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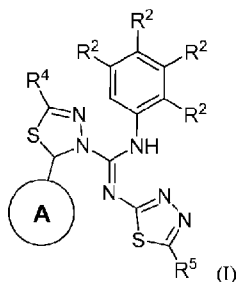
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(54) Title: SECRETIN RECEPTOR AGONISTS AND METHODS OF USE



(57) Abstract: The present application provides compounds of Formula (I) or a pharmaceutically acceptable salt thereof. Pharmaceutical compositions are also provided and are useful for treating and/or preventing heart failure, obesity, type 2 diabetes mellitus, hypertension, functional dyspepsia, cholestasis, and non-alcoholic fatty liver disease.



SECRETIN RECEPTOR AGONISTS AND METHODS OF USE**FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT**

This invention was made with government support under R01 HL133501 awarded by the National Institutes of Health. The government has certain rights in the invention.

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FIELD

This disclosure provides compounds of Formula (I) and pharmaceutically acceptable salts thereof that are useful for treating and/or preventing heart failure (HF), obesity, type 2 diabetes mellitus, hypertension, functional dyspepsia, cholestasis, and non-alcoholic fatty liver disease.

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BACKGROUND

Heart failure (HF) is a major cause of morbidity and mortality, particularly in the elderly, with almost 6 million cases in the United States at this time, and projections to exceed 8 million cases by 2030. Current annual costs (direct and indirect) of \$31 billion (>65 million hospital days) are projected to reach \$70 billion by 2030. HF is the leading cause of hospitalization for Medicare-age patients. While a variety of drugs are effective to acutely correct decompensated HF, this has had little effect to improve prognosis. The clinical course post-hospitalization is particularly unsatisfactory, with rehospitalisation rates of 25% at 1 month and 50% at 6 months, and mortality rates of 30% at 1 year and 50% at 3 years. Even patients with absent or minimal resting signs and symptoms of congestion at hospital discharge who take full advantage of current medications, experience these high rates of readmission and mortality, with this true of those with both preserved and reduced ejection fractions. This clearly represents an enormous unmet medical need.

Secretin is known primarily as a gastrointestinal peptide hormone (27 residues) secreted from intestinal S cells in response to acid in the gut lumen. Its classical physiologic action is to stimulate alkaline secretion from pancreatic and biliary duct cells to neutralize the luminal acidic chyme, acting through the secretin receptor (SecR). Secretin acts through binding to a class B GPCR, SecR. This receptor is prototypic of this small group of peptide-binding GPCRs, including only 15 members, but with many of these possessing important physiologic actions and

representing high priority therapeutic targets. This includes receptors for glucagon, glucagon-like peptide-1 (GLP-1), parathyroid hormone, calcitonin, calcitonin gene-related peptide, gastric insulinotropic peptide, vasoactive intestinal polypeptide, and corticotropin-releasing factor. Like other members of the GPCR superfamily, the class B GPCRs have seven transmembrane segments and couple at their cytosolic face with heterotrimeric G proteins. This small and coherent group all bind moderate length peptides with diffuse pharmacophoric domains. The carboxyl-terminal region of these peptides binds within a groove in a disulphide-bonded amino-terminal extracellular domain, thereby directing the peptide amino terminus into the top of the helical bundle where biological activity is mediated.

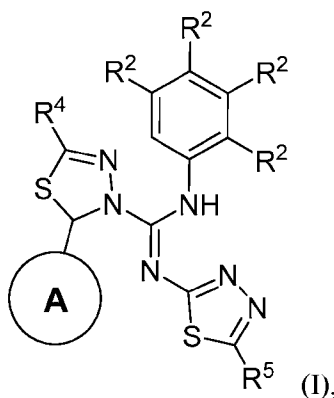
Like all the class B GPCRs, SecR can couple with both Gs and Gq, resulting in cAMP and intracellular calcium responses. The dominant physiologic coupling is with Gs, with the cAMP response at low concentrations of secretin, while the calcium response requires three orders of magnitude more agonist.

The stimulation of the secretin signaling pathway would be beneficial and provide novel treatment approaches for patients with HF and/or obesity, type 2 diabetes mellitus, hypertension, functional dyspepsia, cholestasis, and non-alcoholic fatty liver disease. There are also no secretin-like agonists (other than the peptide itself, that has a very short half-life and that requires parenteral administration), or any positive allosteric modulators of secretin action.

SUMMARY

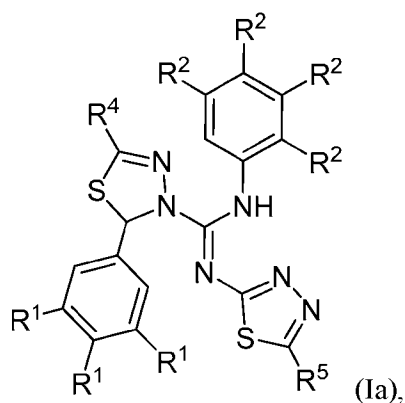
The present disclosure provides, *inter alia*, compounds that stimulate secretin receptor (SecR), with diverse modes of action. Specific scaffolds were identified that have agonist, positive allosteric modulator (PAM) or mixed ago-PAM effect. Stimulation of SecR signaling by agonists/PAMs may result in improved cardiac output, leading to a first-in-class therapeutic approach for the treatment of HF patients. Such compounds would fill a major unmet need for the cardiovascular community, by providing first-in-class agents that would increase secretin agonism and its effects on the heart, peripheral vasculature, islets, adipocytes, and neurons useful for outpatients with HF.

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



or a pharmaceutically acceptable salt thereof, wherein ring A, R², R⁴, and R⁵ are defined as described herein.

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



or a pharmaceutically acceptable salt thereof, wherein R¹, R², R⁴, and R⁵ are defined as described herein.

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

In yet another general aspect, the present disclosure provides a method of
 treating or preventing obesity, type 2 diabetes mellitus, heart failure, hypertension,
 functional dyspepsia, cholestasis, and non-alcoholic fatty liver disease in a subject in
 15 need thereof, comprising administering to the subject a therapeutically effective
 amount of a compound of Formula (I) or (Ia), or a pharmaceutically acceptable salt
 thereof, or a pharmaceutical composition as provided herein.

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,
5 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.

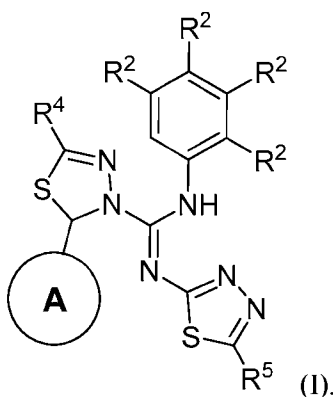
Other features and advantages of the present application will be apparent from the following detailed description, and from the claims.

DETAILED DESCRIPTION

The present disclosure provides, *inter alia*, compounds that are agonists and positive allosteric modulators (PAMs), as well as mixed agonist and PAM activities (ago-PAMs) targeting SecRs able to stimulate the receptor or potentiate effects of natural agonist secretin in systems carrying endogenous SecRs. Pharmaceutical
15 compositions comprising said compounds are also provided, as well as the methods of using these compounds for treating obesity, type 2 diabetes mellitus, heart failure, hypertension, functional dyspepsia, cholestasis, and non-alcoholic fatty liver. Certain embodiments of the compounds, compositions, methods, and combination treatments are disclosed herein.

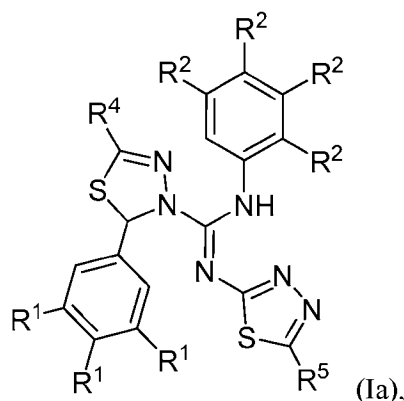
Compounds

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



or a pharmaceutically acceptable salt thereof, wherein ring A, R², R⁴, and R⁵
25 are defined as described herein.

On another general aspect, the present disclosure provides a compound of Formula (Ia):



or a pharmaceutically acceptable salt thereof, wherein R^1 , R^2 , R^4 , and R^5 are defined as described herein.

In some embodiments, ring **A** is selected from phenyl, naphthyl, fluorenyl, dibenzofuranyl, and benzodioxazolyl, each optionally substituted with 1, 2, 3, or 4 R^1 , or ring **A** is thienyl optionally substituted with 1, 2, or 3 R^1 . In some embodiments, ring **A** is selected from phenyl, naphthyl, fluorenyl, dibenzofuranyl, and benzodioxazolyl.

In some embodiments, each R^1 is independently selected from halo, CN, OR^{a1} , SR^{a1} , C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl and pyridinyl. In some embodiments, the phenyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halo, OR^{a1} , C_{1-6} alkyl, and C_{1-6} haloalkyl.

In some embodiments, each R^2 is independently selected from halo, CN, OR^{a1} , SR^{a1} , C_{1-6} alkyl, and C_{1-6} haloalkyl.

In some embodiments, R^4 and R^5 are each independently selected from C_{1-6} alkyl, and phenyl.

In some embodiments, each R^{a1} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, and phenyl.

In some embodiments, R^5 is C_{1-6} alkyl. In some embodiments, R^5 is methyl or ethyl. In some embodiments, R^5 is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, C_{1-6} alkyl, and C_{1-6} haloalkyl. In some embodiments, R^5 is phenyl.

In some embodiments, R^4 is H. In some embodiments, R^4 is C_{1-6} alkyl. In

some embodiments, R⁴ is methyl or ethyl. In some embodiments, R⁴ is phenyl optionally substituted with 1, 2 or 3 substituents each independently selected from halo, C₁₋₆ alkyl, and C₁₋₆ haloalkyl. In some embodiments, R⁴ is phenyl.

In some embodiments, R⁴ and R⁵ are methyl. In some embodiments, R⁴ and R⁵ are ethyl. In some embodiments, R⁴ and R⁵ are phenyl.

In some embodiments, the compound of Formula (I) or Formula (Ia) comprises at least one R² selected from halo, OR^{a1}, C₁₋₆ alkyl, and C₁₋₆ haloalkyl. In some embodiments, the compound of Formula (I) or Formula (Ia) comprises one R², two R², three R², four R², or five R². In some embodiments, at least one R² is methyl. In some embodiments, one R² is methyl. In some embodiments, two R² are methyl. In some embodiments, three R² are methyl. In some embodiments, at least one R² is ethyl. In some embodiments, one R² is ethyl. In some embodiments, two R² are ethyl. In some embodiments, three R² are ethyl. In some embodiments, at least one R² is iso-propyl. In some embodiments, one R² is iso-propyl. In some embodiments, two R² are iso-propyl. In some embodiments, three R² are iso-propyl. In some embodiments, at least one R² is fluoro. In some embodiments, one R² is fluoro. In some embodiments, two R² are fluoro. In some embodiments, three R² are fluoro. In some embodiments, at least one R² is chloro. In some embodiments, one R² is chloro. In some embodiments, two R² are chloro. In some embodiments, three R² are chloro. In some embodiments, at least one R² is bromo. In some embodiments, one R² is bromo. In some embodiments, two R² are bromo. In some embodiments, three R² are bromo. In some embodiments, at least one R² is CF₃. In some embodiments, one R² is CF₃. In some embodiments, two R² are CF₃. In some embodiments, three R² are CF₃. In some embodiments, at least one R² is OCF₃. In some embodiments, one R² is OCF₃. In some embodiments, two R² are OCF₃. In some embodiments, three R² are OCF₃.

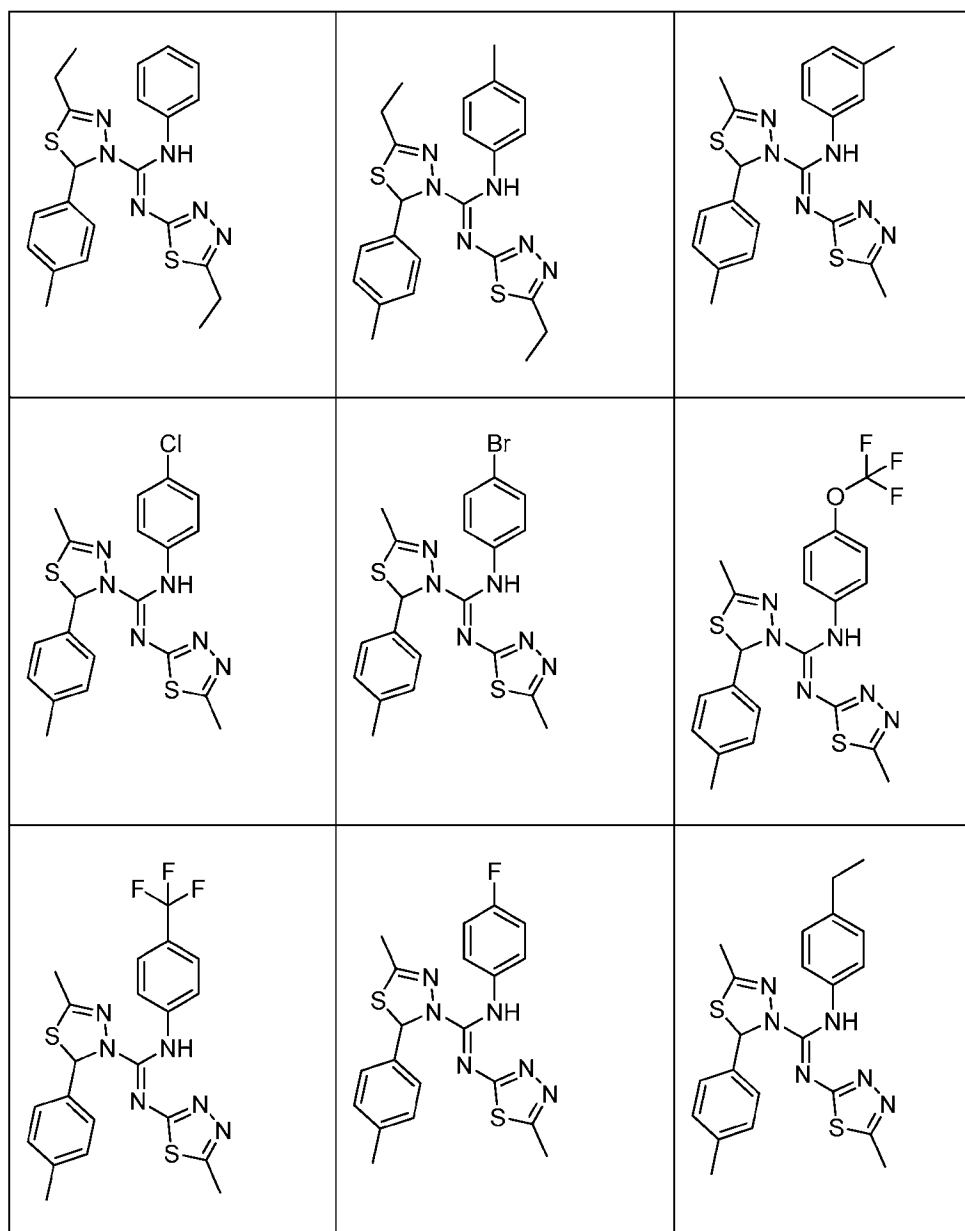
In some embodiments, the compound of Formula (I) or Formula (Ia) comprises at least one R¹ selected from halo, CN, OR^{a1}, SR^{a1}, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and phenyl, and wherein the phenyl in the definition of R¹ is optionally substituted with 1, 2 or 3 substituents each independently selected from halo, OR^{a1}, C₁₋₃ alkyl, and C₁₋₃ haloalkyl. In some embodiments, each R¹ is independently selected from halo, CN, OR^{a1}, SR^{a1}, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and phenyl, and wherein the phenyl in the definition of R¹ is optionally substituted with 1, 2 or 3 substituents each independently selected from halo, OR^{a1}, C₁₋₃ alkyl, and C₁₋₃ haloalkyl. In some embodiments, the compound of Formula (I) or Formula (Ia)

