COMPOUNDS, PHARMACEUTICAL COMPOSITIONS, AND METHODS OF PREPARING COMPOUNDS AND OF THEIR USE

FIELD OF THE INVENTION

The invention relates to compounds and pharmaceutical compositions, their preparation and their use in the treatment of a disease or condition, e.g., cancer, and, in particular, those diseases or conditions (e.g., cancers that harbor CCNE1 amplification/overexpression or FBXW7-mutated cancers) which depend on the activity of membrane-associated tyrosine and threonine-specific cdc2-inhibitory kinase (Myt1) (Gene name PKMYT1).

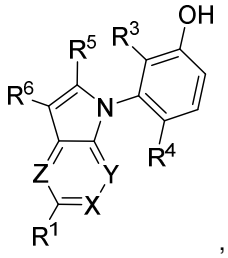
BACKGROUND

DNA is continuously subjected to both endogenous insults (e.g., stalled replication forks, reactive oxygen species) and exogenous insults (UV, ionizing radiation, chemical) that can lead to DNA damage. As a result, cells have established sophisticated mechanisms to counteract these deleterious events that would otherwise compromise genomic integrity and lead to genomic instability diseases such as cancer. These mechanisms are collectively referred to as the DNA damage response (DDR). One component of the overall DDR is the activation of various checkpoint pathways that modulate specific DNA-repair mechanisms throughout the various phases of the cell cycle, which includes the G1, S, G2 and Mitosis checkpoints. A majority of cancer cells have lost their G1 checkpoint owing to p53 mutations and as such, rely on the G2 checkpoint to make the necessary DNA damage corrections prior to committing to enter mitosis and divide into 2 daughter cells.

There is a need for new anti-cancer therapeutic approaches, e.g., those utilizing small-molecules, especially therapies allowing for targeted cancer treatment.

SUMMARY

In one aspect, the disclosure provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

each of X, Y, and Z is independently N or CR^2;

R^1 and each R^2 are independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-8} cycloalkyl,

optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, cyano, $–N(R^7)_2$, $–OR^7$, $–C(O)N(R^8)_2$, $–SO_2N(R^8)_2$, $–SO_2R^{7A}$, or $–Q–R^{7B}$; or R^1 combines with one R^2 that is *vicinal* to R^1 to form an optionally substituted C_{3-6} alkylene;

each of R^3 and R^4 is independently optionally substituted C_{1-6} alkyl or halogen;

R^5 is H or $–N(R^7)_2$;

R^6 is $–C(O)NH(R^8)$, $–C(O)R^{7A}$, or $–SO_2R^{7A}$;

each R^7 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, or $–SO_2R^{7A}$; or two R^7 groups, together with the atom to which both are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

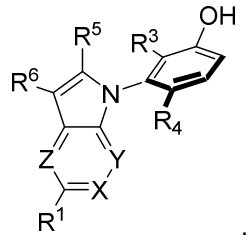
each R^{7A} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl;

each R^{7B} is independently hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-9} heteroaryl, $–N(R^7)_2$, $–C(O)N(R^8)_2$, $–SO_2N(R^8)_2$, $–SO_2R^{7A}$, or optionally substituted alkoxy;

each R^8 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkoxyalkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{1-9} heteroaryl; or two R^8, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

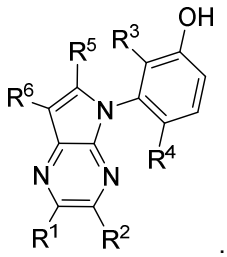
Q is optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{3-8} cycloalkenylene optionally substituted C_{6-10} arylene, optionally substituted C_{2-9} heterocyclylene, or optionally substituted C_{1-9} heteroarylene.

