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(54) Title: INHIBITORS OF DYRK1A

(57) Abstract: The present disclosure provides chemical compounds such as benzimidazole carbamates that are inhibitors of DYRK1A kinase and are useful in treating, e.g., neurodegenerative diseases such as Alzheimer's disease, autoimmune diseases such as inflammatory bowel disease, osteoarthritis, and type-1 diabetes, and cancer (including brain tumors such as glioblastoma and neuroblastoma).



WO 2024/249488 A2

INHIBITORS OF DYRK1A

CLAIM OF PRIORITY

This application claims priority under 35 USC §119(e) to U.S. Patent Application Serial No. 63/504,910, filed on May 30, 2024. The entire contents of the foregoing are
5 hereby incorporated by reference.

TECHNICAL FIELD

This invention relates to benzimidazole carbamate compounds that are, e.g., inhibitors of DYRK1A kinase and are useful in treating, e.g., neurodegenerative diseases such as Alzheimer's disease, autoimmune diseases such as inflammatory bowel disease,
10 osteoarthritis, and type-1 diabetes, and cancer (including brain tumors such as glioblastoma and neuroblastoma).

BACKGROUND

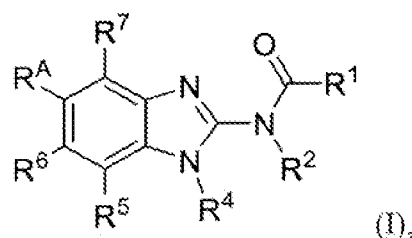
There are numerous deadly diseases affecting current human population. For example, neurodegenerative diseases affect a significant segment of population,
15 especially the elderly. As one example, Alzheimer's disease ("AD"), a neurodegenerative disease that affects approximately 44 million people world-wide, is the sixth leading cause of death with an estimated socioeconomic burden of more than \$200 billion. Neurodegenerative diseases such as AD impose a substantial burden on patients, their family members, the healthcare system, and the society overall. Because of aging
20 population worldwide, neurodegenerative disorders pose an increasing threat to public health.

SUMMARY

The present disclosure is based, at least in part, on a realization that benzimidazole carbamate compounds are potent and selective inhibitors of dual
25 specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A). Without being bound by any particular theory, and as discussed in this disclosure, numerous peer-reviewed scientific publications provide credible evidence that DYRK1A is implicated in pathology of various disorders. For example, as a kinase, DYRK1A promotes phosphorylation of the *Tau* protein, and hyperphosphorylation of *Tau* is a pathological
30 factor in the development of neurodegenerative disorders, including Alzheimer's disease.

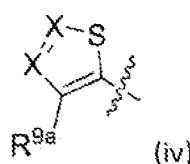
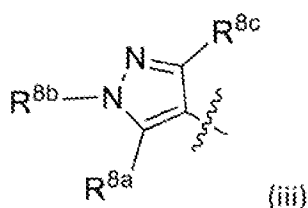
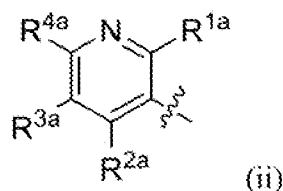
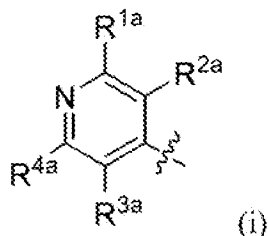
As such, the present disclosure advantageously provides methods of using the benzimidazole carbamate compounds to treat disorders associated with DYRK1A, including neurodegenerative diseases, autoimmune diseases, and cancer. Example embodiments of the benzimidazole carbamate compounds and related treatment methods are described herein.

In one general aspect, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (i), (ii), (iii) and (iv):



R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, $\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , and $\text{S(O)}_2\text{OR}^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, $\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , and $\text{S(O)}_2\text{OR}^{a1}$;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^b is independently selected from Cy^l , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^l , CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^c is selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $S(O)_2NR^{cl}R^{dl}$, and $S(O)_2OR^{al}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

each Cy^l is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} ;

each R^{Cyl} is independently selected from halo, CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^{al} , R^{bl} , R^{cl} , and R^{dl} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^6 ;

R^{8a} , R^{8b} , and R^{8c} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^6 ;

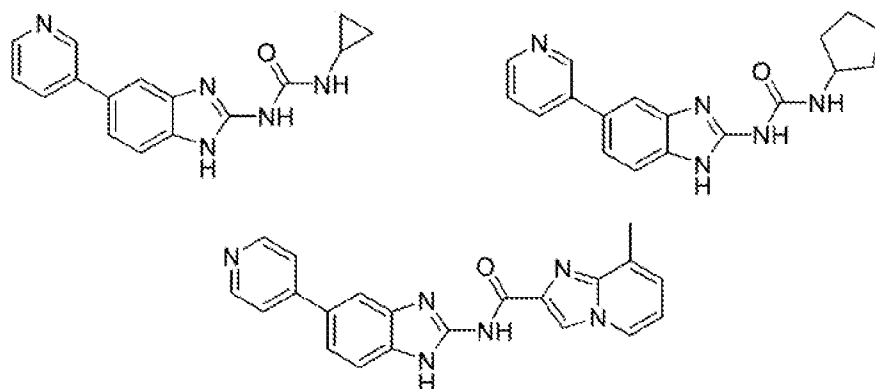
each X is independently selected from N and CR^{9b} , wherein one X is N and the other X is CR^{9b} ;

R^{9a} and R^{9b} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 ;

and

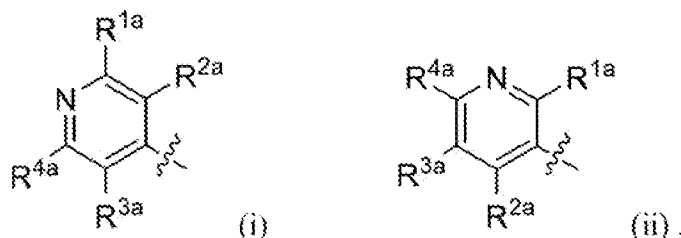
5 each R^8 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino;

provided that the compound of Formula (I) is not any one of the following compounds:

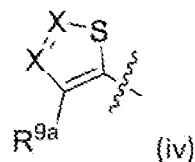


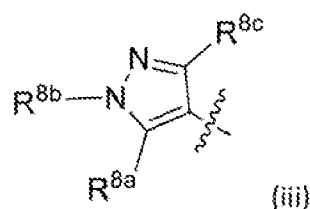
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In some embodiments of the compound of Formula (I), R^A is selected from moiety (i) and (ii):

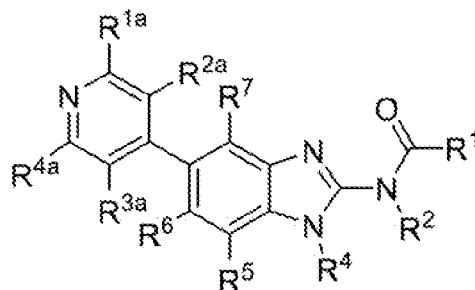


In some embodiments of the compound of Formula (I), R^A is selected from moiety (iii) and (iv):



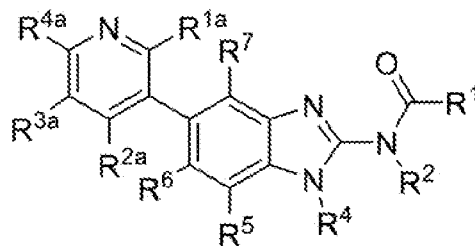


In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:

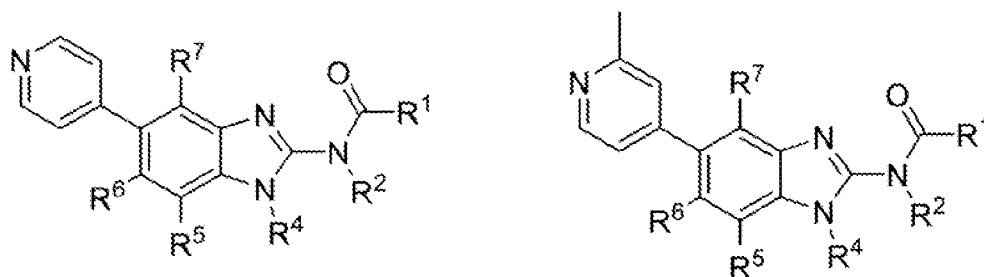


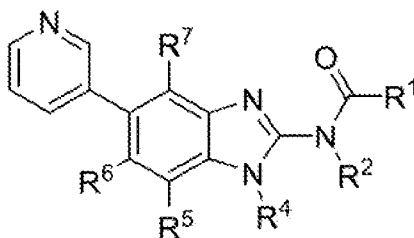
or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, and C₁₋₃ haloalkyl.

In some embodiments, R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently selected from H and C₁₋₃ alkyl.

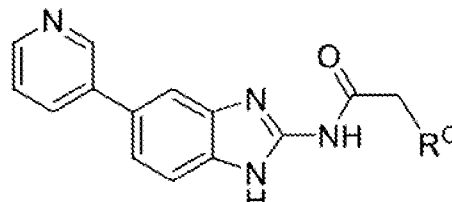
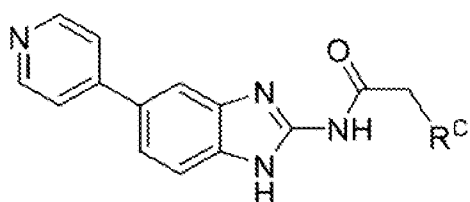
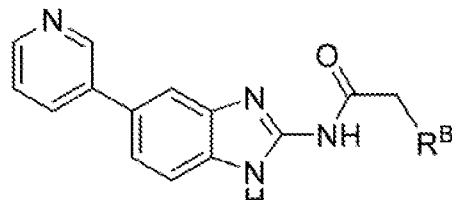
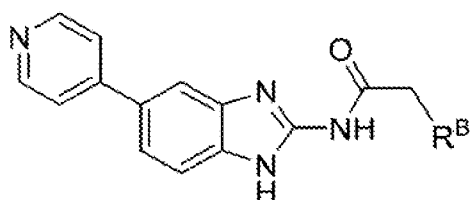
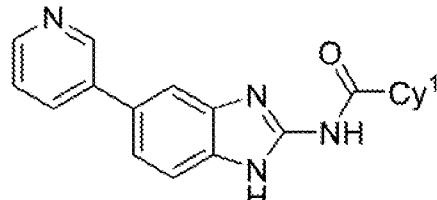
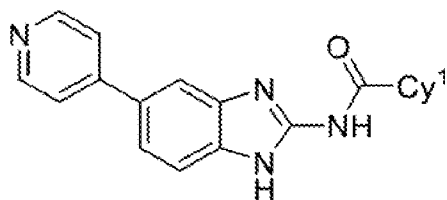
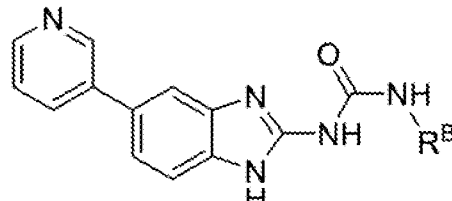
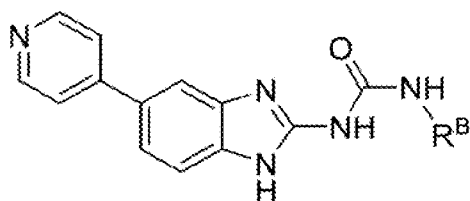
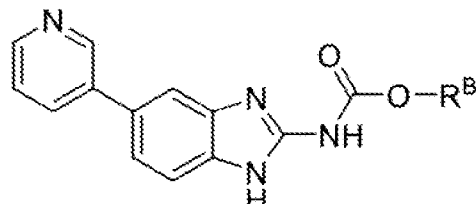
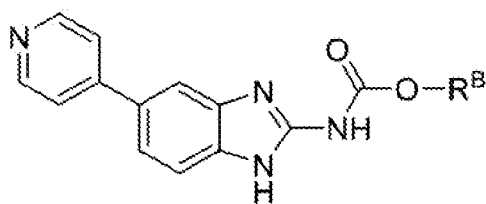
In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:





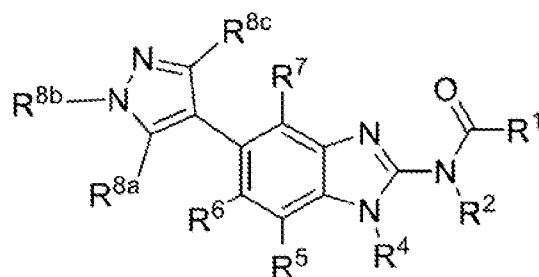
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from:



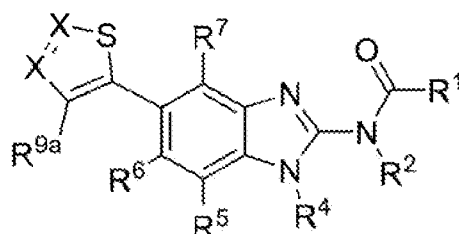
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



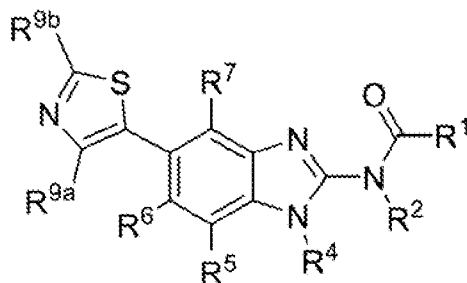
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



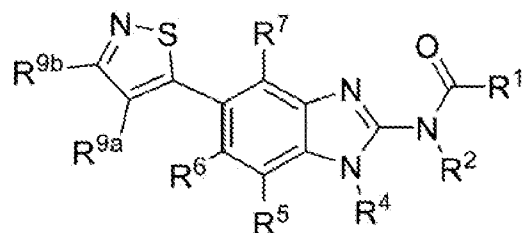
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{8a} , R^{8b} , and R^{8c} are each independently selected from H and C_{1-3} alkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 .

In some embodiments, R^{8a} , R^{8b} , and R^{8c} are each independently selected from H and C_{1-3} alkyl.

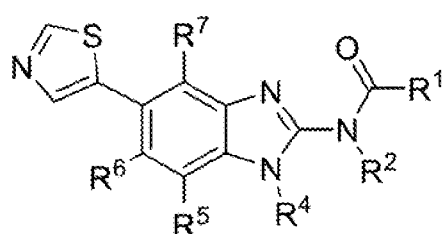
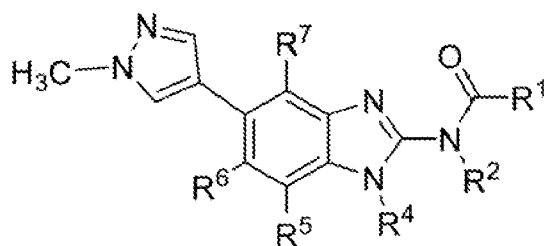
In some embodiments, R^{8a} and R^{8c} are both H and R^{8b} is C_{1-3} alkyl, such as methyl.

In some embodiments, R^{9a} and R^{9b} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9 .

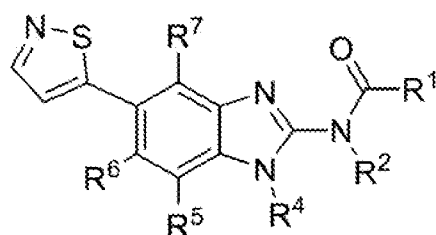
In some embodiments, R^{9a} and R^{9b} are each independently selected from H and C_{1-3} alkyl.

In some embodiments, R^{9a} and R^{9b} are both H.

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:



and



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , and $\text{NR}^{\text{al}}\text{R}^{\text{al}}$.

In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $\text{di}(\text{C}_{1-3}$ alkyl)amino.

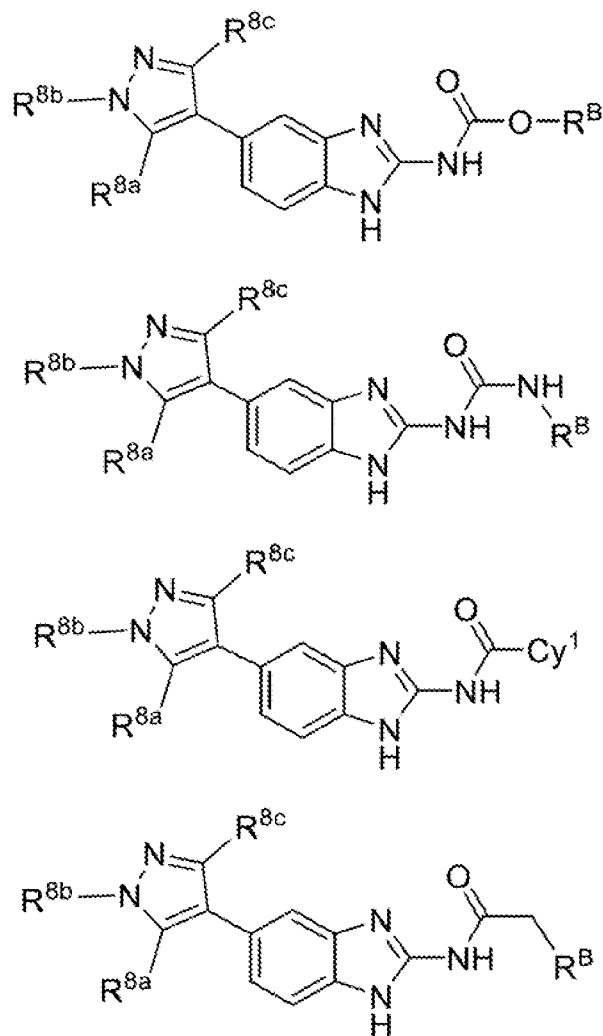
In some embodiments, R^1 is selected from OR^{B} and $\text{NR}^3\text{R}^{\text{B}}$.

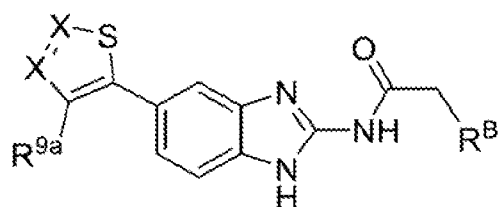
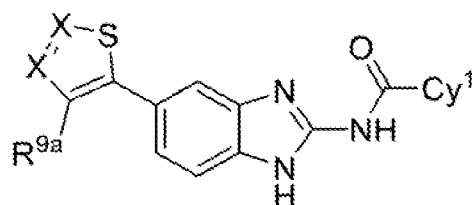
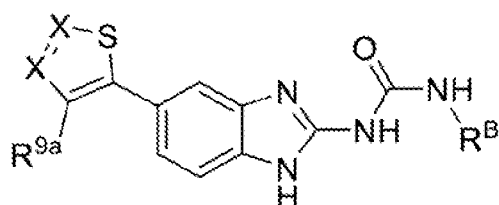
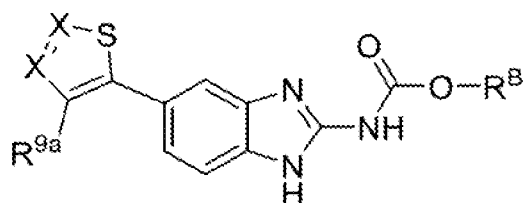
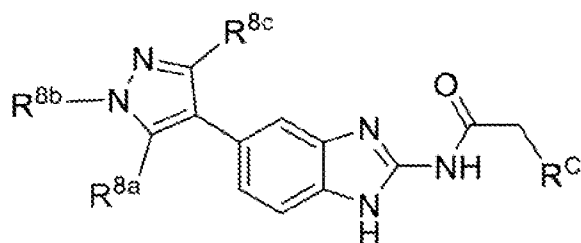
In some embodiments, R^1 is OR^{B} .

In some embodiments, R^1 is NHR^{B} .

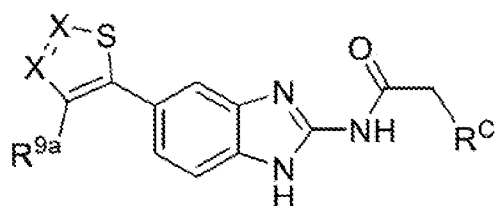
In some embodiments, R^1 is $\text{CH}_2\text{R}^{\text{B}}$.

In some embodiments, the compound of Formula (I) is selected from:





and



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^B is selected from Cy¹ and C₁₋₆ alkyl substituted with Cy¹, OR^{a1}, or NR^{c1}R^{d1}.

In some embodiments, R^B is selected from Cy^1 , C_{1-6} alkyl substituted with Cy^1 , and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.

In some embodiments, R^B is Cy^1 .

In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 .

5 In some embodiments, Cy^1 is selected from C_{6-10} aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

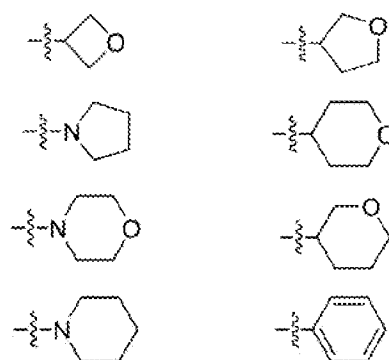
10 In some embodiments, Cy^1 is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

In some embodiments, the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with
15 1 or 2 substituents independently selected from R^{Cy1} .

In some embodiments, R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.

In some embodiments, R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.

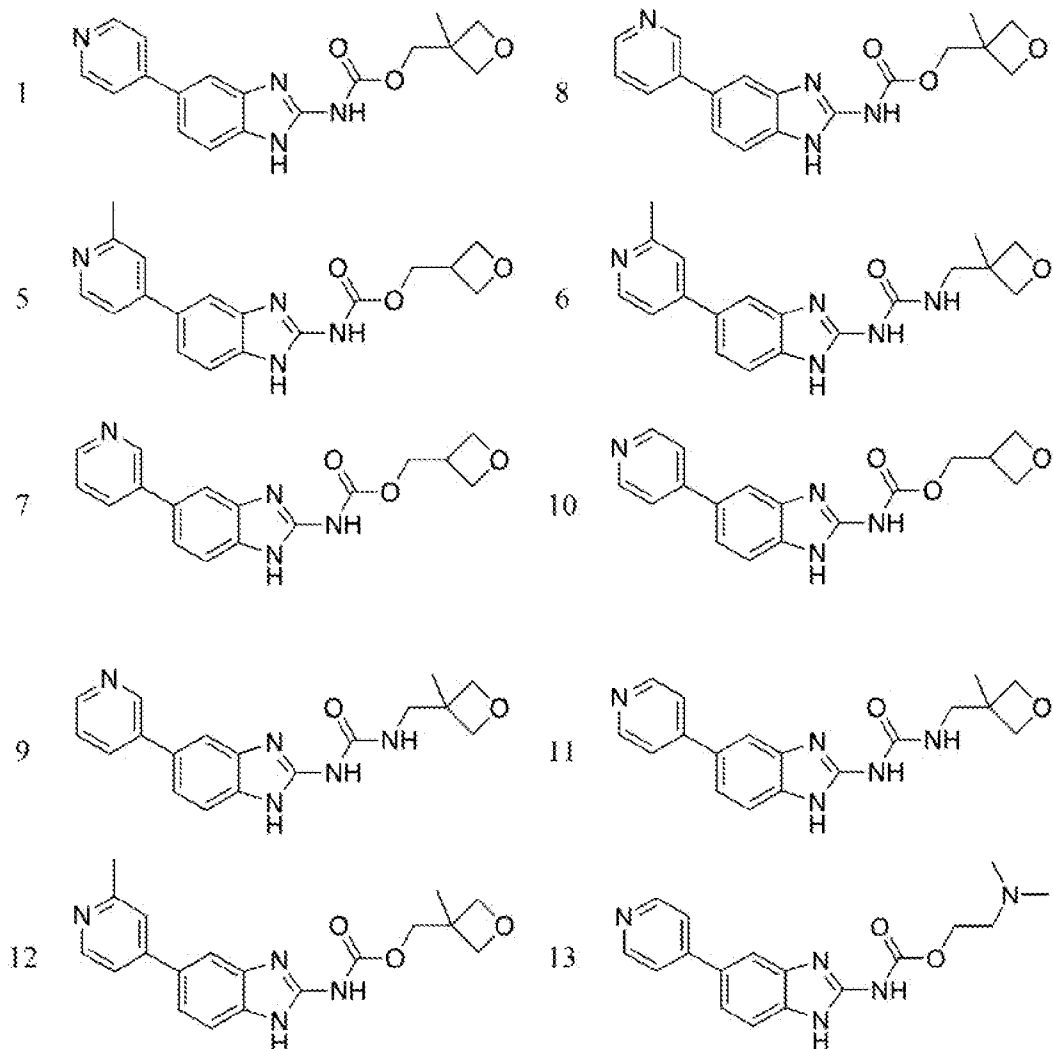
20 In some embodiments, Cy^1 is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cy1} :



In some embodiments, R^B is C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.

In some embodiments, R^B is selected from $CH_2NR^{c1}R^{d1}$, $CH_2CH_2NR^{c1}R^{d1}$, and $CH_2CH_2CH_2NR^{c1}R^{d1}$.

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:



or a pharmaceutically acceptable salt thereof.

In another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another general aspect, the present disclosure provides a method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising same.

In some embodiments, the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astrogliopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.

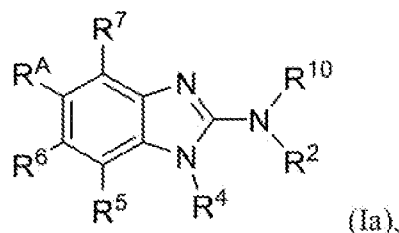
In some embodiments, the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimia, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.

In some embodiments, the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.

In some embodiments, the disease or condition is a cancer selected from brain cancer (e.g., glioblastoma, neuroblastoma), leukemia (e.g., B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.

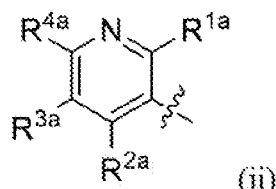
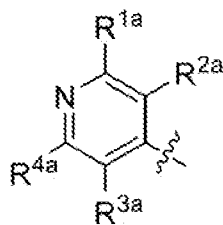
In another general aspect, the present disclosure provides a method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising: (i)

identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and (ii) after (i), administering to the subject a therapeutically effective amount of a compound of Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (i) and (ii):



R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R¹⁰ is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and C(=O)R^l;

R^l is selected from Cy¹, OR^B, NR³R^B, CH₂R^B, and CH₂R^C;

each R^B is independently selected from H, Cy¹, C₁₋₆ alkyl, and C₁₋₆ haloalkyl, wherein said C₁₋₆ alkyl is optionally substituted with Cy¹, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

R^C is selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R², R³, and R⁴ are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R⁵, R⁶ and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy¹, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al},

and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

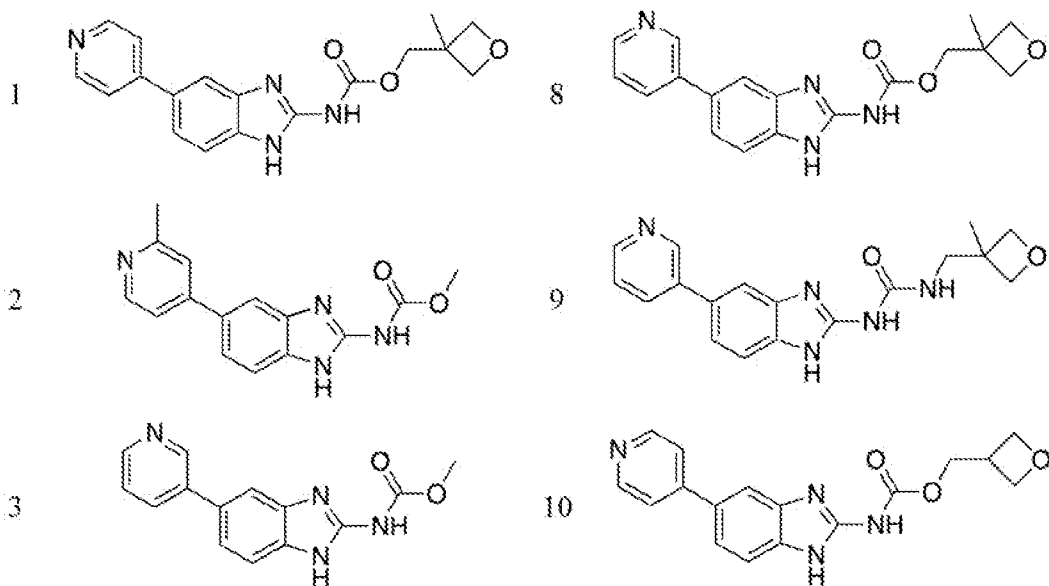
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} ;

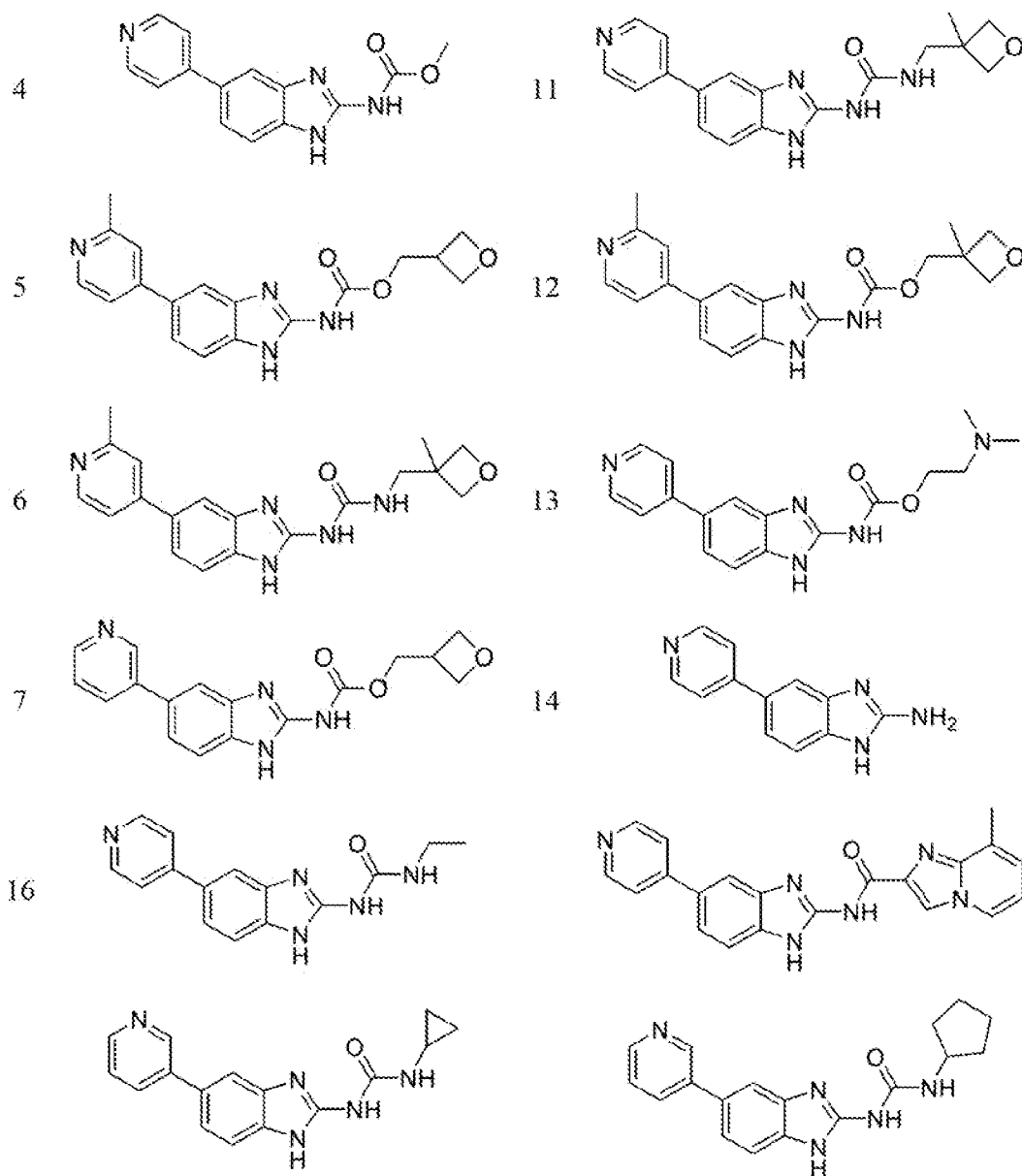
each R^{Cyl} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E ; and

each R^E is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

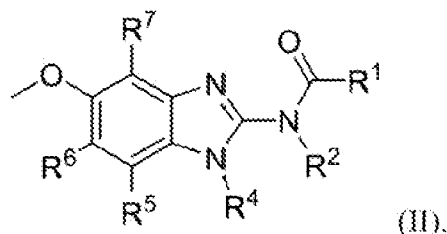
In some embodiments, the compound of Formula (Ia) is selected from any one of the following compounds:





or a pharmaceutically acceptable salt thereof.

In another general aspect, the present disclosure provides a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from OR^B , NR^3R^B , and CH_2R^C ;

each R^B is independently selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from NO_2 , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2OR^{a1}$, and C_{1-6} alkyl substituted with NO_2 , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

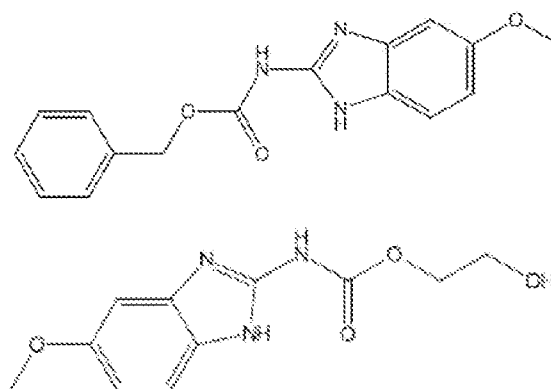
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g ; and

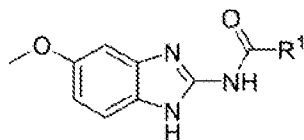
each R^8 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxy carbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino;

provided that the compound of Formula (II) is not any of the following compounds:



In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , and $NR^{c1}R^{d1}$. In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^1 is selected from OR^B and NR^3R^B .

In some embodiments, R^1 is OR^B .

