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PYRIMIDINYL AND 1,3,5-TRIAZINYL BENZIMIDAZOLES AND THEIR USE IN CANCER THERAPY

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See application file for complete search history.

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87 Claims, No Drawings


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PYRIMIDINYL AND 1,3,5-TRIAZINYL BENZIMIDAZOLES AND THEIR USE IN CANCER THERAPY

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(a) to U.S. Provisional Application Nos. 61/223,684, filed Jul. 7, 2009; 61/247,448, filed Sep. 30, 2009; and 61/318,195, filed Mar. 26, 2010; the disclosure of each of which is incorporated herein by reference in its entirety.

FIELD

Provided herein are pyrimidinyl and 1,3,5-triazinyl benzimidazoles, and their pharmaceutical compositions, preparation, and use as agents or drugs for cancer therapy, either alone or in combination with radiation and/or other anticancer drugs.

BACKGROUND

Phosphoinositide-3-kinases (PI3Ks) are a group of lipid kinases, which phosphorylate the 3-hydroxy of phosphoinositides. They are classified into at least three classes (Classes I, II, and III) and play an important role in cellular signaling (Stephens et al., *Curr. Opin. Pharmacol.* 2005, 5, 357). Class I enzymes are further classified into Classes Ia and Ib based on their mechanism of activation; Class Ia PI3Ks are heterodimeric structures consisting of a catalytic subunit (p110α, p110β, or p110δ) in complex with a regulatory p85 subunit, while the class-Ib PI3K (p110γ) is structurally similar but lacks the p85 regulatory subunit, and instead is activated by βγ subunits of heterotrimeric G-proteins (Walker et al., *Mol. Cell.* 2000, 6, 909). The human protein sequence of the p110α isoform is described in Volina et al., *Genomics* 1994, 24, 472; and Stirnivant et al., *Bioorg. Med. Chem. Med.* 1997, 5, 65.

PI3Ks play a variety of roles in normal tissue physiology (Foukas & Shepherd, *Biochem. Soc. Biol.* 2004, 32, 330; Shepherd, *Acta Physiol. Scand.* 2005, 183, 3), with p110α having a specific role in cancer growth, p110β in thrombus formation mediated by integrin α5β3 (Jackson et al., *Nat. Med.* 2005, 11, 507), and p110γ in inflammation, rheumatoid arthritis (Camps et al., *Nat. Med.* 2005, 11, 936) and other chronic inflammation states (Barber et al., *Nat. Med.* 2005, 11, 933). The PI3K enzymes produce phosphoinositide 3,4,5-triphosphate (PIP3) from the corresponding diphosphate (PIP2), thus recruiting AKT (protein kinase B) through its Pleckstrin homology (PH) domain to the plasma membrane. Once bound, AKT is phosphorylated and activated by other membrane bound kinases and is central to a cascade of events that lead to inhibition of apoptosis (Berrie, *Exp. Opin. Invest. Drugs* 2001, 10, 1085).

The p110α isoform is selectively amplified and activated in a number of cancer types (Stephens et al., *Curr. Opin. Pharmacol.* 2005, 5, 357; Stauffer et al., *Curr. Med. Chem.—Anti-Cancer Agents* 2005, 5, 449). In addition, there is a high frequency of non-random mutations in specific sites, primarily in the C2 domain and or the activation loop, of the kinase in several human cancer cell lines, including colon, brain, breast, and stomach (Samuels et al., *Science* 2004, 304, 554). This results in a constitutively active enzyme (Ikenoue et al., *Cancer Res.* 2005, 65, 4562; Kang et al., *Proc. Natl. Acad. Sci. USA* 2005, 102, 802), making p110α one of the most highly mutated oncoproteins found in human tumors. Structural studies have shown that many of the mutations occur at residues lying at the interfaces between p110α and p85α or between the kinase domain of p110α and other domains within the catalytic subunit (Miled et al., *Science* 2007, 317, 239; Huang et al., *Science* 2007, 318, 1744).

While PI3K isoenzymes play important roles in many cellular processes, published experimental studies in mice with human tumor xenografts show that the pan-PI3K inhibitor LY294002 is well-tolerated, reduces signaling through the PI3K pathway, causes reduction of tumor volume, and is more active in cell lines over-expressing mutant forms of p110α than parental control cells (Semb et al., *Clin. Cancer Res.* 2002, 8, 1597; Hu et al., *Cancer Res.* 2002, 62, 1087).

Despite the advances in developing PI3K inhibitors, there is a need for PI3K inhibitors for treatment of cancer.

SUMMARY OF THE DISCLOSURE

Provided herein is a compound of Formula I, IA, or IB:
or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

- each R¹ is independently hydrogen, C₁₋₆ alkyl, —S—C₁₋₆ alkyl, —SO₂—C₁₋₆ alkyl, or —SO₂—C₁₋₆ alkyl; each R² and R³ is independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, C₆₋₁₄ aryl, C₇₋₁₅ alkenyl, heteroaromatic, or heterocyclic; or (c) —C(O)R⁴, —C(O)OR⁵, —C(O)NR⁶R⁷, —C(NR⁸) NR⁶R⁷, —OR⁹; —OC(O)R⁴, —OC(O)OR⁵, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OS(O)R⁴, —OS(O)OR⁵, —OS(O)NR⁶R⁷, —NR⁶R⁷, —NR⁸C(O)R⁹, —NR³C(O)NR⁶R⁷, —NR³C(O)NR⁶R⁷, —NR⁶C(O)R⁹, —NR⁸C(O)R⁹, —OS(O)NR⁶R⁷, —OS(O)NR⁶R⁷, —NR⁶C(O)R⁹, —NR⁸C(O)R⁹, —NR⁶C(O)R⁹, —NR⁸C(O)R⁹, —OS(O)NR⁶R⁷, —OS(O)NR⁶R⁷, —NR⁶C(O)R⁹, —NR⁸C(O)R⁹, —OS(O)NR⁶R⁷, —OS(O)NR⁶R⁷, —NR⁶C(O)R⁹, —NR⁸C(O)R⁹, wherein each R¹, R², R³, or R⁴ is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, C₆₋₁₄ aryl, C₇₋₁₅ alkenyl, heteroaromatic, or heterocyclic, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; and (iii) R¹ and R³ together with the N atom to which they are attached form heterocyclic, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q;

wherein each Q is independently selected from the group consisting of (a) cyano, halo, and nitro; (b) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, C₆₋₁₄ aryl, C₇₋₁₅ alkenyl, heteroaromatic, and heterocyclic; and (c) —C(O)R⁴, —C(O)OR⁵, —C(O)NR⁶R⁷, —C(NR⁸)NR⁶R⁷, —OR⁹; —OC(O)R⁴, —OC(O)OR⁵, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)R⁴, —OC(O)OR⁵, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, —OC(O)NR⁶R⁷, wherein each R¹, R², and R³ is independently (i) hydrogen; (ii) C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₆ alkynyl, or C₆₋₁₄ aryl, heteroaromatic, or heterocyclic, or (iii) R¹ and R³ together with the N atom to which they are attached form heterocyclic.

Also provided herein is a compound of Formula I:
mers, a mixture of two or more diastereomers; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

Provided herein is a method for modulating PI3K activity, comprising contacting a PI3K with a therapeutically effective amount of a compound disclosed herein, e.g., a compound of Formulas I, IA, or IB, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

**DETAILED DESCRIPTION**

To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

The term “subject” refers to an animal, including, but not limited to, a primate (e.g., human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

The terms “treat,” “treating,” and “treatment” are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

The terms “prevent,” “preventing,” and “prevention” are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms: barring a subject from acquiring a disorder, disease, or condition; or reducing a subject’s risk of acquiring a disorder, disease, or condition.

The term “therapeutically effective amount” are meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term “therapeutically effective amount” also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (e.g., a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

The term “pharmacologically acceptable carrier,” “pharmacologically acceptable excipient,” “physiologically acceptable carrier,” or “physiologically acceptable excipient” refers to a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component is “pharmacologically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See, *Remington: The Science and Practice of Pharmacy*, 21st Edition, Lippincott Williams & Wilkins: Philadelphia, Pa., 2005; *Handbook of Pharmaceutical Excipients*, 5th Edition, Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and *Handbook of Pharmaceutical Additives*, 3rd Edition, Ash and Ash Eds.,
express PI3K, increased PI3K expression or degree of intracellular activation; or decreased PI3K expression. A PI3K-mediated condition, disorder or disease may be completely or partially mediated by inappropriate PI3K activity. In particular, a PI3K-mediated condition, disorder or disease is one in which modulation of a PI3K enzyme activity results in some effect on the underlying condition or disorder, e.g., a PI3K inhibitor results in some improvement in at least some of patients being treated.

The term "alkyl" refers to a linear or branched saturated monovalent hydrocarbon radical, wherein the alkyl may optionally be substituted as described herein. As used herein, the term "alkyl" encompasses both linear and branched alkyl, unless otherwise specified. For example, C1-6 alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 20 (C1-20), 1 to 15 (C1-15), 1 to 10 (C1-10), or 1 to 6 (C1-6) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 20 (C3-20), 3 to 15 (C3-15), 3 to 10 (C3-10), or 3 to 6 (C3-6) carbon atoms. As used herein, linear C1-6 and branched C3-6 alkyl groups are also referred as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms, e.g., n-propyl and 2-propyl), butyl (including all isomeric forms, e.g., n-butyl, 2-methylpropyl (isobutyl), 1-methyloctyl (sec-butyl), and 1,1-dimethylpropyl (t-butyl)), pentyl (including all isomeric forms, e.g., n-pentyl, 2-methylbutyl (isopropyl), and 2,2-dimethylpropyl (neopentyl)), hexyl (including all isomeric forms, n-hexyl, 2-methylpentyl (isohexyl), 3-methylpentyl, 2,3-dimethylbutyl, and 2,2-dimethylbutyl (neo-hexyl)), heptyl (including all isomeric forms, e.g., n-heptyl, 2-methylhexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 3-ethylhexyl, and 2,2,3-trimethylbutyl), octyl (including all isomeric forms, e.g., n-octyl, 2-methylheptyl, 3-methylheptyl, 2,5-dimethylhexyl, and 2,2,4-trimethylpentyl (isooctyl)), nonyl (including all isomeric forms, e.g., n-nonyl), decyl (including all isomeric forms, e.g., n-decyl), undecyl (including all isomeric forms, e.g., n-undecyl), dodecyl (including all isomeric forms, e.g., n-dodecyl), tridecyl (including all isomeric forms, e.g., n-tridecyl), tetradecyl (including all isomeric forms, e.g., n-tetradecyl), pentadecyl (including all isomeric forms, e.g., n-pentadecyl), hexadecyl (including all isomeric forms, e.g., n-hexadecyl (palmitic)), heptadecyl (including all isomeric forms, e.g., n-heptadecyl), octadecyl (including all isomeric forms, e.g., n-octadecyl (stearic)), nonadecyl (including all isomeric forms, e.g., n-nonadecyl), and icosyl (including all isomeric forms, e.g., n-icosyl).

The term "alkylene" refers to a linear or branched saturated divalent hydrocarbon radical, wherein the alkylene may optionally be substituted as described herein. For example, C1-6 alkenylene refers to a linear saturated divalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenylene is a linear saturated divalent hydrocarbon radical that has 1 to 20 (C1-20), 1 to 15 (C1-15), 1 to 10 (C1-10), or 1 to 6 (C1-6) carbon atoms, or branched saturated divalent hydrocarbon radical of 3 to 20 (C3-20), 3 to 15 (C3-15), 3 to 10 (C3-10), or 3 to 6 (C3-6) carbon atoms. As used herein, linear C1-6 and branched C3-6 alkenylene groups are also referred as "lower alkenyl." Examples of alkenylene groups include, but are not limited to, methylene, ethylene, propylene (including all isomeric forms), n-propylene, isopropylene, butylene (including all isomeric forms), n-butyl-
lens, isobutylene, 1-butene, pentylene (including all isomeric forms), and hexylene (including all isomeric forms).

The term “heteroalkylene” refers to a linear or branched saturated divalent hydrocarbon radical that contains one or more heteroatoms each independently selected from O, S, and N in the hydrocarbon chain. For example, C\(_{1-8}\) heteroalkylene refers to a linear saturated divalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the heteroalkylene is a linear saturated divalent hydrocarbon radical that has 1 to 20 (C\(_{1-20}\)), 1 to 15 (C\(_{1-15}\)), 1 to 10 (C\(_{1-10}\)), or 1 to 6 (C\(_{1-6}\)) carbon atoms, or branched saturated divalent hydrocarbon radical of 3 to 20 (C\(_{3-20}\)), 3 to 15 (C\(_{3-15}\)), or 3 to 6 (C\(_{3-6}\)) carbon atoms. As used herein, linear C\(_{1-8}\) and branched C\(_{3-8}\) heteroalkylene groups are also referred to as “lower heteroalkylene.” Examples of heteroalkylene groups include, but are not limited to, 
- \(-\text{CH}_2\text{O}H\), \(-\text{CH}_2\text{O}C\text{H}_3\), \(-\text{CH}_2\text{CH}_2\text{O}H\), \(-\text{CH}_2\text{NH}_2\), \(-\text{CH}_2\text{NHCH}_3\), \(-\text{CH}_2\text{CH}_2\text{NH}_2\), \(-\text{CH}_2\text{CH}_2\text{NHCH}_3\), \(-\text{CH}_3\), \(-\text{CH}_2\text{SCH}_3\), and \(-\text{CH}_2\text{CH}_2\text{S}H\).

In certain embodiments, the heteroalkylene may also be optionally substituted as described herein.

The term “alkenyl” refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, carbon-carbon double bonds. The alkenyl may be optionally substituted as described herein. The term “alkenyl” also embraces radicals having “cis” and “trans” configurations, or alternatively, “Z” and “E” configurations, as appreciated by those of ordinary skill in the art. As used herein, the term “alkenyl” encompasses both linear and branched alkenyl, unless otherwise specified. For example, C\(_{2-8}\) alkenyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenyl is a linear monovalent hydrocarbon radical of 2 to 20 (C\(_{2-20}\)), 2 to 15 (C\(_{2-15}\)), 2 to 10 (C\(_{2-10}\)), or 2 to 6 (C\(_{2-6}\)) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 20 (C\(_{3-20}\)), 3 to 15 (C\(_{3-15}\)), or 3 to 6 (C\(_{3-6}\)) carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propen-1-yl, propen-2-yl, allyl, butenyl, and 4-methylbutenyl.

The term “alkenylene” refers to a linear or branched divalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, in another embodiment, one, carbon-carbon double bond(s). The alkenylene may be optionally substituted as described herein. The term “alkenylene” embraces radicals having a “cis” or “trans” configuration or a mixture thereof or, alternatively, a “Z” or “E” configuration or a mixture thereof, as appreciated by those of ordinary skill in the art. For example, C\(_{2-8}\) alkenylene refers to a linear unsaturated divalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated divalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenylene is a linear divalent hydrocarbon radical of 2 to 20 (C\(_{2-20}\)), 2 to 15 (C\(_{2-15}\)), 2 to 10 (C\(_{2-10}\)), or 2 to 6 (C\(_{2-6}\)) carbon atoms, or a branched divalent hydrocarbon radical of 3 to 20 (C\(_{3-20}\)), 3 to 15 (C\(_{3-15}\)), 3 to 10 (C\(_{3-10}\)), or 3 to 6 (C\(_{3-6}\)) carbon atoms. Examples of alkenylene groups include, but are not limited to, ethylene, allylene, propenylene, butylene, and 4-methylbutylene.

The term “heteroalkenylene” refers to a linear or branched divalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, in another embodiment, one, carbon-carbon double bond(s), and which contains one or more heteroatoms each independently selected from O, S, and N in the hydrocarbon chain. The heteroalkenylene may be optionally substituted as described herein. The term “het-
to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazolyl, and triazolyl. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl, benzoisoxazolyl, benzopyryl, benzothiazolyl, benzothiazole, benzothiophenyl, benzotriazolyl, benzoxazolyl, furanopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinylnyl, indolyl, indazolyl, isobenzofuranoyl, isobenzothienyl, isoindolyl, isoquinolinylnyl, isothiokyanoyl, naphthyridinyl, oxazolopyridinyl, pthalalazine, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridinyl, quinolinoyl, quinoxalinyl, quinazolinyl, thiadiazapirimidinyl, and thiopyridinyl. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranoyl, perimidinyl, phenanthridinyl, phenanthroinyl, phena- sarazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xan- thenyl. In certain embodiments, heteroaryl may also be optionally substituted as described herein.

The term “heterocyclic” or “heterocyclic” refers to a monocyclic non-aromatic ring system and/or a monocyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, or N; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclic or heterocyclic group has 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. In certain embodiments, the heterocyclic is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system which may include a fused or bridged ring system, and in which the nitrogen or sulfur atoms may be optionally oxidized, the nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclic may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, azepinyl, benzazepinyl, benzoazinyl, benzofuranoyl, benzopyranoyl, benzoxyranoyl, benzotetrahydrofuranyl, benzotetrahydropyranoyl, benzothiopyranoyl, benzoxazinyl, 2-benzoazinyl, chromanoyl, chromo- nyl, cinnolinyl, coumarinyl, decalyl, dioxinoylquinolinyl, dihydrobenzisothiazinyl, dihydrobenzoxazinyl, dihydrofuryl, dihydroisoxazinyl, dihydrodioxinoyl, dihydropyridyl, dihydropyrazinyl, dihydropyridinyl, dihydroquinolyl, dihydroxyanil, 1,4-dihydropyridinyl, furanoyl, imidazolynyl, imidazolyl, indolyl, indolynyl, isobenzotetrahydrofuranyl, isobenzotetrahydropyranoyl, isochromynyl, isocoumarinyl, isoindolynyl, isoindolyl, isooxazolynyl, isooxazolyl, morpholynyl, octahydroindolyl, octahydroisoxazinyl, oxazolynynyl, oxazolinoyl, oxazolynyl, pyrimidinyl, pyrrolyl, pyrrolinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoxazinyl, tetra- hydropyranoyl, tetrahydrothienyl, thiamorpholynyl, thiazolynynyl, tetrahydroquinoxinyl, and 1,3,5-triazinyl. In certain embodiments, heteroaryl may also be optionally substituted as described herein.

The term “halogen”, “halide” or “halo” refers to fluorine, chlorine, bromine, and/or iodine.

The term “optionally substituted” is intended to mean that a group, such as an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, or heterocyclic, may be substituted with one or more substituents independently selected from, e.g., (a) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, C4-8 aryl, C6-12 alkanoyl, and heteroaryl, and heterocyclic, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; and (b) halo, cyano (—CN), nitro (—NO2), C1-6 alkoxy (—O—R), C1-6 alkyloxy (—O—R), C1-6 alkylthio (—S—R), and the like, wherein R=H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, C3-7 aryl, C6-12 alkanoyl, and heteroaryl, and heterocyclic, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) R5 and R6 together with the N atom to which they are attached form a heteroaryl or heterocyclic, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q. As used herein, all groups that can be substituted are “optionally substituted,” unless otherwise specified.

In one embodiment, each Q is independently selected from the group consisting of (a) cyano, halo, and nitro; and (b) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, C3-7 aryl, heteroaryl, and heterocyclic; and (c) —CN, —NO2, —O—R, —O—R, —NR—R, —N(S)O—R, —NR(NR)2, —C(NR)2NR—R, —C(NR)2NR—R; wherein each R, R5, R6, and R7 is independently (i) hydrogen; (ii) C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, C3-7 cycloalkyl, C3-7 aryl, heteroaryl, or heterocyclic, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) R5 and R6 together with the N atom to which they are attached form a heteroaryl or heterocyclic.

In certain embodiments, “optically active” and “enantio-merically active” refer to a collection of molecules, which has an enantiomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of the desired enantiomer and about 5% or less of the less preferred enantiomer based on the total weight of the racemate in question.

In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (−) are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (−) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or clockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (−), is not related to the absolute configuration of the molecule, R and S.

The term “solvent” refers to a compound provided herein or a salt thereof, which further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

The phrase “an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharma-
centically acceptable salt, solvate, hydrate, or prodrug thereof” has the same meaning as the phrase “a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers of the compound referenced therein; or a pharmacologically acceptable salt, solvate, hydrate, or prodrug of the compound referenced therein, or an enantiomer, a mixture of enantiomers, or a mixture of diastereomers of the compound referenced therein.”

Compounds

In one embodiment, provided herein is a compound of Formula I, IA, or IB:

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmacologically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

each R^1 is independently hydrogen, C_{1-6} alkyl, —S—C_{1-6} alkyl, —SO_2—C_{1-6} alkyl, or —SO_3—C_{1-6} alkyl;

each R^2 and R^3 is independently (a) hydrogen, cyano, halo, or nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} alkanly, heteroaryl, or heterocylly; or (c) —C(O)R^{1a}, —C(O)OR^{1b}, —C(ONR^{1})R^{1b}, —(NR^{1})NR^{1}R^{1b}, —OR^{1a}, —OC(O)R^{1a}, —OC(O)OR^{1a}, —OC(O)NR^{1}R^{1b}, —OC(=NR^{1})NR^{1}R^{1b}, —OS(O)R^{1b}, —OS(O)(NR^{1})R^{1b}, —OS(O)(OR^{1})R^{1b}, —OS(O)(OS)(OR^{1})R^{1b}, —NR^{1}R^{1b}, —NR^{1}OR^{1a}, —NR^{1}OC(O)R^{1a}, —NR^{1}(CO)OR^{1a}, —NR^{1}(C(=NR^{1})N)R^{1a}, —NR^{1}(C(=NR^{1})O)R^{1a}, —NR^{1}(C(=NR^{1})S)R^{1a}, —NR^{1}(S)R^{1a}, —NR^{1}(SO)R^{1a}, —NR^{1}(SO)(NR^{1})R^{1b}, —NR^{1}(SO)(OR^{1})R^{1b}, —NR^{1}(SO)(OS)(OR^{1})R^{1b}, —NR^{1}(S)R^{1a}, —SR^{1a}, —S(O)R^{1a}, —S(O)(R^{1})_2 R^{1b}, —S(O)(OR^{1})R^{1b}, or —S(O)(OS)(OR^{1})R^{1b};

each R^4 and R^5 is independently hydrogen or C_{1-6} alkyl; or R^4 and R^5 are linked together to form a bond, C_{1-6} alkenylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, or C_{2-6} heteroalkylene;

each R^6 is independently C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heteroaryl-C_{1-6} alkyl;

each U is independently a bond, —C(O)—, —C(O)O—, —C(O)NR^{1a}, —O—, —OC(O)O—, —OC(O)NR^{1a}, —NR^{1}—, —NR^{1}C(O)NR^{1a}, —NR^{1}S(O)NR^{1b}, —NR^{1}S(O)ONR^{1b}, —S—, —S(O)—, or —S(O)(R^{1})_2 R^{1b};

each X, Y, and Z is independently N or CR^7, with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R^7 is hydrogen or C_{1-6} alkyl; and

each A, B, D, and E is independently a bond, C, O, N, S, NR^2, CR^2, or CR^2R^10, where each R^2 and R^10 is independently hydrogen, halo, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl; wherein the bonds between A, B, D, and E may be saturated or unsaturated; with the proviso that no more than one of A, B, D, and E are a bond;

each R^{1a}, R^{1b}, R^{1c}, and R^{1d} is independently (i) hydrogen; or (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclylly; wherein each alkyl, alkenylene, heteroalkylene, alkenyl, alkynylene, heteroalkenylene, alkenyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclylly in R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{1a}, R^{1b}, R^{1c}, R^{1d}, R^{10}, R^{11}, R^{12}, R^{13}, or R^{14} is optionally substituted with one or more, in one embodiment, one, two, three, or four groups, each independently selected from (a) cyano, halo, or nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclylly, each of which is further optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; and (c) —C(O)R^{4}, —C(O)OR^{4}, —C(O)NR^{4}R^{5}, —C(NR^{4})R^{5}, —NR^{4}R^{5}, —OR^{4}, —OC(O)R^{4}, —OC(O)OR^{4}, —OC(O)NR^{4}R^{5}, —OC(=NR^{4})NR^{4}R^{5}, —OS(O)R^{4}, —OS(O)NR^{4}R^{5}, —OS(O)(NR^{4})R^{5}, —OR^{4}, —NR^{4}C(O)R^{5}, —NR^{4}(CO)OR^{5}, —NR^{4}(C(=NR^{4})N)R^{5}, —NR^{4}(C(=NR^{4})O)R^{5}, —NR^{4}(C(=NR^{4})S)R^{5}, —NR^{4}(S)R^{5}, —SR^{5}, —S(O)R^{5}, or —S(O)(R^{1})_2 R^{1b};

wherein each Q is independently selected from the group consisting of (a) cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclylly; and (c) —C(O)R^{6}, —C(O)OR^{6}, —C(O)NR^{6}R^{7}, —C(NR^{6})R^{7}, —NR^{6}R^{7}, —OR^{6}, —OC(O)R^{6}, —OC(O)OR^{6}, —OC(O)NR^{6}R^{7}, —OC(=NR^{6})NR^{6}R^{7}, —OS(O)R^{6}, —OS(O)NR^{6}R^{7}, —OS(O)(NR^{6})R^{7}, —OR^{6}, —NR^{6}C(O)R^{7}, —NR^{6}(CO)OR^{7}, —NR^{6}(C(=NR^{6})N)R^{7}, —NR^{6}(C(=NR^{6})O)R^{7}, —NR^{6}(C(=NR^{6})S)R^{7}, —NR^{6}(S)R^{7}, or —NR^{6}(SO)R^{7}, —NR^{6}(SO)(NR^{6})R^{7}, —NR^{6}(SO)(OR^{6})R^{7}, —NR^{6}(SO)(OS)(OR^{6})R^{7}, or —NR^{6}(S)R^{7}, or —NR^{6}(SO)(R^{1})_2 R^{1b}.
(O)R₈, —NR₆S(O)NR₆R₉, —SR₈, —S(O)OR₈, and —S(O)NR₆R₉, wherein each R₈, R₉, R₆, and R₉ is independently (i) hydrogen; (ii) C₆₋₇ alkyl, C₆₋₇ alkenyl, C₆₋₇ alkynyl, C₆₋₇ cycloalkyl, C₆₋₇ aryl, C₆₋₇ aralkyl, heteroaryl, or heterocyclic; or (iii) R₈ and R₉ together with the N atom to which they are attached form heterocyclic.

In another embodiment, provided herein is a compound of Formula I:

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

R₈ is hydrogen, C₁₋₆ alkyl, —S—C₁₋₆ alkyl, —S(O)C₁₋₆ alkyl, or —S(O)₂C₁₋₆ alkyl;

R₉ and R₉ are each independently (a) hydrogen, cyan, halo, or nitro; (b) C₁₋₆ alkyl, C₂₋₇ alkenyl, C₆₋₇ alkynyl, C₆₋₇ cycloalkyl, C₆₋₇ aryl, C₆₋₇ aralkyl, heteroaryl, or heterocyclic; or (c) —(O)R¹¹, —(O)(OR)¹², —(O)NR₆R₉, —(O)NR₆OR¹², —(O)NR₆R₉, —(O)NR₆OR¹², —(O)NR₆R₉, —(O)NR₆OR¹², —(O)NR₆R₉, —(O)NR₆OR¹², —(O)NR₆S(O)R¹³, —(O)NR₆S(O)R¹³, —(O)NR₆S(O)R¹³, or —(O)NR₆S(O)R¹³;

R₉ and R₉ are each independently hydrogen or C₁₋₆ alkyl; R₉ is C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclic—C₁₋₆ alkyl;

R₈ is C₁₋₆ aryl, C₁₋₅ aralkyl, heteroaryl, or heterocyclic—C₁₋₆ alkyl;

U is a bond, —(O)—, —(O)(OR)—, —(O)(OR)², —O—, —OC(O)O—, —OC(O)OR¹⁴, —OC(O)O—, —OC(O)OR¹⁴, —OC(O)O—, —OC(O)OR¹⁴, —OC(O)O—, —OC(O)OR¹⁴, —OC(O)O—, —OC(O)OR¹⁴, —OC(O)O—, —OC(O)OR¹⁴, —OC(O)O—, —OC(O)OR¹⁴, or —OC(O)O—; 

X, Y, and Z are each independently N or CR², with the proviso that at least two of X, Y, and Z are nitrogen atoms; where R₉ is hydrogen or C₁₋₆ alkyl; and each R¹⁴, R¹⁵, R¹⁶, and R¹⁷ is independently (i) hydrogen; or (ii) C₁₋₆ alkyl, C₂₋₇ alkenyl, C₆₋₇ alkynyl, C₆₋₇ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclic; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclic is optionally substituted with one or more groups, each independently selected from (a) cyano, halo, and nitro; (b) C₁₋₆ alkyl, C₂₋₇ alkenyl, C₆₋₇ alkynyl, C₆₋₇ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, and heterocyclic, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; and (c) —(O)R¹⁴, —(O)(OR)¹⁴, —(O)(OR)², —(O)NR₆R₉;
and R^2 are hydrogen, X, Y, and Z are N, and U is a bond. R^4 is not phenyl, pyridinyl, pyrimidinyl, or indolyl.

In another embodiment, provided herein is a compound of Formula II:

In yet another embodiment, provided herein is a compound of Formula III:

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

R^1, R^2, R^3, R^4, R^5, X, Y, and Z are each as defined herein; U is R^6, and NR^1 is not phenyl.

