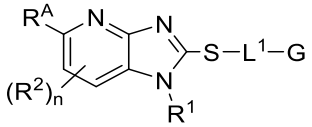
genetic polymorphisms in AMPK are associated with cardiac glycogen deposition, cardiac hypertrophy and Wolff-Parkinson-White syndrome, a condition characterized by electrocardiogram (ECG) abnormalities (see, Burwinkel, B., et al. (2005), Am Journal of Human Genetics, 76(6), 1034-1049). Due to this risk of cardiac hypertrophy, treatment with known AMPK activators, which are systemic in nature, is unsuitable to address the problem of treating IBD, colitis, and other diseases with a leaky gut barrier with a direct AMPK activator.

[0005] Direct AMPK activation in the intestine without systemic engagement has never been demonstrated or proposed until the instant disclosure. All reported direct AMPK activators which have been optimized and entered clinical studies (for example, PF- 06409577 from Pfizer) or extensive preclinical evaluation (for example, MK-3903 and MK-8722 from Merck) are systemic AMPK activators and have been developed for systemic engagement, as is reflected in the routes of administration and biological assays present in patent applications and published manuscripts relating to direct AMPK activators. A delayed-release formulation has been investigated to deliver higher concentrations of the indirect AMPK activator metformin to the colon for treatment of IBD. However, metformin does not optimally activate AMPK, metformin has other activities, and this approach requires specific formulation development. Thus it is not an optimal solution to the problem.

[0006] Disclosed herein is the discovery and development of the first gut-restricted, direct AMPK activators that do not require sophisticated formulations to reach the target tissue and avoid systemic circulation.

BRIEF SUMMARY

[0006a] In an aspect of the present disclosure, there is provided a compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

each R^2 is independently halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

n is 0-2;

L^1 is $–(CR^3R^4)–(CR^5R^6)_m–$, C_3-C_6 cycloalkylene, 3- to 6-membered heterocycloalkylene, phenylene, or monocyclic heteroarylene;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^5 and R^6 is independently hydrogen, halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

m is 0-2;

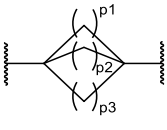
G is $–C(O)OR^7$, $–P(O)(R^8)OR^7$, $–P(O)(OR^7)_2$, or $–S(O)_2OR^7$;

each R^7 is independently hydrogen or C_1-C_4 alkyl;

R^8 is C_1-C_4 alkyl;

R^A is a 6,5-fused bicyclic heteroaryl or a 6,6-fused bicyclic heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{10} groups;

or R^A is $–L^A–A$;

L^A is –C≡C–, or 

, wherein each p1, p2, and p3 is independently 1 or 2;

or L^A is phenylene or monocyclic heteroarylene, which is unsubstituted or substituted with 1, 2, or 3 R^{11} groups;

A is C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups;

each R^{10}, R^{11}, and R^{12} is independently halogen, –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)R^{13}$, $–C(=O)OR^{14}$, $–OC(=O)R^{14}$, $–C(=O)NR^{14}R^{14}$, $–NR^{14}C(=O)R^{14}$, $–NR^{14}C(=O)NR^{14}R^{14}$, $–OC(=O)NR^{14}R^{14}$, $–NR^{14}C(=O)OR^{13}$, $–OC(=O)OR^{13}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

each R^{13} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

or two R^{14} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl;

wherein R^A is not 4-morpholinylphenyl.

[0006b] In another aspsect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0006c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for use as a medicine.

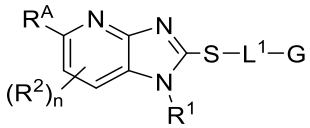
[0006d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the treatment of an adenosine 5'–monophosphate–activated protein kinase (AMPK) associated condition or disorder in a subject in need thereof; wherein the condition or disorder is short bowel syndrome, intestinal failure, intestinal insufficiency, metabolic syndrome, obesity, type 2 diabetes, coronary artery disease, fatty liver, nonalcoholic steatohepatitis (NASH), cirrhosis, hepatic encephalopathy, fibrotic disorders including scleroderma, inflammatory bowel disease including Crohn's disease and ulcerative colitis, psoriasis, celiac disease, necrotizing enterocolitis, gastrointestinal injury resulting from toxic insults such as radiation or chemotherapy, environmental enteric dysfunction, allergy including food allergy, celiac sprue, and childhood allergy, irritable bowel syndrome, spontaneous bacterial peritonitis, ischemic colitis, sclerosing cholangitis, Alzheimer's disease, Parkinson's disease, colorectal cancer, depression, autism, or a combination thereof.

[0006e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the preparation of a medicament for the treatment of gastrointestinal injury resulting from toxic insult in a subject in need thereof.

