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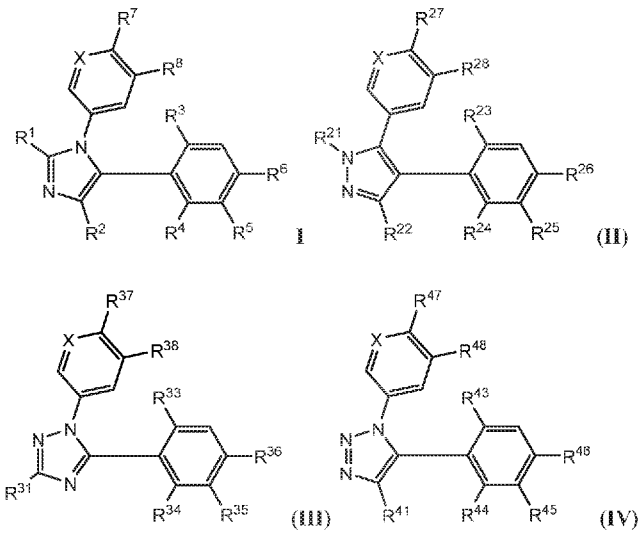
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(54) Title: MULTI-TARGETED HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES



(57) Abstract: The present disclosure provides methods of treating neurodegenerative diseases, peripheral inflammatory conditions, cancers, or parasitic diseases in a subject, comprising administering to the subject a compound of Formula (I), (II), (III), and/or (IV):(I), (II), (III), (IV) or a pharmaceutically acceptable salt thereof, wherein X. R^1-R^8, R^{21}-R^{28}. R^{31}-R^{38}, and R^{41}-R^{48} are as defined herein.

[Continued on next page]

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MULTI-TARGETED HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 62/385,312, filed September 9, 2016, the entirety of which is herein incorporated by reference.

TECHNICAL FIELD

[0002] The disclosure relates to compounds and methods for treating neurodegenerative diseases.

BACKGROUND

[0003] Neurodegeneration is attributed to a variety of diseases, including Alzheimer's disease (AD) which is a multi-factorial disease of the central nervous system (CNS) characterized by progressive and irreversible neurodegeneration. Genetic and histopathological data suggest that the onset and progression of neurodegeneration result from the formation of neurofibrillary tangles (comprised of aggregated tau proteins) and senile plaques (formed from deposits of Aβ peptides). Moreover, neuroinflammation and oxidative stress are invariably associated with the neurodegenerative process.

[0004] Although the precise relationship(s) linking these different neuropathological features remain the focus of intense studies, it is clear that neurodegeneration is a complex, multi-component disease. However, in spite of strong preclinical data, clinical trials aimed at treating neurodegeneration have thus far yielded disappointing results. This raises the possibility that candidate treatments may have to interfere concurrently with more than one neuropathological mechanism to affect disease progression.

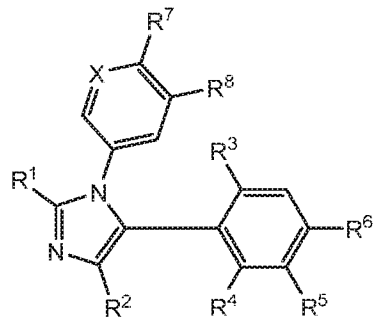
[0005] Neuroinflammation is implicated as a key contributing factor to Aβ plaque deposition through the action of cyclooxygenase (COX) and 5-lipoxygenase (5-LOX)-derived eicosanoids on their cognate receptors in neurons, resulting in increased production of amyloid precursor protein (APP) and Aβ peptides suggesting that inhibitors of COX and 5-LOX enzymes may be useful in reducing Aβ plaque pathology. Furthermore, microtubule-stabilizing agents have been found to attenuate tau pathology. Although brain-penetrant examples of microtubule-stabilizing agents (*e.g.*, epothilone D), inhibitors of COX-1 and/or COX-2 (*e.g.*, SC-560 and coxibs), and

inhibitors of 5-LOX (*e.g.*, zileuton) have been identified, a combination therapy based on three or more compounds would be problematic to develop and test clinically.

[0006] Multi-targeted compounds, especially those that could potentially counter both tau- and Aβ-mediated neurodegeneration, are clearly desirable.

SUMMARY

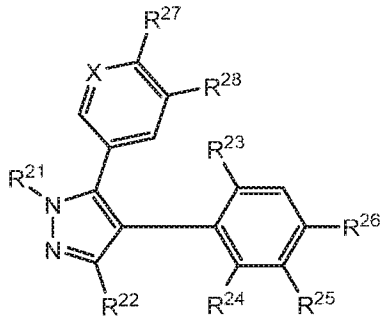
[0007] The present disclosure is directed to methods of treating neurodegenerative diseases, peripheral inflammatory conditions, cancers, or parasitic diseases in a subject, comprising administering to the subject a compound of Formula I:



(I)

[0008] or a pharmaceutically acceptable salt thereof, wherein X is CH or N; R^1 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^2 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^3 is H, F, Cl, or Br; R^4 is H, F, Cl, or Br; R^5 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^6 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^7 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and R^8 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[0009] The present disclosure also relates to methods of treating neurodegenerative diseases, peripheral inflammatory conditions, cancers, or parasitic diseases in a subject, comprising administering to the subject a compound of Formula (**II**):

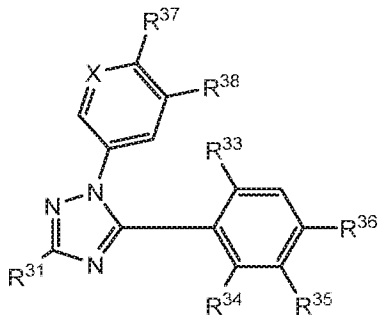


(II)

[0010] or a pharmaceutically acceptable salt thereof, wherein X is CH or N; R^{21} is H or C_{1-6}alkyl; R^{22} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{23} is H, F, Cl, or Br; R^{24} is H, F, Cl, or Br;

R^{25} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{26} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{27} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and R^{28} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

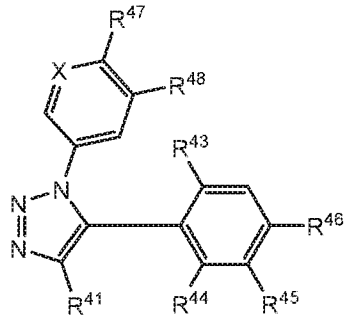
[0011] Further provided are methods of treating neurodegenerative diseases, peripheral inflammatory conditions, cancers, or parasitic diseases in a subject, comprising administering to the subject a compound of Formula (**III**):



(**III**)

[0012] or a pharmaceutically acceptable salt thereof, wherein X is CH or N; R^{31} is H, C_{1-6}alkyl, or C_{1-6}haloalkyl; R^{33} is H, F, Cl, or Br; R^{34} is H, F, Cl, or Br; R^{35} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{36} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{37} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and R^{38} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[0013] The present disclosure also provides methods of treating neurodegenerative diseases in a subject comprising administering to the subject a compound of Formula: (**IV**)



(**IV**)

[0014] or a pharmaceutically acceptable salt thereof, wherein X is CH or N; R^{41} is H or C_{1-6}alkyl; R^{43} is H, F, Cl, or Br; R^{44} is H, F, Cl, or Br; R^{45} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{46} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl; R^{47} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and R^{48} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[0015] Other aspects and embodiments of the invention will be readily apparent from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] The present application is further understood when read in conjunction with the appended drawings. For the purpose of illustrating the subject matter, there are shown in the drawings exemplary embodiments of the subject matter; however, the presently disclosed subject matter is not limited to the specific compositions, methods, devices, and systems disclosed. In addition, the drawings are not necessarily drawn to scale.

[0017] FIG. 1 is a schematic showing a summary of SARs (top) and representative structures exemplifying the different activity profiles exhibited by the 1,5-diarylimidazoles (bottom).

[0018] FIG. 2 are representative dose–response curves in the RBL-1 cell assays. Samples were run in triplicate at each concentration, with the error bars representing standard error of the mean.

[0019] FIG. 3 is a bar graph showing the analysis of Table 12 compounds for their ability to reduce multiple COX and 5-LOX products. The compounds listed in Table 12 were tested at 50 μM in the RBL-1 assay, and COX-derived PGE_2 and PGE_2, as well as 5-LOX-derived LTB_4 and LTC_4, were assessed by LC-MS/MS. All compounds caused appreciable inhibition of all of the measured eicosanoids.

[0020] FIG. 4 are bar graphs showing the concentration response of compounds 64 and 70 in the QBI293 AcTub assay. Compounds 64 and 70 underwent concentration-response testing in triplicate in the QBI cell acetyl tubulin (AcTub) assay from 1-100 μM and the increase in AcTub/μg of cellular homogenate relative to vehicle-treated cells is graphed. The triazolopyrimidine, cevipabulin,1 was tested at 0.1 μM as a positive control. Error bars represent standard error of the mean. **, $p<0.01$ relative to vehicle-treated cells as determined by one-way ANOVA and Dunnett's multiple comparison test.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0021] In the present disclosure the singular forms "a", "an" and "the" include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to "a material" is a reference to at least one of such materials and equivalents thereof known to those skilled in the art, and so forth.

[0022] When a value is expressed as an approximation by use of the descriptor "about" or "substantially" it will be understood that the particular value forms another embodiment. In general, use of the term "about" or "substantially" indicates approximations that can vary depending on the desired properties sought to be obtained by the disclosed subject matter and is

to be interpreted in the specific context in which it is used, based on its function. The person skilled in the art will be able to interpret this as a matter of routine. In some cases, the number of significant figures used for a particular value may be one non-limiting method of determining the extent of the word "about" or "substantially". In other cases, the gradations used in a series of values may be used to determine the intended range available to the term "about" or "substantially" for each value. Where present, all ranges are inclusive and combinable. That is, references to values stated in ranges include every value within that range.

[0023] When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list and every combination of that list is to be interpreted as a separate embodiment. For example, a list of embodiments presented as "A, B, or C" is to be interpreted as including the embodiments, "A," "B," "C," "A or B," "A or C," "B or C," or "A, B, or C."

[0024] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. That is, unless obviously incompatible or excluded, each individual embodiment is deemed to be combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation. Finally, while an embodiment may be described as part of a series of steps or part of a more general structure, each said step may also be considered an independent embodiment in itself.

[0025] The term "alkyl," when used alone or as part of a substituent group, refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms ("C_{1-12}"), preferably 1 to 6 carbons atoms ("C_{1-6}"), in the chain. Examples of alkyl groups include methyl (Me, C_1alkyl) ethyl (Et, C_2alkyl), n-propyl (C_3alkyl), isopropyl (C_3alkyl), butyl (C_4alkyl), isobutyl (C_4alkyl), sec-butyl (C_4alkyl), tert-butyl (C_4alkyl), pentyl (C_5alkyl), isopentyl (C_5alkyl), tert-pentyl (C_5alkyl), hexyl (C_6alkyl), isohexyl (C_6alkyl), and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

[0026] The term "haloalkyl," when used alone or as part of a substituent group, refers to an alkyl group as described above having one, two, or three halogen atoms attached to a single carbon atom. Preferably, the halogen is F. In some embodiments, haloalkyl includes

perfluoroalkyl groups whereby the alkyl group is terminated with a CF_3, CH_2F, or CHF_2. Examples of alkyl groups include CF_3, CHF_2, CH_2F, CH_2CF_3, $CHFCF_3$, CF_2CF_3, CH_2CHF_2, CH_2CH_2F, $CHFCH_3$, CF_2CH_3, $CHFCHF_2$, CF_2CHF_2, among others, and groups that in light of the ordinary skill in the art and the teachings provided herein would be considered equivalent to any one of the foregoing examples.

[0027] When a range of carbon atoms is used herein, for example, C_{1-6}, all ranges, as well as individual numbers of carbon atoms are encompassed. For example, "C_{1-3}" includes C_{1-3}, C_{1-2}, C_{2-3}, C_1, C_2, and C_3.

[0028] The term "halogen" represents chlorine, fluorine, bromine, or iodine. The term "halo" represents chloro, fluoro, bromo, or iodo.

[0029] As used herein, the term "compound(s) of formula (**I**)" includes those compounds of "formula (**I**)," as well as compounds of any of the formula (**I**) subgenera. The term "compound(s) of formula (**II**)" includes those compounds of "formula (**II**)," as well as compounds of any of the formula (**II**) subgenera. The term "compound(s) of formula (**III**)" includes those compounds of "formula (**III**)," as well as compounds of any of the formula (**III**) subgenera. The term "compound(s) of formula (**IV**)" includes those compounds of "formula (**IV**)," as well as compounds of any of the formula (**IV**) subgenera.

[0030] "Pharmaceutically acceptable" means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0031] "Pharmaceutically acceptable salt" refers to a salt of a compound of the disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid,

gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of non-toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0032] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier with which a compound of the disclosure is administered. A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of an agent and that is compatible therewith. Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

[0033] "Subject" includes humans. The terms "human," "patient," and "subject" are used interchangeably herein.

[0034] "Treating" or "treatment" of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (i.e., arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, "treating" or "treatment" refers to delaying the onset of the disease or disorder.