In another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when one of X, Y, and Z is CH=, and U is a bond, R^6 is not phenyl.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when X, Y, and Z is N, and R^5 is C_6H_5 ary1 or heteroaryl, then U is not a bond.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when R^2, R^3, and R^5 are hydrogen, X, Y, and Z are N, and U is a bond, R^6 is not substituted phenyl.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when R^2, R^3, R^4, and R^5 are hydrogen, X, Y, and Z are N, and U is a bond, R^6 is not substituted 3-pyridinyl or 4-pyridinyl.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when R^2, R^3, R^4, and R^5 are hydrogen, X, Y, and Z are N, and U is a bond, R^6 is not substituted 2-indolyl.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when R^2, R^3, and R^5 are hydrogen, X, Y, and Z are N, and U is a bond, R^6 is not phenyl, 3-pyridinyl, 4-pyridinyl, 5-pyrimidinyl, or 4-indolyl.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when R^2, R^3, and R^5 are hydrogen, X, Y, and Z are N, and U is a bond, R^6 is not phenyl, pyridinyl, pyrimidinyl, or indolyl.

In yet another embodiment, provided herein is a compound of Formula II, wherein R^1, R^2, R^3, R^4, R^5, U, X, Y, and Z are each as defined herein, with the proviso that when R^2, R^3, and R^5 are hydrogen, X, Y, and Z are N, and U is a bond, R^6 is not phenyl, pyridinyl, pyrimidinyl, or indolyl.

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;
wherein:

$$R_1, R_2, R_3, R_4, R_5, R_6, X, Y, \text{ and } Z \text{ are each as defined herein;}$$

- $U$ is a bond, $-\text{C(O)}-$, $-\text{C(O)}\text{-}$, $-\text{C(O)}\text{NR}^{12}-$, $-\text{NR}^{12}\text{-}$, $-\text{O}\text{-}$, $-\text{O}\text{(O)}\text{-}$, $-\text{O}\text{(O)}\text{NR}^{12}\text{-}$, $-\text{NR}^{12}\text{-}$, $-\text{NR}^{12}\text{C(O)NR}^{12}\text{-}$, $-\text{NR}^{12}\text{Si(O)}\text{-}$, $-\text{NR}^{12}\text{Si(O)}\text{NR}^{12}\text{-}$, $-\text{NR}^{12}\text{Si(O)}\text{NR}^{12}\text{-}$, $-\text{S}\text{-}$, $-\text{S(O)}\text{-}$, or $-\text{S(O)}\text{O}\text{-}$.

$R^4$ and $R^5$ are each independently (a) hydrogen, cyano, halo, or nitro; (b) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{6-14}$ aryl, $C_{7-13}$ aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents as described herein; and

$m$ is an integer of 1, 2, or 3.

In yet another embodiment, provided herein is a compound of Formula V:

![Chemical Structure](image)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

- $R_1, R_2, R_3, R_4, R_5, R_6, X, Y, \text{ and } Z$ are each as defined herein;
- $A^2$, $A^3$, and $A^4$ are each independently $N$ or $CR^5$ with the proviso that no more than one of $A^2$, $A^3$, and $A^4$ is $N$;
- $R^4$ and $R^5$ are each independently (a) hydrogen, cyano, halo, or nitro; (b) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{6-14}$ aryl, $C_{7-13}$ aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents as described herein;
- $p$ is an integer of 0, 1, 2, or 3; and each $R^8$ is independently (a) hydrogen, cyano, halo, or nitro; (b) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{6-14}$ aryl, $C_{7-13}$ aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents as described herein; or (c) $-\text{C(O)}R^{12}-$, $-\text{COOR}^{12}-$, $-\text{C}NR^{12}R^{12}-$, $-\text{C}NR^{12}R^{12}-$, $-\text{OC}(O)R^{12}-$, $-\text{OC}(O)NR^{12}R^{12}-$, or $-\text{OC}(O)NR^{12}R^{12}-$.

In yet another embodiment, provided herein is a compound of Formula V or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof:

![Chemical Structure](image)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

- $R_1, R_2, R_3, R_4, R_5, R_6, U, X, Y, \text{ and } Z$ are each as defined herein;
- $A^2$, $A^3$, and $A^4$ are each independently $N$ or $CR^5$ with the proviso that no more than one of $A^2$, $A^3$, and $A^4$ is $N$;
- $U$ is a bond, $-\text{C(O)}-$, $-\text{C(O)}\text{-}$, $-\text{C(O)}\text{NR}^{12}-$, $-\text{NR}^{12}\text{-}$, $-\text{O}\text{-}$, $-\text{O}\text{(O)}\text{-}$, $-\text{O}\text{(O)}\text{NR}^{12}\text{-}$, $-\text{NR}^{12}\text{-}$, $-\text{NR}^{12}\text{C(O)NR}^{12}\text{-}$, $-\text{NR}^{12}\text{Si(O)}\text{-}$, $-\text{NR}^{12}\text{Si(O)}\text{NR}^{12}\text{-}$, $-\text{NR}^{12}\text{Si(O)}\text{NR}^{12}\text{-}$, $-\text{S}\text{-}$, $-\text{S(O)}\text{-}$, or $-\text{S(O)}\text{O}\text{-}$.

$R^4$ and $R^5$ are each independently (a) hydrogen, cyano, halo, or nitro; (b) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{6-14}$ aryl, $C_{7-13}$ aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents as described herein; and

$m$ is an integer of 1, 2, or 3.

In yet another embodiment, provided herein is a compound of Formula V, wherein $R_1, R_2, R_3, R_4, R_5, R_6, U, X, Y, \text{ and } Z$, and $p$ are each as defined herein; and

$A^2$, $A^3$, and $A^4$ are each independently $C$, $N$, or $CR^5$; with the proviso that no more than one of $A^2$, $A^3$, and $A^4$ is $N$.

In one embodiment, provided herein is a compound of Formula V wherein $R_1, R_2, R_3, R_4, R_5, R_6, U, X, Y, \text{ and } Z$, and $p$ are each as defined herein, with the proviso that when $X, Y, \text{ and } Z$ is $N$, $A^2$ and $A^4$ are $CR^5$, and $p$ is 0; then $U$ is not a bond.

In certain embodiments, $A^2$ is $C$. In certain embodiments, $A^2$ is $N$. In certain embodiments, $A^3$ is $CR^5$, where $R^5$ is as defined herein. In certain embodiments, $A^4$ is $CH$. In certain embodiments, $A^3$ is $C$. In certain embodiments, $A^3$ is $N$. In certain embodiments, $A^4$ is $CR^5$, where $R^5$ is as defined herein. In certain embodiments, $A^4$ is $CH$. In certain embodiments, $A^4$ is $C$. In certain embodiments, $A^4$ is $N$.

In certain embodiments, $A^2$, $A^3$, and $A^4$ are independently $CR^5$, wherein $R^5$ is as defined herein. In certain embodiments, $A^2$ and $A^4$ are independently $CR^5$, wherein $R^5$ is as defined herein. In certain embodiments, $A^2$, $A^3$, and $A^4$ are independently $CR^5$, and $A^4$ is $N$, wherein $R^5$ is as defined herein.

In yet another embodiment, provided herein is a compound of Formula VI:

![Chemical Structure](image)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

- $R_1, R_2, R_3, R_4, R_5, R_6, U, X, Y, \text{ and } Z$ are each as defined herein;
- $R^4$ is (a) hydrogen, cyano, halo, or nitro; (b) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{3-7}$ cycloalkyl, $C_{6-14}$ aryl, $C_{7-13}$ aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents as described herein; or (c) $-\text{C(O)}R^{12}-$, $-\text{C(O)}\text{-}$, $-\text{C(O)}\text{NR}^{12}R^{12}-$, $-\text{(O)NR}^{12}R^{12}-$, or $-\text{(O)NR}^{12}R^{12}-$.

In yet another embodiment, provided herein is a compound of Formula VI or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

- $R_1, R_2, R_3, R_4, R_5, R_6, U, X, Y, \text{ and } Z$ are each as defined herein; and

$R^4$ is hydrogen.
In certain embodiments, E² and E³ are N, and E⁴ is CR⁶. In certain embodiments, E², E³, and E⁴ are N.

In yet another embodiment, provided herein is a compound of Formula Ia or Ib:
bond. In one embodiment, A is N. In another embodiment, A and D are N. In yet another embodiment, A and D are N, B is CR₂, and the bond between B and D is a double bond, where R² is as defined herein. In yet another embodiment, A and D are N, B is CH₂, and the bond between B and D is a double bond. In yet another embodiment, A is N, B and D are each independently CR₂, and the bond between B and D is a double bond, where R² is as defined herein. In yet another embodiment, A is N, B and D are each independently CHR₂, and the bond between B and D is a single bond. In yet another embodiment, A is N, B and D are each CH₂, and the bond between B and D is a single bond.

In this embodiment, the compound of Formula Ib has the structure of Formula IX:

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein R¹, R², R³, R⁴, R⁵, R⁶, A, B, D, and U are each as defined herein, and the bond between B and D is a single or double bond. In one embodiment, A is N. In another embodiment, A and D are N. In yet another embodiment, A and D are N, B is CR₂, and the bond between B and D is a double bond, where R² is as defined herein. In yet another embodiment, A is N, B and D are each independently CR₂, and the bond between B and D is a double bond. In yet another embodiment, A is N, B and D are each independently CHR₂, and the bond between B and D is a single bond, where R² is as defined herein. In yet another embodiment, A is N, B and D are each CH₂, and the bond between B and D is a single bond.

The groups, R¹, R², R³, R⁴, R⁵, R⁶, A, B, D, E, U, X, Y, Z, m, and p in Formulae provided herein, e.g., Formulae I, IA, IB, Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX, are further defined in the embodiments described herein. All combinations of the embodiments provided herein for such groups are within the scope of this disclosure.

In certain embodiments, R¹ is hydrogen, C₁₋₆ alkyl, —S—C₁₋₆ alkyl, or —SO₂—C₁₋₆ alkyl. In certain embodiments, R¹ is C₁₋₆ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ is C₁₋₆ alkyl, substituted with one or more, in one embodiment, one to three, halo. In certain embodiments, R¹ is C₁₋₆ alkyl, substituted with one to three, in one embodiment, one, two, or three, fluoro groups. In certain embodiments, R¹ is methyl, fluoromethyl, difluoromethyl, or trifluoromethyl. In certain embodiments, R¹ is difluoromethyl. In certain embodiments, R¹ is —S—C₁₋₆ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ is —S(O)—C₁₋₆ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ is methanesulfonyl (—SCH₃). In certain embodiments, R¹ is —S(O)—C₁₋₆ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ is methanesulfonyl (—SOCH₃). In certain embodiments, R¹ is methanesulfonyl (—SO₂CH₃).
(OOR₁ʳ⁻, —NR¹ʳ⁻CO(NR₂ʳ⁻)R₃ʳ⁻, —NR¹ʳ⁻CO(=NR¹⁻R₂⁻)R₃ʳ⁻, —NR¹ʳ⁻CO(NR₂ʳ⁻)R₃ʳ⁻, —NR¹ʳ⁻S(O)R₁ʳ⁻, —NR¹ʳ⁻S(O)R₁ʳ⁻R₂ʳ⁻, —NR¹ʳ⁻S(O)R₁ʳ⁻R₂ʳ⁻R₃ʳ⁻, —NR¹ʳ⁻SO₃H, —SR¹ʳ⁻, —S(OR)₁ʳ⁻, —S(OR)₁ʳ⁻R₂ʳ⁻, or —S(OR)₁ʳ⁻R₂ʳ⁻R₃ʳ⁻), where each R¹ʳ⁻, R₂ʳ⁻, and R₃ʳ⁻ is as defined herein. In certain embodiments, R¹ʳ⁻ is cyano, halo, or nitro. In certain embodiments, R²ʳ⁻ is C₆H₅ alkyl, C₃H₇ alkynl, C₃H₇ alkynyl, C₃H₇ cycloalkyl, C₆H₄ aryl, C₆H₄ alkyl, C₆H₄ alkenyl, C₆H₄ alkenyl, C₆H₄ alkynyl, C₆H₄ ary1, C₆H₄ alkenyl, heteroaryl, or heterocyclyl, optionally substituted with one or more substituents as described herein. 

In certain embodiments, R¹ʳ⁻ is —CO(R₁ʳ⁻), —COOR₁ʳ⁻, —CO(O)R₁ʳ⁻, or —CO(O)OR₁ʳ⁻, while R₁ʳ⁻, R₂ʳ⁻, and R₃ʳ⁻ are each as defined herein. In certain embodiments, R¹ʳ⁻ is —OR₁ʳ⁻, —OC(O)R₁ʳ⁻, —OC(O)OR₁ʳ⁻, or —OC(O)OR₁ʳ⁻, and R₁ʳ⁻, R₂ʳ⁻, and R₃ʳ⁻ are each as defined herein. In certain embodiments, R¹ʳ⁻ is —NR¹⁻R₂ʳ⁻, —NR¹⁻R₂ʳ⁻R₃ʳ⁻, or —NR¹⁻S(O)R₁ʳ⁻, wherein R¹ʳ⁻, R₂ʳ⁻, and R₃ʳ⁻ are each as defined herein. In certain embodiments, R¹ʳ⁻ is —SR¹ʳ⁻, —S(OR)₁ʳ⁻, —S(OR)₁ʳ⁻R₂ʳ⁻, or —S(OR)₁ʳ⁻R₂ʳ⁻, wherein R¹ʳ⁻, R₂ʳ⁻, and R₃ʳ⁻ are each as defined herein. In certain embodiments, R¹ʳ⁻ is methyl, ethyl, or propyl (e.g., n-propyl, isopropyl, or 2-isopropyl), optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is methoxy, ethoxy, propoxy, or isoproxy.

In certain embodiments, R¹ʳ⁻ is hydrogen or C₆H₅ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is hydrogen. In certain embodiments, R¹ʳ⁻ is C₆H₅ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is hydrogen, methyl, ethyl, or propyl (e.g., n-propyl, isopropyl, or 2-isopropyl), optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is methyl, ethyl, n-propyl, or isopropyl.

In certain embodiments, R¹ʳ⁻ is hydrogen or C₆H₅ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is hydrogen. In certain embodiments, R¹ʳ⁻ is C₆H₅ alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is hydrogen, methyl, ethyl, or propyl (e.g., n-propyl, isopropyl, or 2-isopropyl), optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is methyl, ethyl, n-propyl, or isopropyl.

In certain embodiments, R¹ʳ⁻ and R₂ʳ⁻ are both hydrogen. In certain embodiments, R¹ʳ⁻ and R₂ʳ⁻ are linked together to form a bond. In certain embodiments, R¹ʳ⁻ and R₂ʳ⁻ are linked together to form C₆H₅ alkenyl, optionally substituted with one or more substituents. In certain embodiments, R¹ʳ⁻ and R₂ʳ⁻ are linked together to form methylene, ethylene, or propylene, each optionally substituted with one or more substituents.

In certain embodiments, R¹ʳ⁻ is C₆H₄ aryl, C₆H₄ alkyl, heteroaryl, or heteroaryl-C₆H₄ alkyl, each substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is phenyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R¹ʳ⁻ is phenyl, optionally substituted with one or more substituents as described herein. Each independently selected from the group consisting of halo, cyano, amino, and methoxy. In certain embodiments, R¹ʳ⁻ is phenyl, aminophenyl, nitrophenyl, or methoxyphenyl. In certain embodiments, R¹ʳ⁻ is phenyl, 3-aminophenyl, 3-nitrophenyl, or 3-methoxyphenyl.
(methyl)amino, 3-(dimethylamino)propylamino, (3-(dimethylamino)propyl)(methyl)amino, 2-(4-morpholinyl)ethylamino, 2-(4-morpholinyl)ethyl(methyl)amino, 3-(4-morpholinyl)propylamino, (3-(4-morpholinyl)propyl)(methyl)amino, 1-methyl-4-piperidinylamino, (1-methyl-4-piperidinyl)(methyl)amino, 4-methyl-1-piperazinyl, and 4-(dimethylamino)-1-piperidinyl.

In certain embodiments, R\(^3\) is pyrazolyl, methyl-pyrazolyl, [2-(dimethylamino)ethyl]pyrazolyl, [3-(dimethylamino)propyl]pyrazolyl, [2-(4-morpholinyl)ethyl]pyrazolyl, or [3-(4-morpholinyl)propyl]pyrazolyl. In certain embodiments, R\(^3\) is pyrazol-1-yl, 1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-3-yl, 1-methyl-1H-pyrazol-4-yl, 1-methyl-1H-pyrazol-5-yl, 1-[2-(dimethylamino)ethyl]-1H-pyrazol-4-yl, 1-[3-(dimethylamino)propyl]-1H-pyrazol-4-yl, 1-[2-(4-morpholinyl)ethyl]-1H-pyrazol-4-yl, or 1-[3-(4-morpholinyl)propyl]-1H-pyrazol-4-yl.

In certain embodiments, R\(^6\) is imidazolyl or methyl-imidazolyl. In certain embodiments, R\(^6\) is imidazol-1-yl or 1-methyl-1H-imidazol-5-yl.

In certain embodiments, R\(^8\) is thiazoyl, [dimethylamino]methyl-thiazolyl, or (4-morpholinylmethyl)-thiazolyl. In certain embodiments, R\(^8\) is 1,3-thiazol-5-yl, 2-[dimethylamino]methyl]-1,3-thiazol-5-yl, or 2-[4-morpholinylmethyl]-1,3-thiazol-5-yl.

In certain embodiments, R\(^8\) is triazolyl or methyl-1,2,3-triazolyl. In certain embodiments, R\(^8\) is 1-methyl-1H-1,2,3-triazol-4-yl, 1-methyl-1H-1,2,3-triazol-5-yl, or 2-methyl-1H-1,2,3-triazol-4-yl.

In certain embodiments, R\(^8\) is tetrazolyl or methyl-tetrazolyl. In certain embodiments, R\(^8\) is 1-methyl-1H-tetrazol-5-yl or 2-methyl-1H-tetrazol-5-yl.

In certain embodiments, R\(^8\) is pyrazinyl, aminopyrazinyl, or methoxyrazinyl. In certain embodiments, R\(^8\) is 2-pyrazinyl, 5-amino-2-pyrazinyl, 6-amino-2-pyrazinyl, or 6-methoxy-2-pyrazinyl.

In certain embodiments, R\(^8\) is pyridazinyl or methoxypyridazinyl. In certain embodiments, R\(^8\) is pyridazin-3-yl, pyridazin-4-yl, or 6-methoxypyridazin-3-yl.

In certain embodiments, R\(^8\) is pyridinyl, fluoroxyridinyl, chloropyridinyl, amino-pyridinyl, methylamino-pyridinyl, dimethylamino-pyridinyl, [2-(dimethylamino)ethylamino]-pyridinyl, [2-(dimethylaminoethyl)amino]-pyridinyl, [3-(dimethylamino)methylamino]-pyridinyl, [3-(dimethylamino)propyl]methylamino]-pyridinyl, [2-(4-morpholinyl)ethylamino]-pyridinyl, [2-(4-morpholinyl)ethyl(methyl)amino]-pyridinyl, [2-(4-morpholinyl)ethyl(methyl)amino]-pyridinyl, [(3-(4-morpholinyl)propyl)methylamino]-pyridinyl, [(3-(4-morpholinyl)propyl)methylamino]-pyridinyl, [(3-(4-morpholinyl)propyl)amino]-pyridinyl, [(3-(4-morpholinyl)propyl)(methyl)amino]-pyridinyl, [(3-(4-morpholinyl)propyl)(methyl)amino]-pyridinyl, [(3-(4-morpholinyl)propyl)amino]-pyridinyl, [(3-(4-morpholinyl)propyl)(methyl)amino]-pyridinyl, [(3-(4-morpholinyl)propyl)(methyl)amino]-pyridinyl, and [(3-(4-morpholinyl)propyl)(methyl)amino]-pyridinyl.

In certain embodiments, R\(^8\) is pyridinyl.

In certain embodiments, R\(^8\) is pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 2-fluoropyridin-5-yl, 2-chloropyridin-5-yl, 2-amino-5-pyridinyl, 2-methylamino-3-pyridinyl, 2-dimethylamino-5-pyridinyl, 2-[2-(dimethylamino)ethylamino]-5-pyridinyl, 2-[2-(dimethylaminoethyl)amino]-5-pyridinyl, 2-[2-(3-dimethylamino)propylamino]-5-pyridinyl, 2-[2-(4-morpholinyl)propyl](methyl)amino]-5-pyridinyl, 2-[2-(4-morpholinyl)ethylamino]-3-pyridinyl, 2-[(2-(4-morpholino)(ethyl)methyl)amino]-3-pyridinyl, 2-[3-(4-morpholinyl)ethylamino]-3-pyridinyl, 2-[3-(4-morpholinyl)propyl](methyl)amino]-3-pyridinyl, 2-[3-(4-morpholinyl)propyl](methyl)amino]-3-pyridinyl, 6-[4-(methyl-1-piperazinyl)-3-pyridinyl, 6-[4-(dimethylamino)-1-piperidinyl]-3-pyridinyl, 2-[1-(methyl-4-piperidinylamino)-5-pyridinyl, 2-[1-(1-methyl-4-piperidinylamino)(methyl)amino]-5-pyridinyl, 2-methoxy-4-pyrindinyl, 4-methoxy-3-pyridinyl, 5-methoxy-3-pyridinyl, 6-methoxy-3-pyridinyl, 2-[2-(dimethylamino)ethoxy]-4-pyridinyl, 5-[2-(dimethylamino)ethoxy]-4-pyridinyl, 2-[3-(dimethylamino)propoxy]-4-pyridinyl, 2-[3-(dimethylamino)propoxy]-5-pyridinyl, 5-[3-(dimethylamino)propoxy]-3-pyridinyl, 6-[3-(dimethylaminopropoxy)-3-pyridinyl, 6-[1-(methyl-4-piperidinyl)oxy]-3-pyridinyl, 6-[1-(methyl-3-pyrrolidinyl)oxy]-3-pyridinyl, 2-[2-(dimethylamino)ethyl]-3-pyridinyl, and 2-[(2-(methyl)amino)ethyl]-3-pyridinyl. In certain embodiments, R\(^8\) is 3-pyridinyl.

In certain embodiments, R⁵ is heterocyclic quinolinyl. In certain embodiments, R⁶ is quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl, or quinolin-8-yl.

In certain embodiments, R⁷ is heterocyclic C₅₋₅-alkyl, optionally substituted with one or more substituents as described herein. In certain embodiments, R⁷ is heterocyclic (CR₅₋₅R₆₋₆), wherein R₅-R₆ are each as defined herein; p is an integer of 1, 2, or 3, and the heterocyclic is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁷ is heterocyclic (CH₂)ₚ₋₆, wherein p is an integer of 1, 2, or 3, and the heterocyclic is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁷ is imidazolylethyl, pyridinylethyl, or pyridinylmethyl. In certain embodiments, R⁷ is 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(1H-imidazol-4-yl)ethyl, 2-(pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, or 2-(4-pyridinyl)ethyl.

In certain embodiments, each R⁸ is independently (a) hydrogen, cyanato, halo, or nitro; (b) C₁₋₅-alkyl, C₁₋₅-cycloalkyl, C₁₋₅-alkenyl, C₁₋₅-cycloalkenyl, C₁₋₅-aryl, C₁₋₅-cycloalkenyl, heteroarylenyl, or heterocyclyl; or (c) (CR₅₋₅R₆₋₆) wherein R₅-R₆ are each as defined herein; p is an integer of 1, 2, or 3, and the heterocyclic is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁸ is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁸ is heterocyclyl (CR₅₋₅R₆₋₆), wherein R₅-R₆ are each as defined herein; p is an integer of 1, 2, or 3, and the heterocyclic is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁸ is imidazolylethyl, pyridinylethyl, or pyridinylmethyl. In certain embodiments, R⁸ is 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(1H-imidazol-4-yl)ethyl, 2-(pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, or 2-(4-pyridinyl)ethyl.

In certain embodiments, each R⁹ is independently (a) hydrogen, cyanato, halo, or nitro; (b) C₁₋₅-alkyl, C₁₋₅-cycloalkyl, C₁₋₅-alkenyl, C₁₋₅-cycloalkenyl, C₁₋₅-aryl, C₁₋₅-alkenyl, C₁₋₅-cycloalkenyl, heteroarylenyl, or heterocyclyl; or (c) (CR₅₋₅R₆₋₆) wherein R₅-R₆ are each as defined herein; p is an integer of 1, 2, or 3, and the heterocyclic is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁹ is heterocyclic (CR₅₋₅R₆₋₆), wherein R₅-R₆ are each as defined herein; p is an integer of 1, 2, or 3, and the heterocyclic is optionally substituted with one or more substituents as described herein. In certain embodiments, R⁹ is imidazolylethyl, pyridinylethyl, or pyridinylmethyl. In certain embodiments, R⁹ is 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, 2-(1H-imidazol-4-yl)ethyl, 2-(pyridinyl)ethyl, 2-(3-pyridinyl)ethyl, or 2-(4-pyridinyl)ethyl.

In certain embodiments, D is independently a bond. In certain embodiments, D is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, D is N. In certain embodiments, D is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, D is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, E is independently a bond. In certain embodiments, E is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, E is N. In certain embodiments, E is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, E is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, F is independently a bond. In certain embodiments, F is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, F is N. In certain embodiments, F is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, F is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, G is independently a bond. In certain embodiments, G is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, G is N. In certain embodiments, G is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, G is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, H is independently a bond. In certain embodiments, H is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, H is N. In certain embodiments, H is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, H is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, J is independently a bond. In certain embodiments, J is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, J is N. In certain embodiments, J is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, J is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, K is independently a bond. In certain embodiments, K is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, K is N. In certain embodiments, K is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, K is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, L is independently a bond. In certain embodiments, L is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, L is N. In certain embodiments, L is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, L is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, M is independently a bond. In certain embodiments, M is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, M is N. In certain embodiments, M is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, M is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, N is independently a bond. In certain embodiments, N is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, N is N. In certain embodiments, N is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, N is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, O is independently a bond. In certain embodiments, O is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, O is N. In certain embodiments, O is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, O is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, P is independently a bond. In certain embodiments, P is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, P is N. In certain embodiments, P is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, P is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.

In certain embodiments, Q is independently a bond. In certain embodiments, Q is independently a nitrogen, oxygen, or sulfur atom. In certain embodiments, Q is N. In certain embodiments, Q is independently CR₋ₓ or CHR₋ₓ, wherein R₋ₓ is as defined herein. In certain embodiments, Q is independently CR₋ₓ, wherein R₋ₓ is hydrogen, halo, or C₁₋₅-alkyl.
In certain embodiments, X, Y, and Z are nitrogen. In certain embodiments, X and Y are nitrogen, and Z is CH. In certain embodiments, X and Z are nitrogen, and Y is CH. In certain embodiments, Y and Z are nitrogen, and X is CH.

In certain embodiments, m is an integer of 1, 2, or 3. In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3.

In certain embodiments, p is an integer of 0, 1, 2, or 3. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2. In certain embodiments, p is 3.

In one embodiment, provided herein is a compound selected from:

4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(methylsulfonyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(methylsulfonyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine;
N-benzyl-4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
N-benzyl-4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine;
2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-phenylsulfanyl-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-phenylsulfanyl-1,3,5-triazin-2-yl]-1H-benimidazole;
N-(2-chloro-5-pyrimidinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine;
2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-3-yl)-1,3,5-triazin-2-yl]-1H-benimidazole;
N-[3-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)]-4-oxypropyl]-N,N-dimethyamine;
2-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-4,5-bipyrimidine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-4,5-bipyrimidine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-2-methoxy-4,5-bipyrimidine;
2-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-4,5-bipyrimidin-2-amine;
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-3-yl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-3-yl)-1,3,5-triazin-2-yl]-1H-benimidazole-6-ylamine;
2-(difluoromethyl)-4-methoxy-1-[4-(1-methyl-1H-pyrazol-3-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole-6-ylamine;
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-3-yl)-1,3,5-triazin-2-yl]-1H-benimidazole-6-ylamine;
2-(difluoromethyl)-1-[4-(1H-imidazol-1-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-methoxy-1H-benimidazole; and
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-2-pyrimidinyl]-1H-benimidazole-6-ylamine; and enantiomers, mixtures of enantiomers, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.