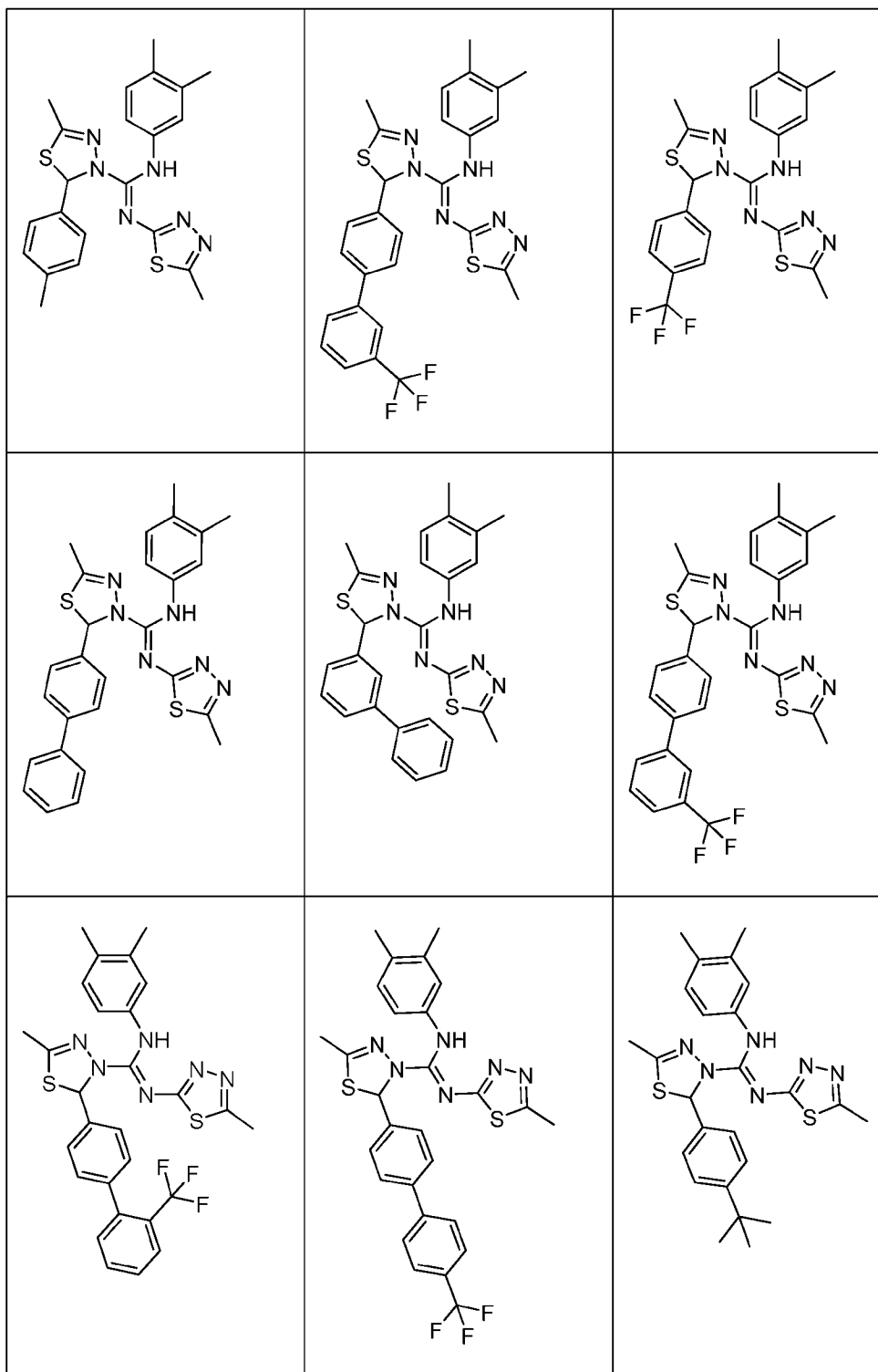
comprises one R¹, two R¹, three R¹, four R¹, or five R¹. In some embodiments, two R¹, three R¹, four R¹, or five R¹ are the same. In some embodiments, two R¹, three R¹, four R¹, or five R¹ are different or different combinations. In some embodiments, at least one R¹ is methyl. In some embodiments, one R¹ is methyl. In some
5 embodiments, two R¹ are methyl. In some embodiments, three R¹ are methyl. In some
embodiments, at least one R¹ is ethyl. In some embodiments, one R¹ is ethyl. In some
embodiments, two R¹ are ethyl. In some embodiments, three R¹ are ethyl. In some
embodiments, at least one R¹ is iso-propyl. In some embodiments, one R¹ is iso-
propyl. In some embodiments, two R¹ are iso-propyl. In some embodiments, three R¹
10 are iso-propyl. In some embodiments, at least one R¹ is tert-butyl. In some
embodiments, one R¹ is tert-butyl. In some embodiments, two R¹ are tert-butyl. In
some embodiments, three R¹ are tert-butyl. In some embodiments, at least one R¹ is
fluoro. In some embodiments, one R¹ is fluoro. In some embodiments, two R¹ are
fluoro. In some embodiments, three R¹ are fluoro. In some embodiments, four R¹ are
15 fluoro. In some embodiments, at least one R¹ is chloro. In some embodiments, one R¹
is chloro. In some embodiments, two R¹ are chloro. In some embodiments, three R¹
are chloro. In some embodiments, at least one R¹ is bromo. In some embodiments,
one R¹ is bromo. In some embodiments, two R¹ are bromo. In some embodiments,
three R¹ are bromo. In some embodiments, at least one R¹ is CF₃. In some
20 embodiments, one R¹ is CF₃. In some embodiments, two R¹ are CF₃. In some
embodiments, three R¹ are CF₃. In some embodiments, at least one R¹ is OCF₃. In
some embodiments, one R¹ is OCF₃. In some embodiments, two R¹ are OCF₃. In
some embodiments, three R¹ are OCF₃. In some embodiments, at least one R¹ is CF₃.
In some embodiments, one R¹ is CH₃. In some embodiments, two R¹ are CH₃. In
25 some embodiments, three R¹ are CH₃. In some embodiments, at least one R¹ is
OCH₃. In some embodiments, one R¹ is OCH₃. In some embodiments, two R¹ are
OCH₃. In some embodiments, three R¹ are OCH₃. In some embodiments, one R¹ is
chloro and two R¹ are fluoro. In some embodiments, one R¹ is fluoro and one R¹ is
CF₃. In some embodiments, one R¹ is fluoro and one R¹ is CN. In some embodiments,
30 two R¹ are fluoro and one R¹ is methyl. In some embodiments, two R¹ are fluoro and
one R¹ is OCH₃.

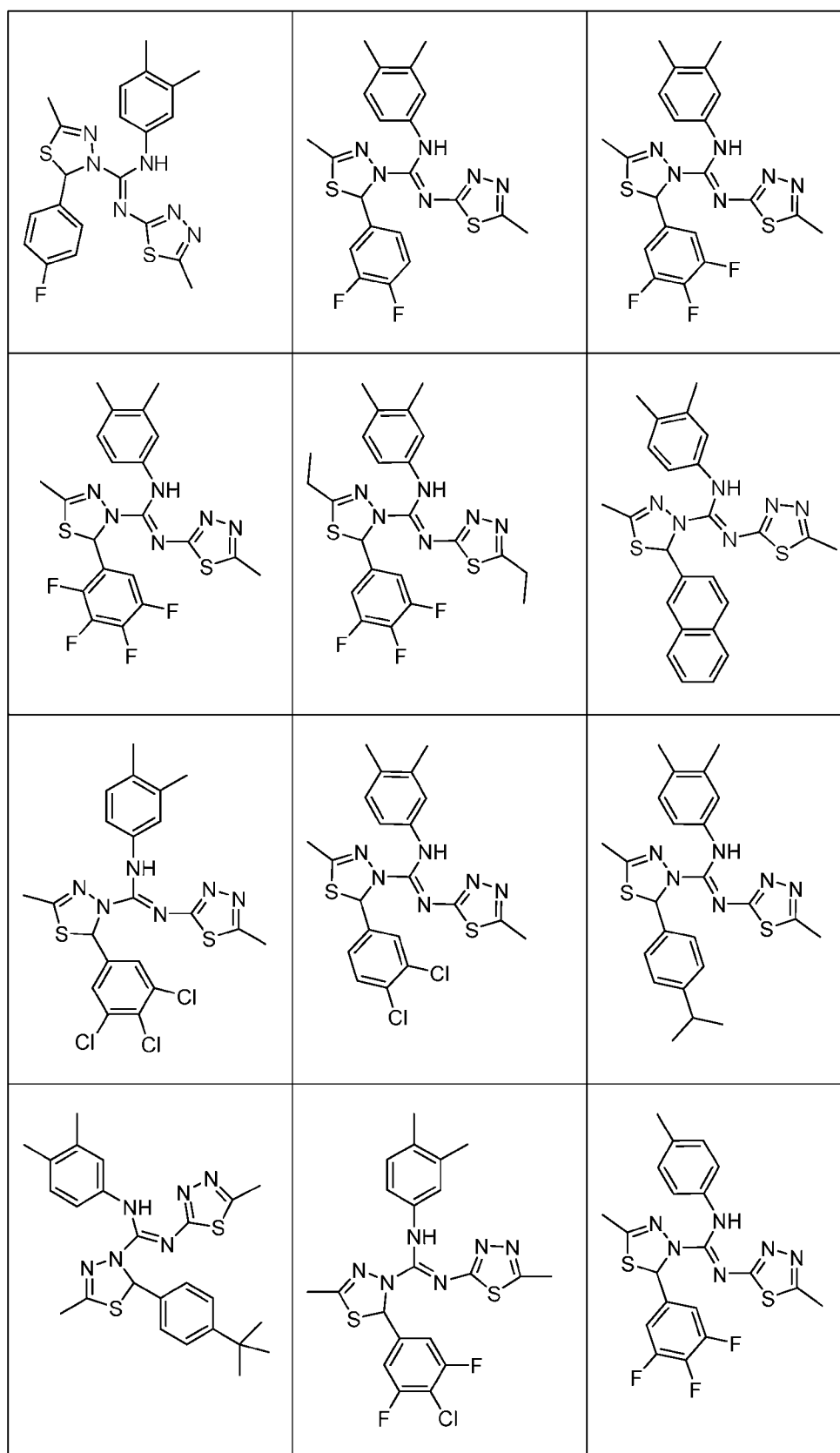
In some embodiments, at least one R¹ is phenyl. In some embodiments, one R¹
is phenyl. In some embodiments, two R¹ are phenyl. In some embodiments, three R¹
are phenyl. In some embodiments, one R¹ is phenyl substituted with fluoro, chloro,

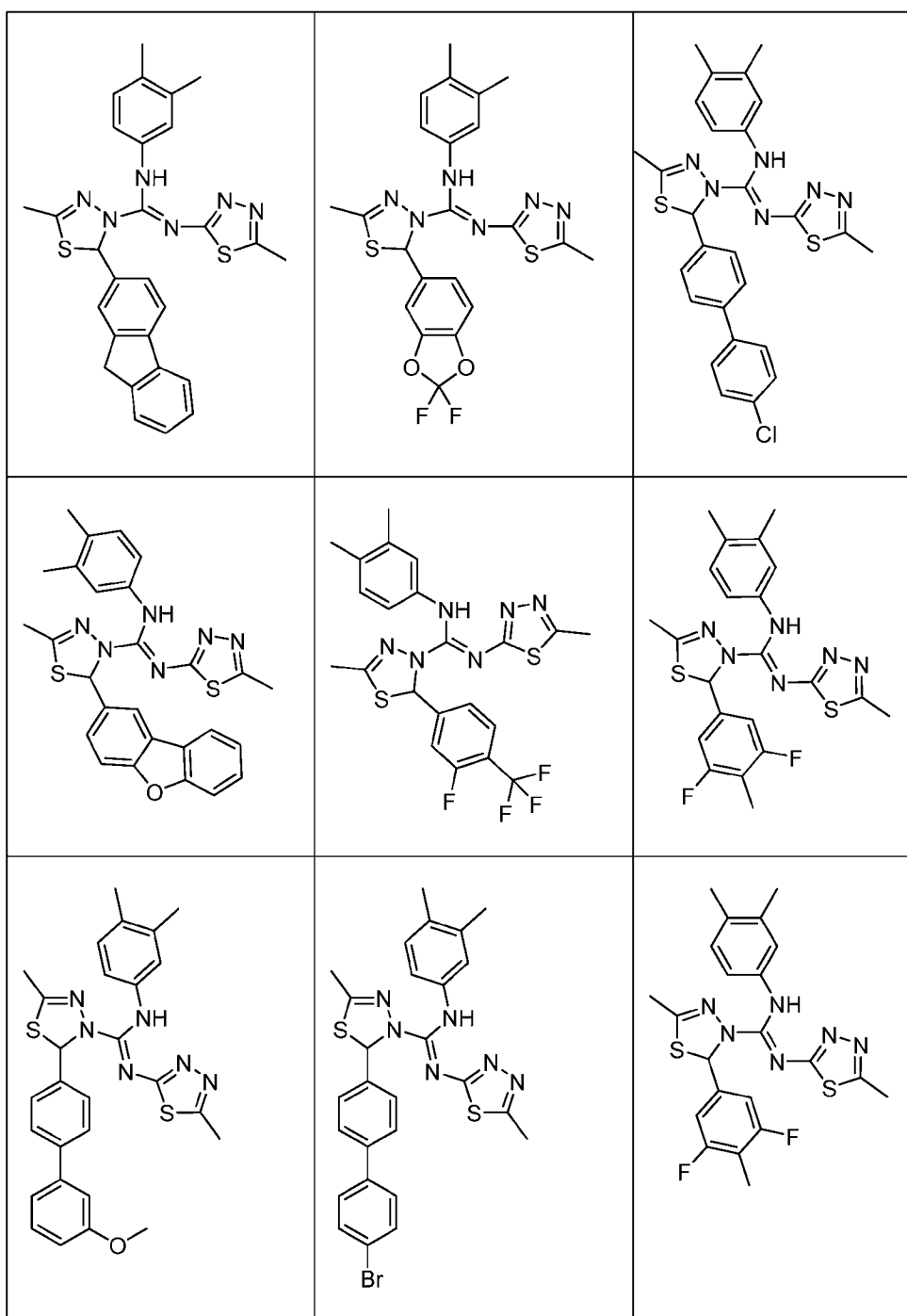
bromo, methyl, OCH₃, or CF₃. In some embodiments, one R¹ is O-phenyl. In some
embodiments, at least one R¹ is phenyl substituted with CF₃. In some embodiments,
one R¹ is phenyl substituted with CF₃. In some embodiments, one R¹ is phenyl
substituted with bromo. In some embodiments, one R¹ is phenyl substituted with
5 chloro. In some embodiments, one R¹ is pyridinyl.