[0035] "Compounds of the present disclosure," and equivalent expressions, are meant to embrace compounds of the Formula (I), (II), (III), and/or (IV) as described herein, which expression includes the pharmaceutically acceptable salts, and the solvates, e.g., hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

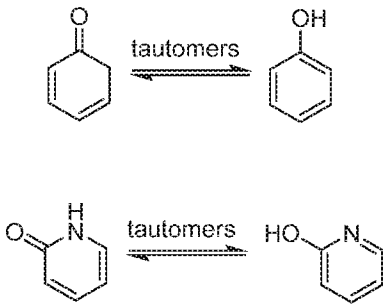
[0036] As used herein, the term "isotopic variant" refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an "isotopic variant" of a compound can be radiolabeled, that is, contain one or more non-

radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitrogen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the disclosure may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. Radiolabeled compounds of the disclosure can be used in diagnostic methods such as Single-photon emission computed tomography (SPECT). The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

[0037] All isotopic variants of the compounds of the disclosure, radioactive or not, are intended to be encompassed within the scope of the disclosure.

[0038] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers," for example, diastereomers, enantiomers, and atropisomers. The compounds of this disclosure may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)-or (*S*)-stereoisomers or as mixtures thereof.

[0039] "Tautomers" refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base.



[0040] Another example of tautomerism is the acid-and nitro-forms of phenyl nitromethane, that are likewise formed by treatment with acid or base.

[0041] Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0042] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Within the present disclosure, any open valency appearing on a carbon, oxygen, or nitrogen atom in any structure described herein indicates the presence of a hydrogen atom. Where a chiral center exists in a structure, but no specific stereochemistry is shown for that center, both enantiomers, separately or as a mixture, are encompassed by that structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0043] The compounds described herein are useful in treating neurodegenerative diseases, in particular, neurodegenerative diseases which are characterized by a tauopathy or compromised microtubule function subject. In some embodiments, the compounds are useful for treating Alzheimer's disease, frontotemporal lobar degeneration, Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration, schizophrenia, Parkinson's disease (PD), PD with dementia, Lewy body disease with dementia, amyotrophic lateral sclerosis, argyrophilic grain disease, chronic traumatic encephalopathy, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, frontotemporal dementia, parkinsonism linked to chromosome 17, Gerstmann-Straussler-Scheinker disease, Guadeloupean parkinsonism, multiple sclerosis, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, white matter tauopathy with globular glial inclusions. In other embodiments, the compounds can be used to treat traumatic brain injury (TBI), especially repetitive TBI (rTBI), such as that due to dementia pugilistica and recurrent football concussions and military closed head injuries such as that due to IEDs, which also is known as chronic traumatic encephalopathy (CTE), with features of tauopathy or AD-like pathology or post-traumatic stress disorder. The compounds described herein are particularly useful in the treatment of Alzheimer's disease.

[0044] The compounds may also be useful in treating peripheral inflammatory conditions. In some embodiments, the compounds useful in treating peripheral inflammatory conditions inhibit

both cyclooxygenase-derived eicosanoid production and lepoxygenase-derived eicosanoid production. In other embodiments, the compounds are not useful in stabilizing microtubules. The peripheral inflammatory conditions which may be treated as described herein include rheumatoid arthritis, Crohn's disease, inflammatory bowel disease (IBD), lupus, asthma, and sepsis. In some embodiments, the peripheral inflammatory conditions is rheumatoid arthritis and Crohn's diease, among others.

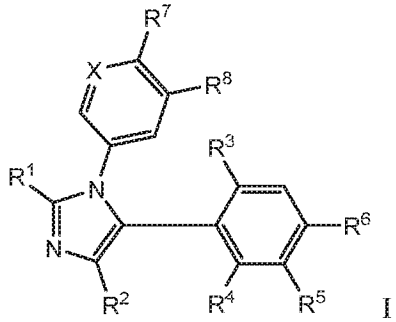
[0045] The compounds may also be useful in treating cancers. In some embodiments, the compounds useful in treating cancer are capable of stabilizing microtubules. The term "cancer" as used herein, refers to neoplastic cells in a patient which have abnormal cell group and invade or have the potential to invade one or more body parts of the patient. In one embodiment, the cancer is a neuroendocrine cancer, adrenal gland cancer, appendix cancer, bladder cancer, blood cancer, brain cancer, bone cancer, breast cancer, bronchus cancer, central nervous system cancer, cervical cancer, chest cancer, colon cancer, esophagael cancer, eye cancer, gallbladder cancer, head cancer, intestininal cancer, kidney cancer, larynx cancer, liver cancer, lung cancer, lymph node cancer, mouth cancer, neck cancer, ovarian cancer, pancreatic cancer, pharynx cancer, pituitary cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicle cancer, throat cancer, thymus cancer, thyroid cancer, uterine cancer, urinary cancer, vaginal cancer, or a leukemia. In some embodiments, the cancer is brain cancer.

[0046] Parasitic diseases may further be treating using the compounds described herein. In some embodiments, the compounds useful in treating parasite infections are those that are capable of stabilizing microtubules. The term "parasitic disease" as used herein refers to a disease resulting from an infection of a parasite. A variety of parasitic diseases may be treated using the compounds as described herein including, without limitation, malaria, leishmaniasis, schistosomiasis, toxoplasmosis, coccidiosis, African trypanosomiasis, Chagas's disease, giardiasis, or amoebiasis.

[0047] These classes of compounds include imidazole compounds of formula **(I)**, pyrazole compounds of formula **(II)**, and triazole compounds of formula **(III)** and **(IV)**, as described herein. As discussed herein, these compounds have microtubule stabilizing properties and/or are inhibitors of eicosanoid synthesis.

[0048] In addition to their stabilizing and inhibiting properties, these compounds were found to exhibit brain penetration properties.

[0049] The present disclosure is related to methods of treating a neurodegenerative disease in a subject comprising administering to the subject a compound of Formula I, or a pharmaceutically acceptable salt thereof:



I

[0050] According to the disclosure X is CH or N. In some embodiments, X is CH. In other embodiments, X is N.

[0051] As described herein, R^1 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^1 is H. In other embodiments, R^1 is F, Cl, or Br. In further embodiments, R^1 is F. In still other embodiments, R^1 is Cl. In yet further embodiments, R^1 is Br. In additional embodiments, R^1 is C_{1-6}alkyl or OC_{1-6}alkyl. In other embodiments, R^1 is C_{1-6}alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In further embodiments, R^1 is OC_{1-6}alkyl such as methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0052] In formula (I), R^2 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^2 is H. In other embodiments, R^2 is F, Cl, or Br. In further embodiments, R^2 is F. In yet other embodiments, R^2 is Cl. In still further embodiments, R^2 is Br. In other embodiments, R^2 is C_{1-6}alkyl or OC_{1-6}alkyl. In further embodiments, R^2 is C_{1-6}alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In further embodiments, R^2 is OC_{1-6}alkyl such as methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0053] R^3 is H, F, Cl, or Br. In some embodiments, R^3 is H. In other embodiments, R^3 is F, Cl, or Br. In further embodiments, R^3 is F. In other embodiments, R^3 is Cl. In additional embodiments, R^3 is Br.

[0054] R^4 is H, F, Cl, or Br. In some embodiments, R^4 is H. In other embodiments, R^4 is F, Cl, or Br. In further embodiments, R^4 is F. In other embodiments, R^4 is Cl. In additional embodiments, R^4 is Br.

[0055] R^5 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^5 is H. In other embodiments, R^5 is F, Cl, or Br. In further embodiments, R^5 is F. In yet other embodiments, R^5 is Cl. In still further embodiments, R^5 is Br. In other embodiments, R^5 is C_{1-6}alkyl or OC_{1-6}alkyl. In further embodiments, R^5 is C_{1-6}alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In further embodiments, R^5 is OC_{1-6}alkyl such as methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

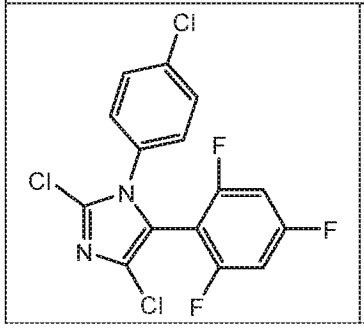
[0056] R^6 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^6 is H. In other embodiments, R^6 is F, Cl, or Br. In further embodiments, R^6 is F. In yet other embodiments, R^6 is Cl. In still further embodiments, R^6 is Br. In other embodiments, R^6 is C_{1-6}alkyl or OC_{1-6}alkyl. In further embodiments, R^6 is C_{1-6}alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In further embodiments, R^6 is OC_{1-6}alkyl such as methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

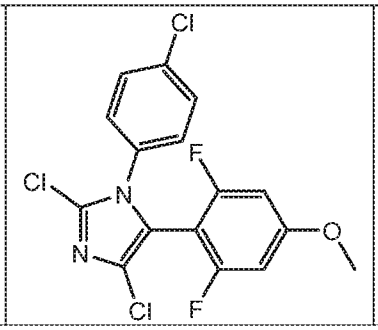
[0057] R^7 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^7 is H. In other embodiments, R^7 is F, Cl, or Br. In further embodiments, R^7 is F. In yet other embodiments, R^7 is Cl. In still further embodiments, R^7 is Br. In other embodiments, R^7 is C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In further embodiments, R^7 is C_{1-6}alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still other embodiments, R^7 is C_{1-6}haloalkyl such as CF_3. In further embodiments, R^7 is OC_{1-6}alkyl such as methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0058] R^8 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^8 is H. In other embodiments, R^8 is F, Cl, or Br. In further embodiments, R^8 is F. In yet other embodiments, R^8 is Cl. In still further embodiments, R^8 is Br. In other embodiments, R^8 is C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In further embodiments, R^8 is C_{1-6}alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still other embodiments, R^8 is C_{1-6}haloalkyl such as CF_3. In further embodiments, R^8 is OC_{1-6}alkyl such as methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0059] Preferred compounds of formula (**I**) include those of Table 1. In some embodiments, these compounds stabilize microtubules.

Table 1





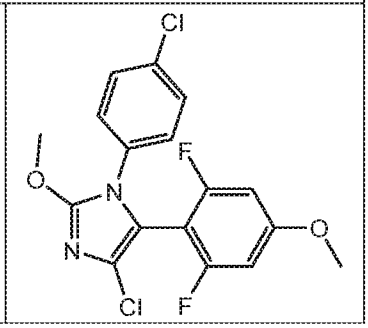


Table 1

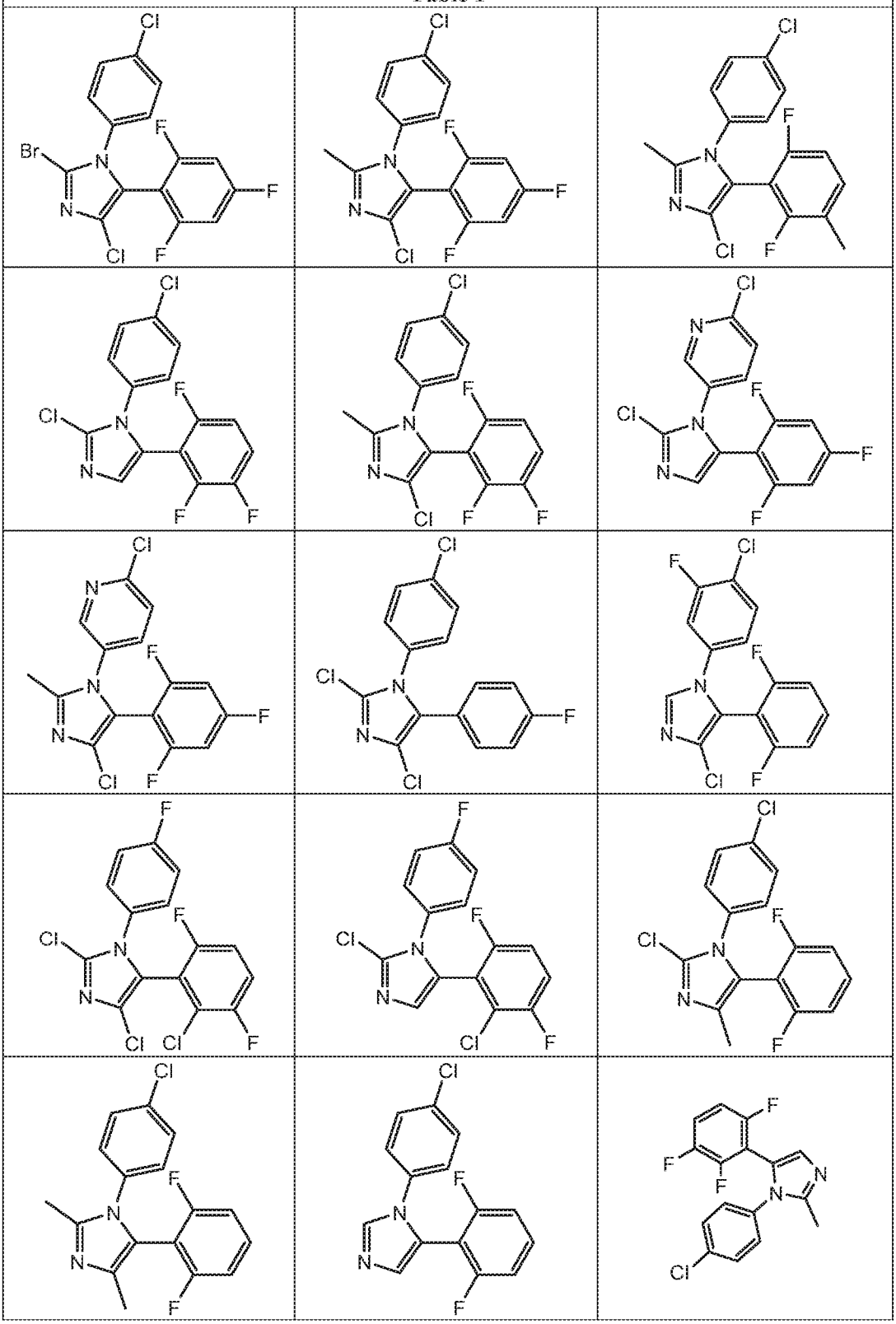
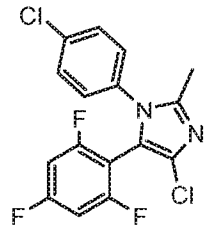
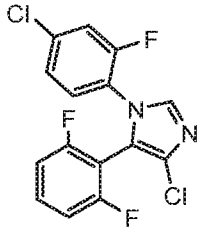
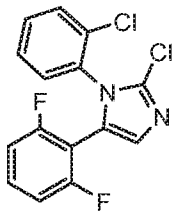
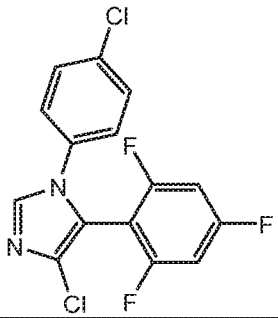
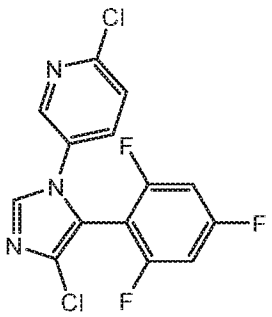
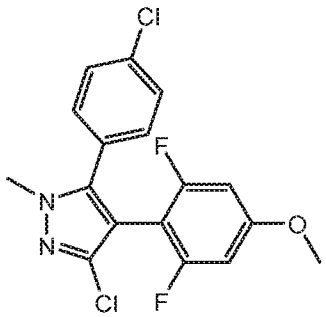
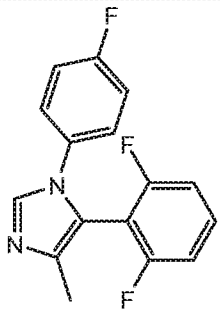
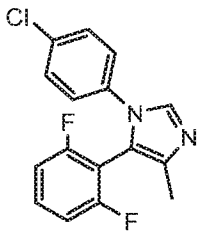
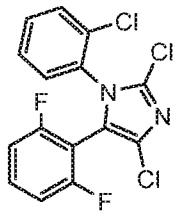