In another embodiment, provided herein is a compound selected from:

N-[4-[6-amino-2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N-(3-pyridinyl)amine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2,5-pyridinediamine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N-[3-(dimethylamino)propyl]-2,5-pyridinediamine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N-[3-(dimethylamino)propyl]-N,N-dimethylamine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-[6-methoxy-3-pyridinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-[6-[3-(dimethylamino)propoxy]-3-pyridinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-[1-methyl-1H-imidazol-5-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-[1-methyl-1H-pyrazol-3-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
2-(difluoromethyl)-1-[4-(1H-imidazol-1-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-methoxy-1H-benimidazole-6-amine;
2-(difluoromethyl)-4-methoxy-1-[4-(1-methyl-1H-pyrazol-3-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
N-[2-[4-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-pyrazol-1-yl]ethyl]-N,N-dimethyamine;
N-[3-[4-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-pyrazol-1-yl]propyl]-N,N-dimethyamine; and
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-1,3,5-triazin-2-yl]-1H-benimidazole-6-ylamine; and enantiomers, mixtures of enantiomers, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.
In yet another embodiment, provided herein is a compound selected from:

2-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-2-pyrimidinamine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-2-pyrimidinamine;
6-[2-(difluoromethyl)-1H-benimidazol-1-yl]-2-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-(difluoromethyl)-1-[4-(4-morpholino)-6-(3-pyridinyl)-1H-benimidazol-1-yl]-2-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
2-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinyl)-4-pyrimidinamine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N[(2-pyridinyl)ethyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholiny)-N-[5-[2-(4-morpholiny)ethoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholiny)-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[2-(4-morpholiny)ethoxy]-4-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[5-[3-(dimethylamino)propoxy]-3-pyridinyl]-1,3,5-triazin-2-amine;
2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(5-pyrimidinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(5-pyrimidinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-[(difluoromethyl)-4-methoxy-1-[4-(2-methoxy-5-pyrimidinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(2-methoxy-5-pyrimidinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-1-[4-(6-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(6-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-1-[4-(5-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(5-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-1-[4-(2-methoxy-4-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(2-methoxy-4-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-1-[4-(1-methyl-1H-pyrazol-4-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(1-methyl-1H-pyrazol-4-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(1,3-thiazol-5-yl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1,3-thiazol-5-yl)-1,3,5-triazin-2-yl]-1H-benimidazole;
N-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2-pyrimidinediamine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2-pyrimidinediamine;
5-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2-pyrimidinediamine;
5-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2-pyrimidinediamine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-(2-pyrazinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-(2-pyrazinyl)-1,3,5-triazin-2-amine;
N-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2,5-pyrazinediamine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2,5-pyrazinediamine;
N-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2,6-pyrazinediamine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-[4-morpholinyl]-1,3,5-triazin-2-yl]-2,6-pyrazinediamine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-(6-methoxy-2-pyrazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-(6-methoxy-2-pyrazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
6-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-pyrazinaminime;
6-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-pyrazinaminime;
2-(difluoromethyl)-1-[4-(6-methoxy-2-pyrazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
2-(difluoromethyl)-4-methoxy-1-[4-(6-methoxy-2-pyrazinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benimidazole;
N-[4-[6-amino-2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N-(3-pyridinyl)amine;
anesthetics, mixtures of disinfectants, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.
In yet another embodiment, provided herein is a compound selected from:
N-[4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-quinoxalinamine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(5-pyridinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-[4-(methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-[6-fluoro-3-pyridinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
N-(6-chloro-3-pyridinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-(6-methoxy-4-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine;
and esterans, mixtures of esterans, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof.
In still another embodiment, provided herein is a compound selected from:
4-[4-(2-(difluoromethyl)-4-methoxy-1H-benzol[d]imidazol-1-yl)-7-(pyridin-3-yl)-6,7-dihydro-5H-pyrrrolo[2,3-d]pyrimidin-2-yl]morpholine;
4-[4-(2-(difluoromethyl)-4-methoxy-1H-benzol[d]imidazol-1-yl)-7-(pyridin-3-yl)-6,7-dihydro-5H-pyrrrolo[2,3-d]pyrimidin-2-yl]morpholine;
4-[6-(2-(difluoromethyl)-4-methoxy-1H-benzol[d]imidazol-1-yl)-9-(pyridin-3-yl)-9H-1-purin-2-yl]morpholine;
4-[7-(2-(difluoromethyl)-4-methoxy-1H-benzol[d]imidazol-1-yl)-3-(pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl]morpholine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzol[d]imidazol-1-yl)-9-(pyridin-3-yl)-9H-1-purin-6-yl]morpholine;
45 4-(6-(2-(difluoromethyl)4-methoxy-1H-benzimidazolyl)-3-(pyridin-3-yl)-3H-[1,1,2,3,4]triazolo[4,5-d]pyrimidin-7-yl)morpholine; 2-(6-(2-(difluoromethyl)4-methoxy-1H-benzimidazolyl)-3-(pyridin-3-yl)-3H-[1,1,2,3,4]triazolo[4,5-d]pyrimidin-7-yl)-6-(4-morpholinyl)-9-(5-pyrimidinyl)-9H-purine; and an entamnitor, mixtures of entamnitors, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof. 

The compounds provided herein are intended to encompass all possible stereoisomers, unless a particular stereochirality is specified. Where the compound provided herein contains an alkyl or alkenylene group, the compound may exist as one or a mixture of geometric cis/trans (or Z/E) isomers. Where structural isomers are interconvertible, the compound may exist as a single enantiomer or a mixture of enantiomers. This can take the form of proton tautomerism in the compound that contains, for example, an amine, keto, or oxime group; or so-called valence tautomerism in the compound that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

The compounds provided herein may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, e.g., a racemic mixture of two enantiomers; or a mixture of two or more diastereomers. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization in vivo, to administration of the compound in its (S) form. Conventional techniques for the preparation/isolation of individual enantiomers include synthesis from a suitable optically pure precursor, asymmetric synthesis from achiral starting materials, or resolution of an enantiomer mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

When the compound provided herein contains an acidic or basic moiety, it may also be provided as a pharmaceutically acceptable salt (see, Berge et al., J. Pharm. Sci. 1977, 66, 119; and “Handbook of Pharmaceutical Salts, Properties, and Use,” Stahl and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002). Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroterephthalic acid, acetylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzene-sulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfonic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, fumaric acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-glucaric acid, D-glucuronic acid, L-glutamic acid, c-oxoglutaric acid, glycine acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (+)-L-malic acid, maleic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-prolylamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfonic acid, tannic acid, (+)-L-tartaric acid, thioctric acid, p-toluenesulfonic acid, undeceylenic acid, and valeric acid. Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benzamide, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, disoproplamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methylglucamine, hydrobromide, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methyamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxymethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethyamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and trimethanolamine.

In certain embodiments, the compounds provided herein are pharmacologically acceptable salts of the compounds with one or more of hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, and isothionic acids; or with one or more of potassium carbonate, sodium or potassium hydroxide, ammonia, triethyamine, and triethanolamine.


Methods of Synthesis

The compound provided herein can be prepared, isolated, or obtained by any method known to one of skill in the art, and the following examples are only representative and do not exclude other related procedures.

For example, the compounds of Formula 1 can be prepared via aromatic substitution of a halo-1,3,5-triazine or halopyrimidine, e.g., chloro-1,3,5-triazine 1, with HUR® (Method A), as illustrated in Scheme 1, where U is N, O, or S.

The compounds of Formula 1 where U is a direct bond can be prepared via the replacement of a halo group of a halo-1, 3,5-triazine or halopyrimidine with an R® group, e.g., via Suzuki coupling by using a boronic acid or boronate ester of R® under palladium catalyzed reaction conditions (Method B), as illustrated in Scheme 2, where R is hydrogen or alkyl.

The halo-1,3,5-triazine or halo-pyrimidine used in Methods A and B can also be prepared, isolated, or obtained by any method known to one of skill in the art. For example, the halo-1,3,5-triazine can be prepared via aromatic substitution reactions of chlorotriazine with two different amines, compounds 2 and 4, as shown in Scheme 3.
The compounds of Formula I can be prepared by the modification of existing compounds of Formula I (Method D), such as illustrated in Scheme 6, wherein R₁⁴, R₂⁴, R₃⁴, R₄², R₅¹, R₆¹, and U¹⁴ are defined as R¹, R², R³, R⁴, R⁵, R⁶, and U, respectively, but at least one of R¹, R₂, R₃, R⁴, R⁵, R₆, or U¹⁴ is different from R¹, R², R₃, R⁴, R⁵, R₆, or U.

The compounds of Formula I, Ia, or Ib can also be prepared as shown in Scheme 7.
Pharmaceutical Compositions

In one embodiment, provided herein is a pharmaceutical composition comprising a compound of Formula I, IA, or IB as defined herein, and a pharmaceutically acceptable excipient, adjuvant, carrier, buffer, or stabiliser.

In one embodiment, the pharmaceutically acceptable excipient, adjuvant, carrier, buffer, or stabiliser is non-toxic and does not interfere with the efficacy of the active ingredient. The precise nature of the carrier or other material will depend on the route of administration, which may be oral or by injection, such as cutaneous, subcutaneous, or intravenous injection.

In another embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, and one or more pharmaceutically acceptable excipients or carriers. Where pharmaceutical compositions may be formulated for intravenous, cutaneous or subcutaneous injection, the active ingredient will be in the form of a parenterally acceptable aqueous solution, which is pyrogen-free and has a suitable pH, isotonicity, and stability. Those of relevant skill in the art are well able to prepare suitable solutions using, for example, isotonic vehicles, such as Sodium Chloride injection, Ringer’s injection, or Lactated Ringer’s injection. Preservatives, stabilisers, buffers, antioxidants, and/or other additives may be included as required.

In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise the compound provided herein, and one or more pharmaceutically acceptable excipients or carriers. The pharmaceutical compositions provided herein that are formulated for oral administration may be in tablet, capsule, powder, or liquid form. A tablet may comprise a solid carrier or an adjuvant. Liquid pharmaceutical compositions generally comprise a liquid carrier such as water, petroleum, animal or vegetable oils, or mineral oil or synthetic oil. Physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol may be included. A capsule may comprise a solid carrier such as gelatin.

In yet another embodiment, the pharmaceutical compositions are provided in a dosage form for topical administration, which comprise the compound provided herein, and one or more pharmaceutically acceptable excipients or carriers.

The pharmaceutical compositions can also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be
The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage forms. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

The pharmaceutical compositions provided herein can be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations.

In another embodiment, the pharmaceutical compositions provided herein further comprise one or more chemotherapeutic agents as defined herein.

In yet another embodiment, provided herein is the use of a compound of Formula I, IA, or IB in the manufacture of a medicament for the treatment of cancer. In certain embodiments, the medicament is in tablet, capsule, powder, or liquid form. In certain embodiments, the medicament is formulated as described herein.

A. Oral Administration

The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions may contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

Binders or granulants impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulants include, but are not limited to, starches, such as corn starch, potato starch, and pregelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginate; extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidine (PVP), Veegum, larch arboagelactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-HP-101, AVICEL-HP-103, AVICEL RC-581, AVICEL-HP-105 (FMC Corp., Marcus Hook, Pa.); and mixtures thereof. Suitable fillers include, but are not limited to, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrose, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

Suitable diluents include, but are not limited to, dirols phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

Suitable disintegrants include, but are not limited to, agar, bentonite, celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; alginates; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium laurel sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laurate; agar; starch; lycopodium; silica or silica gels, such as AERO-SIL® 200 (W.R. Grace Co., Baltimore, Md.) and CAB-O-SIL® (Cabot Co. of Boston, Mass.); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, Mass.), and asbestoses-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on
alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, sorbitol, saccharin, and artificial sweeteners, such as saccharin and aspartame.

Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Vee gum, acacia, sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monostearate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets. Sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammnoniated shellac, and cellulose acetate phthalate. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxypropylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft gelatin capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl)acetel of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal, and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydralcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, e.g., water, to be measured conveniently for administration.

Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxyethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiourea, and thiodiuretanes. The pharmaceutical compositions provided herein for oral administration can also be provided in the forms of liposomes, micelles, microspheres, or nanoparticles. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

The pharmaceutical compositions provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.
Coloring and flavoring agents can be used in all of the above dosage forms.

The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intramuscular, intraspinal, intracranial, intramucosal, intranasal, intravascular, and subcutaneous administration.

The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (see, Remington: The Science and Practice of Pharmacy, supra).

The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butadiol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, N-methyl-2-pyrrolidone, N,N-dimethylacetamide, and dimethyl sulfoxide.

Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycine, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those described herein, including sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan mononoleate 80, and triethanolamine oleate. Suitable seques-
tering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin, and sulfobutyl ether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, Kans.).

When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and lyopodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

Suitable inner matrices include, but are not limited to, polyethylene, methacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polysisoprene, polysisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymers, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyl oxyethanol copolymers.

C. Topical Administration

The pharmaceutical compositions provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes (intra)dermal, conjunctival, intraocular, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.
The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irritations, sprays, suppositories, bandages, and dermal patches. The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, Calif.), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, Ore.).

The pharmaceutical compositions provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxyystenin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glycerol monostearate, lanolin, and stearic acid (see, Remington: The Science and Practice of Pharmacy, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

Suitable cream base can be oil-in-water or water-in-oil. Suitable cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the “internal” phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsion in a cream formulation may be nonionic, anionic, cationic, or amphoteric surfactant.

Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include, but are not limited to, crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, and CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose gums; such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

The pharmaceutical compositions provided herein can be administered rectally, urethrally, vaginally, or per vaginam in the forms of suppositories, pessaries, bougies, poultrie or cataplasms, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes, as described in Remington: The Science and Practice of Pharmacy, supra.

Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerolgelatin, cariowax (polyoxyethylene glycol), spermaceti, paraffin, white and yellow wax, and appropriate mixtures of mono-, di-, and triglycerides of fatty acids, and hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, and polyacrylic acid. Combinations of the various vehicles can also be used. Rectal and vaginal suppositories may be prepared by compressing or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

The pharmaceutical compositions provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

The pharmaceutical compositions provided herein can be administered intraocularly or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,2-tributylfluorothane or 1,1,2,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a biodegradable agent, including chitosan or cyclodextrin.

Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein; a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oleic acid.

The pharmaceutical compositions provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminutes method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, superfine fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

Capsules, blisters, and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as i-leucine, mannitol, or magnesium stearate. The lactose may be unhydrous or in the form of the monohydrate. Other suitable excipients or carriers include, but are not
61 limited to, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/parenteral administration can further comprise a suitable flavor, such as menthol and levomenthol; and/or sweeteners, such as saccharin and saccharin sodium. The pharmaceutical compositions provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

D. Modified Release
The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate release dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix control release devices, osmotic control release devices, multiparticulate control release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphism of the active ingredient(s).

Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,553; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

1. Matrix Control Release Devices
The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using a matrix controlled release device known to those skilled in the art (see, Takada et al. in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz Ed., Wiley, 1999).

In certain embodiments, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including, but not limited to, synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageeans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphates, such as lecithin; alginates; propylene glycol alginates; gelatin; collagen; celluloses, such as ethyl cellulose (EC), methylthyl cellulose (MCC), carboxymethyl cellulose (CMC), CMC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMC, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCT), and ethyl hydroxyethyl cellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®R, Rohn America, Inc., Piscataway, N.J.); poly(2-hydroxyethyl-methacrylate); polyacrylics; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly(D(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methyl methacrylate, ethyl methacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chlorides.

In certain embodiments, the pharmaceutical compositions provided herein are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device include, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polystyrene, polysisobutylene, polybutadiene, polymethylmethacrylate, polylubutylmethacrylate, chlorinated polyethylene, polyvinyl chloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene-propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers, ethylene-vinyl alcohol copolymers, ethylene/vinyl acetate/vinyl alcohol terpolymers, ethylene/vinylvinyl alcohol copolymers, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

The pharmaceutical compositions provided herein in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, and melt-granulation followed by compression.

2. Osmotic Control Release Devices
The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including, but not limited to, one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) a core which contains an active ingredient; and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents is water-swellable hydrophilic polymers, which are also referred to as "osmoparimeters" and "hydrogels." Suitable water-swellable hydrophilic polymers as osmotic agents include, but are not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium...
algin, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carmagnan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxethyl, cellulose (CEC), sodium alginate, polyacrylphil, gelatin, xanthan gum, and sodium starch glycolate.

The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfate, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluene-sulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ (SPI Pharma, Lewes, Del.) can be used to provide faster delivery during the first two hours of the desired therapeutic effect, and gradually and continually release the remainder of the amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing. Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating include plasticized, uncoated, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylacetone, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCA, poly(acrylic) acid and esters, and poly-(methacrylic) acid and esters and copolymers thereof, starch, dextrin, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polyanhydrides, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

Suitable membranes can also be a hydrophilic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Patent No. 5,798,119. Such hydrophilic but water-vapor permeable membranes are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating processes, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

The total amount of the active ingredient(s) released and the release rate can substantially be modulated by the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (see, Remington: The Science and Practice of Pharmacy, supra; Santus and Baker, J. Controlled Release 1995, 35, 1-21; Verma et al., Drug Development and Industrial Pharmacy 2000, 26, 695-708; Verma et al., J. Controlled Release 2002, 79, 7-27).

In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. See, U.S. Patent No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

In certain embodiments, the pharmaceutical compositions provided herein are formulated as EDC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticle Controlled Release Devices

The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated as a multiparticle controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticles can be made by the processes known to those skilled in the art, including wet- and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray coating seed cores. See, for example, Multiparticle Oral Drug Delivery; Marcel Dekker: 1994; and Pharmaceutical Pelletization Technology; Marcel Dekker: 1989.
Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as emeric polymers, water-swellable, and water-soluble polymers. The multiparticulates can further processed as a capsule or a tablet.

4. Targeted Delivery

The pharmaceutical compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, those disclosed in U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

Methods of Use

In one embodiment, provided is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition associated with PI3K activity in a subject, which comprises administering to the subject a therapeutically effective amount of the compound provided herein, e.g., a compound of Formula I, IA, or IB, including an enhancer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In another embodiment, provided is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition responsive to the modulation of PI3K activity in a subject, which comprises administering to the subject a therapeutically effective amount of the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enhancer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In yet another embodiment, provided is a method of treating, preventing, or ameliorating one or more symptoms of a disorder, disease, or condition mediated by PI3K activity in a subject, which comprises administering to the subject a therapeutically effective amount of the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enhancer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In yet another embodiment, provided is a method of treating, preventing, or ameliorating one or more symptoms of cancer in a subject, which comprises administering to the subject a therapeutically effective amount of the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enhancer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In yet another embodiment, provided herein are uses of the compound provided herein, e.g., a compound of Formula I, IA, or IB, including an enhancer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

In yet another embodiment, provided herein are uses of the compound provided herein, e.g., a compound of Formula I, IA, or IB, including an enhancer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered daily in a single dose or divided doses for a total daily dose sufficient to achieve a plasma concentration of the compound at steady state ranging from about 0.001 to about 100, from about 0.01 to about 10, from about 0.1 to about 5, or from about 0.1 to about 1 μM. As used herein, the term “plasma concentration at steady state” is the concentration reached after a period of administration of a compound. Once steady state is reached, there are minor peaks and troughs on the time dependent curve of the plasma concentration of the compound administered.

In certain embodiments, the compound selectively targets the p110α subunit of PI3K. In certain embodiments, the compound selectively inhibits the PI3K via its interaction with its p110α subunit. In certain embodiments, the compound selectively alkylates the p110α subunit of PI3K.

In certain embodiments, the p110α subunit of PI3K, and in certain embodiments, the p110α subunit of PI3K is a Class I kinase. In certain embodiments, the p110α subunit of PI3K is a Class I kinase. In certain embodiments, the PI3K is a Class I kinase.

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enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve a C_{max} ranging from about 0.1 to about 100, from about 0.2 to about 50, from about 0.5 to about 25, or from about 1 to about 10 μM.

In certain embodiments, the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve a C_{max} ranging from about 0.1 to about 100, from about 0.2 to about 50, from about 1 to about 20, or from about 1 to about 10 μg/ml.

In certain embodiments, the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve an AUC ranging from about 1 to about 1,000, from about 10 to about 500, from about 20 to about 250, or from about 50 to about 100 μg•hr/ml.

In certain embodiments, the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve an AUC ranging from about 1 to about 1,000, from about 10 to about 500, from about 20 to about 250, or from about 50 to about 100 μM•hr.

The disorders, diseases, or conditions treatable with the compound provided herein, include, but are not limited to, (1) inflammatory or allergic diseases, including systemic anaphylaxis and hypersensitivity disorders, cutaneous dermatitis, urticaria, drug allergies, insect sting allergies, food allergies (including celiac disease and the like), and mastocytosis; (2) inflammatory bowel diseases, including Crohn’s disease, ulcerative colitis, ileitis, and enteritis; (3) vasculitis, and Behcet’s syndrome; (4) psoriasis and inflammatory dermatoses, including dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria, viral cutaneous pathogens including those derived from human papillomavirus, HIV or RLV infection, bacterial, fungal, and other parasitic cutaneous pathogens, and cutaneous lupus erythematosus; (5) asthma and respiratory allergic diseases, including allergic asthma, exercise induced asthma, allergic rhinitis, otitis media, allergic conjunctivitis, hypersensitivity lung diseases, and chronic obstructive pulmonary disease; (6) autoimmune diseases, including arthritis (including rheumatoid and psoriatic), systemic lupus erythematosus, type 1 diabetes, myasthenia gravis, multiple sclerosis, Graves’ disease, and glomerulonephritis; (7) graft reaction (including allograft rejection and graft-v-host disease), e.g., skin graft reaction, solid organ transplant reaction, bone marrow transplant rejection; (8) fever; (9) cardiovascular disorders, including acute heart failure, hypotension, hypertension, angina pectoris, myocardial infarction, cardiomyopathy, congestive heart failure, atherosclerosis, coronary artery disease, restenosis, and vascular stenosis; (10) cerebrovascular disorders, including traumatic brain injury, stroke, ischemic reperfusion injury and aneurysm; (11) cancers of the breast, skin, prostate, cervix, uterus, ovary, testes, bladder, lung, liver, larynx, oral cavity, colon and gastrointestinal tract (e.g., esophagus, stomach, pancreas), brain, thyroid, blood, and lymphatic system; (12) fibrosis, connective tissue disease, and sarcoidosis, (13) genital and reproductive conditions, including erectile dysfunction; (14) gastrointestinal disorders, including gastritis, ulcers, nausea, pancreatitis, and vomiting; (15) neurologic disorders, including Alzheimer’s disease; (16) sleep disorders, including insomnia, narcolepsy, sleep apnea syndrome, and Pickwick Syndrome; (17) pain; (18) renal disorders; (19) ocular disorders, including glaucoma; and (20) infectious diseases, including HIV.

In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroblastemia leukemias and myeloplastic syndrome or a remission thereof (such as anemia, thrombocytopenia, neutropenia, neutrophilia or pancytopenia); refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelogenous leukemia (CML); (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin’s disease and non-Hodgkin’s disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, non-secretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary plasmacytoma, and extramedullary plasmacytoma; (6) Waldenström’s macroglobulinemia; (7) monoclonal gamopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing’s sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosseous sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi’s sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma, nongliatal glioma, acoustic neuroma, craniothymyglioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget’s disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, phaeochromocytoma and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but not limited to, Cushing’s disease, prolactin-secreting tumor, acromegaly, and diabetes insipidus; (17) eye cancer, including, but not limited to, ocular melanoma such as iris melanoma, choroidal melanoma, and ciliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget’s disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine
cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polyloid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma, fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer, including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, papillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinant tumor, seminoma, anaplastic, classic (typical); spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penile cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentigious melanoma; (37) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or ureter); (40) Wilms’ tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangioendotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (See Fishman et al., 1985, Medicine, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy et al., 1997, Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

Depending on the disorder, disease, or condition to be treated, and the subject’s condition, the compounds or pharmaceutical compositions provided herein can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, IV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration and can be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants, and vehicles appropriate for each route of administration. Also provided is administration of the compounds or pharmaceutical compositions provided herein in a depot formulation, in which the active ingredient is released over a predefined time period.

In the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions described herein, an appropriate dosage level generally is ranging from about 0.001 to 100 mg per kg subject body weight per day (mg/kg per day), from about 0.01 to about 75 mg/kg per day, from about 0.1 to about 50 mg/kg per day, from about 0.5 to about 25 mg/kg per day, or from about 1 to about 20 mg/kg per day, which can be administered in single or multiple doses. Within this range, the dosage can be ranging from about 0.005 to about 0.05, from about 0.05 to about 0.5, from about 0.5 to about 5.0, from about 1 to about 15, from about 1 to about 20, or from about 1 to about 50 mg/kg per day.

For oral administration, the pharmaceutical compositions provided herein can be formulated in the form of tablets containing from about 1.0 to about 1,000 mg of the active ingredient, in one embodiment, about 1, about 5, about 10, about 15, about 20, about 25, about 50, about 75, about 100, about 150, about 200, about 250, about 300, about 400, about 500, about 600, about 750, about 800, about 900, and about 1,000 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The pharmaceutical compositions can be administered on a regimen of 1 to 4 times per day, including once, twice, three times, and four times per day.

It will be understood, however, that the specific dose level and frequency of dosage for any particular patient can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Also provided herein are methods of modulating PI3K activity, comprising contacting a PI3K enzyme with the compound provided herein, e.g., the compound of Formula I, IA, or IB, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In one embodiment, the PI3K enzyme is inside a cell.

In certain embodiments, the PI3K is a wild PI3K. In certain embodiments, the PI3K is a PI3K mutant.

In certain embodiments, the PI3K is a Class I kinase. In certain embodiments, the PI3K is p110α, p110β, p110δ, or p110γ. In certain embodiments, the PI3K is a wild type of a Class I kinase. In certain embodiments, the PI3K is a mutant of a Class I kinase.


In certain embodiments, the PI3K is a Class IV kinase. In certain embodiments, the PI3K is a wild type of a Class IV kinase. In certain embodiments, the PI3K is a mutant of a Class IV kinase. In certain embodiments, the PI3K is mTOR, ATM, ATR, or DNA-PK. In certain embodiments, the PI3K is mTOR.

In certain embodiments, the compounds provided herein, e.g., a compound of Formula I, IA, or IB, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt,
solvent, hydrate, or prodrg thereof, show inhibitory activity against a PI3K and a mutant thereof.

In certain embodiments, the compounds provided herein, e.g., a compound of Formula 1, 1A, or 1B, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrg thereof, show inhibitory activity against a wild type of a PI3K. In certain embodiments, the PI3K is p110α. In certain embodiments, the PI3K is mTOR.

In certain embodiments, the compounds provided herein, e.g., a compound of Formula 1, 1A, or 1B, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrg thereof, show inhibitory activity against a PI3K mutant. In certain embodiments, the PI3K mutant is a PI3K mutant. In certain embodiments, the PI3K mutant is a p110α mutant. In certain embodiments, the p110α mutant is C420R, E542K, E545A, E545K, Q546K, 1800L, M1043I, H1047L, or H1047Y.

The compounds provided herein, e.g., a compound of Formula 1, 1A, or 1B, including an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrg thereof, can also be combined or used in combination with other agents or therapies useful in the treatment, prevention, or amelioration of one or more symptoms of the disorders, diseases, or conditions for which the compounds provided herein are useful, including asthma, allergic rhinitis, eczema, psoriasis, atopic dermatitis, fever, sepsis, systemic lupus erythematosus, diabetes, rheumatoid arthritis, multiple sclerosis, atherosclerosis, transplant rejection, inflammatory bowel disease, cancer, infectious diseases, and those pathologies noted herein.

Suitable other therapeutic agents can also include, but are not limited to, (1) alpha-adrenergic agents; (2) antiarrhythmic agents; (3) anti-inflammatory agents; (4) antibiotics, such as anthracyclines, bleomycins, mitomycin, daunomycin, and plicamycin; (5) anticancer agents and cytotoxic agents, e.g., alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazines; (6) anticoagulants, such as acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione, warfarin, and ximelagatran; (7) anti-diabetic agents, such as biguanides (e.g., metformin), glucosidase inhibitors (e.g., acarbose), insulin, meglitindes (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, and glipizide), thiazolidinediones (e.g., troglitazone, rosiglitazone, and pioglitazone), and PPAR-gamma agonists; (8) antifungal agents, such as amorphol, amphotericin B, anidulafungin, bifonazole, butenafine, butoconazole, caspofungin, ciclopirox, clotrimazole, econazole, fencnazole, filipin, fluconazole, itraconazole, ketoconazole, miconafungin, miconazole, naftifine, nystatin, oxiconazole, ravucconazole, posaconazole, rimocidin, sertaconazole, sulconazole, terbinafine, terconazole, tioconazole, and voriconazole; (9) antiinflammatory agents, e.g., non-steroidal anti-inflammatory agents, such as aceclofenac, acemetacin, amoxicillin, aspirin, azapropazone, benorilate, bromfenac, caprofen, celecoxib, choline magnesium salicylate, diclofenac, diflunisal, etodolac, etoricoxib, fiasilamine, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, ketorolac, lornoxicom, loxoprofen, lumicoxib, meclofenamic acid, melaminic acid, meloxicam, metamizole, methyl salicylate, magnesium salicylate, nabumetone, naproxen, nimesulide, oxyphenbutazone, parecoxib, phe- nylbutazone, piroxicam, salicylic salicylate, sulindac, sulfispyrazone, suprofen, tenoxicam, tiaprofenic acid, and toluene; (10) antimetabolites, such as folate antagonists, purine analogues, and pyrimidine analogues; (11) anti-platelet agents, such as GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, and tirofiban), P2Y12 (e.g., clopidogrel, ticlopidine and CS-747), cilostazol, dipryidamole, and aspirin; (12) antiproliferatives, such as methotrexate, FK506 (tacrolimus), and mycophenolate mofetil; (13) anti-TNF antibodies or soluble TNF receptor, such as etanercept, rupamycin, and leflunomide; (14) α2P inhibitors; (15) β-adrenergic agents, such as carvedilol and metoprolol; (16) bile acid sequestrants, such as questran; (17) calcium channel blockers, such as amiodipine besylate; (18) chemotherapeutic agents; (19) cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib; (20) cyclopentors; (21) cytokine drugs, such as azathioprine and cyclophosphamide; (22) diuretics, such as chlorothiazide, hydrochlorothiazide, flu- methiazide, hydroflumethiazide, bendroflumethiazide, methyl- chlorothiazide, trichlorothiazide, polychlorothiazide, ben- zothiazide, ethacrynic acid, furosemide, chlorothiazide, farosine, muzolinate, bumetanide, triamterene, amlodipine, and spironolactone; (23) endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; (24) enzymes, such as L-asparaginase; (25) Factor VIIa Inhibitors and Factor Xa Inhibitors; (26) farnesyl-protein transferase inhibitors; (27) fibrates; (28) growth factor inhibitors, such as modulators of PDGF activity; (29) growth hormone secretagogues; (30) HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, sitavastatin, or niasstatin), and ZD-4522 (also known as rosuvastatin, atorvastatin, or visastatin); neutral endothelio- dase (NEP) inhibitors; (31) hormonal agents, such as glucocorticoids (e.g., cortisone), estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; (32) immunosuppressants; (33) mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; (34) microtubule-disruptor agents, such as taxanes and colchicine; (35) microtubule-stabilizing agents, such as paclitaxel, docetaxel, and epothilones A-F; (36) MTP Inhibitors; (37) niasin; (38) phosphodiesterase inhibitors, such as PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors (e.g., sildenafil, tadalaflu, and vardenafill); (39) plant-derived products, such as vinca alkaloids, epipodophyllotoxins, and taxanes; (40) platelet activating factor (PAF) antagonists; (41) platinum coordination complexes, such as cisplatin, carboplatin, and carbo- platinum; (42) potassium channel openers; (43) prenyl-protein transferase inhibitors; (44) protein tyrosine kinase inhibitors; (45) renin inhibitors; (46) quinolone synthetase inhibitors; (47) steroids, such as aldosterone, beclometasone, betamethasone, defluorocortisone, hydrocortisone (cortisol), prednisolone, prednisone, methylprednisolone, dexamethasone, and triamcinolone; (48) TNF-α inhibitors, such as nadinap; (49) thrombin inhibitors, such as hirudin; (50) thrombolytic agents, such as anistre- plase, reteplase, tenecteplase, tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prouroki- nase, and anisoylated plasminogen streptokinase activator complex (APSAC); (51) thromboxane receptor antagonists, such as ifetroban; (52) topoisomerase inhibitors; (53) vasopressin peptide inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and enepatrilat; and (54) other miscellaneous agents, such as, hydroxyurea, procarbazine, mitotane, hex- amethylmelamine, and gold compounds.