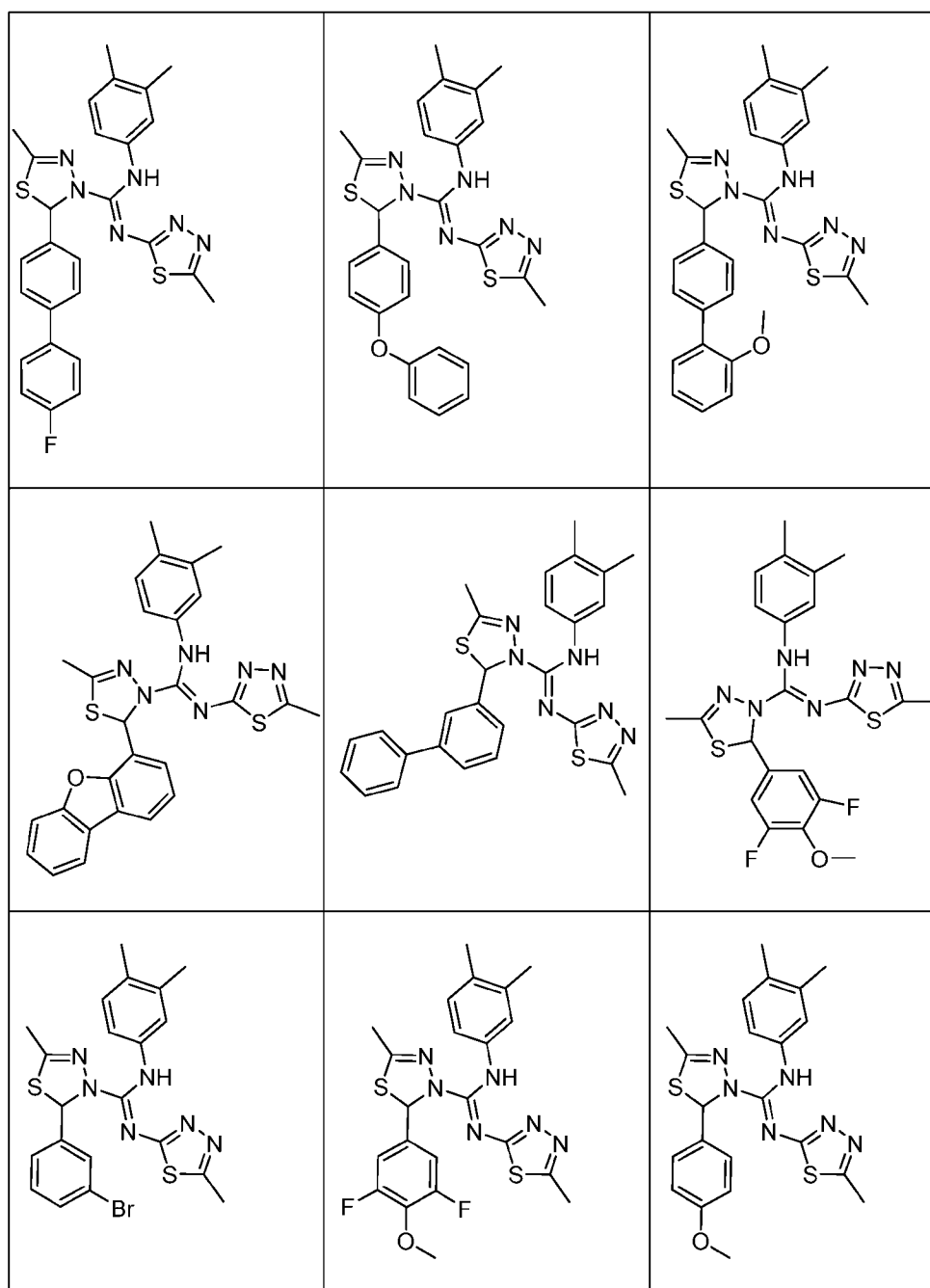
In some embodiments, the compound is selected from:

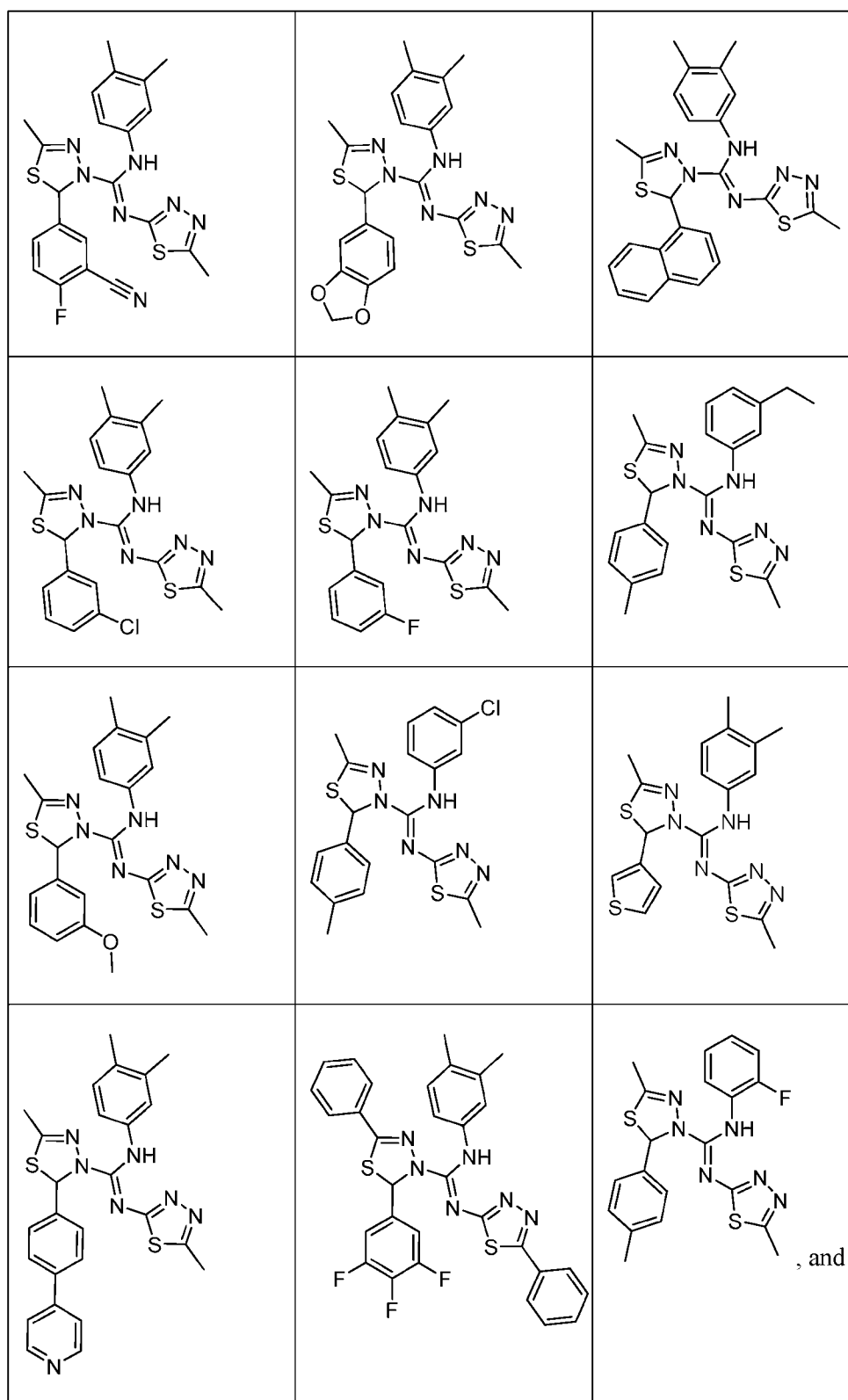


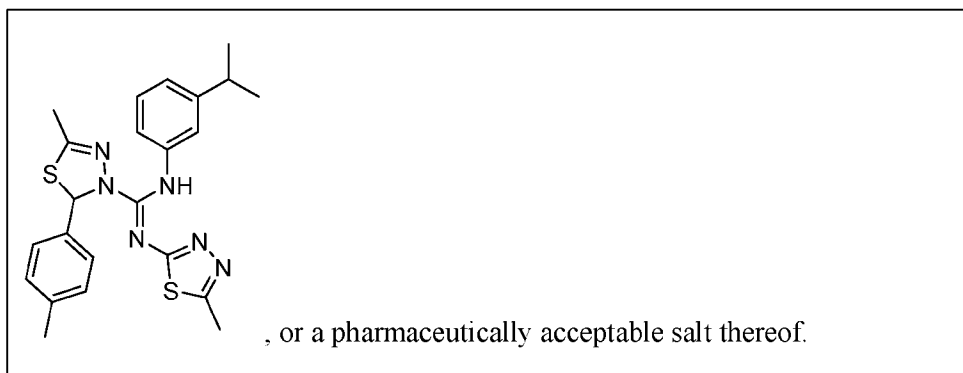












Pharmaceutically acceptable salts

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-*D*-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt is not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid,

methanesulfonic acid, and ethanesulfonic acid; and acidic amino acids such as aspartic acid and glutamic acid. In some embodiments, the compounds of Formula (I) or (Ia), or pharmaceutically acceptable salts thereof, are substantially isolated.

5 **Compositions and Methods of use**

The present application also provides pharmaceutical compositions comprising an effective amount of a compound of the present disclosure (e.g., Formula (I) or Formula (Ia)) disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The carrier(s) are “acceptable” in
10 the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Some embodiments provide a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of
15 a compound of Formula (I) or Formula (Ia), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same. Some embodiments provide a method of treating cancer in a subject previously determined to have cancer, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I) or Formula (Ia), or a pharmaceutically acceptable salt
20 thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating obesity, type 2 diabetes mellitus, heart failure, hypertension, functional dyspepsia, cholestasis, and/or non-alcoholic fatty liver disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a
25 pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same. Some embodiments provide a method of treating obesity, type 2 diabetes mellitus, heart failure, hypertension, functional dyspepsia, cholestasis, and/or non-alcoholic fatty liver disease in a subject previously determined to have obesity, type 2 diabetes mellitus, heart failure, hypertension, functional dyspepsia, cholestasis,
30 and/or non-alcoholic fatty liver disease, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating obesity in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of

a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating type 2 diabetes mellitus in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating heart failure in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating hypertension in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating functional dyspepsia in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Some embodiments provide a method of treating non-alcoholic fatty liver disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition comprising same.

Definitions

As used herein, the term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation, for example, within experimental variability and/or statistical experimental error, and thus the number or numerical range may vary up to $\pm 10\%$ of the stated number or numerical range.

At various places in the present specification, substituents of compounds of the disclosure are disclosed in groups or in ranges. It is specifically intended that the disclosure 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.

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
5 substituent, e.g., oxo, can replace two hydrogen atoms. It is to be understood that substitution at a given atom is limited by valency.

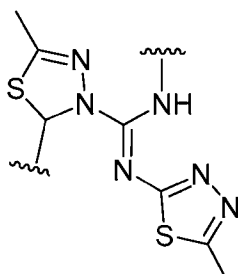
Throughout the definitions, the term “C_{n-m}” indicates a range which includes the endpoints, wherein n and m are integers and indicate the number of carbons. Examples include C₁₋₄, C₁₋₆, and the like.

10 The term “halo” or “halogen” refers to any radical of fluorine, chlorine, bromine or iodine.

The term “alkyl” refers to a fully saturated hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁₋₆ alkyl indicates that the group may have from 1 to 6 (inclusive)
15 carbon atoms in it. Any atom can be optionally substituted, e.g., by one or more substituents. Examples of alkyl groups include, without limitation, methyl, ethyl, *n*-propyl, *isopropyl*, and *tert*-butyl.

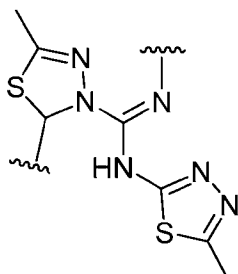
As used herein, the term “haloalkyl”, employed alone or in combination with other terms, refers to an alkyl group having from one halogen atom to 2s+1 halogen
20 atoms which may be the same or different, where “s” is the number of carbon atoms in the alkyl group, wherein the alkyl group has n to m carbon 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.

In addition, the compounds generically or specifically disclosed herein are
25 intended to include all tautomeric forms. Thus, by way of example, a compound



containing the moiety:

encompasses the tautomeric form



containing the moiety:

The compounds provided herein may encompass various stereochemical forms. The compounds also encompass enantiomers (e.g., R and S isomers), diastereomers, as well as mixtures of enantiomers (e.g., R and S isomers) including racemic mixtures and mixtures of diastereomers, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry (e.g., a “flat” structure) and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound. Likewise, unless otherwise indicated, when a disclosed compound is named or depicted by a structure that specifies the stereochemistry (e.g., a structure with “wedge” and/or “dashed” bonds) and has one or more chiral centers, it is understood to represent the indicated stereoisomer of the compound.

The term “pharmaceutically acceptable excipient” means a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, carrier, solvent, or encapsulating material. In one embodiment, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, e.g., Remington: The Science and Practice of*

Pharmacy, 21st ed.; Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients, 6th ed.*; Rowe *et al.*, Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009; *Handbook of Pharmaceutical Additives, 3rd ed.*; Ash and Ash Eds.; Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, FL, 2009.

The term “pharmaceutically acceptable salt” refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In certain instances, pharmaceutically acceptable salts are obtained by reacting a compound described herein, with acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. In some instances, pharmaceutically acceptable salts are obtained by reacting a compound having acidic group described herein with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, *N*-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like, or by other methods previously determined. The pharmacologically acceptable salt is not specifically limited as far as it can be used in medicaments. Examples of a salt that the compounds described herein form with a base include the following: salts thereof with inorganic bases such as sodium, potassium, magnesium, calcium, and aluminum; salts thereof with organic bases such as methylamine, ethylamine and ethanolamine; salts thereof with basic amino acids such as lysine and ornithine; and ammonium salt. The salts may be acid addition salts, which are specifically exemplified by acid addition salts with the following: mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, and ethanesulfonic acid; acidic amino acids such as aspartic acid and glutamic acid.

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

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, 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 disease; for example, inhibiting a disease, condition or disorder in a subject 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 a subject who is experiencing or displaying the pathology or symptomatology of the 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 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

All reactions involving air and moisture-sensitive reagents and solvents were performed under a nitrogen atmosphere using standard chemical techniques.

Anhydrous solvents were purchased and freshly used from Sigma-Aldrich or EMD Biosciences. All organic reagents were used as purchased. All starting materials and intermediates were purchased from Sigma Aldrich (St. Louis, MO) or Combi Blocks Inc. (San Diego, CA) unless otherwise indicated. ¹H and ¹³C chemical shifts are reported in δ values in ppm in the corresponding solvent. All solvents used for chromatography on the synthetic materials were Fisher Scientific HPLC grade, and

the water was Millipore Milli-Q PP filtered. UPLC/MS analysis of synthetic materials was completed on a Waters Acquity system, which consists of a ACQ-QSM sample manager, a ACQ-FTN binary gradient module, a ACQ-PDA UV/vis detector, and a ACQ-SQD2 mass detector, all controlled with MassLynx software. An Acquity UPLC-HSS T3 1.8 μ M, 2.1 x 50 mm column, and a stepwise gradient {5% [(MeOH + 0.05% FA) in (water + 0.05% FA)] to 100% [(MeOH + 0.05% FA) in (water + 0.05% TFA)] for 3.5 min.} was used for analytical UPLC/MS of all intermediate and final compounds. The final compounds were purified by preparative HPLC chromatography using a Shimadzu preparative HPLC which was composed of a Kromasil 100-5 μ M C18 30 x 100 mm preparative column, CBM-20A controller, 2 – each LC-20A pumps, SPD-20A PDA detector, FCR-10AF fraction collector and a SIL10AP auto sampler. All NMR spectra for the synthetic materials were recorded on a Bruker DRX-500 MHz instrument or a JEOL 400 MHz instrument. The MestReNova 7 program was used to process and interpret NMR spectra. High Resolution Mass Spectrometry (HRMS) spectra were carried out on an Agilent 6224A Accurate-Mass Time-of-Flight (TOF) LC/MS system with ESI. All synthesized final compounds were determined to be $\geq 95\%$ unless otherwise noted (by UV at 254 nm) purity by UPLC chromatography. Compound identity was verified by ^1H NMR and HRMS, and additionally by ^{13}C NMR for Compound 20.

The compounds disclosed herein can be synthesized according to the procedures disclosed in Wermann et al., “Bis(1,3,4-Thiadiazolo)-1,3,5-triazinium Halides: Access to Highly Substituted Aromatic Guanidines,” Synlett, 2003, 10: 1459–1462, which is incorporated herein by reference in its entirety, or according to the scheme described below and adapted from Example 1 or Example 20.