Table 1

[0060] Other preferred compounds of formula (**I**) include those in Table 2. In some embodiments, these compounds inhibit cyclooxygenase-derived eicosanoid production and stabilize microtubules.

Table 2

[0061] Further preferred compounds of formula (**I**) include those in Table 3. In some embodiments, these compounds inhibit 5-lipoxygenase-derived eicosanoid production and stabilize microtubules.

Table 3

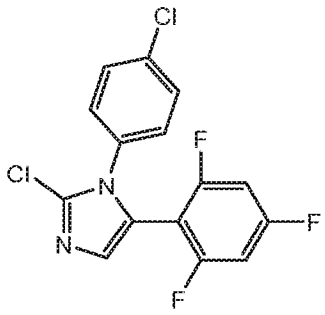
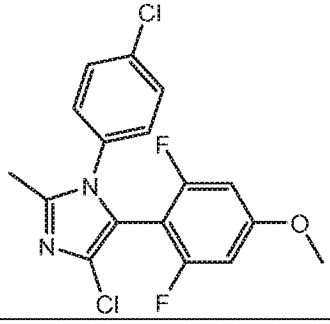
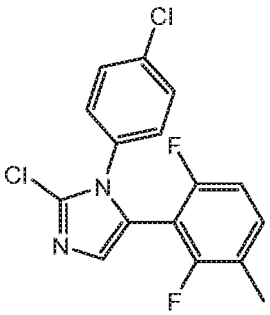
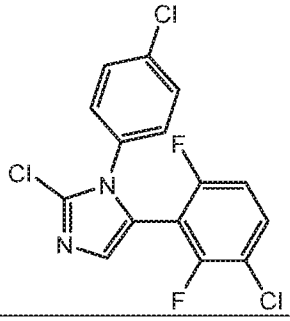
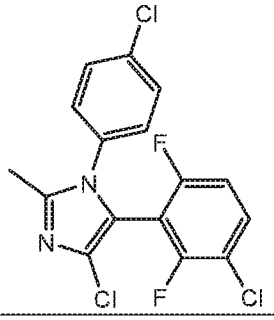
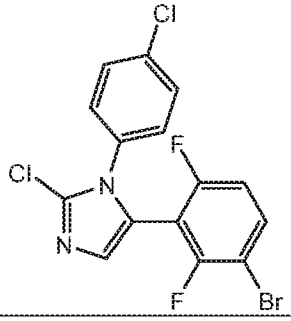
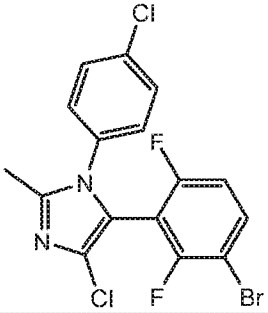
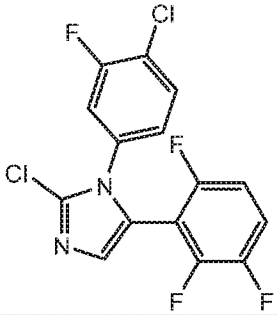
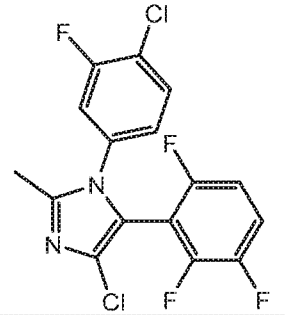
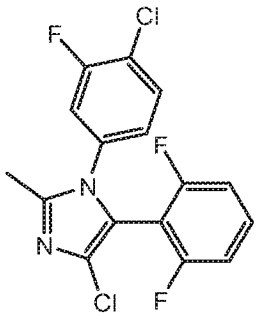
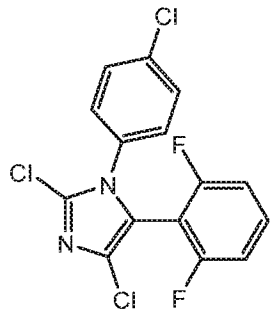
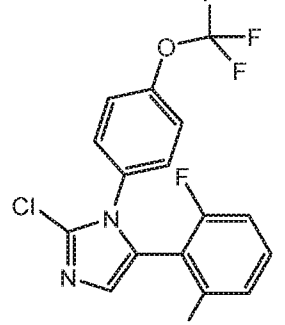
		
		
		
		

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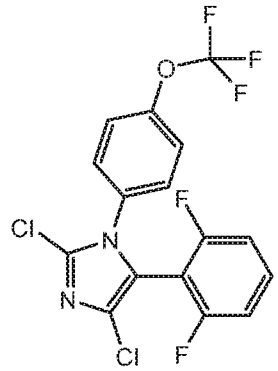
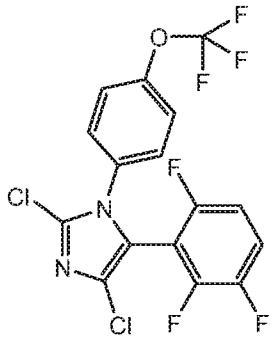
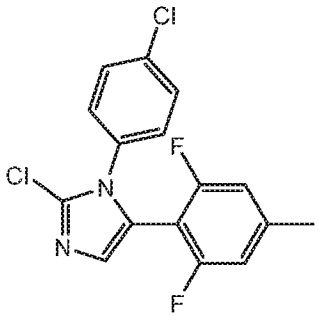
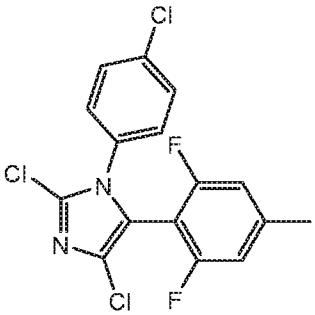
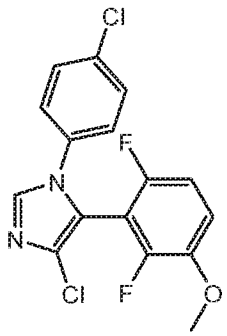
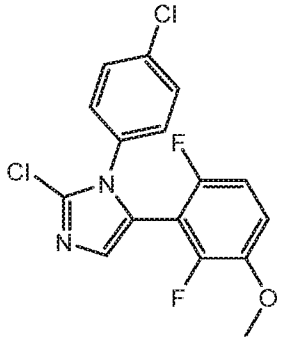
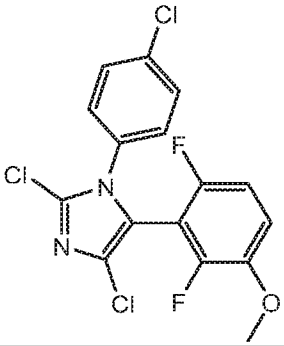
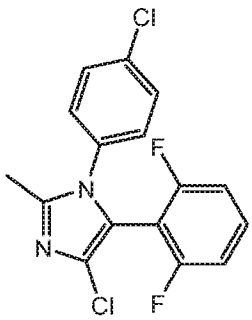
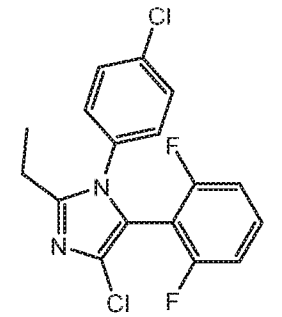
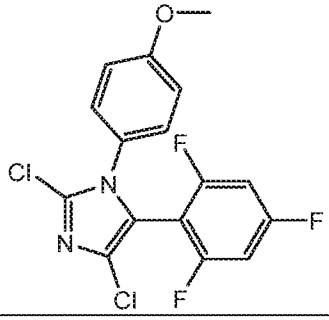
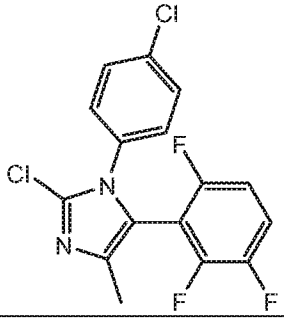
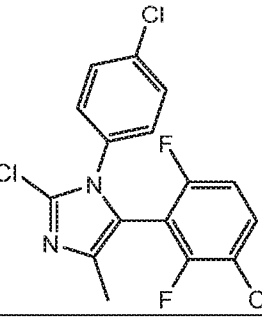
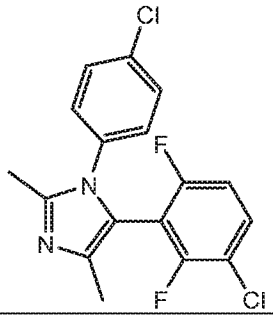
		
		
		
		

Table 3		
		

[0062] Additional preferred compounds of formula (I) are those in Table 4. In some embodiments, these compounds inhibit cyclooxygenase-derived eicosanoid production, inhibit 5-lipoxygenase-derived eicosanoid production and stabilize microtubules.