In certain embodiments, the other therapies that may be used in combination with the compounds provided herein include, but are not limited to, surgery, endocrine therapy, biologic response modifiers (e.g., interferons, interleukins,
and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, and agents to attenuate any adverse effects (e.g., antiemetics).

In certain embodiments, the other therapeutic agents that may be used in combination with the compounds provided herein include, but are not limited to, alkylating drugs (methylthioalkylamine, chlorambucil, cyclophosphamide, melphalan, and ifosfamide), antimetabolites (cytarabine (also known as cytosine arabinoside or Ara-C), HDAC (high dose cytarabine), and methotrexate), purine antagonists and pyrimidine antagonists (6-mercaptopurine, 5-fluorouracil, cytarabine, and gemcitabine), spindle poisons (vinblastine, vincristine, and vinorelbine), podophyllotoxins (etoposide, irinotecan, and topotecan), antibodies (daunornubicin, doxorubicin, bleomycin, and mitomycin), nitrosoureas (armustin and lomustine), enzymes (asparaginase), and hormones (tamoxifen, leuprolide, flutamide, and megestrol), imatinib, adramycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies; see, e.g., the Office of Cancer Drugs of the FDA approved ology drugs at http://www.fda.gov/cder/cancer/drglist.htm and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

In another embodiment, the method provided herein comprises administration of a compound of Formula I, IA, or IB, together with administering one or more chemotherapeutic agents and/or therapies selected from: alkylating agents (e.g., cisplatin, carboplatin; antimetabolites (e.g., methotrexate and 5-FU); antitumor antibiotics (e.g., adramycin and bleomycin); antitumor vegetable alkaloids (e.g., taxol and etoposide); antitumor hormones (e.g., dexamethasone and tamoxifen); antitumour immunological agents (e.g., interferon α, β, and γ); radiation therapy; and surgery. In certain embodiments, the one or more chemotherapeutic agents and/or therapies are administered to the subject before, during, or after the administration of the compound of Formula I, IA, or IB as defined herein.

Such other agents, or drugs, can be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with the compounds provided herein, e.g., a compound of Formula I, IA, or IB, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof. When the compound provided herein is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound provided herein can be utilized, but is not required. Accordingly, the pharmaceutical compositions provided herein include those that also contain one or more other active ingredients or therapeutic agents, in addition to the compound provided herein.

The weight ratio of the compound provided herein to the second active ingredient can be varied, and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when the compound provided herein is combined with a NSAID, the weight ratio of the compound to the NSAID can range from about 1,000:1 to about 1:1,000, or about 200:1 to about 1:200. Combinations of the compound provided herein and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

The compounds provided herein can also be provided as an article of manufacture using packaging materials well known to those of skill in the art. See, e.g., U.S. Pat. Nos. 5,323,907; 5,052,558; and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

Provided herein also are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the kits provided herein include a container and a dosage form of the compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

In certain embodiments, the kits also include a container comprising a dosage form of the compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a container comprising one or more other therapeutic agents(s) described herein.

Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer’s Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer’s Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, benzyl benzoate.

The disclosure will be further understood by the following non-limiting examples.

EXAMPLES

As herein used, the symbols and conventions used in these processes, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviations may be used in the examples and throughout the specification: g (grams); mg (milligrams); mL (milliliters); µL (microliters); M (molar); mM (millimolar); µM (micromolar); eq. (equivalent); Hz (Hertz); MHz (megahertz); mmol (millimoles); hr or hrs (hours); min (minutes); mp (melting point); HRMS (high resolution mass spectrometry); FAB, (fast atom bombardment); aq. (aqueous); DMF (dimethylformamide); DMSO (dimethylsulfoxide); DMSO-d₆ (deuterated dimethylsulfoxide); EtOH (ethanol); EtOAc (ethyl acetate); i-Pr₂O (disopropyl ether); MeOH (methanol); THF (tetrahydrofuran); DIPEA (N,N-dioisopropylethylamine); DMAP (dimethylaminopyridine); HCO₂H (acetic acid); LDA (lithium diisopropyl-
Synthesis of 4-[(2-(difluoromethyl)-4-methoxy-1H-benzoimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. 2-Amino-3-methoxynitrobenzene (15.10 g. 0.09 mol) was hydrogenated over palladium on carbon in methanol, and the solution was filtered through celite into a methanolic HCl solution. The solvent was removed under vacuum and the resulting hydrochloride salt was combined with difluoroacetic acid (19.2 g, 0.18 mol) and 4 M HCl (100 mL). The mixture was heated under reflux for 3 hr, diluted with water, decolorized with charcoal, and filtered through celite. Neutralization of aqueous ammonia gave 2-difluoromethyl-4-methoxy-1H-benzoimidazole (15.2 g, 84%) as a solid: ¹H NMR (CDCl₃) δ 9.95-9.70 (m, 3H, exchangeable with D₂O, 1H), 7.44 (br d, J= 7.9 Hz, 0.4H), 7.31-7.24 (m, 1H), 7.12 (br d, J= 8.0 Hz, 0.5H), 6.89 (t, J= 53.8 Hz, 1H), 6.82-6.74 (m, 1H), 4.03 and 3.98 (2s, 3H).

A mixture of 3.96 g (20 mmol) of the above benzimidazole, 4.70 g (20 mmol) of 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine, and 22 g (80 mmol) of powdered K₂CO₃ in 150 mL of DMF at room temperature was stirred rapidly for 3 hr and then diluted with water. The resulting precipitate was collected, washed with water, and then with cold ethanol, and dried to give 6.82 g (86%) of 4-[1-(4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzoimidazole: mp (CHCl₃/MeOH) 263-265° C.; ¹H NMR (CDCl₃) δ 7.99 (d, J= 8.4 Hz, 1H), 7.48 (t, J= 53.4 Hz, 1H), 7.40 (t, J= 8.3 Hz, 1H), 6.86 (d, J= 8.1 Hz, 1H), 4.05 (s, 3H), 3.96 (m, 4H), 3.82 (m, 4H); Anal. Calcd. for C₆H₁₂F₂N₂O₂: C, 48.4; H, 3.8; N, 21.2. Found: C, 48.3; H, 3.8; N, 21.1%.

To a solution of 3-aminopyridine (1.88 g, 20 mmol) in 100 mL THF was added LDA (10 mL, 2 M in THF; 20 mmol) and to the resulting suspension was added 1.99 g (5 mmol) of 1-(4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzoimidazole at room temperature. After 5 min, the mixture was neutralized with acetic acid and diluted with water. After the pH was made slightly alkaline with Na₂CO₃, the precipitate was collected, washed with

Example 1

The compound was synthesized according to Method A. 1-[4-Chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzoimidazole (U.S. Pat. Appl. Publ. No. US 2007/244110) (0.183 g, 0.5 mmol) was added to a mixture of 3-aminopyridine (0.20 g, 2 mmol) and LDA (1 mL, 2 M in THF, 2 mmol) in 10 mL THF at room temperature. After 5 min, the mixture was neutralized with HCl acid, diluted with water, extracted with EtOAc, and dried (Na₂SO₄). Chromatography on alumina eluting with CH₃Cl/EtOAc (4:1) gave a solid, which was recrystallized from i-Pr₂O to give 92 mg (43% yield) of 4-[1-(4-chloro-6-(4-morpholinyl)-1H-benzoimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine: mp (i-Pr₂O) 228-230° C.; ¹H NMR (CDCl₃) δ 8.86 (br, 1H), 8.42 (d, J= 2.0 Hz, 1H), 8.38 (d, J= 6.2 Hz, 1H), 7.98 (d, J= 8.2 Hz, 1H), 7.89 (dd, J= 6.2, 2.9 Hz, 1H), 7.58 (br t, J= 11 Hz, 1H), 7.42 (m, 2H), 7.34 (dd, J= 8.3, 4.7 Hz, 1H), 7.28 (m, exchangeable with D₂O, 1H), 3.93 (m, 4H), 3.82 (m, 4H); Anal. Calcd. for C₆H₁₄F₂N₂O₂: C, 56.6; H, 4.3; N, 26.4. Found: C, 56.5; H, 4.4; N, 26.1%.

Example 2

The compound was synthesized according to Method A. 2-Amino-3-methoxynitrobenzene (15.10 g, 0.09 mol) was hydrogenated over palladium on carbon in methanol, and the solution was filtered through celite into a methanolic HCl solution. The solvent was removed under vacuum and the resulting hydrochloride salt was combined with difluoroacetic acid (19.2 g, 0.18 mol) and 4 M HCl (100 mL). The mixture was heated under reflux for 3 hr, diluted with water, decolorized with charcoal, and filtered through celite. Neutralization of aqueous ammonia gave 2-difluoromethyl-4-methoxy-1H-benzoimidazole (15.2 g, 84%) as a solid: ¹H NMR (CDCl₃) δ 9.95-9.70 (m, 3H, exchangeable with D₂O, 1H), 7.44 (br d, J= 7.9 Hz, 0.4H), 7.31-7.24 (m, 1H), 7.12 (br d, J= 8.0 Hz, 0.5H), 6.89 (t, J= 53.8 Hz, 1H), 6.82-6.74 (m, 1H), 4.03 and 3.98 (2s, 3H).

A mixture of 3.96 g (20 mmol) of the above benzimidazole, 4.70 g (20 mmol) of 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine, and 22 g (80 mmol) of powdered K₂CO₃ in 150 mL of DMF at room temperature was stirred rapidly for 3 hr and then diluted with water. The resulting precipitate was collected, washed with water, and then with cold ethanol, and dried to give 6.82 g (86%) of 4-[1-(4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzoimidazole: mp (CHCl₃/MeOH) 263-265° C.; ¹H NMR (CDCl₃) δ 7.99 (d, J= 8.4 Hz, 1H), 7.48 (t, J= 53.4 Hz, 1H), 7.40 (t, J= 8.3 Hz, 1H), 6.86 (d, J= 8.1 Hz, 1H), 4.05 (s, 3H), 3.96 (m, 4H), 3.82 (m, 4H); Anal. Calcd. for C₆H₁₂F₂N₂O₂: C, 48.4; H, 3.8; N, 21.2. Found: C, 48.3; H, 3.8; N, 21.1%.

To a solution of 3-aminopyridine (1.88 g, 20 mmol) in 100 mL THF was added LDA (10 mL, 2 M in THF; 20 mmol) and to the resulting suspension was added 1.99 g (5 mmol) of 1-(4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzoimidazole at room temperature. After 5 min, the reaction was neutralized with acetic acid and diluted with water. After the pH was made slightly alkaline with Na₂CO₃, the precipitate was collected, washed with...
hot water, and dried. Recrystallization from EtOH (using CHCl₃ to aid initial solubility) gave 1.65 g (73% yield) of 4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine: mp 221-223°C; `H NMR (CDCl₃) 8.868 (br, 1H), 8.42 (d, J=2.0 Hz, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.92 (d, J=8.1 Hz, 1H), 7.48 (br t, J=6.6 Hz, 1H), 7.35-7.31 (m, 2H), 7.22 (m, exchangeable with D₂O, 1H), 6.82 (d, J=8.0 Hz, 1H), 4.04 (s, 3H), 3.92 (m, 4H), 3.81 (m, 4H); Anal. Calcld. for C₂₈H₂₃F₅N₇O₅: C, 55.5; H, 4.4; N, 24.7. Found: C, 55.5; H, 4.4; N, 24.4.

A suspension of 4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine in MeOH was treated with a slight excess of methanesulfonic acid, to give a clear solution. Addition of EtOAc gave a precipitate, which was collected by filtration and washed with EtOAc. Recrystallization from MeOH/EtOAc gave 4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine methanesulfonate: mp 279-282°C; `H NMR (d₆-DMSO-d₆) δ 10.63 (s, exchangeable with D₂O, 1H), 9.19 (s, 1H), 8.55 (d, J=5.5 Hz, 1H), 8.53 (m, 1H), 8.08 (m, 1H), 7.90 (dd, J=8.5, 5.4 Hz, 1H), 7.82 (br t, J=5.30 Hz, 1H), 7.43 (t, J=8.2 Hz, 1H), 6.98 (d, J=7.8 Hz, 1H), 4.56 (br m, exchangeable with D₂O, 1H), 3.99 (s, 3H), 3.86 (m, 4H), 3.75 (m, 4H); Anal. Calcld. for C₂₉H₂₄F₆N₇O₇S: C, 48.0; H, 4.4; N, 20.4. Found: C, 47.8; H, 4.4; N, 20.2%.

Example 3

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. A mixture of 2-(methylsulfonyl)-1H-benzimidazole (1.64 g, 10 mmol), 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine (2.35 g, 10 mmol), and powdered K₂CO₃ (11 g, 80 mmol) in DMF (50 mL) was stirred at room temperature for 1 hr. The mixture was diluted with water and the resulting precipitate was collected, washed with water and then ethanol, and dried to give 3.56 g (98% yield) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(methylsulfonyl)-1H-benzimidazole: mp (CHCl₃/EtOH) 260-261°C; `H NMR (CDCl₃) 8.42 (br dd, J=7.0, 1.9 Hz, 1H), 7.65 (br dd, J=6.8, 1.9 Hz, 1H), 7.30 (m, 2H), 4.06 (m, 2H), 3.95 (m, 2H), 3.84 (m, 2H), 3.80 (m, 2H), 2.74 (s, 3H); Anal. Calcld. for C₉H₁₀CN₂O₃S: C, 49.65; H, 4.2; N, 23.2. Found: C, 49.8; H, 4.1; N, 23.1%. A solution of 3-aminopyridine (2 g, 21 mmol) in 100 mL THF was treated with 10.6 mL (21 mmol) 2 M LDA in THF to give a suspension which was treated with 1.81 g (5 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(methylsulfonyl)-1H-benzimidazole at room temperature. After 5 min, the mixture was neutralized with HOAc and diluted with water to give 1.65 g (78%) of 4-[2-(methylsulfonyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine: mp (CHCl₃/EtOH) 240-241°C; `H NMR (CDCl₃) 8.85 (br s, 1H), 8.39 (d, J=4.0 Hz, 1H), 8.34 (d, J=7.5 Hz, 1H), 8.02 (d, J=7.3 Hz, 1H), 7.66 (dd, J=7.0, 0.5 Hz, 1H), 7.32 (dd, J=8.5, 4.9 Hz, 1H), 7.28 (dt, J=7.3, 1.1 Hz, 1H), 7.22 (t, J=7.4 Hz, 1H), 7.15 (br s, exchangeable with D₂O, 1H), 4.05 (m, 2H), 3.90 (m, 2H), 3.81 (m, 4H), 2.73 (s, 3H); Anal. Calcld. for C₂₉H₂₃F₅N₇O₅S: C, 57.1; H, 4.8; N, 26.65. Found: C, 57.0; H, 4.9; N, 27.0%.

Example 4

Synthesis of 4-[2-(methylsulfonyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine
The compound was synthesized according to Method D.
A solution of 0.421 g (1 mmol) of 4-[2-(methylsulfonyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine (from Example 4) in 130 mL acetonitrile and 20 mL HOAc was treated with 1 g KMnO₄ in 10 mL water at room temperature. After 30 min, the reaction was decolorized withaq. Na₂S₂O₃ solution and the acetonitrile was removed under vacuum. The residue was diluted with water and the pH adjusted to neutral to give a precipitate which was dissolved in CHCl₃ and dried. Chromatography on alumina, eluting with CHCl₃/MeOH (1:1) gave 140 mg (31%) of 4-[2-(methylsulfonyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine: mp (MeOH) 208-211°C; 1H NMR (CDCl₃) δ 8.88 (s, 1H), 8.38 (dd, J = 7.4, 1.4 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.77 (dd, J = 7.3, 1.2 Hz, 1H), 7.46-7.38 (m, 3H); 2H after D₂O exchange), 7.31 (dd, J = 8.3, 4.7 Hz, 1H), 4.08 (m, 2H), 3.83 (m, 2H), 3.76 (m, 4H), 3.62 (s, 3H); Anal. Calcd. for C₁₅H₁₈N₃O₃S 0.5H₂O: C, 52.0; H, 4.6; N, 24.3. Found: C, 51.8; H, 4.6; N, 24.3%.

Example 6

Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine

The compound was synthesized according to Method A.
A mixture of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (92 mg, 0.25 mmol) and aniline (58 mg, 0.625 mmol) in dioxane (5 mL) was heated under reflux for 1 hr and cooled. Dilution with water gave a white precipitate, which was recrystallised from MeOH to give 52 mg (49% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine: mp 171-174°C; 1H NMR (CDCl₃) δ 8.40 (m, 1H), 7.89 (m, 1H), 7.58 (t, J = 5.4 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.43-7.38 (m, 4H), 7.20 (t, J = 7.3 Hz, 1H), 7.09 (br, exchangeable with D₂O, 1H), 3.93 (m, 4H), 3.81 (m, 4H); Anal. Calcd. for C₂₂H₁₉F₂N₄O: C, 59.6; H, 4.5; N, 23.2. Found: C, 59.6; H, 4.5; N, 23.3%.

Example 7

Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine

The compound was synthesized according to Method A.
A mixture of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (92 mg, 0.25 mmol) and benzylamine (67 mg, 0.625 mmol) in dioxane (5 mL) was heated under reflux for 5 min and cooled. The mixture was diluted with water to give a white precipitate, which was recrystallised from EtOH to give 73 mg (67% yield) of N-benzyl-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine: mp 185-188°C; 1H NMR (CDCl₃) (rotamers) δ 8.41 and 8.28 (2d, J = 7.4 and 7.7 Hz).
Example 9

Synthesis of N-benzyl-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. A mixture of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (92 mg, 0.25 mmol) and N-methylbenzylamine (76 mg, 0.625 mmol) in dioxane (5 mL) was heated under reflux for 5 min and cooled. The mixture was diluted with water to give a white precipitate, which was recrystallised from EtOH to give N-benzyl-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-1,3,5-triazin-2-amine: mp 147-150°C; 'H NMR (CDCl₃) (rotamers) δ 8.45 and 8.22 (2d, J = 7.6 and 7.9 Hz, 1H), 7.90 and 7.85 (2d, J = 8.3 and 7.7 Hz, 1H), 7.68 and 7.44 (2t, J = 53.7 and 53.6 Hz, 1H), 7.43-7.25 (m, 7H), 4.92 and 4.90 (2s, 2H), 3.95-3.75 (m, 8H), 3.22 and 3.20 (2s, 3H); Anal. Calc. for C₅₂H₅₃F₃N₅O: C, 61.2; H, 5.2; N, 21.7. Found: C, 61.45; H, 5.2; N, 21.93%.

Example 10

Synthesis of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-phenoxo-1,3,5-triazin-2-yl]-1H-benzimida zole

The compound was synthesized according to Method A. Phenol (200 mg, 21 mmol) and NaOH (85 mg, 21 mmol) were combined in water to give a clear solution, which was then evaporated to dryness. 1-[4-Chloro-6-(4-morpholinyl)-

Example 11

Synthesis of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(phenylsulfonyl)-1,3,5-triazin-2-yl]-1H-benzimidazole

The compound was synthesized according to Method A. Thiophenol (230 mg, 2.1 mmol) and NaOH (85 mg, 2.1 mmol) were combined in water to give a clear solution, which was then evaporated to dryness. 1-[4-Chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (184 mg, 0.5 mmol) and tris[2-[2-methoxyethoxyethyl]amine (TDA-1; 16 mg, 0.05 mmol) were added and the mixture was heated under reflux in dioxane (10 mL) for 2 h. After cooling, the mixture was diluted with water to give a white solid, which was collected and recrystallised from MeOH to give 93 mg (44% yield) of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-phenoxo-1,3,5-triazin-2-yl]-1H-benzimidazole: mp 228-231°C; 'H NMR (CDCl₃) δ 8.06 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.49 (br t, J = 7.9 Hz, 2H), 7.36 (br t, J = 7.5 Hz, 2H), 7.30 (dt, J = 7.6, 1.1 Hz, 1H), 7.22 (m, 2H), 7.11 (t, J = 5.6 Hz, 1H), 3.99-3.93 (m, 4H), 3.86-3.79 (m, 4H); Anal. Calc. for C₅₂H₅₃F₃N₅O: C, 59.4; H, 4.3; N, 19.8. Found: C, 59.65; H, 4.2; N, 19.9%.
The compound was synthesized according to Method D. A solution of 0.1 g (0.23 mmol) of 2-(dihalomethyl)-1-[4-(4-morpholinyl)-6-(phenylsulfonyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (from Example 11) in 10 mL acetone and 10 mL H₂OAc was treated with portions of 4% aq. KMnO₄ until the color remained. The mixture was then decolorized with aq. Na₂SO₃ solution, neutralized with aq. NH₃, and extracted with CH₂Cl₂. Chromatography on silica eluting with CH₂Cl₂/EtOAc (9:1) gave 26 mg (24% yield) of 2-(dihalomethyl)-1-[4-(4-morpholinyl)-6-(phenylsulfonyl)-1,3,5-triazin-2-yl]-1H-benzimidazole: mp (EtOH) 237-239°C (C); ¹H NMR (CDCl₃) δ 8.13 (dd, J=8.4, 1.2 Hz, 2H), 7.99 (d, J=7.7 Hz, 1H), 7.86 (d, J=7.5 Hz, 1H), 7.80 (dt, J=7.5, 1.8 Hz, 1H), 7.67 (t, J=7.8 Hz, 2H), 7.41 (dt, J=7.8, 1.3 Hz, 1H), 7.35 (dt, J=7.8, 1.3 Hz, 1H), 7.13 (t, J=5.3 Hz, 3H), 4.04 (m, 2H), 3.98 (m, 2H), 3.84 (m, 4H); Anal. Calc. for C₂₂H₂₈F₂N₂O₅S·C₅, 53.4; H, 3.8; N, 17.8. Found: C, 53.4; H, 3.8; N, 18.0%.

Example 13
Synthesis of 4-[2-(dihalomethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amime

The compound was synthesized according to Method A. A stirred mixture of 1-(4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl)-2-(dihalomethyl)-1H-benzimidazole (0.183 g, 0.5 mmol) and 3-aminoethylpyridine (0.135 g, 1.25 mmol) in 10 mL dioxane was heated under gentle reflux for 5 min. After cooling, the mixture was diluted with water to give an oily solid, which was recrystallized from MeOH to give 0.13 g (59% yield) of 4-[2-(dihalomethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinylmethyl)1,3,5-triazin-2-amime: mp 160-161°C (C); ¹H NMR (CDCl₃) (rotamers) δ 8.61 (d, J=4.4 Hz, 1H), 8.42 and 8.32 (2d, J=7.6 and 8.4 Hz, 1H), 7.89-7.87 (m, 1H), 7.70 (dt, J=7.7, 1.65 Hz, 1H), 7.65 and 7.59 (2t, J=5.3 and 5.5 Hz, I), 7.43-7.37 (m, 2H), 7.34 (trb, J=8.7 Hz, 1H), 7.24 (tr, J=6.2 Hz, 1H), 6.55 and 6.41 (2m, exchangeable with D₂O, 1H), 4.82 and 4.78 (2d, J=5.3 and 5.1 Hz, 2H), 3.88 (m, 4H), 3.78 (m, 4H); Anal. Calc. for C₂₃H₂₆F₂N₄O·C, 57.5; H, 4.6; N, 25.6. Found: C, 57.7; H, 4.5; N, 25.7%.

Example 15
Synthesis of 4-[2-(dihalomethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyridinylmethyl)-1,3,5-triazin-2-amime

The compound was synthesized according to Method A. A stirred mixture of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(dihalomethyl)-1H-benzimidazole (0.183 g, 0.5 mmol) and 2-aminomethylpyridine (0.135 g, 1.25 mmol) in 10 mL dioxane was heated gently until a clear solution was obtained. After cooling, the mixture was diluted with water to give an oily solid, which was recrystallized from aqueous MeOH to give 0.11 g (50% yield) of 4-[2-(dihalomethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amime: mp 192-193°C (C); ¹H NMR (CDCl₃) (rotamers) δ 88.65 (d, J=1.8 Hz, 1H), 8.57 (dd, J=4.7, 1.0 Hz, 1H), 8.40 and 8.25 (2d, J=7.5 and 5.5 Hz, 1H), 7.88 (m, 1H), 7.70 (d, J=7.7 Hz, 1H), 7.62 (t, J=5.4 Hz, 1H), 7.43-7.37 (m, 2H), 7.30 (dd, J=7.9, 4.8, 0.7 Hz, 1H), 5.75 and 5.64 (2m, exchangeable with D₂O, 1H), 4.76 and 4.69 (2d, J=5.7 and 5.8 Hz, 2H), 3.87 (m, 4H), 3.78 (m, 4H); Anal. Calc. for C₂₃H₂₆F₂N₄O·C, 57.5; H, 4.6; N, 25.6. Found: C, 57.5; H, 4.5; N, 25.6%.
0.5 mmol) and 4-aminomethylpyridine (0.135 g, 1.25 mmol) in 10 mL of dioxane was heated under gentle reflux for 5 min, before being cooled and diluted with water. The mixture was extracted with CH$_2$Cl$_2$ and the organic layer was dried with Na$_2$SO$_4$. Chromatography on alumina, eluting with CH$_2$Cl$_2$/EtOAc (9:1), followed by chromatography on silica, eluting with CH$_2$Cl$_2$/EtOAc (3:2) gave 56 mg (26% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyrindinyl)-1,3,5-triazin-2-amine: mp 188-190°C; $^1$H NMR (CDCl$_3$, rotamers) 88.60 (br s, 2H), 8.42 and 8.13 (2d, J=7.4 and 8.0 Hz, 1H), 7.88 (m, 1H), 7.64 (t, J$_{HF}$=5.6 Hz, 1H), 7.44-7.25 (m, 4H), 5.78 and 5.71 (2 m, exchangeable with D$_2$O, 1H), 4.74 and 4.70 (2 d, J=6.0 and 6.0 Hz, 2H), 3.19-3.69 (m, 8H).

Example 16

Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrindinyl)-1,3,5-triazin-2-amine

The proposed compound was synthesized according to Method A. To 0.224 g (2.38 mmol) of 2-aminopyridine in THF (3 mL) was added 2.5 mL of lithium bis(trimethylsilyl)amide (1 M solution in THF) and the mixture was stirred for 10 min. A solution of 0.204 g (0.56 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in THF (4 mL) was added and the mixture was stirred for 1 hr. The resulting mixture was neutralized with acetic acid, diluted with water and extracted with EtOAc. The organic layer was washed with water and aqueous NH$_4$$_2$CO$_3$, dried. After removal of the solvent, the residue was purified by chromatography on alumina, eluting with CH$_2$Cl$_2$/EtOAc (1:5) to give an orange powder. Recrystallization from EtOH/CH$_2$Cl$_2$ gave 31.5 mg (13% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrindinyl)-1,3,5-triazin-2-amine: mp 230-232°C; $^1$H NMR (CDCl$_3$) δ 8.41-8.37 (m, 2H), 8.20 (d, J=8.4 Hz, 1H), 8.12 (br s, 1H), 7.91-7.89 (m, 1H), 7.75 (td, J=7.5, 1.8 Hz, 1H), 7.60 (t, J$_{HF}$=5.5 Hz, 1H), 7.45-7.39 (m, 2H), 7.05 (dd, J=7.3, 4.9, 0.9 Hz, 1H), 3.96-3.94 (m, 4H), 3.85-3.82 (m, 4H); HRMS (FAB$^+$) M$^+$ Calcd. for C$_{20}$H$_{14}$F$_2$N$_8$NaO: m/z 447.1466; Found: m/z 447.1464.