In some embodiments, R^1 is NHR^B .

In some embodiments, R^B is selected from Cy^1 and C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$.

In some embodiments, R^B is selected from Cy^1 , C_{1-6} alkyl substituted with Cy^1 , and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.

In some embodiments, R^B is Cy^1 .

In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 .

In some embodiments, Cy^1 is selected from C_{6-10} aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

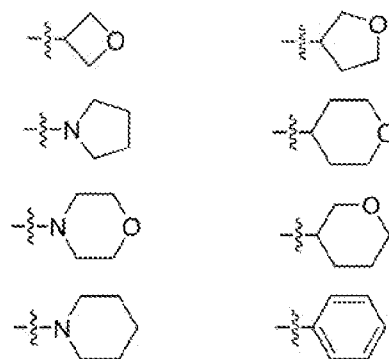
In some embodiments, Cy^1 is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

In some embodiments, the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .

In some embodiments, R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.

In some embodiments, R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.

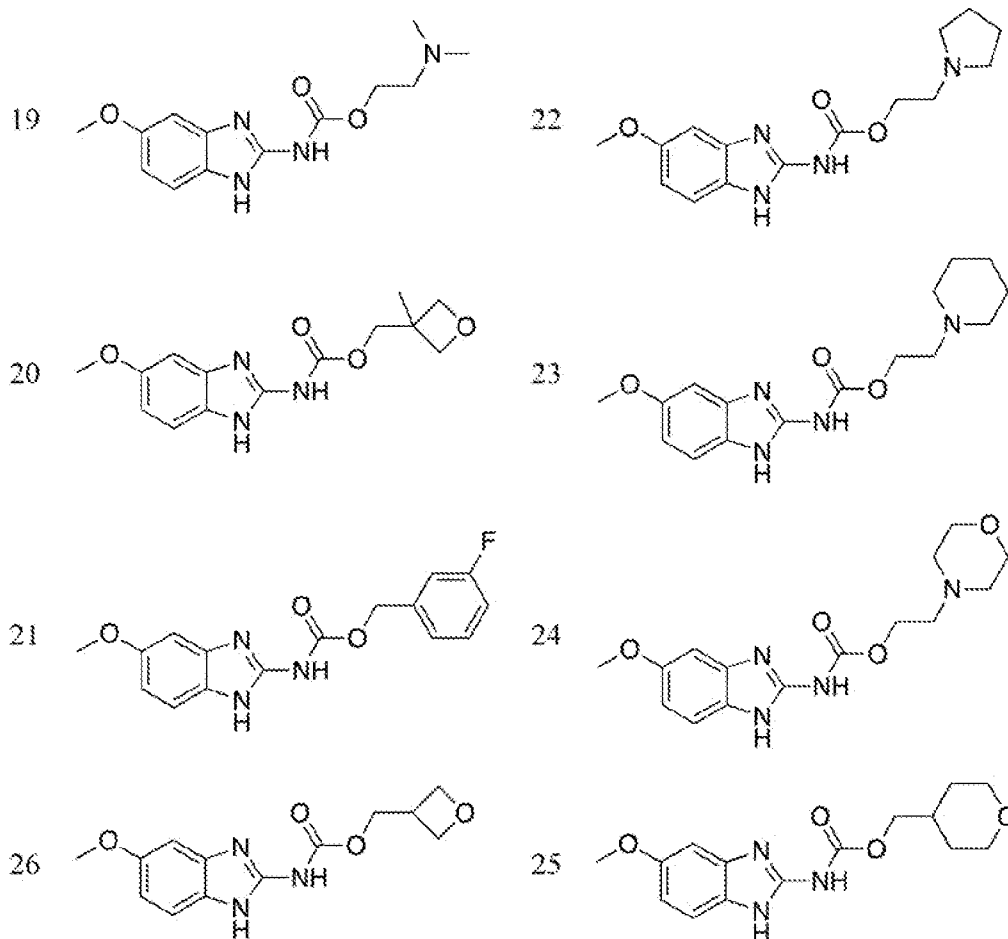
In some embodiments, Cy^1 is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cy1} :



In some embodiments, R^B is C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.

In some embodiments, R^B is selected from $CH_2NR^{c1}R^{d1}$, $CH_2CH_2NR^{c1}R^{d1}$, and $CH_2CH_2CH_2NR^{c1}R^{d1}$.

In some embodiments, the compound of Formula (II) is selected from any one of the following compounds:



or a pharmaceutically acceptable salt thereof.

In another general aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula (II), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another general aspect, the present disclosure provides a method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising same.

In some embodiments, the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager

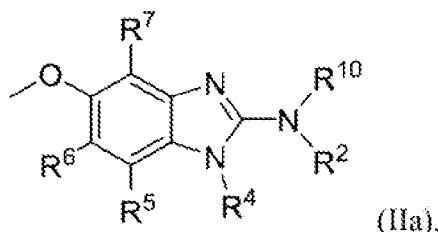
syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astrogliopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.

In some embodiments, the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimía, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.

In some embodiments, the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.

In some embodiments, the disease or condition is a cancer selected from brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.

In another general aspect, the present disclosure provides a method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising: (i) identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and (ii) after (i), administering to the subject a therapeutically effective amount of a compound of Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein:

R^{10} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and $C(=O)R^1$;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^B is independently selected from H, Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

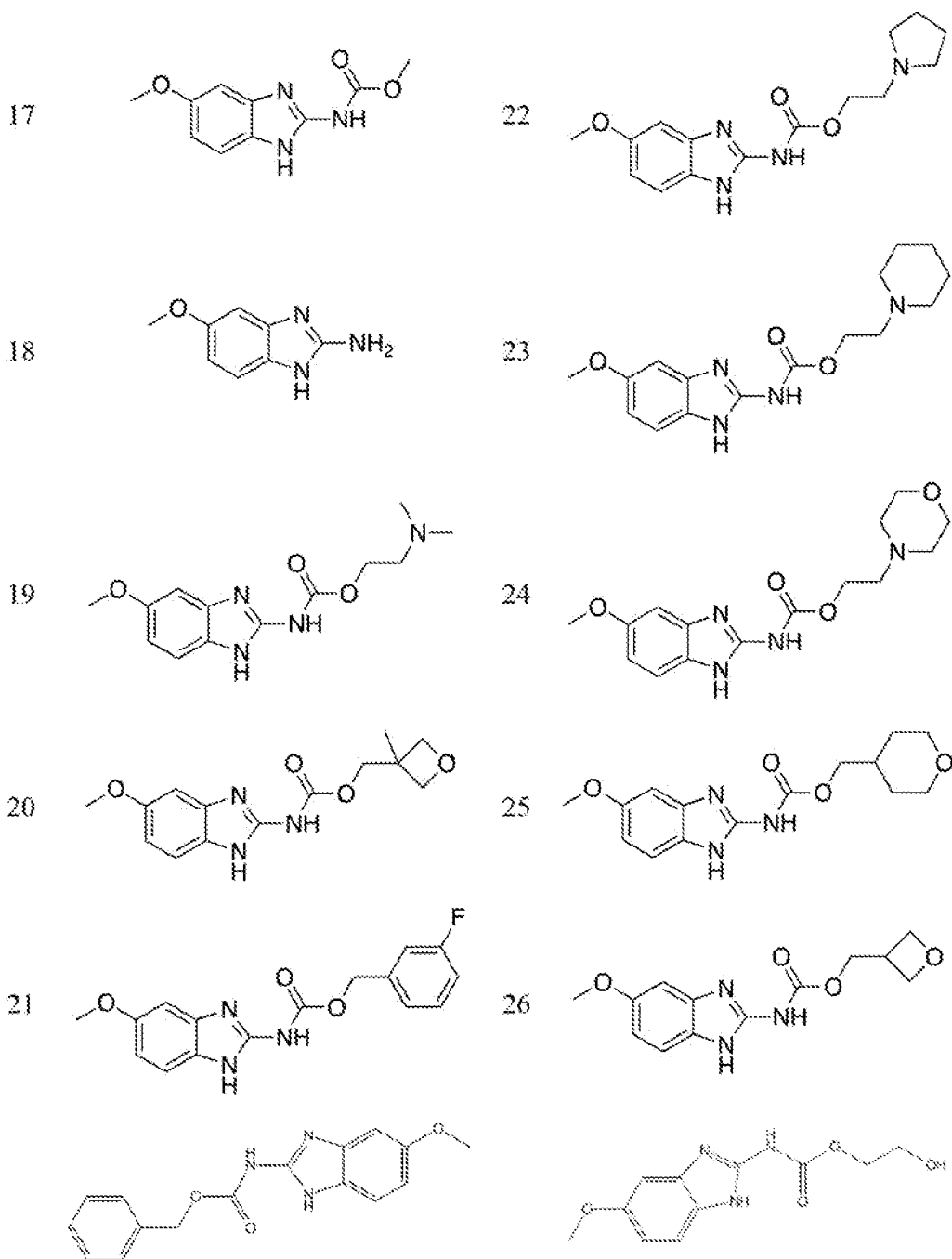
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

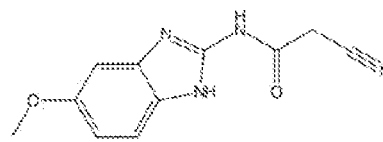
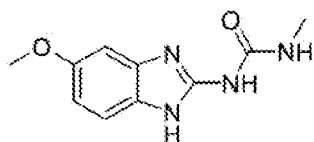
each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E ; and

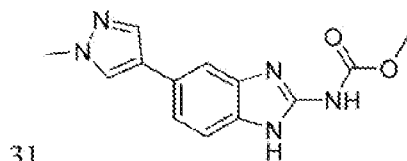
each R^8 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

In some embodiments, the compound of Formula (IIa) is selected from any one of the following compounds:

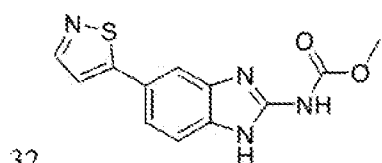




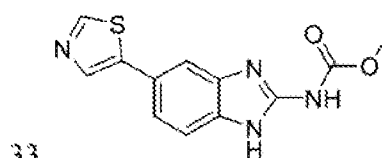
In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:



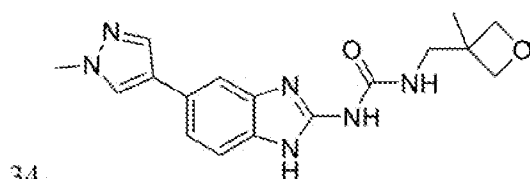
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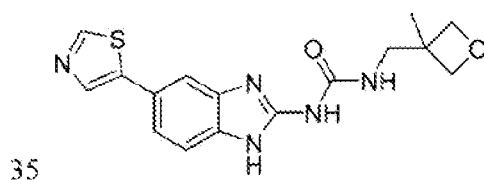


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and



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or a pharmaceutically acceptable salt thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present application belongs. Methods and materials are described herein for use in the present application; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and

other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Other features and advantages of the present application will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION

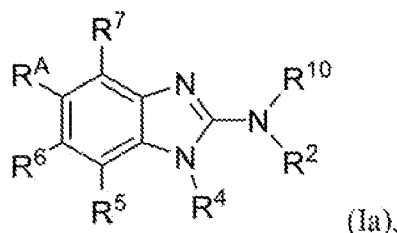
The present disclosure provides chemical compounds (*e.g.*, organic heterocyclic compounds). Without being bound by any theory or speculation, it is believed that in one example, compounds of this disclosure potently and selectively inhibit kinase enzyme DYRK1A and/or phosphorylation of the Tau protein. Certain embodiments of these compounds, methods of using these compounds to inhibit DYRK1A (*e.g.*, *in vitro*, *in vivo*, or *ex vivo*) and to treat associated disorders and conditions (*e.g.*, diseases where DYRK1A is implicated in pathology such as Alzheimer's disease, inflammation, and cancer) are described herein. Example embodiments of pharmaceutical compositions containing these compounds and combination treatment methods are also provided.

Therapeutic compounds

In a general aspect, the present disclosure provides benzoimidazole (*e.g.*, benzo[d]imidazole) compound having a substituent in the 5-position (*e.g.*, a substituted pyridine, a methoxy, or a substituted benzoyl moiety). Example embodiments of these compounds are provided herein.

Pyridine-containing benzoimidazole compounds

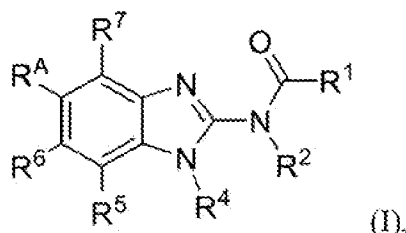
In some embodiments, the present disclosure provides a compound of Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein R^{10} , R^2 , R^4 , R^5 , R^6 , R^7 , and R^A (*e.g.*, as described herein for Formula Ia or Formula I).

In some embodiments, R^{10} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and $C(=O)R^1$. In some embodiments, R^{10} is H. In some embodiments, R^{10} is C_{1-3} alkyl. In some embodiments, R^{10} is haloalkyl. In some embodiments, R^{10} is $C(=O)R^1$.

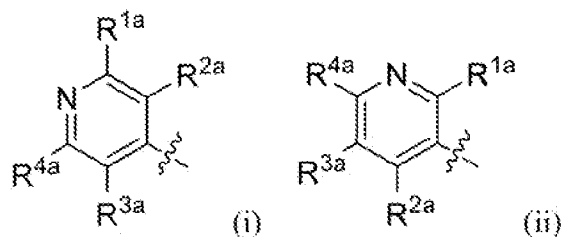
In some embodiments, the compound of Formula (Ia) has Formula (I):



or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula (Ia) or Formula (I):

R^A is selected from moiety (i) and (ii):



R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^B is independently selected from H, Cy^1 , C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy¹, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy¹, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl};

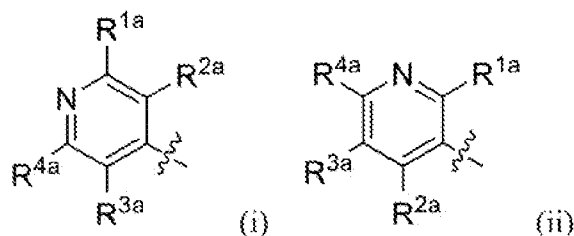
each R^{Cyl} is independently selected from halo, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

R^{al} , R^{bl} , R^{cl} , and R^{dl} are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from halo, CN, OH, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, carboxy, C₁₋₃ alkoxy carbonyl, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino.

In some embodiments of Formula (Ia) or Formula (I):

R^A is selected from moiety (i) and (ii):



R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R¹ is selected from Cy¹, OR^B, NR^{3B}R^B, CH₂R^B, and CH₂R^C;

each R^b is independently selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^c is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} ;

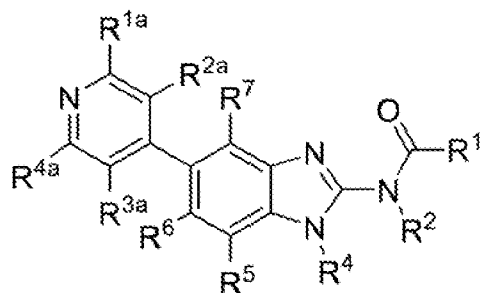
each R^{Cyl} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^6 ; and

each R^8 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

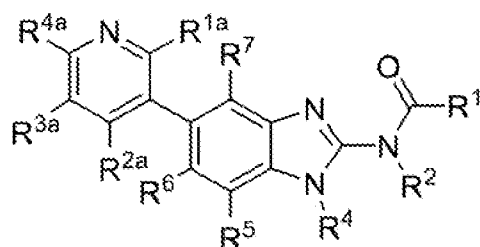
In some embodiments, R^A is a moiety of formula (i). In some embodiments, R^A is a moiety of formula (ii).

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{1a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and $\text{S}(\text{O})_2\text{OR}^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and $\text{S}(\text{O})_2\text{OR}^{a1}$.

In some embodiments, R^{2a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and $\text{S}(\text{O})_2\text{OR}^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and $\text{S}(\text{O})_2\text{OR}^{a1}$.

In some embodiments, R^{3a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and $\text{S}(\text{O})_2\text{OR}^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and $\text{S}(\text{O})_2\text{OR}^{a1}$.

In some embodiments, R^{4a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{R}^{b1}$, $\text{C}(\text{O})\text{NR}^{c1}\text{R}^{d1}$, $\text{S}(\text{O})_2\text{NR}^{c1}\text{R}^{d1}$, $\text{C}(\text{O})\text{OR}^{a1}$, and

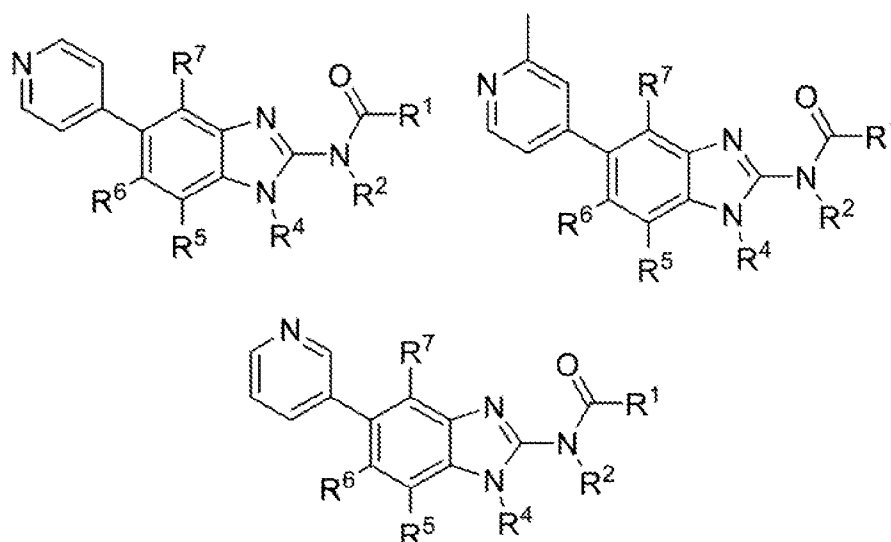
$S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl.

In some embodiments, R^{1a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{2a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{3a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{4a} is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl.

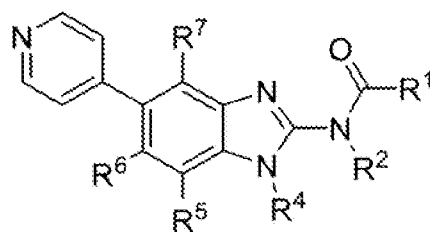
In some embodiments, R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H and C_{1-3} alkyl. In some embodiments, R^{1a} is selected from H and C_{1-3} alkyl. In some embodiments, R^{1a} is C_{1-3} alkyl. In some embodiments, R^{2a} is selected from H and C_{1-3} alkyl. In some embodiments, R^{2a} is C_{1-3} alkyl. In some embodiments, R^{3a} is selected from H and C_{1-3} alkyl. In some embodiments, R^{3a} is C_{1-3} alkyl. In some embodiments, R^{4a} is selected from H and C_{1-3} alkyl. In some embodiments, R^{4a} is C_{1-3} alkyl. In some embodiments, R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each H.

In some embodiments, the compound of Formula (Ia) or Formula (I) is selected from any one of the following compounds:



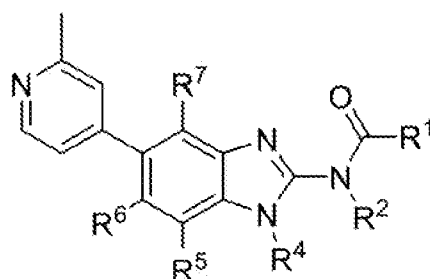
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



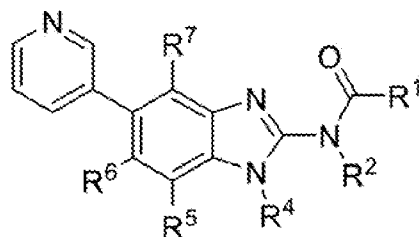
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$.

In some embodiments, R^5 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^5 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^6 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^6 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^7 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^7 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{a1} , $NR^{c1}R^{d1}$, $C(O)NR^{c1}R^{d1}$, and $C(O)OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{a1} , $NR^{c1}R^{d1}$, $C(O)NR^{c1}R^{d1}$, and $C(O)OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$.

5 In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $C(O)NR^{c1}R^{d1}$, and $C(O)OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , and $NR^{c1}R^{d1}$, wherein said C_{1-3} alkyl is
10 optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$.

In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , and $NR^{c1}R^{d1}$.

In some embodiments, at least one of R^5 , R^6 , and R^7 is C_{1-3} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$.

15 In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $di(C_{1-3}$ alkyl)amino.

In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.

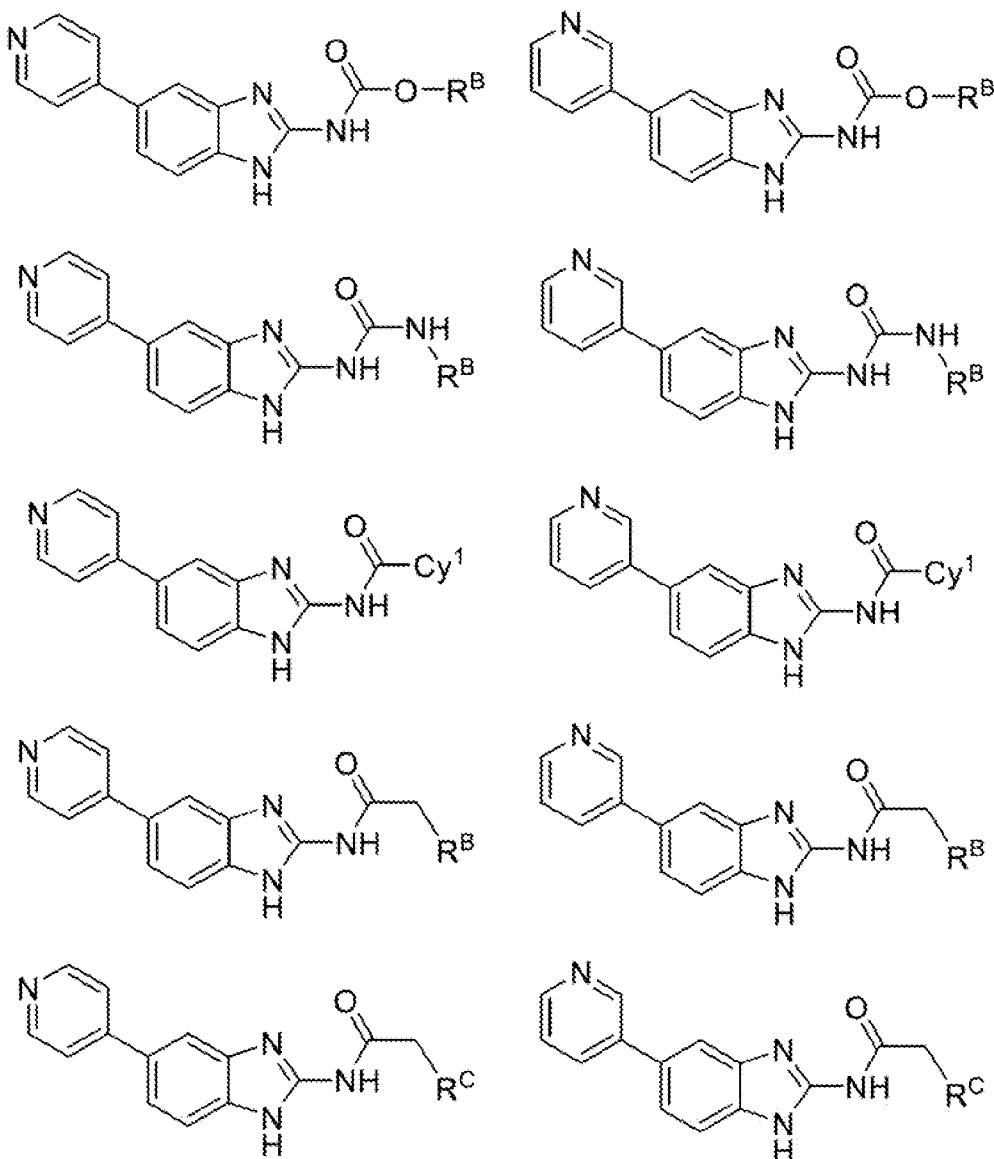
20 In some embodiments, R^5 , R^6 and R^7 are each H. In some embodiments, R^5 is not Cy^1 . In some embodiments, R^5 is not $C(O)NR^{c1}R^{d1}$. In some embodiments, R^5 is not $C(O)OR^{a1}$.

In some embodiments, R^2 , R^3 , and R^4 are each independently selected from H and C_{1-3} alkyl. In some embodiments, R^2 is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In
25 some embodiments, R^3 is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^4 is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^2 is selected from H and C_{1-3} alkyl. In some embodiments, R^3 is selected from H and C_{1-3} alkyl. In some embodiments, R^4 is selected from H and C_{1-3} alkyl. In some embodiments, R^2 , R^3 , and R^4 are each H.

30 In some embodiments, R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C . In some embodiments, R^1 is Cy^1 . In some embodiments, R^1 is OR^B . In some

embodiments, R^1 is NR^3R^B . In some embodiments, R^1 is CH_2R^B . In some embodiments, R^1 is CH_2R^C . In some embodiments, R^1 is selected from OR^B and NR^3R^B .

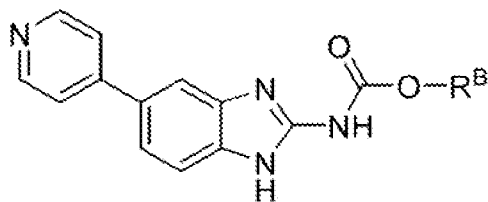
In some embodiments, the compound of Formula (Ia) or Formula (I) is selected from:



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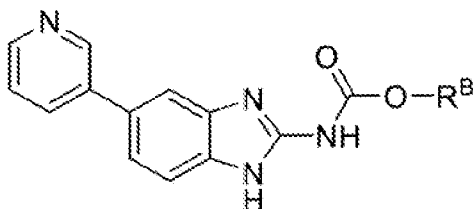
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



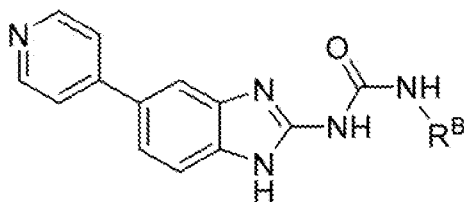
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



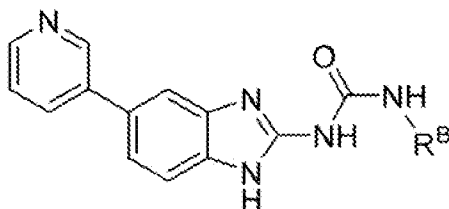
5 or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

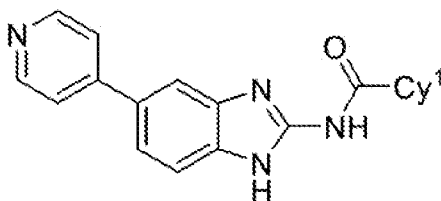
In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



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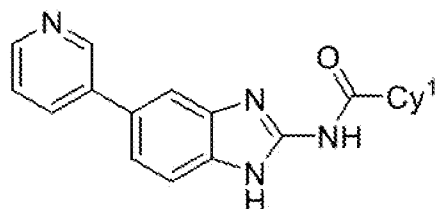
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



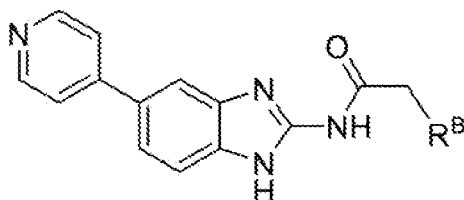
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

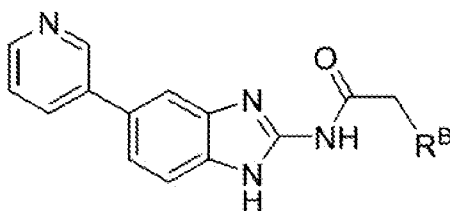
In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



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or a pharmaceutically acceptable salt thereof.

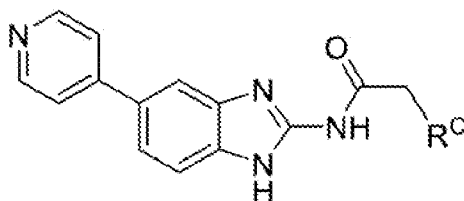
In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

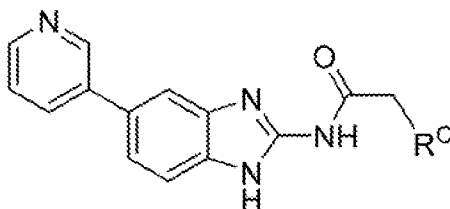
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In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (Ia) or Formula (I) has formula:



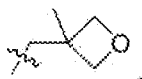
or a pharmaceutically acceptable salt thereof.

In some embodiments, R^B is selected from H, Cy^1 , C_{1-6} alkyl (*e.g.*, methyl, ethyl, propyl, or *n*-butyl), and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$,
 5 or $S(O)_2OR^{a1}$.

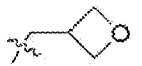
In some embodiments, R^B is selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$. In some embodiments, R^B is selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$. In some embodiments,
 10 R^B is selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$.

In some embodiments, R^B is H. In some embodiments, R^B is Cy^1 . In some embodiments, R^B is C_{1-6} haloalkyl. In some embodiments, R^B is C_{1-6} alkyl optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$,
 15 $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$. In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$. In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$. In some embodiments, R^B is selected from Cy^1 and C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$. In some embodiments, R^B is selected from Cy^1 , C_{1-6} alkyl substituted with Cy^1 , and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$. In some embodiments, R^B
 20 is R^B is C_{1-6} alkyl substituted with Cy^1 .

In some embodiments, R^B is a moiety of formula:



In some embodiments, R^B is a moiety of formula:



In some embodiments, R^B is C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$. In some embodiments, R^B is selected from $CH_2NR^{c1}R^{d1}$, $CH_2CH_2NR^{c1}R^{d1}$, and $CH_2CH_2CH_2NR^{c1}R^{d1}$.

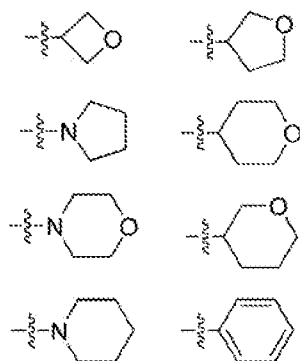
In some embodiments, R^C is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$. In some embodiments, R^C is
 30

CN or NO₂. In some embodiments, R^C is OR^{a1} or NR^{c1}R^{d1}. In some embodiments, R^C is OR^{a1}. In some embodiments, R^C is NR^{c1}R^{d1}. In some embodiments, R^C is S(O)₂R^{b1}, C(O)NR^{c1}R^{d1}, S(O)₂NR^{c1}R^{d1}, C(O)OR^{a1}, or S(O)₂OR^{a1}.

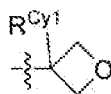
In some embodiments, Cy¹ is selected from C₆₋₁₀ aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1}. In some embodiments, Cy¹ is C₆₋₁₀ aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1}. In some embodiments, Cy¹ is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1}. In some embodiments, the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1}.

In some embodiments, R^{Cy1} is selected from halo, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy. In some embodiments, R^{Cy1} is selected from halo, NO₂, C₁₋₃ alkyl, and C₁₋₃ alkoxy. In some embodiments, R^{Cy1} is C₁₋₃ alkyl.

In some embodiments, Cy¹ is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cy1}:



In some embodiments, Cy¹ is a moiety of formula:

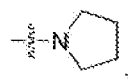


In some embodiments, Cy¹ is a moiety of formula:



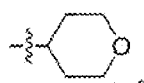
which is optionally substituted with R^{Cy1}.

In some embodiments, Cy^1 is a moiety of formula:



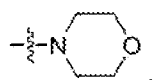
which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



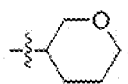
which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



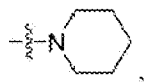
which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



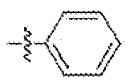
which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



which is optionally substituted with R^{Cy1} .