[0007] Disclosed herein, in some examples, are adenosine 5'–monophosphate–activated protein kinase (5' AMP–activated protein kinase, AMPK) activators useful for the treatment of conditions or disorders associated with AMPK. In some examples, the condition or disorder is associated with the gut-brain axis. In some examples, the condition or disorder is associated with systemic infection and inflammation from having a leaky gut barrier. In some examples, the AMPK activators are gut-restricted or selectively modulate AMPK located in the gut. In some examples, the condition or disorder is selected from the group consisting of: central nervous system (CNS) disorders including mood disorders, anxiety, depression, affective disorders, schizophrenia, malaise, cognition disorders, addiction, autism, epilepsy, neurodegenerative disorders, Alzheimer's disease, and Parkinson's disease, Lewy Body dementia, episodic cluster headache, migraine, pain; metabolic conditions including diabetes and its complications such as chronic kidney disease/diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, cardiovascular disease, metabolic syndrome, obesity, dyslipidemia, and

nonalcoholic steatohepatitis (NASH); eating and nutritional disorders including hyperphagia, cachexia, anorexia nervosa, short bowel syndrome, intestinal failure, intestinal insufficiency and other eating disorders; inflammatory disorders and autoimmune diseases such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, checkpoint inhibitor-induced colitis, psoriasis, celiac disease and enteritis, including chemotherapy-induced enteritis or radiation-induced enteritis; necrotizing enterocolitis; gastrointestinal injury resulting from toxic insults such as radiation or chemotherapy; diseases/disorders of gastrointestinal barrier dysfunction including environmental enteric dysfunction; spontaneous bacterial peritonitis; allergy including food allergy, celiac sprue, and childhood allergy; graft vs. host disease; functional gastrointestinal disorders such as irritable bowel syndrome, functional dyspepsia, functional abdominal bloating/distension, functional diarrhea, functional constipation, and opioid-induced constipation; gastroparesis; nausea and vomiting; disorders related to microbiome dysbiosis, and other conditions involving the gut-brain axis.

[0008] Disclosed herein, in some examples, is a compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

each R^2 is independently halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

n is 0-2;

L^1 is $–(CR^3R^4)–(CR^5R^6)_m–$, C_3-C_6 cycloalkylene, 3- to 6-membered heterocycloalkylene, phenylene, or monocyclic heteroarylene;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^5 and R^6 is independently hydrogen, halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

m is 0-2;

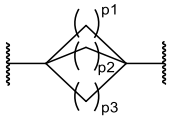
G is $–C(O)OR^7$, $–P(O)(R^8)OR^7$, $–P(O)(OR^7)_2$, or $–S(O)_2OR^7$;

each R^7 is independently hydrogen or C_1-C_4 alkyl;

R^8 is C_1-C_4 alkyl;

R^A is a 6,5-fused bicyclic heteroaryl or a 6,6-fused bicyclic heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{10} groups;

or R^A is $–L^A–A$;

L^A is –C≡C–, or 

, wherein each p1, p2, and p3 is independently 1 or 2;

or L^A is phenylene or monocyclic heteroarylene, which is unsubstituted or substituted with 1, 2, or 3 R^{11} groups;

A is C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups;

each R^{10}, R^{11}, and R^{12} is independently halogen, –CN, –OH, –OR^{13}, –$NR^{14}R^{14}$, –$C(=O)R^{13}$, –$C(=O)OR^{14}$, –$OC(=O)R^{14}$, –$C(=O)NR^{14}R^{14}$, –$NR^{14}C(=O)R^{14}$, –$NR^{14}C(=O)NR^{14}R^{14}$, –$OC(=O)NR^{14}R^{14}$, –$NR^{14}C(=O)OR^{13}$, –$OC(=O)OR^{13}$, –$OSO_2OR^{14}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

each R^{13} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

or two R^{14} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl;

wherein R^A is not 4-morpholinylphenyl.

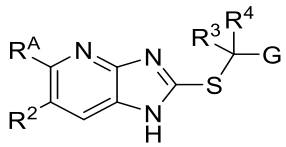
[0009] Any combination of the groups described above or below for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0010] In some examples of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, R^1 is hydrogen or methyl; and each R^2 is independently –F, –Cl, –CN, methyl, ethyl, isopropyl, or –CF_3. In some examples, R^1 is hydrogen; R^2 is –F, –Cl, or –CN; and n is 1.