Example 17

Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyrindinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. A mixture of 0.048 g (0.51 mmol) of 4-aminopyridine and 0.095 g (0.26 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in DMSO (1.5 mL) was heated at 120°C for 1 hr. The reaction mixture was cooled to room temperature and water was added. The solid was collected by filtration and washed with water to give 0.022 g (20% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyrindinyl)-1,3,5-triazin-2-amine: mp (MeOH) 222-224°C; $^1$H NMR (DMSO-d$_6$) δ 10.30 (br s, 1H), 8.59-8.46 (m, 3H), 7.91-7.86 (m, 4H), 7.55-7.44 (m, 2H), 3.88 (br s, 4H), 3.77-3.76 (m, 4H); HRMS (FAB$^+$) M$^+$ Calcd. for C$_{20}$H$_{14}$F$_2$N$_8$NaO: m/z 447.1466; Found: m/z 447.1464; HRMS (FAB$^+$) MH$^+$ Calcd. for C$_{20}$H$_{14}$F$_2$N$_8$NO: m/z 425.1644; Found: m/z 425.1629.

Example 18

Synthesis of N-[4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-quinolinamine

The compound was synthesized according to Method A. To a solution of 0.323 g (2.24 mmol) of 3-aminquinoline in THF (5 mL) at 0°C was added 1.6 mL of NaHMDS (2 M solution in THF), and the mixture was stirred for 15 min. A solution of 0.280 g (0.77 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in THF (4 mL) was added and the resulting mixture was stirred for 1 hr at RT. The resulting mixture was neutralized with acetic acid, diluted with water, and extracted with EtOAc. The organic layer was washed sequentially with water andaq. NH$_4$NO$_3$, dried, and concentrated. Chromatography
on alumina, eluting first with hexanes/EtOAc (1:1), and then CH₂Cl₂/EtOAc (1:3) gave a pink powder. Recrystallization from ethanol gave 0.167 g (46% yield) of N-[4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-3-quinoxalinamine: mp 270-273°C; ¹H NMR (CDCl₃) δ 9.08 (br s, 1H), 8.48-8.43 (m, 2H), 8.12 (d, J = 8.4 Hz, 1H), 7.93-7.90 (m, 1H), 7.80 (dd, J = 8.0, 1.1 Hz, 1H), 7.69 (d, J = 6.9, 1.4 Hz, 1H), 7.61-7.41 (m, 4H), 7.30 (d, J = 5.3 Hz, 1H), 3.97-3.95 (m, 4H), 3.83 (s, 4H); Anal. Calcd. for C₂₆H₂₈F₂N₆O·C: 60.75; H: 4.2; N: 23.6. Found: C: 60.7; H: 4.2; N: 23.5%.

Example 19

Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrimidinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. To a solution of 0.214 g (2.25 mmol) of 2-aminopyrimidine in THF (4 mL) at 0°C, was added 1.25 mL of NaH (1.0 M solution in THF) and the mixture was stirred for 20 min. A solution of 0.275 g (0.75 mmol) of 4-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in THF (4 mL) was added, and the resulting mixture was stirred for 1 hr at RT. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NH₃, dried and concentrated. Chromatography on alumina, eluting first with hexanes/EtOAc (4:1), then with CH₂Cl₂/EtOAc (1:3) gave an orange powder. Recrystallization from ethanol gave 0.008 g (31% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrimidinyl)-1,3,5-triazin-2-amine: mp 261-263°C; ¹H NMR (CDCl₃) 88.69-8.67 (m, 3H), 8.34 (t, J = 5.3 Hz, 1H), 8.07 (br s, 1H), 7.91 (dd, J = 7.9, 0.9 Hz, 1H), 7.49-7.40 (m, 2H), 7.05 (t, J = 4.8 Hz, 1H), 3.96 (m, 4H), 3.83 (m, 4H); Anal. Calcd. for C₂₆H₂₈F₂N₆O·C: 53.65; H: 4.0; N: 29.6. Found: C: 53.6; H: 4.1; N: 29.4%.

Example 20

Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. To a solution of 0.186 g (1.96 mmol) of 5-aminopyrimidine in THF (4 mL) at 0°C, was added 1.1 mL of NaH (1.0 M solution in THF), and the mixture was stirred for 15 min. A solution of 0.238 g (0.65 mmol) of 4-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in THF (5 mL) was added and the resulting mixture was stirred for 1 hr at RT. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NH₃, dried and concentrated. Chromatography on alumina, eluting first with CH₂Cl₂/EtOAc (1:9) and then with CH₂Cl₂/EtOAc (1:3) to CH₂Cl₂/EtOAc (7:3) gave an off-white powder. Recrystallization from ethanol gave 0.123 g (47% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine: mp 290-292°C; ¹H NMR (CDCl₃) 89.07 (s, 2H), 9.02 (s, 1H), 8.37 (d, J = 7.2 Hz, 1H), 7.89 (dd, J = 7.7, 1.5 Hz, 1H), 7.57 (t, J = 5.3 Hz, 1H), 7.47-7.40 (m, 2H), 7.11 (s, 1H), 3.95-3.92 (m, 4H), 3.83 (br s, 4H); Anal. Calcd. for C₂₆H₂₈F₂N₆O·C: 53.65; H: 4.1; N: 29.6. Found: C: 53.4; H: 4.2; N: 29.4%.
Synthesis of 4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrazinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. To a solution of 0.219 g (2.33 mmol) of 3-aminoaziridine in THF (5 mL) at 0°C, was added 1.3 mL of NaOMe (2 M solution in THF), and the mixture was stirred for 15 min. A solution of 0.238 g (0.65 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benimidazol-6 (6 mL) was added, and the resulting mixture was stirred for 1 hr at RT. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NH₄Cl, dried and concentrated. Chromatography on alumina, eluting first with hexanes/EtOAc (1:1) and then with CH₂Cl₂/EtOAc (1:4) to CH₂Cl₂/EtOAc (1:1) gave a white powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.170 g (54% yield) of 4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrazinyl)-1,3,5-triazin-2-amine: mp 247-252°C; ²H NMR (CDCl₃) 8.95-6.59 (s, 2H), 8.10 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.4 Hz, 1H), 7.35 (t, J=4.2 Hz, 1H), 7.28 (m, 2H), 3.85 (d, J=4.2 Hz, 4H); Anal. Caled. for C₂₀H₁₇F₂N₃O₂: C, 53.65; H, 4.11; N, 29.6%. Found: C, 53.9; H, 3.8; N, 29.7%.

Synthesis of 4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyrazinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. A mixture of 0.063 g (0.486 mmol) of 6-chloro-3-pyridazinamine (J. Med. Chem. 2006, 49, 4409-4424), 0.022 g (0.55 mmol) of NaOH, and 0.045 g of 10% Pd/C in ethanol (15 mL) was stirred under an atmosphere of hydrogen for 18 hrs. After filtration through celite, the solvent was concentrated to give 0.046 g (95.5% yield) of 3-aminopyrazidine. ²H NMR (DMSO-d₆) 88.39 (dd, J=4.4, 1.2 Hz, 1H), 7.21 (dd, J=8.8, 4.4 Hz, 1H), 6.74 (dd, J=9.2, 1.6 Hz, 1H), 6.26 (br s, 2H).

To a solution of 0.159 g (1.67 mmol) of 3-aminopyrazidine in THF (3 mL) at 0°C, was added 0.93 mL of NaHMDS (2 M solution in THF), and the mixture was stirred for 15 min. A solution of 0.317 g (0.84 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benimidazol-6 (6 mL) was added, and the resulting mixture was stirred for 1 hr at RT. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NH₄Cl, dried and concentrated. Chromatography on alumina, eluting first with hexanes/EtOAc (8:2) then with CH₂Cl₂/EtOAc (1:1) gave a white powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.065 g (18% yield) of 4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine: mp 271-273°C; ²H NMR (DMSO-d₆) 8.11-6.16 (br s, 1H), 8.98 (dd, J=4.7, 1.4 Hz, 1H), 8.67 (d, J=8.0 Hz, 1H), 8.61 (d, J=8.4 Hz, 1H), 8.08 (t, J=5.8 Hz, 1H), 7.86 (dd, J=7.7, 0.7 Hz, 1H), 7.73 (dd, J=9.1, 4.7 Hz, 1H), 7.53-7.43 (m, 2H), 3.86 (s, 4H), 3.75 (s, 4H); Anal. Caled. for C₂₀H₁₇F₂N₃O₂C: C, 53.65; H, 4.11; N, 29.6. Found: C, 53.7; H, 4.2; N, 29.5%.

Synthesis of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(3-pyridinylxyloxy)-1,3,5-triazin-2-yl]-1H-benimidazole

The compound was synthesized according to Method A. A mixture of 0.301 g (3.16 mmol) of 3-hydroxyprizidine and 0.132 g (3.30 mmol) of NaOH was stirred in water until a clear solution was obtained. The water was removed and the residue was combined with a mixture of 0.301 g (3.16 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benimidazole and 0.02 g (0.06 mmol) of tris[2-(2-methoxycethoxy)ethyl]amine (TDA-1) in dioxane (12 mL). The resulting mixture was heated under reflux for 2 hr before being cooled, and diluted with water. The resulting precipitate was collected by filtration, and recrystallized from methanol to give 0.160 g (50% yield) of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(3-pyridinylxyloxy)-1,3,5-triazin-2-yl]-1H-benimidazole: mp 229-231°C; ²H NMR (CDCl₃) 88.63-8.60 (m, 2H), 8.12 (dd, J=7.1, 1.4 Hz, 1H), 7.87 (dd, J=7.1, 1.4 Hz, 1H), 7.59 (dd, J=8.3, 2.7, 1.4 Hz, 1H), 7.45 (dd, J=8.2, 4.6, 0.3 Hz, 1H), 7.41-7.34 (m, 2H), 7.25 (t, J=5.6 Hz, 1H), 3.99-3.96 (m, 2H), 3.89-3.83 (m, 4H).
Synthesis of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-(1-methyl-1H-pyrazol-4-yl)-6-(4-morpholynyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A.

A mixture of 0.996 g (8.82 mmol) of 4-nitropyrazole (J. Med. Chem. 2005, 48, 5780-5793) and 1.33 g (10.6 mmol) of dimethylnitrile in 10 mL of 1 M NaOH was heated at 35°C for 48 h. The reaction mixture was cooled to RT and the supernatant was filtered, washed with water, and dried to give 0.561 g (50% yield) of 1-methyl-4-nitro-1H-pyrazole: 1H NMR (DMSO-d6) 8.85 (s, 1H), 8.22 (s, 1H), 3.91 (s, 3H). A mixture of 0.144 g (1.14 mmol) 1-methyl-4-nitro-1H-pyrazole, 0.017 g (0.07 mmol) platinum oxide, and ethyl acetate (5 mL) in ethanol (15 mL) was stirred under 2 atmospheres of hydrogen for 14 h. The catalyst was removed by filtration through a pad of celite and the solvent was removed to give 0.080 mg (73% yield) of 4-amino-1-methyl-1H-pyrazole as a purple residue, which was used in the next step without further purification: 1H NMR (DMSO-d6) 6.98 (s, 1H), 6.88 (s, 1H), 3.76 (br s, 2H), 3.65 (s, 3H).

A mixture of 0.405 g (4.27 mmol) of 4-amino-1-methylpyrazole and 0.695 g (1.90 mmol) of 1-[4-chloro-6-(4-morpholynyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in DMSO (5 mL) was heated at 125°C for 45 minutes. The reaction mixture was cooled to room temperature and water was added. The solid was collected by filtration, washed with water, and dried. Chromatography on alumina, eluting with hexanes/EtOAc (1:1) gave a brown powder. Recrystallization from ethanol/CH2Cl2 gave 0.145 g (18% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-(1-methyl-1H-pyrazol-4-yl)-6-(4-morpholynyl)-1,3,5-triazin-2-amine: mp 225-226°C; 1H NMR (DMSO-d6) (rotamers) δ 10.00 (s, 1H), 9.73 (s, 0.2H), 8.60 (d, J=8.0 Hz, 1H), 8.29 (d, J=7.6 Hz, 0.2H), 7.92 (t, J=6.8 Hz, 1H), 7.86-7.80 (m, 2.6H), 7.68 (t, J=5.2 Hz, 0.2H), 7.59 (s, 1H), 7.52-7.42 (m, 2.9H), 3.85-3.82 (m, 8.4H), 3.75-3.73 (m, 4.8H); Anal. Calcd. for C30H30F6N8O2: C, 55.5; H, 4.4; N, 24.7; Found: C, 55.5; H, 4.4; N, 24.5%.

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-(2-methoxy-3-pyridinyl)-6-(4-morpholynyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method B.

A solution of 0.134 g (1.08 mmol) of 3-amino-4-methoxy-2-pyridinyl in THF (3 mL) was added 0.5 mL of butyllithium (2.5 M solution in hexanes), and the mixture was stirred for 15 min. A solution of 0.133 g (0.36 mmol) of 1-[4-chloro-6-(4-morpholynyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole in THF (6 mL) was added and the resulting mixture was stirred for 1 hr. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NaHCO3, dried, and concentrated. Chromatography on alumina, eluting with hexanes/EtOAc (1:1) and then with CH2Cl2/EtOAc (2:3) gave a white powder. Recrystallization from ethanol/CH2Cl2 gave 0.078 g (48% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-(4-methoxy-3-pyridinyl)-6-(4-morpholynyl)-1,3,5-triazin-2-amine: mp 161-162°C; 1H NMR (DMSO-d6) 8.43 (br s, 1H), 8.61-8.37 (m, 3H), 8.73-8.71 (m, 2H), 7.41 (brs, 2H), 7.20 (d, J=5.6 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 4H); Anal. Calcd. for C30H29F6N8O2: C, 55.5; H, 4.4; N, 24.7; Found: C, 55.5; H, 4.4; N, 24.5%.
The compound was synthesized according to Method A. To a solution of 0.121 g (0.98 mmol) of 3-amino-4-methoxyppyridine in THF (3 mL) was added 0.44 mL of butyl-lithium (2.5 M solution in hexanes), and the mixture was stirred for 15 min. A solution of 0.128 g (0.32 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benimidazolone in THF (6 mL) was added and the resulting mixture was stirred for 1 hr. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NaH₂PO₄, dried, and concentrated. Chromatography on alumina, eluting first with hexanes/EtOAc (8:2) and then with CH₂Cl₂/EtOAc (2:1) to CH₂Cl₂/EtOAc (1:1) gave a yellow powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.065 g (42% yield) of 4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-(4-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine: mp 239-241°C; ¹H NMR (CDCl₃) δ 8.43 (br s, 1H), 8.31 (d, J=5.6 Hz, 1H), 7.96 (d, J=8.2 Hz, 1H), 7.54 (t, J=5.4 Hz, 1H), 7.39-7.35 (m, 2H), 6.89 (d, J=5.6 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 4.05 (s, 3H), 3.80 (s, 2H), 3.32-3.80 (m, 4H); Anal. Calc'd. for C₂₂H₂₂F₂N₂O₅: C, 54.5; H, 4.6; N, 23.1. Found: C, 54.4; H, 4.5; N, 22.9.%.

Example 28

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-(6-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. To a solution of 0.310 g (2.50 mmol) of 5-amino-2-methoxyppyridine in THF (3 mL) at 0°C, was added 1.35 mL of lithium diisopropylamide (2 M solution in benzene/heptanes/THF), and the mixture was stirred for 20 min. A solution of 0.240 g (0.61 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazolone in THF (5 mL) was added, and the resulting mixture was stirred for 1 hr at RT. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed sequentially with water and aq. NaH₂PO₄, dried, and concentrated. Chromatography on alumina, eluting first with hexanes/EtOAc (1:1) and then CH₂Cl₂/EtOAc (1:3) gave a brown powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.135 g (40% yield) of 4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-(6-fluoro-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine: mp 261-263°C; ¹H NMR (CDCl₃) δ 88.44 (br s, 1H), 8.03-8.01 (m, 1H), 7.90 (brs, 1H), 7.61-7.31 (m, 2H), 7.07 (br, s, 1H), 6.99 (dd, J=8.3, 3.4 Hz, 1H), 6.83 (d, J=8.0 Hz, 1H), 4.06 (s, 4H), 3.93-3.88 (m, 4H), 3.80 (s, 4H); Anal. Calc'd. for C₂₁H₁₉F₂N₂O₅: C, 53.4; H, 4.05; N, 23.7. Found: C, 53.5; H, 4.6; N, 23.8%.

Example 30

Synthesis of N-(6-chloro-3-pyridinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine
The compound was synthesized according to Method A. To 0.246 g (1.92 mmol) of 5-amino-2-chloropyridine in THF (4 mL) was added 0.85 mL of n-butyllithium (2.5 M solution in hexanes), and the mixture was stirred for 10 min. A solution of 0.260 g (0.66 mmol) of 1-[4-chloro-6-(4-morpholino)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (Example 2) in THF (5 mL) was added. The resulting mixture was stirred at room temperature for 1 hr. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed successively with water and aqueous NH₄OH, and dried. Removal of the solvent and chromatography of the residue on alumina eluting first with hexanes/EtOAc (1:1) and then with CH₂Cl₂/EtOAc (1:5) gave a brown powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.016 g (5% yield) of N-(6-chloro-3-pyridinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-1,3,5-triazin-2-amine: mp 260-262°C; ¹H NMR (CDCl₃) 88.69 (s, 1H), 7.95-7.90 (m, 2H), 7.48 (t, J=53.5 Hz, 1H), 7.37-7.33 (m, 2H), 7.11 (s, 1H), 6.83 (d, J=8.0 Hz, 1H), 4.05 (s, 3H), 3.94-3.87 (m, 4H), 3.81 (m, 4H); Anal. Calcd. for C₂₃H₁₉F₂N₅O₂: C, 51.6; H, 3.9; N, 22.9; Cl, 7.25. Found: C, 52.1; H, 3.9; N, 22.5; Cl, 7.1%.

Example 31

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N(5-pyrimidinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A. To 0.282 g (2.25 mmol) of 4-amino-6-methylpyrimidine in THF (4 mL) was added 1.30 mL of NaHMDS (2 M solution in THF), and the mixture was stirred for 10 min. A solution of 0.297 g (0.75 mmol) of 1-[1-(4-chloro-6-(4-morpholino)-1,3,5-triazin-2-yl)-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (Example 2) in THF (5 mL) was added. The resulting mixture was stirred at room temperature for 1 hr. After neutralization with acetic acid, the mixture was diluted with water, and extracted with EtOAc. The organic layer was washed successively with water and aqueous NH₄OH, and dried. Removal of the solvent, followed by chromatography on silica eluting with CH₂Cl₂/EtOAc (1:1) gave a yellow powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.105 g (30% yield) of 4-(2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl)-N-(6-methylpyrimidin-4-yl)-6-morpholino-1,3,5-triazin-2-amine: mp 256-259°C; ¹H NMR (CDCl₃) 88.52 (s, 1H), 7.96-7.94 (m, 2H), 7.59 (s, 1H), 7.49 (t, J=53.5 Hz, 1H), 7.36 (d, J=8.4 Hz, 1H), 6.84 (d, J=8.1 Hz, 1H), 4.06 (s, 3H), 3.99-3.96 (m, 4H), 3.84 (s, 4H); HRMS (FAI MH⁺) Calcd. for C₂₁H₂₆F₂N₅O₃: m/z 486.1808. Found: m/z 486.1808.

Example 33

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N(3-pyridinyl)-1,3,5-triazin-2-amine
The compound was synthesized according to Method A. To 0.215 g (2.26 mmol) of 3-aminopyrazidine (Example 23) in THF (4 mL) was added 1.30 mL of NaHIMDS (2 M solution in THF), and the mixture was stirred for 10 min. A solution of 0.297 g (0.75 mmol) of 1-[4-chloro-6-(4-morpholiny)1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (Example 2) in THF (5 mL) was added. The resulting mixture was stirred at room temperature for 1 hr. After neutralization with acetic acid, the mixture was diluted with water and extracted with EtOAc. The organic layer was washed successively with water and aqueous NH₃, and dried. Removal of the solvent, followed by chromatography on silica eluting with CH₂Cl₂/EtOAc (1:3) gave a white powder. Recrystallization from ethanol/CH₂Cl₂ gave 0.103 g (30% yield) of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholiny)N-(3-pyridazinyl)-1,3,5-triazin-2-amine: mp 261-263°C (C); 1H NMR (DMso-d₆) δ 11.13 (s, 1H), 8.97 (s, 1H), 8.38 (d, J=8.4 Hz, 1H), 8.20 (d, J=8.4 Hz, 1H), 8.05 (t, J=5.9 Hz, 2H), 7.73 (dd, J=9.1, 4.7 Hz, 1H), 7.41 (t, J=8.3 Hz, 1H), 6.97 (d, J=7.8 Hz, 1H), 3.98 (s, 3H), 3.85 (s, 4H), 3.75 (s, 4H); Anal. Calcd. for C₂₃H₁₈F₂N₂O: C, 52.7; H, 4.2; N, 27.7%. Found: C, 52.7; H, 4.25; N, 27.7%.

Example 34

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-(6-methoxy-3-pyridazinyl)-6-(4-morpholiny)1,3,5-triazin-2-amine

The compound was synthesized according to Method A. To 0.186 g (1.96 mmol) of 5-aminopyrimidine in THF (4 mL) was added 1.1 mL of NaHIMDS (2 M solution in THF) at 0°C, and the mixture was stirred for 15 min. A solution of 0.238 g (0.65 mmol) of 1-[4-chloro-6-(4-morpholiny)1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole in THF (5 mL) was added and the resulting mixture was stirred for 1 hr at room temperature. The resulting mixture was neutralized with acetic acid, diluted with water, and extracted with EtOAc. The organic layer was washed with water, and aqueous NH₃, and dried. Removal of the solvent, followed by chromatography on alumina, eluting with CH₂Cl₂/EtOAc (1:9), then CH₂Cl₂/EtOAc (1:3), gave an off-white powder. Recrystallization from ethanol gave 0.123 g (47% yield) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholiny)N-(5-pyrimidinyl)-1,3,5-triazin-2-amine: mp 290-292°C (C); 1H NMR (CDCl₃) 89.07 (s, 2H), 9.02 (s, 1H), 8.37 (d, J=7.2 Hz, 1H), 7.89 (dd, J=7.7, 1.5 Hz, 1H), 7.57 (t, J=5.7 Hz, 1H), 7.47-7.40 (m, 2H), 7.11 (s, 1H), 3.95-3.92 (m, 4H), 3.83 (brs, 4H); Anal. Calcd. for C₂₃H₁₈F₂N₂O: C, 53.65; H, 4.0; N, 29.6%. Found: C, 53.4; H, 4.2; N, 29.4%.

To 99 mg (0.23 mmol) of the above compound in CH₂Cl₂ (3 mL) was added 16 µL (0.25 mmol) of methanesulfonic acid in MeOH (0.5 mL). The mixture was stirred for 5 min and concentrated in vacuo to give a white powder. Recrystallization from MeOH/EtOAc gave 85 mg (71%) of 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholiny)N-(5-pyrimidinyl)-1,3,5-triazin-2-amine: mp 163-166°C (C); 1H NMR (DMso-d₆) δ 10.32 (s, 1H), 9.13 (s, 2H), 8.92 (s, 1H), 8.56 (br s, 1H), 8.13-7.77 (m, 2H), 7.53-7.43 (m, 2H), 3.85 (s, 4H), 3.76-3.69 (m, 4H), 2.35 (s, 3H); Anal. Calcd. for C₂₃H₁₈F₂N₂O: C, 45.6; H, 4.1; N, 23.9%. Found: C, 45.2; H, 4.35; N, 23.8%.
Example 36

Synthesis of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyrimidine-1,3,5-triazin-2-yl)-2,5-pyridinediamine

The compound was synthesized according to Method A.

To 0.225 g (2.37 mmol) of 4-aminopyrimidine in THF (3 mL) was added 1.30 mL of NaOMe (2 M solution in THF) and the mixture was stirred for 10 min. A solution of 0.320 g (0.81 mmol) of 1-(4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl)-2-(difluoromethyl)-4-methoxy-1H-benzimidazole in THF (5 mL) was added and the resulting mixture was stirred for 1 hr. The reaction mixture was neutralized with acetic acid, diluted with water and extracted with EtOAc. The organic layer was washed with water andaq. NH₄OH, and dried. Removal of the solvent, followed by chromatography on silica, eluting first with hexanes-EtOAc (1:1), then CH₂Cl₂/EtOAc (1:1) to CH₂Cl₂/EtOAc (1:3) gave a white powder. Recrystallization from EtOH/CH₂Cl₂ gave 0.058 g (16% yield) of 4-[2-(difluoromethyl)-4-methoxy-1H-benzoimidazol-1-yl]-6-(4-morpholinyl)-N-(4-pyrimidine-1,3,5-triazin-2-yl)-2,5-pyridinediamine: mp 234-236°C; 1H NMR (CDCl₃) δ 89.81 (d, J = 1.0 Hz, 1H), 86.65 (d, J = 5.8 Hz, 1H), 8.23 (dd, J = 5.8, 1.3 Hz, 1H), 7.99 (s, 1H), 7.93 (dd, J = 8.3, 0.5 Hz, 1H), 7.47 (t, Jₚₚ = 53.4 Hz, 1H), 7.38 (t, J = 8.2 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 4.06 (s, 3H), 3.97-3.96 (m, 4H), 3.86-3.84 (m, 4H); Anal. Calcd. for C₃₃H₂₄F₂N₄O₂: C, 51.7; H, 4.15; N, 27.3%. Found: C, 51.7; H, 4.15; N, 27.3%.

Example 37

Synthesis of N²-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2,5-pyridinediamine

The compound was synthesized according to Method A.

To 0.652 g (4.69 mmol) of 2-amino-5-nitropyridine in THF (5 mL) was added 3.5 mL of NaOMe (2 M solution in THF) at 0°C. After 20 min a solution of 1.085 g (4.97 mmol) of di-tert-butyl dicarbonate in THF (6 mL) was added and the mixture was slowly warmed to room temperature overnight. Water was added, and the mixture was extracted with EtOAc (3 x 40 mL) and the mixture was stirred under hydrogen (40 mL/Hg) for 4 hrs. The reaction mixture was filtered through celite, washed with MeOH and concentrated to give 0.277 g (99% yield) of tert-butyld-5-nitropyridin-2-yl-carbamate as a white powder: 1H NMR (CDCl₃) δ 10.02 (s, 1H), 9.66 (s, 1H), 8.54 (s, 1H), 8.17-7.80 (m, 3H), 7.39 (d, J = 8.7 Hz, 1H), 6.97-6.93 (m, 1H), 3.98 (s, 3H), 3.82 (s, 4H), 3.74-3.72 (m, 4H), 1.48 (s, 9H).

To 0.033 g (0.06 mmol) of the above carbamate in CH₂Cl₂ (3 mL) was added 0.1 mL (1.30 mmol) of trifluoroacetic acid, the mixture was stirred for 5 hrs and the mixture was diluted with CH₂Cl₂ andaq. NH₄OH, and the organic layer was washed with brine, dried (Na₂SO₄), and concentrated. The residue was recrystallized from EtOH/CH₂Cl₂ to give 0.013 g (49% yield) of N²-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2,5-pyridinediamine, as a brown powder: mp 267-270°C; 1H NMR (CDCl₃) δ 8.97-9.49 (m, 1H), 8.18-7.27 (m, 5H), 6.96 (d, J = 7.6 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 5.87-5.75 (m, 2H), 3.98 (s, 3H), 3.81 (s, 4H), 3.71 (s, 4H); HRMS (ESI) M+H⁺ Calcd. for C₂₃H₂₂F₂N₄O₂: m/z 470.1859. Found: m/z 470.1867.

Example 38

Synthesis of N²-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N²-methyl-2,5-pyridinediamine
The compound was synthesized according to Method A. To 0.652 g (4.69 mmol) of 2-amino-5-nitropyridine in THF (5 mL) was added 3.5 mL of NaHMDSS (2M solution in THF) at 0°C. After 20 min, a solution of 1.085 g (4.97 mmol) of di-tert-butyl dicarbonate in THF (6 mL) was added, and the mixture was slowly warmed to room temperature overnight. Water was added, and the mixture was extracted with EtOAc (×4). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated. Purification by flash column chromatography on silica, eluting with hexanes-EtOAc (7:3), gave 0.695 g (62% yield) of tert-butyl-5-nitro-2-pyridinylcarbamate as an orange powder: $^1$H NMR (CDCl$_3$) 09.19 (dd, J = 2.8, 0.5 Hz, 1H), 8.93 (br s, 1H), 8.46 (ddd, J = 9.4, 2.8, 0.5 Hz, 1H), 8.20 (dd, J = 9.5, 0.5 Hz, 1H), 1.59 (s, 9H); LCMS (APCI$^+$) m/z: 238 (M+H$^+$, 100%).