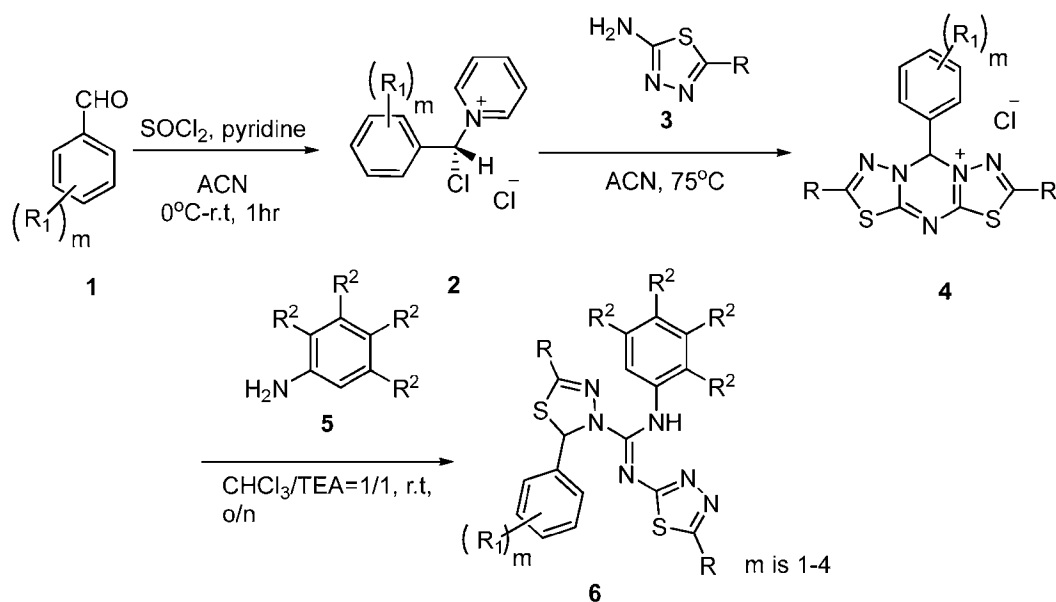
As used throughout the description, the following abbreviations, unless otherwise indicated, shall be understood to correlate to the identifying information shown below:

Abbreviations:

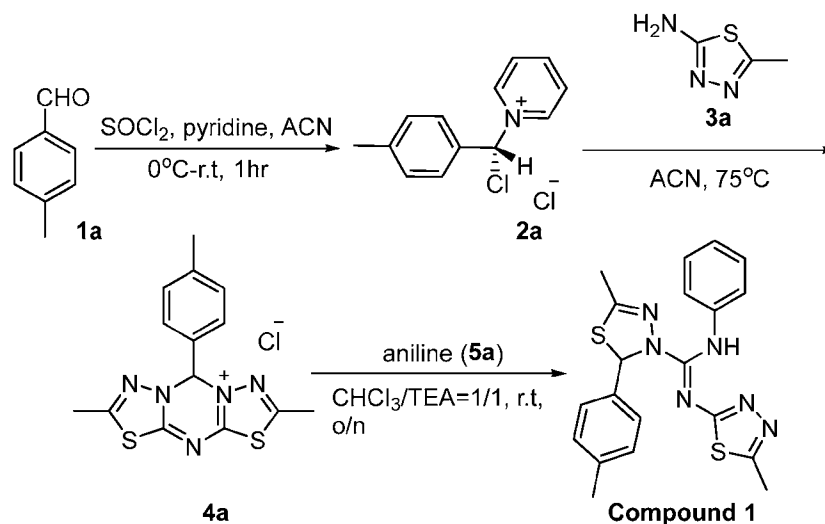
ACN	acetonitrile
DCM	dichloromethane
DMSO	dimethylsulfoxide
DMSO- d_6	dimethylsulfoxide- d_6

	ESI	electrospray ionization
	Et ₂ O	diethyl ether
	FA	formic acid
	HPLC	high pressure liquid chromatography
5	HRMS	high resolution mass spectrometry
	LC/MS	liquid chromatography-mass spectrometry
	MeOH	methyl alcohol
	min	minutes
	MS	mass spectrometry
10	NMR	nuclear magnetic resonance
	o/n	overnight
	Prep-HPLC	preparative high pressure liquid chromatography
	rt	room temperature
	TEA	triethylamine
15	UPLC	ultra performance liquid chromatography

General Synthesis of 1,3,4-thiadiazole-3(2H)-carboximidamide Compounds



Example 1 – synthesis of (Z)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-N'-phenyl-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 1)



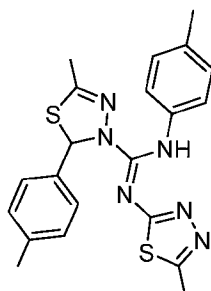
Step 1: To a solution of SOCl_2 (3.97 g, 33.3 mmol) in ACN (20 mL) was added pyridine (2.6 g, 33.3 mmol) slowly at 0 °C. Then 4-methylbenzaldehyde (**1a**) (2 g, 16.7 mmol) was added and the resulting mixture was stirred to room temperature for 1 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel column (DCM/MeOH = 20/1) to afford (*R*)-1-(chloro(*p*-tolyl)methyl)pyridin-1-ium chloride (**2a**) (3 g, yield: 71%) as yellow oil.

Step 2: A mixture of (*R*)-1-(chloro(*p*-tolyl)methyl)pyridin-1-ium chloride (**2a**) (3 g, 11.85 mmol) and 5-methyl-1,3,4-thiadiazol-2-amine (**3a**) (2.1 g, 23.7 mmol) in ACN (30 mL) was stirred at 75 °C overnight. The mixture was concentrated under reduced pressure and the residue was purified by reversed column (ACN/ H_2O) to afford 2,6-dimethyl-9-(*p*-tolyl)-9H-bis([1,3,4]thiadiazolo)[3,2-*a*:2',3'-*d*][1,3,5]triazin-8-ium (**4a**) (1.5 g, yield: 36%) as yellow solid.

Step 3: A mixture of aniline (**5a**) (26.4 mg, 0.284 mmol) and 2,6-dimethyl-9-(*p*-tolyl)-9H-bis([1,3,4]thiadiazolo)[3,2-*a*:2',3'-*d*][1,3,5]triazin-8-ium (**4a**) (30 mg, 0.284 mmol) in CHCl_3 /TEA (2 mL/2 mL) was stirred at room temperature overnight. The analytical HPLC of the mixture was very complicated containing multiple peaks. The mixture was concentrated under reduced pressure and the residue was purified by Prep-HPLC to afford (Z)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-N',2-di-*p*-tolyl-1,3,4-thiadiazole-3(2H)-carboximidamide (**compound 1**) (19 mg, yield: 16%) as white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.57 (s, 1H), 7.23-7.21 (m, 3H), 7.19-

7.14 (m, 4H), 6.98-6.96 (m, 3H), 6.93-6.90 (m, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H). MS: m/z 409 $[M+H]^+$.

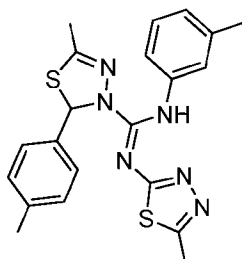
Example 2: (Z)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-N',2-di-p-tolyl-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 2)



^1H NMR (400 MHz, DMSO- d_6): δ 9.51 (s, 1H), 7.16 – 7.22 (m, 5H), 6.97 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H). MS: m/z 423 $[M+H]^+$.

10

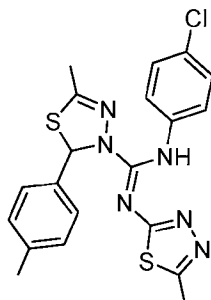
Example 3: (Z)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-N'-(m-tolyl)-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 3)



^1H NMR (400 MHz, DMSO- d_6): δ 9.50 (s, 1H), 7.16 – 7.22 (m, 5H), 7.02 – 7.06 (m, 1H), 6.72 – 6.77 (m, 3H), 2.33 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H). MS: m/z 423 $[M+H]^+$.

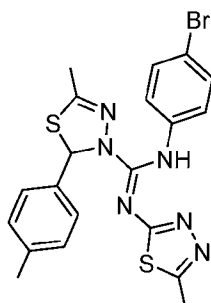
15

Example 4: (Z)-N'-(4-chlorophenyl)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 4)



5 ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.68 (s, 1H), 7.16 – 7.22 (m, 7H), 6.96 – 6.98 (m, 2H), 2.34 (s, 3H), 2.28 (s, 3H), 2.23 (s, 3H). MS: m/z 444 $[\text{M}+\text{H}]^+$.

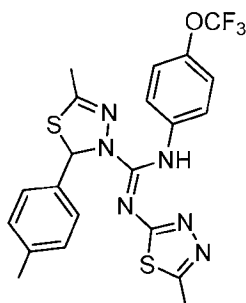
Example 5: (Z)-N'-(4-bromophenyl)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 5)



10 ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.67 (s, 1H), 7.32 – 7.34 (m, 2H), 7.12-7.22 (m, 5H), 6.89 – 6.92 (bm, 2H), 2.35 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H). MS: m/z 488 $[\text{M}+\text{H}]^+$.

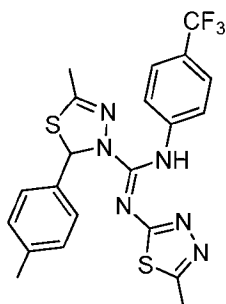
15

Example 6: (Z)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-N'-(4-(trifluoromethoxy)phenyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 6)



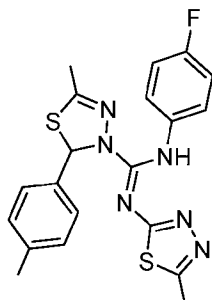
5 ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.73 (s, 1H), 7.11-7.20 (m, 2H), 7.04-7.06 (m, 3H), 6.95-7.08 (m, 4H) 2.23 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H). MS: m/z 493 $[\text{M}+\text{H}]^+$.

10 **Example 7: (Z)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-N'-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 7)**



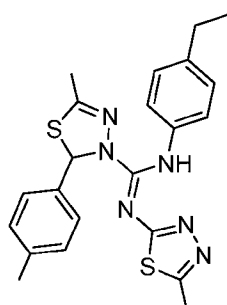
15 ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.89 (b, 1H), 7.49-7.52-7.16 (m, 2H), 7.17-7.24 (d, , 5H), 7.07-7.09 (b, 2H), 2.33, (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H). MS: m/z 477. $[\text{M}+\text{H}]^+$.

Example 8: (Z)-N'-(4-fluorophenyl)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 8)



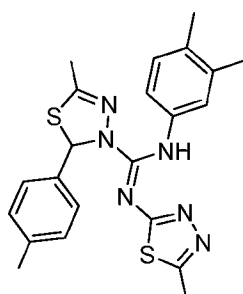
¹H NMR (400 MHz, DMSO-*d*₆): δ 9.65 (s, 1H), 87.19-7.23 (m, 5H), 7.02-7.04 (m, 4H), 2.36 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H). MS: *m/z* 427. [M+H]⁺.

Example 9: (Z)-N'-(4-ethylphenyl)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 9)



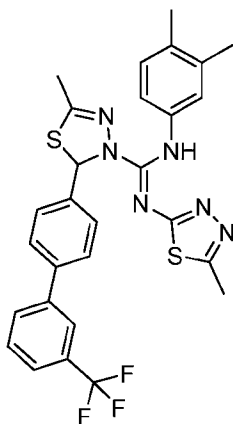
¹H NMR (400 MHz, DMSO-*d*₆): δ 9.52 (s, 1H), 7.16-7.22 (m, 5H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.2 Hz, 6H), 2.49-2.51 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 1.07-1.11 (t, *J* = 7 Hz, 3H). MS: *m/z* 437 [M+H]⁺.

Example 10: (Z)-N'-(3,4-dimethylphenyl)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(p-tolyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 10)



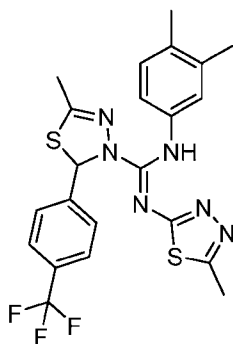
^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.44 (s, 1H), 7.16-7.23 (m, 5H), 6.92 (d, J = 8.0 Hz, 1H), 6.75 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H). MS: m/z 437 $[\text{M}+\text{H}]^+$.

5 **Example 11: (E)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(3'(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 11)**



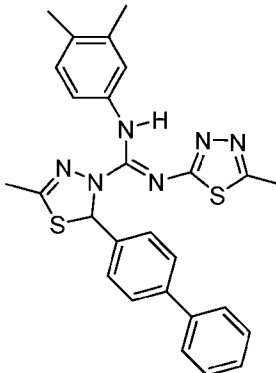
10 ^1H NMR (400 MHz, CD_3OD): δ 8.52 (s, 1H), 7.90-8.05 (m, 2H), 7.75-7.77 (m, 4H), 7.42-7.45 (m, 2H), 7.29 (s, 1H), 6.80-6.89 (m, 1H), 6.70-6.76 (m, 2H), 2.49 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H), 2.07 (s, 3H). MS: m/z 567 $[\text{M}+\text{H}]^+$.

15 **Example 12: (E)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(4-(trifluoromethyl)phenyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 12)**



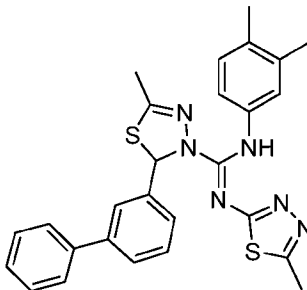
^1H NMR (400 MHz, CD_3OD): δ 9.35 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.32 (s, 1H), 6.89-6.91 (m, 1H), 6.75-6.73 (m, 2H), 2.48 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 2.07 (s, 3H). MS: m/z 491. $[\text{M}+\text{H}]^+$.

Example 13: (E)-2-([1,1'-biphenyl]-4-yl)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 13)



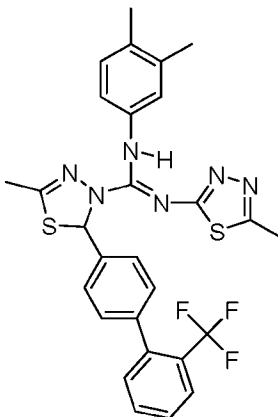
5 ^1H NMR (400 MHz, CD_3OD): δ 9.61 (s, 1H), 7.64-7.76 (m, 3H), 7.35-7.45 (m, 6H), 7.35 (s, 1H), 6.91-6.94 (b, 1H), 6.90 (s, 1H), 6.77-6.99 (b, 1H), 2.49 (3H), 2.48 (s, 3H), 2.47 (s, 3H), 2.07 (s, 3H). MS: m/z 501 $[\text{M}+\text{H}]^+$.

10 **Example 14: (E)-2-([1,1'-biphenyl]-3-yl)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 14)**



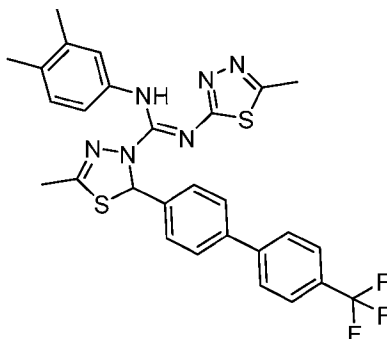
15 ^1H NMR (400 MHz, CD_3OD): δ 9.50 (s, 1H), 7.55-7.60 (m, , 3H), 7.40-7.51 (m, 3H), 7.30-7.36 (m, 3H), 6.85-6.89 (b, 1H), 6.76 (s, 1H), 6.70-6.73 (b, 1H), 6.53 (s, 1H), 2.349 (s, 3H), 2.48 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H).). MS: m/z 501 $[\text{M}+\text{H}]^+$.