[0011] In some examples of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, L^1 is –(CR^3R^4)–$(CR^5R^6)_m$–; R^3 and R^4 are each independently hydrogen, methyl, or –CF_3; each R^5 and R^6 is independently hydrogen, –F, –CN, methyl, or –CF_3; each R^7 is independently hydrogen, methyl, or ethyl; and R^8 is methyl. In some examples, L^1 is –(CR^3R^4)–$(CR^5R^6)_m$–; R^3 and R^4 are each independently hydrogen

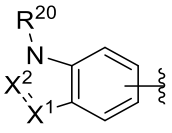
or methyl; m is 0; and G is –C(O)OH, –P(O)(Me)OH, –P(O)(OEt)(OH), –P(O)(OH)$_2$, or –S(O)$_2$OH. In some examples, L^1 is –CH$_2$–, –CHMe–, or –CMe$_2$–; and G is –C(O)OH.

[0012] In some examples, the compound of Formula (I), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, is a compound of Formula (II):



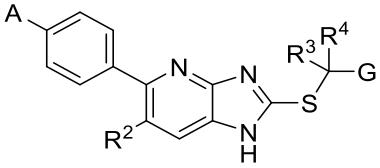
Formula (II),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

[0013] In some examples of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, R^A is a 6,5-fused bicyclic heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{10} groups; and each R^{10} is independently halogen, –CN, –OH, –OR^{13}, –NR^{14}R^{14}, –C(=O)OR^{14}, –C(=O)NR^{14}R^{14}, C$_1$-C$_6$ alkyl, or C$_1$-C$_6$ fluoroalkyl. In some examples, R^A is ; X^1 and X^2 are each independently CH, C–R^{10}, or N; and R^{20} is hydrogen or C$_1$-C$_6$ alkyl.

[0014] In some examples of a compound of Formula (I) or (II), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, R^A is –L^A–A. In some examples, L^A is phenylene or monocyclic heteroarylene, which is unsubstituted or substituted with 1, 2, or 3 R^{11} groups; and each R^{11} is independently halogen, –CN, –OH, –OR^{13}, –NR^{14}R^{14}, –C(=O)OR^{14}, –C(=O)NR^{14}R^{14}, C$_1$-C$_6$ alkyl, or C$_1$-C$_6$ fluoroalkyl. In some examples, L^A is unsubstituted phenylene.

[0015] In some examples, the compound of Formula (I) or (II), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, is a compound of Formula (III):



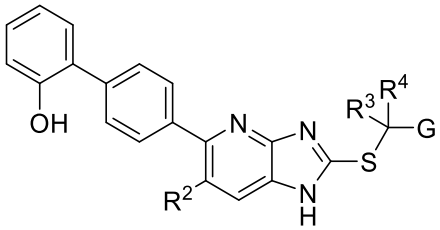
Formula (III),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

[0016] In some examples of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, A is C$_3$-C$_8$ cycloalkyl or C$_6$-C$_{10}$ aryl which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups. In some examples, A is phenyl which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; and each R^{12} is independently halogen, –CN, –OH, –OR^{13}, –NR^{14}R^{14}, –C(=O)OR^{14}, –

$C(=O)NR^{14}R^{14}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl. In some examples, A is phenyl which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; and each R^{12} is independently –F, –Cl, –Br, –CN, –OH, –OMe, $–NH_2$, $–C(=O)OH$, $–C(=O)NH_2$, $–OSO_2OH$, methyl, or $–CF_3$. In some examples, A is phenyl, which is unsubstituted or substituted with a –OH group.

[0017] In some examples, the compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, is a compound of Formula (IV):



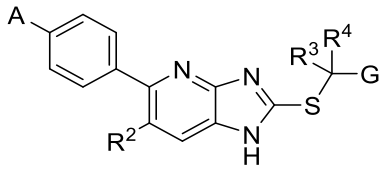
Formula (IV),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

[0018] In some examples of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, A is 3- to 8-membered heterocycloalkyl or 5- to 10-membered heteroaryl, which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups. In some examples, A is monocyclic heteroaryl or 3- to 6-membered heterocycloalkyl, which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; and each R^{12} is independently –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)OR^{14}$, $–C(=O)NR^{14}R^{14}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl. In some examples, A is 6-membered heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; or A is 5- to 6-membered heterocycloalkyl which is substituted with 1, 2, or 3 R^{12} groups; and each R^{12} is independently –CN, –OH, –OMe, $–NH_2$, $–C(=O)OH$, $–C(=O)NH_2$, $–OSO_2OH$, methyl, or $–CF_3$. In some examples, A is pyridinyl, which is unsubstituted or substituted by a –OH group; or A is pyrrolidinyl or piperidinyl, which is substituted with 1 or 2 groups selected from –OH and $–C(=O)OH$.

[0019] In some examples of a compound of Formula (I), (II), or (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, each R^{13} is independently C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl; and each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl; or two R^{14} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl.