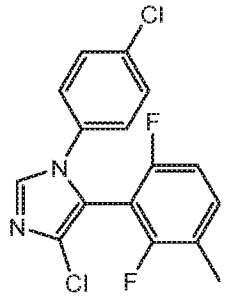
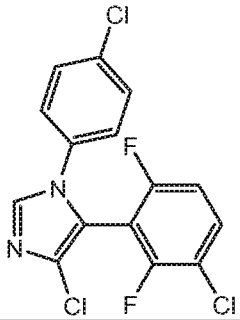
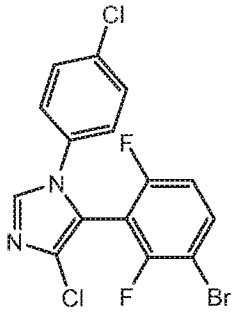
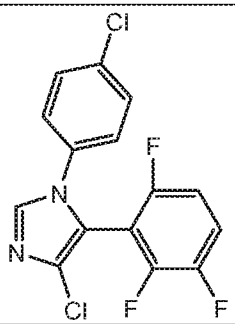
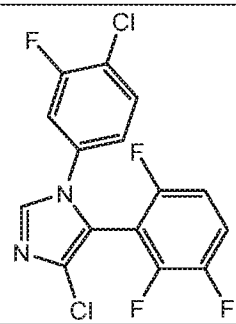
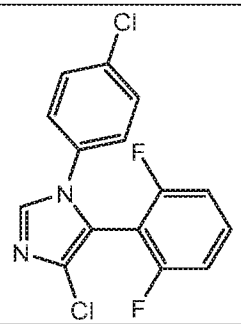
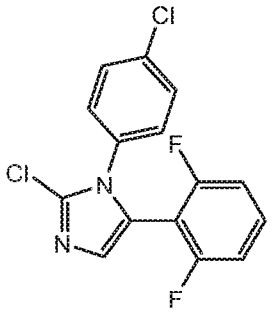
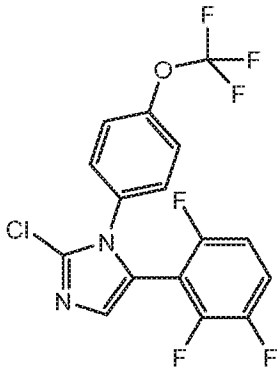
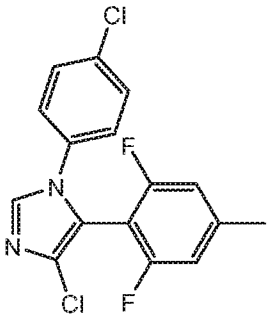
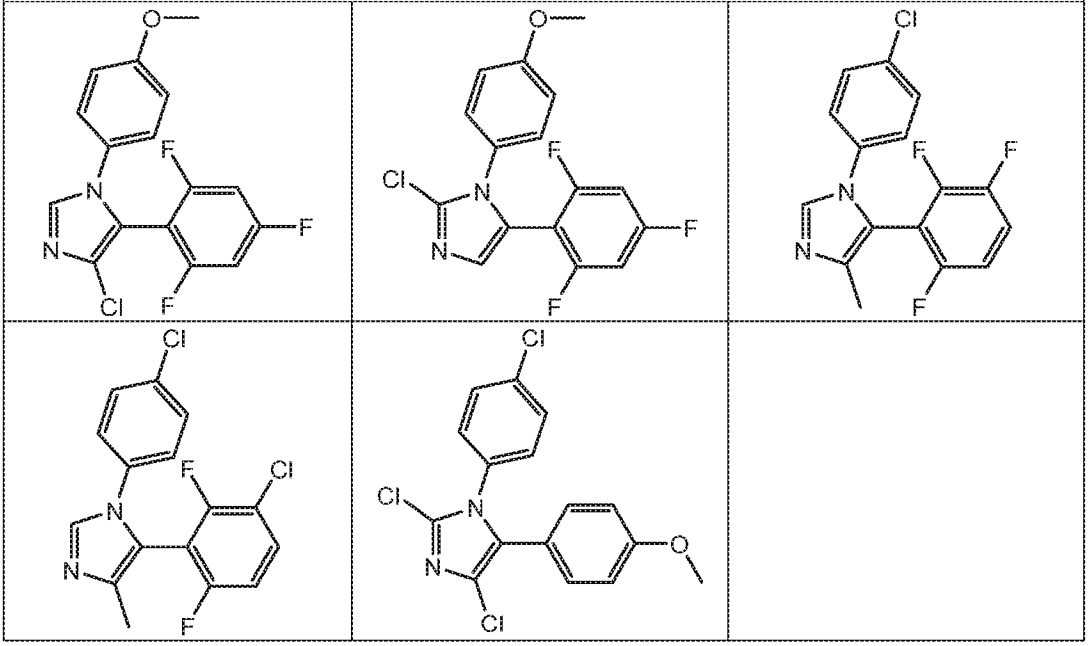
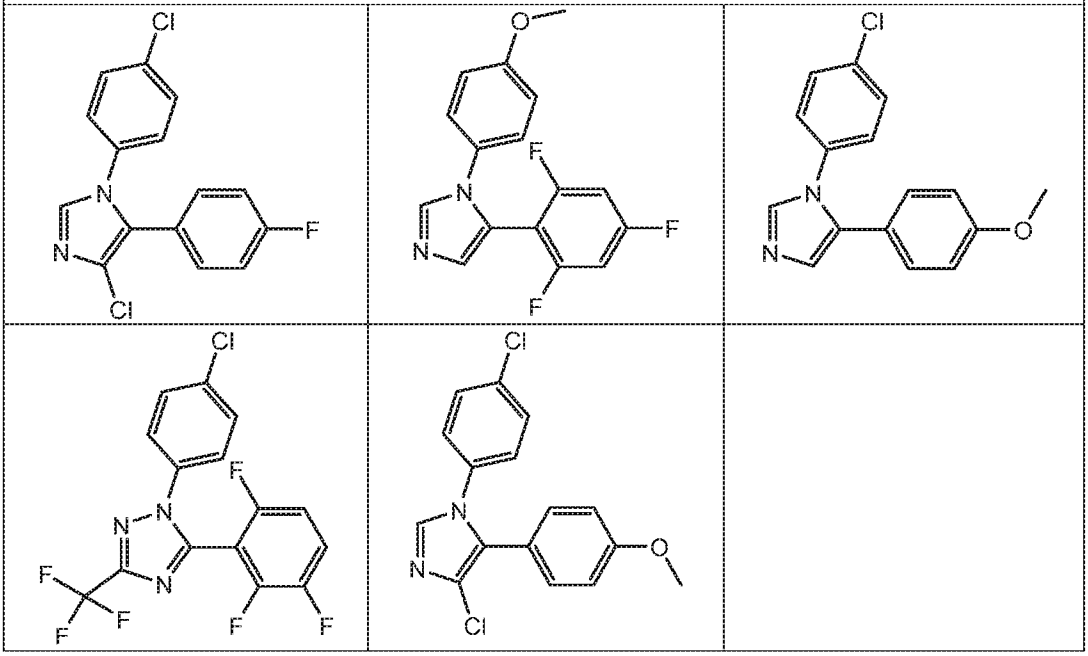
Table 4		
		
		
		

Table 4



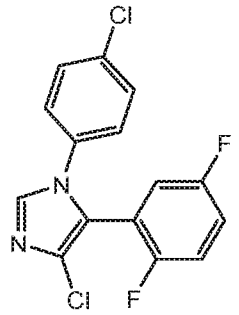
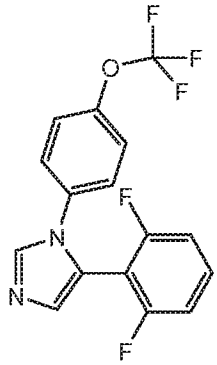
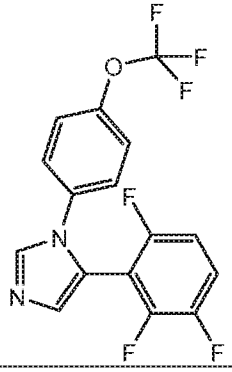
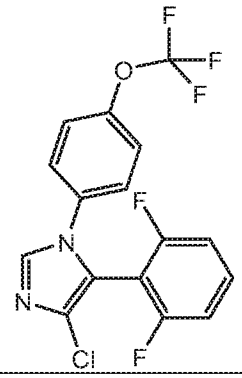
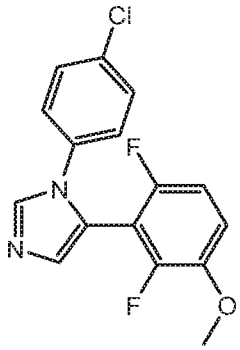
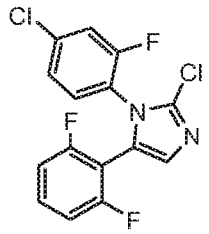
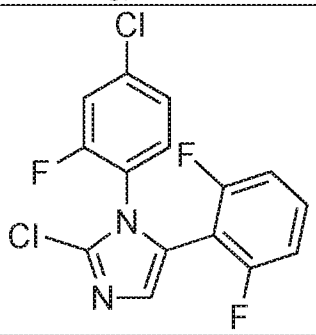
[0063] Other preferred compounds of formula (I) are those in Table 5. In some embodiments, these compounds inhibit cyclooxygenase-derived eicosanoid production.

Table 5



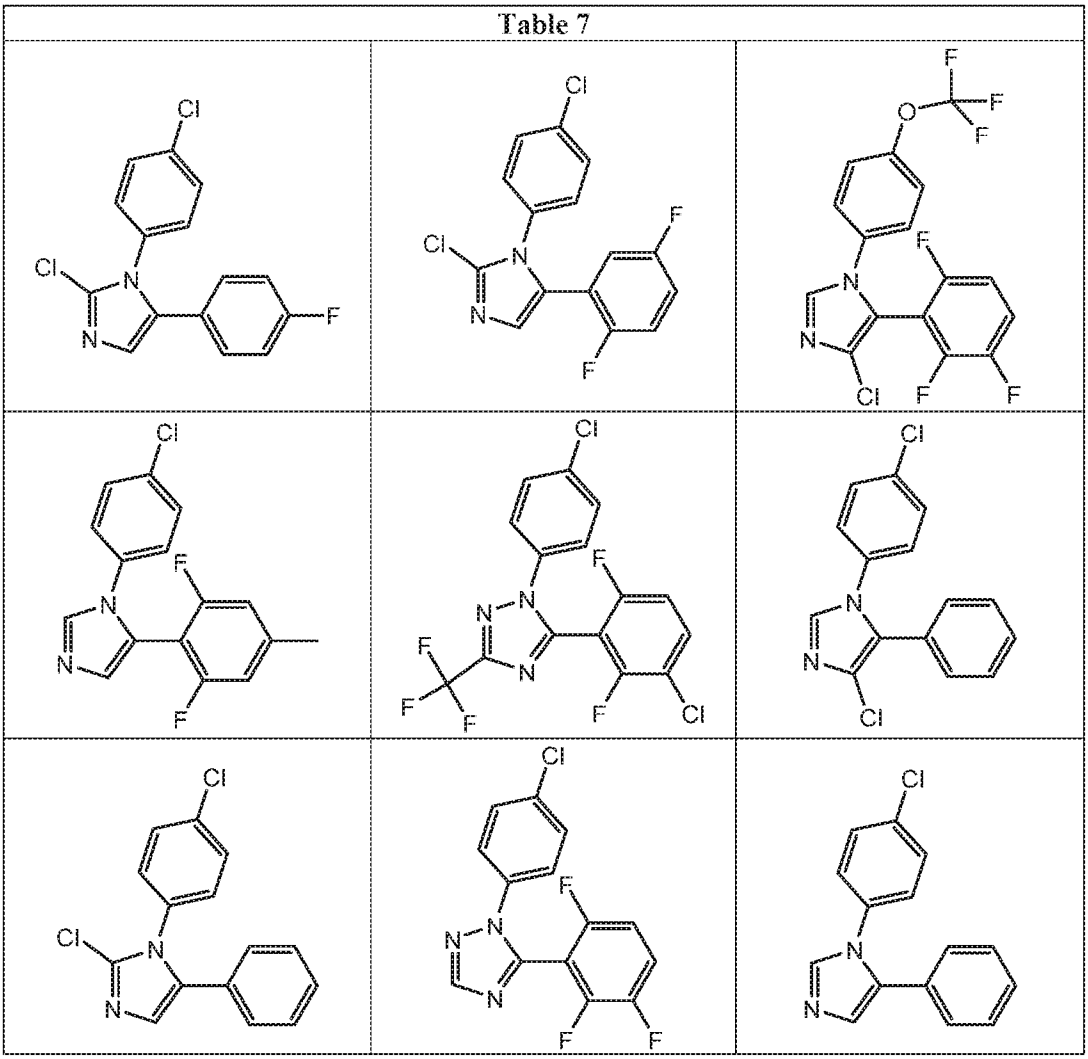
[0064] Further preferred compound of formula (I) include those in Table 6. In some embodiments, these compounds inhibit 5-lipoxygenase-derived eicosanoid production.

Table 6

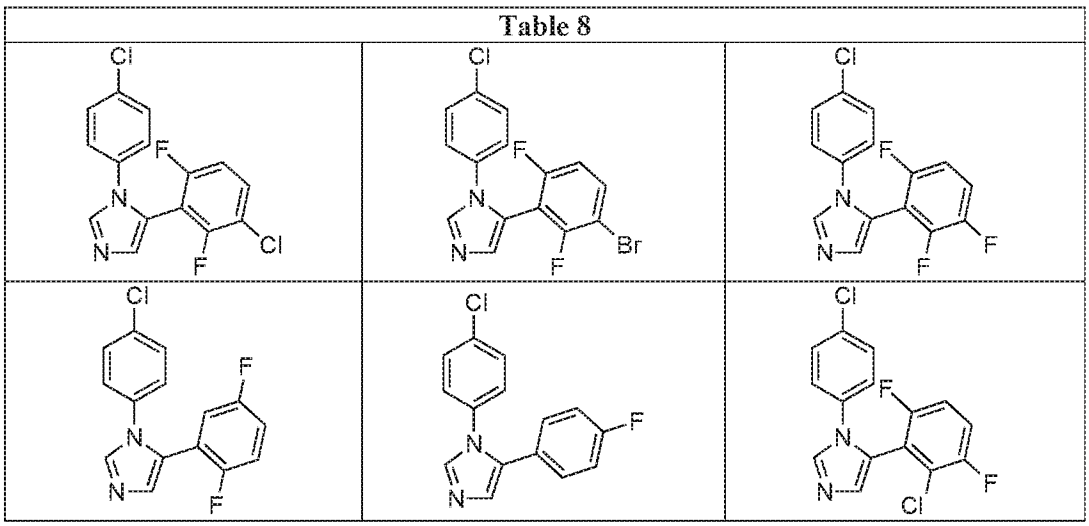
[0065] Additional preferred compounds of formula (**I**) are those in Table 7. In some embodiments, these compounds inhibit cyclooxygenase-derived eicosanoid production and 5-lipoxygenase-derived eicosanoid production.