Example 15: (E)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 15)



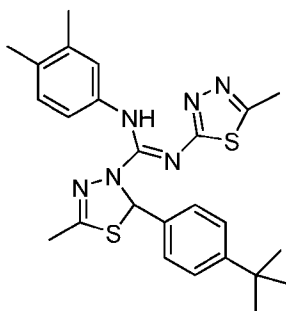
¹H NMR (400 MHz, CD₃OD): δ 9.48 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.59-7.68 (m, 4H), 7.36-7.40 (m, 2H), 7.27-7.31 (m, 2H), 7.87-7.91 (m, 1H), 6.76 (s, 1H), 6.65-6.70 (m, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H). MS: m/z 567 [M+H]⁺.

Example 16: (E)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 16)



¹H NMR (400 MHz, CD₃OD): δ 8.02 (s, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.29-7.16 (m, 6H), 6.85 (s, 1H), 2.48 (s, 3H), 2.31 (s, 3H), 2.37 (s, 3H), 2.23 (s, 3H), 2.08 (s, 3H). MS: m/z 567 [M+H]⁺.

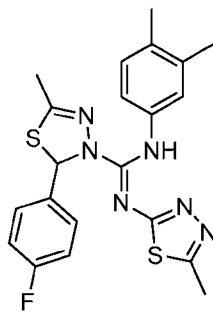
Example 17: (E)-2-(4-(tert-butyl)phenyl)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 17)



^1H NMR (400 MHz CD_3OD): δ 9.51 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8$ Hz, 2H), 7.21 (s, 1H), 6.85-6.89 (m, 1H), 6.76 (s, 1H), 6.73-6.77 (m, 1H), 2.49 (s, 3H), 2.31 (s, 3H), 2.30 (s, 3H), 2.07 (s, 3H). MS: m/z 479 $[\text{M}+\text{H}]^+$.

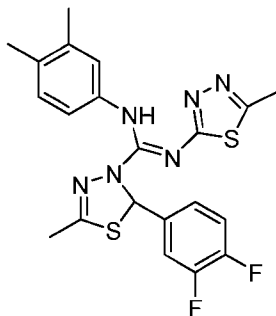
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Example 18: (E)-N-(3,4-dimethylphenyl)-2-(4-fluorophenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 18)



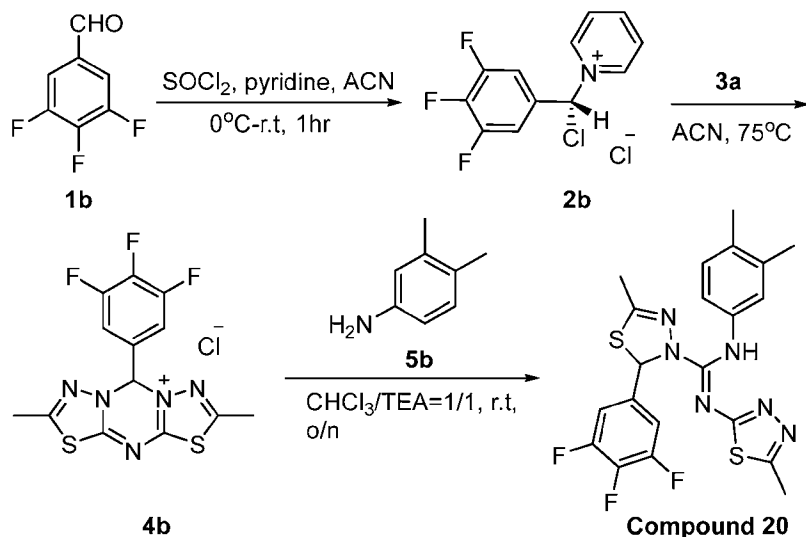
10 ^1H NMR (400 MHz, CD_3OD): δ 9.35 (s, 1H), 7.75 (d, $J = 8.0$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.32 (s, 1H), 6.89-6.91 (m, 1H), 6.75-6.73 (m, 2H), 2.48 (s, 3H), 2.30 (s, 3H), 2.20 (s, 3H), 2.07 (s, 3H). MS: m/z 441 $[\text{M}+\text{H}]^+$.

Example 19: (E)-2-(3,4-difluorophenyl)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 19)



¹H NMR (400 MHz, CD₃OD): δ 9.45 (s, 1H), 7.35-7.49 (m, 2H), 7.19 (bm, 2H), 6.86-6.88 (bm, 1H), 6.86.61-6.715 (m, 2H), 2.46 (s, 3H), 2.28 (s, 3H), 2.17 (s, 3H), 2.04 (s, 3H). MS: m/z 459 [M+H]⁺.

Example 20: (E)-N-(3,4-dimethylphenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(3,4,5-trifluorophenyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 20)



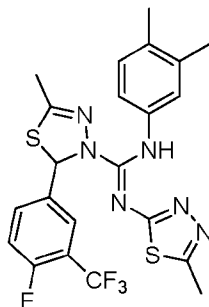
Step 1: To a solution of SOCl₂ (1.5 mL, 20.6 mmol) in ACN (20 mL) was added pyridine (3.0 mL, 37.5 mmol) slowly at 0 °C. Then 3,4,5-trifluorobenzaldehyde (**1b**) (3 g, 18.7 mmol) was added and the resulting mixture was stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure and the

solid was suspended in a minimum of ACN. The solid was filtered, washed with Et₂O, and dried under vacuum to afford (R)-1-(chloro(3,4,5-trifluorophenyl)methyl)pyridin-1-ium chloride (**2b**) (3.2 g, yield: 58 %) as white precipitate. ¹H NMR (400 MHz, CD₃OD): δ 9.32 (d, *J* = 6.0 Hz, 2H), 8.77 (t, *J* = 7.7 Hz, 1H), 8.24 (t, *J* = 7.1 Hz, 2H), 8.09 (s, 1H), 7.67 (dd, *J* = 8.0, 6.2 Hz, 2H). MS: *m/z* 259 [M+H]⁺.

Step 2: A mixture of (R)-1-(chloro(3,4,5-trifluorophenyl)methyl)pyridin-1-ium chloride (**2b**) (3.2 g, 10.9 mmol) and 5-methyl-1,3,4-thiadiazol-2-amine (**3a**) (2.5 g, 21.8 mmol) in ACN (30 mL) was stirred at 75 °C overnight. The resulting mixture was concentrated under reduced pressure and the solid was suspended in a minimum of ACN. The solid was filtered, washed with Et₂O, and dried under vacuum. Then the solid was suspended in a minimum of CH₂Cl₂ and stirred at rt overnight. The solid was again filtered, washed with Et₂O, and dried under vacuum to afford 2,6-dimethyl-9-(3,4,5-trifluorophenyl)-9H-bis([1,3,4]thiadiazolo)[3,2-*a*:2',3'-d][1,3,5]triazin-8-ium chloride (**4b**) (1.8 g, yield: 42%) as white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.88 (s, 1H), 7.70 – 7.59 (m, 2H), 2.63 (s, 6H). MS: *m/z* 358 [M+H]⁺.

Step 3: A mixture of 3,4-dimethylaniline (**5b**) (309 mg, 2.6 mmol) and 2,6-dimethyl-9-(3,4,5-trifluorophenyl)-9H-bis([1,3,4]thiadiazolo)[3,2-*a*:2',3'-d][1,3,5]triazin-8-ium chloride (**4b**) (1 g, 2.6 mmol) in CHCl₃/TEA (15 mL/15 mL) was stirred at room temperature overnight. The solvent was removed under vacuum. The desired product was purified by chromatography (0-40% EtOAc/Hexanes), affording Compound 20 (125 mg) as a light-yellow solid. The obtained product was further purified by Prep-HPLC to afford (Z)-N'-(3,4-dimethylphenyl)-5-methyl-N-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(3,4,5-trifluorophenyl)-1,3,4-thiadiazole-3(2H)-carboximidamide (**compound 20**) (85 mg, yield: 7%) as white solid. ¹H NMR (400 MHz, CD₃OD): δ 7.21-7.12 (m, 3H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.79-6.68 (m, 3H), 2.30 (s, 3H), 2.28 (s, 3H), 2.11 (s, 6H). MS: *m/z* 477 [M+H]⁺. ¹³C NMR (101 MHz, CD₃OD): δ 208.11, 200.02, 165.20, 151.60, 138.23, 130.92, 124.12, 120.29, 111.66, 92.21, 73.93, 71.35, 71.21, 69.29, 67.01, 64.26, 62.17, 19.74, 19.11, 16.41, 15.60.

Example 21: (E)-N-(3,4-dimethylphenyl)-2-(4-fluoro-3-(trifluoromethyl)phenyl)-5-methyl-N'-(5-methyl-1,3,4-thiadiazol-2-yl)-1,3,4-thiadiazole-3(2H)-carboximidamide (Compound 29)



¹H NMR (400 MHz, CD₃OD): δ 8.02 (s, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.29-7.16 (m, 6H), 6.85 (s, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.16 (s, 3H). MS: m/z 509 [M+H]⁺.

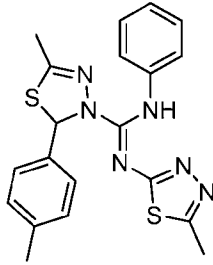
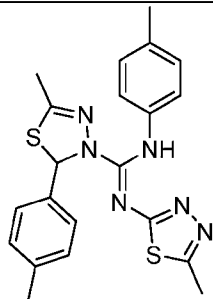
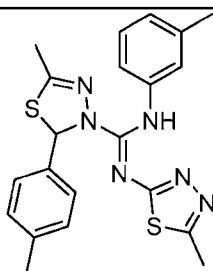
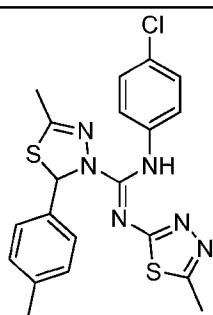
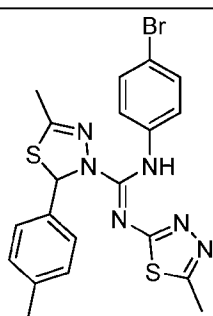
Example 35 – Bioactivity of the Exemplified Compounds

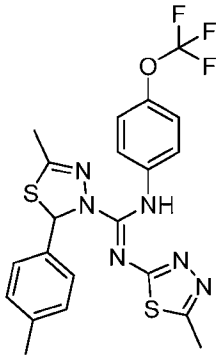
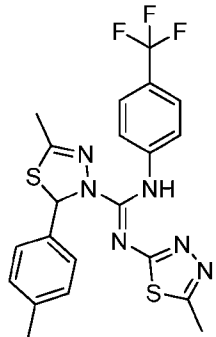
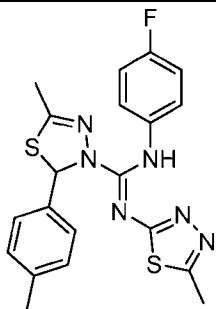
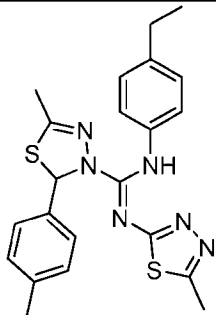
hSecR agonist assay

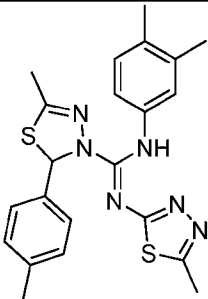
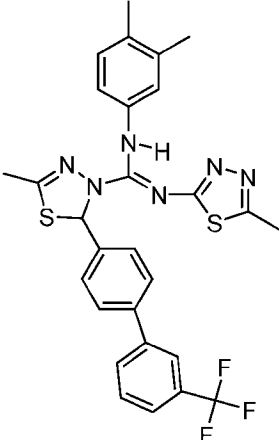
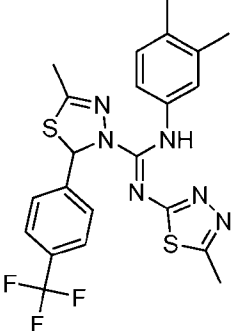
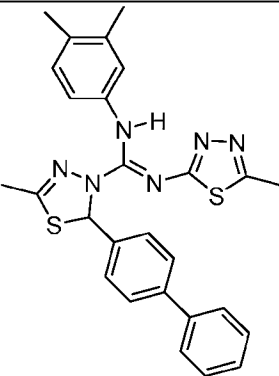
Compounds were dispensed by acoustic dispenser Echo 555 to reach final concentration of 50 μ M or less in dosage response in columns 5 through 40. Positive control of 100 pM final concentration secretin FL peptide was dispensed to column 1 and 2 with Echo, and matching DMSO was dispensed to rest of the assay wells. Stimulation buffer was prepared, containing 0.5 mM IBMX, 0.08% BSA, 5 mM HEPES pH 7.3, and HBSS. hSecR CHO cells were detached with Tryple and resuspended in stimulation buffer, and 800 cells per well were dispensed to Corning 3725 assay plate at 5 μ L volume with Nanodrop Combi dispenser. After 30 minutes incubation at room temperature, 4 μ L of anti cAMP-cryptate and cAMP-d2 mixture from Cisbio 20k Gs Dynamic kit were dispensed by Combi and the plate was mixed by centrifugation at 1k rpm for 1 minute. After 30 more minutes, the plate was read on PHERAstar FS with HTRF optical module.

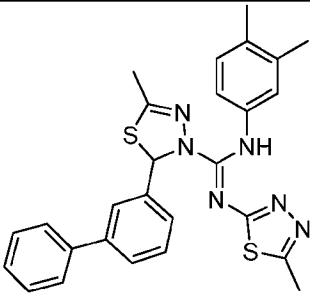
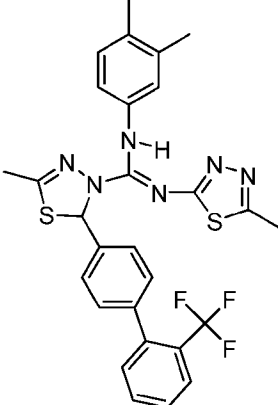
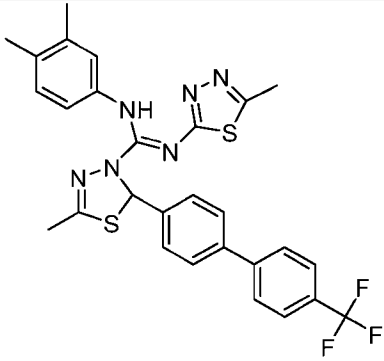
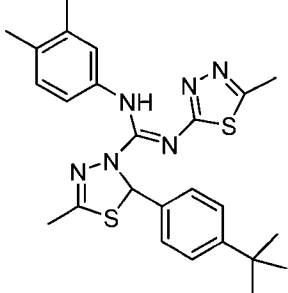
The potency ranges in **Table A** are as follows: EC₅₀ = less than 200 nM = A; EC₅₀ = 201 nM – 1000 nM = B; EC₅₀ = 1001 – 5000 nM = C; EC₅₀ = 5001 – 20000 nM = D. EC₅₀ = > 20000 nM = E

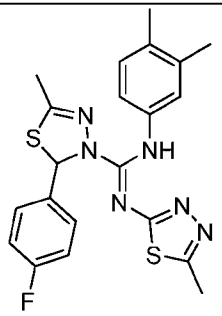
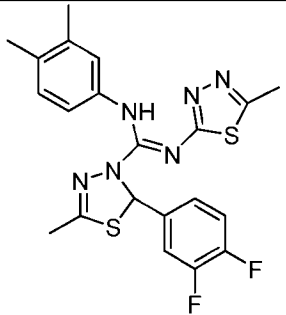
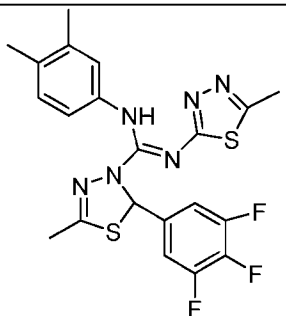
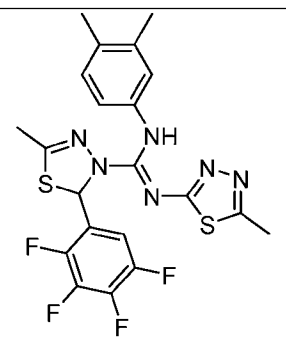
Table A. hSecR EC₅₀ and m/z Values.