[0020] Also disclosed herein, in some example is a compound of Formula (III):



Formula (III),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^2 is independently halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

G is $–C(O)OR^7$, $–P(O)(R^8)OR^7$, $–P(O)(OR^7)_2$, or $–S(O)_2OR^7$;

each R^7 is independently hydrogen or C_1-C_4 alkyl;

R^8 is C_1-C_4 alkyl;

A is C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, which is substituted with 1, 2, or 3 R^{12} groups;

each R^{12} is independently halogen, –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)R^{13}$, $–C(=O)OR^{14}$, $–OC(=O)R^{14}$, $–C(=O)NR^{14}R^{14}$, $–NR^{14}C(=O)R^{14}$, $–NR^{14}C(=O)NR^{14}R^{14}$, $–OC(=O)NR^{14}R^{14}$, $–NR^{14}C(=O)OR^{13}$, $–OC(=O)OR^{13}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

each R^{13} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

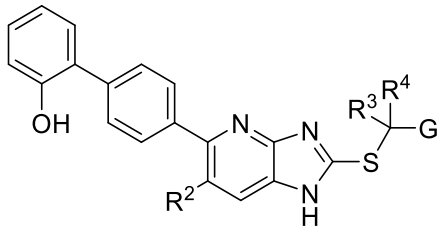
each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

or two R^{14} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl.

[0021] In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, each R^2 is independently –F, –Cl, –CN, methyl, ethyl, isopropyl, or $–CF_3$; R^3 and R^4 are each independently hydrogen, methyl, or $–CF_3$; each R^7 is independently hydrogen, methyl, or ethyl; and R^8 is methyl. In some examples, R^2 is –F, –Cl, or –CN; R^3 and R^4 are each independently hydrogen or methyl; and G is –C(O)OH, –P(O)(Me)OH, –P(O)(OEt)(OH), $–P(O)(OH)_2$, or $–S(O)_2OH$. In some examples, L^1 is $–CH_2–$, –CHMe–, or $–CMe_2–$; and G is –C(O)OH.

[0022] In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, A is C_6-C_{10} aryl which is substituted with 1, 2, or 3 R^{12} groups. In some examples, A is phenyl which is substituted with 1, 2, or 3 R^{12} groups. In some examples, each R^{12} is independently –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)OR^{14}$, $–C(=O)NR^{14}R^{14}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or monocyclic heteroaryl. In some examples, each R^{12} is independently –F, –Cl, –Br, –CN, –OH, –OMe, $–NH_2$, $–C(=O)OH$, $–C(=O)NH_2$, $–CH_3$, $–CH_2CH_3$, $–CH_2CH_2CH_3$, $–CH(CH_3)_2$, $–CH_2CH_2CH_2CH_3$, $–CH_2CH(CH_3)_2$, $–CH(CH_3)(CH_2CH_3)$, $–CH_2CH_2C(CH_3)_3$, $–CF_3$, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, or tetrazolyl. In some examples, A is phenyl which is substituted with a –OH group and is optionally substituted with one other group selected from $–CH_2CH_2C(CH_3)_3$ and triazolyl.

[0023] In some examples, the compound of Formula (III) is a compound of Formula (IV)



Formula (IV),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. In some examples, each R^2 is independently –F, –Cl, –CN, methyl, ethyl, isopropyl, or $–CF_3$; R^3 and R^4 are each independently hydrogen, methyl, or $–CF_3$; each R^7 is independently hydrogen, methyl, or ethyl; and R^8 is methyl. In some examples, R^2 is –F, –Cl, or –CN; R^3 and R^4 are each independently hydrogen or methyl; and G is $–C(O)OH$, $–P(O)(Me)OH$, $–P(O)(OEt)(OH)$, $–P(O)(OH)_2$, or $–S(O)_2OH$. In some examples, L^1 is $–CH_2–$, –CHMe–, or $–CMe_2–$; and G is $–C(O)OH$.

[0024] In some examples of a compound of Formula (III), or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, A is 3- to 6-membered heterocycloalkyl, which is substituted with 1, 2, or 3 R^{12} groups. In some examples, each R^{12} is independently –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)OR^{14}$, $–C(=O)NR^{14}R^{14}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl. In some examples, A is pyrrolidinyl or piperidinyl, which is substituted with 1 or 2 groups selected from –OH and $–C(=O)OH$. In some examples, R^2 is –F, –Cl, or –CN; R^3 and R^4 are each independently hydrogen or methyl; and G is $–C(O)OH$, $–P(O)(Me)OH$, $–P(O)(OEt)(OH)$, $–P(O)(OH)_2$, or $–S(O)_2OH$.