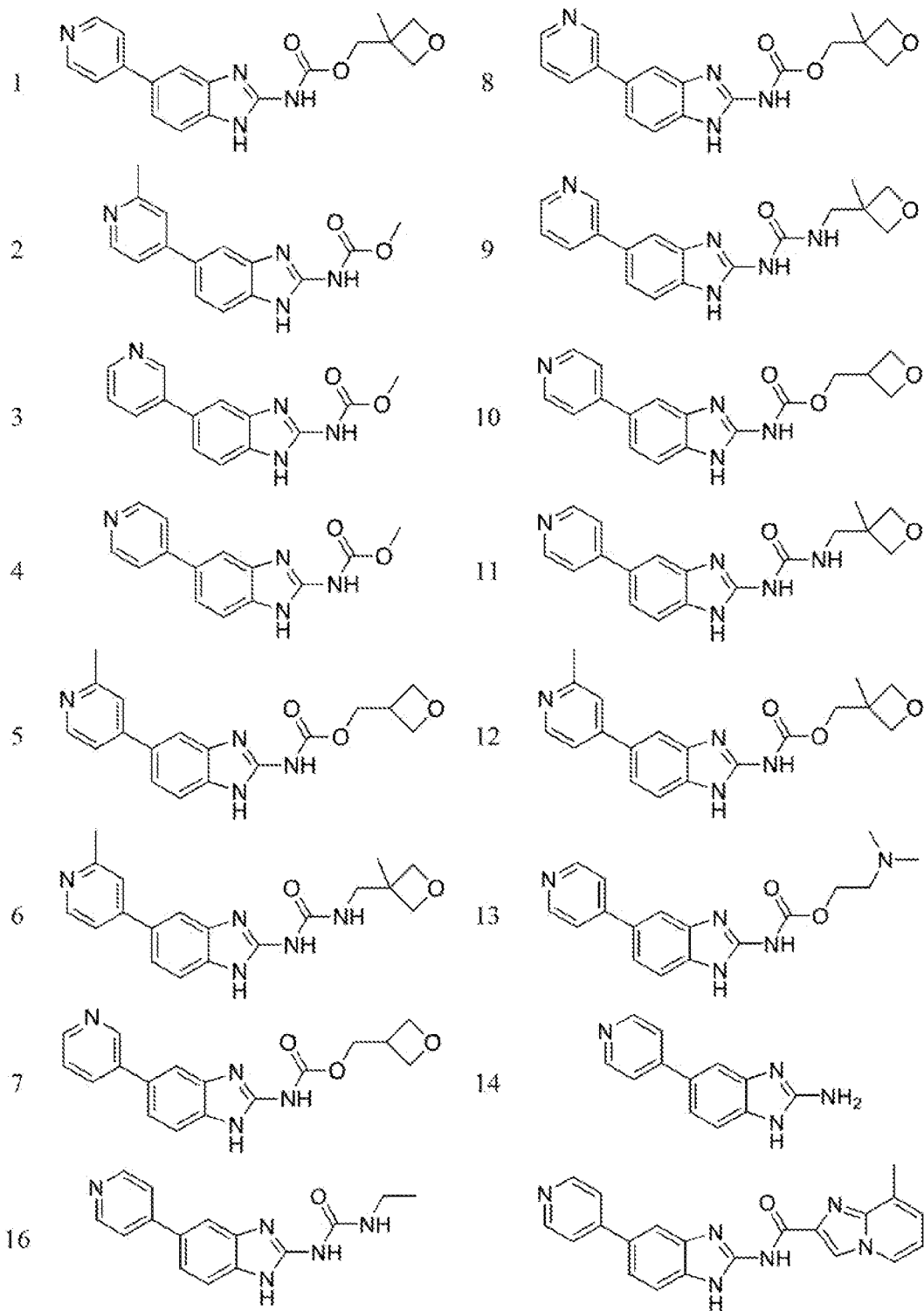
In some embodiments, Cy^1 is a moiety of formula:

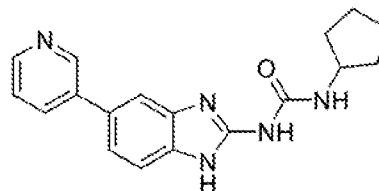
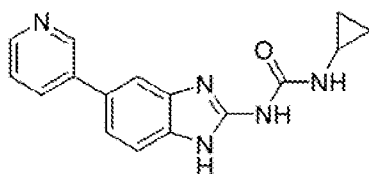


which is optionally substituted with R^{Cy1} .

In some embodiments, R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{a1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{b1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{c1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{d1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl.

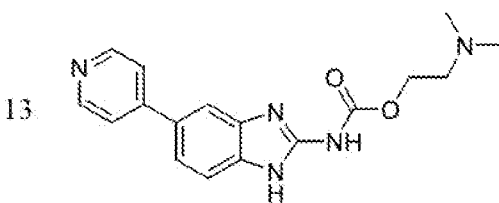
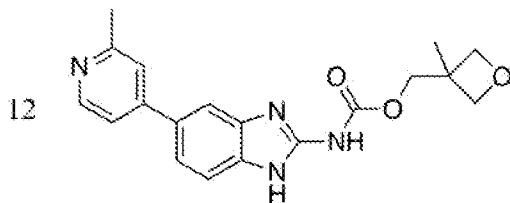
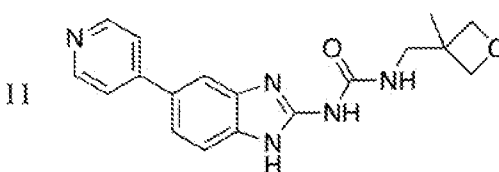
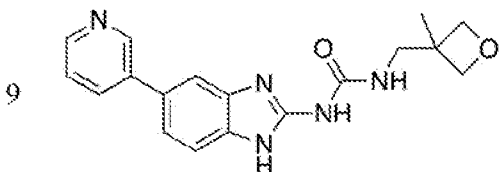
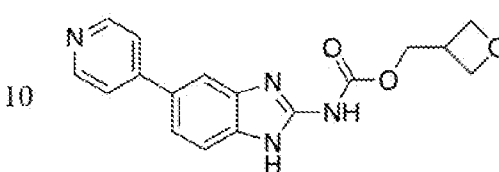
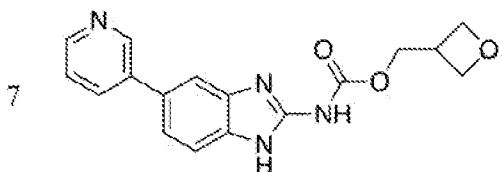
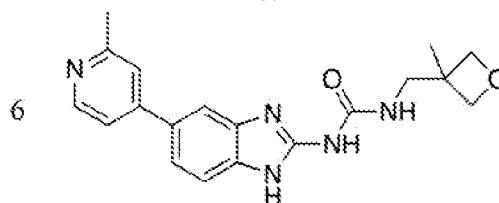
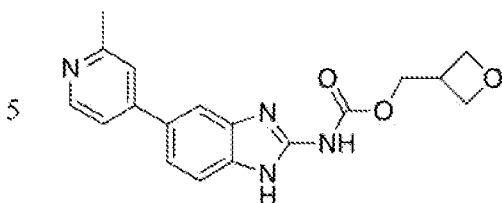
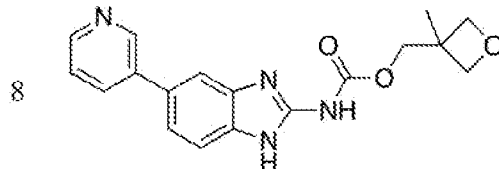
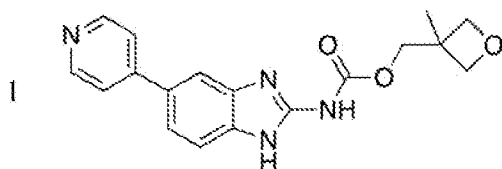
In some embodiments, the compound of Formula (Ia) is selected from any one of the following compounds:





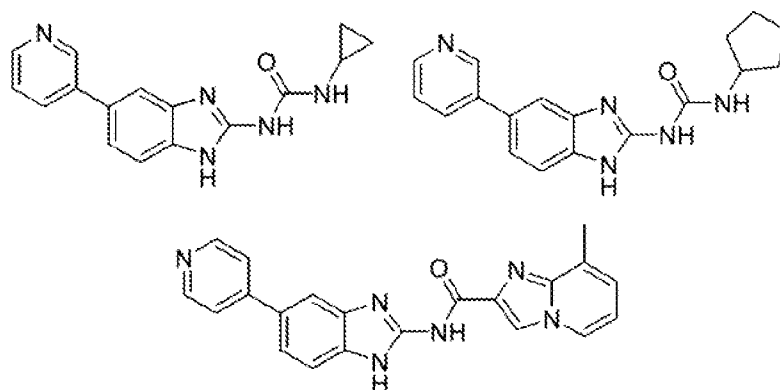
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:



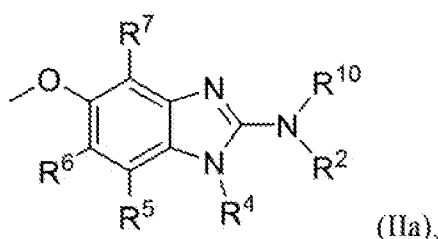
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (I) is not any one of the following compounds:



Methoxy-containing benzoimidazole compounds

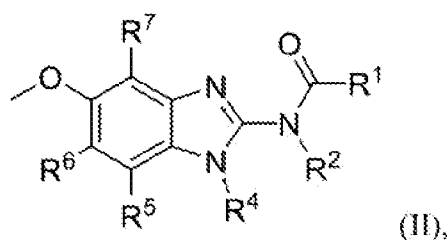
In some embodiments, the present disclosure provides a compound of Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein R^{10} , R^2 , R^4 , R^5 , R^6 , and R^7 (e.g., as described herein for Formula IIa or Formula II).

In some embodiments, R^{10} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and $C(=O)R^1$. In some embodiments, R^{10} is H. In some embodiments, R^{10} is C_{1-3} alkyl. In some embodiments, R^{10} is haloalkyl. In some embodiments, R^{10} is $C(=O)R^1$.

In some embodiments, the compound of Formula (IIa) has Formula (II):



or a pharmaceutically acceptable salt thereof.

In some embodiments of Formula (IIa) or Formula (II):

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C .

each R^B is independently selected from H, Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} ;

each R^{Cyl} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E ; and

each R^E is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

In some embodiments of Formula (IIa) or Formula (II):

R^1 is selected from OR^B , NR^3R^B , and CH_2R^C ;

each R^B is independently selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from NO_2 , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, $\text{S(O)}_2\text{OR}^{\text{al}}$, and C_{1-6} alkyl substituted with NO_2 , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, or $\text{S(O)}_2\text{OR}^{\text{al}}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$;

each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} ;

each R^{Cyl} is independently selected from halo, CN, NO_2 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, or $\text{S(O)}_2\text{OR}^{\text{al}}$;

R^{al} , R^{bl} , R^{cl} , and R^{dl} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^{e} ; and

each R^{e} is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and $\text{di(C}_{1-3}\text{ alkyl)amino}$.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{C(O)}\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{C(O)}\text{OR}^{\text{al}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$.

In some embodiments, R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, $\text{S(O)}_2\text{R}^{\text{bl}}$, $\text{S(O)}_2\text{NR}^{\text{cl}}\text{R}^{\text{dl}}$, and $\text{S(O)}_2\text{OR}^{\text{al}}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents

independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁵ is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy^l, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^l, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁵ is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, S(O)₂NR^{cl}R^{dl}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁶ is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy^l, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^l, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁶ is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, S(O)₂NR^{cl}R^{dl}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁷ is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy^l, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^l, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁷ is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, S(O)₂NR^{cl}R^{dl}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}.

In some embodiments, R⁵, R⁶ and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy^l, OR^{al}, NR^{cl}R^{dl}, C(O)NR^{cl}R^{dl}, and

C(O)OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with Cy¹, CN, NO₂, OR^{al}, or NR^{cl}R^{dl}.

In some embodiments, R⁵, R⁶ and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, Cy¹, OR^{al}, NR^{cl}R^{dl}, C(O)NR^{cl}R^{dl}, and C(O)OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with Cy¹, CN, NO₂, OR^{al}, or NR^{cl}R^{dl}.

In some embodiments, R⁵, R⁶ and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, C(O)NR^{cl}R^{dl}, and C(O)OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with Cy¹, CN, NO₂, OR^{al}, or NR^{cl}R^{dl}.

In some embodiments, R⁵, R⁶ and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, and NR^{cl}R^{dl}, wherein said C₁₋₃ alkyl is optionally substituted with Cy¹, CN, NO₂, OR^{al}, or NR^{cl}R^{dl}.

In some embodiments, R⁵, R⁶, and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, and NR^{cl}R^{dl}.

In some embodiments, at least one of R⁵, R⁶, and R⁷ is C₁₋₃ alkyl substituted with Cy¹, CN, NO₂, OR^{al}, or NR^{cl}R^{dl}.

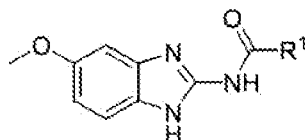
In some embodiments, R⁵, R⁶, and R⁷ are each independently selected from H, halo, CN, OH, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino.

In some embodiments, R⁵, R⁶, and R⁷ are each independently selected from H, halo, CN, OH, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, and C₁₋₃ haloalkoxy.

In some embodiments, R⁵, R⁶ and R⁷ are each H. In some embodiments, R⁵ is not Cy¹. In some embodiments, R⁵ is not C(O)NR^{cl}R^{dl}. In some embodiments, R⁵ is not C(O)OR^{al}.

In some embodiments, R², R³, and R⁴ are each independently selected from H and C₁₋₃ alkyl. In some embodiments, R² is selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl. In some embodiments, R³ is selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl. In some embodiments, R⁴ is selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl. In some embodiments, R² is selected from H and C₁₋₃ alkyl. In some embodiments, R³ is selected from H and C₁₋₃ alkyl. In some embodiments, R⁴ is selected from H and C₁₋₃ alkyl. In some embodiments, R², R³, and R⁴ are each H.

In some embodiments, the compound of Formula (IIa) or Formula (II) has formula:



or a pharmaceutically acceptable salt thereof.

5 In some embodiments, R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C .

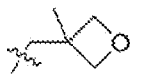
In some embodiments, R^1 is Cy^1 . In some embodiments, R^1 is OR^B . In some embodiments, R^1 is NR^3R^B . In some embodiments, R^1 is NHR^B . In some embodiments, R^1 is CH_2R^B . In some embodiments, R^1 is CH_2R^C . In some embodiments, R^1 is selected from OR^B and NR^3R^B . In some embodiments, R^1 is selected from OR^B and NHR^B .

10 In some embodiments, R^B is selected from H, Cy^1 , C_{1-6} alkyl (e.g., methyl, ethyl, propyl, or *n*-butyl), and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$.

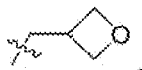
15 In some embodiments, R^B is selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$. In some embodiments, R^B is selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , or $NR^{c1}R^{d1}$. In some embodiments, R^B is selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$.

20 In some embodiments, R^B is H. In some embodiments, R^B is Cy^1 . In some embodiments, R^B is C_{1-6} haloalkyl. In some embodiments, R^B is C_{1-6} alkyl optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$. In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$. In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$. In some embodiments, R^B is selected from Cy^1 and C_{1-6} alkyl substituted with Cy^1 , OR^{a1} , or $NR^{c1}R^{d1}$. In some embodiments, R^B is selected from Cy^1 , C_{1-6} alkyl substituted with Cy^1 , and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$. In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 .

In some embodiments, R^B is a moiety of formula:



In some embodiments, R^B is a moiety of formula:



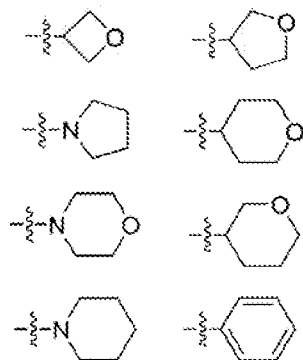
5 In some embodiments, R^B is C_{1-6} alkyl substituted with $NR^{cl}R^{dl}$. In some embodiments, R^B is selected from $CH_2NR^{cl}R^{dl}$, $CH_2CH_2NR^{cl}R^{dl}$, and $CH_2CH_2CH_2NR^{cl}R^{dl}$.

In some embodiments, R^C is selected from CN , NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$. In some embodiments, R^C is
 10 CN or NO_2 . In some embodiments, R^C is OR^{al} or $NR^{cl}R^{dl}$. In some embodiments, R^C is OR^{al} . In some embodiments, R^C is $NR^{cl}R^{dl}$. In some embodiments, R^C is $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$.

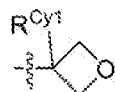
In some embodiments, Cy^1 is selected from C_{6-10} aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents
 15 independently selected from R^{Cyl} . In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} . In some embodiments, Cy^1 is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} . In some embodiments, the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of
 20 which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} .

In some embodiments, R^{Cyl} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy. In some embodiments, R^{Cyl} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy. In some embodiments, R^{Cyl} is C_{1-3} alkyl.

In some embodiments, Cy^1 is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cy1} :



In some embodiments, Cy^1 is a moiety of formula:

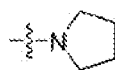


5 In some embodiments, Cy^1 is a moiety of formula:



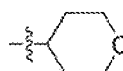
which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



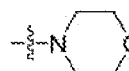
10 which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



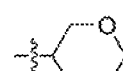
which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



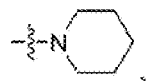
15 which is optionally substituted with R^{Cy1} .

In some embodiments, Cy^1 is a moiety of formula:



which is optionally substituted with R^{Cy1} .

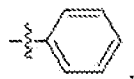
In some embodiments, Cy^1 is a moiety of formula:



which is optionally substituted with R^{Cy1} .

5

In some embodiments, Cy^1 is a moiety of formula:

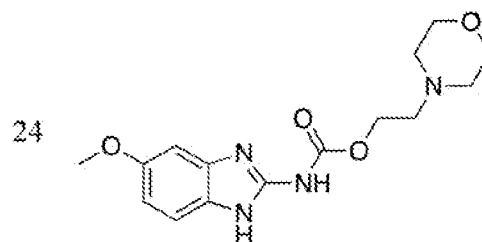
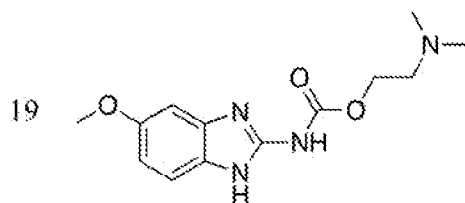
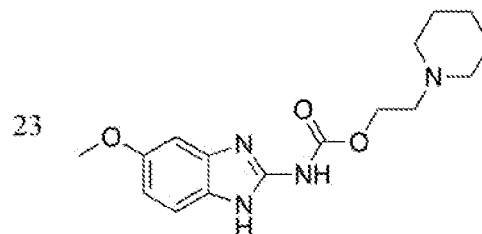
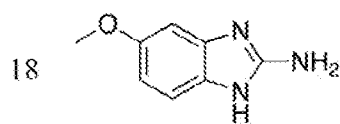
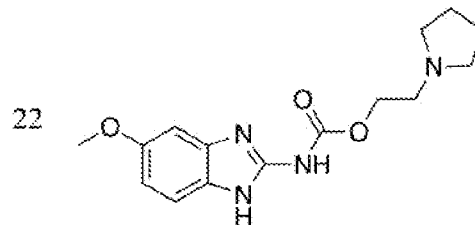
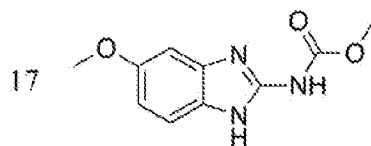


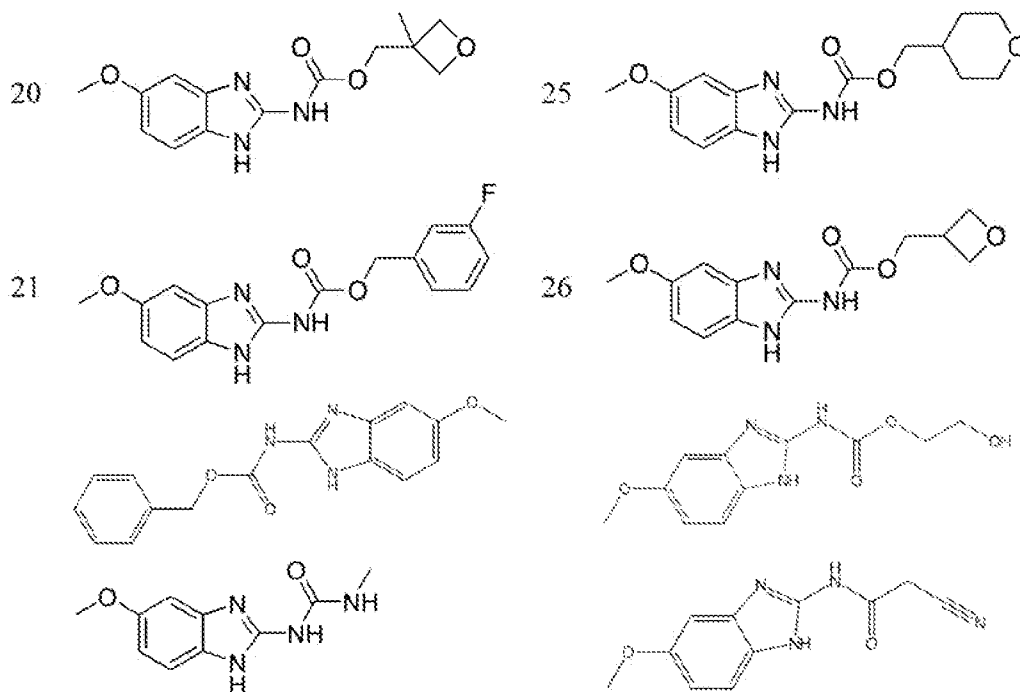
which is optionally substituted with R^{Cy1} .

10

In some embodiments, R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{a1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{b1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{c1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl. In some embodiments, R^{d1} is selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl.

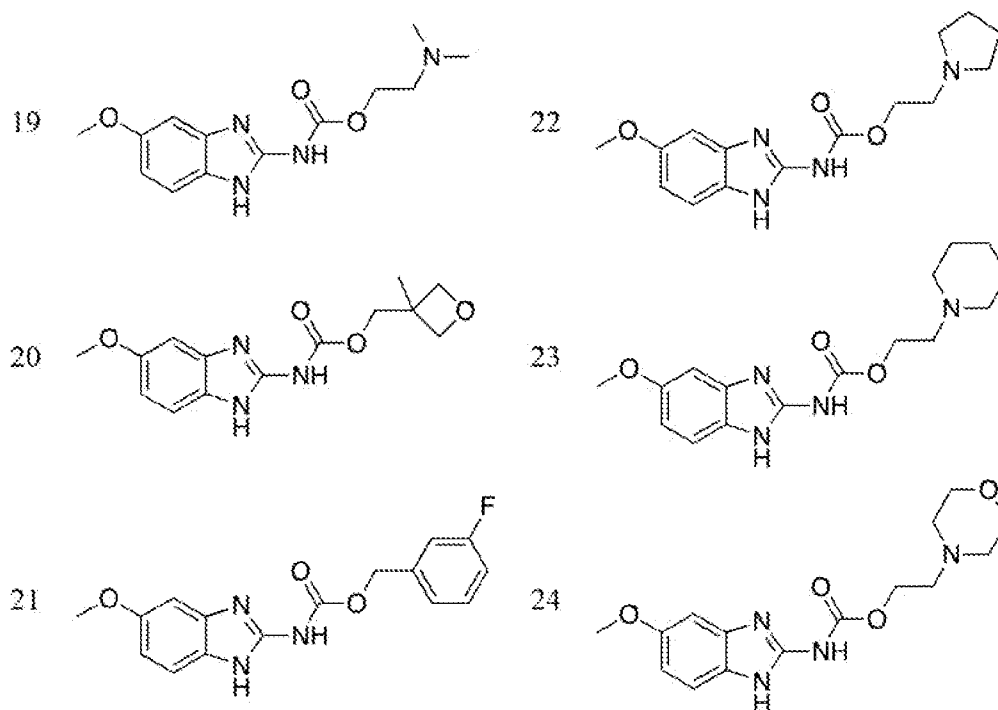
In some embodiments, the compound of Formula (IIa) is selected from any one of the following compounds:

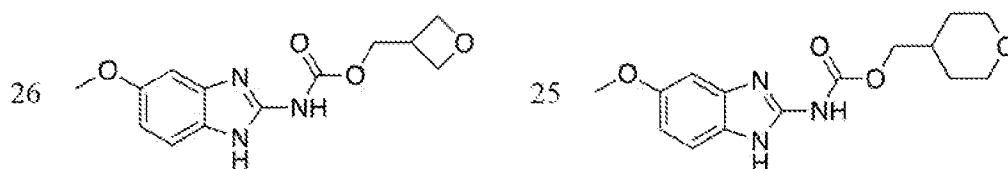




or a pharmaceutically acceptable salt thereof.

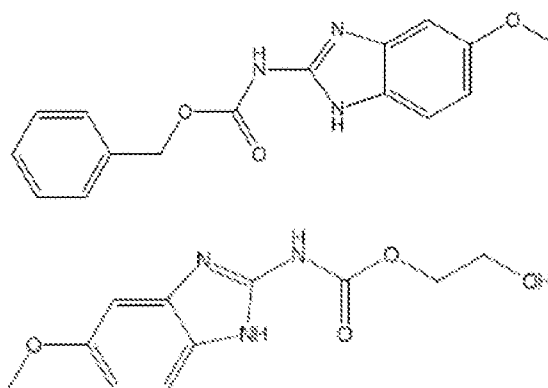
In some embodiments, the compound of Formula (II) is selected from any one of the following compounds:





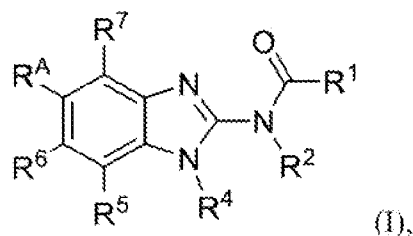
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound of Formula (II) is not any of the following compounds:



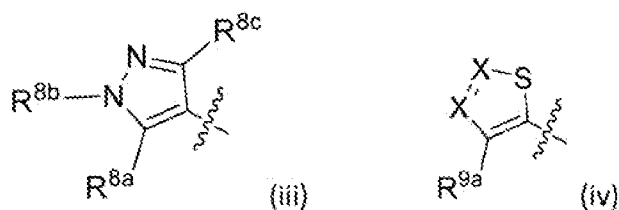
5-membered heteroaryl-containing benzoimidazole compounds

In some embodiments, the present disclosure provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (iii) and (iv):



R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^b is independently selected from Cy^l , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^l , CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^c is selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $S(O)_2NR^{cl}R^{dl}$, and $S(O)_2OR^{al}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

each Cy^l is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} ;

each R^{Cyl} is independently selected from halo, CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^{8a} , R^{8b} , and R^{8c} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 ;

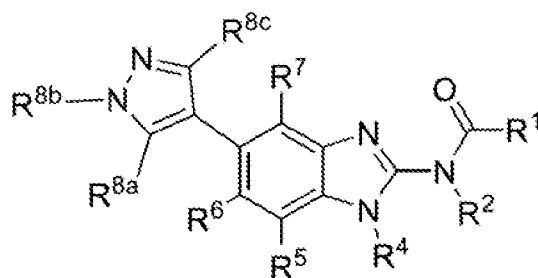
each X is independently selected from N and CR^{9b} , wherein one X is N and the other X is CR^{9b} ;

R^{9a} and R^{9b} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 ;

and

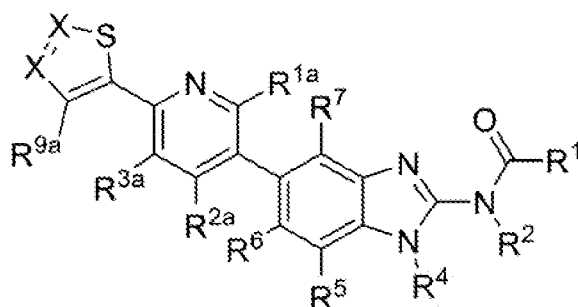
each R^8 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

In some embodiments, the compound has formula:



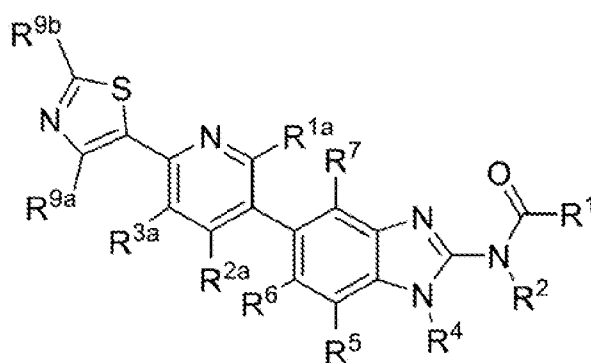
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



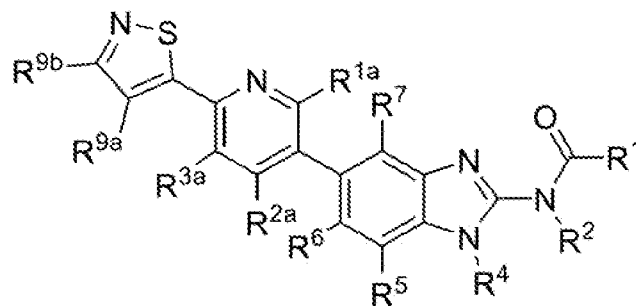
or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound has formula:



or a pharmaceutically acceptable salt thereof.

In some embodiments, R^{8a} , R^{8b} , and R^{8c} are each independently selected from H and C_{1-3} alkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 .

In some embodiments, R^{8a} , R^{8b} , and R^{8c} are each independently selected from H and C_{1-3} alkyl.

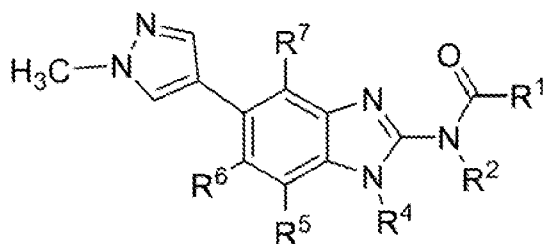
In some embodiments, R^{8a} and R^{8c} are both H and R^{8b} is C_{1-3} alkyl, such as methyl.

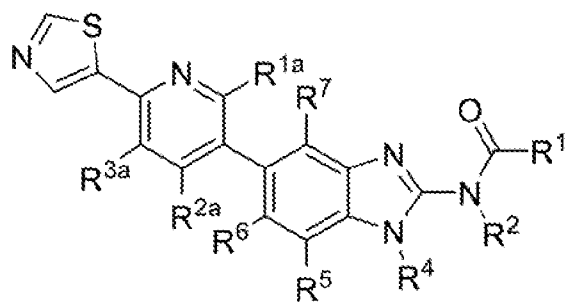
In some embodiments, R^{9a} and R^{9b} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^9 .

In some embodiments, R^{9a} and R^{9b} are each independently selected from H and C_{1-3} alkyl.

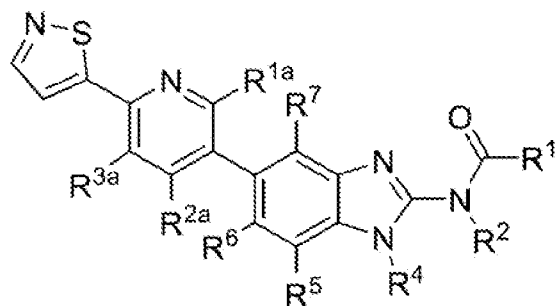
In some embodiments, R^{9a} and R^{9b} are both H.

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:





and



or a pharmaceutically acceptable salt thereof.

5 In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , and $\text{NR}^{\text{c1}}\text{R}^{\text{d1}}$.

In some embodiments, R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $\text{di}(\text{C}_{1-3} \text{ alkyl})\text{amino}$.

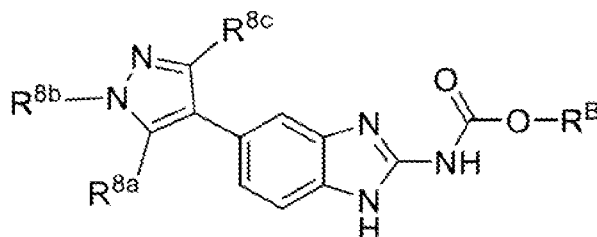
10 In some embodiments, R^1 is selected from OR^{B} and $\text{NR}^3\text{R}^{\text{B}}$.

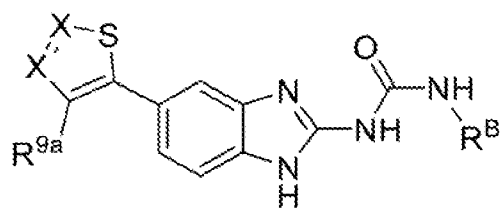
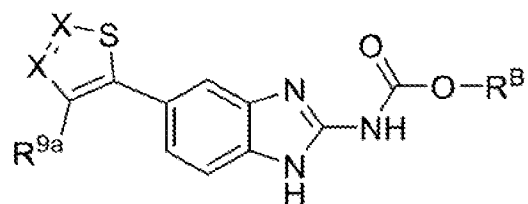
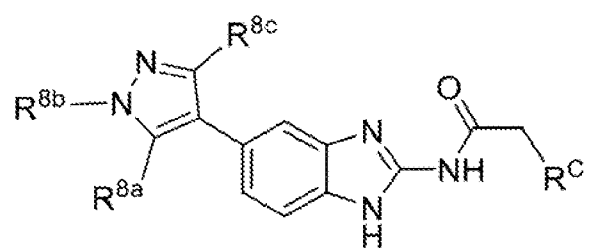
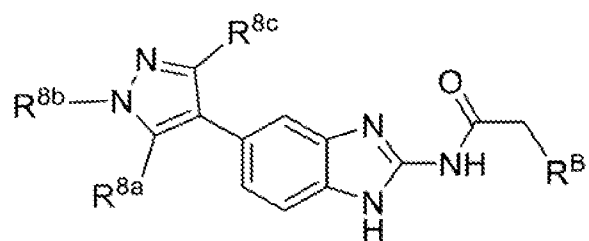
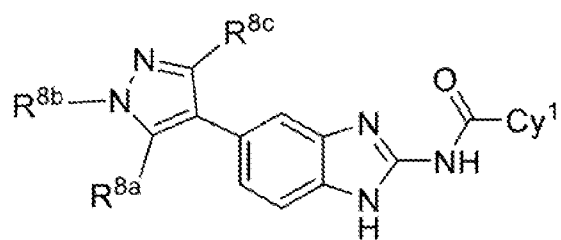
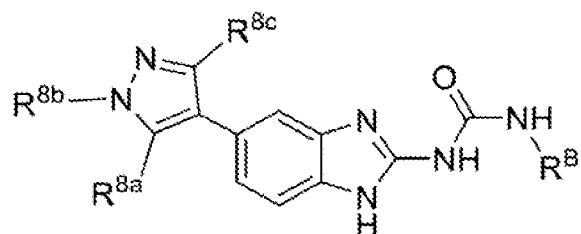
In some embodiments, R^1 is OR^{B} .

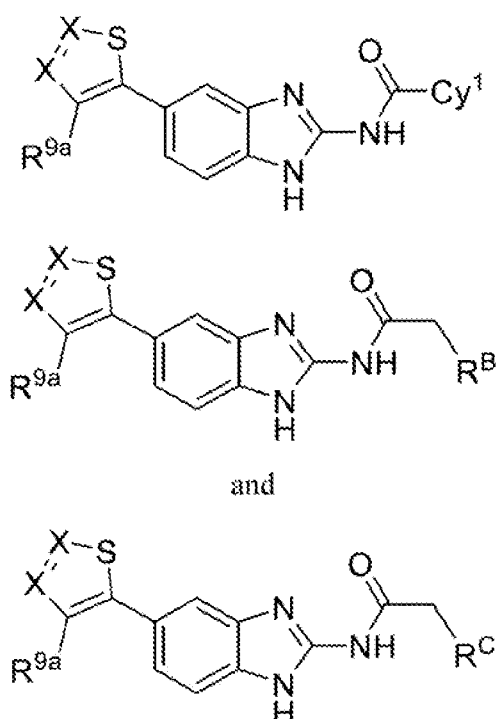
In some embodiments, R^1 is NHR^{B} .