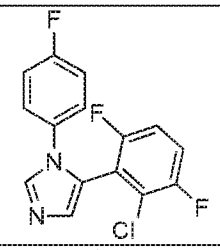
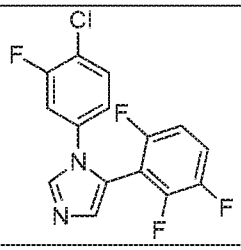
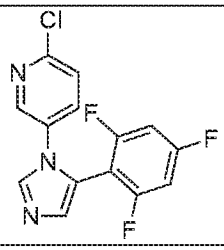
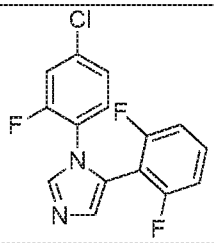
Table 7



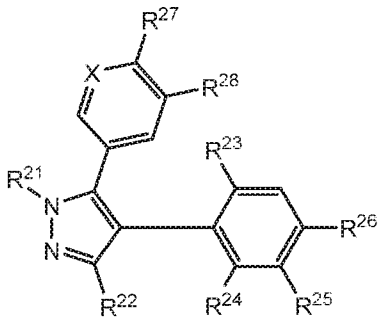
[0066] Yet further preferred compounds of formula (**I**) are those in Table 8.

Table 8



[0067] Also provided are methods of treating neurodegenerative diseases in a subject comprising administering to the subject a compound of Formula (**II**), or a pharmaceutically acceptable salt thereof:



(**II**)

[0068] According to the disclosure, X is CH or N. In some embodiments, X is CH. In other embodiments, X is N.

[0069] R^{21} is H or C_{1-6}alkyl. In some embodiments, R^{21} is H. In other embodiments, R^{21} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl.

[0070] R^{22} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{22} is H. In other embodiments, R^{22} is F. In further embodiments, R^{22} is Cl. In yet other embodiments, R^{22} is Br. In additional embodiments, R^{22} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{22} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0071] R^{23} is H, F, Cl, or Br. In some embodiments, R^{23} is H. In other embodiments, R^{23} is F. In further embodiments, R^{23} is Cl. In additional embodiments, R^{23} is Br.

[0072] R^{24} is H, F, Cl, or Br. In some embodiments, R^{24} is H. In other embodiments, R^{24} is F. In further embodiments, R^{24} is Cl. In additional embodiments, R^{24} is Br.

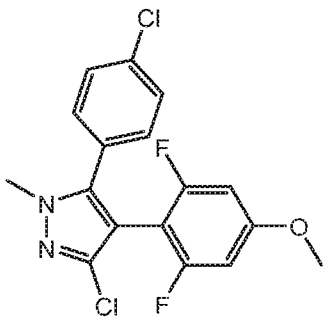
[0073] R^{25} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{25} is H. In other embodiments, R^{25} is F. In further embodiments, R^{25} is Cl. In yet other embodiments, R^{25} is Br. In additional embodiments, R^{25} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{25} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0074] R^{26} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{26} is H. In other embodiments, R^{26} is F. In further embodiments, R^{26} is Cl. In yet other embodiments, R^{26} is Br. In additional embodiments, R^{26} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{26} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0075] R^{27} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^{27} is H. In other embodiments, R^{27} is F. In further embodiments, R^{27} is Cl. In yet other embodiments, R^{27} is Br. In additional embodiments, R^{27} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{27} is C_{1-6}haloalkyl, for example, CF_3. In still further embodiments, R^{27} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

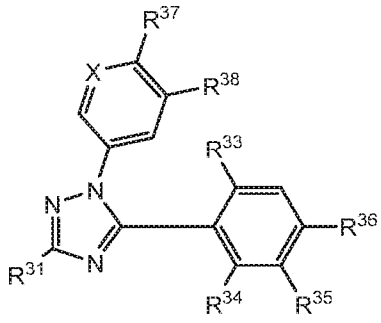
[0076] R^{28} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^{28} is H. In other embodiments, R^{28} is F. In further embodiments, R^{28} is Cl. In yet other embodiments, R^{28} is Br. In additional embodiments, R^{28} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{28} is C_{1-6}haloalkyl, for example, CF_3. In still further embodiments, R^{28} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0077] In some embodiments, the compound of formula (**II**) is the following.



In some embodiments, this compound stabilizes microtubules and inhibits cyclooxygenase-derived eicosanoid production.

[0078] Further provided are methods of treating neurodegenerative diseases in a subject comprising administering to the subject a compound of Formula (**III**), or a pharmaceutically acceptable salt thereof:



(III)

[0079] According to the disclosure, X is CH or N. In some embodiments, X is CH. In other embodiments, X is N.

[0080] R^{31} is H, C_{1-6}alkyl, or C_{1-6}haloalkyl. In some embodiments, R^{31} is H. In additional embodiments, R^{31} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{31} is C_{1-6}haloalkyl, for example, CF_3.

[0081] R^{33} is H, F, Cl, or Br. In some embodiments, R^{33} is H. In other embodiments, R^{33} is F. In further embodiments, R^{33} is Cl. In yet other embodiments, R^{33} is Br.

[0082] R^{34} is H, F, Cl, or Br. In some embodiments, R^{34} is H. In other embodiments, R^{34} is F. In further embodiments, R^{34} is Cl. In yet other embodiments, R^{34} is Br.

[0083] R^{35} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{35} is H. In other embodiments, R^{35} is F. In further embodiments, R^{35} is Cl. In yet other embodiments, R^{35} is Br. In additional embodiments, R^{35} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{35} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0084] R^{36} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{36} is H. In other embodiments, R^{36} is F. In further embodiments, R^{36} is Cl. In yet other embodiments, R^{36} is Br. In additional embodiments, R^{36} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{36} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

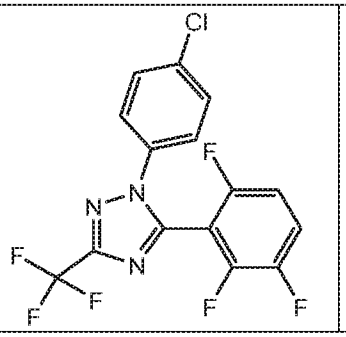
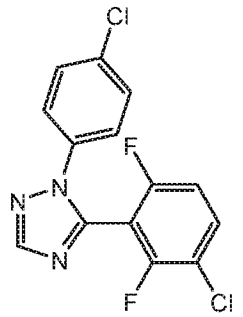
[0085] R^{37} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^{37} is H. In other embodiments, R^{37} is F. In further embodiments, R^{37} is Cl. In yet other embodiments, R^{37} is Br. In additional embodiments, R^{37} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{37} is C_{1-6}haloalkyl, for example, CF_3. In

still further embodiments, R^{37} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

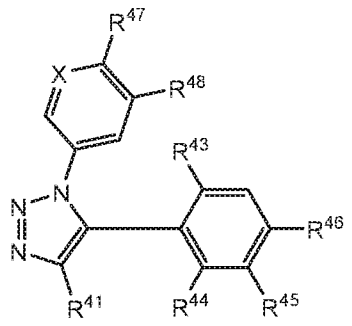
[0086] R^{38} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^{38} is H. In other embodiments, R^{38} is F. In further embodiments, R^{38} is Cl. In yet other embodiments, R^{38} is Br. In additional embodiments, R^{38} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{38} is C_{1-6}haloalkyl, for example, CF_3. In still further embodiments, R^{38} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0087] Some preferred compounds of formula (**III**) are provided in Table 9. In some embodiments, these compounds inhibit cyclooxygenase-derived eicosanoid production and 5-lipoxygenase-derived eicosanoid production.

Table 9

[0088] Also provided are methods of treating neurodegenerative diseases in a subject comprising administering to the subject a compound of Formula (**IV**, or a pharmaceutically acceptable salt thereof:



(**IV**)

[0089] According to the disclosure, X is CH or N. In some embodiments, X is CH. In other embodiments, X is N.

[0090] R^{41} is H or C_{1-6}alkyl. In some embodiments, R^{41} is H. In other embodiments, R^{41} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl.

[0091] R^{43} is H, F, Cl, or Br. In some embodiments, R^{43} is H. In other embodiments, R^{43} is F. In further embodiments, R^{43} is Cl. In yet other embodiments, R^{43} is Br.

[0092] R^{44} is H, F, Cl, or Br. In some embodiments, R^{44} is H. In other embodiments, R^{44} is F. In further embodiments, R^{44} is Cl. In yet other embodiments, R^{44} is Br.

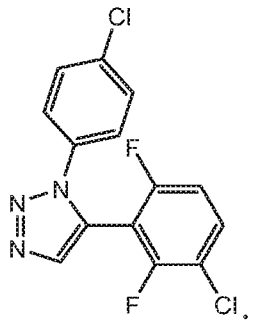
[0093] R^{45} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{45} is H. In other embodiments, R^{45} is F. In further embodiments, R^{45} is Cl. In yet other embodiments, R^{45} is Br. In additional embodiments, R^{45} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{45} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0094] R^{46} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl. In some embodiments, R^{46} is H. In other embodiments, R^{46} is F. In further embodiments, R^{46} is Cl. In yet other embodiments, R^{46} is Br. In additional embodiments, R^{46} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In still further embodiments, R^{46} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0095] R^{47} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^{47} is H. In other embodiments, R^{47} is F. In further embodiments, R^{47} is Cl. In yet other embodiments, R^{47} is Br. In additional embodiments, R^{47} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{47} is C_{1-6}haloalkyl, for example, CF_3. In still further embodiments, R^{47} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0096] R^{48} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl. In some embodiments, R^{48} is H. In other embodiments, R^{48} is F. In further embodiments, R^{48} is Cl. In yet other embodiments, R^{48} is Br. In additional embodiments, R^{48} is C_{1-6}alkyl, for example, methyl, ethyl, propyl, butyl, pentyl, or hexyl. In other embodiments, R^{48} is C_{1-6}haloalkyl, for example, CF_3. In still further embodiments, R^{48} is OC_{1-6}alkyl, for example, methoxy, ethoxy, propoxy, butoxy, pentoxy, or hexoxy.

[0097] A preferred compound of formula (**IV**) is the following compound.



In some embodiments, this compound inhibits 5-lipoxygenase-derived eicosanoid production.

[0098] In treatment methods according to the disclosure, an effective amount of a pharmaceutical agent according to the disclosure is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. An "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic benefit in patients in need of such treatment for the designated disease, disorder, or condition. Effective amounts or doses of the compounds of the present disclosure may be ascertained by routine methods such as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the compound, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician. An example of a dose is in the range of from about 0.001 to about 200 mg of compound per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

[0099] The compounds of the disclosure are used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions of the disclosure. A pharmaceutical composition of the disclosure comprises: (a) an effective amount of at least one compound in accordance with the disclosure; and (b) a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition contains a compound of formula (**I**), or a pharmaceutically acceptable salt thereof. In other embodiments, the pharmaceutical composition contains a compound of formula (**II**) , or a pharmaceutically acceptable salt thereof. In further embodiments, the pharmaceutical composition contains a compound of formula (**III**), or a pharmaceutically acceptable salt thereof. In additional embodiments, the pharmaceutical composition contains a compound of formula (**IV**), or a pharmaceutically acceptable salt thereof.

In yet other embodiments, the pharmaceutical composition contains more than one compound disclosed herein, for example, compounds of formula (I), (II), (III), and (IV) , or pharmaceutically acceptable salts thereof.

[00100] In addition, the compounds of the disclosure may be used in combination with additional active ingredients in the treatment of the above conditions. The additional active ingredients may be coadministered separately with a compound of the disclosure or included with such an agent in a pharmaceutical composition according to the disclosure. In an exemplary embodiment, additional active ingredients are those that are known or discovered to be effective in the treatment of any of the diseases or disorders described herein. In some embodiments, the additional active agent is a cholinesterase inhibitor, memantine, or ergoloid, or any combinations of the foregoing. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an active agent according to the disclosure), decrease one or more side effects, or decrease the required dose of the active agent according to the disclosure.

[00101] Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

[00102] The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

[00103] For oral administration, the compounds of the disclosure can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the compounds may be formulated to yield a dosage of, e.g., from about 0.05 to about 100 mg/kg daily, or from about 0.05 to about 35 mg/kg daily, or from about 0.1 to about 10 mg/kg daily. For example, a total daily dosage of about 5 mg to 5 g daily may be accomplished by dosing once, twice, three, or four times per day.

[00104] Oral tablets may include a compound according to the disclosure mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol,

sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay absorption in the gastrointestinal tract, or may be coated with an enteric coating.

[00105] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, compounds of the disclosure may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the compound of the disclosure with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

[00106] Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

[00107] The active agents of this disclosure may also be administered by non-oral routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the compounds of the disclosure may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms will be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses may range from about 1 to 1000 µg/kg/minute of compound, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[00108] For topical administration, the compounds may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of

administering the compounds of the disclosure may utilize a patch formulation to affect transdermal delivery.

[00109] Compounds of the disclosure may alternatively be administered in methods of this disclosure by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

[00110] Also provided herein are kits or packages of pharmaceutical formulations containing one or more compounds of formula (I), (II), (III), and (IV) (or salts thereof), or pharmaceutical compositions described herein. The kits may be organized to indicate a single formulation or combination of formulations to be taken at each desired time. The composition may also be sub-divided to contain appropriate quantities of one or more compound of formula (I), (II), (III), and (IV). For example, the unit dosage can be packaged compositions, e.g., packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids.