[0025] Disclosed herein, in some examples, are pharmaceutical compositions comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

[0026] Disclosed herein, in some examples, are methods of treating an adenosine 5'–monophosphate–activated protein kinase (AMPK) associated condition or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. In some examples, the condition or disorder involves the gut-brain axis. In some examples, the condition or disorder is a nutritional disorder. In some examples, the condition or disorder is short bowel syndrome, intestinal failure, or intestinal insufficiency. In some examples, the condition or disorder is associated with systemic infection and inflammation from having a leaky gut barrier. In some examples, the condition or disorder is metabolic syndrome, obesity, type 2 diabetes, coronary artery disease, fatty liver, nonalcoholic steatohepatitis (NASH), cirrhosis, hepatic encephalopathy, fibrotic disorders including scleroderma, inflammatory bowel disease including Crohn's disease, ulcerative colitis, and checkpoint inhibitor-induced colitis, psoriasis, celiac disease, necrotizing enterocolitis, gastrointestinal injury resulting from toxic insults such as radiation or chemotherapy, environmental enteric dysfunction, allergy including food allergy, celiac sprue, and childhood allergy, graft vs. host disease, irritable bowel syndrome, spontaneous bacterial peritonitis, ischemic colitis, sclerosing cholangitis, Alzheimer's disease, Parkinson's disease, cancer including colorectal cancer, depression, autism, or a combination thereof.

[0027] Also disclosed herein, in some examples, are methods of treating gastrointestinal injury resulting from toxic insult, the method comprising administering to the subject a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof. In some examples, the toxic insult is from radiation, chemotherapy, or a combination thereof. In some examples, the toxic insult is radiation-induced. In some examples, the toxic insult is chemotherapy-induced.

[0028] Also disclosed herein, in some examples, is the use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, as a medicine.

[0029] Also disclosed herein, in some examples, is the use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the treatment of an adenosine 5'–monophosphate–activated protein kinase (AMPK) associated condition or disorder in a subject in need thereof. In some examples, the condition or disorder involves the gut-brain axis. In some examples, the condition or disorder is a

nutritional disorder. In some examples, the condition or disorder is short bowel syndrome, intestinal failure, or intestinal insufficiency. In some examples, the condition or disorder is associated with systemic infection and inflammation from having a leaky gut barrier. In some examples, the condition or disorder is metabolic syndrome, obesity, type 2 diabetes, coronary artery disease, fatty liver, nonalcoholic steatohepatitis (NASH), cirrhosis, hepatic encephalopathy, fibrotic disorders including scleroderma, inflammatory bowel disease including Crohn's disease, ulcerative colitis, and checkpoint inhibitor-induced colitis, psoriasis, celiac disease, necrotizing enterocolitis, gastrointestinal injury resulting from toxic insults such as radiation or chemotherapy, environmental enteric dysfunction, allergy including food allergy, celiac sprue, and childhood allergy, graft vs. host disease, irritable bowel syndrome, spontaneous bacterial peritonitis, ischemic colitis, sclerosing cholangitis, Alzheimer's disease, Parkinson's disease, cancer including colorectal cancer, depression, autism, or a combination thereof.

[0030] Also disclosed herein, in some examples, is the use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the treatment of gastrointestinal injury resulting from toxic insult in a subject in need thereof. In some examples, the toxic insult is from radiation, chemotherapy, or a combination thereof. In some examples, the toxic insult is radiation-induced. In some examples, the toxic insult is chemotherapy-induced.

[0031] Also disclosed herein, in some examples, is the use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the preparation of a medicament for the treatment of the diseases disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

[0032] This disclosure is directed, at least in part, to AMPK activators useful for the treatment of conditions or disorders involving the gut-brain axis. In some embodiments, the AMPK activators are gut-restricted compounds. In some embodiments, the AMPK activators are agonists, super agonists, full agonists, or partial agonists.

[0033] Compounds disclosed herein directly activate AMPK in the intestine without systemic engagement. The preferred compounds are more potent, efficacious at lower doses, and have decreased systemic exposure compared to other previously-known AMPK activators.

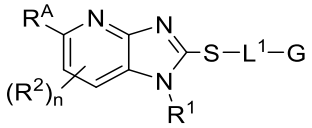
Definitions

[0034] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those

CLAIMS

We Claim:

1. A compound of Formula (I):



Formula (I),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1 is hydrogen or C_1-C_4 alkyl;

each R^2 is independently halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

n is 0-2;

L^1 is $–(CR^3R^4)–(CR^5R^6)_m–$, C_3-C_6 cycloalkylene, 3- to 6-membered heterocycloalkylene, phenylene, or monocyclic heteroarylene;

R^3 and R^4 are each independently hydrogen, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

each R^5 and R^6 is independently hydrogen, halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

m is 0-2;

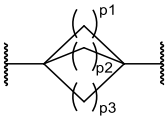
G is $–C(O)OR^7$, $–P(O)(R^8)OR^7$, $–P(O)(OR^7)_2$, or $–S(O)_2OR^7$;

each R^7 is independently hydrogen or C_1-C_4 alkyl;