In some embodiments, R^1 is $\text{CH}_2\text{R}^{\text{B}}$.

In some embodiments, the compound of Formula (I) is selected from:







or a pharmaceutically acceptable salt thereof.

In some embodiments, R^B is selected from Cy^1 and C_{1-6} alkyl substituted with Cy^1 , OR^{d1} , or $NR^{c1}R^{d1}$.

In some embodiments, R^B is selected from Cy^1 , C_{1-6} alkyl substituted with Cy^1 ,
 5 and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.

In some embodiments, R^B is Cy^1 .

In some embodiments, R^B is C_{1-6} alkyl substituted with Cy^1 .

In some embodiments, Cy^1 is selected from C_{6-10} aryl and 3-10 membered
 10 heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents
 independently selected from R^{Cy1} .

In some embodiments, Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2
 substituents independently selected from R^{Cy1} .

In some embodiments, Cy^1 is 3-10 membered heterocycloalkyl, optionally
 substituted with 1 or 2 substituents independently selected from R^{Cy1} .

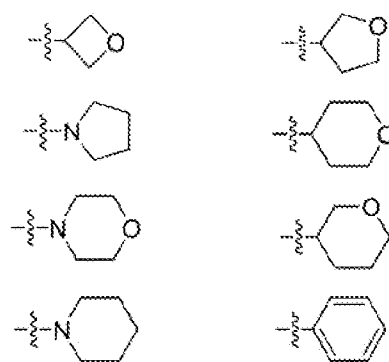
In some embodiments, the 3-10 membered heterocycloalkyl is selected from
 15 oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl,

morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl} .

In some embodiments, R^{Cyl} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.

5 In some embodiments, R^{Cyl} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.

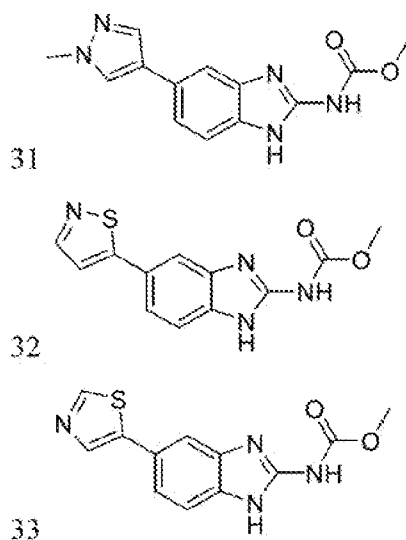
In some embodiments, Cyl is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cyl} :

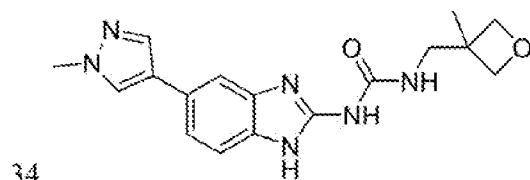


In some embodiments, R^B is C_{1-6} alkyl substituted with $NR^{cl}R^{dl}$.

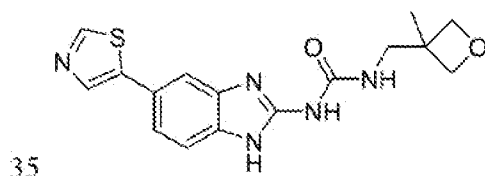
10 In some embodiments, R^B is selected from $CH_2NR^{cl}R^{dl}$, $CH_2CH_2NR^{cl}R^{dl}$, and $CH_2CH_2CH_2NR^{cl}R^{dl}$.

In some embodiments, the compound of Formula (I) is selected from any one of the following compounds:





and



or a pharmaceutically acceptable salt thereof.

6 *Pharmaceutically acceptable salts*

In some embodiments, a salt of a compound of this disclosure is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

10 In some embodiments, acids commonly employed to form pharmaceutically acceptable salts of the compounds of this disclosure include inorganic acids such as hydrogen bisulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid, fumaric acid,
 15 gluconic acid, glucuronic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, *para*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate,
 20 monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate,
 25 phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate,

phenylbutyrate, citrate, lactate, *l*-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

In some embodiments, bases commonly employed to form pharmaceutically acceptable salts of the compounds of this disclosure include hydroxides of alkali metals, including sodium, potassium, and lithium; hydroxides of alkaline earth metals such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, organic amines such as unsubstituted or hydroxyl-substituted mono-, di-, or tri-alkylamines, dicyclohexylamine; tributyl amine; pyridine; N-methyl, N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-OH-(C₁-C₆)-alkylamine), such as N,N-dimethyl-N-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; morpholine; thiomorpholine; piperidine; pyrrolidine; and amino acids such as arginine, lysine, and the like. In some embodiments, the compounds, or pharmaceutically acceptable salts thereof, are substantially isolated.

Methods of use

Protein phosphorylation, catalyzed by protein kinases, is one of the major intracellular mechanisms which cells use to regulate their structural and enzymatic proteins. Reversible phosphorylation/dephosphorylation is involved in essentially all physiological events, and abnormal phosphorylations and kinase activities have been observed under many pathological situations. Among the 518 human kinases, dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is a conserved eukaryotic serine/threonine protein kinase that belongs to the DYRK family (which includes also DYRK1B, DYRK2, DYRK3, and DYRK4). DYRK kinases belong to the CMGC group which includes cyclin-dependent kinases (CDK), mitogen-activated protein kinases (MAP kinases), glycogen synthase kinases (GSK), and Ccd2-like kinases (CLK). Like many members of the CMGC group, the phosphorylation/dephosphorylation of a conserved tyrosine regulates the catalytic activity of the kinase. In DYRK1A, the Tyr321 residue has been described to be autophosphorylated in the activation loop allowing stabilization of the active conformation of DYRK1A. In its mature form, DYRK1A is then

able to phosphorylate various protein targets (involved in various physiological functions) on their serine or threonine residues. DYRK1A is involved in cell cycle and differentiation regulation, β -cell regeneration, T cell regulation, cytoskeleton stabilization, brain neurodevelopment, and synaptic activities. See Nguyen, *Expert Opin. Ther. Pat.*, 2017, 11, 1183-1199, and references discussed therein.

Accordingly, in some embodiments, the present disclosure provides compounds as described herein, or pharmaceutically acceptable salts thereof, that modulate (*e.g.*, inhibit) DYRK1A in a cell. In some embodiments, the present disclosure provides a method of modulating (*e.g.*, inhibiting) DYRK1A in a cell, the method comprising contacting the cell with a compound as described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the method includes contacting the cell *in vitro*, *in vivo*, or *ex vivo*. In some embodiments, the compound modulates DYRK1A selectively (*e.g.*, the compound is at least about 2 $\times$, about 5 $\times$, about 10 $\times$, about 100 $\times$, or about 1,000 $\times$ selective to DYRK1A as compared to DYRK1B, DYRK2, DYRK3, and/or DYRK4, CLK1, CLK2, CLK3, CLK4, or any other kinase or protein target). As discussed herein, DYRK1A is involved in pathology of numerous debilitating conditions (*e.g.*, the disease or condition may include overexpression, abnormal function, persistent activation, *etc.*, of DYRK1A, *e.g.*, in a cell or tissue affected by the disease). See, for example, *J. Med. Chem.*, 2021, 64, 11709–11728, attesting to the fact that DYRK1A regulates the proliferation and differentiation of neuronal progenitor cells during brain development, and as such, inhibitors of DYRK1A are useful in treating Down syndrome and Alzheimer's disease, among other neurodegenerative conditions. Inhibition of DYRK1A is also clinically relevant in treatment of metabolic disorders (*e.g.*, diabetes), myocardial Infarction, inflammatory disorders (*e.g.*, inflammatory bowel disease), cancer (*e.g.*, glioblastoma, leukemia, because DYRK1A's function mediates cancer cell cycle), as well as other conditions. See, *e.g.*, *Int. J. Mol. Sci.*, 2021, 22, 6047 and Young *et al.*, *Circulation Research*, 2022, 130, 1345–1361, among others, all of which are incorporated herein by reference in their entirety.

Accordingly, in some embodiments, the method provides a method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition (*e.g.*, the disease or condition responsive to inhibition of DYRK1A in a cell, a

tissue, and/or an organ affected by the disease or condition), the method comprising administering to a subject (e.g., in need thereof) a therapeutically effective amount of a compound as described herein, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is human. In some embodiments, the subject is male or female. In some embodiments, the subject is from about 18 to about 75 years old, or from 35 to about 75 years old, or from about 45 to about 75 years old, or from about 55 to about 75 years old. In some embodiments, the method includes a step of identifying a mammal in need of treatment. In one example, the step includes identifying a subject diagnosed with the disease or condition (e.g., by diagnosing the subject with the disease or by identifying the subject that was already diagnosed with disease by another person). For example, the diagnosis can be performed by a lab technician, a diagnostician, a treating physician, a primary care physician, or a specialty physician such as an oncologist or a memory care specialist. The diagnosis can be performed on the basis of laboratory tests (e.g., MRI imaging or testing a specimen obtained from the mammal for a disease biomarker), a clinical observation, or both.

In some embodiments, this disclosure provides a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in treating a disease, disorder, or condition. In some embodiments, this disclosure provides a use of a compound as described herein, or a pharmaceutically acceptable salt thereof, for treating a disease, disorder, or condition. In some embodiments, this disclosure provides a compound as described herein, or a pharmaceutically acceptable salt thereof, for use (or a use of a compound as described herein, or a pharmaceutically acceptable salt thereof) in the manufacture of a medicament for treating a disease, disorder, or condition. Example embodiments of diseases, disorders, or conditions are described herein.

Neurodegenerative diseases

In neuropathology, neurodegeneration is often featured by accumulation in brain cells and intracellular spaces of insoluble protein aggregates, such as α -synuclein fibrils, amyloid- β plaques, and tau tangles, as well as by marked neuroinflammation. Together, these pathologies lead to a reduction of brain volume and brain cell number, degeneration of neurons, dysfunction of microglia, and the development of various neurodegenerative

disorders. Numerous scientific publications attest to the well-established principle that modulating (*e.g.*, inhibiting) DYRK1A in cells (*e.g.*, brain cells such as neurons and/or glia) is an art-accepted model that is well-known to reliably correlate with the clinical treatment of neurodegenerative disorders. See, for example, *J. Neurochem*, 2015, 133, 440–451, which is incorporated herein by reference in its entirety, and which shows that DYRK1A is implicated in the generation of Tau and amyloid aggregates and related pathologies and is associated with onset of, *e.g.*, Down Syndrome, Alzheimer's disease, and other synucleinopathies, amyloidopathies, and/or tauopathies. See also *Front. Behav. Neurosci.*, 10, 104 (discussing treatment of, *e.g.*, dementia, Pick's disease, Parkinson's, Phelan-McDermid syndrome, autism, and CDKL5 deficiency disorder, among others).

Accordingly, in some embodiments, the disease or disorder treatable by a compound of this disclosure is a neurodegenerative disorder. Suitable examples of neurodegenerative disorders include synucleinopathies, amyloidopathies, and/or tauopathies. For example, synucleinopathies include dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, and Bradbury-Eggleston syndrome. Suitable examples of amyloidopathies include premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), and dementia associated with HD. Suitable examples of tauopathies include Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astrogliaopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.

Metabolic diseases

Numerous scientific publications attest to the well-established principle that modulating (*e.g.*, inhibiting) DYRK1A in cells (*e.g.*, insulin-producing β -cells) is an

art-accepted model that is well-known to reliably correlate with the clinical treatment of metabolic disorders. See, for example, *J. Med. Chem.*, 2021, 64, 2901–2922, and *J. Med. Chem.*, 2020, 63, 2958–2973, which are incorporated herein by reference in their entirety, and which show that inhibition of DYRK1A promotes regeneration of functional insulin-producing human β -cells in people with diabetes (*e.g.*, type 1 diabetes, type 2 diabetes) and/or hyperglycerimia. See also *Int. J. Mol. Sci.*, 2021, 22, 6047 (discussing treatment of, *e.g.*, abnormal folate/methionine metabolism-related disorders). Accordingly, in some embodiments, the disease or disorder treatable by a compound of this disclosure is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimia, and hypermethioninemia. Additional examples of metabolic disorders include familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.

Autoimmune and inflammatory conditions

Numerous scientific publications attest to the well-established principle that modulating (*e.g.*, inhibiting) DYRK1A in immune cells (*e.g.*, T-cells) is an art-accepted model that is well-known to reliably correlate with the clinical treatment of inflammatory and autoimmune diseases (*e.g.*, systemic autoimmunity, mucosal inflammation, osteoarthritis). See, for example, *eLife*, 2015, 4, e05920, which is incorporated herein by reference in its entirety, and which shows that inhibition of DYRK1A enhances T_{reg} differentiation and impairs Th17 differentiation. An inflammatory disease can be either an acute or chronic inflammatory condition and can result from infections or non-infectious causes.

Accordingly, in some embodiments, the disease or disorder treatable by a compound of this disclosure is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease. Additional examples of inflammatory disorders include atherosclerosis, arteriosclerosis, polymyalgia

rheumatica (PMR), gouty arthritis, degenerative arthritis, tendonitis, bursitis, cystic
 fibrosis, arthroseitis, Sjogren's syndrome, giant cell arteritis, progressive systemic
 sclerosis (scleroderma), ankylosing spondylitis, polymyositis, dermatomyositis,
 pemphigus, pemphigoid, myasthenia gravis, sclerosing cholangitis, Crohn's disease,
 5 ulcerative colitis, pernicious anemia, inflammatory dermatoses, usual interstitial
 pneumonitis (UIP), asbestosis, silicosis, bronchiectasis, berylliosis, talcosis,
 pneumoconiosis, sarcoidosis, desquamative interstitial pneumonia, lymphoid interstitial
 pneumonia, giant cell interstitial pneumonia, cellular interstitial pneumonia, extrinsic
 allergic alveolitis, Wegener's granulomatosis, inflammatory dermatoses, delayed-type
 10 hypersensitivity reactions (*e.g.*, poison ivy dermatitis), pneumonia, respiratory tract
 inflammation, Adult Respiratory Distress Syndrome (ARDS), encephalitis, immediate
 hypersensitivity reactions, asthma, hayfever, allergies, acute anaphylaxis, rheumatic
 fever, glomerulonephritis, pyelonephritis, cellulitis, cystitis, chronic cholecystitis,
 ischemia (ischemic injury), reperfusion injury, allograft rejection, host-versus-graft
 15 rejection, appendicitis, arteritis, blepharitis, bronchiolitis, bronchitis, cervicitis,
 cholangitis, chorioamnionitis, conjunctivitis, dacryoadenitis, dermatomyositis,
 endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis,
 fibrositis, gastritis, gastroenteritis, gingivitis, ileitis, iritis, laryngitis, myelitis,
 myocarditis, nephritis, omphalitis, oophoritis, orchitis, osteitis, otitis, pancreatitis,
 20 parotitis, pericarditis, pharyngitis, pleuritis, phlebitis, pneumonitis, proctitis, prostatitis,
 rhinitis, salpingitis, sinusitis, stomatitis, synovitis, testitis, tonsillitis, urethritis,
 urocystitis, uveitis, vaginitis, vasculitis, vulvitis, vulvovaginitis, angitis, chronic
 bronchitis, osteomyelitis, optic neuritis, temporal arteritis, transverse myelitis, necrotizing
 fasciitis, and necrotizing enterocolitis.

25 Accordingly, in some embodiments, the disease or disorder treatable by a
 compound of this disclosure is an autoimmune disease selected from autoimmune
 thyroiditis, glomerulonephritis, necrotizing vasculitis, lymphadenitis, periarteritis nodosa,
 systemic lupus erythematosus, systemic sclerosis, dermatomyositis/polymyositis, anti-
 phospholipid antibody syndrome, scleroderma, pemphigus vulgaris, uveitis, Reiter's
 30 syndrome, ankylosing spondylitis, Lyme disease, Guillain-Barre syndrome, and
 cardiomyopathy.

Cancer

Numerous scientific publications attest to the well-established principle that modulating (*e.g.*, inhibiting) DYRK1A in cells (*e.g.*, cancer cells) is an art-accepted model that is well-known to reliably correlate with the clinical treatment of various cancer types. See, *e.g.*, PLoS ONE, 8, 11, e81803, which is incorporated herein by reference in its entirety, among many other publications discussing DYRK1A's involvement in the pathology of cancer, such as brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer. Additional exemplary cancers include acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (*e.g.*, cholangiocarcinoma), bladder cancer, breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer), brain cancer (*e.g.*, meningioma, glioblastomas, glioma (*e.g.*, astrocytoma, oligodendroglioma), medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (*e.g.*, cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (*e.g.*, colon cancer, rectal cancer, colorectal adenocarcinoma), connective tissue cancer, epithelial carcinoma, ependymoma, endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma), esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma), Ewing's sarcoma, ocular cancer (*e.g.*, intraocular melanoma, retinoblastoma), familial hypereosinophilia, gall bladder cancer, gastric cancer (*e.g.*, stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), germ cell cancer, head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease, hemangioblastoma, hypopharynx cancer, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma), liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma),

lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung), leiomyosarcoma (LMS), mastocytosis (*e.g.*, systemic mastocytosis), muscle cancer, myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (*e.g.*, polycythemia vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *aka.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor), osteosarcoma (*e.g.*, bone cancer), ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), islet cell tumors), penile cancer (*e.g.*, Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), plasma cell neoplasia, paraneoplastic syndromes, intraepithelial neoplasms, prostate cancer (*e.g.*, prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (*e.g.*, appendix cancer), soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), eposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, small intestine cancer, sweat gland carcinoma, synovioma, testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma), thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer, and vulvar cancer (*e.g.*, Paget's disease of the vulva).

Compositions, formulations, and routes of administration

The present application also provides pharmaceutical compositions comprising an effective amount of a compound of the present disclosure disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The pharmaceutical composition may also comprise any one of the additional therapeutic

agents described herein. In certain embodiments, the application also provides pharmaceutical compositions and dosage forms comprising any one the additional therapeutic agents described herein. The carrier(s) are "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a
5 pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of the present application include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human
10 serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate,
15 polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol, and wool fat.

The compositions or dosage forms may contain any one of the compounds and therapeutic agents described herein in the range of 0.005% to 100% with the balance made up from the suitable pharmaceutically acceptable excipients. The contemplated
20 compositions may contain 0.001%-100% of any one of the compounds and therapeutic agents provided herein, in one embodiment 0.1-95%, in another embodiment 75-85%, in a further embodiment 20-80%, wherein the balance may be made up of any pharmaceutically acceptable excipient described herein, or any combination of these excipients.

Routes of administration and dosage forms

The pharmaceutical compositions of the present application include those suitable for any acceptable route of administration. Acceptable routes of administration include, but are not limited to, buccal, cutaneous, endocervical, endosinusal, endotracheal, enteral, epidural, interstitial, intra-abdominal, intra-arterial, intrabronchial, intrabursal,
30 intracerebral, intracisternal, intracoronary, intradermal, intraductal, intraduodenal, intradural, intraepidermal, intraesophageal, intragastric, intragingival, intraileal,

intralymphatic, intramedullary, intrameningeal, intramuscular, intranasal, intraovarian, intraperitoneal, intraprostatic, intrapulmonary, intrasinal, intraspinal, intrasynovial, intratesticular, intrathecal, intratubular, intratumoral, intrauterine, intravascular, intravenous, nasal, nasogastric, oral, parenteral, percutaneous, peridural, rectal, respiratory (inhalation), subcutaneous, sublingual, submucosal, topical, transdermal, transmucosal, transtracheal, ureteral, urethral and vaginal.

Compositions and formulations described herein may conveniently be presented in a unit dosage form, *e.g.*, tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. *See*, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000). Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In some embodiments, any one of the compounds and therapeutic agents disclosed herein are administered orally. Compositions of the present application suitable for oral administration may be presented as discrete units such as capsules, sachets, granules or tablets each containing a predetermined amount (*e.g.*, effective amount) of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, *etc.* Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption. In the case of tablets for oral use, carriers that are commonly used include lactose, sucrose, glucose, mannitol, and silicic acid and starches. Other acceptable excipients may include: *a*) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, *b*) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, *c*) humectants such as glycerol, *d*) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, *e*) solution retarding agents such as

paraffin, *f*) absorption accelerators such as quaternary ammonium compounds, *g*) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, *h*) absorbents such as kaolin and bentonite clay, and *i*) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added. Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions or infusion solutions which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, saline (*e.g.*, 0.9% saline solution) or 5% dextrose solution, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets. The injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are

natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of the present application may be administered
5 in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of the present application with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax, and polyethylene glycols.

10 The pharmaceutical compositions of the present application may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents
15 known in the art. *See*, for example, U.S. Patent No. 6,803,031. Additional formulations and methods for intranasal administration are found in Ilium, L., *J Pharm Pharmacol*, 56:3-17, 2004 and Ilium, L., *Eur J Pharm Sci* 11:1-18, 2000.

The topical compositions of the present disclosure can be prepared and used in the form of an aerosol spray, cream, emulsion, solid, liquid, dispersion, foam, oil, gel,
20 hydrogel, lotion, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, towelette, soap, or other forms commonly employed in the art of topical administration and/or cosmetic and skin care formulation. The topical compositions can be in an emulsion form. Topical administration of the pharmaceutical compositions of the present application is especially useful when the desired treatment involves areas or organs
25 readily accessible by topical application. In some embodiments, the topical composition comprises a combination of any one of the compounds and therapeutic agents disclosed herein, and one or more additional ingredients, carriers, excipients, or diluents including, but not limited to, absorbents, anti-irritants, anti-acne agents, preservatives, antioxidants, coloring agents/pigments, emollients (moisturizers), emulsifiers, film-forming/holding
30 agents, fragrances, leave-on exfoliants, prescription drugs, preservatives, scrub agents,

silicones, skin-identical/repairing agents, slip agents, sunscreen actives, surfactants/detergent cleansing agents, penetration enhancers, and thickeners.

Dosages and regimens

In the pharmaceutical compositions of the present application, a compound of the present disclosure is present in an effective amount (*e.g.*, a therapeutically effective amount). Effective doses may vary, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

In some embodiments, an effective amount of the compound can range, for example, from about 0.001 mg/kg to about 500 mg/kg (*e.g.*, from about 0.001 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 200 mg/kg; from about 0.01 mg/kg to about 150 mg/kg; from about 0.01 mg/kg to about 100 mg/kg; from about 0.01 mg/kg to about 50 mg/kg; from about 0.01 mg/kg to about 10 mg/kg; from about 0.01 mg/kg to about 5 mg/kg; from about 0.01 mg/kg to about 1 mg/kg; from about 0.01 mg/kg to about 0.5 mg/kg; from about 0.01 mg/kg to about 0.1 mg/kg; from about 0.1 mg/kg to about 200 mg/kg; from about 0.1 mg/kg to about 150 mg/kg; from about 0.1 mg/kg to about 100 mg/kg; from about 0.1 mg/kg to about 50 mg/kg; from about 0.1 mg/kg to about 10 mg/kg; from about 0.1 mg/kg to about 5 mg/kg; from about 0.1 mg/kg to about 2 mg/kg; from about 0.1 mg/kg to about 1 mg/kg; or from about 0.1 mg/kg to about 0.5 mg/kg). In some embodiments, an effective amount of a compound is about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, or about 5 mg/kg. The foregoing dosages can be administered on a daily basis (*e.g.*, as a single dose or as two or more divided doses, *e.g.*, once daily, twice daily, thrice daily) or non-daily basis (*e.g.*, every other day, every two days, every three days, once weekly, twice weekly, once every two weeks, once a month).

Selected definitions

As used herein, the term “about” means “approximately” (*e.g.*, plus or minus approximately 10% of the indicated value).

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such

groups and ranges. For example, the term “C₁₋₆ alkyl” is specifically intended to individually disclose methyl, ethyl, C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl.

At various places in the present specification various aryl, heteroaryl, cycloalkyl, and heterocycloalkyl rings are described. Unless otherwise specified, these rings can be attached to the rest of the molecule at any ring member as permitted by valency. For example, the term “a pyridine ring” or “pyridinyl” may refer to a pyridin-2-yl, pyridin-3-yl, or pyridin-4-yl ring.

It is further appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

The term “aromatic” refers to a carbocycle or heterocycle having one or more polyunsaturated rings having aromatic character (*i.e.*, having $(4n + 2)$ delocalized π (pi) electrons where n is an integer).

The term “ n -membered” where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n . For example, piperidinyl is an example of a 6-membered heterocycloalkyl ring, pyrazolyl is an example of a 5-membered heteroaryl ring, pyridyl is an example of a 6-membered heteroaryl ring, and 1,2,3,4-tetrahydro-naphthalene is an example of a 10-membered cycloalkyl group.

As used herein, the phrase “optionally substituted” means unsubstituted or substituted. The substituents are independently selected, and substitution may be at any chemically accessible position. As used herein, the term “substituted” means that a hydrogen atom is removed and replaced by a substituent. A single divalent substituent, *e.g.*, oxo, can replace two hydrogen atoms. It is to be understood that substitution at a given atom is limited by valency.

Throughout the definitions, the term “C _{n - m} ” indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C₁₋₄, C₁₋₆, and the like.

As used herein, the term “C_{n-m} alkyl”, employed alone or in combination with other terms, refers to a saturated hydrocarbon group that may be straight-chain or branched, having n to m carbons. Examples of alkyl moieties include, but are not limited to, chemical groups such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *tert*-butyl, isobutyl, *sec*-butyl; higher homologs such as 2-methyl-1-butyl, *n*-pentyl, 3-pentyl, *n*-hexyl, 1,2,2-trimethylpropyl, and the like. In some embodiments, the alkyl group contains from 1 to 6 carbon atoms, from 1 to 4 carbon atoms, from 1 to 3 carbon atoms, or 1 to 2 carbon atoms.

As used herein, the term “C_{n-m} haloalkyl”, employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen atoms which may be the same or different, where “s” is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon atoms. In some embodiments, the haloalkyl group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “C_{n-m} alkoxy”, employed alone or in combination with other terms, refers to a group of formula -O-alkyl, wherein the alkyl group has n to m carbons. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), butoxy (e.g., *n*-butoxy and *tert*-butoxy), and the like. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, “C_{n-m} haloalkoxy” refers to a group of formula -O-haloalkyl having n to m carbon atoms. An example haloalkoxy group is OCF₃. In some embodiments, the haloalkoxy group is fluorinated only. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

As used herein, the term “amino” refers to a group of formula -NH₂.

As used herein, the term “C_{n-m} alkylamino” refers to a group of formula -NH(alkyl), wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkylamino groups include, but are not limited to, N-methylamino, N-ethylamino, N-propylamino (e.g., N-(*n*-propyl)amino and N-isopropylamino), N-butylamino (e.g., N-(*n*-butyl)amino and N-(*tert*-butyl)amino), and the like.

As used herein, the term “di(C_{n-m}-alkyl)amino” refers to a group of formula -N(alkyl)₂, wherein the two alkyl groups each has, independently, n to m carbon atoms. In some embodiments, each alkyl group independently has 1 to 6, 1 to 4, or 1 to 3 carbon atoms.

5 As used herein, the term “C_{n-m} alkoxy carbonyl” refers to a group of formula -C(O)O-alkyl, wherein the alkyl group has n to m carbon atoms. In some embodiments, the alkyl group has 1 to 6, 1 to 4, or 1 to 3 carbon atoms. Examples of alkoxy carbonyl groups include, but are not limited to, methoxy carbonyl, ethoxy carbonyl, propoxy carbonyl (e.g., *n*-propoxy carbonyl and isopropoxy carbonyl), butoxy carbonyl
10 (e.g., *n*-butoxy carbonyl and *tert*-butoxy carbonyl), and the like.

As used herein, the term “carboxy” refers to a -C(O)OH group.

As used herein, “halo” refers to F, Cl, Br, or I. In some embodiments, a halo is F, Cl, or Br.

As used herein, the term “aryl,” employed alone or in combination with other
15 terms, refers to an aromatic hydrocarbon group, which may be monocyclic or polycyclic (e.g., having 2, 3 or 4 fused rings). The term “C_{n-m} aryl” refers to an aryl group having from n to m ring carbon atoms. Aryl groups include, e.g., phenyl, naphthyl, anthracenyl, phenanthrenyl, indanyl, indenyl, and the like. In some embodiments, aryl groups have from 6 to 10 carbon atoms. In some embodiments, the aryl group is phenyl or naphthyl.

20 As used herein, “cycloalkyl” refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and/or alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups and spirocycles. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by 1 or 2 independently selected oxo or sulfide groups (e.g., C(O) or C(S)). Also included in the definition of cycloalkyl are
25 moieties that have one or more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons
30 (C₃₋₁₀). In some embodiments, the cycloalkyl is a C₃₋₁₀ monocyclic or bicyclic cycloalkyl. In some embodiments, the cycloalkyl is a C₃₋₇ monocyclic cycloalkyl.

Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbornyl, norpinyl, norcarnyl, adamantyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

As used herein, "heteroaryl" refers to a monocyclic or polycyclic aromatic heterocycle having at least one heteroatom ring member selected from sulfur, oxygen, and nitrogen. In some embodiments, the heteroaryl ring has 1, 2, 3, or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, any ring-forming N in a heteroaryl moiety can be an N-oxide. In some embodiments, the heteroaryl is a 5-10 membered monocyclic or bicyclic heteroaryl having 1, 2, 3 or 4 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a 5-6 monocyclic heteroaryl having 1 or 2 heteroatom ring members independently selected from nitrogen, sulfur and oxygen. In some embodiments, the heteroaryl is a five-membered or six-membered heteroaryl ring. A five-membered heteroaryl ring is a heteroaryl with a ring having five ring atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary five-membered ring heteroaryls are thienyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, 1,2,3-triazolyl, tetrazolyl, 1,2,3-thiadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-triazolyl, 1,2,4-thiadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-triazolyl, 1,3,4-thiadiazolyl, and 1,3,4-oxadiazolyl. A six-membered heteroaryl ring is a heteroaryl with a ring having six ring atoms wherein one or more (*e.g.*, 1, 2, or 3) ring atoms are independently selected from N, O, and S. Exemplary six-membered ring heteroaryls are pyridyl, pyrazinyl, pyrimidinyl, triazinyl and pyridazinyl.

As used herein, "heterocycloalkyl" refers to non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N, or S. Included in heterocycloalkyl are monocyclic 4-, 5-, 6-, 7-, 8-, 9- or 10-membered heterocycloalkyl groups. Heterocycloalkyl groups can also include spirocycles. Example heterocycloalkyl groups include pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranyl, tetrahydropuran, oxetanyl, azetidiny, morpholino, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidiny, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl,

benzazapene, and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by 1 or 2 independently selected oxo or sulfido groups (*e.g.*, C(O), S(O), C(S), or S(O)₂, *etc.*). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some
5 embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. Also included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings fused (*i.e.*, having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of piperidine, morpholine, azepine, *etc.* A heterocycloalkyl group containing a
10 fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl having 1 or 2 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members. In some embodiments, the heterocycloalkyl is a monocyclic or bicyclic 4-10 membered
15 heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members.

At certain places, the definitions or embodiments refer to specific rings (*e.g.*, an azetidine ring, a pyridine ring, *etc.*). Unless otherwise indicated, these rings can be attached to any ring member provided that the valency of the atom is not exceeded. For
20 example, an azetidine ring may be attached at any position of the ring, whereas a pyridin-3-yl ring is attached at the 3-position.

As used herein, the term “oxo” refers to an oxygen atom as a divalent substituent, forming a carbonyl group when attached to a carbon (*e.g.*, C=O), or attached to a heteroatom forming a sulfoxide or sulfone group.

25 The term “compound” as used herein is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified.

The compounds described herein can be asymmetric (*e.g.*, having one or more
30 stereocenters). All stereoisomers, such as enantiomers and diastereomers, are intended unless otherwise indicated. Compounds of the present invention that contain

asymmetrically substituted carbon atoms can be isolated in optically active or racemic forms. Methods on how to prepare optically active forms from optically inactive starting materials are known in the art, such as by resolution of racemic mixtures or by stereoselective synthesis. Many geometric isomers of olefins, C=N double bonds, N=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. In some embodiments, the compound has the (*R*)-configuration. In some embodiments, the compound has the (*S*)-configuration.

Compounds provided herein also include tautomeric forms. Tautomeric forms result from the swapping of a single bond with an adjacent double bond together with the concomitant migration of a proton. Tautomeric forms include prototropic tautomers which are isomeric protonation states having the same empirical formula and total charge. Example prototropic tautomers include ketone – enol pairs, amide - imidic acid pairs, lactam – lactim pairs, enamine – imine pairs, and annular forms where a proton can occupy two or more positions of a heterocyclic system, for example, 1H- and 3H-imidazole, 1H-, 2H- and 4H- 1,2,4-triazole, 1H- and 2H- isoindole, and 1H- and 2H-pyrazole. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution.

As used herein, the term “cell” is meant to refer to a cell that is *in vitro*, *ex vivo* or *in vivo*. In some embodiments, an *ex vivo* cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

As used herein, the term “contacting” refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, “contacting” the DYRK1A with a compound of the invention includes the administration of a compound of the present invention to an individual or patient, such as a human, having DYRK1A, as well as, for example, introducing a compound of the invention into a sample containing a cellular or purified preparation containing the DYRK1A.

As used herein, the term “individual”, “patient”, or “subject” used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

5 As used herein, the phrase “effective amount” or “therapeutically effective amount” refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

As used herein the term “treating” or “treatment” refers to 1) inhibiting the
10 disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology), or 2) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the
15 disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

As used herein, the term “preventing” or “prevention” of a disease, condition or disorder refers to decreasing the risk of occurrence of the disease, condition or disorder in a subject or group of subjects (e.g., a subject or group of subjects predisposed to or susceptible to the disease, condition or disorder). In some embodiments, preventing a
20 disease, condition or disorder refers to decreasing the possibility of acquiring the disease, condition or disorder and/or its associated symptoms. In some embodiments, preventing a disease, condition or disorder refers to completely or almost completely stopping the disease, condition or disorder from occurring.