To 0.378 g (1.58 mmol) of the above nitro compound in DME (6 mL) at 0°C, was added 0.067 g (2.80 mmol) of sodium hydride. After 20 min, 0.12 mL (1.93 mmol) of methyl iodide was added, and the mixture was stirred for 2 hrs. Water was added, and the mixture was extracted with EtOAc (×4). The combined organic layer was washed successively with 1M HCl sat, NaHCO$_3$ solution, and brine, dried (Na$_2$SO$_4$), and concentrated, to give 0.40 g (99% yield) of tert-butyl methyl[5-nitro-2-pyridinyl]carbamate: $^1$H NMR (CDCl$_3$) 09.19 (d, J = 2.7 Hz, 1H), 8.36 (dd, J = 9.4, 2.7 Hz, 1H), 8.14 (dd, J = 9.4, 0.3 Hz, 1H), 3.50 (s, 3H), 1.57 (s, 9H); LCMS (APCI$^+$) m/z: 253 (M+H$^+$, 100%).

To 0.40 g (1.58 mmol) of the above nitro compound in MeOH (25 mL) was added 0.4 g of 10% Pd/C and the mixture was stirred under hydrogen (40 in 1at) for 4 hrs. After filtration through celite the reaction mixture was concentrated, to give 0.36 g (97% yield) of tert-butyl 5-amino-2-pyridinyl(methyl)carbamate, as a yellow oil. $^1$H NMR (DMSO-d$_6$) 87.70 (dd, J = 2.9, 0.5 Hz, 1H), 7.07 (d, J = 8.6 Hz, 1H), 6.93 (d, J = 8.6, 2.9 Hz, 1H), 3.12 (s, 3H), 1.39 (s, 9H).

The compound was synthesized according to Method A. To 0.314 g (1.99 mmol) of 2-chloro-5-nitropyridine in MeOH (1 mL) was added 5 mL of dimethylamine (2M solution in MeOH) at 0°C, and the mixture was warmed to room temperature. The reaction mixture was concentrated and extracted with EtOAc. The organic layer was washed successively with sat. NaHCO$_3$ solution and brine, dried (Na$_2$SO$_4$), and concentrated to give 0.313 g (94% yield) of 2-dimethylamino-5-nitropyridine as an orange powder: $^1$H NMR (CDCl$_3$) 89.06 (d, J = 2.7 Hz, 1H), 8.20 (dd, J = 9.5, 2.7 Hz, 1H), 6.46 (dd, J = 9.5, 0.4 Hz, 1H), 3.23 (s, 6H); LCMS (APCI$^+$) m/z: 168 (M+H$^+$, 100%).

A mixture of 0.312 g (1.87 mmol) of the above nitro compound and 0.205 g of 10% Pd/C in methanol (40 mL) was stirred under hydrogen (25 in 1at) for 5 hrs. The reaction mixture was filtered through celite, and the solvent was concentrated, to give 0.236 g (92% yield) of N$_2$N$_2$-dimethyl-2,5-pyridinediamine: $^1$H NMR (CDCl$_3$) 87.78 (d, J = 2.9 Hz, 1H), 6.98 (dd, J = 8.8, 2.9 Hz, 1H), 6.45 (dd, J = 8.8, 0.5 Hz, 1H), 2.99 (s, 6H); LCMS (APCI$^+$) m/z: 138 (M+H$^+$, 100%).

To 0.236 g (1.72 mmol) of the above diamine in THF (3.5 mL) was added 0.79 mL of n-butyllithium (2.5 M solution in hexanes) and the mixture was stirred for 10 min. A solution of 0.271 g (0.58 mmol) of 2-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benimidazole (5 mL) was added, and the resulting mixture was stirred for 1 hr. The reaction mixture was neutralized with acetic acid, diluted with water, and extracted with EtOAc. The organic layer was washed with water and aq. NH$_3$, and dried. The solvent was removed under vacuum, and the product mixture was purified by flash column chromatography, eluting with CH$_2$Cl$_2$:EtOAc (3:1), to give 0.075 g (13% yield) of 5-[4-(2-difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]amine$^-$[2-pyridinyl(methyl)carbamate, as a yellow powder: $^1$H NMR (CDCl$_3$) 80.11 (s, 1H), 8.68-7.41 (m, 5H), 7.61 (d, J = 9.0 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H), 3.98 (s, 3H), 3.83 (s, 4H), 3.74-3.73 (m, 4H), 3.29 (s, 3H), 1.47 (s, 9H); LCMS (APCI$^+$) m/z: 585 (M+H$^+$, 100%).

To 0.0750 g (0.13 mmol) of the above carbamate in CH$_2$Cl$_2$ (3 mL) was added 0.1 mL (1.30 mmol) of trifluoroacetic acid and the mixture was stirred for 5 hrs. After dilution with CH$_2$Cl$_2$, the mixture was treated with H$_2$O and aq. NH$_3$, and the organic layer was washed with brine, dried (Na$_2$SO$_4$), and concentrated. The residue was recrystallized from EtOH/CH$_2$Cl$_2$ to give 0.0472 g (75% yield) of N$_2$N$_2$-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N$_2$N$_2$-methyl-2,5-pyridinediamine: mp 218-221°C; $^1$H NMR (CDCl$_3$) 88.31-7.73 (m, 2H), 7.62 (dd, J = 8.8, 2.6 Hz, 1H), 7.56-7.51 (m, 2H), 6.82-6.80 (m, 2H), 6.46 (d, J = 8.8 Hz, 1H), 4.67 (br s, 1H), 4.04 (s, 3H), 3.89 (s, 4H), 3.79 (s, 4H), 2.96 (s, 3H); HRMS (ESI) M+H$^+$ Calcd. for C$_{22}$H$_{22}$F$_3$N$_5$O$_7$: m/z 484.2. Found: m/z 484.216.

Example 39

Synthesis of N$_2$N$_2$-[4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N$_2$N$_2$-dimethyl-2,5-pyridinediamine
Example 40

Synthesis of 4-[[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-(2-methoxy-5-pyrimidinyl)-6-(4-morpholino)-1,3,5-triazin-2-amine

The compound was synthesized according to Method A.

To a solution of sodium methoxide (0.090 g of sodium) in MeOH (12 mL) was added 0.486 g (3.03 mmol) of 2-chloro-5-nitropyrimidine and the mixture was heated under reflux for 1 hr. After cooling, the mixture was concentrated in vacuo, extracted with EtOAc, and washed with water. The aqueous layer was extracted with CHCl₃ and the combined organic layers were dried (Na₂SO₄) and concentrated, to give 0.347 g (75% yield) of 2-methoxy-5-nitropyrimidine as a yellow powder: ¹H NMR (CDCl₃) δ 8.31 (s, 2H), 4.17 (s, 3H); LCMS (APCI⁺) m/z: 156 (MH⁺, 100%).

To 0.342 g (2.20 mmol) of the above nitro compound in MeOH (20 mL) was added 0.30 g of 10% Pd/C and the mixture was stirred under hydrogen (25 in/Hg) for 18 hrs. The reaction mixture was filtered through celite, and concentrated, to give 0.274 g (100% yield) of 5-amino-2-methoxy-pyrimidine as a colorless oil: ¹H NMR (DMSO-d₆) δ 8.05 (s, 2H), 3.94 (s, 3H); LCMS (APCI⁺) m/z: 126 (MH⁺, 100%).

To 0.274 g (2.19 mmol) of the above amino compound in THF (5 mL) was added 1.25 mL of NaHMDMS (2 M solution in THF) and the mixture was stirred for 10 min. A solution of 0.31 g (0.78 mmol) of 1-[4-chloro-6-(4-morpholino)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole in THF (5 mL) was added and the resulting mixture was stirred for 90 min. The reaction mixture was neutralized with acetic acid, diluted with water, and extracted with EtOAc. The organic layer was washed with water and dried. The crude residue was then purified by chromatography on silica, eluting with hexanes/EtOAc (6:4), to give 0.49 g (60% yield) of 5-amino-2-chloropyrimidine as a yellow powder: ¹H NMR (DMSO-d₆) δ 8.03 (s, 2H); LCMS (APCI⁺) m/z: 130 (MH⁺, 100%).

A mixture of 0.28 g (0.71 mmol) of 1-[4-chloro-6-(4-morpholino)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (0.076 g, 0.56 mmol) of the above amine, 0.026 g (0.04 mmol) of BINAP, 0.01 g (0.04 mmol) of Pd(OAc)₂, and 0.266 g (0.82 mmol) of Cs₂CO₃ in 1,4-dioxane (4 mL) was heated at 100°C for 3 hrs under nitrogen. The mixture was cooled to room temperature, sat. NaHCO₃ solution was added, and the resulting mixture was extracted with EtOAc (4×). The organic layer was washed with brine, dried (Na₂SO₄), and concentrated. Chromatography on silica, eluting with CH₂Cl₂/EtOAc (6:1), gave 0.10 g (36% yield) of N-(2-chloro-5-pyrimidinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-1,3,5-triazin-2-amine, as a white powder: mp 298°C (decomp.); ¹H NMR (DMSO-d₆) δ 10.43 (s, 1H), 9.08 (s, 2H), 8.09-7.69 (m, 2H), 7.42 (t, J=8.0 Hz, 1H), 6.98 (d, J=7.6 Hz, 1H), 3.98 (s, 3H), 3.83 (s, 3H), 3.75-3.73 (m, 4H); Anal. Calcd. for C₂₉H₁₅Cl₂N₆O₂: C, 50.0; H, 2.1; N, 32.7. Found: C, 49.2; H, 2.3; N, 32.5%.
Example 42

Synthesis of N²-[4-[(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N²-[2-(dimethylamino)ethyl]-N²-methyl-2,5-pyrimidinediamine

The compound was synthesized according to Method D. To 0.101 g (0.21 mmol) of N-(2-chloro-5-pyrindinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine (Example 41) in EtOH (5 mL) was added 0.28 mL (2.14 mmol) of N,N,N'-trimethylthelyenediamine, and the mixture was heated at 120°C in a sealed tube for 1.5 hrs. Concentration of the solvent, followed by chromatography on silica, eluting first with CH₂Cl₂/EtOAc (1:3), and then with CH₂Cl₂/Methanol/Pyridine (95:5:1), gave N²-[4-[(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N²-[2-(dimethylamino)ethyl]-N²-methyl-2,5-pyrimidinediamine as a brownish oil, which solidified under vacuum: mp 96-98°C; ¹H NMR (CDCl₃) δ 8.47 (s, 1H), 8.36 (s, 1H), 8.05-7.31 (m, 3H), 7.00-6.61 (m, 2H), 4.04 (s, 3H), 3.90-3.79 (m, 10H), 3.22 (s, 3H), 2.97-2.89 (m, 2H), 2.33 (s, 6H); HRMS (EI) M+H⁺ Calcd. for C₅₆H₆₂F₂N₁₂O₂: m/z 556.2703. Found: m/z 556.2694.

Example 43

Synthesis of N²-[4-[(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N²-[3-(dimethylamino)propyl]-N²-methyl-2,5-pyrimidinediamine

The compound was synthesized according to Method D. To a solution of 99 mg (0.23 mmol) of N-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine (Example 22) in DMF (2 mL) was added NaH (95%, 7.9 mg, 0.31 mmol), and after 10 min iodomethane (15 μL, 0.24 mmol) was added, and the resulting mixture was stirred for 2 hrs. Water was added, and the mixture was extracted with EtOAc (3×). The organic layer was washed with brine, dried (Na₂SO₄), and concentrated. Chromatography on silica, eluting first with CH₂Cl₂/EtOAc (1:1) and then with CH₂Cl₂/EtOAc (1:2), gave a white powder (0.082 g), which was recrystallized from CH₂Cl₂/EtOH to give 0.073 g (72% yield) of N-[4-[(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine: mp 202-205°C; ¹H NMR (DMSO-d₆) δ 89.14 (s, 1H), 8.83 (s, 2H), 8.18 (br s, 1H), 7.89-7.87 (m, 1H), 7.41-7.37 (m, 3H), 3.91 (s, br, 2H), 3.80-3.75 (m, 6H), 3.66 (s, 3H); Anal. Calcd. for C₂₆H₂₃F₂N₈O₂: C, 54.7; H, 4.4; N, 28.6. Found: C, 54.7; H, 4.4; N, 29.1%.
Example 45

Synthesis of 4-(2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl)-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine

The compound was synthesized according to Method D. To a solution of 0.1033 g (0.23 mmol) of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine (Example 32) in DMF (2 mL) was added NaI (95%, 8.7 mg, 0.34 mmol), and after 10 min isodinethane (15 μL, 0.24 mmol) was added, and the resulting mixture was stirred for 2 hrs. Water was added and the mixture was extracted with EtOAc (4×). The organic layer was washed with brine, dried (Na₂SO₄), and concentrated. Chromatography on silica, eluting with CH₃Cl/CH₂Cl₂/MeOH (1:1:2) gave a white powder which was recrystallized from CH₂Cl₂/CH₃OH (4:1) to give 0.061 g (50% yield) of 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine: mp 214-217°C; ¹H NMR (DMSO-d₆) δ 8.13 (s, 1H), 8.98 (s, 2H), 7.66-7.28 (m, 3H), 6.93 (d, J=8.0 Hz, 1H), 3.98 (s, 3H), 3.82-3.70 (m, 8H), 3.59 (s, 3H); HRMS (ESI) M+H⁺. Calcd for C₂₅H₂₅F₂N₂O₂: m/z 470.1859. Found: m/z 470.1852.

Example 46

Synthesis of 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-4-pyrimidinamine

The compound was synthesized according to Method A. 1-(4,6-Dichloro-2-pyrimidinyl)-2-(difluoromethyl)-1H-benzimidazole (International Publ. No. WO 2002/088112, the disclosure of which is incorporated herein by reference in its entirety) (0.315 g, 1 mmol) was added to a mixture of 3-aminopyridine (0.28 g, 3 mmol) and LDA (1.5 mL, 2 M in THF, 3 mmol) in 10 mL THF at room temperature. After 10 min, the mixture was neutralized with H₂OAc, diluted with water, extracted with EtOAc, and dried (Na₂SO₄). Chromatography on silica, eluting with CH₂Cl₂/CH₂Cl₂/MeOH (3:2) gave a solid, which was recrystallized from 1-chloro-4-(2-methylpentane) to give 0.252 g (67% yield) of 6-chloro-2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-(3-pyridinyl)-4-pyrimidinamine: mp (i-Pr₂O) 233-236°C; ¹H NMR (DMSO-d₆) δ 10.42 (br, 1H), 8.72 (d, J=2.3 Hz, 1H), 8.43 (dd, J=4.7, 1.4 Hz, 1H), 8.26 (m, 1H), 8.01 (dd, J=8.3, 2.5, 1.5 Hz, 1H), 7.86 (m, 1H), 7.62 (t, J=8.3 Hz, 1H), 7.48-7.42 (m, 3H), 6.86 (s, 1H); Anal. Calc. for C₂₅H₂₅F₂N₂O₂: C, 54.8; H, 3.0; N, 22.55. Found: C, 54.75; H, 3.0; N, 22.7%.

The above compound was refuxed with morpholine in THF to give 280 mg (98% yield) of 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-4-pyrimidinamine: mp (i-Pr₂O) 192-194°C; ¹H NMR (DMSO-d₆) δ 8.63 (br, 1H), 8.69 (d, J=2.4 Hz, 1H), 8.27 (dd, J=4.7, 1.4 Hz, 1H), 8.23 (dd, J=4.7, 2.8 Hz, 1H), 7.98 (ddd, J=8.3, 2.6, 1.5 Hz, 1H), 7.83 (td, J=6.4, 2.8 Hz, 1H), 7.70 (t, J=8.3 Hz, 1H), 7.42-7.39 (m, 2H), 7.36 (dd, J=8.6, 4.8 Hz, 1H), 6.00 (s, 1H), 3.74 (m, 4H), 3.59 (m, 4H).

Example 47

Synthesis of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole

The compound was synthesized according to Method B. A mixture of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-1H-benzimidazole (0.183 g, 0.5 mmol), 3-pyridylboronic acid (92 mg, 0.75 mmol), PdCl₂ (dpf) (28 mg), and aq. Na₂CO₃ (2M, 4 mL) in dioxane (20 mL) was heated under reflux under nitrogen for 1 hr. After cooling, the mixture was diluted with water, extracted with CH₂Cl₂, and dried. Chromatography on silica, eluting with CH₂Cl₂/MeOH (1:1), gave 0.13 g (64% yield) of 2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole: mp (MeOH) 190-191°C; ¹H NMR (DMSO-d₆) δ 9.59 (d, J=1.6 Hz, 1H), 8.85 (dd, J=4.8, 1.7 Hz, 1H), 8.75 (td, J=8.0, 1.9 Hz, 1H), 8.50 (d, J=8.2 Hz, 1H), 7.90 (d, J=7.9 Hz, 1H), 7.86 (t, J=8.2 Hz, 1H), 7.65 (ddd, J=8.0, 4.8, 0.7 Hz, 1H), 7.59 (dt, J=7.8, 1.1 Hz, 1H), 7.49 (dt, J=7.6, 1.1 Hz,
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The compound was synthesized according to Method B.

Reaction of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (Example 47) with tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (WO 2006/021881) by a similar procedure to Example 47 gave a mixture of 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-4-yl)-1,3,5-triazin-2-yl]-1H-benzimidazole and 2-(difuoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-4-yl)-1,3,5-triazin-2-yl]-1H-benzimidazole in 55% yield: mp (CH₂Cl₂/MeOH) 289-291°C; 'H NMR (DMSO-d₆) δ 8.13 (s, 1H), 8.52 (d, J = 1.5 Hz, 1H), 7.74 (s, J₂=52.8 Hz, 1H), 7.63 (m, J = 8.0 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H), 7.45 (s, 1H), 4.08 (br, 2H), 3.83 (br, 2H); Anal. Calcd. for C₃₁H₂₆F₂N₂O₂: C, 54.96; H, 4.32; N, 22.14.

Example 49

Synthesis of 5-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-pyridinamine

The compound was synthesized according to Method B.

A mixture of 0.30 g (0.75 mmol) of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole, 0.21 g (0.95 mmol) of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinamine, and 0.057 g (0.08 mmol) of PdCl₂(dppf) in a mixture of 1,4-dioxane (30 mL) and 2M Na₂CO₃ solution (6 mL) was heated at 100°C for 5 hrs under nitrogen. After cooling, the mixture was concentrated, diluted with water, and extracted with EtOAc (x4). The organic layer was washed with brine, dried (Na₂SO₄), and concentrated. Chromatography on silica, eluting first with CH₂Cl₂-EtOAc (1:3) and then with CH₂Cl₂-EtOAc (1:3), gave an off-white powder, which was recrystallized from CH₂Cl₂-EtOH to give 0.144 g (43% yield) of 5-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-pyridinamine: mp 259-261°C; 'H NMR (DMSO-d₆) δ 9.04 (d, J = 2.2 Hz, 1H), 8.32 (dd, J = 8.8, 2.4 Hz, 1H), 8.04 (d, J = 8.3 Hz, 1H), 7.79 (t, J₂=52.8 Hz, 1H), 7.47 (t, J = 8.2 Hz, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.85 (s, 2H), 6.57 (d, J = 8.8 Hz, 1H), 4.04-4.00 (m, 5H), 3.89 (br s, 2H), 3.76 (s, 4H); Anal. Calcd. for C₃₁H₂₆F₂N₂O₂: C, 54.45; H, 4.6; N, 24.22. Found: C, 54.8; H, 4.2; N, 24.2%.

Example 50

Synthesis of 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-4-yl)-1,3,5-triazin-2-yl]-1H-benzimidazole

The compound was synthesized according to Method B.

The mixture with TFA in CH₂Cl₂, as for previous examples, gave 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-4-yl)-1,3,5-triazin-2-yl]-1H-benzimidazole in 55% yield: mp (CH₂Cl₂/MeOH) 289-291°C; 'H NMR (DMSO-d₆) δ 8.13 (s, 1H), 8.60 (d, J = 1.4 Hz, 1H), 8.24 (d, J = 1.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.84 (s, J₂=52.8 Hz, 1H), 7.46 (s, J = 8.2 Hz, 1H), 6.99 (d, J = 7.9 Hz, 1H), 4.01 (br, 2H), 3.99 (s, 3H), 3.88 (br,
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2H), 3.76 (br, 4H); Anal. Calcd. for C_{13}H_{18}F_{2}N_{2}O_{2}: C, 53.3; H, 4.2; N, 26.2. Found: C, 53.1; H, 4.3; N, 26.0%.

Example 51

Synthesis of 2-(difluoromethyl)-1-[4-(4-morpholino)-6-(3-pyridinyl)-2-pyrimidinyl]-1H-benzimidazole

\[ \text{CHF}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{CH}_2 \]

The compound was synthesized according to Method B. Using a similar procedure to Example 47, reaction of 1-[4-chloro-6-(4-morpholino)-2-pyrimidinyl]-2-(difluoromethyl)-1H-benzimidazole (International Publ. No. WO 2008/032028, the disclosure of which is incorporated herein by reference in its entirety) and 3-pyridinylboronic acid gave 2-(difluoromethyl)-1-[4-(4-morpholino)-6-(3-pyridinyl)-2-pyrimidinyl]-1H-benzimidazole in 77% yield: mp (CH\textsubscript{3}Cl\textsubscript{2}/hexanes) 172-179\degree C; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}) \delta 9.44 (d, J=2.2 Hz, 1H), 8.75 (dd, J=4.8, 1.5 Hz, 1H), 8.61 and 8.59 (2m, 1H), 8.39 (d, J=8.20 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.82 (t, J=5.28 Hz, 1H), 7.62 (dd, J=8.0, 4.8 Hz, 1H), 7.35-7.51 (m, 2H), 7.46-7.42 (m, 1H), 3.88-3.84 (m, 4H), 3.79-3.77 (m, 4H); Anal. Calcd. for C\textsubscript{23}H\textsubscript{18}F\textsubscript{2}N\textsubscript{2}O\textsubscript{2}: C, 59.1; H, 4.8; N, 15.6. Found: C, 49.0; H, 4.4; N, 15.0%.

Example 52

Synthesis of 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholino)-6-(3-pyridinyl)-2-pyrimidinyl]-1H-benzimidazole

\[ \text{CHF}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{O} \]

The compound was synthesized according to Method B. Reaction of 1-(4,6-dichloro-2-pyrimidinyl)-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (International Publ. No. WO 2005/095389, the disclosure of which is incorporated herein by reference in its entirety) with a ten-fold excess of morpholine in THF at room temperature gave 51 mg (89% yield) of 1-[4-chloro-6-(4-morpholino)-2-pyrimidinyl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole: mp (CH\textsubscript{3}Cl\textsubscript{2}/MeOH) 261-263\degree C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \delta 7.90 (dd, J=8.4, 0.7 Hz, 1H), 7.47 (t, J=5.3 Hz, 1H), 7.37 (t, J=8.2 Hz, 1H), 6.82 (d, J=7.7 Hz, 1H), 6.47 (s, 1H), 4.07 (s, 3H), 3.84 (m, 4H), 3.73 (m, 4H); Anal. Calcd. for C\textsubscript{13}H\textsubscript{18}F\textsubscript{2}N\textsubscript{2}O\textsubscript{2}: C, 51.6; H, 4.1; N, 17.7. Found: C, 51.7; H, 4.1; N, 17.9%.

Example 53

Synthesis of 2-(difluoromethyl)-1-[4-(6-methoxy-3-pyridyl)-6-(4-morpholino)-1,3,5-triazin-2-yl]-1H-benzimidazole

\[ \text{CHF}_2 \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{O} \]

The compound was synthesized according to Method B. Reaction of 6-methoxy-3-pyridinylboronic acid and 1-[4-chloro-6-(4-morpholino)-2-pyrimidinyl]-2-(difluoromethyl)-1H-benzimidazole (International Publ. No. WO 2008/032028, the disclosure of which is incorporated herein by reference in its entirety), as in Example 47, gave 2-(difluoromethyl)-1-[4-(6-methoxy-3-pyridyl)-6-(4-morpholino)-1,3,5-triazin-2-yl]-1H-benzimidazole in 81% yield: mp (CH\textsubscript{3}Cl\textsubscript{2}/hexanes) 224-226\degree C; \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}) \delta 9.09 (dd, J=2.1, 0.5 Hz, 1H), 8.54 (dd, J=8.8, 2.5 Hz, 1H), 8.37 (d, J=8.2 Hz, 1H), 7.87 (d, J=7.9 Hz, 1H), 7.80 (t, J=5.28 Hz, 1H), 7.53 (td, J=7.7, 1.1 Hz, 1H), 7.45 (d, J=8.2 Hz, 1H), 7.42 (br s, 1H), 7.02 (d, J=8.7, 0.4 Hz, 1H), 3.96 (s, 3H), 3.86-3.83 (m, 4H), 3.79-3.76 (m, 4H); Anal. Calcd. for C\textsubscript{21}H\textsubscript{18}F\textsubscript{2}N\textsubscript{2}O\textsubscript{2}: C, 60.3; H, 4.6; N, 19.2. Found: C, 60.4; H, 4.7; N, 19.5%.
Example 54

Synthesis of N-[3-(5-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-4-pyrimidinyl]-2-pyridinyl]oxypropyl]-N,N-dimethylamine

The compound was synthesized according to Method B. Similarly, reaction of 1-[4-chloro-6-(4-morpholinyl)-2-pyrimidinyl]-2-(difluoromethyl)-1H-benzimidazole and N,N-dimethyl-3-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridinyl]oxy]-1-propanamine, as in Example 47, gave N-[3-(5-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-4-pyrimidinyl]-2-pyridinyl]oxy)propyl]-N,N-dimethylamine in 33% yield: mp (CH<sub>2</sub>Cl<sub>2</sub>/hexanes) 140-141°C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 9.07 (d, J=2.2 Hz, 1H), 8.53 (dd, J=8.8, 2.5 Hz, 1H), 8.37 (d, J=8.2 Hz, 1H), 7.87 (d, J=7.9 Hz, 1H), 7.80 (t, J=5.8 Hz, 1H), 7.52 (dt, J=7.8, 1.0 Hz, 1H), 7.30 (dd, J=8.1, 1.0 Hz, 1H), 7.42 (s, 1H), 7.00 (d, J=8.7 Hz, 1H), 4.39 (t, J=6.6 Hz, 2H), 3.85-3.84 (m, 4H), 3.76-3.76 (m, 4H), 2.39 (t, J=7.1 Hz, 2H), 2.17 (s, 6H), 1.89 (quintet, 2H); Anal. Calcld. for C<sub>26</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 61.3; H, 5.7; N, 19.2. Found: C, 61.0; H, 5.5; N, 19.1%.

Example 55

Synthesis of 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-4,5'-bipyrimidine

The compound was synthesized according to Method B. A mixture of 1-[4-chloro-6-(4-morpholinyl)-2-pyrimidinyl]-2-(difluoromethyl)-1H-benzimidazole (200 mg, 0.547 mmol), pyrimidine-5-boronic acid (203 mg, 1.64 mmol), PdCl<sub>2</sub>(dpf) (45 mg, 0.0551 mmol), and aq. K<sub>2</sub>CO<sub>3</sub> (2M, 4 mL) in 1,4-dioxane (20 mL) was refluxed under nitrogen for 2.5 hrs. Additional pyrimidine-5-boronic acid (203 mg, 1.64 mmol) and PdCl<sub>2</sub>(dpf) (23 mg, 0.0282 mmol) were added, and the mixture was refluxed for additional 16.5 hrs under nitrogen. The mixture was cooled to room temperature, diluted with H<sub>2</sub>O, extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x), and the combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvents were removed under vacuum. Chromatography on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/hexanes gave 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-4,5'-bipyrimidine (89 mg, 75%); mp 222-224°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.38 (s, 2H), 9.36 (s, 1H), 7.92 (dd, J=8.4, 0.6 Hz, 1H), 7.40 (t, J=5.6 Hz, 1H), 7.38 (t, J=8.2 Hz, 1H), 6.86 (s, 1H), 6.84 (d, J=7.7 Hz, 1H), 4.07 (s, 3H), 3.89 (m, 4H), 3.85 (m, 4H); Anal. Calcld. for C<sub>26</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>2</sub>: C, 57.0; H, 4.5; N, 21.9. Found: C, 56.95; H, 4.45; N, 22.0%.
Example 57

Synthesis of 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-2'-methoxy-4, 5'-bipyrimidine

The compound was synthesized according to Method B.

Similarly to Example 56, a mixture of 1-[4-chloro-6-(4-morpholinyl)-2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-2'-methoxy-4, 5'-bipyrimidine (148 mg, 0.374 mmol), 2-methoxy-5-pyrimidinylboronic acid (211 mg, 1.52 mmol), PdCl$_2$ (dpff) (40 mg, 0.055 mmol) and aq. K$_2$CO$_3$ (2M, 4 mL) in 1,4-dioxane (20 mL) was refluxed under nitrogen for 24 hrs. After cooling to room temperature, the mixture was diluted with H$_2$O, and the combined organic layers were dried (Na$_2$SO$_4$), and the solvents were removed under vacuum. Chromatography on silica, eluting with CH$_2$Cl$_2$/MeOH (100:0 to 98:2), followed by recrystallization from CH$_2$Cl$_2$/MeOH/Pr$_2$O gave 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-2'-methoxy-4, 5'-bipyrimidine (61 mg, 35%) mp 238-241°C; $^1$H NMR (CDCl$_3$): δ 9.13 (s, 2H), 7.91 (d, J=8.1 Hz, 1H), 7.49 (t, J$_{1,2}$=53.6 Hz, 1H), 7.37 (t, J=8.2 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.77 (s, 1H), 4.13 (s, 3H), 4.07 (s, 3H), 3.75 (dd, J=5.6, 3.7 Hz, 4H), 3.82 (m, 4H). Anal. Calcd. for C$_{24}$H$_{22}$F$_2$N$_4$O$_4$: C, 56.3; H, 4.5; N, 20.9. Found: C, 56.1; H, 4.3; N, 20.6%.