R^8 is C_1-C_4 alkyl;

R^A is a 6,5-fused bicyclic heteroaryl or a 6,6-fused bicyclic heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{10} groups;

or R^A is $–L^A–A$;

L^A is –C≡C–, or , wherein each p1, p2, and p3 is independently 1 or 2;

or L^A is phenylene or monocyclic heteroarylene, which is unsubstituted or substituted with 1, 2, or 3 R^{11} groups;

A is C_3-C_8 cycloalkyl, 3- to 8-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups;

each R^{10}, R^{11}, and R^{12} is independently halogen, –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)R^{13}$, $–C(=O)OR^{14}$, $–OC(=O)R^{14}$, $–C(=O)NR^{14}R^{14}$, $–NR^{14}C(=O)R^{14}$, $–NR^{14}C(=O)NR^{14}R^{14}$, $–OC(=O)NR^{14}R^{14}$, $–NR^{14}C(=O)OR^{13}$, $–OC(=O)OR^{13}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, C_2-C_6

alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl;

each R^{13} is independently C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, 3- to 6-membered heterocycloalkyl, phenyl, or monocyclic heteroaryl; and

or two R^{14} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl;

wherein R^A is not 4-morpholinylphenyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1 is hydrogen or methyl;

each R^2 is independently –F, –Cl, –CN, methyl, ethyl, isopropyl, or $–CF_3$;

L^1 is $–(CR^3R^4)–(CR^5R^6)_m–$;

R^3 and R^4 are each independently hydrogen, methyl, or $–CF_3$;

each R^5 and R^6 is independently hydrogen, –F, –CN, methyl, or $–CF_3$;

each R^7 is independently hydrogen, methyl, or ethyl; and

R^8 is methyl.

3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^1 is hydrogen;

R^2 is –F, –Cl, or –CN;

n is 1;

L^1 is $–(CR^3R^4)–(CR^5R^6)_m–$;

R^3 and R^4 are each independently hydrogen or methyl;

m is 0; and

G is –C(O)OH, –P(O)(Me)OH, –P(O)(OEt)(OH), $–P(O)(OH)_2$, or $–S(O)_2OH$.

4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

R^A is a 6,5-fused bicyclic heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{10} groups; and

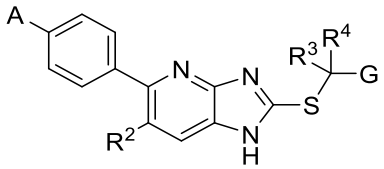
each R^{10} is independently halogen, –CN, –OH, –OR^{13}, –$NR^{14}R^{14}$, –C(=O)OR^{14}, –C(=O)$NR^{14}R^{14}$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl;

or R^A is –L^A–A;

L^A is phenylene or monocyclic heteroarylene, which is unsubstituted or substituted with 1, 2, or 3 R^{11} groups; and

each R^{11} is independently halogen, –CN, –OH, –OR^{13}, –$NR^{14}R^{14}$, –C(=O)OR^{14}, –C(=O)$NR^{14}R^{14}$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl.

5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, having the structure of Formula (III):



Formula (III),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

A is phenyl which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; and

each R^{12} is independently halogen, –CN, –OH, –OR^{13}, –$NR^{14}R^{14}$, –C(=O)OR^{14}, –C(=O)$NR^{14}R^{14}$, –OSO_2OR^{14}, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or monocyclic heteroaryl.

7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

each R^{12} is independently –F, –Cl, –Br, –CN, –OH, –OMe, –NH_2, –C(=O)OH, –C(=O)NH_2, –CH_3, –CH_2CH_3, –$CH_2CH_2CH_3$, –$CH(CH_3)_2$, –$CH_2CH_2CH_2CH_3$, –$CH_2CH(CH_3)_2$, –$CH(CH_3)(CH_2CH_3)$, –$CH_2CH_2C(CH_3)_3$, –CF_3, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, triazolyl, or tetrazolyl.

8. The compound of claim 5, wherein:

R^2 is halogen, –CN, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^3 and R^4 are each independently hydrogen or methyl;

G is –C(O)OR^7, –P(O)(R^8)OR^7, –P(O)(OR^7)$_2$, or –S(O)$_2OR^7$;

each R^7 is independently hydrogen or C_1-C_4 alkyl;

R^8 is C_1-C_4 alkyl;

A is phenyl which is substituted with 1, 2, or 3 R^{12} groups;

each R^{12} is independently halogen, –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)OR^{14}$, $–C(=O)NR^{14}R^{14}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, or monocyclic heteroaryl;

each R^{13} is independently C_1-C_6 alkyl; and

each R^{14} is independently hydrogen or C_1-C_6 alkyl.