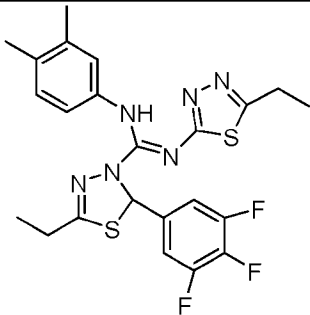
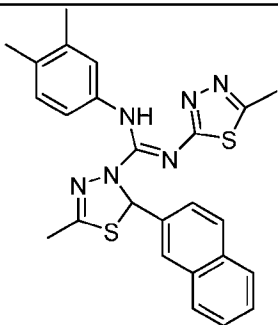
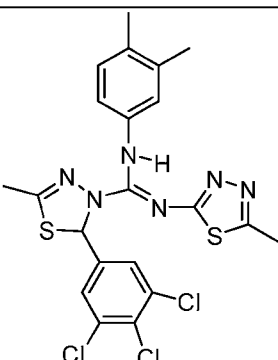
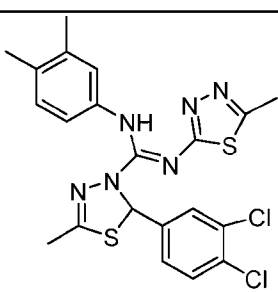
Compound No.	Structure	(M+H) ⁺	EC ₅₀
1		409	D
2		423	C
3		423	C
4		443	C
5		488	D

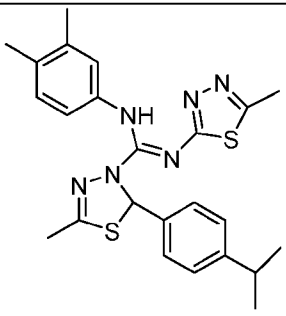
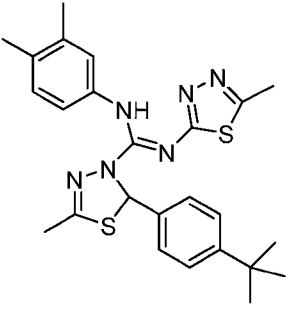
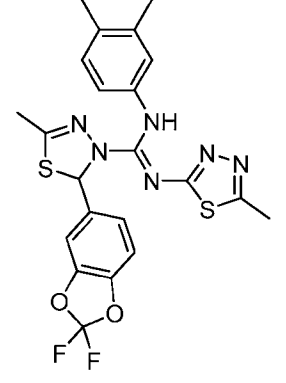
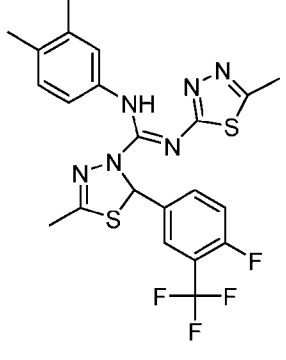
6		493	E
7		477	D
8		427	D
9		437	E

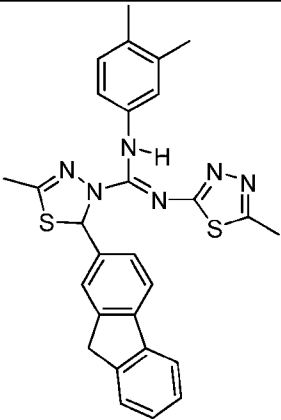
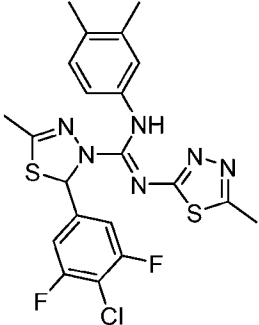
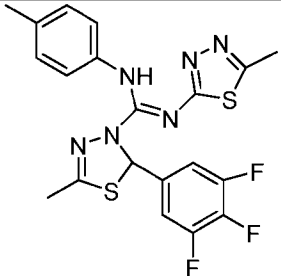
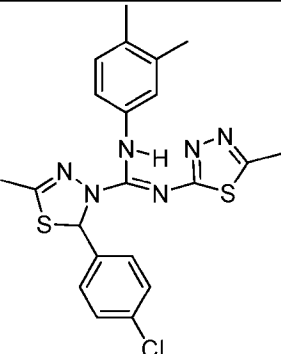
10		437	B
11		567	B
12		491	B
13		501	B

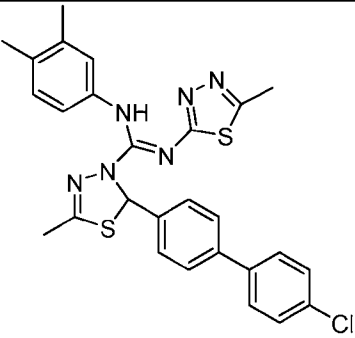
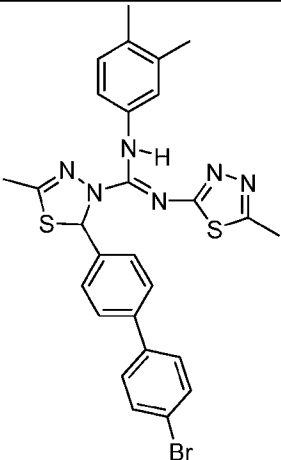
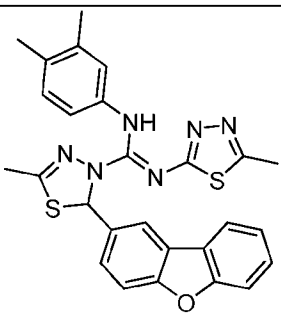
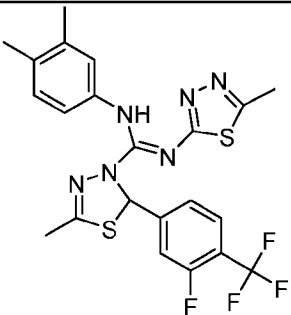
14		501	C
15		567	B
16		567	A
17		479	B

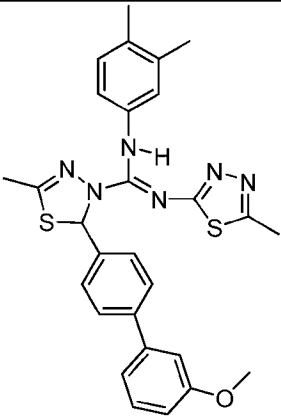
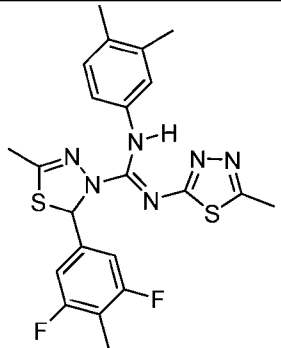
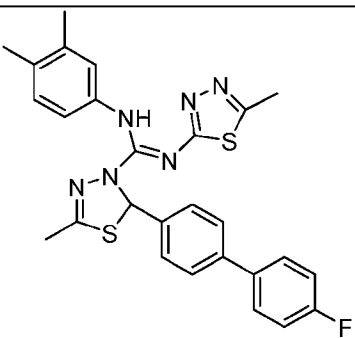
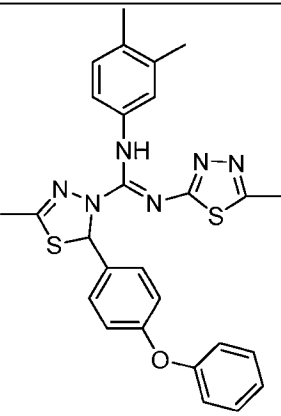
18		441	B
19		459	B
20		477	A
21		495	B

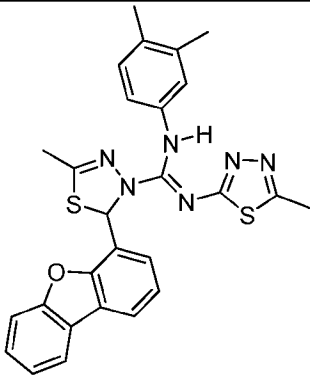
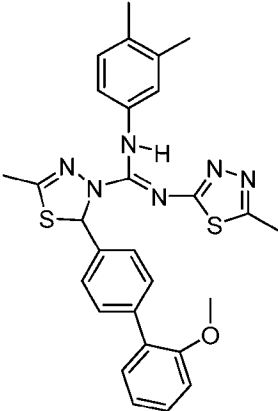
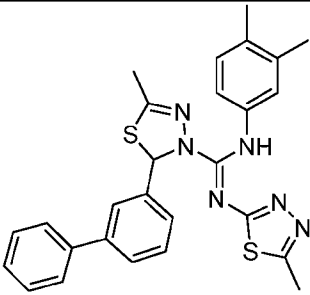
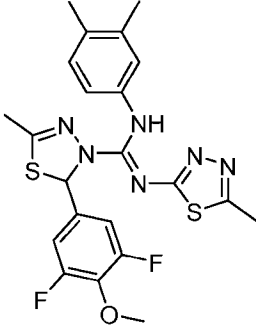
22		505	A
23		473	B
24		525	B
25		491	B

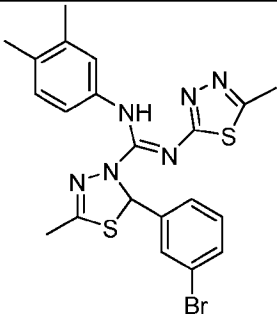
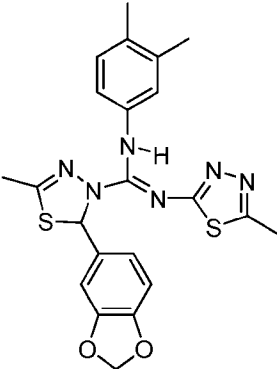
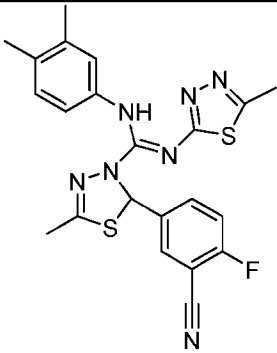
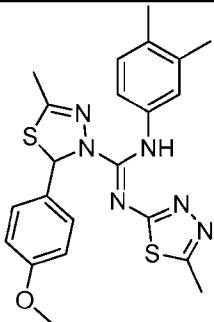
26		465	B
27		479	B
28		503	B
29		509	B

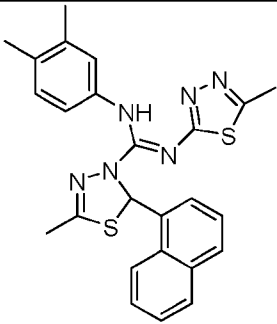
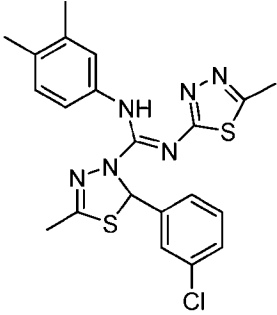
30		511	B
31		494	B
32		463	B
33		457	B

34		533	B
35		577	B
36		513	B
37		509	B

38		529	B
39		473	B
40		517	B
41		515	B

42		513	B
43		529	C
44		499	C
45		489	C

46		501	C
47		467	C
48		466	C
49		453	C

50		473	C
51		457	C

5

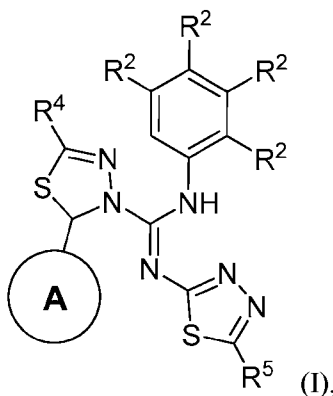
OTHER EMBODIMENTS

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

10 the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

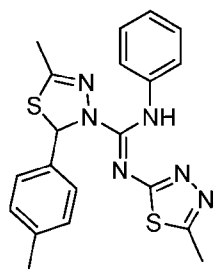
ring **A** is selected from phenyl, naphthyl, fluorenyl, dibenzofuranyl, and benzodioxazolyl, each optionally substituted with 1, 2, 3, or 4 R^1 , or ring **A** is thienyl optionally substituted with 1, 2, or 3 R^1 ;

each R^1 is independently selected from halo, CN, OR^{a1} , SR^{a1} , C_{1-6} alkyl, C_{1-6} haloalkyl, phenyl, and pyridinyl, and wherein the phenyl in the definition of R^1 is optionally substituted with 1, 2 or 3 substituents each independently selected from halo, OR^{a1} , C_{1-6} alkyl, and C_{1-6} haloalkyl;

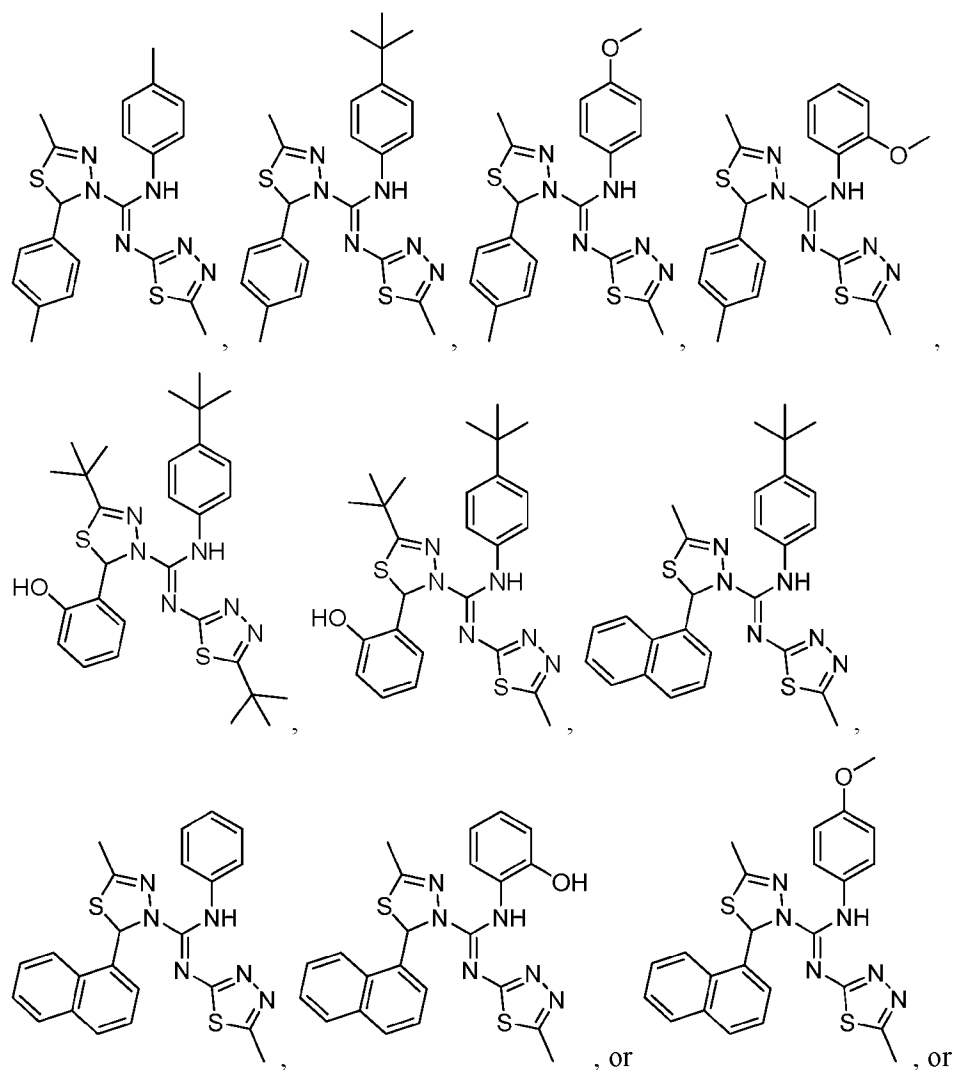
each R^2 is selected from halo, CN, OR^{a1} , SR^{a1} , C_{1-6} alkyl, and C_{1-6} haloalkyl;

R^4 and R^5 are each independently selected from C_{1-6} alkyl, and phenyl; and

each R^{a1} is independently selected from H, C_{1-6} alkyl, C_{1-6} haloalkyl, and

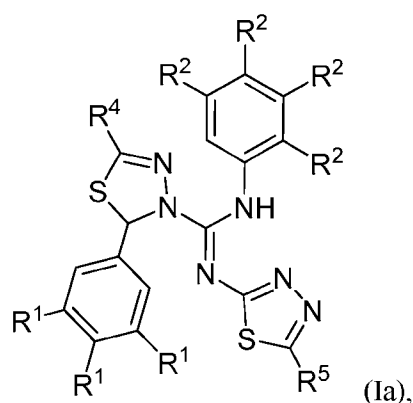


phenyl, with the proviso the compound is not



a pharmaceutically acceptable salt thereof.

