N-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-morpholin-4-ylpyridin-3-yl}methanesulfonamide
N-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-[(1-methylethyl)oxy]pyridin-3-yl}methanesulfonamide
N-{5-[4-(6,6-dimethyl-5,6,7,8-tetrahydroquinazolin-4-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepin-7-yl]-2-hydroxypyridin-3-yl}methanesulfonamide, and
4-[6,6-dimethyl-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4-yl]-7-(2-methyl-1*H*-imidazo[4,5-*b*]pyridin-6-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine

optionally as a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition which comprises a compound, optionally as pharmaceutically acceptable salt thereof, of Claim 1 and a pharmaceutically acceptable carrier, excipient, or diluent.

3. A method for treating a disease, disorder, or syndrome which method comprises administering to a patient a therapeutically effective amount of a compound of Claim 1, optionally as a pharmaceutically acceptable salt thereof, or administering to a patient a pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, optionally as a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, excipient, or diluent.

4. The method of Claim 3 where the disease is cancer.

5. The method of Claim 4 where the cancer is breast cancer, mantle cell lymphoma, renal cell carcinoma, acute myelogenous leukemia, chronic myelogenous leukemia, NPM/ALK-transformed anaplastic large cell lymphoma, diffuse large B cell lymphoma, rhabdomyosarcoma, ovarian cancer, endometrial cancer, cervical cancer, non small cell lung carcinoma, small cell lung carcinoma, adenocarcinoma, colon cancer, rectal cancer, gastric carcinoma, hepatocellular carcinoma, melanoma, pancreatic cancer, prostate carcinoma, thyroid carcinoma, anaplastic large cell lymphoma, hemangioma, glioblastoma, or head and neck cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/035639

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/14 C07D417/14 C07D471/04 C07D513/04
A61K31/553 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2004/248890 A1 (GONZALEZ JESUS E [US] ET AL GONZALEZ III JESUS E [US] ET AL) 9 December 2004 (2004-12-09) pages 4,144; example 656	1-5
Y	WO 2009/042092 A1 (MERCK & CO INC [US]; CHANG RONALD K [US]; DI MARCO CHRISTINA NG [US];) 2 April 2009 (2009-04-02) pages 1,47; example 151	1-5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 2010	12/08/2010

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/035639

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004248890 A1	09-12-2004	US 2010160316 A1	24-06-2010
		US 2006217377 A1	28-09-2006
WO 2009042092 A1	02-04-2009	EP 2205085 A1	14-07-2010