9. The compound of claim 8, wherein:

R^2 is –F, –Cl, or –CN; and

G is $–C(O)OH$, $–P(O)(Me)OH$, $–P(O)(OEt)(OH)$, $–P(O)(OH)_2$, or $–S(O)_2OH$.

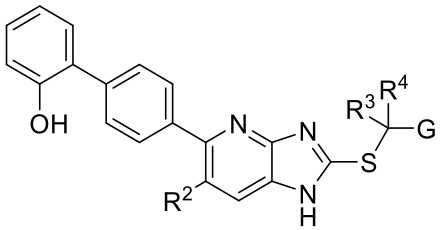
10. The compound of claim 8, wherein:

R^2 is –Cl;

R^3 and R^4 are each hydrogen; and

G is $–C(O)OH$, $–P(O)(Me)OH$, $–P(O)(OEt)(OH)$, or $–P(O)(OH)_2$.

11. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, having the structure of Formula (IV):



Formula (IV),

or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

12. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

A is monocyclic heteroaryl or 3- to 6-membered heterocycloalkyl, which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; and

each R^{12} is independently –CN, –OH, $–OR^{13}$, $–NR^{14}R^{14}$, $–C(=O)OR^{14}$, $–C(=O)NR^{14}R^{14}$, $–OSO_2OR^{14}$, C_1-C_6 alkyl, or C_1-C_6 fluoroalkyl.

13. The compound of claim 9, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

A is 6-membered heteroaryl which is unsubstituted or substituted with 1, 2, or 3 R^{12} groups; or

A is 5- to 6-membered heterocycloalkyl which is substituted with 1, 2, or 3 R^{12} groups; and

each R^{12} is independently –CN, –OH, –OMe, $–NH_2$, $–C(=O)OH$, $–C(=O)NH_2$, $–OSO_2OH$, methyl, or $–CF_3$.

14. The compound of any one of claims 1-13, wherein:

G is –C(O)OH.

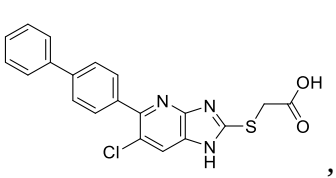
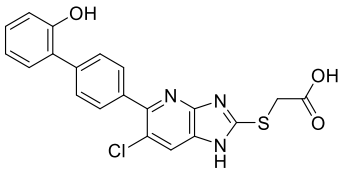
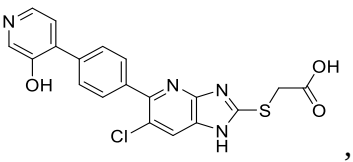
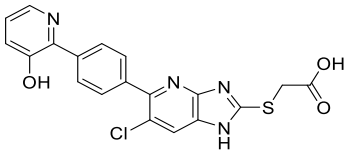
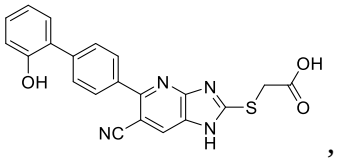
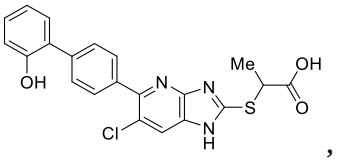
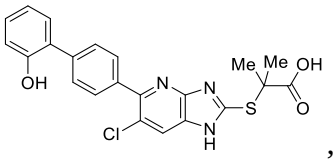
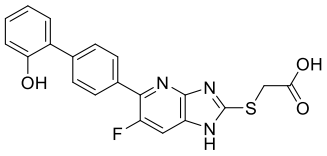
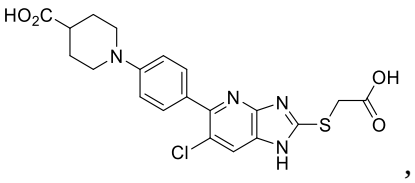
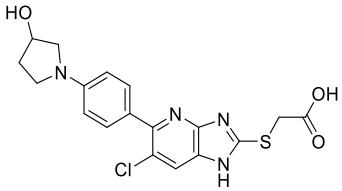
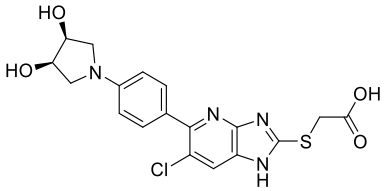
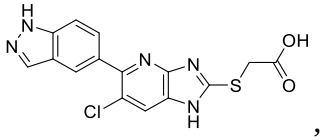
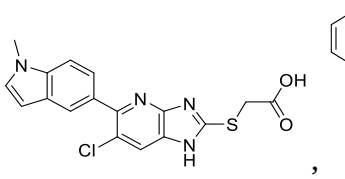
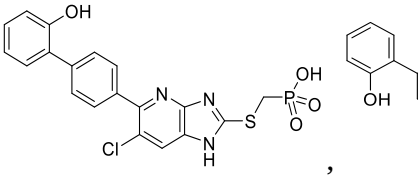
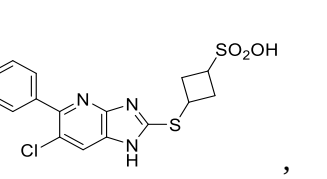
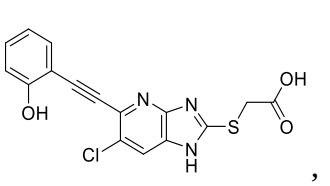
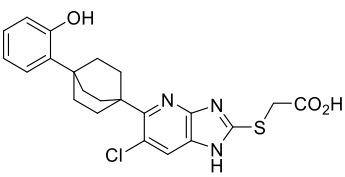
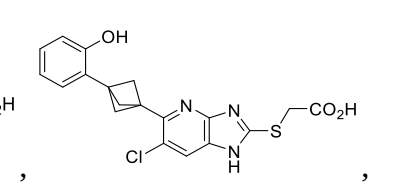
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, wherein:

each R^{13} is independently C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl; and

each R^{14} is independently hydrogen, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, or 3- to 6-membered heterocycloalkyl;

or two R^{14} on the same nitrogen atom are taken together with the nitrogen to which they are attached to form a 3- to 6-membered *N*-heterocycloalkyl.

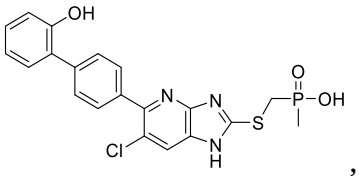
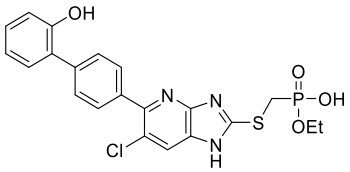
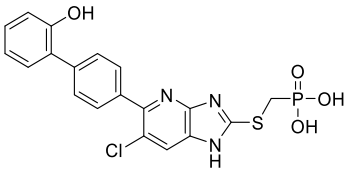
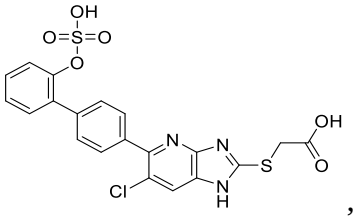
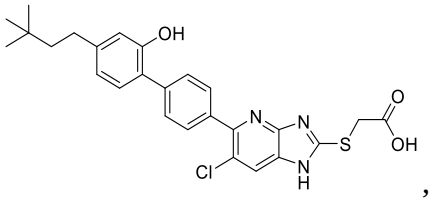
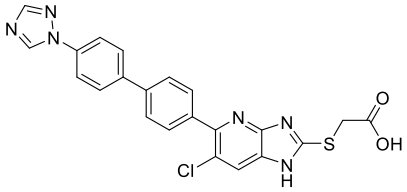
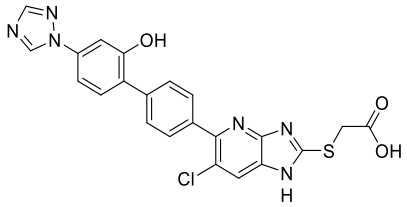
16. The compound of claim 1, selected from:


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, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof.

17. A pharmaceutical composition comprising a compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, and at least one pharmaceutically acceptable excipient.

18. A compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for use as a medicine.

19. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the treatment of an adenosine 5'–monophosphate–activated protein kinase (AMPK) associated condition or disorder in a subject in need thereof; wherein the condition or disorder is short bowel syndrome, intestinal failure, intestinal insufficiency, metabolic syndrome, obesity, type 2 diabetes, coronary artery disease, fatty liver, nonalcoholic steatohepatitis (NASH), cirrhosis, hepatic encephalopathy, fibrotic disorders including scleroderma, inflammatory bowel disease including Crohn's disease and ulcerative colitis, psoriasis, celiac disease, necrotizing enterocolitis, gastrointestinal injury resulting from toxic insults such as radiation or chemotherapy, environmental enteric dysfunction, allergy including food allergy, celiac sprue, and childhood allergy, irritable bowel syndrome, spontaneous bacterial peritonitis, ischemic colitis, sclerosing cholangitis, Alzheimer's disease, Parkinson's disease, colorectal cancer, depression, autism, or a combination thereof.

20. Use of a compound of any one of claims 1-16, or a pharmaceutically acceptable salt, solvate, stereoisomer, or prodrug thereof, for the preparation of a medicament for the treatment of gastrointestinal injury resulting from toxic insult in a subject in need thereof.