[00111] Suitably, the kit contains packaging or a container with the one or more compound of formula (I), (II), (III), and (IV) formulated for the desired delivery route. Suitably, the kit contains instructions on dosing and an insert regarding the one or more compound of formula (I), (II), (III), and (IV). Optionally, the kit may further contain instructions for monitoring circulating levels of product and materials for performing such assays including, e.g., reagents, well plates, containers, markers or labels, and the like. Such kits are readily packaged in a manner suitable for treatment of a desired indication. For example, the kit may also contain instructions for use of the delivery device. Other suitable components to include in such kits will be readily apparent to one of skill in the art, taking into consideration the desired indication and the delivery route. The doses are repeated daily, weekly, or monthly, for a predetermined length of time or as prescribed.

[00112] The one or more compound of formula (I), (II), (III), and (IV) or composition described herein can be a single dose or for continuous or periodic discontinuous administration. For continuous administration, a package or kit can include the compound in each dosage unit (e.g., solution, lotion, tablet, pill, or other unit described above or utilized in drug delivery). When the one or more compound of formula (I), (II), (III), and (IV) is to be delivered with periodic discontinuation, a package or kit can include placebos during periods when the one or more compound of formula (I), (II), (III), and (IV) is not delivered. When varying concentrations of a composition, of the components of the composition, or of relative ratios of the one or more compound of formula (I), (II), (III), and (IV) or other agents within a composition over time is desired, a package or kit may contain a sequence of dosage units, so varying.

[00113] A number of packages or kits are known in the art for the use in dispensing pharmaceutical agents for oral use. In one embodiment, the package has indicators for each period. In another embodiment, the package is a labeled blister package, dial dispenser package, or bottle.

[00114] The packaging means of a kit may itself be geared for administration, such as an inhalant, syringe, pipette, eye dropper, or other such like apparatus, from which the formulation may be applied to an infected area of the body, such as the lungs, injected into a subject, or even applied to and mixed with the other components of the kit.

[00115] The one or more compound of formula **(I)**, **(II)**, **(III)**, and **(IV)** or composition of these kits also may be provided in dried or lyophilized forms. When reagents or components are provided as a dried form, reconstitution generally is by the addition of a suitable solvent. It is envisioned that the solvent also may be provided in another packaging means.

[00116] The kits may include a means for containing the vials in close confinement for commercial sale such as, e.g., injection or blow-molded plastic containers into which the desired vials are retained.

[00117] Irrespective of the number or type of packages, the kits also may include, or be packaged with a separate instrument for assisting with the injection/administration or placement of the ultimate complex composition within the body of an animal. Such an instrument may be an inhalant, syringe, pipette, forceps, measuring spoon, eye dropper or any such medically approved delivery means. Other instrumentation includes devices that permit the reading or monitoring of reactions *in vitro*.

[00118] In one embodiment, a pharmaceutical kit is provided and contains one or more compound of formula **(I)**, **(II)**, **(III)**, and **(IV)**. The one or more compound of formula **(I)**, **(II)**, **(III)**, and **(IV)** may be in the presence or absence of one or more of the carriers or excipients described above. The kit may optionally contain an additional active agent as described above and/or instructions for administering the additional active agent and the one or more compound of formula **(I)**, **(II)**, **(III)**, and **(IV)** to a subject.

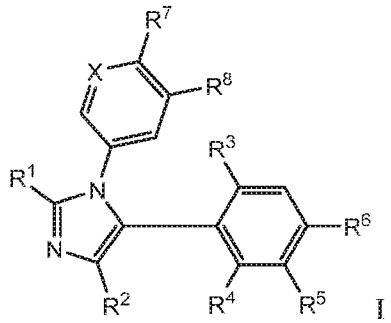
[00119] In a further embodiment, a pharmaceutical kit is provided and contains an additional active agent in a first dosage unit, one or more compound of formula **(I)**, **(II)**, **(III)**, and **(IV)** selected from those described herein in a second dosage unit, and one or more of the carriers or excipients described above in a third dosage unit. The kit may optionally contain instructions for administering the additional active agent and/or one or more compound of formula **(I)**, **(II)**, **(III)**, and **(IV)** to a subject.

[00120] The following Examples are provided to illustrate some of the concepts described within this disclosure. While each Example is considered to provide specific individual embodiments of composition, methods of preparation and use, none of the Examples should be considered to limit the more general embodiments described herein.

[00121] In the following examples, efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C, pressure is at or near atmospheric.

[00122] Aspects

[00123] Aspect 1: A method of treating a neurodegenerative disease in a subject comprising administering to the subject a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^1 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^2 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^3 is H, F, Cl, or Br;

R^4 is H, F, Cl, or Br;

R^5 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^6 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^7 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

R^8 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[00124] Aspect 2: The method of aspect 1, wherein X is CH.

[00125] Aspect 3: The method of aspect 1, wherein X is N.

[00126] Aspect 4: The method of any one of the preceding aspects, wherein R^1 is H.

[00127] Aspect 5: The method of any one of aspects 1 to 3, wherein R^1 is F, Cl, or Br.

[00128] Aspect 6: The method of any one of aspects 1 to 3, wherein R^1 is C_{1-6}alkyl or OC_{1-6}alkyl.

[00129] Aspect 7: The method of any one of the preceding aspects wherein R^2 is H.

[00130] Aspect 8: The method of any one of aspects 1 to 6, wherein R^2 is F, Cl, or Br.

[00131] Aspect 9: The method of any one of aspects 1 to 6, wherein R^2 is C_{1-6}alkyl or OC_{1-6}alkyl.

[00132] Aspect 10: The method of any one of the preceding aspects, wherein R^3 is H.

[00133] Aspect 11: The method of any one of aspects 1 to 9, wherein R^3 is F, Cl, or Br.

[00134] Aspect 12: The method of any one of the preceding aspects, wherein R^4 is H.

[00135] Aspect 13: The method of any one of aspects 1 to 11, wherein R^4 is F, Cl, or Br.

[00136] Aspect 14: The method of any one of the preceding aspects, wherein R^5 is H.

[00137] Aspect 15: The method of any one of aspects 1 to 13, wherein R^5 is F, Cl, or Br.

[00138] Aspect 16: The method of any one of aspects 1 to 13, wherein R^5 is C_{1-6}alkyl or OC_{1-6}alkyl.

[00139] Aspect 17: The method of any one of the preceding aspects, wherein R^6 is H.

[00140] Aspect 18: The method of any one of aspects 1 to 16, wherein R^6 is F, Cl, or Br.

[00141] Aspect 19: The method of any one of aspects 1 to 16, wherein R^6 is C_{1-6}alkyl or OC_{1-6}alkyl.

[00142] Aspect 20: The method of any one of the preceding aspects, wherein R^7 is H.

[00143] Aspect 21: The method of any one aspects 1 to 19, wherein R^7 is F, Cl, or Br.

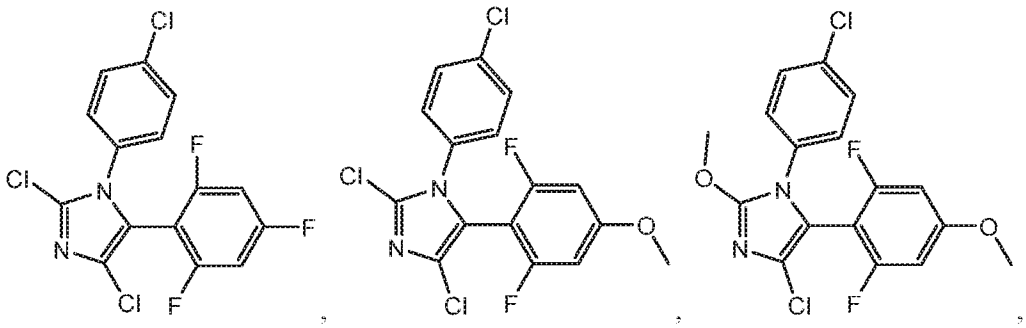
[00144] Aspect 22: The method of any one of aspects 1 to 19, wherein R^7 is C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

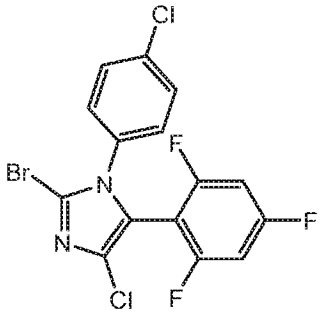
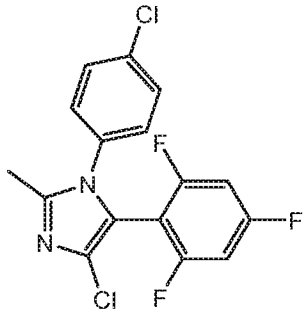
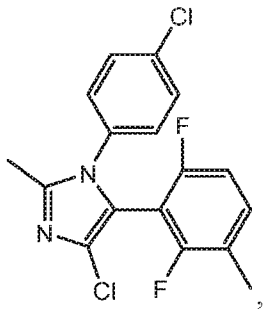
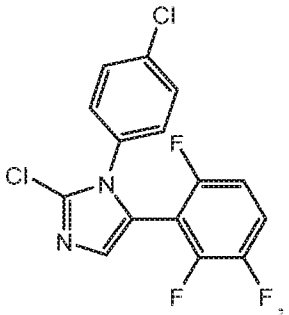
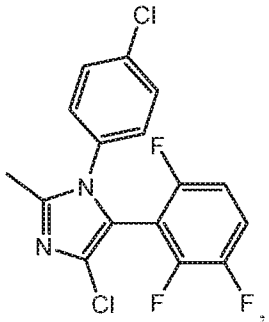
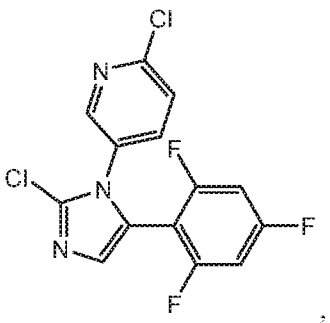
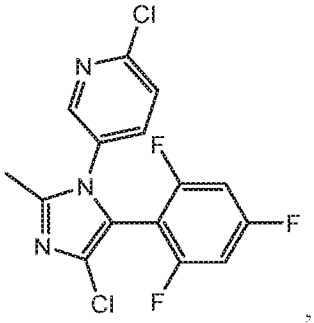
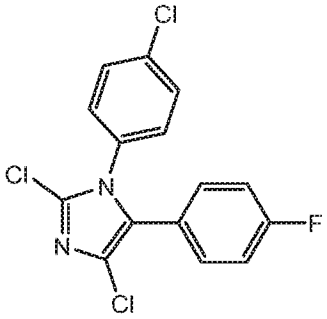
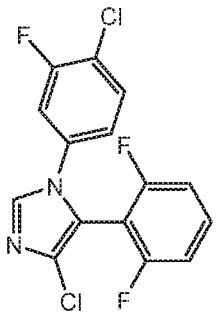
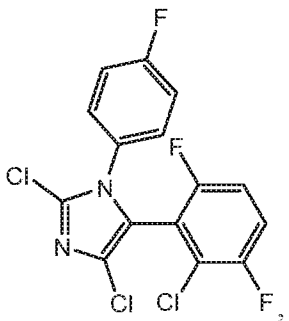
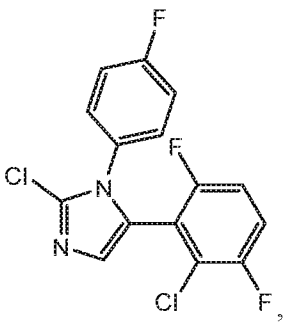
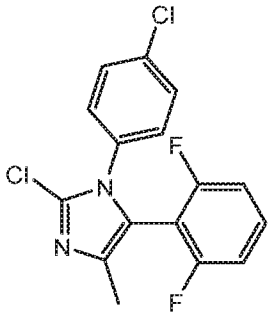
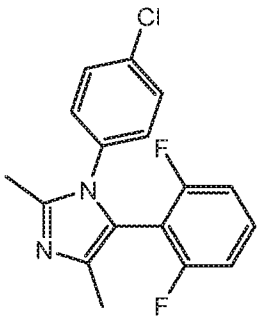
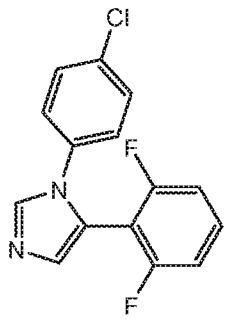
[00145] Aspect 23: The method of any one of the preceding aspects, wherein R^8 is H.

[00146] Aspect 24: The method of any one of aspects 1 to 22, wherein R^8 is F, Cl, or Br.