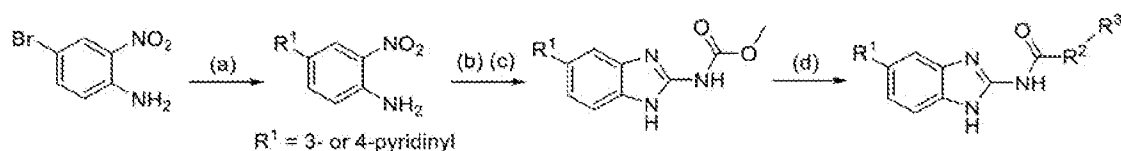
EXAMPLES

25 Materials and methods

General. All reagents and solvents were purchased from commercially available sources and used without further purification. All reactions were carried out according to the indicated procedures and conditions. Flash Chromatography was performed on an Interchim PuriFlash 430 with cartridges filled with Silica gel 15 μ m (PF-50SIHC).
30 Agilent 1200 was used for Prep LC purification with Thermo Scientific C18 column,

particle size 5 μm , dimensions 250 mm $\times$ 21.2 mm. Reactions were monitored by HPLC analysis and/or thin-layer chromatography (TLC) on silica-coated glass with the indicated eluent. The compounds were visualized by UV light (254 nm). LC/MS analysis was performed on an Agilent 1260 HPLC/UV (λ = 220 nm and/or 254 nm) system coupled with Agilent 6130 Single Quadrupole Mass Spectrometer. High-resolution mass spectrometry (HRMS) was performed on an Agilent 6530 QTOF Mass Spectrometer with 1290 Infinity Binary LC (mass accuracy 1 ppm with internal calibrant) in the positive mode that utilizes electrospray ionization (ESI). Compounds for analysis were dissolved in 100% DMSO and separated on C₁₈ cartridge (particle size 2.6 μm , dimensions: 100 mm $\times$ 2.1 mm, 0.3 mL/min flow rate, 5 μL injection volume) using acetonitrile/water mobile phase with 0.1% formic acid as a modifier. The gradient started at 0% acetonitrile, held for 1 min, and linearly increased to 97% acetonitrile over 10 min, with 2 min hold at 97% acetonitrile and subsequent re-equilibration to the original conditions in a total of 17 min. All compounds reported were obtained in a purity of > 95% at 254 nm wavelength. Nuclear magnetic resonance (¹H NMR) spectra were recorded on a Varian Mercury plus NMR spectrometer operating at 400 MHz frequencies for ¹H, using a 5 mm ASW PFG probe capable of detecting ¹H and ¹³C nuclei. The proton chemical shifts (ppm) were referenced to the DMSO-*d*₆ residual solvent peaks and indicated in parts per million (ppm). The splitting patterns are abbreviated as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), quin (quintet), sxt (sextet), br (broad), and m (multiplet).

Example 1 – preparation of exemplified pyridine-based compounds



Scheme 1: reagents and conditions: (a) 4-pyridinylboronic acid, PdCl₂(dppf), Na₂CO₃, dioxane:H₂O = 5:2, 8 h, 95 °C; (b) H₂, 10% Pd/C (wet), MeOH, 8 h, rt; (c) 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea, MeOH, MW, 80 W, 5 min $\times$ 10; (d) R³-R²-H (R²: O, NH, N(C₁₋₃ alkyl)), anhydrous pyridine, o/n, 95 °C.

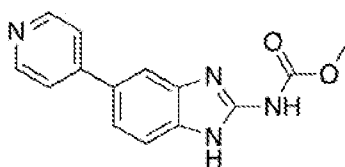
Procedure For The Synthesis of Methyl Carbamates

Step b: to 2-nitro-4-aniline intermediate (1.0 eq.) in MeOH (0.1 M), Pd/C (1.0 equiv. 10 wt.% Pd/C, pre-wetted) was added and then a H₂-filled balloon attached to a 3-way valve was attached. The flask's atmosphere was repeatedly evacuated under vacuum and back-filled with H₂. The reaction was stirred for 24 h then filtered through Celite, rinsing with additional MeOH. The solvent was removed under reduced pressure and the product was placed under high vacuum to yield benzene-1,2-diamine intermediates as an off-white solid (quantitative yield) for the next step without further purification.

Step c: benzene-1,2-diamine compound (1.0 eq.) was dissolved in MeOH (0.5 M) and 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (1.1 eq.) was added. The mixture was exposed to microwave irradiation (80 W) for 5 min, 10 times (5 min cooling interval). Once the reaction was completed (monitored by TLC), the reaction mixture was concentrated under reduced pressure and residual oil was triturated with MeCN three times, filtered, and dried *in vacuo* to give the desired compound.

Step d: in a flame dried glassware, a methyl carbamate (1.0 eq.) was dissolved in anhydrous pyridine (0.2 M). To this solution, corresponding alcohol (10 eq.) was added as indicated in Scheme 1 and the reaction proceeded at 95 °C for o/n under argon. Once the reaction was completed (monitored by HPLC), the solvent was removed *in vacuo* utilizing toluene as an azeotrope. The residual oil was purified by silica gel chromatography with 10% MeOH in DCM and dried *in vacuo* to give the desired compound. Compound was further purified by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid as the mobile phase. Collected fractions were dried in a Speed-Vac concentrator to yield >95 % purity.

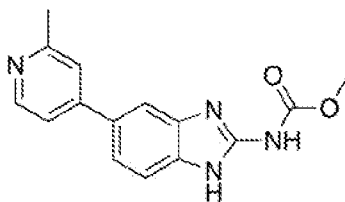
Methyl (5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 4)



Product was obtained as an off-white solid; $R_f = 0.51$ (10% MeOH/DCM); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 7.9$ min; ¹H NMR (400 MHz, 25 °C, DMSO-*d*₆) δ 11.22 (br s, 2H), 8.6-8.45 (m, 3H), 7.8-

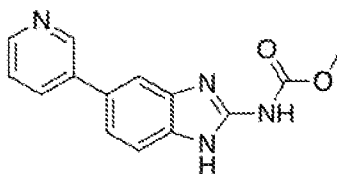
7.65 (m, 3H), 7.54 (t, 2H, $J = 1.4$ Hz), 3.8 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{14}H_{13}N_4O_2$ 269.1033; found 269.1018.

Methyl (5-(2-methylpyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 2)



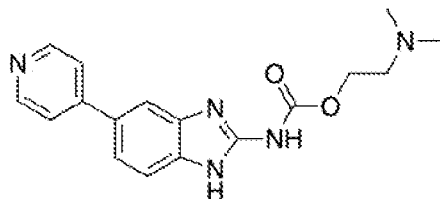
Product was obtained using general methods (scheme 1) as an off-white solid; $R_f = 0.53$ (10% MeOH/DCM); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 8.4$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.71 (s, 2H), 8.44 (d, 1H, $J = 5.3$ Hz), 7.78 (d, 1H, $J = 1.3$ Hz), 7.55 (s, 1H), 7.50 (s, 2H), 7.47 (dd, 1H, $J = 5.3, 1.8$ Hz), 3.77 (s, 3H), 2.53 (s, 3H); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{15}H_{14}N_4O_2$ 283.1190; found 283.1185.

Methyl (5-(pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 3)



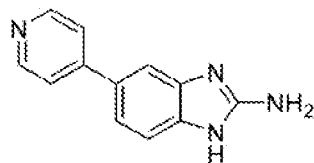
Product was obtained as an off-white solid; $R_f = 0.52$ (10% MeOH/DCM); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 7.8$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 10.75 (d, 2H, $J = 10.8$ Hz), 8.82 (d, 1H, $J = 2.4$ Hz), 8.51 (d, 1H, $J = 4.8$ Hz), 7.99 (dt, 1H, $J = 7.9, 1.9$ Hz), 7.44 (dd, 1H, $J = 8.0, 4.8$ Hz), 7.28 (dd, 1H, $J = 8.1, 1.8$ Hz), 7.21 (d, 1H, $J = 1.6$ Hz), 7.04 (d, 1H, $J = 8.0$ Hz), 3.35 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{14}H_{13}N_4O_2$ 269.1033; found 269.1023.

2-(dimethylamino)ethyl (5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate
(*cmpd 13*)



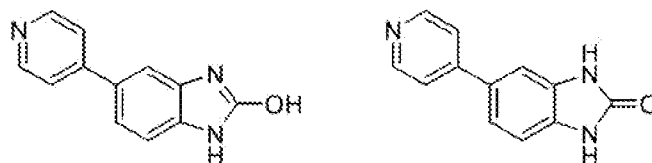
Compound was obtained following the general procedure as an off-white solid; $R_f = 0.36$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 min, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 8.3$ min; ^1H NMR (400 MHz, 25 °C, DMSO- d_6) δ 8.57 (d, 2H, $J = 5.0$ Hz), 7.79 (s, 1H), 7.66 (d, 2H, $J = 4.7$ Hz), 7.50 (s, 2H), 4.27 (t, 2H, $J = 5.7$ Hz), 2.62 (t, 2H, $J = 5.7$ Hz), 2.52 (s, 6H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{17}H_{20}N_5O_2$ 326.1612; found 326.1604.

5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-amine (*cmpd 14*)



Compound was isolated as a minor product of step d reaction (scheme 1) by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid as the mobile phase. Title compound was obtained as an off-white solid; $R_f = 0.33$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 7.6$ min; ^1H NMR (400 MHz, 25 °C, DMSO- d_6) δ 10.81 (s, 2H), 8.57 (m, 2H), 7.63 (m, 2H), 7.39 (dd, ^1H , $J = 8.0, 1.8$ Hz), 7.3 (d, ^1H , $J = 1.6$ Hz), 7.05 (d, ^1H , $J = 8.2$ Hz); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{12}H_{10}N_3O$ 212.0818; found 212.0820.

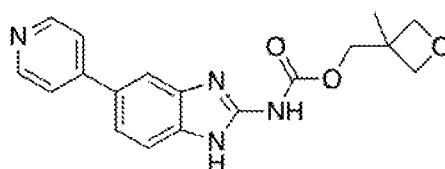
5-(Pyridin-4-yl)-1H-benzo[d]imidazol-2-ol (*cmpd 15*)



Compound was isolated as a minor product of step d reaction (scheme 1), and further purified by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid

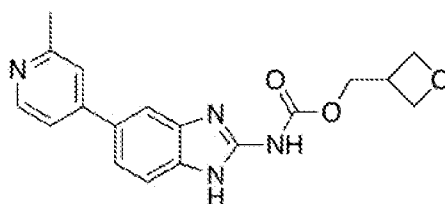
as the mobile phase. Product was obtained as an off-white solid; $R_f = 0.33$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97 % H_2O/ACN with 0.1% formic acid): $t_R = 7.6$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 10.81 (s, 2H), 8.57 (m, 2H), 7.63 (m, 2H), 7.39 (dd, 1H, $J = 8.0, 1.8$ Hz), 7.3 (d, 1H, $J = 1.6$ Hz), 7.05 (d, 1H, $J = 8.2$ Hz); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{12}H_{10}N_3O$ 212.0818; found 212.0820.

(3-methyloxetan-3-yl)methyl (5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 1)



Compound was obtained using general methods and further purified by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid as the mobile phase. Product was obtained as an off-white solid; $R_f = 0.39$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.6$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.74 (br s, 2H) 8.59 (d, 2H, $J = 6.3$ Hz), 7.81 (s, 1H), 7.68 (d, 2H, $J = 5.9$ Hz), 7.52 (s, 2H), 4.48 (d, 2H, $J = 5.9$ Hz), 4.37 – 4.18 (m, 4H), 1.33 (s, 3H); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{18}H_{19}N_4O_3$ 339.1452; found 339.1468.

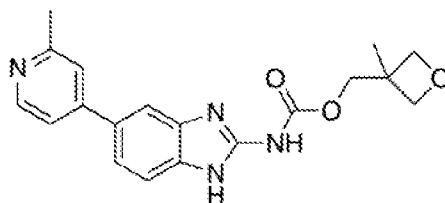
Oxetan-3-ylmethyl (5-(2-methylpyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 5)



Product was obtained using general methods (scheme 1) as an off-white solid; $R_f = 0.57$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.0$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.74 (s, 2H), 8.45 (d, 1H, $J = 5.2$ Hz), 7.79 (d, 1H, $J = 1.3$ Hz), 7.54 (d, 1H, $J = 1.8$ Hz),

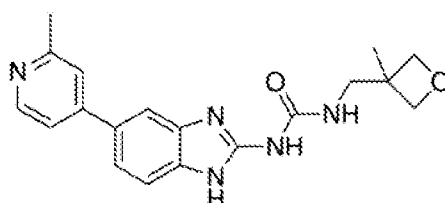
7.50 (d, 2H, $J = 1.2$ Hz), 7.46 (dd, 1H, $J = 5.3, 1.8$ Hz), 4.68 (dd, 2H, $J = 7.9, 6.1$ Hz), 4.42 (t, 4H, $J = 5.9$ Hz), 3.35 (dd, 1H, $J = 7.8, 6.3$ Hz), 2.52 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{18}H_{19}N_4O_3$ 339.1452; found 339.1455.

(3-methyloxetan-3-yl)methyl (5-(2-methylpyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 12)



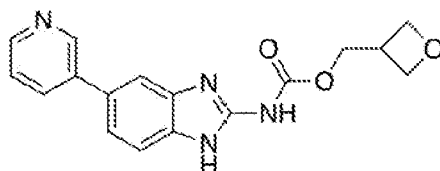
Product was obtained using general methods (scheme 1) as an off-white solid; HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.2$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.75 (s, 3H), 8.45 (d, 1H, $J = 5.3$ Hz), 7.78 (d, 1H, $J = 1.2$ Hz), 7.55 – 7.45 (m, 4H), 4.48 (d, 2H, $J = 5.8$ Hz), 4.30 – 4.27 (m, 4H), 2.53 (s, 3H), 1.33 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{19}H_{21}N_4O_3$ 353.1608; found 353.1610.

1-((3-Methyloxetan-3-yl)methyl)-3-(5-(2-methylpyridin-4-yl)-1H-benzo[d]imidazol-2-yl)urea (cmpd 6)



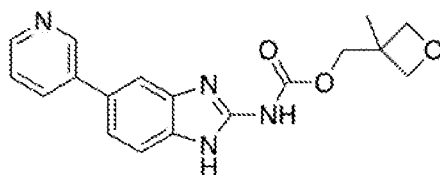
Product was obtained using general methods (scheme 1) as an off-white solid; $R_f = 0.34$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.5$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 12.12 (br s, 1H), 8.44 (t, 1H, $J = 4.7$ Hz), 7.83 (d, 1H, $J = 21.2$ Hz), 7.57 – 7.40 (m, 6H), 4.43 – 4.23 (m, 2H), 3.94 – 3.83 (m, 2H), 3.37 (s, 2H), 2.52 (s, 3H), 1.02 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{19}H_{22}N_5O_2$ 352.1768; found 352.1771.

Oxetan-3-ylmethyl (5-(pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 7)



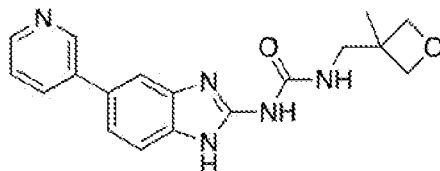
Product was obtained using general methods (scheme 1) as an off-white solid; R_f = 0.35 (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O /ACN with 0.1% formic acid): t_R = 9.1 min; ^1H NMR (400 MHz, 25 °C, DMSO- d_6) δ 11.74 (s, 2H), 8.87 (d, 1H, J = 2.4 Hz), 8.52 (d, 1H, J = 4.7 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.71 (s, 1H), 7.52 – 7.42 (m, 3H), 4.70 – 4.66 (m, 2H), 4.42 (t, 4H, J = 5.9 Hz), 3.37 – 3.30 (m, 1H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{17}H_{17}N_4O_3$ 325.1295; found 325.1288.

(3-methyloxetan-3-yl)methyl (5-(pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 8)



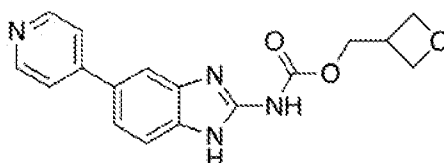
Product was obtained using general methods (scheme 1) as an off-white solid; R_f = 0.56 (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O /ACN with 0.1% formic acid): t_R = 8.7 min; ^1H NMR (400 MHz, 25 °C, DMSO- d_6) δ 12.05 (s, 2H), 8.91 (d, 1H, J = 2.4 Hz), 8.56 (d, 1H, J = 4.7 Hz), 8.14 – 8.10 (m, 1H), 7.74 (d, 1H, J = 1.7 Hz), 7.55 – 7.45 (m, 3H), 4.48 (d, 2H, J = 5.9 Hz), 4.30 – 4.27 (m, 4H), 1.33 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{18}H_{19}N_4O_3$ 339.1452; found 339.1454.

1-((3-methyloxetan-3-yl)methyl)-3-(5-(pyridin-3-yl)-1H-benzo[d]imidazol-2-yl)urea (cmpd 9)



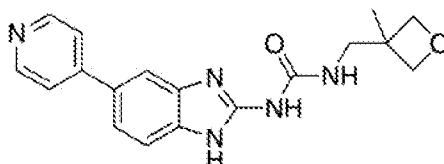
Product was obtained using general methods (scheme 1) as an off-white solid; R_f = 0.40 (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid); t_R = 9.0 min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 12.10 (br s, 1H), 8.87 (s, 1H), 8.52 (s, 1H), 8.20 (br s, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.76 (s, 1H), 7.53 – 7.39 (m, 4H), 3.95 – 3.84 (m, 2H), 3.38 (s, 2H), 3.15 (d, 1H, J = 11.7 Hz), 2.94 (d, 1H, J = 11.6 Hz), 1.02 (s, 3H); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{18}H_{20}N_5O_2$ 338.1612; found 338.1611.

Oxetan-3-ylmethyl (5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 10)



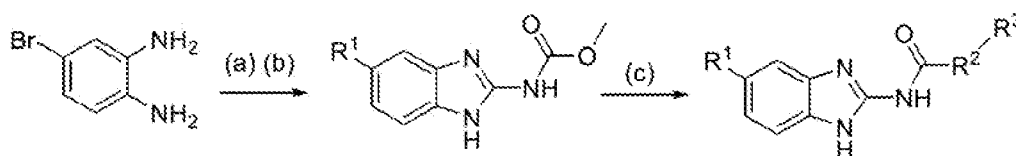
Product was obtained as an off-white solid; R_f = 0.43 (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid); t_R = 8.8 min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.72 (s, 2H), 8.60 – 8.58 (m, 3H), 7.81 (t, 1H, J = 1.2 Hz), 7.69 – 7.67 (m, 2H), 7.52 (t, 2H, J = 1.5 Hz), 4.68 (dd, 2H, J = 7.9, 6.1 Hz), 4.42 (t, 4H, J = 6.1 Hz), 3.35 (dt, 1H, J = 8.1, 6.3 Hz); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{17}H_{17}N_4O_3$ 325.1295; found 325.1301.

1-((3-Methyloxetan-3-yl)methyl)-3-(5-(pyridin-4-yl)-1H-benzo[d]imidazol-2-yl)urea (cmpd 11)



Product was obtained as an off-white solid; $R_f = 0.38$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.1$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.72 (br s, 1H), 9.96 (br s, 1H), 8.59 – 8.57 (m, 2H), 7.79 (s, 1H), 7.67 (s, 2H), 7.49 (br s, 3H), 4.41 (d, 2H, $J = 5.8$ Hz), 4.24 (d, 2H, $J = 5.8$ Hz), 3.42 (d, 2H, $J = 6.0$ Hz), 1.27 (s, 3H); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{18}H_{20}N_5O_2$ 338.1612; found 338.1614.

Compounds 1-15 described in Example 1 can also be prepared using method and procedures generically depicted in Scheme 2, below, using 4-bromobenzene-1,2-diamine as the starting material.

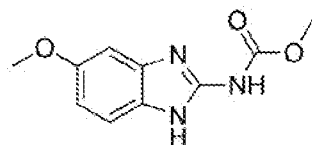


Scheme 2: reagents and conditions: (a) $R^1-B(OH)_2$ (R^1 is Ar, Het, $Ar(C=O)$, or $Het(C=O)$), $Pd(dppf)Cl_2$, Na_2CO_3 , dioxane: H_2O =5:2, 8h, 115 °C; (b) 1,3-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea, acetic acid, glacial, 50 °C, 1 h; (c) R^3-R^2-H (R^2 : O, NH, $N(C_{1-3} \text{ alkyl})$), anhydrous pyridine, 8 h, 95 °C.

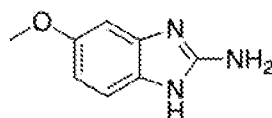
Example 2a - preparation of exemplified 5-methoxy-based compounds

The following benzo[d]imidazole compounds having a methoxy substituent in position 5 on the phenyl ring were prepared according to the methods and procedures similar to those provided for pyridine-containing compounds in Example 1.

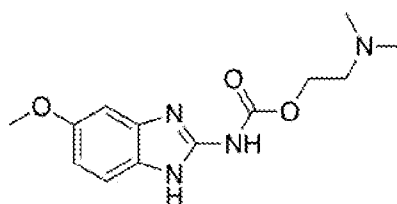
Methyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (compd 17)



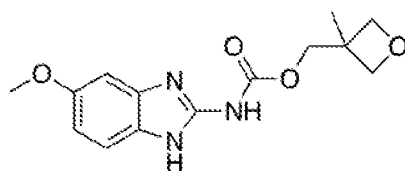
Compound was obtained as an off-white solid; $R_f = 0.57$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 8.4$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.53 (br s, 2H), 7.25 (d, 1H, $J = 8.6$ Hz), 6.94 (d, 1H, $J = 2.3$ Hz), 6.67 (dd, 1H, $J = 8.6, 2.3$ Hz), 3.72 (s, 6H); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{10}H_{12}N_3O_3$ 222.0873; found 222.0873.

5-Methoxy-1H-benzo[d]imidazol-2-amine (compd 18)

Compound was isolated as a minor by-product, and purified by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid as the mobile phase. Product was obtained as an off-white solid; $R_f = 0.18$ (EtOAc:MeOH:H₂O = 7:2:1); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 9.7$ min; ¹H NMR (400 MHz, 25 °C, DMSO-*d*₆) δ 6.99 (d, 1H, $J = 8.6$ Hz), 6.72 (d, 1H, $J = 2.7$ Hz), 6.50 (dd, 1H, $J = 8.6, 2.3$ Hz), 6.39 (br s, 2H), 3.7 (s, 3H); HRMS (ESI) m/z : $[M + H]^+$ calcd for C₈H₁₀N₂O 164.0818; found 164.0817.

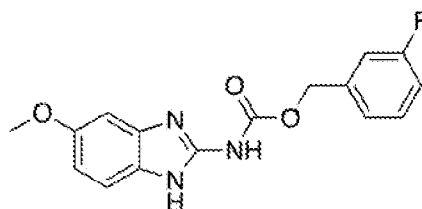
2-(Dimethylamino)ethyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (compd 19)

Compound was further purified by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid as the mobile phase. Product was obtained as a brown solid; $R_f = 0.55$ (10% MeOH/DCM); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 9.4$ min; ¹H NMR (400 MHz, 25 °C, DMSO-*d*₆) δ 7.26 (d, 1H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 2.7$ Hz), 6.69 (dd, 1H, $J = 8.8, 2.5$ Hz), 4.25 (t, 2H, $J = 5.9$ Hz), 3.74 (s, 3H), 2.62 (t, 2H, $J = 5.7$ Hz), 2.27 (s, 6H); HRMS (ESI) m/z : $[M + H]^+$ calcd for C₁₃H₁₉N₄O₃ 279.1452; found 279.1455.

(3-Methyloxetan-3-yl)methyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (compd 20)

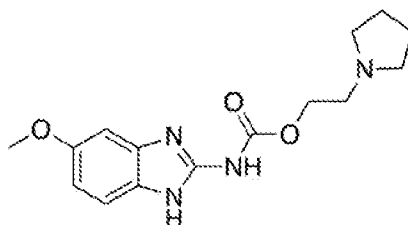
Compound was further purified by Prep-LC using a 5-100% gradient of MeCN in water 0.1% formic acid as the mobile phase. Product was obtained as an off-white solid; $R_f = 0.57$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.0$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.71 (m, 2H), 7.26 (d, 1H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 2.7$ Hz), 6.69 (dd, 1H, $J = 8.6$, 2.7 Hz), 4.46 (d, 2H, $J = 5.9$ Hz), 4.26 (m, 4H), 3.74 (s, 3H), 1.31 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{14}H_{18}N_3O_4$ 292.1292; found 292.1295.

3-Fluorobenzyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 21)



Compound was obtained as an off-white solid; $R_f = 0.57$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 9.1$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 11.62 (br s, 2H, $J =$ Hz), 7.44 (m, 1H), 7.27 (t, 3H, $J = 8.6$ Hz), 7.18 (m, 1H), 6.95 (d, 1H, $J = 2.3$ Hz), 6.69 (dd, 1H, $J = 8.8$, 2.5 Hz), 5.23 (s, 2H), 3.73 (s, 3H); HRMS (ESI) m/z : $[M+H]^+$ calcd for $C_{16}H_{15}FN_3O_3$ 316.1092; found 316.1091.

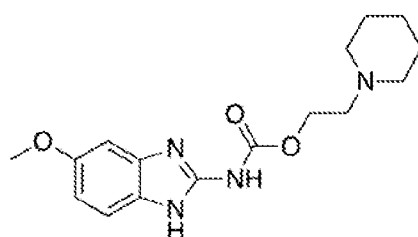
2-(Pyrrolidin-1-yl)ethyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 22)



Product was obtained as an off-white solid; $R_f = 0.25$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O/ACN with 0.1% formic acid): $t_R = 8.0$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 7.26 (d, 1H, $J = 8.6$ Hz), 6.94 (d, 2H, $J = 2.5$ Hz), 6.68 (dd, 1H, $J = 8.6$, 2.5 Hz), 4.26 (t, 2H, $J = 5.8$ Hz), 3.74 (s, 3H), 2.77 (t, 2H,

$J = 5.8$ Hz), 2.60 – 2.56 (m, 4H), 1.72 – 1.69 (m, 4H); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{15}H_{21}N_4O_3$ 305.1608; found 305.1611.

2-(Piperidin-1-yl)ethyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (compd 23)

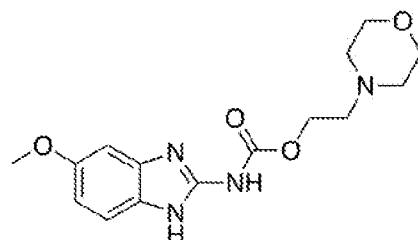


5

Product was obtained as an off-white solid; $R_f = 0.28$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O /ACN with 0.1% formic acid): $t_R = 8.4$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 7.26 (d, 1H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 2.4$ Hz), 6.69 (dd, 1H, $J = 8.6, 2.4$ Hz), 4.27 (t, 2H, $J = 5.8$ Hz), 3.74 (s, 3H), 2.68 (t, 2H, $J = 5.8$ Hz), 2.53 (d, 4H, $J = 5.0$ Hz), 1.52 (p, 4H, $J = 5.6$ Hz), 1.40 (q, 2H, $J = 6.1$ Hz); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{16}H_{23}N_4O_3$ 319.1765; found 319.1764.

10

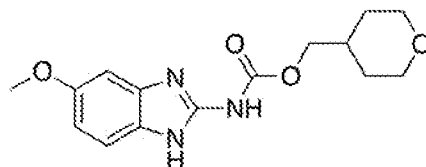
2-Morpholinoethyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (compd 24)



15

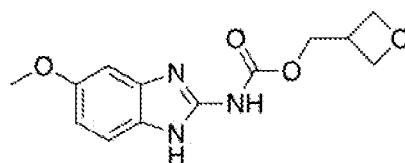
Product was obtained as an off-white solid; $R_f = 0.67$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O /ACN with 0.1% formic acid): $t_R = 7.9$ min; ^1H NMR (400 MHz, 25 °C, $DMSO-d_6$) δ 7.26 (d, 1H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 2.4$ Hz), 6.68 (dd, 1H, $J = 8.6, 2.4$ Hz), 4.26 (t, 2H, $J = 5.8$ Hz), 3.74 (s, 3H), 3.58 – 3.55 (m, 4H), 2.60 (t, 2H, $J = 5.7$ Hz), 2.45 (t, 4H, $J = 4.8$ Hz); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{15}H_{21}N_4O_4$ 321.1557; found 321.1565.

(Tetrahydro-2H-pyran-4-yl)methyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 25)



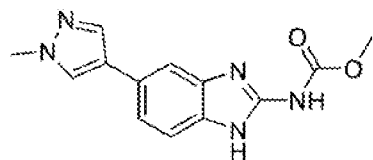
Product was obtained as an off-white solid; $R_f = 0.67$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O /ACN with 0.1% formic acid): $t_R = 9.4$ min; ^1H NMR (400 MHz, $25^\circ C$, $DMSO-d_6$) δ 11.44 (s, 2H), 7.26 (d, 1H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 2.4$ Hz), 6.68 (dd, 1H, $J = 8.6, 2.4$ Hz), 3.86 (ddd, 2H, $J = 11.5, 4.5, 1.8$ Hz), 3.74 (s, 3H), 3.34 – 3.27 (m, 4H), 1.92 (ddt, 1H, $J = 11.5, 8.5, 4.3$ Hz), 1.60 (ddd, 2H, $J = 12.9, 4.1, 1.9$ Hz), 1.29 (qd, 2H, $J = 12.5, 4.9$ Hz); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{15}H_{20}N_3O_4$ 306.1448; found 306.1447.

Oxetan-3-ylmethyl (5-methoxy-1H-benzo[d]imidazol-2-yl)carbamate (cmpd 26)



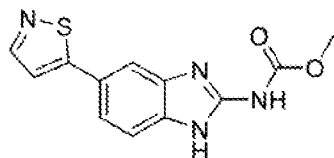
Product was obtained as a brown solid; $R_f = 0.67$ (10% MeOH/DCM); HPLC analysis (C_{18} reverse phase, 17 mins, 0-97% H_2O /ACN with 0.1% formic acid): $t_R = 8.9$ min; ^1H NMR (400 MHz, $25^\circ C$, $DMSO-d_6$) δ 7.26 (d, 1H, $J = 8.7$ Hz), 6.95 (d, 1H, $J = 2.4$ Hz), 6.69 (dd, 1H, $J = 8.7, 2.4$ Hz), 4.67 (dd, 2H, $J = 7.9, 6.0$ Hz), 4.42 – 4.36 (m, 4H), 3.74 (s, 3H), 3.31 (ddq, 1H, $J = 14.4, 8.0, 6.5$ Hz); HRMS (ESI) m/z : $[M + H]^+$ calcd for $C_{13}H_{16}N_3O_4$ 278.1135; found 278.1134.

Example 2b - 5-(5-membered heteroaryl)-based compounds

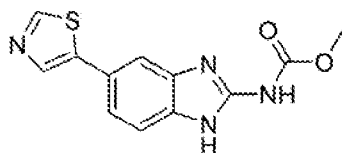


Methyl (5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-2-yl)carbamate (31)

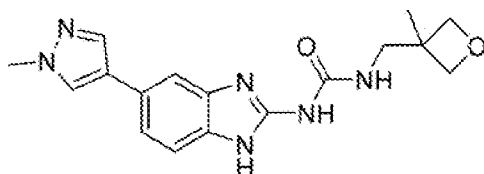
(101.3 mg, 88%). HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): *t_R* = 5.21 min; ¹H NMR (400 MHz, CD₃OD) δ 11.54 (br s, 2H), 8.02 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H), 3.75 (s, 3H).

**Methyl (5-(isothiazol-5-yl)-1H-benzo[d]imidazol-2-yl)carbamate (32) (25.5 mg, 75%).**

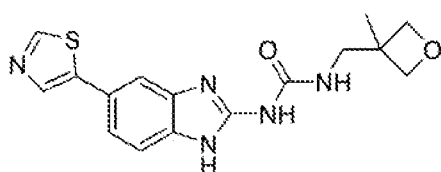
HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): *t_R* = 5.83 min; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.74 (br s, 3H), 8.54 (d, *J* = 1.8 Hz, 1H), 7.76 (s, 1H), 7.69 (d, *J* = 1.8 Hz, 1H), 7.52 – 7.43 (m, 2H), 3.77 (s, 3H). HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₂H₁₀N₄O₂S 275.0597; found 275.0595.

**Methyl (5-(thiazol-5-yl)-1H-benzo[d]imidazol-2-yl)carbamate (33) (16.3 mg, 23%).**

HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): *t_R* = 5.48 min; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.66 (br s, 2H), 9.00 (s, 1H), 8.19 (s, 1H), 7.67 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.41 (dd, *J* = 8.3, 1.6 Hz, 1H), 3.77 (s, 3H). HRMS (ESI) *m/z*: [M + H]⁺ calcd for C₁₂H₁₀N₄O₂S 275.0597; found 275.0595.



1-((5-(1-methyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazol-2-yl)-3-((3-methyloxetan-3-yl)methyl)urea (**34**) was obtained as an off-white solid (99.3 mg, 0.36 mmol). $R_f = 0.31$ (7% MeOH/DCM); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 5.46$ min; ^1H NMR (400 MHz, DMSO- d_6) δ 11.42 (br s, 1H), 9.81 (br s, 1H), 8.00 (s, 1H), 7.75 (s, 1H), 7.66 (br s, 1H), 7.50 (d, $J = 1.2$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.23 (d, $J = 9.6$ Hz, 1H), 4.41 (d, $J = 5.8$ Hz, 2H), 4.24 (d, $J = 5.8$ Hz, 2H), 3.85 (s, 3H), 3.41 (d, $J = 6.1$ Hz, 2H), 1.27 (s, 3H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for C₁₇H₂₀N₆O₂ 341.1271; found 341.1271.