Example 58

Synthesis of 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-4,5'-bipyrimidine-2'-amine

The compound was synthesized according to Method B.

Similar to Example 57, a mixture of 1-[4-chloro-6-(4-morpholinyl)-2-pyrimidinyl]-2-(difluoromethyl)-1H-benzimidazole (200 mg, 0.547 mmol), 5-(4,4,5,5-tetramethylyl-1,3,2-dioxaborolan-2-yl)-2-pyrimidinylamine (302 mg, 1.38 mmol), PdCl$_2$ (dpff) (45 mg, 0.0551 mmol) and aq. K$_2$CO$_3$ (2M, 4 mL) in 1,4-dioxane (20 mL) was refluxed under nitrogen for 24 hrs. The mixture was cooled to room temperature, diluted with H$_2$O, extracted with CH$_2$Cl$_2$ (4x), and the combined organic extracts were dried (Na$_2$SO$_4$), and the solvents were removed under vacuum. Chromatography on alumina, eluting with CH$_2$Cl$_2$/EtOAc (100:0 to 80:20) to CH$_2$Cl$_2$/MeOH (100:0 to 98:5:1.5), followed by recrystallization from CH$_2$Cl$_2$/MeOH/MePr$_2$O gave 2-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-4,5'-bipyrimidine-2'-amine (157 mg, 66% yield), mp 281-285°C; $^1$H NMR (DMSO-d$_6$): δ 9.09 (s, 2H), 8.35 (d, J=8.2 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H), 7.79 (t, J$_{1,2}$=52.8 Hz, 1H), 7.52 (t, J=7.5 Hz, 1H), 7.43 (t, J=7.5 Hz, 1H), 7.32 (s, 1H), 7.24 (s, 2H), 3.82 (m, 4H). 3.75 (m, 4H).

Example 59

Synthesis of 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-9-(3-pyridinyl)-9H-purine

The compound was synthesized by a modification of Method C.

A mixture of 4-(2,6-dichloro-5-nitro-4-pyrimidinyl)morpholine (U.S. Pat. Appl. Publ. No. 2009/0181963, the disclosure of which is incorporated herein by reference in its entirety) (1.89 g, 6.36 mmol) and 3-amino pyridine (0.68 g, 7.22 mmol) in THF at -70°C was treated with 7.2 mL of LiHMDS (1M solution in THF, 2 eq.) and the mixture was stirred at that temperature for 1.5 hrs, and then allowed to warm to room temperature. The solvent was removed and the crude product was extracted with 0.5 mL HCl. After filtration, the aqueous solution was made basic with sat. Na$_2$CO$_3$ to precipitate, which was collected by filtration, and dried, to give 1.12 g (52% yield) of 2-chloro-6-(4-morpholinyl)-5-nitro-N-(3-pyridinyl)-4-pyrimidinamine mp (aq. MeOH):>310°C; $^1$H NMR (CDCl$_3$): δ 10.19 (br s, 1H), 8.74 (d, J=2.5 Hz, 1H), 8.45 (d, J=4.8 Hz, 1H), 8.12 (dd, J=8.3, 2.6, 1.5 Hz, 1H), 7.35 (dd, J=8.4, 4.8 Hz, 1H), 3.81 (m, 4H), 3.61 (m, 4H).

A mixture of 0.23 g of the above nitro compound (0.68 mmol), 0.147 g (0.74 mmol) of 2-difluoromethyl-4-methoxy-1H-benzimidazole (Example 2) and 0.38 g (2.75 mmol) of powdered K$_2$CO$_3$ in 4 mL of DMSO was heated at 120°C for 4 hrs. The reaction mixture was diluted with water, and extracted with EtOAc (×4). The combined organic layers were washed with brine, dried, and concentrated. The residue was purified by chromatography on silica, eluting first with hexanes/EtOAc (1:1), and then with CH$_2$Cl$_2$/EtOAc (2:1), to
give 0.253 g (75% yield) of 3-[[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-5-nitro-N-(3-pyridyl)-4-pyrindimidine, as a yellow powder. ²H NMR (CDCl₃) δ 10.26 (s, 1H), 8.72 (d, J = 2.4 Hz, 1H), 8.60 (dd, J = 4.8, 1.4 Hz, 1H), 7.95 (d, J = 8.3, 2.4, 1.6 Hz, 1H), 7.46 (d, J = 8.3, 0.6 Hz, 1H), 7.40 (d, J = 8.3, 4.8 Hz, 1H), 7.18 (s, J = 7.8 Hz, 1H), 7.11 (s, J = 5.5 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.83 (s, 3H), 3.98 (t, J = 4.5 Hz, 4H), 3.70 (t, J = 4.5 Hz, 4H).

To 0.253 g (0.51 mmol) of the above nitro compound in MeOH (30 mL) was added 0.15 g of 5% Pd on activated carbon, and the mixture was stirred under hydrogen (30 in Hg) for 1.5 hrs. The reaction mixture was filtered through celite and concentrated, to give 0.203 g of crude 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N⁴-(3-pyridyl)-4-pyrindiminediameine. ³H NMR (DMSO-d₆) δ 8.81 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.27 (dd, J = 4.7, 1.5 Hz, 1H), 8.02 (d, J = 8.3, 2.4, 1.5 Hz, 1H), 7.64 (dd, J = 8.3, 0.6 Hz, 1H), 7.56 (t, J = 5.3 Hz, 1H), 7.34 (dd, J = 8.3, 4.7, 0.5 Hz, 1H), 7.25 (s, J = 8.3 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 4.79 (s, 2H), 3.96 (s, 3H), 3.82 (t, J = 4.5 Hz, 4H), 3.24 (t, J = 4.5 Hz, 4H).

A mixture of 0.155 g (0.33 mmol) of the above diamine, trimethyl orthoformate (2.05 g, 22.6 mmol) and p-toluene-sulfonate monohydrate (0.05 g, 0.26 mmol) was heated at 95°C for 4 hrs. The reaction mixture was cooled to room temperature, concentrated, and the product was recrystallized from CH₂Cl₂/MeOH, to give 0.113 g (54% over 2 steps) of 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-9-(3-pyridyl)-9H-purine, as an off-white powder: mp 229-231°C; ¹H NMR (CDCl₃) δ 8.97 (d, J = 2.4 Hz, 1H), 8.76 (dd, J = 4.8, 1.5 Hz, 1H), 8.19 (dd, J = 8.2, 2.4, 1.5 Hz, 1H), 8.09 (s, 1H), 7.77 (dd, J = 8.3, 0.6 Hz, 1H), 7.57 (dd, J = 8.3, 4.8, 0.7 Hz, 1H), 7.41 (t, J = 5.5 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 4.44 (s, br, 4H), 4.05 (s, 3H), 3.91 (t, J = 4.8 Hz, 4H).

Example 60

Synthesis of 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-9-(5-pyrimidinyl)-9H-purine

The compound was synthesized by a modification of Method C.

To 0.482 g (5.06 mmol) of 5-aminopyrimidine in THF (30 mL) was added 2.90 mL of NaHMDS (2 M solution in THF) at 0°C, and the mixture was stirred for 10 min. A solution of 0.5924 g (2.12 mmol) of 4-(2,6-dichloro-5-nitro-4-pyrimidinyl)morpholine (U.S. Pat. Appl. Publ. No. 2009/0181963, the disclosure of which is incorporated herein by reference in its entirety) in THF (5 mL) was added, and the resulting mixture was stirred for 15 min. The reaction mixture was neutralized with acetic acid, diluted with water, and extracted with EtOAc. The organic layer was washed with water and aq. NH₄Cl, dried, and concentrated. Chromatography on silica, eluting with hexanes/EtOAc (8:2), gave 0.465 g (65% yield) of 2-chloro-6-(4-morpholino)-5-nitro-N-(5-pyrimidinyl)-4-pyrindimidine as a white powder: ¹H NMR (DMSO-d₆) δ 10.34 (s, 1H), 9.86 (s, 1H), 9.82 (s, 2H), 3.70 (t, J = 4.8 Hz, 4H), 3.50 (t, J = 4.8 Hz, 4H).

A mixture of 0.465 g (1.38 mmol) of the above nitro compound, 0.368 g (1.86 mmol) of 2-difluoromethyl-4-methoxy-1H-benzimidazole (Example 2) and 0.762 g (5.52 mmol) of powdered K₂CO₃ in 5 mL of DMSO was heated at 120°C for 8 hrs. The reaction mixture was diluted with water, and extracted with EtOAc (x4). The organic layer was washed with brine, dried, and concentrated. Chromatography on silica, eluting first with hexanes/EtOAc (7:3) and then with CH₂Cl₂/EtOAc (1:2), gave 0.592 g (86% yield) of 2-[2-(difluoromethyl)-7-methoxy-2,3-dihydro-1H-benzimidazol-1-yl]-6-(4-morpholino)-5-nitro-N-(5-pyrimidinyl)-4-pyrindimidine, as a yellow powder: ¹H NMR (CDCl₃) δ 10.26 (s, 1H), 9.16 (s, 1H), 8.98 (s, 2H), 7.38 (dd, J = 8.4, 0.6 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H), 7.12 (t, J = 5.3 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 4.01 (s, 3H), 3.87 (t, J = 4.8 Hz, 4H), 3.70 (t, J = 4.8 Hz, 4H).

To 0.162 g (0.33 mmol) of the above nitro compound in THF (40 mL) was added 0.2 g of 5% Pd on activated carbon, and the mixture was stirred under hydrogen (40 in Hg) for 17 hrs. The reaction mixture was filtered through celite, and concentrated, to give 0.155 g of crude 2-[2-(difluoromethyl)-7-methoxy-2,3-dihydro-1H-benzimidazol-1-yl]-6-(4-morpholino)-N⁴-(5-pyrimidinyl)-4-pyrindiminediameine: ¹H NMR (CDCl₃) δ 88.97-8.92 (m, 3H), 7.76 (s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.43 (t, J = 5.3 Hz, 1H), 7.28-7.26 (m, 1H), 6.97 (s, 2H), 6.76 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 3.88 (t, J = 4.6 Hz, 4H), 3.36 (t, J = 4.6 Hz, 4H).

A mixture of the above crude diamine (0.155 g, 0.33 mmol), trimethyl orthoformate (2.5 mL, 22.8 mmol) and p-toluene-sulfonate monohydrate (0.05 g, 0.26 mmol) was heated at 95°C for 3 hrs. The reaction mixture was cooled and concentrated, and the residue was purified by chromatography on silica, eluting with CH₂Cl₂/EtOAc (1:3), to give 0.115 g (73% over 2 steps) of 2-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-9-(5-pyrimidinyl)-9H-purine as a yellow powder: mp 248-251°C; ¹H NMR (CDCl₃) δ 89.34 (s, 1H), 9.23 (s, 2H), 8.09 (s, 1H), 7.73 (dd, J = 8.4, 0.6 Hz, 1H), 7.41 (t, J = 5.5 Hz, 1H), 7.34 (t, J = 8.2 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 4.43 (brs, 4H), 4.05 (s, 3H), 3.91 (t, J = 4.8 Hz, 4H); Anal. Calcd. for C₂₃H₁₅F₂N₄O₇: 0.09EtOAc: C, 55.1; H, 4.1; N, 25.9. Found: C, 55.05; H, 4.00; N, 25.5%.
Example 61

Synthesis of 6-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9-(3-pyridinyl)-9H-purine

NaH (148 mg, 6.17 mmol) was added to a solution of 2-difluoromethyl-4-methoxy-1H-benzimidazole (Example 2) (638 mg, 3.22 mmol) in DMF (10 ml) at 0°C. and the mixture was warmed to room temperature and stirred for 45 min.

2,6-Dichloro-9-tetrahydro-2H-pyran-2-yl-9H-purine (800 mg, 2.93 mmol) was then added and the resulting mixture was stirred at room temperature for 5 days, quenched with H₂O, and extracted with EtOAc (2x). The combined organic extracts were washed with H₂O (3x), dried (Na₂SO₄), and the solvent was removed under vacuum. Chromatography on silica, eluting with hexanes/EtOAc (100:0 to 60:40), gave 2-chloro-6-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-9-tetrahydro-2H-pyran-2-yl-9H-purine (645 mg, 51%). ¹H NMR (CDCl₃) δ 8.38 (s, 1H), 7.52 (d, J=5.4 Hz, 1H), 7.37-7.31 (m, 2H), 6.84 (m, 1H), 5.86 (dd, J=10.7, 2.5 Hz, 1H), 4.23 (dd, J=10.0, 3.8, 1.8 Hz, 1H), 4.07 (s, 3H), 3.83 (dt, J=11.7, 2.8 Hz, 1H), 2.26 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.91-1.69 (m, 3H).

A mixture of the above chloro compound (629 mg, 1.45 mmol) and morpholine (0.65 ml, 7.43 mmol) in absolute EtOH (30 ml) was heated at 70°C for 17 hrs. The solvent was removed under vacuum and the residue diluted with H₂O. The resulting precipitate was filtered, washed with H₂O and aq. MeOH, and dried to give 6-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9-tetrahydro-2H-pyran-2-yl-9H-purine (633 mg, 90%) which was used in the next step without purification. ¹H NMR (CDCl₃) δ 8.01 (s, 1H), 7.30 (t, J=5.7 Hz, 1H), 7.32-7.23 (m, 2H), 6.80 (dd, J=7.8, 0.7 Hz, 1H), 5.67 (dd, J=10.0, 2.6 Hz, 1H), 4.19 (m, 1H), 4.06 (s, 3H), 3.88 (m, 4H), 3.83-3.75 (m, 5H), 2.17-2.05 (m, 5H), 1.88-1.67 (m, 3H).

A mixture of the above pyranyl compound (625 mg, 1.29 mmol) in HCl saturated EtOAc (50 ml) was stirred at 0°C for 30 min, warmed to room temperature, and stirred for 24 hrs. The solid was filtered, washed with H₂O and dried to give 6-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9H-purine (435 mg, 84%) which was used in the next step without purification. ¹H NMR (DMSO-d₆) δ 13.21 (br s, 1H), 8.30 (s, 1H), 7.51 (t, J=5.2 Hz, 1H), 7.33 (t, J=8.1 Hz, 1H), 7.27 (d, J=8.1 Hz, 1H), 6.94 (d, J=7.4 Hz, 1H), 4.01 (s, 3H), 3.74-3.71 (m, 8H).

trans-N,N'-Dimethylcylohexane-1,2-diamine (0.04 ml, 0.254 mmol) in DMF (6 ml) was added to a mixture of the above purine (155 mg, 0.386 mmol), 3-isopropyridine (158 mg, 0.748 mmol), CuI (37 mg, 0.194 mmol), and Cs₂CO₃ (264 mg, 0.811 mmol) under nitrogen. After heating the mixture at 95-100°C for 2 hrs, additional CuI (37 mg, 0.194 mmol) and trans-N,N'-dimethylcylohexane-1,2-diamine (0.04 mL, 0.254 mmol) were added, and the mixture was heated at 105-110°C for 2 days under nitrogen. At this time, additional 3-isopropyridine (80 mg, 0.350 mmol), CuI (37 mg, 0.194 mmol), and trans-N,N'-dimethylcylohexane-1,2-diamine (0.05 mL, 0.190 mmol) were added and the reaction mixture was heated for an additional 24 hrs under nitrogen. The mixture was then cooled to room temperature, diluted with CH₂Cl₂ and filtered through celite. The solvents were removed. Chromatography on silica, eluting with CH₂Cl₂/MeOH (100:0 to 98:2), followed by chromatography on silica eluting with hexanes/EtOAc (67:33 to 20:80), gave 6-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9-(3-pyridinyl)-9H-purine (62 mg, 34%). mp 206-209°C; ¹H NMR (CDCl₃) δ 8.12 (d, J=2.4 Hz, 1H), 8.74 (dd, J=4.8, 1.4 Hz, 1H), 8.14-8.11 (m, 2H), 7.57 (dd, J=8.3, 4.8, 0.7 Hz, 1H), 7.33 (t, J=8.3, 5.7 Hz, 1H), 7.37-7.28 (m, 2H), 6.83 (dd, J=7.8, 0.8 Hz, 1H), 4.08 (s, 3H), 3.89 (m, 4H), 3.79 (m, 4H).

Example 62

Synthesis of 6-[2-(Difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9-(5-pyrimidinyl)-9H-purine

The compound was synthesized by a modification of Method C.

trans-N,N'-Dimethylcylohexane-1,2-diamine (0.071 mL, 0.450 mmol) in DMF (5 ml) was added to a mixture of 6-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9H-purine (180 mg, 0.448 mmol), 5-bromopyrimidine (356 mg, 2.24 mmol), CuI (85 mg, 0.448 mmol), and Cs₂CO₃ (321 mg, 0.986 mmol) under nitrogen, and the mixture was heated at 100-105°C for 3 days. The mixture was cooled to room temperature, diluted with CH₂Cl₂, and filtered through celite. The celite plug was washed with CH₂Cl₂ and CH₂Cl₂/MeOH (9:1) before the solvents were removed under vacuum. Chromatography on silica, eluting with hexanes/EtOAc (70:30 to 20:80), followed by recrystallization from EtOAc/hexanes, gave 6-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-2-[4-morpholiny]-9-(5-pyrimidinyl)-9H-purine (113 mg, 53%); mp (EtOAc/hexanes) 238-240°C; ¹H NMR (CDCl₃) δ 9.47 (s, 2H), 9.30 (s, 1H), 8.89 (s, 1H), 7.53 (t, J=5.6 Hz, 1H), 7.37 (t, J=8.1 Hz, 1H), 7.29 (dd, J=8.4, 0.7 Hz, 1H), 6.97 (d, J=7.5 Hz, 1H), 4.02 (s, 3H), 3.80 (m, 4H), 3.72 (m, 4H). Anal. Calc.: for C₂₂H₁₇F₂N₆O₂: C, 55.1; H, 4.0; N, 26.3. Found: C, 55.3; H, 4.1; N, 26.5.
Example 63

Synthesis of 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-1H-benzimidazole

The compound was synthesized according to Method A. A mixture of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazole (Example 2) (0.49 mg, 1.22 mmol), 1H-pyrazole (1.0 g, 14.7 mmol), and DIPEA (3 mL) was heated to 120°C for 40 min, cooled to 20°C, and diluted with water (50 mL). The resulting precipitate was collected by filtration, washed with water, and dried. Chromatography on silica, eluting with CH3Cl2/ EtOAc (4:1), gave 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-1H-benzimidazole (428 mg, 82%): mp (CH3Cl2/hexanes) 274-277°C; 1H NMR (DMSO-d6) δ 8.79 (dd, J = 2.8, 0.5 Hz, 1H), 8.14 (dd, J = 8.3, 0.5 Hz, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.88 (t, J = 52.8 Hz, 1H), 7.49 (t, J = 8.2 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.70 (dd, J = 2.8, 1.5 Hz, 1H), 4.01 (m, 2H), 4.00 (s, 3H), 3.93 (m, 2H), 3.80-3.75 (m, 4H); Anal. Calc. for C14H12F2N4O2: C, 53.3; H, 4.2; N, 26.2. Found: C, 53.1; H, 4.1; N, 25.9%.

Example 64

Synthesis of 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-ylamine

The compound was synthesized according to Method A. A mixture of 2,3-diamino-5-nitroanisole (Horner et al., Annelin 1953, 579, 212) (1.10 g, 6 mmol) and difluorocetic acid (2.31 g, 24 mmol) in polyphosphoric acid (PPA) (50 g) was heated at 130°C in an oil bath for 1 hr. The hot solution was poured into water, and the pH was adjusted to neutral with cooling to give 2-(difluoromethyl)-4-methoxy-6-nitro-1H-benzimidazole (1.35 g, 91%); mp (EtOH/H2O) 192-194°C; 1H NMR (DMSO-d6) δ 14.18 (br, exchangeable with D2O, 1H), 8.18 (br, 1H), 7.65 (dd, J = 1.4 Hz, 1H), 7.30 (t, JH=JF=52.9 Hz, 1H), 4.07 (s, 3H); Anal. Calc. for C10H12F2N4O2: C, 44.45; H, 2.9; N, 17.3. Found: C, 44.75; H, 3.0; N, 17.3%.

A solution of 2-(difluoromethyl)-4-methoxy-6-nitro-1H-benzimidazole (1.22 g, 5 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd on C (50 mg). After filtration to remove the catalyst Pd/C, the solution was evaporated to dryness. The residue was combined with di-tert-butyl dicarbonate (3.2 g, 15 mmol) in dioxane (20 mL), and the mixture was heated under reflux for 5 hrs. The reaction was cooled, and the solvent was removed under vacuum and the residue was dissolved in MeOH (30 mL) containing aqueous NaOH (2 M, 1.5 mL, 5 equiv.). The mixture was stirred at room temperature for 1 hr, neutralized with HOAc, and evaporated to dryness. The residue was extracted with EtOAc, washed with NaHCO3 solution, and dried over Na2SO4. Chromatography on silica, eluting with CH3Cl2/EtOAc (9:1), gave 1.54 g (98% yield) of tert-butyl 2-(difluoromethyl)-4-methoxy-1H-benzimidazol-6-yl-carbamate: mp (i-Pr2O) 189-191°C; 1H NMR (DMSO-d6) δ 13.0 (br, exchangeable with D2O, 1H), 9.31 (br s, exchangeable with D2O, 1H), 7.42 (br s, 1H), 7.15 (t, JH=JF=53.4 Hz, 1H), 6.90 (br, 1H), 5.90 (s, 3H), 1.49 (s, 9H); Anal. Calc. for C18H14F2N4O2: C, 53.7; H, 5.5; N, 13.4. Found: C, 53.9; H, 5.6; N, 13.4%.

A mixture of the above benzimidazole (0.47 g, 1.5 mmol), 2,4-dichloro-6-(4-morpholinyl)-1,3,5-triazine (0.35 g, 1.5 mmol), and powdered K2CO3 (0.83 g, 6 mmol) in DMP (10 mL) was stirred at room temperature for 30 min. The reaction mixture was then diluted with water. The resulting precipitate was collected, washed with water and then MeOH, and dried to give 0.45 g (59% yield) of tert-butyl 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazol-6-yl-carbamate: mp (CH3Cl2/MeOH) 300°C; 1H NMR (CDCl3) δ 8.45 (d, J = 0.6 Hz, 1H), 7.57 (t, JH=JF=53.6 Hz, 1H), 6.67 (br, exchangeable with D2O, 1H), 6.63 (d, J = 0.9 Hz, 1H), 4.11 (m, 2H), 4.02 (s, 3H), 3.97 (m, 2H), 3.88 (m, 2H), 3.82 (m, 2H), 1.52 (s, 9H); Anal. Calc. for C24H18F2N4O2: C, 49.3; H, 4.7; N, 19.15. Found: C, 49.4; H, 4.8; N, 19.2%.

Reaction of the above chloro compound with 1H-pyrazole, as in Example 63, gave tert-butyl 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-ylcarbamate in 85% yield: mp (CH3Cl2/hexanes) 252-254°C; 1H NMR (DMSO-d6) δ 9.62 (s, 1H), 8.84 (d, J = 2.3 Hz, 1H), 8.71 (br s, 1H), 7.98 (d, J = 1.0 Hz, 1H), 7.93 (t, JH=JF=53.2 Hz, 1H), 6.93 (d, J = 1.7 Hz, 1H), 6.68 (dd, J = 2.8, 1.5 Hz, 1H), 4.08 (m, 2H), 4.01 (m, 2H), 3.93 (s, 3H), 3.81-3.76 (m, 4H), 1.52 (s, 9H); Anal. Calc. for C24H18F2N4O2: C, 53.0; H, 5.0; N, 23.2. Found: C, 53.2; H, 5.2; N, 23.0%.

To a solution of the above carbamate (284 mg, 0.52 mmol) in CH3Cl2 (5 mL) was added TFA (5 mL). The reaction mixture was stirred at 20°C for 30 hrs, basified withaq. NH4OH, and the CH3Cl2 was removed under vacuum. The resulting precipitate was collected by filtration, washed with water, and dried. Recrystallization from CH3Cl2/MeOH gave 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-ylamine in 91% yield.
Example 65

Synthesis of 2-(Difluoromethyl)-4-methoxy-1-[4-(1-methyl-1H-pyrazol-3-yl)-6-(4-morpholino)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-ylamine

The compound was synthesized according to Method B. A mixture of tert-butyl 1-[4-chloro-6-(4-morpholino)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazol-6-yl-carbamate (Example 64) (313 mg, 0.61 mmol), 1-methyl-1H-pyrazol-4-ylboronic acid (155 mg, 1.22 mmol), and 2 M K₂CO₃ (4.1 mL) in 1,4-dioxane (20 mL) was degassed with N₂ for 30 min and then Pd(dppf)Cl₂ (30 mg) was added, and the mixture was degassed for a further 10 min. The reaction mixture was heated under reflux for 1 hr, cooled to 20°C, diluted with water, and extracted with CH₂Cl₂ (20 mL × 3). The combined CH₂Cl₂ extracts were dried (Na₂SO₄) and the solvents were removed to give a crude product which was purified by chromatography on silica, eluting with CH₂Cl₂/EtOAc (4:1) to give tert-butyl 2-(difluoromethyl)-4-methoxy-1-[4-(1-methyl-1H-pyrazol-3-yl)-6-(4-morpholino)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-yl-carbamate (233 mg, 69% yield); mp (CH₂Cl₂/hexanes) 224-227°C; ¹H NMR (DMSO-d₆) δ 9.60 (s, 1H), 8.75 (s, 1H), 8.64 (s, 1H), 8.28 (m, 1H), 7.82 (t, JHF = 53.1 Hz, 1H), 6.92 (d, J = 1.7 Hz, 1H), 3.99-3.96 (m, 4H), 3.96 (s, 3H), 3.92 (s, 3H), 3.76 (m, 4H), 1.53 (s, 9H); Anal. Calcd. for C₂₉H₂₅F₂N₆O₂S: C, 45.4; H, 4.5; N, 22.4. Found: C, 45.3; H, 4.5; N, 22.3.

Deprotection of the above carbamate with TFA/CH₂Cl₂ as in Example 64 gave 2-(difluoromethyl)-4-methoxy-1-[4-(1-methyl-1H-pyrazol-3-yl)-6-(4-morpholino)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-ylamine in 96% yield.

Example 66

Synthesis of 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholino)-6-((1H-pyrazol-4-yl)-1,3,5-triazin-2-yl)]-1H-benzimidazol-6-ylamine

The compound was synthesized according to Method B. Similarly to Example 50, reaction of tert-butyl 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholino)-6-(1H-pyrazol-1-yl)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-yl-carbamate with tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (WO 2006/021881) gave a mixture of tert-butyl 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholino)-6-(1H-pyrazol-4-yl)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-yl-carbamate and tert-butyl 4-[6-[(tert-butyloxycarbonylamino)-2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-1,3,5-triazin-2-yl]-1H-pyrazole-1-carboxylate. Deprotection of the mixture with CH₂Cl₂/TFA for 20 hrs at 20°C gave 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholino)-6-(1H-pyrazol-3-yl)-1,3,5-triazin-2-yl]-1H-benzimidazol-6-ylamine, which was treated with methanesulfonic acid in MeOH, to give the methanesulfonate salt in 50% overall yield; mp (MeOH/EtOAc) >300°C; ¹H NMR (DMSO-d₆) δ 8.48 (s, 2H), 7.88 (br s, 1H), 7.79 (t, J = 52.9 Hz, 1H), 6.76 (br d, J = 1.3 Hz, 1H), 4.01 (m, 2H), 3.99 (s, 3H), 3.76 (m, 4H), 2.34 (s, 3H); Anal. Calcd. for C₂₉H₂₅F₂N₆O₂S: C, 44.5; H, 4.3; N, 23.4. Found: C, 44.5; H, 4.5; N, 23.1.

Example 67

Synthesis of 2-(Difluoromethyl)-1-[4-(1H-imidazol-1-yl)-6-(4-morpholino)-1,3,5-triazin-2-yl]-4-methoxy-1H-benzimidazole

The compound was synthesized according to Method B.
The compound was synthesized according to Method A. Similarly to Example 63, reaction of 1-[4-chloro-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazol-6-ylcarbamate and imidazole at 120°C for 1 hr gave 2-(difluoromethyl)-1-[4-(1H-imidazol-1-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-4-methoxy-1H-benzimidazole in 71% yield: mp (CH₂Cl₂/hexanes) 272-275°C; ¹H NMR (DMSO-d₆) δ 8.74 (s, 1H), 8.04 (t, J=1.4 Hz, 1H), 8.00 (d, J=7.8 Hz, 1H), 7.78 (t, J=1.5 Hz, 1H), 7.50 (t, J=8.3 Hz, 1H), 7.22 (dd, J=1.5, 0.8 Hz, 1H), 7.02 (dd, J=7.8 Hz, 1H), 4.03 (m, 2H), 4.00 (s, 3H), 3.94 (m, 2H), 3.80-3.75 (m, 4H); Anal. Calcld. for C₁₉H₁₈F₂N₄O₂: C, 53.3; H, 4.2; N, 26.2. Found: C, 53.6; H, 4.3; N, 26.7%.