In some examples, the compound is enriched for the atropisomer of formula (IA):



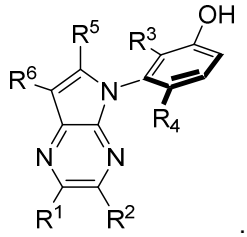
(IA)

In some examples, X is CR^2. In some examples, the compound is of formula (II):



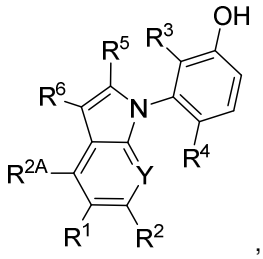
(II)

In some examples, the compound is enriched for the atropisomer of formula (IIA):



(IIA)

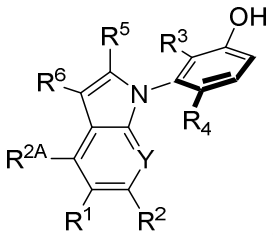
In some examples, the compound is of formula (III):



(III)

wherein R^{2A} is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, $–N(R^7)_2$, $–OR^7$, $–C(O)N(R^8)_2$, $–SO_2N(R^8)_2$, $–SO_2R^{7A}$, or $–Q–R^{7B}$.

In some examples, the compound is enriched for the atropisomer of formula (IIIA):



(IIIA)

In some examples, R^{2A} is hydrogen, optionally substituted C_{1-6} alkyl, or halogen.

In some examples, R^3 is optionally substituted C_{1-6} alkyl. In some examples, R^3 is halogen. In some examples, R^4 is optionally substituted C_{1-6} alkyl. In some examples, R^4 is halogen (e.g., chlorine).

In some examples, R^2 is hydrogen. In some examples, R^2 is optionally substituted C_{1-6} alkyl. In some examples, R^2 is optionally substituted methyl or optionally substituted isopropyl. R^2 is halogen.

In some examples, R^1 is hydrogen. In some examples, R^1 is halogen. In some examples, R^1 is chlorine or bromine. In some examples, R^1 is optionally substituted C_{1-6} alkyl. In some examples, R^1 is optionally substituted methyl, optionally substituted ethyl, optionally substituted isopropyl, or optionally substituted butyl. In some examples, R^1 is optionally substituted C_{1-9} heteroaryl. In some examples, R^1 is 1,3-thiazolyl, 1,2-thiazolyl, 1,3-oxazolyl, benzo-1,3-thiazolyl, benzo-1,3-oxazolyl, indolyl, benzimidazolyl, pyridyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, or pyrazolyl, wherein R^1 is optionally substituted with substituents as defined for optionally substituted C_{1-9} heteroaryl. In some examples, R^1 is optionally substituted C_{3-8} cycloalkyl. In some examples, R^1 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein R^1 is optionally substituted with substituents as defined for optionally substituted C_{3-8} cycloalkyl. In some examples, R^1 is optionally substituted C_{2-9} heterocyclyl. In some examples, R^1 is 1,2,3,6-tetrahydropyridinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, oxa-aza-spiro[3,3]heptane, or oxa-aza-bicyclo[3.2.1]octane, wherein R^1 is optionally substituted with substituents as defined for optionally substituted C_{2-9} heterocyclyl. In some examples, R^1 is optionally substituted C_{3-8} cycloalkyl. In some examples, R^1 is optionally substituted cyclohexenyl or optionally substituted cyclopentenyl. In some examples, R^1 is optionally substituted C_{6-10} aryl. In some examples, R^1 is optionally substituted phenyl.

In some examples, R^1 is $–Q–R^{7B}$. In some examples, Q is optionally substituted C_{2-6} alkynylene. In some examples, Q is optionally substituted C_{1-6} alkylene. In some examples, Q is optionally substituted C_{6-10} arylene. In some examples, R^{7B} is optionally substituted C_{2-9} heterocyclyl. In some examples, R^{7B} is optionally substituted C_{6-10} aryl.

In some examples, R^1 is optionally substituted with one, two, or three groups independently selected from the group consisting of methyl, difluoromethyl, trifluoromethyl, fluorine, chlorine, bromine, amino, hydroxyl, cyano, oxo, -C(O)NH_2, -C(O)NH(Me), -C(O)$N(Me)_2$, -$(CH_2)_n$-C(O)OH, and -$(CH_2)_n$-C(O)Ot-Bu, wherein n is 0 or 1.

In some examples, R^1 is $–N(R^7)_2$. In some examples, R^1 is diethylamino.

In some examples, R^5 is hydrogen. In some examples, R^5 is $–N(R^7)_2$. In some examples, R^5 is $–NH_2$. In some examples, R^6 is $–C(O)NH(R^8)$. In some examples, R^6 is $–C(O)NH_2$. In some examples, R^6 is –C(O)NH(Me). In some examples, R^6 is $–SO_2R^{7A}$. In some examples, R^6 is $–SO_2Me$.