1-((3-methyloxetan-3-yl)methyl)-3-(5-(thiazol-5-yl)-1H-benzo[d]imidazol-2-yl)urea (**35**) (15.7 mg, 84%). $R_f = 0.49$ (10% MeOH/DCM); HPLC analysis (C18 reverse phase, 17 mins, 0-97% H₂O/ACN with 0.1% formic acid): $t_R = 5.64$ min; ^1H NMR (400 MHz, CD₃OD) δ 8.89 (s, 1H), 8.10 (d, $J = 10.1$ Hz, 3H), 7.67 (s, 1H), 7.44 (s, 2H), 4.58 (d, $J = 6.0$ Hz, 2H), 4.39 (d, $J = 6.0$ Hz, 2H), 3.50 (s, 2H), 1.36 (s, 3H). HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for C₁₆H₂₁N₅O₂S 344.1176; found 344.1175.

All compounds disclosed herein can be prepared in a manner analogous to the one disclosed above in the Examples.

Example 3 - benzimidazole carbamates as high affinity DYRK1A kinase inhibitors – inhibition of *Tau* phosphorylation

Introduction: the dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) is implicated in the pathology of AD. DYRK1A is upregulated in the brain tissue of AD patients, and as a trisomy gene it is the underlying cause of Down Syndrome with increased risk of developing AD. DYRK1A catalyzes the phosphorylation of the amyloid precursor and tau proteins, two major pathological effectors involved in the formation of amyloid plaques and neurofibrillary tangle, and consequentially

neuroinflammation in AD. The experimental data provided in the examples provides credible evidence that DYRK1A inhibitors of this disclosure are useful as therapeutics for neurodegenerative disorders such as tauopathies, including AD.

Methods: a competitive binding assay was used as the primary screen to measure the binding affinity (K_D) to DYRK1A. Selectivity against DYRK1B/2 as well as the related CLK1-4 was determined by comparison of the K_D in each of the enzymes. Cellular activity of representative compounds was obtained by measuring the p-Tau levels in HEK293 cells expressing human full-length DYRK1A and Tau.

Results: a exemplified benzimidazole carbamates were synthesized as described in the examples and tested for their K_D to the DYRK1A protein, including a number of highly active DYRK1A inhibitors. Among them, five (5) compounds were shown to bind to DYRK1A with K_D of < 1 nM: 2 (K_D : 720 pM), 11 (K_D : 330 pM), 5 (K_D : 330 pM), 1 (K_D : 170 pM), and 12 (K_D : 140 pM). Furthermore, compound 1 showed 15 to 90-fold selectivity over DYRK1B/2 and CLK1-4 kinases, and potently inhibited Tau phosphorylation in the HEK293 cellular assay (IC_{50} : 26 nM).

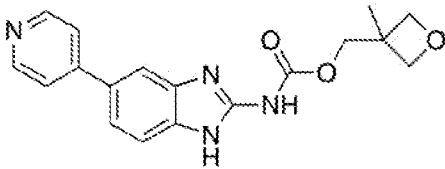
T-cell Inflammation Inhibition Assay Protocol: Day 1, High binding plates were coated with anti-CD3 (clone UCHT-1, 2 μ g/mL) and isotype IgG1 using PBS 1x and incubated overnight at 4 °C. Day 2: Cryopreserved PBMCs were drip thawed and diluted to the appropriate density and seeded into U bottom 96-well polypropylene plates (1.2 $\times$ 10⁵ cells per well) with 228 μ L per well of culture medium (RPMI 1640, 10% heat-inactivated FBS, 1% penicillin/streptomycin, 2 mM L-glutamine). Cells were incubated at 37 °C, 5% CO₂ for 1 hour prior to the addition of test compounds. Test compounds were solubilized in DMSO and further diluted to 20 $\times$ with cell culture medium. Compounds were added to the PBMCs in volumes of 12 μ L (1 $\times$) in triplicate and incubated for 1 hour at 37 °C, 5% CO₂. For reference compound, 12 μ L of dexamethasone (100 nM) was added to the control wells according to the plate map and incubated for 1 hour at 37 °C, 5% CO₂. After 1 hour incubation, 200 μ L of cells (1 $\times$ 10⁵) treated with test compounds or controls were transferred to the anti-CD3 coated plates and incubated for 24 hours at 37 °C, 5% CO₂. For positive and negative controls, transferred 200 μ L (1 $\times$ 10⁵) of cells to the coated plate with anti-CD3 or isotype IgG1. Plates were centrifuged at 200 $\times$ g for 10 minutes. Cell culture supernatants were collected

and stored at -80 °C until needed for analysis. Cytokine levels in each sample were determined using Luminex methodology, per the manufacturer's protocol. Luminex assessment of cytokine levels in cell culture supernatants in tissue culture medium, was performed per manufacturer's protocol using the Human Cytokine/Chemokine Magnetic bead panel from Millipore Sigma (catalogue No. HCYTOMAG-60K) with standards range 3.2, 16, 80, 400, 2,000, 10,000 pg/mL. Cytokines Measured: The following cytokines were measured for a complete cytokine response profile. Human panel, T cell (neat): IL-2, IL-17, IFN γ .

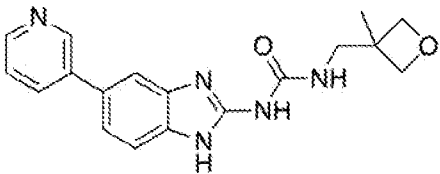
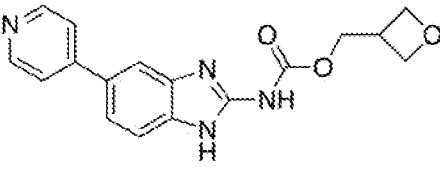
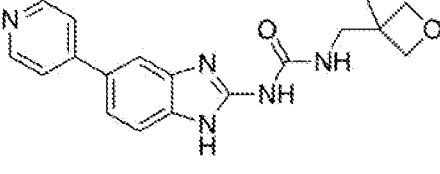
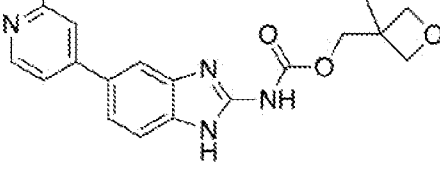
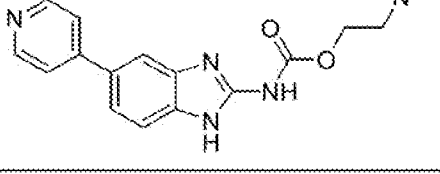
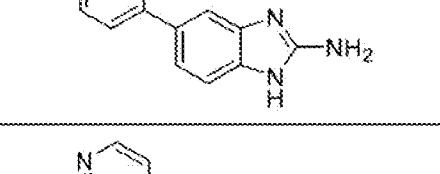
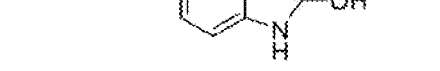
Kinase assays. For most assays, kinase-tagged T7 phage strains were prepared in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage and incubated with shaking at 32 °C until lysis. The lysates were centrifuged and filtered to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for 30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1 $\times$ binding buffer (20% SeaBlock, 0.17 $\times$ PBS, 0.05% Tween 20, 6 mM DTT). Test compounds were prepared as 111 $\times$ stocks in 100% DMSO. K_{as} were determined using an 11-point 3-fold compound dilution series with three DMSO control points. All compounds for K_a measurements are distributed by acoustic transfer (non-contact dispensing) in 100% DMSO. The compounds were then diluted directly into the assays such that the final concentration of DMSO was 0.9%. All reactions performed in polypropylene 384-well plate. Each was a final volume of 0.02 mL. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1 $\times$ PBS, 0.05% Tween 20). The beads were then re-suspended in elution buffer (1 $\times$ PBS, 0.05% Tween 20, 0.5 μ M non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

Kinase Cellular Assay: HEK293 human embryonic kidney cells were transiently co-transfected with vectors encoding full-length human DYRK1A and *Tau*. Cells were dispensed into 96-well plates at a number previously determined by cell titration and signal optimization for the DYRK1A assay. Compounds were diluted to 200× final assay concentration in DMSO. Eight 3-fold or 4-fold serial dilutions were prepared for each compound in 100% DMSO. Compounds were then diluted in tissue culture medium to 10× final assay concentration and 5% DMSO. Compounds were added to the cells in 96-well plates (10-fold dilution in medium) for a final concentration of 1× compound and 0.5% DMSO. For positive (high signal) controls, cells were treated with 0.5% DMSO alone. For negative (low signal) controls, cells were treated with 20 μM harmine including 0.5% DMSO final concentration. Cells were incubated with compound at 37 °C for 2 hours. Cells were lysed, and lysates were transferred to an ELISA plate that had been previously coated with antibody to capture the substrate (human *Tau*). Plates were washed then incubated with an antibody to detect phosphorylation of *Tau*. Plates were washed then incubated with HRP-linked secondary antibody. Plates were washed, then HRP substrate was added. Absorbance was read at 450 nm. Per cent inhibition values were calculated from absorbance readings based on positive and negative control values, and according to the following formula: (%INH = ((positive control – sample)/(positive control – negative control))×100. Z' values were calculated based on the following formula: $1 - [(3 \times \text{standard deviation of positives} + 3 \times \text{standard deviation of negatives}) / (\text{average positive} - \text{average negative})]$. Per cent inhibition values were plotted vs. the log of compound concentrations utilizing GraphPad Prism software. IC₅₀s were determined after utilizing sigmoidal dose response curve fitting to generate the curves.

Table 1a

No.	Structure	DYRK1A K _D /IC ₅₀ (nM)	p- <i>Tau</i> IC ₅₀ (nM)	% inh at 5 μM		
				IL2	IL17	INFγ
1		0.17	37			

2		0.72	280	46.5 42.3	22.8 35.9	31.4 11.5
3		242				
4		0.84				
5		0.33	55	78.2 59.3	47.8 51.8	58.8 46
6		13.3	827	38.9 35.8	9.3 7.3	30 -
7		91		36.9 43.4	- -	24.4 -
8		76				

9		23,012				
10		0.44	26	76.1 59.8	35 30.4	57.5 39.9
11		0.33				
12		0.14				
13		3.5				
14		45				
15		37				

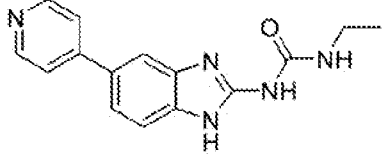
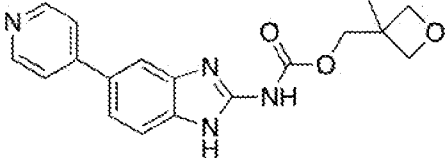
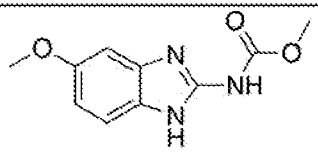
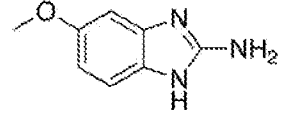
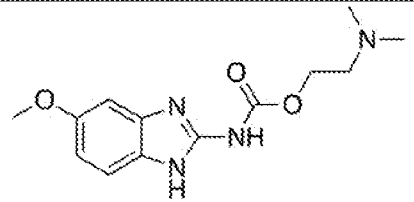
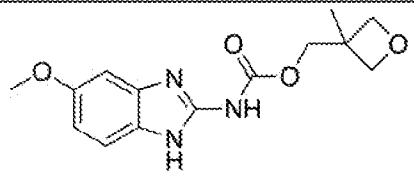
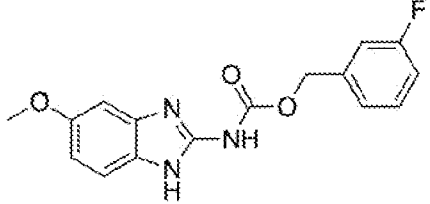
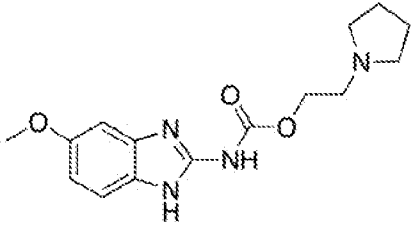
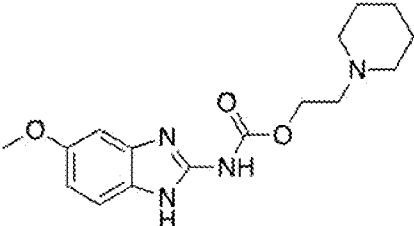
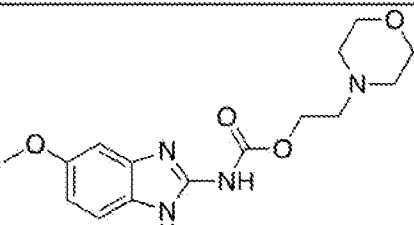
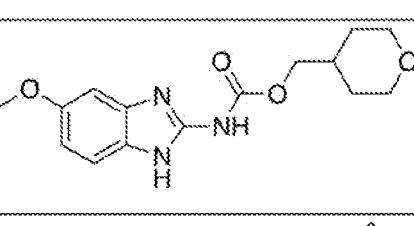
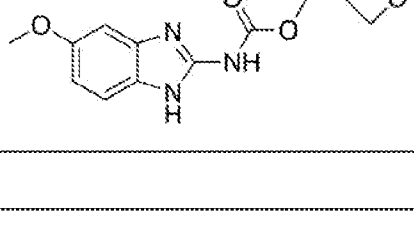
16				
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Table 1b

No.	Structure	%inh at 10 μ M	%inh at 1 μ M	%inh at 0.1 μ M
1		100%	100%	100%
17		69%	NT	NT
18		11%	NT	NT
19		51%	NT	NT
20		96.4	63%	NT
21		69%	NT	NT

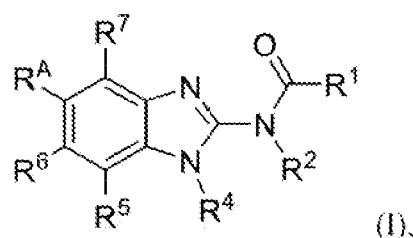
22				
23				
24				
25				
26				
31				
32				
33				
34				
35				

NT: not tested

The experimental results show that the 5-pyridyl group-containing compounds show high binding affinity in the kinase assays. These compounds are highly active at about 0.1 μ M, about 1 μ M, or about 10 μ M concentration.

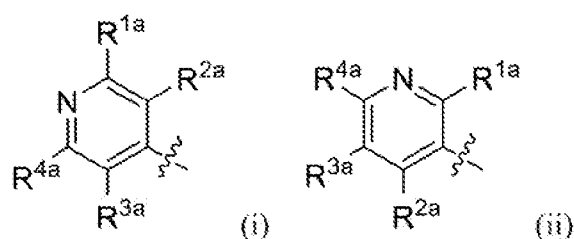
5 Exemplary embodiments:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (i) and (ii):



R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R^1 is selected from Cy^l, OR^B, NR³R^B, CH₂R^B, and CH₂R^C;

each R^B is independently selected from Cy^l, C₁₋₆ haloalkyl, and C₁₋₆ alkyl substituted with Cy^l, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

R^C is selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R², R³, and R⁴ are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R^5 is selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $S(O)_2NR^{c1}R^{d1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

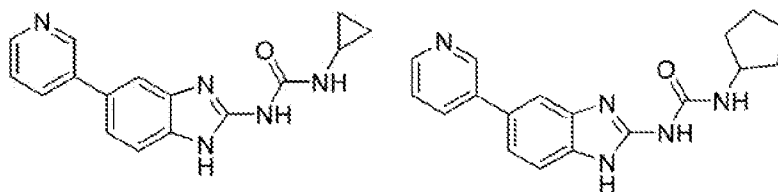
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

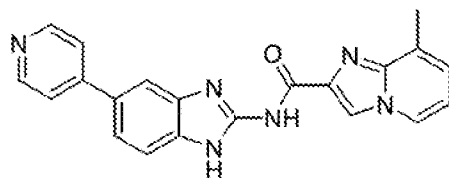
each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^2 ; and

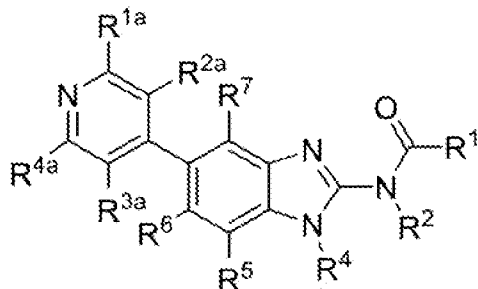
each R^2 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino;

provided that the compound of Formula (I) is not any one of the following compounds:



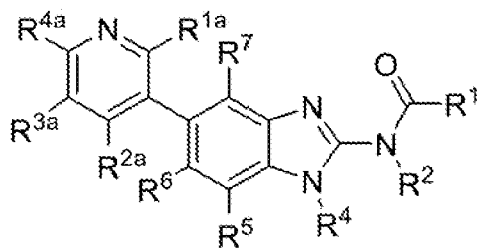


2. The compound of embodiment 1, having formula:



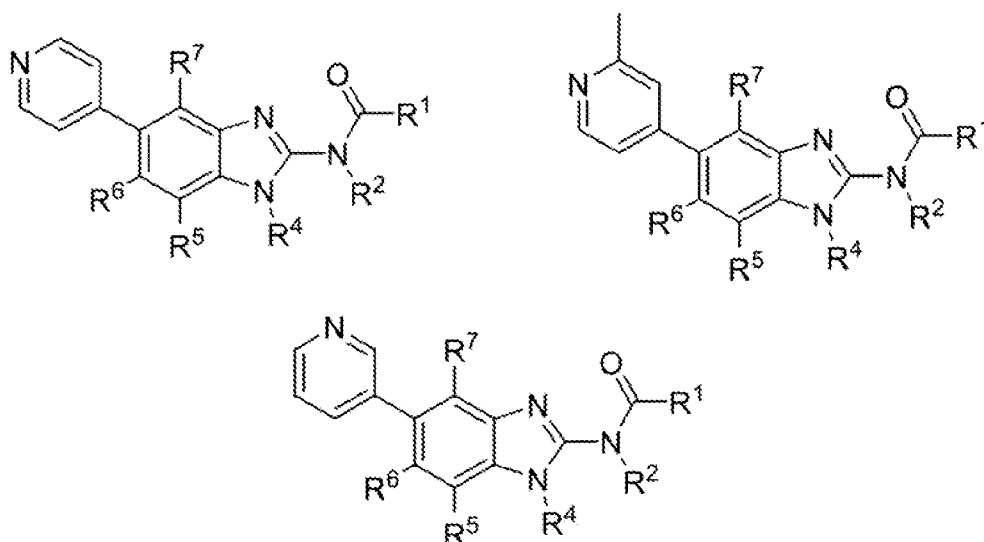
or a pharmaceutically acceptable salt thereof.

3. The compound of embodiment 1, having formula:



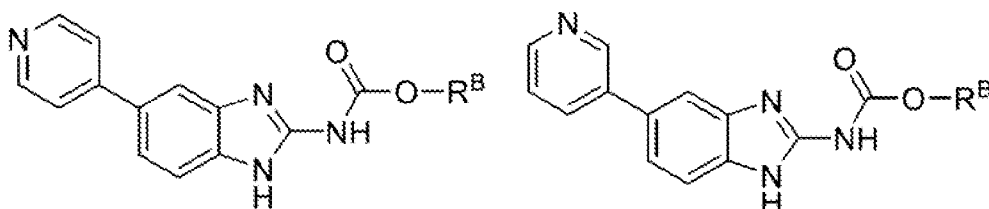
or a pharmaceutically acceptable salt thereof.

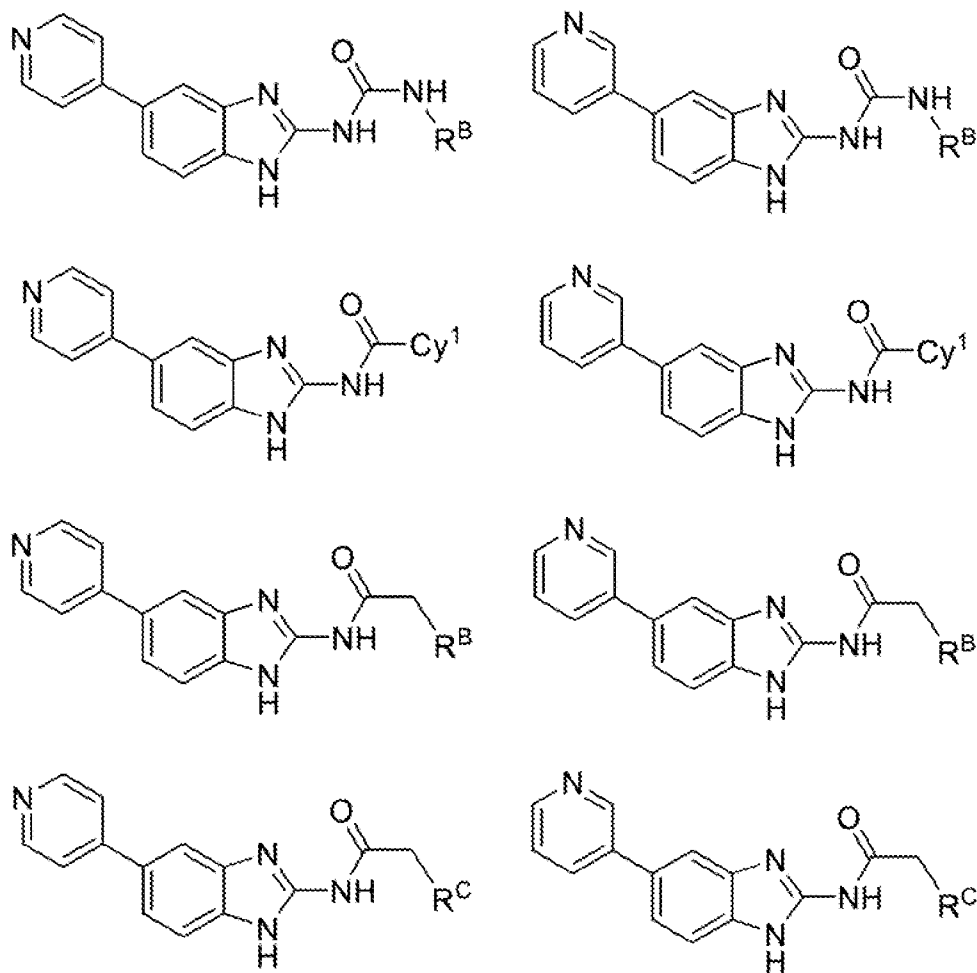
4. The compound of any one of embodiments 1-3, wherein R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl.
5. The compound of any one of embodiments 1-3, wherein R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H and C_{1-3} alkyl.
6. The compound of embodiment 1, wherein the compound of Formula (I) is selected from any one of the following compounds:



or a pharmaceutically acceptable salt thereof.

7. The compound of any one of embodiments 1-6, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{A1} , and $\text{NR}^{\text{C1}}\text{R}^{\text{A1}}$.
8. The compound of any one of embodiments 1-6, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $\text{di}(\text{C}_{1-3}$ alkyl)amino.
9. The compound of any one of embodiments 1-8, wherein R^1 is selected from OR^{B} and $\text{NR}^3\text{R}^{\text{B}}$.
10. The compound of embodiment 9, wherein R^1 is OR^{B} .
11. The compound of embodiment 9, wherein R^1 is NHR^{B} .
12. The compound of any one of embodiments 1-8, wherein R^1 is $\text{CH}_2\text{R}^{\text{B}}$.
13. The compound of any one of embodiments 1-8, wherein the compound of Formula (I) is selected from:

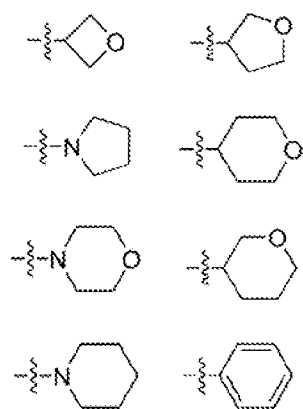




or a pharmaceutically acceptable salt thereof.

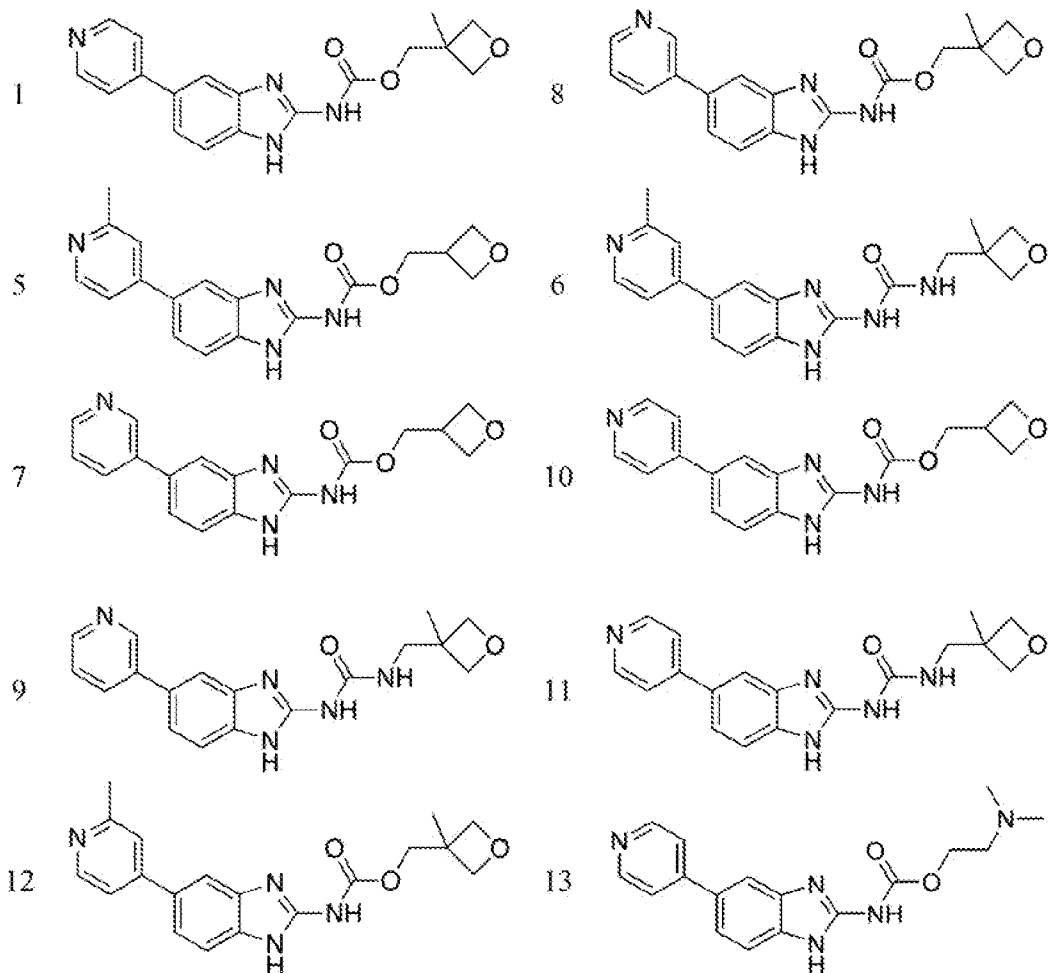
14. The compound of any one of embodiments 1-13, wherein R^B is selected from Cy^1 and C₁₋₆ alkyl substituted with Cy^1 , OR^{al}, or NR^{cl}R^{dl}.
15. The compound of embodiment 14, wherein R^B is selected from Cy^1 , C₁₋₆ alkyl substituted with Cy^1 , and C₁₋₆ alkyl substituted with NR^{cl}R^{dl}.
16. The compound of embodiment 15, wherein R^B is Cy^1 .
17. The compound of embodiment 15, wherein R^B is C₁₋₆ alkyl substituted with Cy^1 .
18. The compound of any one of embodiments 1-17, wherein Cy^1 is selected from C₆₋₁₀ aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl}.

19. The compound of embodiment 18, wherein Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
20. The compound of embodiment 18, wherein Cy^1 is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
21. The compound of embodiment 20, wherein the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
22. The compound of any one of embodiments 1-21, wherein R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.
23. The compound of any one of embodiments 1-21, wherein R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.
24. The compound of any one of embodiments 1-23, wherein Cy^1 is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cy1} :



25. The compound of any one of embodiments 1-13, wherein R^B is C_{1-6} alkyl substituted with $NR^{C1}R^{d1}$.

26. The compound of embodiment 25, wherein R^B is selected from $CH_2NR^{c1}R^{d1}$, $CH_2CH_2NR^{c1}R^{d1}$, and $CH_2CH_2CH_2NR^{c1}R^{d1}$.
27. The compound of embodiment 1, wherein the compound of Formula (I) is selected from any one of the following compounds:

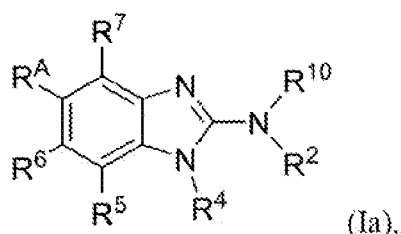


or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of embodiments 1-28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
29. A method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any

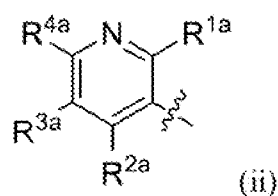
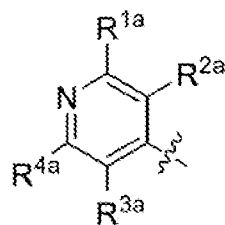
- one of embodiments 1-28, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 29.
30. The method of embodiment 30, wherein the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astrogliopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.
31. The method of embodiment 30, wherein the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimia, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.
32. The method of embodiment 30, wherein the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.

33. The method of embodiment 30, wherein the disease or condition is a cancer selected from brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.
34. A method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising:
- identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and
 - after (i), administering to the subject a therapeutically effective amount of a compound of Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (i) and (ii):



R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, $\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , and $\text{S(O)}_2\text{OR}^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $\text{NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{R}^{b1}$, $\text{C(O)NR}^{c1}\text{R}^{d1}$, $\text{S(O)}_2\text{NR}^{c1}\text{R}^{d1}$, C(O)OR^{a1} , and $\text{S(O)}_2\text{OR}^{a1}$;

R^{10} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and C(=O)R^1 ;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^B is independently selected from H, Cy^I , C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with Cy^I , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^I , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^I , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

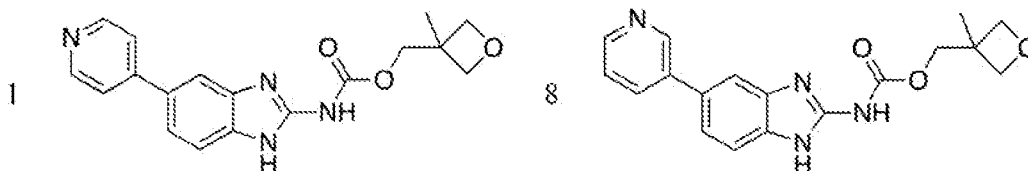
each Cy^I is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{CyI} ;

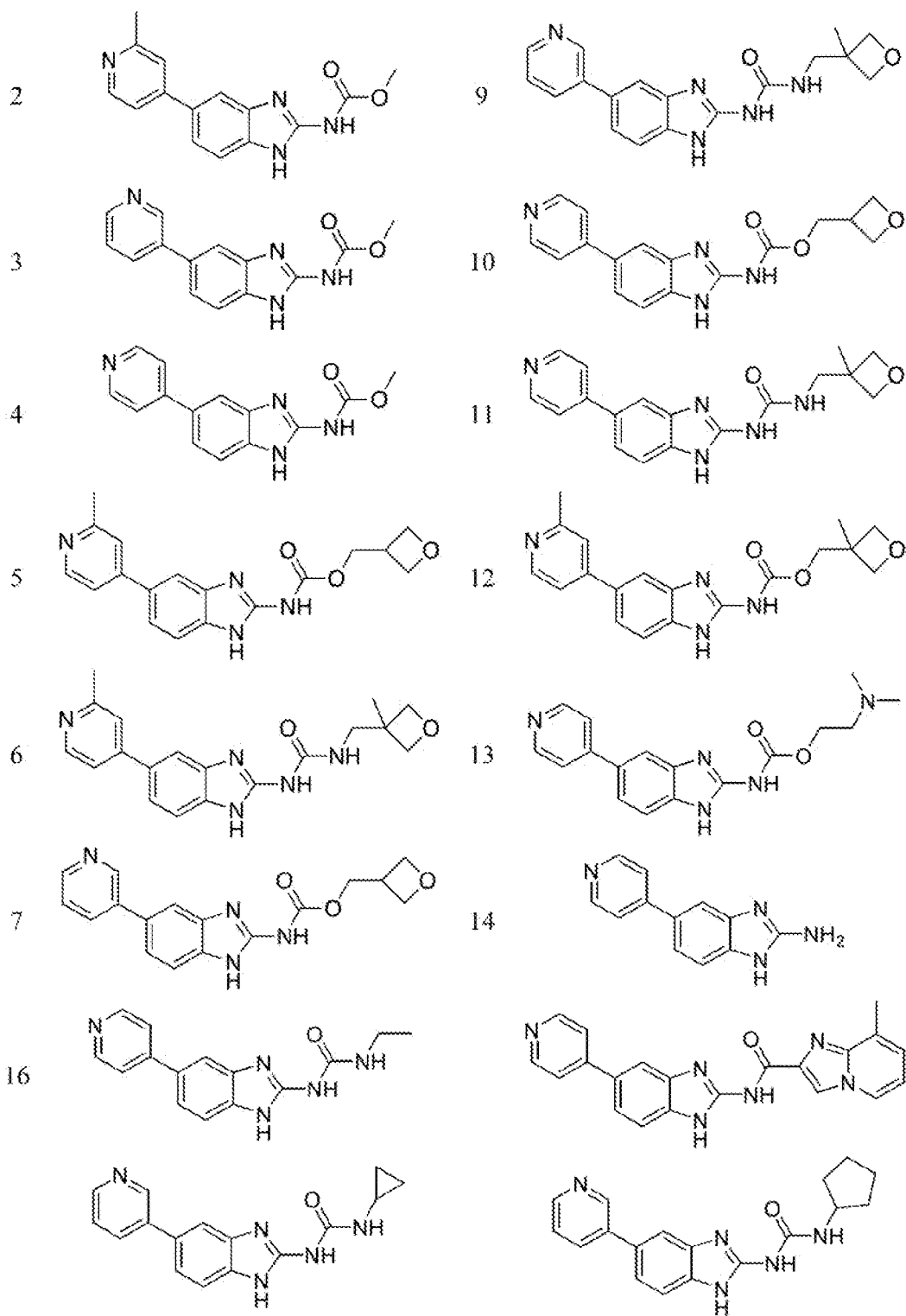
each R^{CyI} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E ; and

each R^E is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

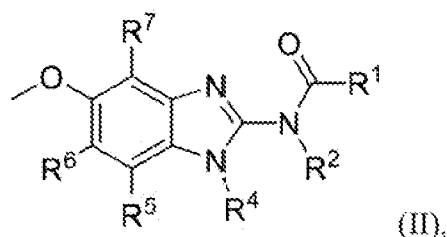
35. The method of embodiment 35, wherein the compound of Formula (Ia) is selected from any one of the following compounds:





or a pharmaceutically acceptable salt thereof.

36. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from OR^B , NR^3R^B , and CH_2R^C ;

each R^B is independently selected from Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from NO_2 , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, $S(O)_2OR^{a1}$, and C_{1-6} alkyl substituted with NO_2 , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

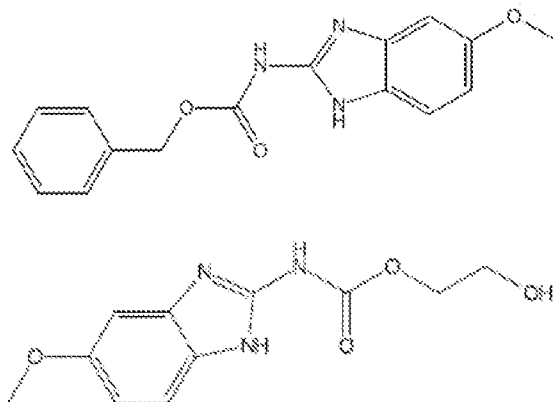
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

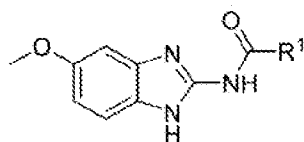
R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E ; and

each R^2 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino;

provided that the compound of Formula (II) is not any of the following compounds:



37. The compound of embodiment 36, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{d1} , and $NR^{c1}R^{d1}$.
38. The compound of embodiment 36, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.
39. The compound of embodiment 36, wherein the compound has formula:

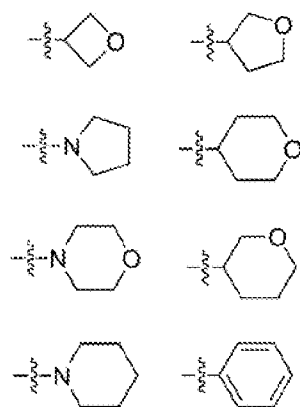


or a pharmaceutically acceptable salt thereof.

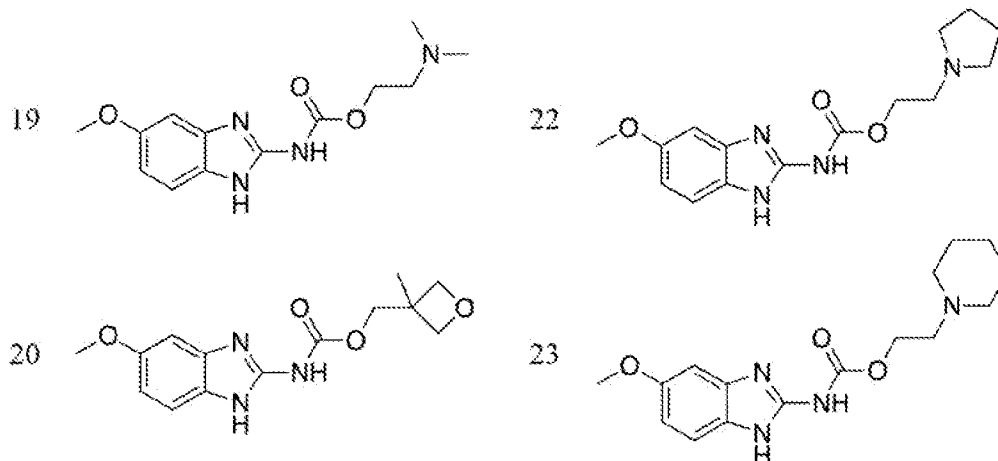
40. The compound of any one of embodiments 36-39, wherein R^1 is selected from OR^B and NR^3R^B .
41. The compound of embodiment 40, wherein R^1 is OR^B .
42. The compound of embodiment 40, wherein R^1 is NHR^B .

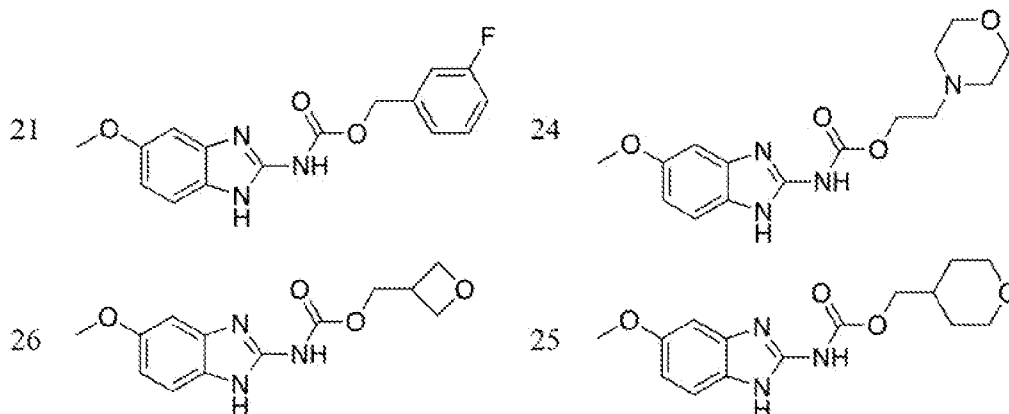
43. The compound of any one of embodiments 36-42 wherein R^B is selected from Cy^I and C_{1-6} alkyl substituted with Cy^I , OR^{d1} , or $NR^{c1}R^{d1}$.
44. The compound of embodiment 43, wherein R^B is selected from Cy^I , C_{1-6} alkyl substituted with Cy^I , and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.
45. The compound of embodiment 44, wherein R^B is Cy^I .
46. The compound of embodiment 44, wherein R^B is C_{1-6} alkyl substituted with Cy^I .
47. The compound of any one of embodiments 36-46, wherein Cy^I is selected from C_{6-10} aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{CyI} .
48. The compound of embodiment 47, wherein Cy^I is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{CyI} .
49. The compound of embodiment 47, wherein Cy^I is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{CyI} .
50. The compound of embodiment 49, wherein the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{CyI} .
51. The compound of any one of embodiments 36-50, wherein R^{CyI} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.
52. The compound of any one of embodiments 36-50, wherein R^{CyI} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.

53. The compound of any one of embodiments 36-46, wherein Cy^I is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{CyI} :



54. The compound of any one of embodiments 36-46, wherein R^B is C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.
55. The compound of embodiment 54, wherein R^B is selected from $CH_2NR^{c1}R^{d1}$, $CH_2CH_2NR^{c1}R^{d1}$, and $CH_2CH_2CH_2NR^{c1}R^{d1}$.
56. The compound of embodiment 36, wherein the compound of Formula (II) is selected from any one of the following compounds:





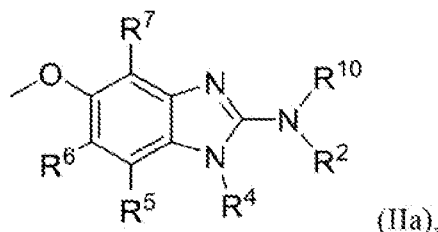
or a pharmaceutically acceptable salt thereof.

57. A pharmaceutical composition comprising a compound of any one of embodiments 36-56, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
58. A method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments 36-56, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of embodiment 57.
59. The method of embodiment 58, wherein the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astroglialopathy, Richardson

syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.

60. The method of embodiment 58, wherein the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimia, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.
61. The method of embodiment 58, wherein the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.
62. The method of embodiment 58, wherein the disease or condition is a cancer selected from brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.
63. A method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising:
 - (i) identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and

(ii) after (i), administering to the subject a therapeutically effective amount of a compound of Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein:

R^{10} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and $C(=O)R^1$;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^B is independently selected from H, Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^C is selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

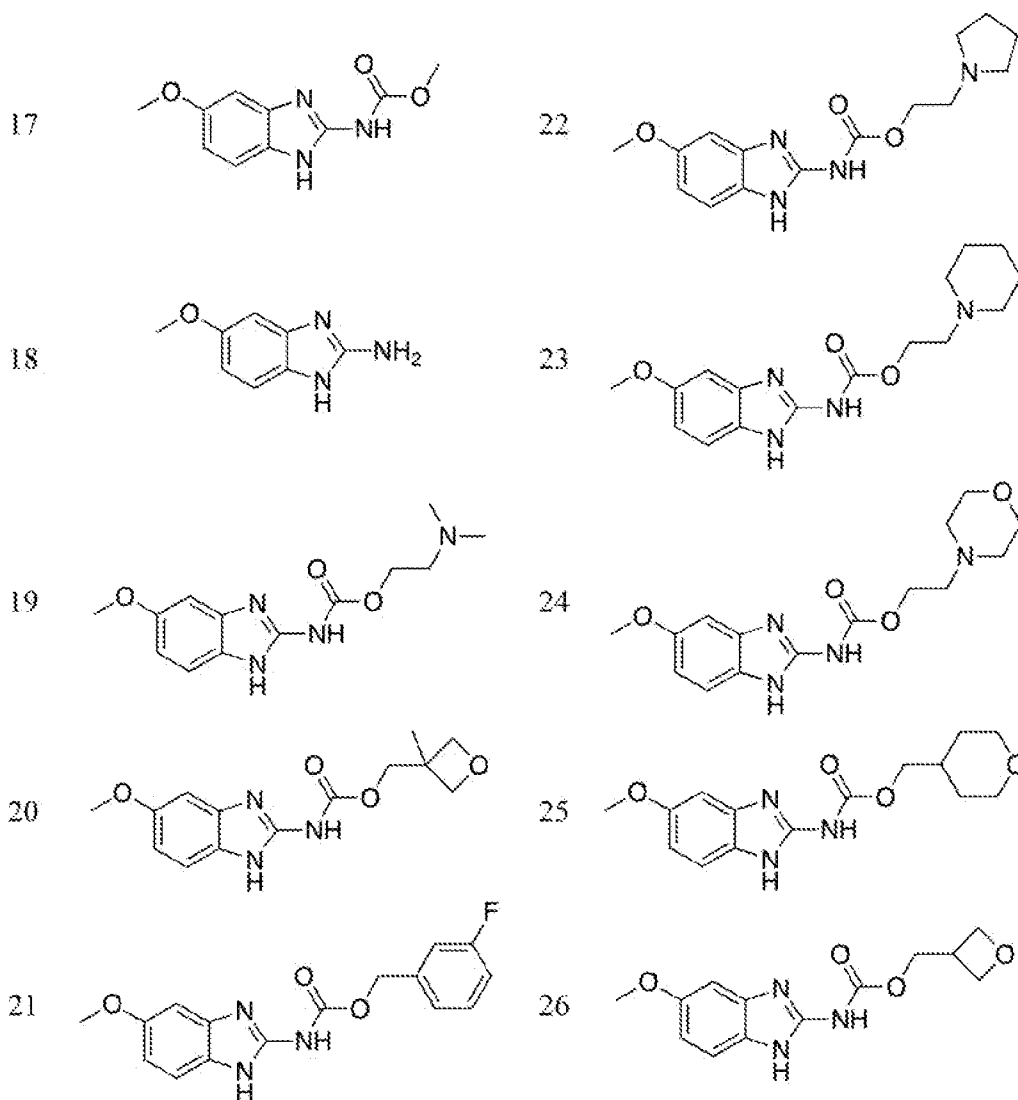
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

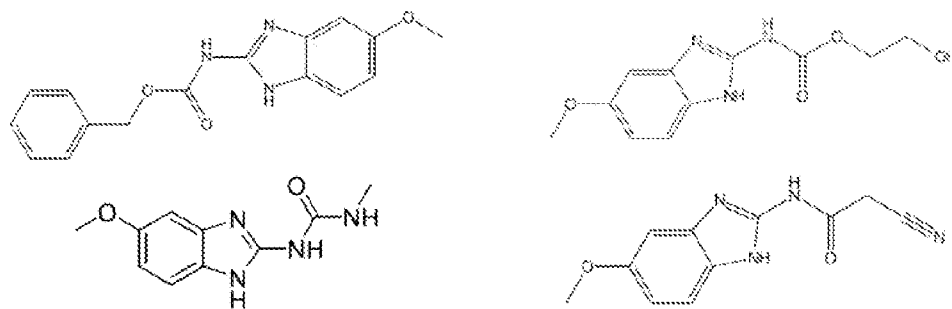
each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E , and

each R^E is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxy carbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

64. The method of embodiment 63, wherein the compound of Formula (IIa) is selected from any one of the following compounds:





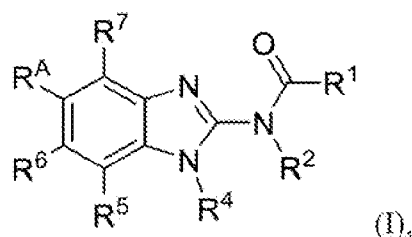
or a pharmaceutically acceptable salt thereof.

OTHER EMBODIMENTS

It is to be understood that while the present application has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the present application, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

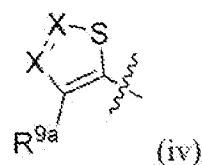
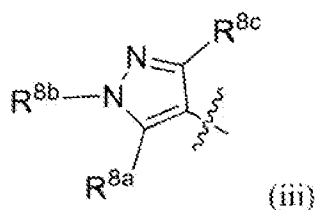
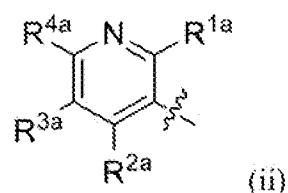
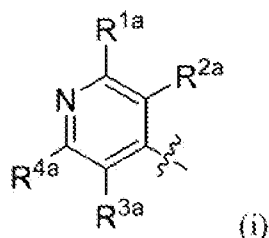
WHAT IS CLAIMED IS:

I. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (i), (ii), (iii) and (iv):



R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R^1 is selected from Cy^l, OR^B, NR³R^B, CH₂R^B, and CH₂R^C;

each R^B is independently selected from Cy^l, C₁₋₆ haloalkyl, and C₁₋₆ alkyl substituted with Cy^l, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

R^C is selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R^2 , R^3 , and R^4 are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R^5 is selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{a1}, NR^{c1}R^{d1}, S(O)₂R^{b1}, S(O)₂NR^{c1}R^{d1}, and S(O)₂OR^{a1}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{a1}, NR^{c1}R^{d1}, S(O)₂R^{b1}, C(O)NR^{c1}R^{d1}, S(O)₂NR^{c1}R^{d1}, C(O)OR^{a1}, and S(O)₂OR^{a1};

R^6 and R^7 are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{a1}, NR^{c1}R^{d1}, S(O)₂R^{b1}, C(O)NR^{c1}R^{d1}, S(O)₂NR^{c1}R^{d1}, C(O)OR^{a1}, and S(O)₂OR^{a1}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{a1}, NR^{c1}R^{d1}, S(O)₂R^{b1}, C(O)NR^{c1}R^{d1}, S(O)₂NR^{c1}R^{d1}, C(O)OR^{a1}, and S(O)₂OR^{a1};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1};

each R^{Cy1} is independently selected from halo, CN, NO₂, OR^{a1}, NR^{c1}R^{d1}, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with CN, NO₂, OR^{a1}, NR^{c1}R^{d1}, S(O)₂R^{b1}, C(O)NR^{c1}R^{d1}, S(O)₂NR^{c1}R^{d1}, C(O)OR^{a1}, or S(O)₂OR^{a1};

R^{a1}, R^{b1}, R^{c1}, and R^{d1} are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

R^{8a}, R^{8b}, and R^{8c} are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

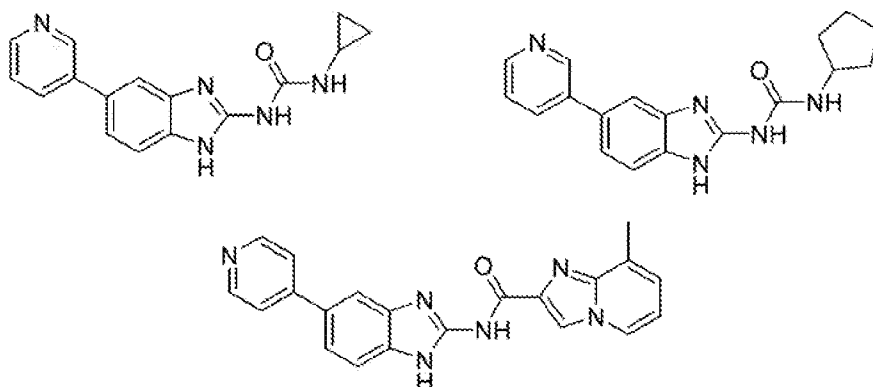
each X is independently selected from N and CR^{9b}, wherein one X is N and the other X is CR^{9b};

R^{9a} and R^{9b} are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g;

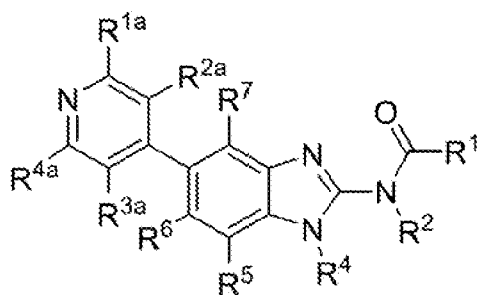
and

each R^8 is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxy carbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino;

provided that the compound of Formula (I) is not any one of the following compounds:

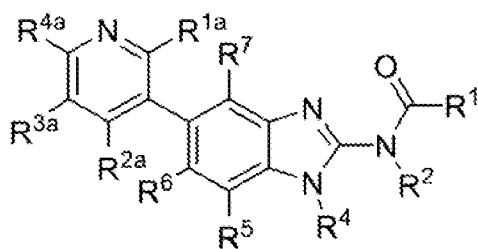


2. The compound of claim 1, having formula:



or a pharmaceutically acceptable salt thereof.

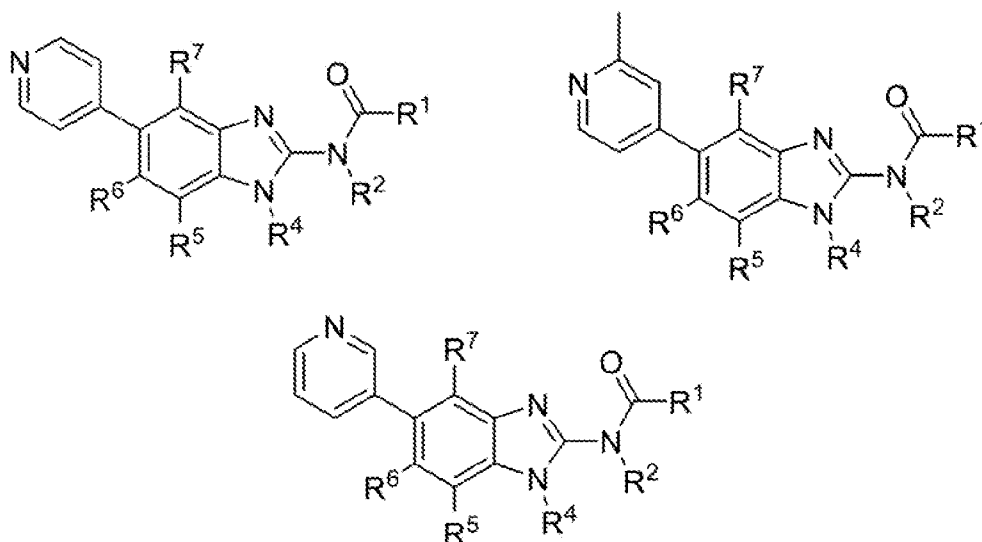
3. The compound of claim 1, having formula:



or a pharmaceutically acceptable salt thereof.

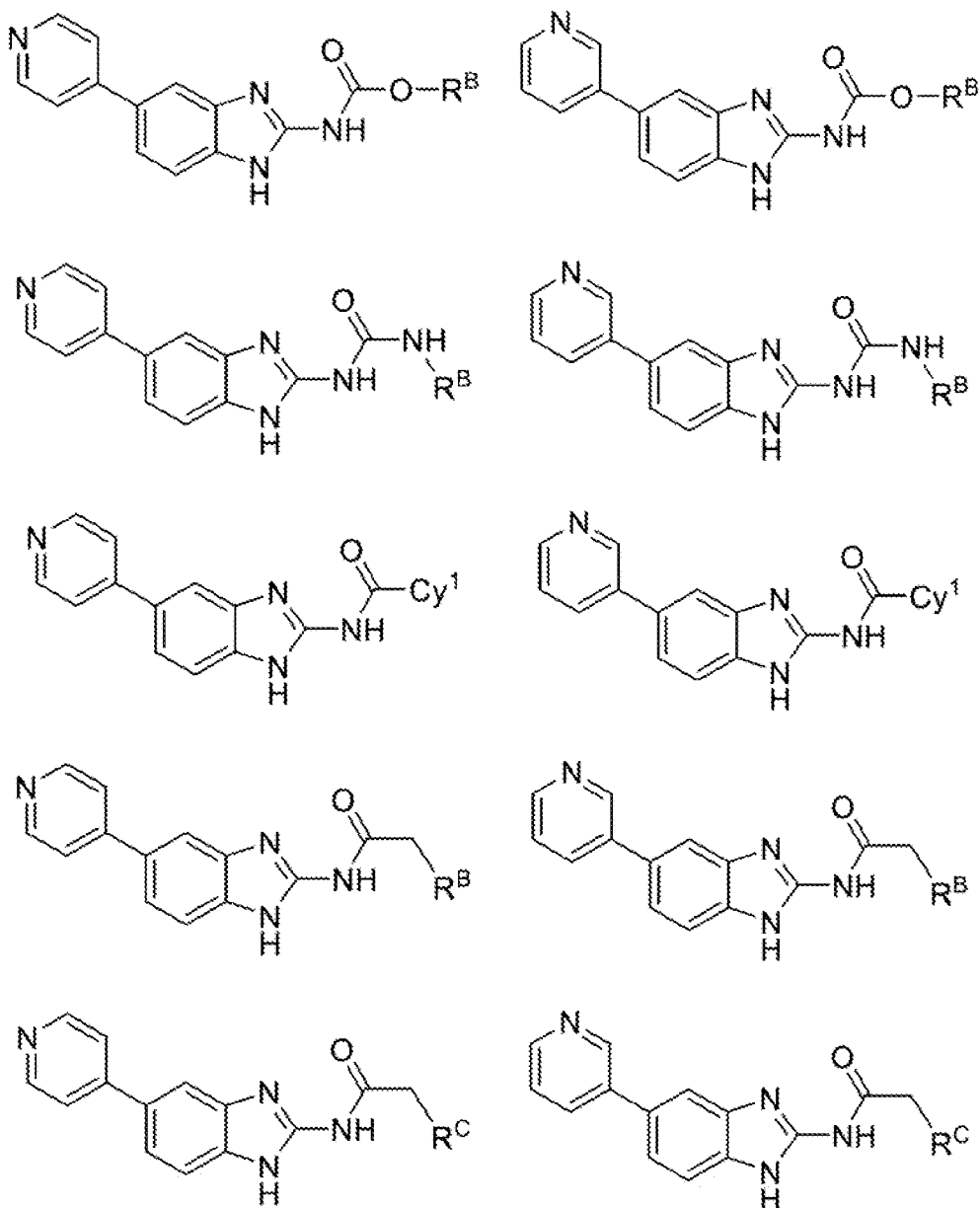
4. The compound of any one of claims 1-3, wherein R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, and C_{1-3} haloalkyl.

5. The compound of any one of claims 1-3, wherein R^{1a} , R^{2a} , R^{3a} , and R^{4a} are each independently selected from H and C_{1-3} alkyl.
6. The compound of claim 1, wherein the compound of Formula (I) is selected from any one of the following compounds:



or a pharmaceutically acceptable salt thereof.

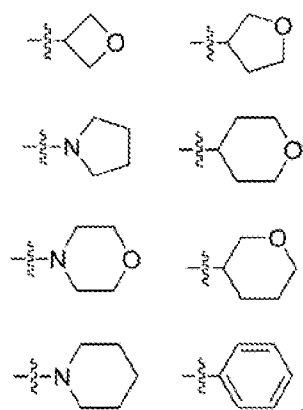
7. The compound of any one of claims 1-6, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , and $NR^{c1}R^{d1}$.
8. The compound of any one of claims 1-6, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $di(C_{1-3}$ alkyl)amino.
9. The compound of any one of claims 1-8, wherein R^1 is selected from OR^B and NR^3R^B .
10. The compound of claim 9, wherein R^1 is OR^B .
11. The compound of claim 9, wherein R^1 is NHR^B .
12. The compound of any one of claims 1-8, wherein R^1 is CH_2R^B .
13. The compound of any one of claims 1-8, wherein the compound of Formula (I) is selected from:



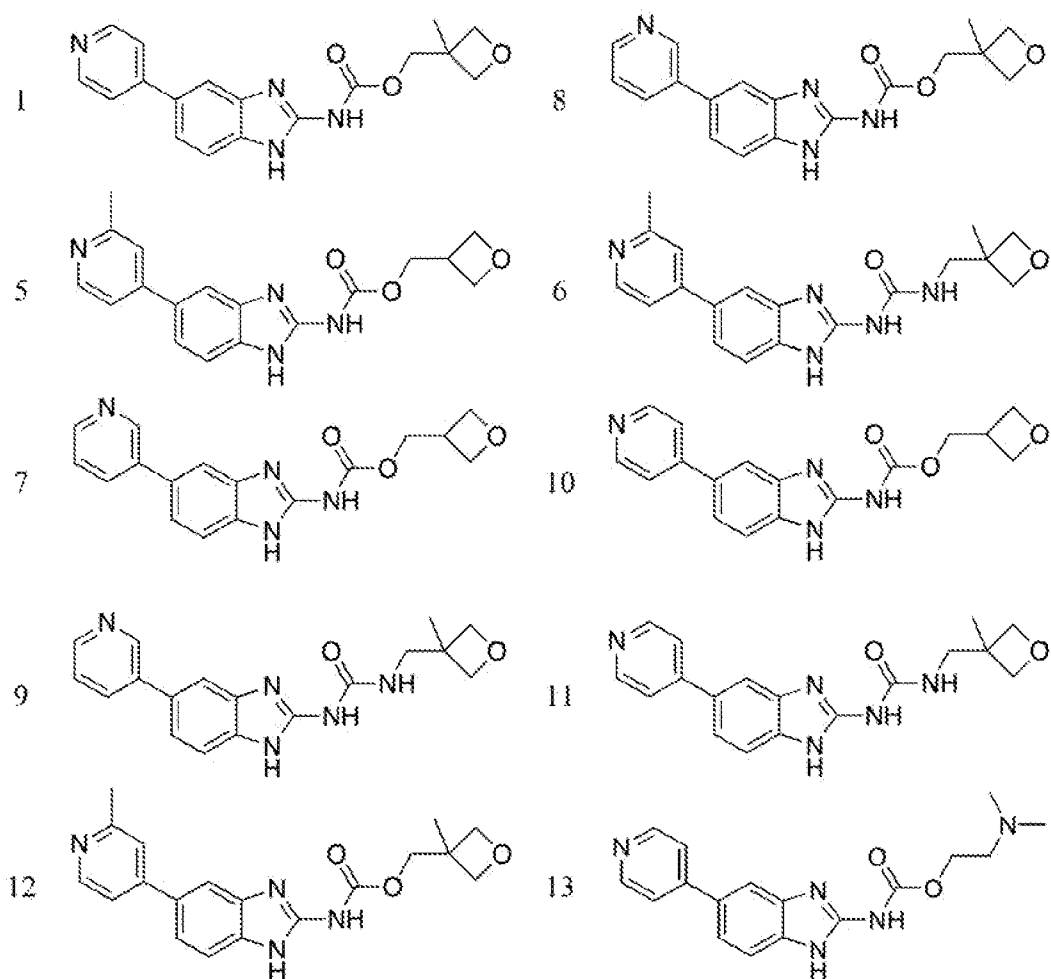
or a pharmaceutically acceptable salt thereof.

14. The compound of any one of claims 1-13, wherein R^B is selected from Cy¹ and C₁₋₆ alkyl substituted with Cy¹, OR^{sl}, or NR^{sl}R^{dl}.
15. The compound of claim 14, wherein R^B is selected from Cy¹, C₁₋₆ alkyl substituted with Cy¹, and C₁₋₆ alkyl substituted with NR^{sl}R^{dl}.
16. The compound of claim 15, wherein R^B is Cy¹.

17. The compound of claim 15, wherein R^B is C_{1-6} alkyl substituted with Cy^1 .
18. The compound of any one of claims 1-17, wherein Cy^1 is selected from C_{6-10} aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
19. The compound of claim 18, wherein Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
20. The compound of claim 18, wherein Cy^1 is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
21. The compound of claim 20, wherein the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholinyl, pyrrolidinyl, and oxazolidinyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
22. The compound of any one of claims 1-21, wherein R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.
23. The compound of any one of claims 1-21, wherein R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.
24. The compound of any one of claims 1-23, wherein Cy^1 is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cy1} :



25. The compound of any one of claims 1-13, wherein R^B is C_{1-6} alkyl substituted with $NR^{cl}R^{dl}$.
26. The compound of claim 25, wherein R^B is selected from $CH_2NR^{cl}R^{dl}$, $CH_2CH_2NR^{cl}R^{dl}$, and $CH_2CH_2CH_2NR^{cl}R^{dl}$.
27. The compound of claim 1, wherein the compound of Formula (I) is selected from any one of the following compounds:



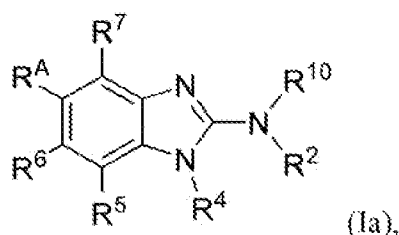
or a pharmaceutically acceptable salt thereof.

28. A pharmaceutical composition comprising a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

29. A method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-28, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 29.
30. The method of claim 30, wherein the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astrogliopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.
31. The method of claim 30, wherein the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimia, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.
32. The method of claim 30, wherein the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis,

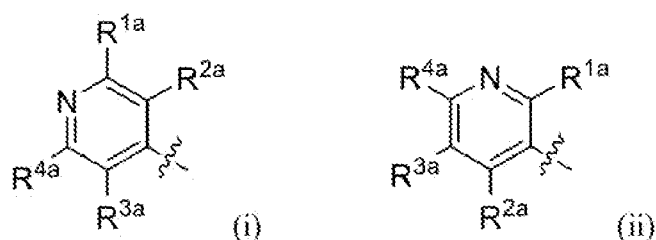
systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.

33. The method of claim 30, wherein the disease or condition is a cancer selected from brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.
34. A method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising:
- identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and
 - after (i), administering to the subject a therapeutically effective amount of a compound of Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein:

R^A is selected from moiety (i) and (ii):



R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

R¹⁰ is selected from H, C₁₋₃ alkyl, C₁₋₃ haloalkyl, and C(=O)R^l;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^B is independently selected from H, Cy^1 , C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein said C_{1-6} alkyl is optionally substituted with Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^C is selected from CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, Cy^1 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from Cy^1 , CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, and $S(O)_2OR^{a1}$;

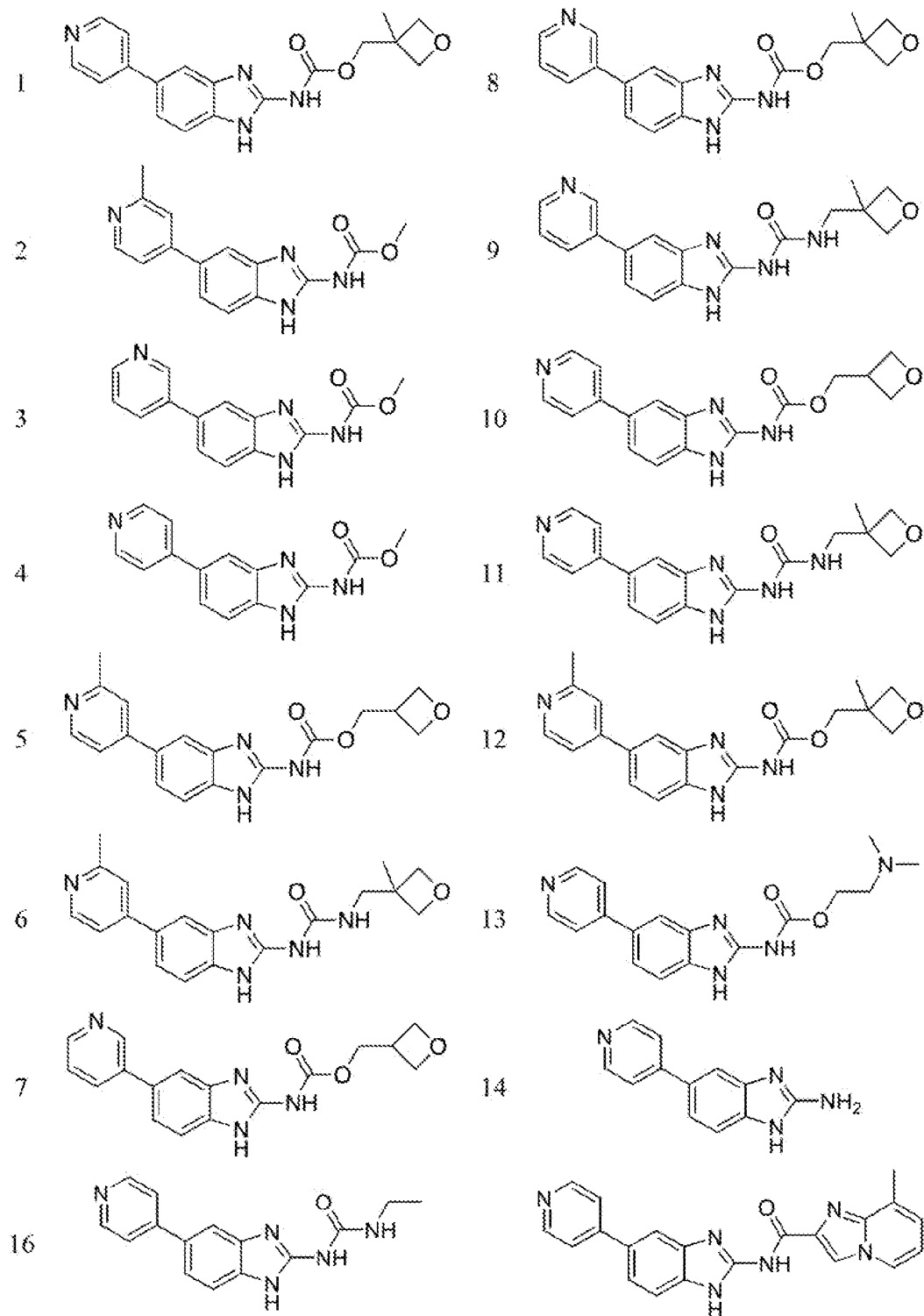
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

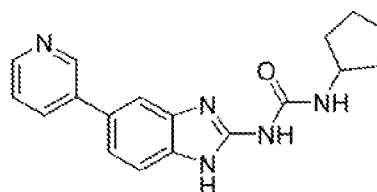
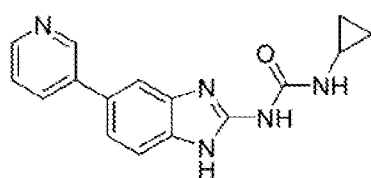
each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{a1} , $NR^{c1}R^{d1}$, $S(O)_2R^{b1}$, $C(O)NR^{c1}R^{d1}$, $S(O)_2NR^{c1}R^{d1}$, $C(O)OR^{a1}$, or $S(O)_2OR^{a1}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E ; and

each R^E is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

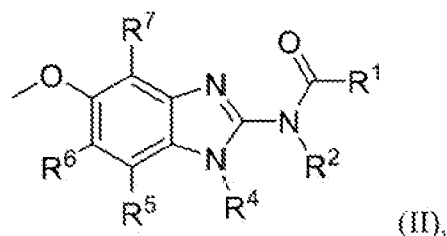
35. The method of claim 35, wherein the compound of Formula (Ia) is selected from any one of the following compounds:





or a pharmaceutically acceptable salt thereof.

36. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from OR^B, NR³R^B, and CH₂R^C;

each R^B is independently selected from Cy¹, C₁₋₆ haloalkyl, and C₁₋₆ alkyl substituted with Cy¹, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

R^C is selected from NO₂, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, S(O)₂OR^{al}, and C₁₋₆ alkyl substituted with NO₂, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

R², R³, and R⁴ are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl;

R⁵, R⁶, and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al}, wherein said C₁₋₃ alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, and S(O)₂OR^{al};

each Cy¹ is independently selected from C₆₋₁₀ aryl, C₃₋₁₀ cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cyl};

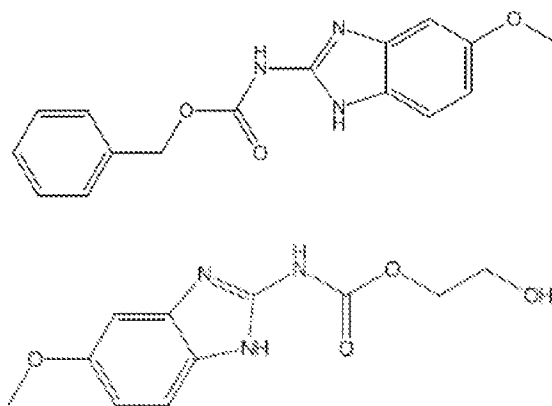
each R^{Cyl} is independently selected from halo, CN, NO₂, OR^{al}, NR^{cl}R^{dl}, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with

CN, NO₂, OR^{al}, NR^{cl}R^{dl}, S(O)₂R^{bl}, C(O)NR^{cl}R^{dl}, S(O)₂NR^{cl}R^{dl}, C(O)OR^{al}, or S(O)₂OR^{al};

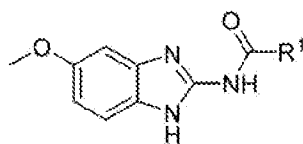
R^{al}, R^{bl}, R^{cl}, and R^{dl} are each independently selected from H, C₁₋₃ alkyl, and C₁₋₃ haloalkyl, wherein said C₁₋₃ alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^g; and

each R^g is independently selected from halo, CN, OH, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, carboxy, C₁₋₃ alkoxycarbonyl, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino;

provided that the compound of Formula (II) is not any of the following compounds:



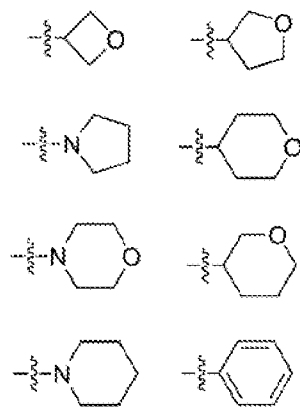
37. The compound of claim 36, wherein R⁵, R⁶, and R⁷ are each independently selected from H, halo, CN, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, OR^{al}, and NR^{cl}R^{dl}.
38. The compound of claim 36, wherein R⁵, R⁶, and R⁷ are each independently selected from H, halo, CN, OH, NO₂, C₁₋₃ alkyl, C₁₋₃ haloalkyl, C₁₋₃ alkoxy, C₁₋₃ haloalkoxy, amino, C₁₋₃ alkylamino, and di(C₁₋₃ alkyl)amino.
39. The compound of claim 36, wherein the compound has formula:



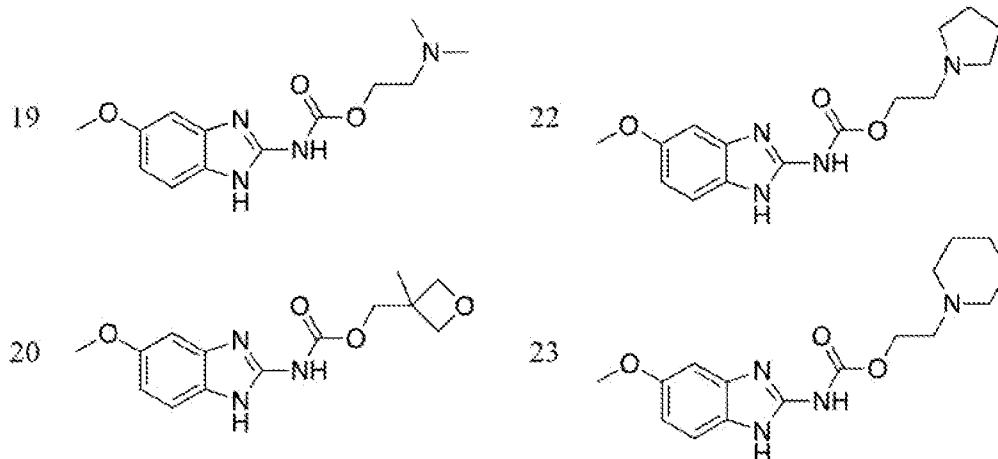
or a pharmaceutically acceptable salt thereof.

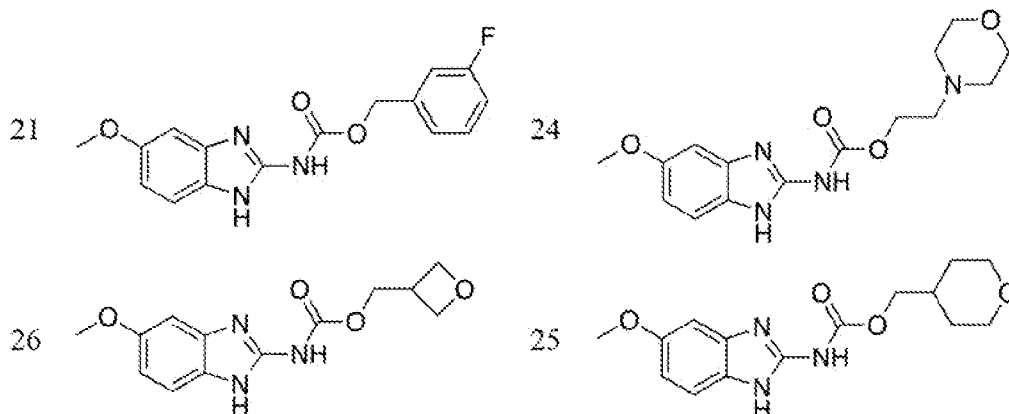
40. The compound of any one of claims 36-39, wherein R^1 is selected from OR^B and NR^3R^B .
41. The compound of claim 40, wherein R^1 is OR^B .
42. The compound of claim 40, wherein R^1 is NHR^B .
43. The compound of any one of claims 36-42 wherein R^B is selected from Cy^1 and C_{1-6} alkyl substituted with Cy^1 , OR^{d1} , or $NR^{c1}R^{d1}$.
44. The compound of claim 43, wherein R^B is selected from Cy^1 , C_{1-6} alkyl substituted with Cy^1 , and C_{1-6} alkyl substituted with $NR^{c1}R^{d1}$.
45. The compound of claim 44, wherein R^B is Cy^1 .
46. The compound of claim 44, wherein R^B is C_{1-6} alkyl substituted with Cy^1 .
47. The compound of any one of claims 36-46, wherein Cy^1 is selected from C_{6-10} aryl and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
48. The compound of claim 47, wherein Cy^1 is C_{6-10} aryl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
49. The compound of claim 47, wherein Cy^1 is 3-10 membered heterocycloalkyl, optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
50. The compound of claim 49, wherein the 3-10 membered heterocycloalkyl is selected from oxiranyl, oxetanyl, tetrahydrofuranyl, 1,3-dioxolanyl, tetrahydropyranyl, 1,3-dioxanyl, morpholiny, pyrrolidiny, and oxazolidiny, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} .
51. The compound of any one of claims 36-50, wherein R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, and C_{1-3} haloalkoxy.
52. The compound of any one of claims 36-50, wherein R^{Cy1} is selected from halo, NO_2 , C_{1-3} alkyl, and C_{1-3} alkoxy.

53. The compound of any one of claims 36-46, wherein Cy^1 is selected from any one of the following moieties, each of which is optionally substituted with 1 or 2 independently selected R^{Cyl} :



54. The compound of any one of claims 36-46, wherein R^B is C_{1-6} alkyl substituted with $NR^{cl}R^{dl}$.
55. The compound of claim 54, wherein R^B is selected from $CH_2NR^{cl}R^{dl}$, $CH_2CH_2NR^{cl}R^{dl}$, and $CH_2CH_2CH_2NR^{cl}R^{dl}$.
56. The compound of claim 36, wherein the compound of Formula (II) is selected from any one of the following compounds:



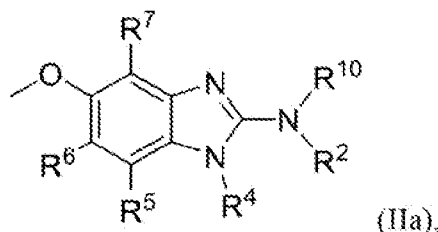


or a pharmaceutically acceptable salt thereof.

57. A pharmaceutical composition comprising a compound of any one of claims 36-56, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
58. A method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 36-56, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 57.
59. The method of claim 58, wherein the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Leu Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic

- encephalopathy (CTE), aging-related tau astrogliaopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.
60. The method of claim 58, wherein the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycerimia, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.
61. The method of claim 58, wherein the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis, systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.
62. The method of claim 58, wherein the disease or condition is a cancer selected from brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.
63. A method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising:
- (i) identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and

(ii) after (i), administering to the subject a therapeutically effective amount of a compound of Formula (IIa):



or a pharmaceutically acceptable salt thereof, wherein:

R^{10} is selected from H, C_{1-3} alkyl, C_{1-3} haloalkyl, and $C(=O)R^1$;

R^1 is selected from Cy^1 , OR^B , NR^3R^B , CH_2R^B , and CH_2R^C ;

each R^B is independently selected from H, Cy^1 , C_{1-6} haloalkyl, and C_{1-6} alkyl substituted with Cy^1 , CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^C is selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

R^2 , R^3 , and R^4 are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl;

R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$, wherein said C_{1-3} alkyl is optionally substituted with 1 or 2 substituents independently selected from CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, and $S(O)_2OR^{al}$;

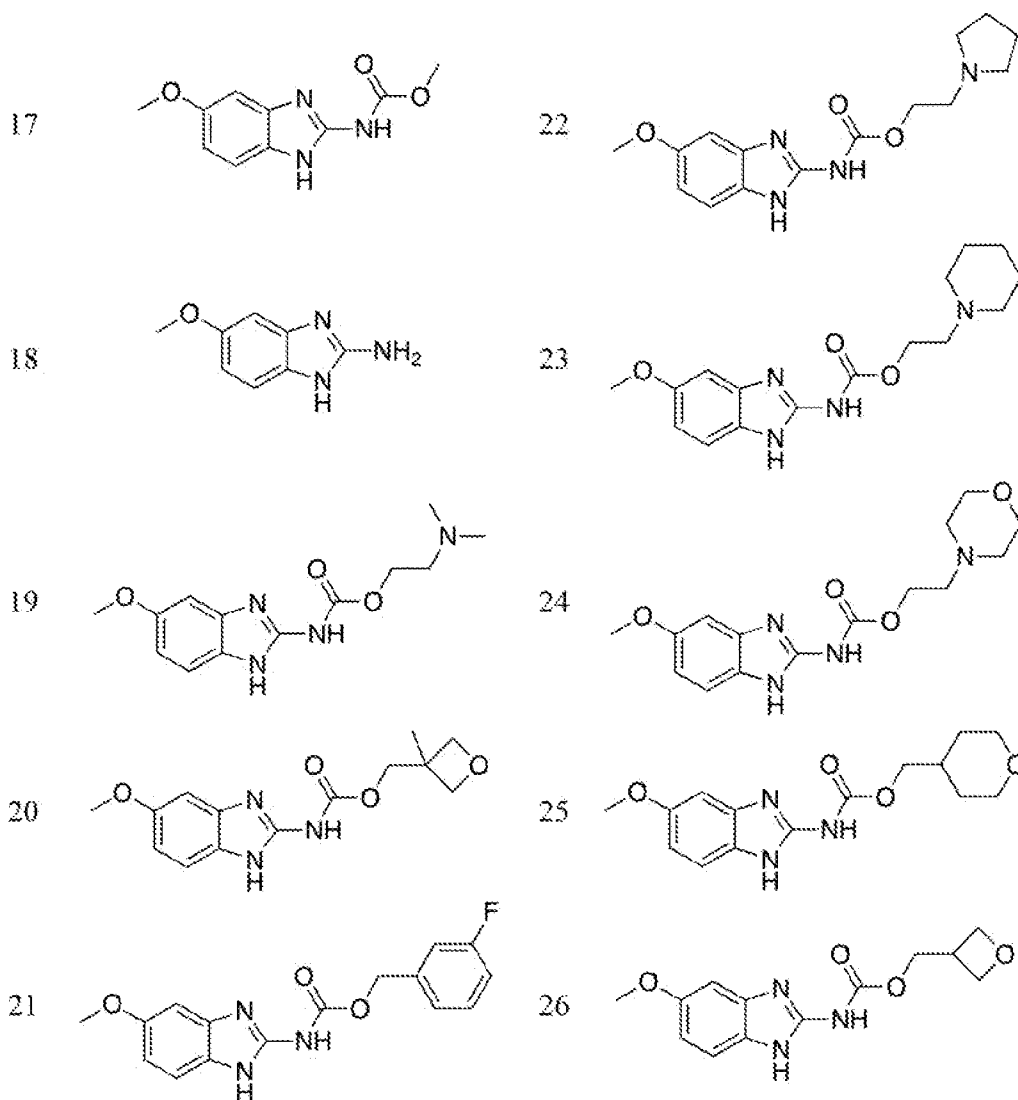
each Cy^1 is independently selected from C_{6-10} aryl, C_{3-10} cycloalkyl, 5-14 membered heteroaryl, and 3-10 membered heterocycloalkyl, each of which is optionally substituted with 1 or 2 substituents independently selected from R^{Cy1} ;

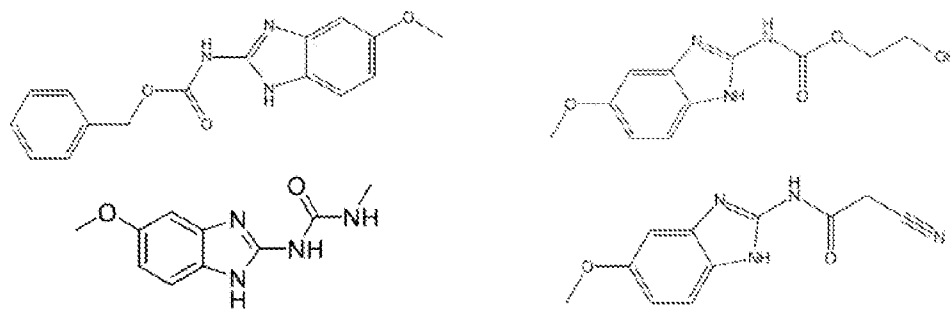
each R^{Cy1} is independently selected from halo, CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with CN, NO_2 , OR^{al} , $NR^{cl}R^{dl}$, $S(O)_2R^{bl}$, $C(O)NR^{cl}R^{dl}$, $S(O)_2NR^{cl}R^{dl}$, $C(O)OR^{al}$, or $S(O)_2OR^{al}$;

R^{a1} , R^{b1} , R^{c1} , and R^{d1} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^E , and

each R^E is independently selected from halo, CN, OH, C_{1-3} alkoxy, C_{1-3} haloalkoxy, carboxy, C_{1-3} alkoxycarbonyl, amino, C_{1-3} alkylamino, and di(C_{1-3} alkyl)amino.

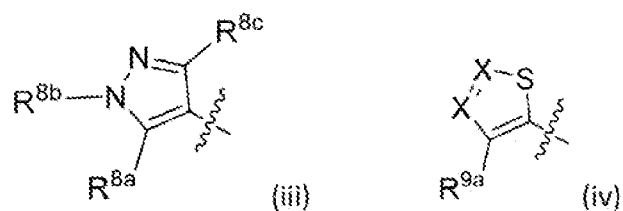
64. The method of claim 63, wherein the compound of Formula (IIa) is selected from any one of the following compounds:



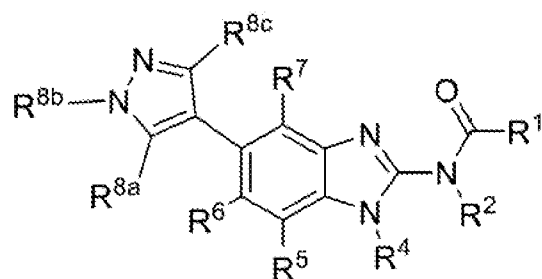


or a pharmaceutically acceptable salt thereof.

65. The compound of claim 1, wherein R^A is selected from moiety (iii) and (iv):

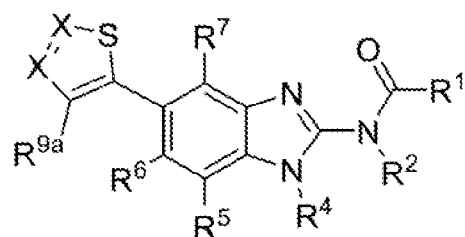


66. The compound of claim 65, wherein the compound has the formula



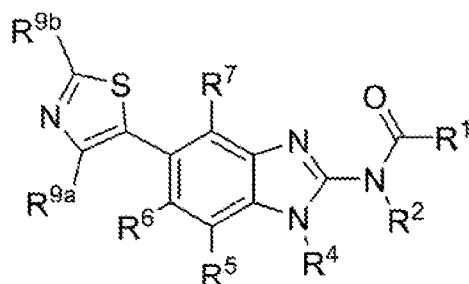
or a pharmaceutically acceptable salt thereof.

67. The compound of claim 65, wherein the compound has the formula



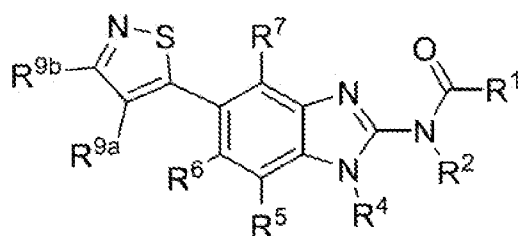
or a pharmaceutically acceptable salt thereof.

68. The compound of claim 67, wherein the compound has the formula



or a pharmaceutically acceptable salt thereof.

69. The compound of claim 67, wherein the compound has the formula



or a pharmaceutically acceptable salt thereof.

70. The compound of claim 66, wherein R^{8a} , R^{8b} , and R^{8c} are each independently selected from H and C_{1-3} alkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 .

71. The compound of claim 66, wherein R^{8a} , R^{8b} , and R^{8c} are each independently selected from H and C_{1-3} alkyl.

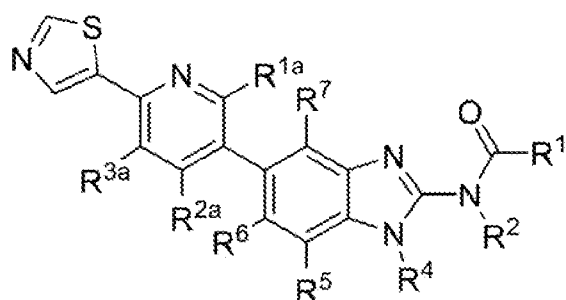
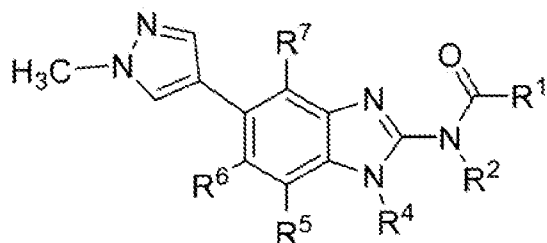
72. The compound of claim 66, wherein R^{8a} and R^{8c} are both H and R^{8b} is C_{1-3} alkyl.

73. The compound of claim 67, wherein R^{9a} and R^{9b} are each independently selected from H, C_{1-3} alkyl, and C_{1-3} haloalkyl, wherein said C_{1-3} alkyl is optionally substituted with 1, 2, or 3 substituents independently selected from R^8 .

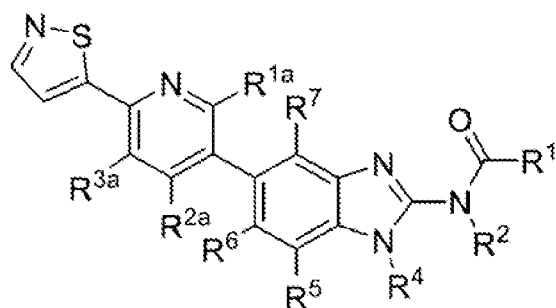
74. The compound of claim 67, wherein R^{9a} and R^{9b} are each independently selected from H and C_{1-3} alkyl.

75. The compound of claim 67, wherein R^{9a} and R^{9b} are both H.

76. The compound of claim 65, wherein the compound is selected from any one of the following compounds:



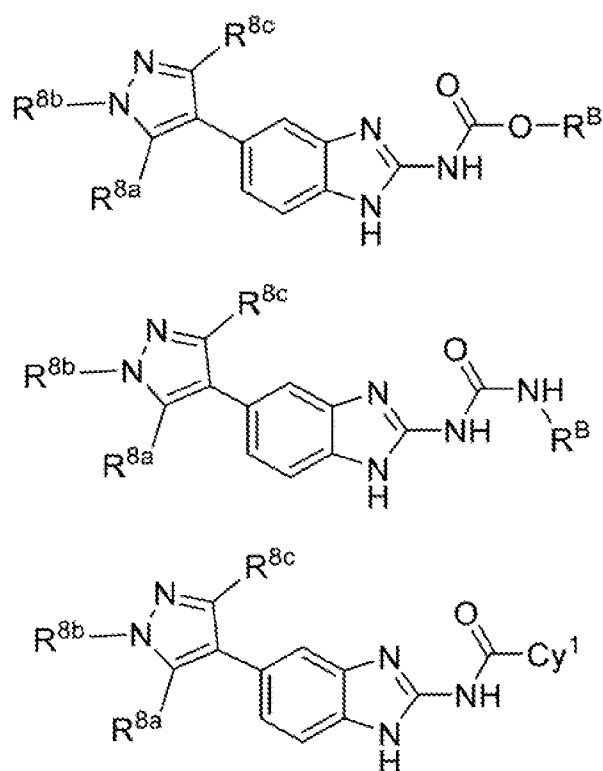
and

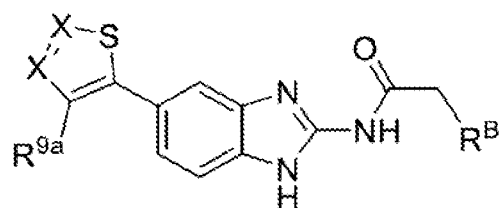
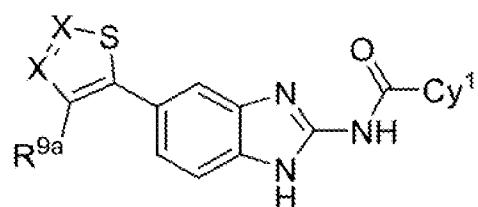
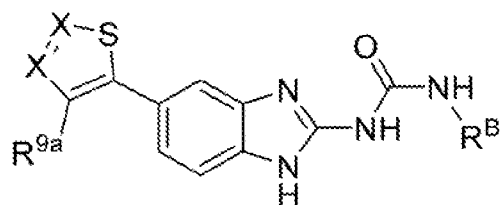
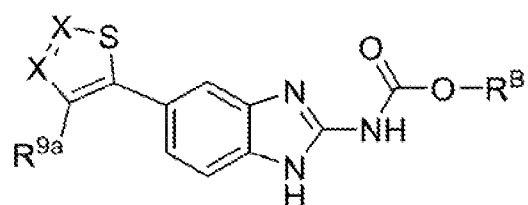
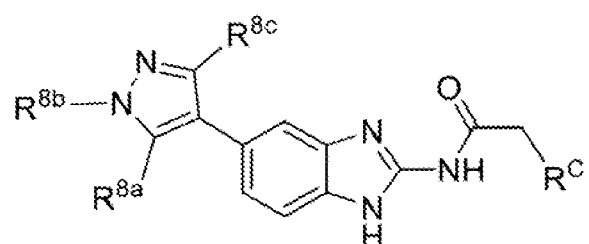
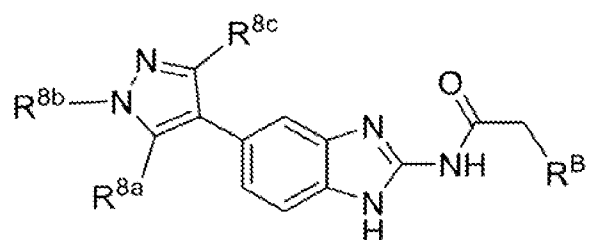


or a pharmaceutically acceptable salt thereof.

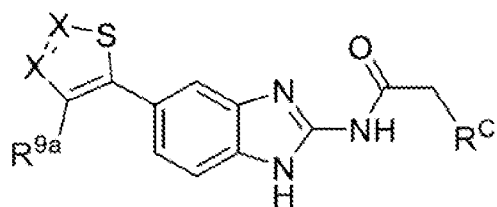
77. The compound of claim 65, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, OR^{a1} , and $NR^{c1}R^{d1}$.

78. The compound of claim 65, wherein R^5 , R^6 , and R^7 are each independently selected from H, halo, CN, OH, NO_2 , C_{1-3} alkyl, C_{1-3} haloalkyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, amino, C_{1-3} alkylamino, and $\text{di}(\text{C}_{1-3}$ alkyl)amino.
79. The compound of claim 65, wherein R^1 is selected from OR^B and NR^3R^B .
80. The compound of claim 65, wherein R^1 is OR^B .
81. The compound of claim 65, wherein R^1 is NHR^B .
82. The compound of claim 65, wherein R^1 is CH_2R^B .
83. The compound of claim 65, wherein the compound of Formula (I) is selected from:



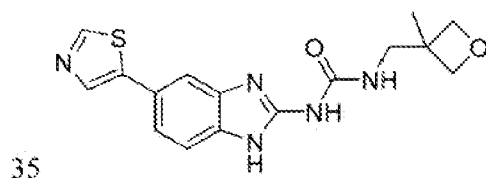
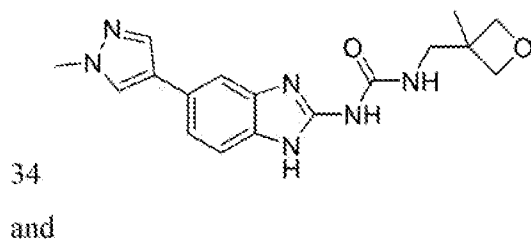
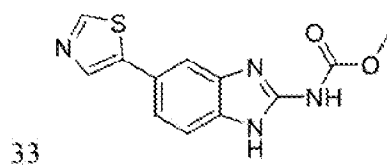
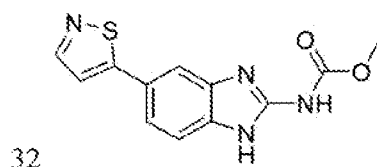
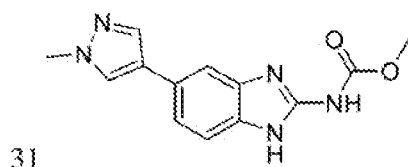


and



or a pharmaceutically acceptable salt thereof.

- 84 The compound of claim 65, wherein the compound is selected from any one of the following compounds:



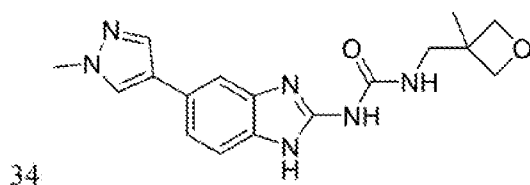
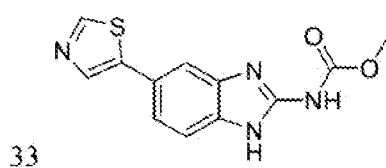
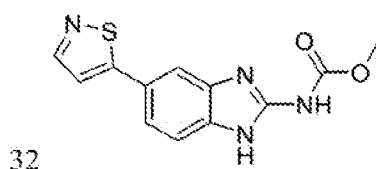
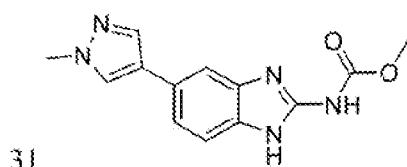
or a pharmaceutically acceptable salt thereof.

85. A pharmaceutical composition comprising a compound of any one of claims 65-84, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

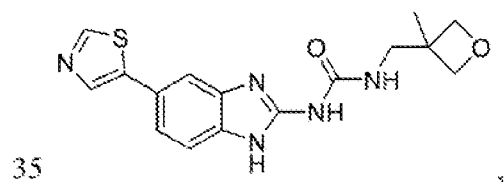
86. A method of treating a disease or condition where DYRK1A is implicated in pathology of the disease or condition, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 65-84, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 85.
87. The method of claim 86, wherein the disease or condition is a neurodegenerative disease selected from dementia with Lewy bodies, Parkinson's disease (PD), multiple system atrophy (MSA), pure autonomic failure (PAF), PD with dementia, olivopontocerebellar atrophy (OPCA), striatonigral degeneration (SND), neuroaxonal dystrophy, Shy-Drager syndrome, Hallervorden-Spatz syndrome, Bradbury-Eggleston syndrome, premature aging, cerebral amyloid angiopathy, Alzheimer's disease (AD), familial AD (FAD), dementia associated with AD or FAD, frontotemporal lobar degeneration (FTD), dementia associated with FTD, amyotrophic lateral sclerosis (ALS, aka Lou Gehrig's disease), Huntington's disease (HD), dementia associated with HD, Pick's disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, primary age-related tauopathy, neurofibrillary tangle dementia, chronic traumatic encephalopathy (CTE), aging-related tau astrogliopathy, Richardson syndrome, cerebellar ataxia, globular glial tauopathy, and argyrophilic grain disease.
88. The method of claim 86, wherein the disease or condition is a metabolic disorder selected from type 1 diabetes, type 2 diabetes, hyperglycemia, hypermethioninemia, familial hypercholesterolemia, Gaucher disease, Hunter syndrome, Krabbe disease, maple syrup urine disease, metachromatic leukodystrophy, mitochondrial encephalopathy, lactic acidosis, stroke-like episodes (MELAS), Niemann-Pick, phenylketonuria (PKU), porphyria, Tay-Sachs disease, and Wilson's disease.
89. The method of claim 86, wherein the disease or condition is an inflammatory disorder selected from arthritis, rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory arthritis, inflammatory bowel disease, osteoarthritis, inflammatory joint disease, systemic lupus erythematosus, osteoporosis, ulcerative colitis,

systemic autoimmunity, sepsis, dermatomyositis, multiple sclerosis, myasthenia gravis, Hashimoto thyroiditis, and Grave's disease.

90. The method of claim 86, wherein the disease or condition is a cancer selected from brain cancer (*e.g.*, glioblastoma, neuroblastoma), leukemia (*e.g.*, B cell acute lymphoblastic leukemia), breast cancer, and pancreatic cancer.
91. A method of treating a disease or condition where overexpression and/or enhanced activity of DYRK1A is implicated in pathology of the disease or condition, the method comprising:
- (i) identifying a subject diagnosed with the disease or condition responsive to inhibition of DYRK1A in a cell, a tissue, and/or an organ affected by the disease or condition; and
 - (ii) after (i), administering to the subject a therapeutically effective amount of a compound of any one of claims 65-84, or a pharmaceutically acceptable salt thereof.
92. The method of claim 91, wherein the compound is selected from any one of the following compounds:



and



or a pharmaceutically acceptable salt thereof.