Example 68

Synthesis of 2-(Difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-6-ylamine

The compound was synthesized according to Method B. A mixture of tert-butyl 2-(difluoromethyl)-4-methoxy-1H-benzimidazol-6-ylcarbamate (Example 64) (3.13 g, 10 mmol), 4-(2,6-dichloro-4-pyrimidinyl)morpholine (2.64 g, 11 mmol), and potassium K₂CO₃ (5 g, 40 mmol) in 30 ml DMF was heated at 100°C for 8 hrs. The mixture was cooled and diluted with water to give a precipitate which was collected and dried. Chromatography on silica eluting with CH₂Cl₂/EtOAc (19:1) gave tert-butyl 1-[4-chloro-6-(4-morpholinyl)-2-pyrimidinyl]-2-(difluoromethyl)-4-methoxy-1H-benzimidazol-6-ylcarbamate (2.49 g, 44% yield): mp (i-Pr₂O) 233-236°C; ¹H NMR (CDCl₃) δ 8.30 (s, 1H), 7.57 (t, J=8.3 Hz, 1H), 6.64 (m, 1H), 6.63 (d, J=1.8 Hz, 1H), 6.43 (s, 1H), 4.01 (s, 3H), 3.88-3.85 (m, 4H), 3.82-3.77 (s, 4H), 1.52 (s, 9H); Anal. Calcld. for C₁₉H₁₈F₂N₄O₂: C, 51.7; H, 4.9; N, 16.9%. Reaction of the above chloro compound (0.41 g, 0.8 mmol) with 3-pyridinylboronic acid (0.15 g, 12 mmol) as in Example 47, followed by chromatography on alumina eluting with CH₂Cl₂/EtOAc (4:1), gave tert-butyl 2-(difluoromethyl)-4-methoxy-1-[4-(4-morpholinyl)-6-(3-pyridinyl)-2-pyrimidinyl]-1H-benzimidazol-6-ylcarbamate (0.22 g, 50% yield): ¹H NMR (DMSO-d₆) δ 9.53 (s, 1H), 9.45 (d, J=1.7 Hz, 1H), 8.74 (d, J=4.7, 1.6 Hz, 1H), 8.66 (dd, J=8.3, 1.9 Hz, 1H), 8.54 (br s, 1H), 7.75 (t, J=8.3 Hz, 1H), 7.59 (dd, J=8.0, 4.8, 0.5 Hz, 1H), 7.51 (s, 1H), 6.91 (d, J=1.7 Hz, 1H), 3.95 (s, 3H), 3.92-3.88 (m, 4H), 3.81-3.78 (m, 4H), 1.51 (s, 9H).

Example 69

Biological Activity

A. Inhibition of Isolated Enzyme

Compounds were evaluated for their ability to inhibit Class I PI 3-kinase enzymes p110α/p85, p110α/p55, and p110γ/p55. Reaction mixtures comprising 0.1 μg of a recombinant enzyme, 10 μg of L-α-phosphatidylserinol, and 2x Lipid Kinase Buffer (40 mM Tris-HCl, pH 7.4, 200 mM NaCl, 1 mM EDTA), which contains either DMSO only as a control or the test compound in DMSO (the final DMSO concentration is 1%), were activated by the addition of an ATP mix (5 mM MgCl₂, 100 μM ATP, and 0.1 μL [γ³²P]ATP). Reactions were incubated at room temperature for 1 hr and then stopped by the addition of 1M HCl. The lipids were then extracted using a two step procedure. Firstly, 200 μL of chloroform/methanol (1:1) was added, the biphasic reactions mixed and centrifuged briefly, and the organic phase was removed and discarded. Following this, 80 μL of methanol:HCl (1:1) was added and the same procedure followed. The organic phase (70 μL) was then transferred to a clean 1.6 ml tube and the reactions were dried using a Speedvac, with no heating, for 30 mM. The reactions were spotted onto TLC plates (Merck Ltd) and developed for 1 hr in propanol:1:2 M acetic acid (13:7). The TLC plates were then dried at room temperature and quantified using a phosphorimager (StormImager, Amersham). Nine compound concentrations were used for each test compound to determine its IC₅₀ value. Each experiment was performed twice and the average IC₅₀ value is used herein. The results are summarized in Table 1.

B. Cellular Growth Inhibition

The compounds were evaluated against two early passage human cell lines NFB3 and NZO9 (Marshall et al., Oncol. Res. 2004, 14, 297). The cells were grown in ITS medium (a modified minimal essential medium supplemented insulin, transferrin, selenite, and 5% fetal bovine serum) and grown on 96-well tissue culture plates under an atmosphere of 5% O₂, 5% CO₂, and 90% N₂. Individual wells contained 500-1,000 cells (depending on the growth rate) in a volume of 150 μL. Compounds were added at 10-fold concentration steps to a maximum of 20 μM and plates were incubated for five days, with [³²P]-thymidine being added over the last 6 hrs. Cells were harvested and incorporated radioactivity measured. Duplicate samples were analyzed for each compound dose with multiple control samples. Data were fitted by a least-squares method to an exponential of the form y=yₒ+a exp(-bt), where y is the radioactivity (corrected for background and normalized to 100% of the control), x is the radiation dose, and yₒ, a, and b are variables, and the IC₅₀ value defined as the compound concentration reducing [³²P]-thymidine levels by 50%. The results are summarized in Table 1.
### TABLE 1

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*Note: A = 0.1 μM; B = 0.1-1.0 μM; C = 0.1-10 μM; D = >10 μM

The examples set forth above are provided to give those of ordinary skill in the art a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent application were specifically and individually indicated to be incorporated herein by reference.
each R⁴ and R⁵ is independently hydrogen or C₁₋₅ alkyl; or R⁴ and R⁵ are linked together to form a bond, C₈₋₁₅ alkylene, C₁₋₅ heteroalkylene, C₂₋₅ alkenyle, or C₂₋₅ heteroalkenylene;

each R⁶ is independently C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heteroaryl-C₁₋₅ alkyl;

each U is independently —C(O) —O, —O(O) —O, —OC(O) —O, —OC(O) —NR¹ —O, —NR¹ —O, —NR¹ —S(O) —O, —NR¹ —S(O) —O, —NR¹ —S(O) —O, —NR¹ —S(O) —O, —S(O) —NR¹ —O, —S(O) —O, or —S(O) —O;

each X, Y, and Z is N;

each A, B, D, and E is independently a bond, C, O, N, S, NR², CR³, or CNR⁴, where each R¹ and R² is independently hydrogen, halo, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl, wherein the bonds between A, B, D, and E may be saturated or unsaturated; with the proviso that no more than one of A, B, D, and E is a bond; and R¹ and R² is independently (i) hydrogen; or (ii) C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₆₋₁₄ aryl, or C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl;

wherein each alkyl, alkenyl, heteroalkenyl, alkenyl, heteroalkenyl, alkenyl, heteroalkenyl, alkenyl, heteroalkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, or R¹⁰ is optionally substituted with one or more groups, each independently selected from (a) cyano, halo, and nitro; (b) C₁₋₅ alkyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₆₋₁₄ aryl, or C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl, each of which is further optionally substituted with one or more substituents Q; and (c) —C(O)R², —C(O)OR², —C(O)NR²R⁴, —C(NR²)R⁴, —C(O)NR²R⁴, —OR², —OC(O)R², —OC(O)OR², —OC(O)OR², —OC(O)NR²R⁴, —OS(O)R², —OS(O)OR², —OS(O)OR², —NR²R⁴, —NR²R⁴, —NR²C(O)R⁴, —NR²C(O)NR²R⁴, —NR²C(O)NR²R⁴, —NR²C(O)NR²R⁴, —S(O)R², —S(O)R², and —S(O)R², wherein each R¹, R², R³, R⁴, and R⁶ is independently (i) hydrogen; (ii) C₁₋₅ alkyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₆₋₁₄ aryl, or C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q; or (iii) R³ and R⁶ together with the N atom to which they are attached form heterocyclyl, optionally substituted with one or more substituents Q;

wherein each Q is independently selected from the group consisting of (a) cyano, halo, and nitro; (b) C₁₋₅ alkyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₆₋₁₄ aryl, or C₇₋₁₅ aralkyl, heteroaryl, and heterocyclyl; and (c) —C(O)R², —C(O)OR², —C(O)NR²R⁴, —C(NR²)NR²R⁴, —NR²R⁴, —NR²R⁴, —NR²C(O)R⁴, —NR²C(O)NR²R⁴, —NR²C(O)NR²R⁴, —NR²C(O)NR²R⁴, —S(O)R², —S(O)R², and —S(O)R², wherein each R¹, R², R³, and R⁶ is independently (i) hydrogen; (ii) C₁₋₅ alkyl, C₂₋₅ alkynyl, C₃₋₅ cycloalkyl, C₆₋₁₄ aryl, or C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; or (iii) R³ and R⁶ together with the N atom to which they are attached form heterocyclyl; or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof.
3. The compound of claim 1 having the structure of Formula VIII:

![Chemical Structure]

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof.

4. The compound of claim 1 having the structure of Formula IX:

![Chemical Structure]

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof.

5. The compound of claim 1, wherein A is N.
6. The compound of claim 1, wherein B is N.
7. The compound of claim 1, wherein B is CH or CH₂.
8. The compound of claim 1, wherein D is N.
9. The compound of claim 1, wherein D is CH or CH₂.

10. The compound of claim 1, wherein R⁶ is C₆₋₁₄ aryl, optionally substituted with one or more substituents Q.

11. The compound of claim 10, wherein R⁵ is phenyl, optionally substituted with one or more substituents, each independently selected from the group consisting of halo, cyano, nitro, amino, hydroxyl, and methoxy.

12. The compound of claim 10, wherein R⁵ is phenyl, aminophenyl, nitrophenyl, or methoxyphenyl.

13. The compound of claim 1, wherein R⁵ is C₇₋₁₅ aralkyl, optionally substituted with one or more substituents Q.

14. The compound of claim 13, wherein R⁵ is —(CR⁴R⁶)m-C₆₋₁₄ aryl, and each R⁴ and R⁶ are independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₅ alkyl, C₂₋₆ alkyl, C₃₋₇ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; and m is an integer of 1, 2, or 3; and where each alkyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q.

15. The compound of claim 13, wherein R⁵ is benzyl, optionally substituted with one or more substituents Q.

16. The compound of claim 13, wherein R⁵ is benzyl or phenyl-ethyl, each optionally substituted with one or more substituents Q.

17. The compound of claim 1, wherein R⁶ is heteroaryl, optionally substituted with one or more substituents Q.

18. The compound of claim 17, wherein R⁶ is pyrazolyl, imidazolyl, thiazolyl, 1,2,3-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, or quinolinyl, each optionally substituted with one or more substituents Q.

19. The compound of claim 17, wherein each substituent is independently —L-(CR⁴R⁶)n—R⁷, where R⁷ and R⁸ are each independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₅ alkyl, C₂₋₆ alkyl, C₃₋₇ cycloalkyl, C₆₋₁₄ aryl, C₇₋₁₅ aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; R⁸ is hydrogen, —NR⁹R¹⁰, or heterocyclyl; L is a bond, —O—, or —N(R¹¹)—; R⁷, R⁹, and R¹⁰ are each independently hydrogen or C₁₋₅ alkyl; and n is an integer of 0, 1, 2, or 3; and where each alkyl and heterocyclyl is independently, optionally substituted with one or more substituents Q.

20. The compound of claim 19, wherein L is a bond, —O—, —NH—, or —N(CH₃)—.

21. The compound of claim 19, wherein R⁷ and R⁸ are hydrogen.

22. The compound of claim 19, wherein R⁷ is hydrogen, methylamino, dimethylamino, pyrrolidinyl, piperidinyl, or morpholinyl, wherein the pyrrolidinyl, piperidinyl, and morpholinyl are independently, optionally substituted with methyl.

23. The compound of claim 17, wherein each substituent is independently selected from the group consisting of amino, fluoro, chloro, methyl, (dimethylamino)methyl, (dimethylamino)ethyl, (dimethylamino)propyl, morpholinylmethyl, (morpholinyl)ethyl, (morpholinyl)propyl, methoxy, (dimethylamino)ethoxy, (dimethylamino)propoxy, (morpholinyl)ethoxy, (morpholinyl)propoxy, (methyl-piperidinyl)oxy, (methyl-pyrrolidinyl)-oxy, methylamino, dimethylamino, (dimethylamino)ethylamino, (dimethylamino)propylamino, (dimethylamino)propyl(methyl)amino, (morpholinyl)ethylamino, (morpholinyl)propylamino, (methyl-piperidinyl)(methyl)amino, methyl-piperidinylmethylamino (methyl-piperidinyl)-(methyl)amino, methyl-piperazinyl, and (dimethylamino)-piperidinyl.

24. The compound of claim 18, wherein R⁶ is pyridinyl.

25. The compound of claim 24, wherein R⁷ is 3-pyridinyl.

26. The compound of claim 1 having the structure of Formula III:

![Chemical Structure]
or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof;

wherein:

R<sup>a</sup> is (a) hydrogen, cyano, halo, or nitro; (b) C<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkyloxy, C<sub>6</sub>-<sub>14</sub> aryl, C<sub>6</sub>-<sub>15</sub> aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (e) —C(O) R<sup>1a</sup>, —C(O)OR<sup>1b</sup>, —C(O)NR<sup>1c</sup>R<sup>1d</sup>, —C(NR<sup>4</sup>)R<sup>1e</sup>, —NR<sup>1f</sup> R<sup>1g</sup>, —OR<sup>1h</sup>, —OC(O)R<sup>1i</sup>, —OC(O)NR<sup>1j</sup>R<sup>1k</sup>, —NR<sup>1l</sup>SO(O)R<sup>1m</sup>, —NR<sup>1n</sup>SO(O)NR<sup>1o</sup>R<sup>1p</sup>, —NR<sup>1q</sup> —S(O)R<sup>1r</sup>, —S(O)NR<sup>1s</sup>R<sup>1t</sup>, or —S(O)NR<sup>1u</sup>R<sup>1v</sup>

R<sup>b</sup> is (a) hydrogen, cyano, halo, or nitro; (b) C<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkyloxy, C<sub>6</sub>-<sub>14</sub> aryl, C<sub>6</sub>-<sub>15</sub> aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (e) —C(O) R<sup>1a</sup>, —C(O)OR<sup>1b</sup>, —C(O)NR<sup>1c</sup>R<sup>1d</sup>, —C(NR<sup>4</sup>)R<sup>1e</sup>, —NR<sup>1f</sup> R<sup>1g</sup>, —OR<sup>1h</sup>, —OC(O)R<sup>1i</sup>, —OC(O)NR<sup>1j</sup>R<sup>1k</sup>, —NR<sup>1l</sup>SO(O)R<sup>1m</sup>, —NR<sup>1n</sup>SO(O)NR<sup>1o</sup>R<sup>1p</sup>, —NR<sup>1q</sup> —S(O)R<sup>1r</sup>, —S(O)NR<sup>1s</sup>R<sup>1t</sup>, or —S(O)NR<sup>1u</sup>R<sup>1v</sup>

and

p is an integer of 0, 1, 2, or 3.

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof;

wherein:

R<sup>a</sup> is (a) hydrogen, cyano, halo, or nitro; (b) C<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkyloxy, C<sub>6</sub>-<sub>14</sub> aryl, C<sub>6</sub>-<sub>15</sub> aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (e) —C(O) R<sup>1a</sup>, —C(O)OR<sup>1b</sup>, —C(O)NR<sup>1c</sup>R<sup>1d</sup>, —C(NR<sup>4</sup>)R<sup>1e</sup>, —NR<sup>1f</sup> R<sup>1g</sup>, —OR<sup>1h</sup>, —OC(O)R<sup>1i</sup>, —OC(O)NR<sup>1j</sup>R<sup>1k</sup>, —NR<sup>1l</sup>SO(O)R<sup>1m</sup>, —NR<sup>1n</sup>SO(O)NR<sup>1o</sup>R<sup>1p</sup>, —NR<sup>1q</sup> —S(O)R<sup>1r</sup>, —S(O)NR<sup>1s</sup>R<sup>1t</sup>, or —S(O)NR<sup>1u</sup>R<sup>1v</sup>

R<sup>b</sup> is (a) hydrogen, cyano, halo, or nitro; (b) C<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkyloxy, C<sub>6</sub>-<sub>14</sub> aryl, C<sub>6</sub>-<sub>15</sub> aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (e) —C(O) R<sup>1a</sup>, —C(O)OR<sup>1b</sup>, —C(O)NR<sup>1c</sup>R<sup>1d</sup>, —C(NR<sup>4</sup>)R<sup>1e</sup>, —NR<sup>1f</sup> R<sup>1g</sup>, —OR<sup>1h</sup>, —OC(O)R<sup>1i</sup>, —OC(O)NR<sup>1j</sup>R<sup>1k</sup>, —NR<sup>1l</sup>SO(O)R<sup>1m</sup>, —NR<sup>1n</sup>SO(O)NR<sup>1o</sup>R<sup>1p</sup>, —NR<sup>1q</sup> —S(O)R<sup>1r</sup>, —S(O)NR<sup>1s</sup>R<sup>1t</sup>, or —S(O)NR<sup>1u</sup>R<sup>1v</sup>

and

p is an integer of 0, 1, 2, or 3.

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof;

wherein:

A<sup>2</sup>, A<sup>3</sup>, and A<sup>4</sup> are each independently C, N, or CR<sup>8</sup>; with the proviso that no more than one of A<sup>2</sup>, A<sup>3</sup>, and A<sup>4</sup> is N; each R<sup>4</sup> and R<sup>5</sup> are each independently (a) hydrogen, cyano, halo, or nitro; (b) C<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkyloxy, C<sub>6</sub>-<sub>15</sub> aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (e) —C(O) R<sup>1a</sup>, —C(O)OR<sup>1b</sup>, —C(O)NR<sup>1c</sup>R<sup>1d</sup>, —C(NR<sup>4</sup>)R<sup>1e</sup>, —NR<sup>1f</sup> R<sup>1g</sup>, —OR<sup>1h</sup>, —OC(O)R<sup>1i</sup>, —OC(O)NR<sup>1j</sup>R<sup>1k</sup>, —NR<sup>1l</sup>SO(O)R<sup>1m</sup>, —NR<sup>1n</sup>SO(O)NR<sup>1o</sup>R<sup>1p</sup>, —NR<sup>1q</sup> —S(O)R<sup>1r</sup>, —S(O)NR<sup>1s</sup>R<sup>1t</sup>, or —S(O)NR<sup>1u</sup>R<sup>1v</sup>

and

p is an integer of 0, 1, 2, or 3.

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof;

wherein:

A<sup>2</sup>, A<sup>3</sup>, and A<sup>4</sup> are each independently C, N, or CR<sup>8</sup>; with the proviso that no more than one of A<sup>2</sup>, A<sup>3</sup>, and A<sup>4</sup> is N; each R<sup>4</sup> and R<sup>5</sup> are each independently (a) hydrogen, cyano, halo, or nitro; (b) C<sub>1</sub>-<sub>6</sub> alkyl, C<sub>2</sub>-<sub>6</sub> alkenyl, C<sub>2</sub>-<sub>6</sub> alkyloxy, C<sub>6</sub>-<sub>14</sub> aryl, C<sub>6</sub>-<sub>15</sub> aralkyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (e) —C(O) R<sup>1a</sup>, —C(O)OR<sup>1b</sup>, —C(O)NR<sup>1c</sup>R<sup>1d</sup>, —C(NR<sup>4</sup>)R<sup>1e</sup>, —NR<sup>1f</sup> R<sup>1g</sup>, —OR<sup>1h</sup>, —OC(O)R<sup>1i</sup>, —OC(O)NR<sup>1j</sup>R<sup>1k</sup>, —NR<sup>1l</sup>SO(O)R<sup>1m</sup>, —NR<sup>1n</sup>SO(O)NR<sup>1o</sup>R<sup>1p</sup>, —NR<sup>1q</sup> —S(O)R<sup>1r</sup>, —S(O)NR<sup>1s</sup>R<sup>1t</sup>, or —S(O)NR<sup>1u</sup>R<sup>1v</sup>

and

p is an integer of 0, 1, 2, or 3.
34. The compound of claim 29 having the structure of Formula VI:

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof.

35. The compound of claim 1 having the structure of Formula VII:

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof;

wherein:

E², E³, and E⁴ are each independently C, N, O, S, CR, or NR,

each R¹ and R⁶ is independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₅ alkyl, C₂₋₅ alkenyl, C₆₋₁₅ aryl, or C₆₋₁₅ alkenyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q;

each R⁵ is independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₅ alkyl, C₂₋₅ alkenyl, C₆₋₁₅ aryl, or C₆₋₁₅ alkenyl, heteroaryl, or heterocyclyl; each optionally substituted with one or more substituents Q; or (c) —C(O)R¹, —C(O)OR¹, —C(NR²)NR³R⁴R⁵, —OR¹, —OC(O)R¹, —OS(O)R¹, —OS(O)R¹, —OS(O)R¹, —OS(O)R¹, —NR²R⁴R⁵, —NR²C(O)OR¹, —NR²C(O)NR³R⁴R⁵, —NR²C(O)NR³R⁴R⁵, —NR²C(O)NR³R⁴R⁵, —S(O)R¹, —S(O)R¹, —S(O)R¹, and p is an integer of 0, 1, 2, or 3.

36. The compound of claim 35, wherein E², E³, and E⁴ are CR⁻.

37. The compound of claim 35, wherein E² and E⁴ are CR⁻, and E³ is NR⁵, O, or S.

38. The compound of claim 35, wherein E² and E³ are N, and E⁴ is CR⁻.

39. The compound of claim 35, wherein E², E³, and E⁴ are N.

40. The compound of claim 29, wherein R⁵ is hydrogen.

41. The compound of claim 29, wherein R⁵ is L(=CR⁶R⁷)⁻, where R⁶ and R⁷ are each independently (a) hydrogen, cyano, halo, or nitro; (b) C₁₋₅ alkyl, C₂₋₅ alkenyl, C₆₋₁₅ aryl, C₆₋₁₅ alkenyl, heteroaryl, or heterocyclyl; R⁷ is hydrogen, —NR⁸R⁹, or heterocyclyl; L is a bond, —O—, or —N(R¹⁰)R¹¹—; R⁸, R⁹, and R¹⁰ are each independently hydrogen or C₁₋₅ alkyl, and n is an integer of 0, 1, 2, or 3.

42. The compound of claim 41, wherein L is a bond, —O—, or —N(CH₃)₁₀—.

43. The compound of claim 41, wherein R⁶ and R⁷ are hydrogen.

44. The compound of claim 41, wherein R⁵ is hydrogen, methylamino, dimethylamino, pyridinyl, piperidinyl, or morpholyl, wherein the pyridinyl, piperidinyl, and morpholyl are independently, optionally substituted with methyl.

45. The compound of claim 41, wherein R⁵ is independently selected from the group consisting of amino, fluoro, chloro, methyl, (dimethylamino)methyl, (dimethylamino)ethyl, (dimethylamino)propyl, morpholinylmethyl, (morpholinyl)ethyl, (morpholinyl)propyl, methoxy, (dimethylamino)ethoxy, (morpholinyl)ethoxy, (morpholinyl)propoxy, (methyl-piperidinyl)oxy, (methyl-pyridinyl)oxy, methylamino, dimethylamino, (dimethylamino)ethylamino, (dimethylamino)methylamino, (dimethylamino)propylamino, (dimethylamino)propyl, (methylamino), (morpholinyl)(methyl)amino, (morpholinyl)(methyl)amino, (morpholinyl)propylamino, (morpholinyl)propyl, methyl-piperidinylamino, methyl-piperazinyl, and (dimethylamino)piperidinyl.

46. The compound of claim 27, wherein R⁴ and R⁶ are hydrogen.

47. The compound of claim 1, wherein R¹ is C₁₋₅ alkyl, —S—C₁₋₅ alkyl or —SO₂—C₁₋₅ alkyl, where each alkyl is optionally substituted with one to three halo.

48. The compound of claim 47, wherein R⁴ is methyl, fluoromethyl, difluoromethyl, trifluoromethyl, methane-sulfonyl, or methanesulfonyl.

49. The compound of claim 47, wherein R⁴ is difluoromethyl.

50. The compound of claim 47, wherein R¹ is methane-sulfonyl.

51. The compound of claim 47, wherein R¹ is methane-sulfonyl.

52. The compound of claim 1, wherein R² is hydrogen, C₁₋₅ alkyl, or —O—C₁₋₅ alkyl, where each alkyl is optionally substituted with one or more substituents Q.

53. The compound of claim 52, wherein R² is hydrogen.

54. The compound of claim 52, wherein R² is methoxy.

55. The compound of claim 1, wherein R³ is hydrogen, amino, or C₁₋₅ alkyl, optionally substituted with one or more substituents Q.

56. The compound of claim 55, wherein R³ is hydrogen.
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N^2-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-2,5-pyrindinediamine;

N^2-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N^3-[3-(dimethylamino)propyl]-2,5-pyrindinediamine;

N^2-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-yl]-N^3-[3-(dimethylamino)propyl]-N^5-methyl-2,5-pyrindinediamine;

4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-(6-methoxy-3-pyridinyl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[3-(dimethylamino)propoxy]-3-pyridinyl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridazinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-(1-methyl-1H-imidazol-5-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine; and

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-(1-methyl-1H-pyrazol-5-yl)-6-(4-morpholinyl)-1,3,5-triazin-2-amine; and enaminetors, mixtures of enaminetors, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts and prodrugs thereof.

The compound of claim 1 selected from the group consisting of:

4-[methoxy-2-(methylsulfonyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(3-pyridinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyridinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-(2-pyridinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-phenyl-1,3,5-triazin-2-amine:

N-benzyl-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;

N-benzyl-4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-1,3,5-triazin-2-amine;

2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-phenoxo]-1,3,5-triazin-2-yl]-1H-benzimidazole;

2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-phenylsulfanyl]-1,3,5-triazin-2-yl]-1H-benzimidazole;

2-(difluoromethyl)-1-[4-(4-morpholinyl)-6-(phenylsulfanyl)-1,3,5-triazin-2-yl]-1H-benzimidazole;

N-(2-chloro-5-pyrimidinyl)-4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine;

4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholinyl)-N-(5-pyrimidinyl)-1,3,5-triazin-2-amine;

and enaminetors, mixtures of enaminetors, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts and prodrugs thereof.
139 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(4-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(4-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(2-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(3-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(4-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-methyl-6-(4-morpholino)-N-(4-pyridinylmethyl)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine; 4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[6-[(2-dimethylamino)ethyl]oxy]3-pyridinyl]-6-(4-morpholino)-1,3,5-triazin-2-amine.
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145 4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-[2-(1-methyl-3-pyridinyl)oxy]-5-pyrimidinyl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benimidazol-1-yl]-N-[2-(1-methyl-3-pyridinyl)oxy]-5-pyrimidinyl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(dimethylamino)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[2-(dimethylamino)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[2-(dimethylamino)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[2-(dimethylamino)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(4-morpholiny)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benimidazol-1-yl]-N-[2-(4-morpholiny)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(4-morpholiny)ethyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(3-dimethylamino)propyl]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
N-[4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-6-(4-morpholiny)-1,3,5-triazin-2-yl]-2,5-pyrimidinediamine;
N-[4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholiny)-1,3,5-triazin-2-yl]-2,5-pyrimidinediamine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-4-methoxy-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-[2-(difluoromethyl)-1H-benzimidazol-1-yl]-N-[2-(pyrazinyl)]-1H-pyrazol-4-yl]-6-(4-morpholiny)-1,3,5-triazin-2-amine;
4-(2-(difluoromethyl))-4-methoxy-1H-benzimidazol-1-yl)-N-(6-methoxypyrimidin-4-yI)-6-morpholino-1,3,5-triazin-2-amine;
4-[(2-(difluoromethyl))-4-methoxy-1H-benzimidazol-1-yl]-6-(4-morpholino)-N-(3-pyridazinyl)-1,3,5-triazin-2-amine; and
4-[2-(difluoromethyl))-4-methoxy-1H-benzimidazol-1-yl]-N-(6-methoxy-3-pyridazinyl)-6-(4-morpholino)-1,3,5-triazin-2-amine;
and enantiomers, mixtures of enantiomers, or mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts and prodrugs thereof.

71. A pharmaceutical composition comprising the compound of claim 1, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or prodrug thereof; and one or more pharmaceutically acceptable carriers.

72. The pharmaceutical composition of claim 71, further comprising a second therapeutic agent.

73. The pharmaceutical composition of claim 71, wherein the composition is formulated as oral, parenteral, or intravenous dosage form.

74. The pharmaceutical composition of claim 71, wherein the composition is formulated as oral, parenteral, or intravenous dosage form.

75. The pharmaceutical composition of claim 74, wherein the oral dosage form is a tablet or capsule.

76. The compound of claim 14, wherein m is 2.

77. The compound of claim 76, wherein each R^4 is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents Q.

78. The compound of claim 76, wherein each R^4 is independently hydrogen or methyl.

79. The compound of claim 76, wherein each R^4 is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents Q.

80. The compound of claim 76, wherein each R^4 is independently hydrogen or methyl.

81. The compound of claim 76, wherein each R^4 and R^6 is independently hydrogen or methyl.

82. The compound of claim 27, wherein m is 2.

83. The compound of claim 82, wherein each R^4 is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents Q.

84. The compound of claim 82, wherein each R^4 is independently hydrogen or methyl.

85. The compound of claim 82, wherein each R^4 is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more substituents Q.

86. The compound of claim 82, wherein each R^4 is independently hydrogen or methyl.

87. The compound of claim 82, wherein each R^4 and R^6 is independently hydrogen or methyl.