In some examples, the compound selected from the group consisting of compounds 1-328 (e.g., compounds 1-288) and pharmaceutically acceptable salts thereof.

In another aspect, there is provided a compound selected from the group consisting of compounds 1-328 and pharmaceutically acceptable salts thereof.

In another aspect, the disclosure provides a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In some examples, the composition is isotopically enriched in deuterium.

In yet another example, the disclosure provides a method of inhibiting Myt1 in a cell expressing Myt1, the method comprising contacting the cell with the compound disclosed herein.

In some examples, the cell is overexpressing CCNE1. In some examples, the cell is in a subject.

In still another example, the disclosure provides a method of treating a subject in need thereof comprising administering to the subject the compound disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition disclosed herein.

In some examples, the subject is suffering from, and is in need of a treatment for, a disease or condition having the symptom of cell hyperproliferation. In some examples, the disease or condition is a cancer. In some examples, the cancer is a cancer overexpressing CCNE1.

In still another example, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a Myt1 inhibitor, wherein the cancer has been previously identified as a cancer overexpressing *CCNE1*.

In another example, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a Myt1 inhibitor, wherein the cancer is a cancer overexpressing *CCNE1*.

In yet another example, the disclosure provides a method of inducing cell death in a cancer cell overexpressing *CCNE1*, the method comprising contacting the cell with an effective amount of a Myt1 inhibitor.

In some examples, the cell is in a subject. In some examples, the Myt1 inhibitor is the compound disclosed herein or a pharmaceutically acceptable salt thereof. In some examples, the cancer overexpressing CCNE1 is uterine cancer, ovarian cancer, breast cancer, stomach cancer, esophageal cancer, lung cancer, or endometrial cancer.

In still another example, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a Myt1 inhibitor, wherein the cancer has been previously identified as a cancer having an inactivating mutation in the *FBXW7* gene.

In another example, the disclosure provides a method of treating a cancer in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a Myt1 inhibitor, wherein the cancer has an inactivating mutation in the *FBXW7* gene.

In yet another example, the disclosure provides a method of inducing cell death in an FBXW7-mutated cancer cell, the method comprising contacting the cell with an effective amount of a Myt1 inhibitor.

In some examples, the cell is in a subject. the cancer is uterine cancer, colorectal cancer, breast cancer, lung cancer, or esophageal cancer. In some examples, the Myt1 inhibitor is the compound disclosed herein, or a pharmaceutically acceptable salt thereof.

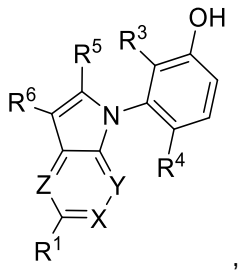
ABBREVIATIONS

Abbreviations and terms that are commonly used in the fields of organic chemistry, medicinal chemistry, pharmacology, and medicine and are well known to practitioners in these fields are used herein. Representative abbreviations and definitions are provided below:

Ac is acetyl [$CH_3C(O)$-], Ac_2O is acetic anhydride; AcOH is acetic acid; APC is antigen-presenting cell; aq. is aqueous; 9-BBN is 9-borabicyclo[3.3.1]nonane; BINAP is (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl); Bn is benzyl; BOC is tert Butyloxycarbonyl; CDI is carbonyldiimidazole; DCM is dichloromethane; DIAD is diisopropylazodicarboxylate; DIBAL is diisobutylaluminum hydride; DIPEA is diisoproplyethyl amine; DMA is dimethylacetamide; DMAP is 4-dimethylaminopyridine; DMF is N,N-dimethylformamide; DMSO is dimethyl sulfoxide; dppf is 1,1'-bis(diphenylphosphino)ferrocene; EDAC (or EDC) is 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide HCl; ESI is electrospray ionization mass spectrometry; Et_2O is diethyl ether; Et_3N is triethylamine; Et is ethyl; EtOAc is ethyl acetate; EtOH is ethanol; 3-F-Ph is 3-fluorophenyl, HATU is (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; HCl is hydrochloric acid; HOBt is 1-hydroxybenzotriazole; HPLC is high performance liquid chromatography; LCMS is HPLC with mass spectral detection; LiHMDS is lithium bis(trimethylsilyl)amide; LG is leaving group; M is molar; mCPBA is metachloroperbenzoic acid; mmol is millimole; Me is methyl; MeCN is acetonitrile; MeOH is methanol; Ms is methanesulfonyl; MS is mass spectrometry; N is normal; NaHMDS is sodium hexamethyldisiliazide; NaOAc is sodium acetate; NaOtBu is sodium tert-butoxide; NMO is N-methylmorpholine N-oxide; NMP is N-methyl pyrrolidinone; NMR is nuclear magnetic resonance spectroscopy; $Pd_2(dba)_3$ is tris(dibenzylideneacetone)dipalladium; $PdCl_2(PPh_3)_2$ is dichlorobis-(triphenylphosphene) palladium; PG Denotes an unspecified protecting group; Ph is phenyl; PhMe is toluene; PPh_3 is triphenylphosphine; PMB is para-methoxybenzyl; rt is room temperature; RBF is round-bottom flask; RuPhos Pd G1 is chloro-(2-Dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2-aminoethyl)phenyl]palladium(II); SEM is [2-(trimethylsilyl)ethoxy]methyl; SFC is supercritical fluid chromatography; S_NAr is nucleophilic aromatic substitution; TBAB is tetrabutyl ammonium bromide; TBAF is tetrabutyl ammonium fluoride; TBS is tert-butyldimethylsilyl; tBu is tert-butyl; Tf is triflate; TFA is trifluoroacetic acid; THF is tetrahydrofuran; THP is tetrahydropyran; TLC is thin layer chromatography; TMAD is tetramethylazodicarboxamide; TMS is trimethylsilyl; TPAP is tetrapropylammonium perruthenate; Ts is *p*-toluenesulfonyl; UPLC is ultra performance liquid chromatography.

CLAIMS

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

each of X, Y, and Z is independently N or CR^2;

R^1 and each R^2 are independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, cyano, $–N(R^7)_2$, $–OR^7$, $–C(O)N(R^8)_2$, $–SO_2N(R^8)_2$, $–SO_2R^{7A}$, or $–Q–R^{7B}$; or R^1 combines with one R^2 that is *vicinal* to R^1 to form an optionally substituted C_{3-6} alkylene;

each of R^3 and R^4 is independently optionally substituted C_{1-6} alkyl or halogen;

R^5 is H or $–N(R^7)_2$;

R^6 is $–C(O)NH(R^8)$, $–C(O)R^{7A}$, or $–SO_2R^{7A}$;

each R^7 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, or $–SO_2R^{7A}$; or two R^7 groups, together with the atom to which both are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

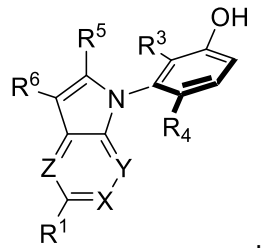
each R^{7A} is independently optionally substituted C_{1-6} alkyl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{6-10} aryl;

each R^{7B} is independently hydroxyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{1-9} heteroaryl, $–N(R^7)_2$, $–C(O)N(R^8)_2$, $–SO_2N(R^8)_2$, $–SO_2R^{7A}$, or optionally substituted alkoxy;

each R^8 is independently hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkoxyalkyl, optionally substituted C_{6-10} aryl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{3-8} cycloalkyl, or optionally substituted C_{1-9} heteroaryl; or two R^8, together with the atom to which they are attached, combine to form an optionally substituted C_{2-9} heterocyclyl;

Q is optionally substituted C_{1-6} alkylene, optionally substituted C_{2-6} alkenylene, optionally substituted C_{2-6} alkynylene, optionally substituted C_{3-8} cycloalkylene, optionally substituted C_{3-8} cycloalkenylene optionally substituted C_{6-10} arylene, optionally substituted C_{2-9} heterocyclylene, or optionally substituted C_{1-9} heteroarylene.