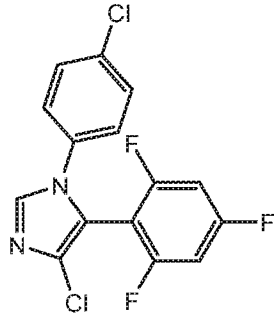
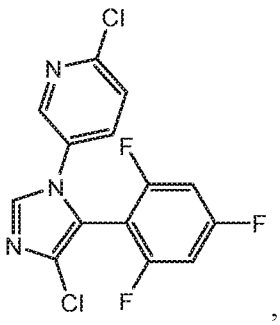
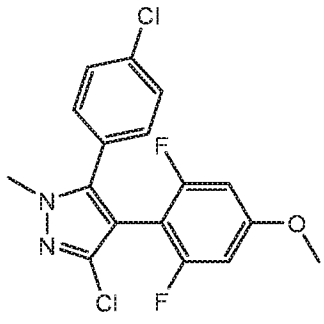
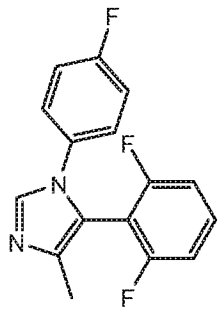
[00147] Aspect 25: The method of any one of aspects 1 to 22, wherein R^8 is C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[00148] Aspect 26: The method of aspect 1, wherein the compound of formula (**I**) is:



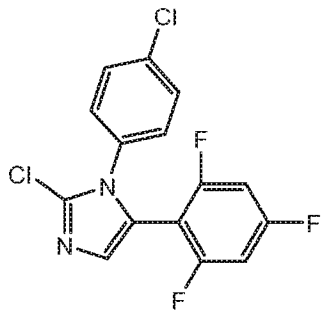
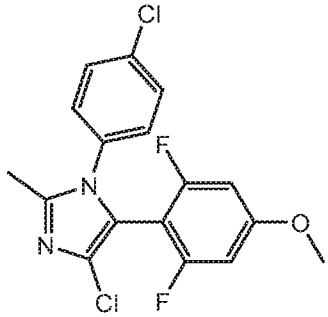
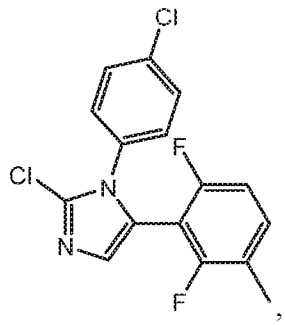
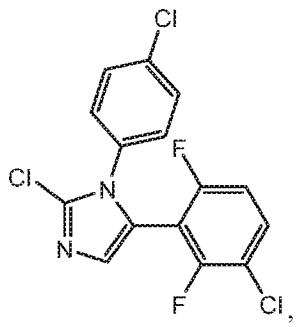
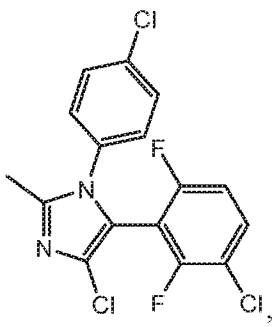
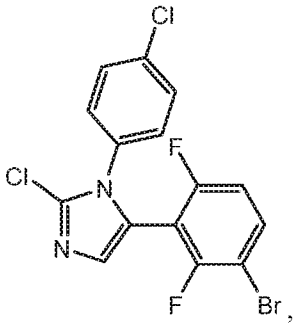

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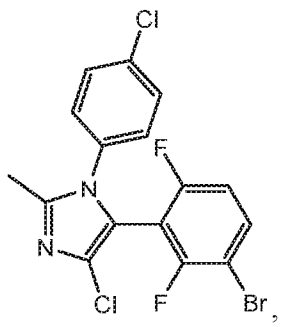
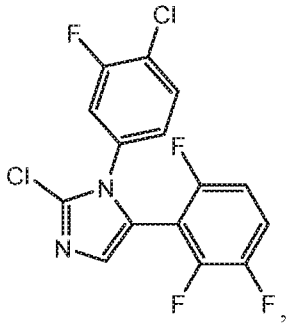
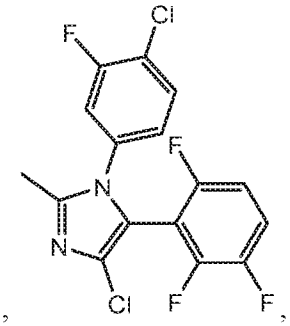
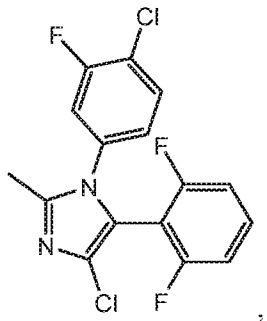
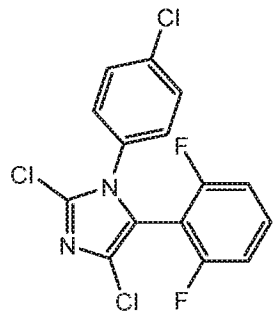
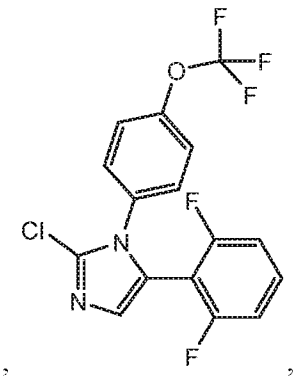
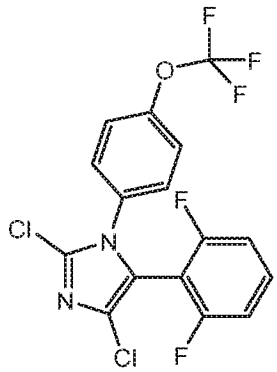
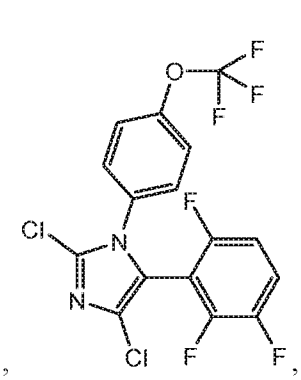
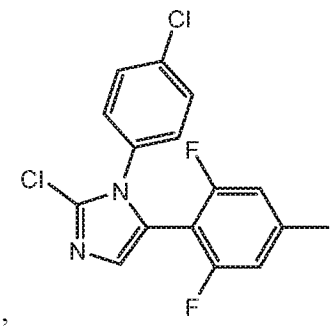
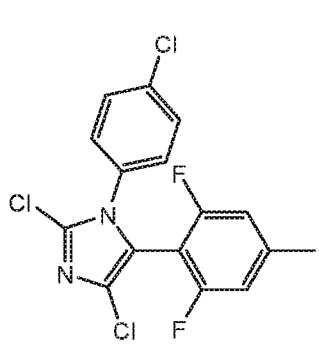
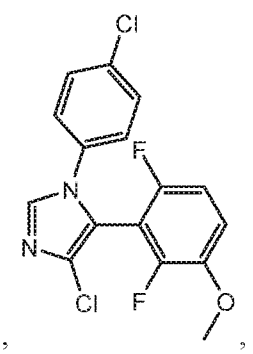
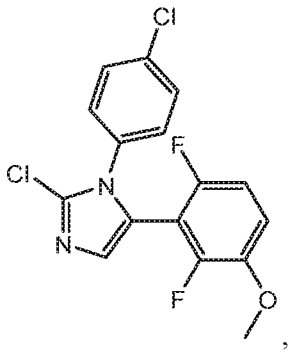
[00149] Aspect 27: The method of aspect 1, wherein the compound of formula (**I**) is:

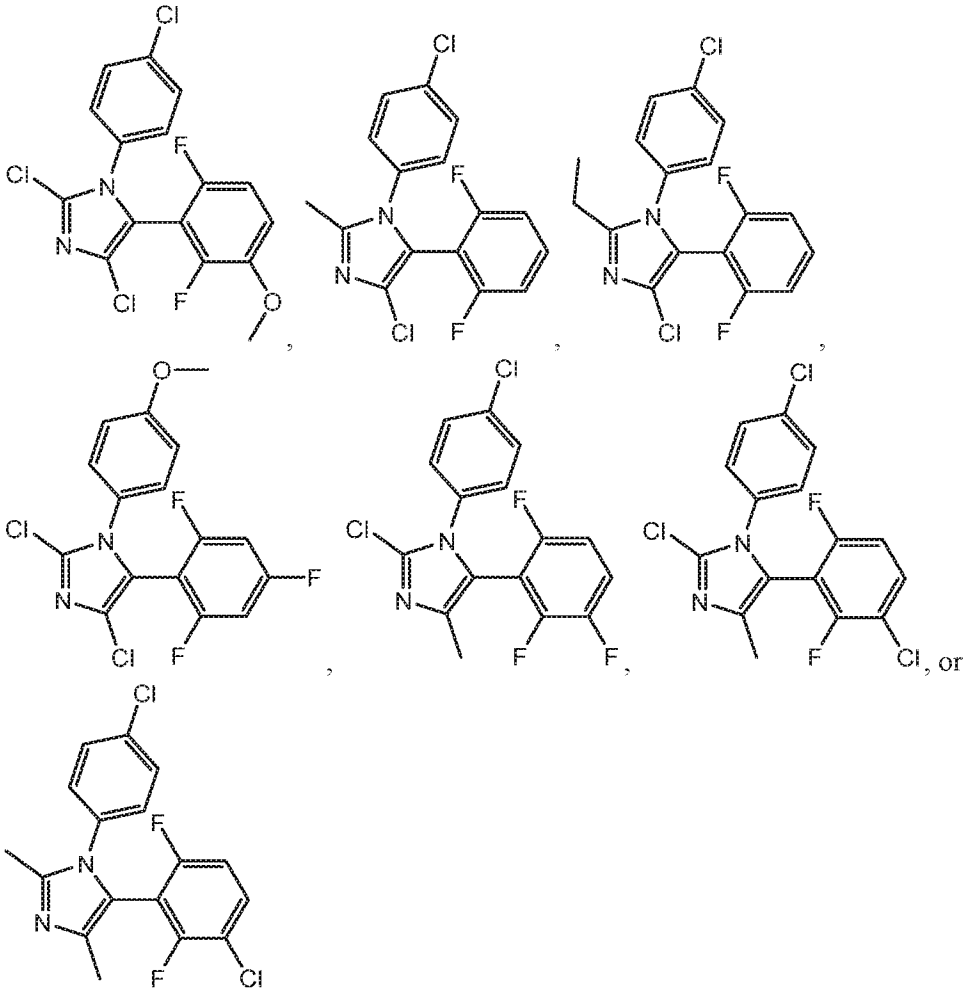

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, or


or a pharmaceutically acceptable salt thereof.

[00150] Aspect 28: The method of aspect 1, wherein the compound of formula (**I**) is:

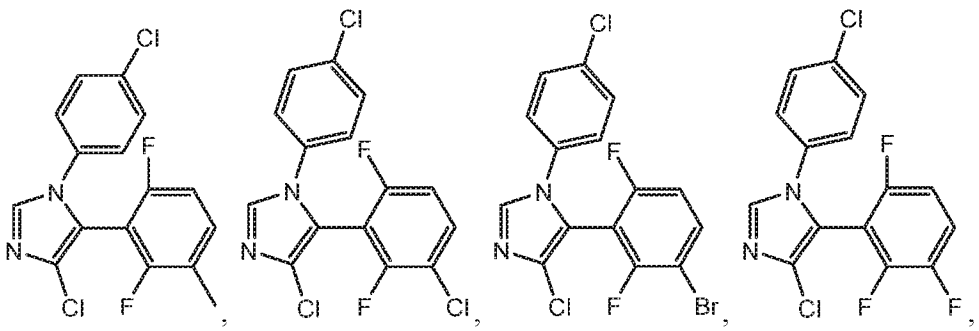

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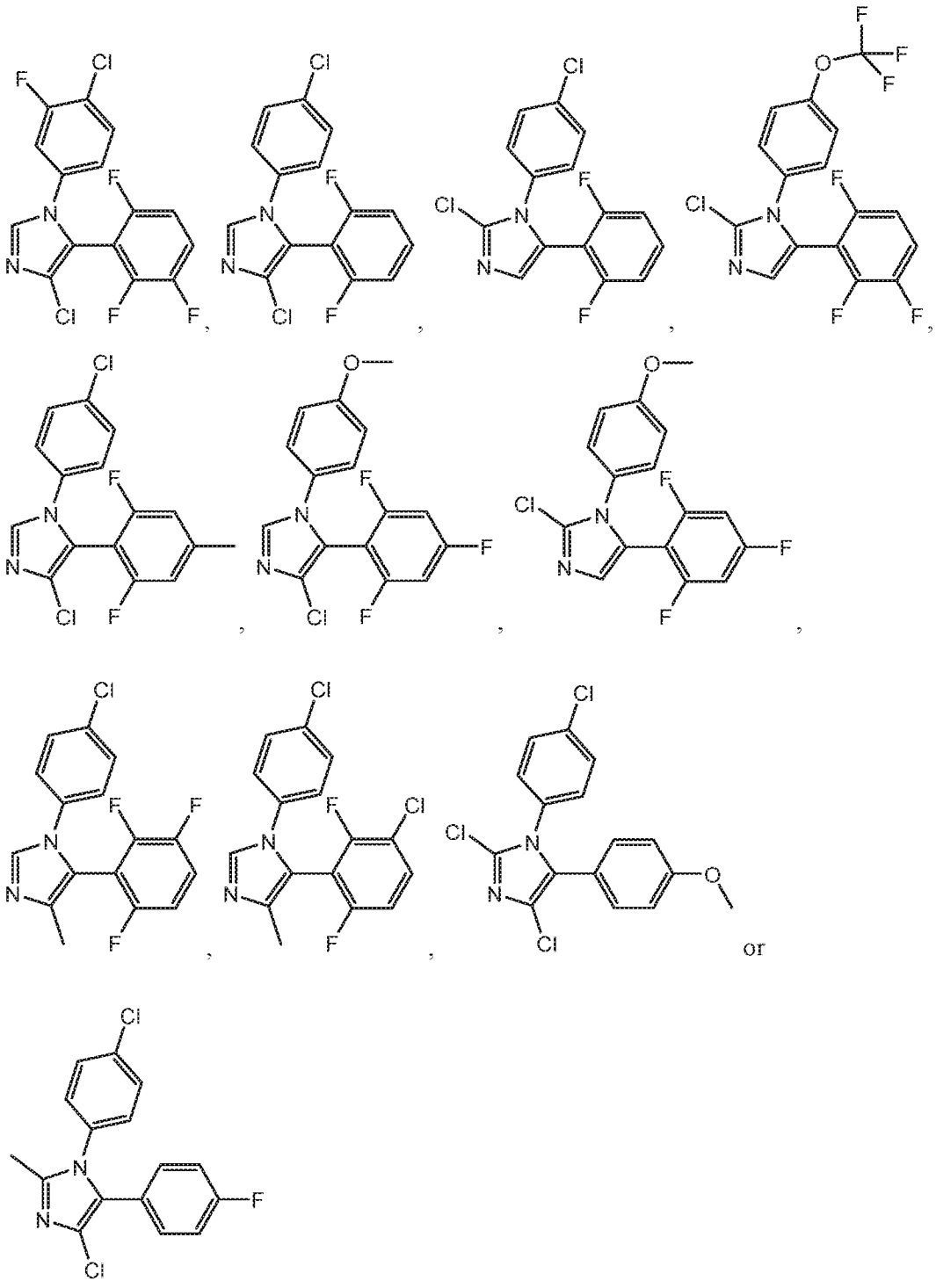















or a pharmaceutically acceptable salt thereof.