- The compound of claim 1, wherein ring A is selected from phenyl, naphthyl, fluorenyl, dibenzofuranyl, and benzodioxazolyl, each substituted with 1, 2, 3, or 4 R¹.
- The compound of claim 2, wherein ring A is phenyl substituted with 1, 2, 3, or 4 R¹.
- The compound of claim 1, wherein ring A is thienyl substituted with 1, 2, or 3 R¹.
- The compound of claim 1, wherein compound of Formula (I) is a compound of Formula (Ia):

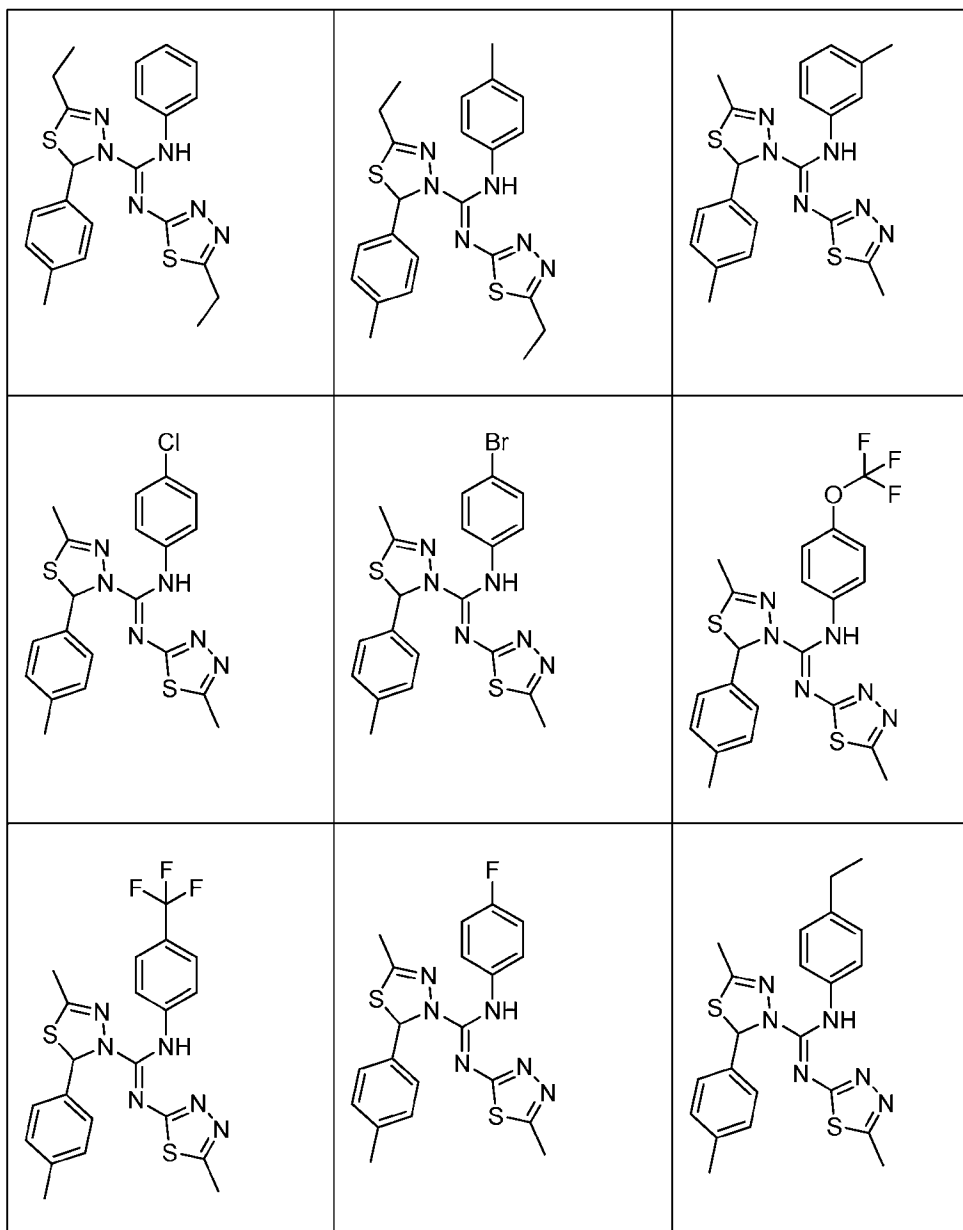


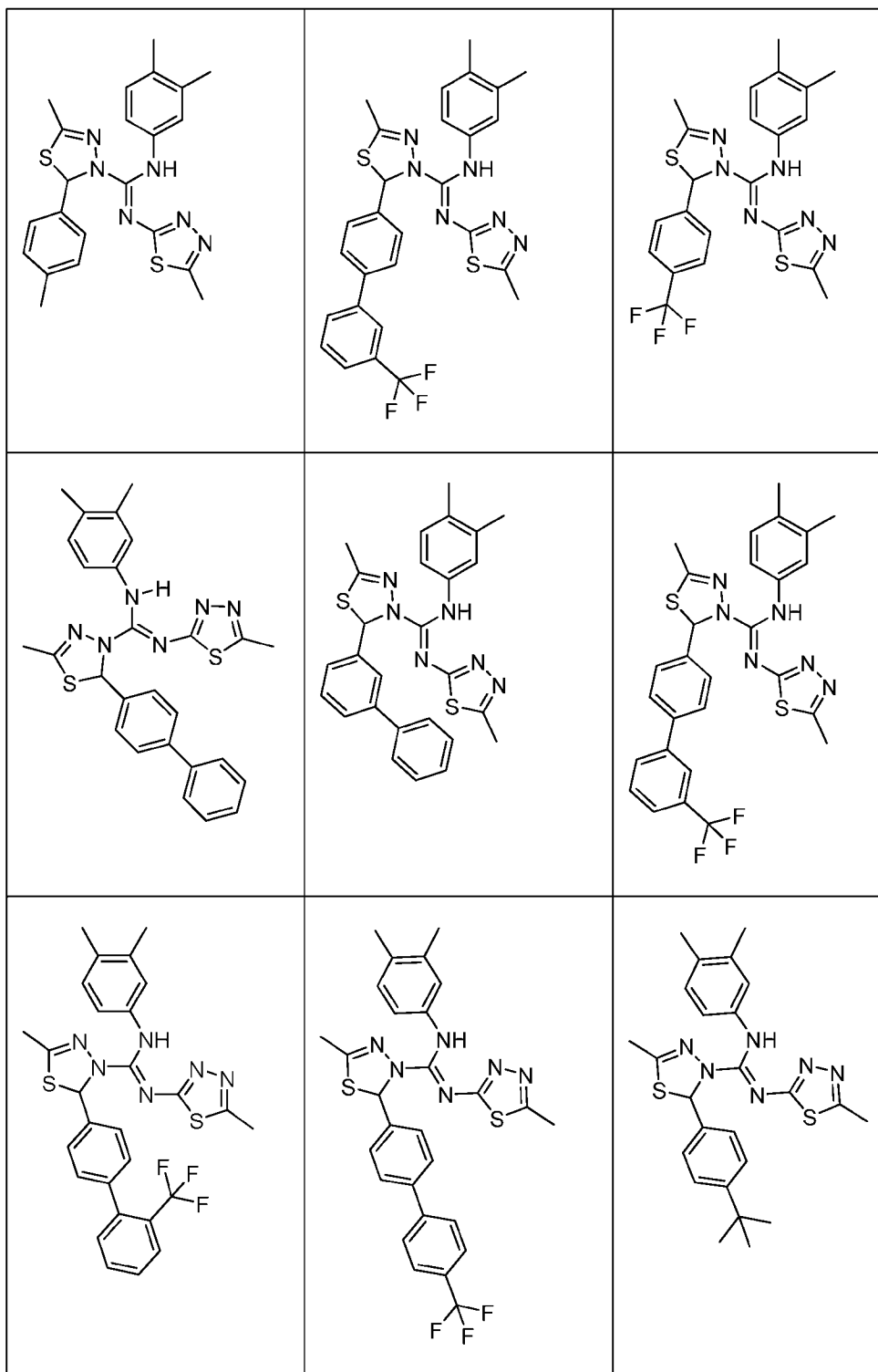
or a pharmaceutically acceptable salt thereof.

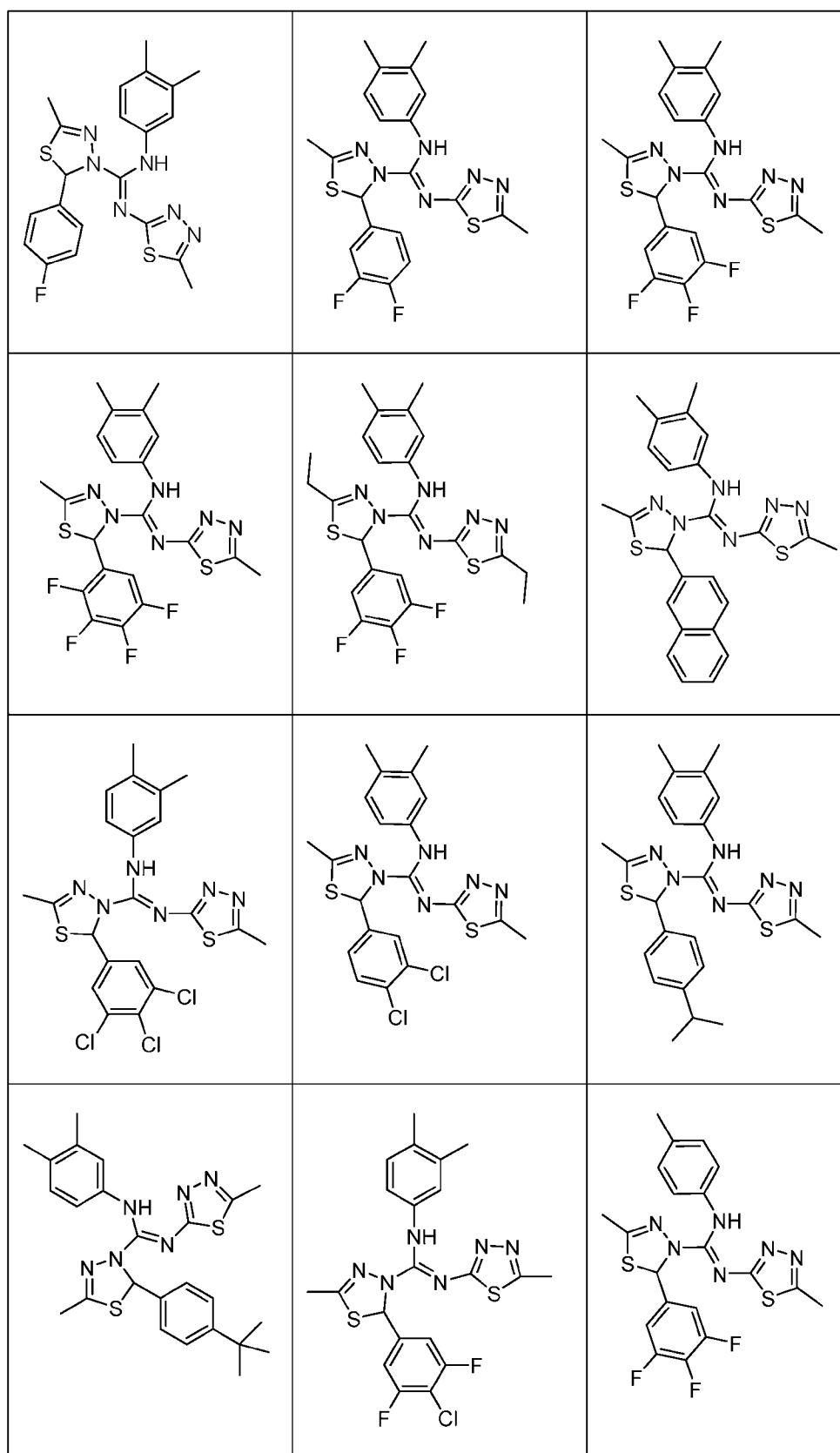
6. The compound of any of the preceding claims, wherein R^5 is C_{1-6} alkyl.
7. The compound of any of the preceding claims, wherein R^5 is C_{1-3} alkyl.
8. The compound of claim 7, wherein R^5 is methyl.
9. The compound of claim 7, wherein R^5 is ethyl.
10. The compound of any one of claims 1-6, wherein R^5 is phenyl or methyl.
11. The compound of claim 10, wherein R^5 is phenyl.
12. The compound of any of the preceding claims, wherein R^4 is C_{1-3} alkyl.
13. The compound of claim 12, wherein R^4 is methyl.
14. The compound of claim 12, wherein R^4 is ethyl.
15. The compound of any one of claims 1-11, wherein R^4 is phenyl or methyl.
16. The compound of claim 15, wherein R^4 is phenyl.
17. The compound of any one of claims 1-6, wherein R^4 and R^5 are methyl or ethyl.
18. The compound of any one of claims 1-6, wherein R^4 and R^5 are phenyl.
19. The compound of any one of the preceding claims, comprising at least one R^2 selected from halo, OR^{a1} , C_{1-6} alkyl, and C_{1-6} haloalkyl.
20. The compound of any one of claims 1-19, wherein one R^2 is methyl.