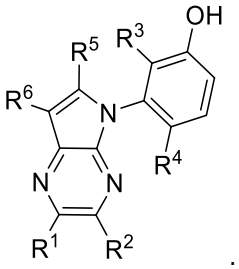
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is enriched for the atropisomer of formula (IA):



(IA)

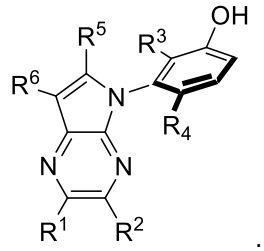
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X is CR^2.

4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (II):



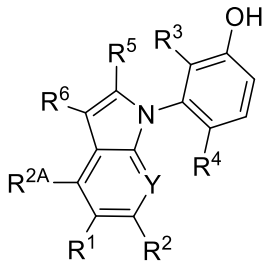
(II)

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein the compound is enriched for the atropisomer of formula (IIA):



(IIA)

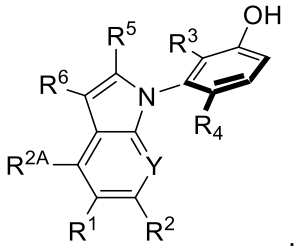
6. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (III):



(III)

wherein R^{2A} is hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, optionally substituted C_{3-8} cycloalkyl, optionally substituted C_{3-8} cycloalkenyl, optionally substituted C_{2-9} heterocyclyl, optionally substituted C_{2-9} heterocyclyl C_{1-6} alkyl, optionally substituted C_{6-10} aryl, optionally substituted C_{1-9} heteroaryl, optionally substituted C_{1-9} heteroaryl C_{1-6} alkyl, halogen, $–N(R^7)_2$, $–OR^7$, $–C(O)N(R^8)_2$, $–SO_2N(R^8)_2$, $–SO_2R^{7A}$, or $–Q–R^{7B}$.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein the compound is enriched for the atropisomer of formula (IIIA):



(IIIA)

8. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{2A} is hydrogen, optionally substituted C_{1-6} alkyl, or halogen.

9. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is optionally substituted C_{1-6} alkyl or halogen.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is optionally substituted C_{1-6} alkyl or chlorine.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen, optionally substituted methyl, optionally substituted isopropyl, or halogen.

12. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is hydrogen, chlorine, bromine, optionally substituted methyl, optionally substituted ethyl, optionally substituted isopropyl, optionally substituted butyl, optionally substituted 1,3-thiazolyl, optionally substituted 1,2-thiazolyl, optionally substituted 1,3-oxazolyl, optionally substituted benzo-1,3-thiazolyl, optionally substituted benzo-1,3-oxazolyl, optionally substituted indolyl, optionally substituted benzimidazolyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted pyrimidyl, optionally substituted pyrazinyl, optionally substituted pyridazinyl, optionally substituted pyrazolyl, optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl, optionally substituted cyclohexyl, optionally substituted 1,2,3,6-tetrahydropyridinyl, optionally substituted piperidinyl, optionally substituted morpholinyl, optionally substituted piperazinyl, optionally substituted thiomorpholinyl, optionally substituted oxa-aza-spiro[3,3]heptane, optionally substituted oxa-aza-bicyclo[3.2.1]octane, optionally substituted phenyl, $–Q–R^{7B}$, or diethylamino.

13. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is $–Q–R^{7B}$, wherein Q, is optionally substituted C_{2-6} alkynylene, C_{1-6} alkylene, or C_{6-10} arylene; and R^{7B} is optionally substituted C_{2-9} heterocyclyl, or optionally substituted C_{6-10} aryl.

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is optionally substituted with one, two, or three groups independently selected from the group consisting of methyl, difluoromethyl, trifluoromethyl, fluorine, chlorine, bromine, amino, hydroxyl, cyano, oxo, $-C(O)NH_2$, $-C(O)NH(Me)$, $-C(O)N(Me)_2$, $-(CH_2)_n-C(O)OH$, and $-(CH_2)_n-C(O)Ot\text{-}Bu$, wherein n is 0 or 1.

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen or $–NH_2$.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^6 is $–C(O)NH_2$, $–C(O)NH(Me)$ or $–SO_2Me$.

17. A compound selected from the group consisting of compounds 1-328 and pharmaceutically acceptable salts thereof.

18. The compound of claim 17, wherein the compound is selected from the group consisting of compounds 1-288 and pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition comprising the compound of claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.