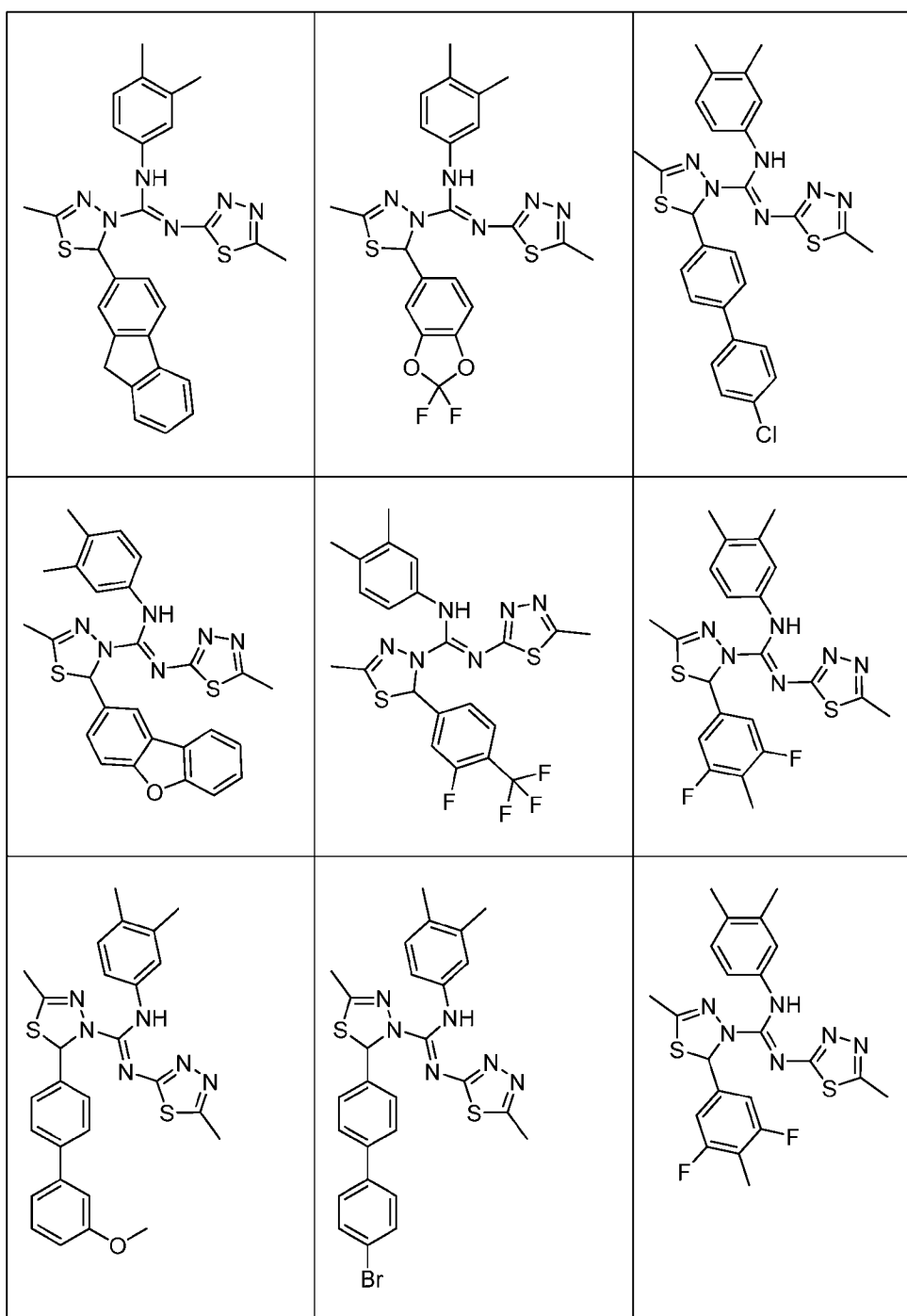
21. The compound of any one of claims 1-19, wherein two R^2 are methyl.
22. The compound of any one of claims 1-19, wherein one R^2 is ethyl.
23. The compound of any one of claims 1-19, wherein one R^2 is iso-propyl.
24. The compound according to any one of claims 1-19, wherein one R^2 is fluoro.
25. The compound of any one of claims 1-19, wherein one R^2 is chloro.
26. The compound of any one of claims 1-19, wherein one R^2 is bromo.
27. The compound of any one of claims 1-19, wherein one R^2 is CF_3 .
28. The compound of any one of claims 1-19, wherein one R^2 is OCF_3 .
29. The compound of any one of claims 2-28, wherein each R^1 is independently selected from halo, CN, OR^{a1} , SR^{a1} , C_{1-6} alkyl, C_{1-6} haloalkyl, and phenyl, and wherein the phenyl in the definition of R^1 is optionally substituted with 1, 2 or 3 substituents each independently selected from halo, OR^{a1} , C_{1-3} alkyl, and C_{1-3} haloalkyl.
30. The compound of any one of claims 2-29, wherein one R^1 is methyl.
31. The compound of any one of claims 2-29, wherein one R^1 is iso-propyl or tert-butyl.
32. The compound of any one of claims 2-29, wherein one or two R^1 are fluoro.
33. The compound of any one of claims 2-29, wherein three R^1 are fluoro.
34. The compound of any one of claims 2-29, wherein one R^1 is chloro.
35. The compound of any one of claims 2-29, wherein two or three R^1 are chloro.
36. The compound of any one of claims 2-29, wherein one R^1 is chloro and two R^1 are fluoro.
37. The compound of any one of claims 2-29, wherein one R^1 is bromo.
38. The compound of any one of claims 2-29, wherein one R^1 is CF_3 .

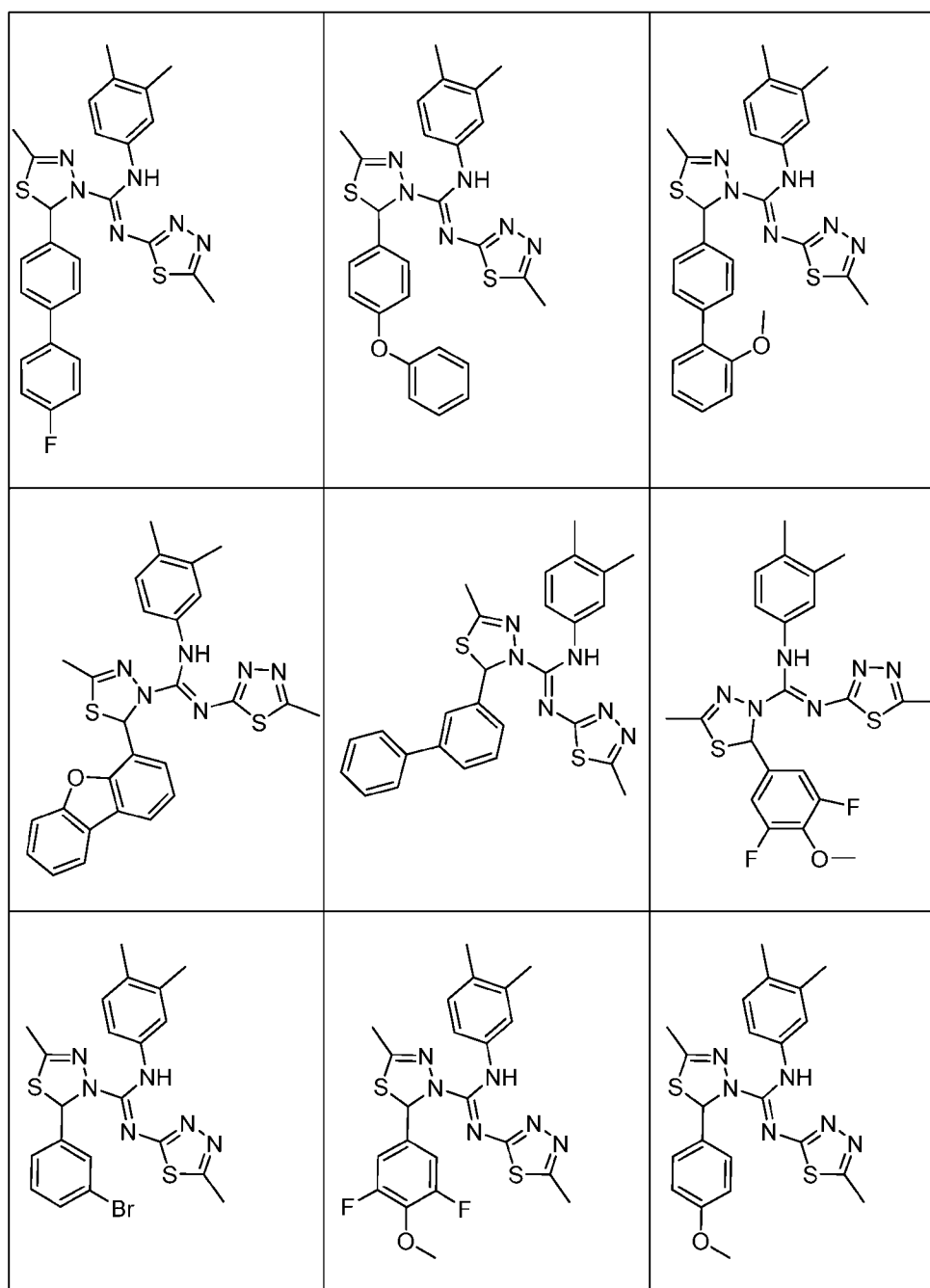
39. The compound of any one of claims 2-29, wherein one R¹ is fluoro and one R¹ is CF₃.
40. The compound of any one of claims 2-29, wherein one R¹ is fluoro and one R¹ is CN.
41. The compound of any one of claims 2-29, wherein two R¹ are fluoro and one R¹ is methyl.
42. The compound of any one of claims 2-29, wherein two R¹ are fluoro and one R¹ is OCH₃.
43. The compound of any one of claims 2-29, wherein one R¹ is OCF₃.
44. The compound of any one of claims 2-29, wherein one R¹ is phenyl.
45. The compound of to any one of claims 2-29, wherein one R¹ is phenyl substituted with fluoro, chloro, bromo, methyl, OCH₃, or CF₃.
46. The compound of any one of claims 2-29, wherein one R¹ is O-phenyl.
47. The compound of any one of claims 2-29, wherein one R¹ is phenyl substituted with CF₃.
48. The compound of any one of claims 2-29, wherein one R¹ is phenyl substituted with bromo.
49. The compound of any one of claims 2-29, wherein one R¹ is phenyl substituted with chloro.
50. The compound of claim 1, wherein the compound is selected from:

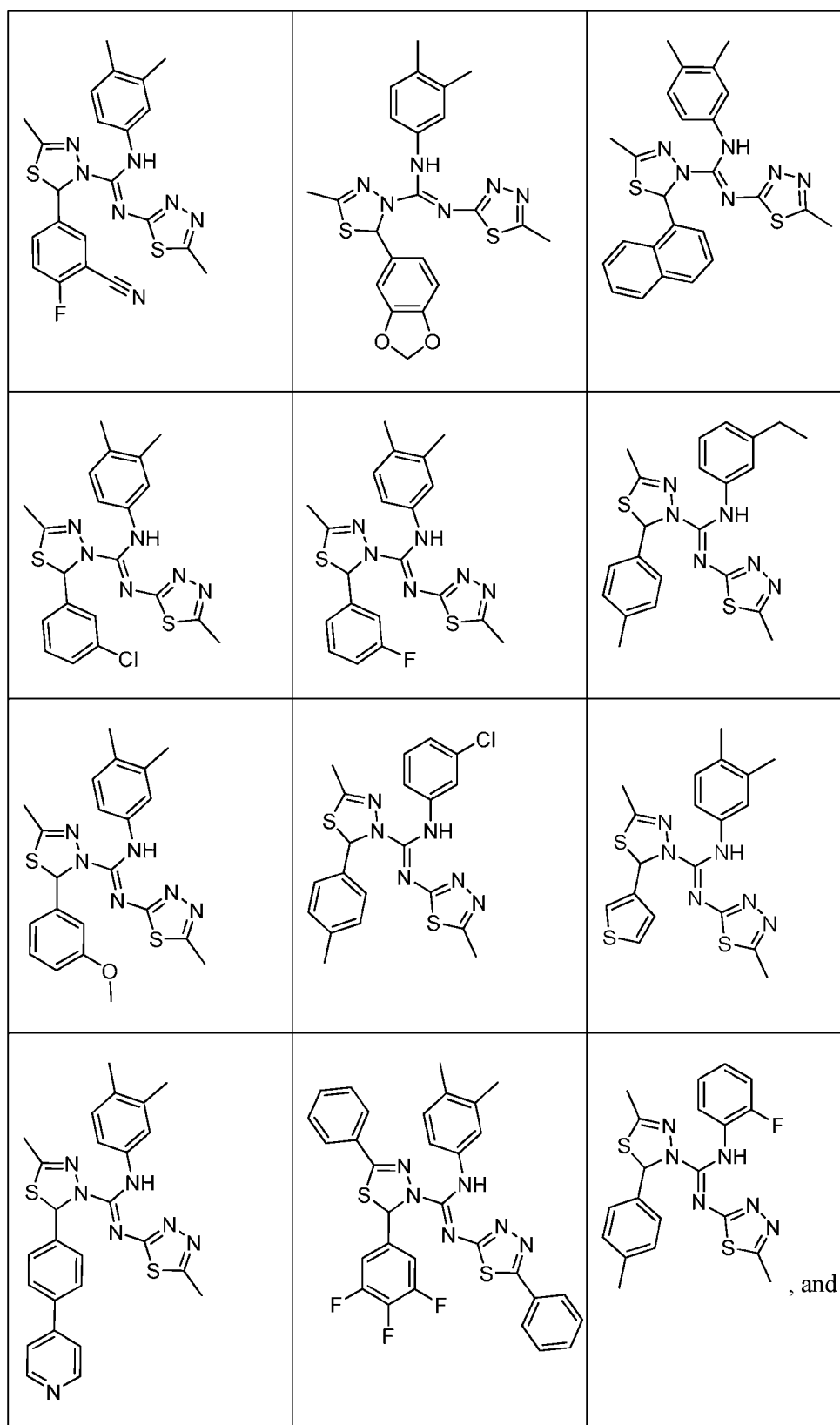


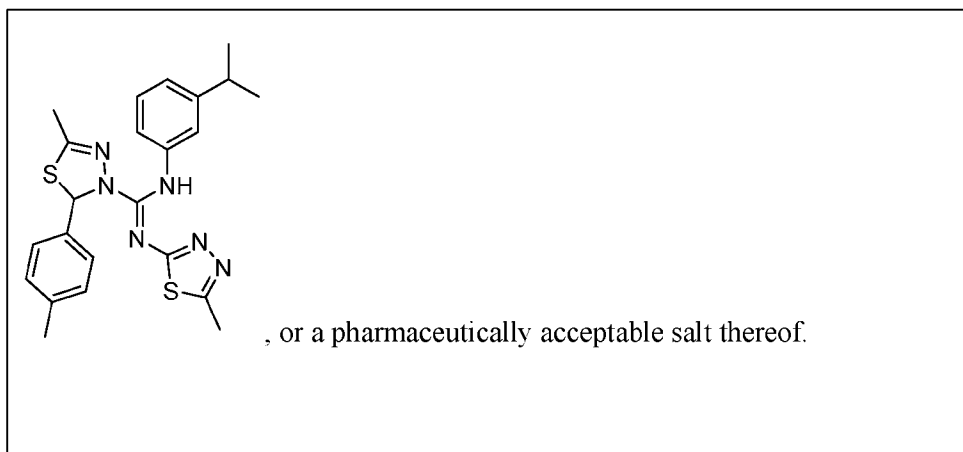












51. A pharmaceutical composition comprising a compound of any one of claims 1-50, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
52. A method of treating a disease selected from obesity, type 2 diabetes mellitus, heart failure, hypertension, functional dyspepsia, cholestasis, and non-alcoholic fatty liver disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-50, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 51.
53. A method of treating a disease mediated by stimulation of secretin receptor (SecR), comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-50, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 51.

INTERNATIONAL SEARCH REPORT

 International application No.
PCT/US2024/058250

A. CLASSIFICATION OF SUBJECT MATTER

C07D 285/135 (2006.01) A61K 31/433 (2006.01) A61P 43/00 (2006.01) C07D 417/14 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REGISTRY and CAPLUS: structure search based on claim 1; keywords: secretin receptor agonist

Google search: secretin receptor agonist

USPATFULL, PCTFULL, EPFULL: "secretin receptor agonist"

Espacenet and IP Australia internal databases: applicant and inventor names

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "D" document cited by the applicant in the international application "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search 4 March 2025	Date of mailing of the international search report 04 March 2025
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaaustralia.gov.au	Authorised officer Chetan Makani AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 2 6283 2896

INTERNATIONAL SEARCH REPORT Information on patent family members		International application No. PCT/US2024/058250	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2020/211772 A1	22 October 2020	WO 2020211772 A1	22 Oct 2020
		US 2023099367 A1	30 Mar 2023
End of Annex			
Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001. Form PCT/ISA/210 (Family Annex)(July 2019)			