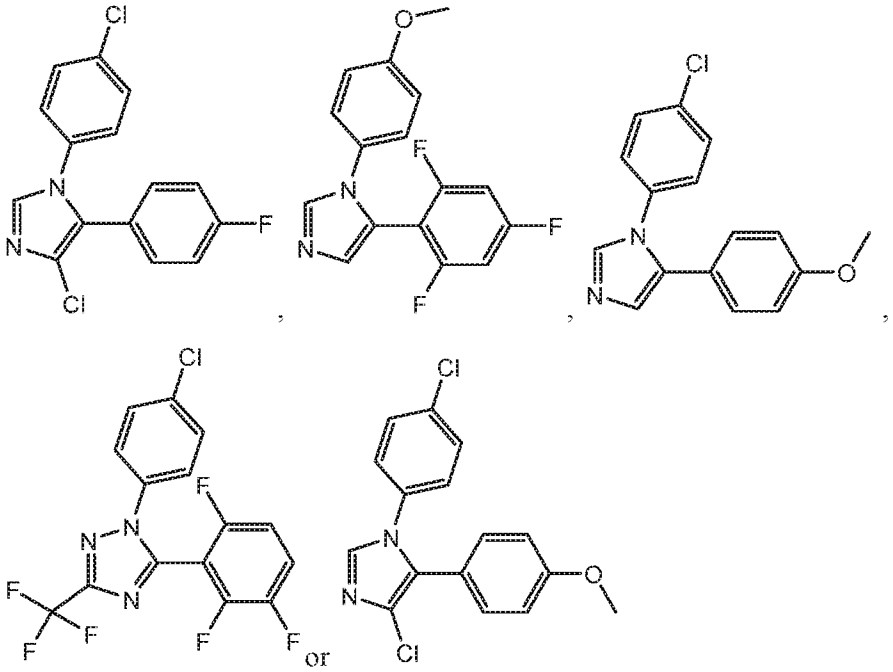
[00151] Aspect 29: The method of aspect 1, wherein the compound of formula (**I**) is:





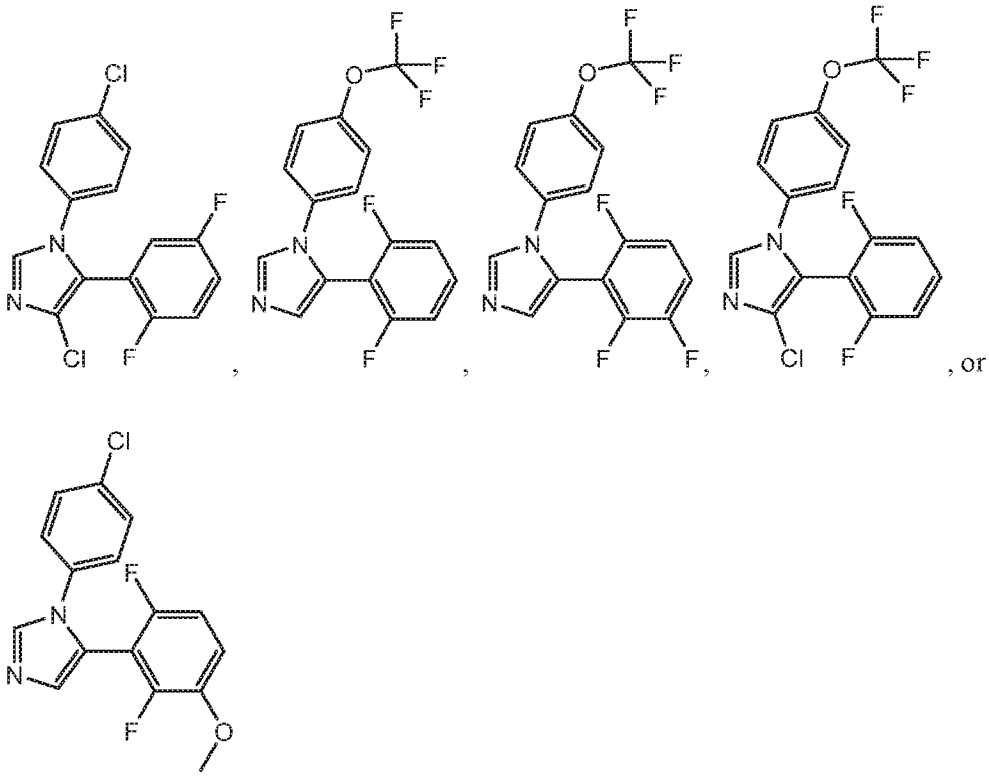
or a pharmaceutically acceptable salt thereof.

[00152] Aspect 30: The method of aspect 1, wherein the compound of formula **(I)** is:



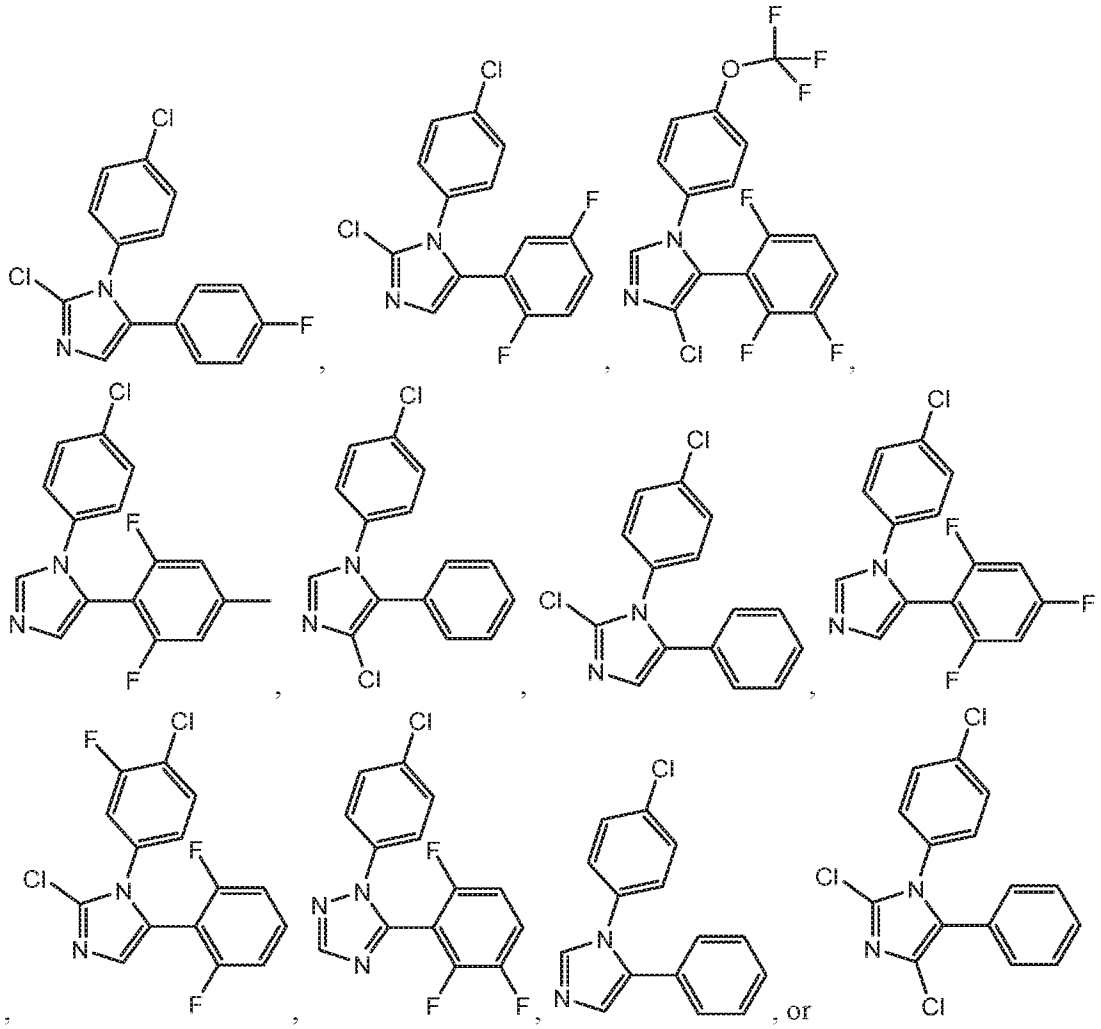
or a pharmaceutically acceptable salt thereof.

[00153] Aspect 31: The method of aspect 1, wherein the compound of formula (**I**) is:



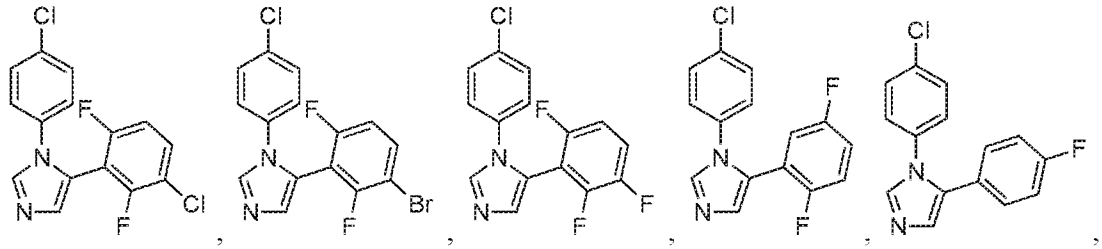
or a pharmaceutically acceptable salt thereof.

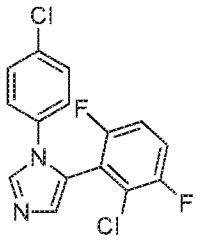
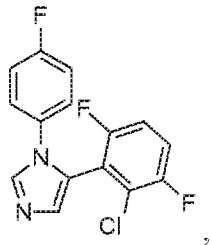
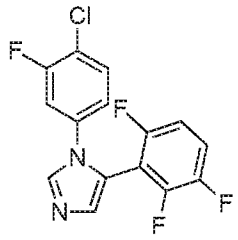
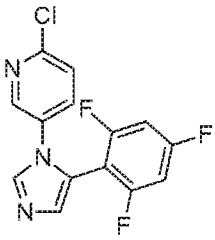
[00154] Aspect 32: The method of aspect 1, wherein the compound of formula (**I**) is:

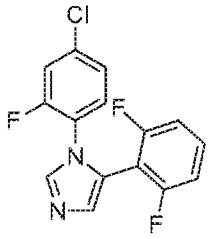


or a pharmaceutically acceptable salt thereof.

[00155] Aspect 33: The method of aspect 1, wherein the compound of formula (**I**) is:

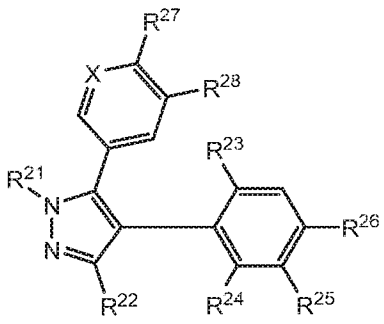






, or


;

or a pharmaceutically acceptable salt thereof.

[00156] Aspect 34: A method of treating a neurodegenerative disease in a subject comprising administering to the subject a compound of Formula (II):


(II)

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^{21} is H or C_{1-6}alkyl;

R^{22} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{23} is H, F, Cl, or Br;

R^{24} is H, F, Cl, or Br;

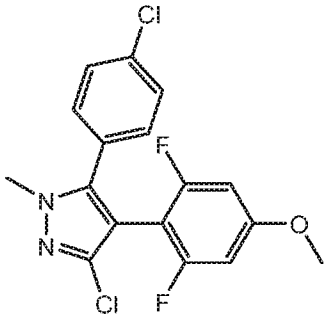
R^{25} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{26} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{27} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

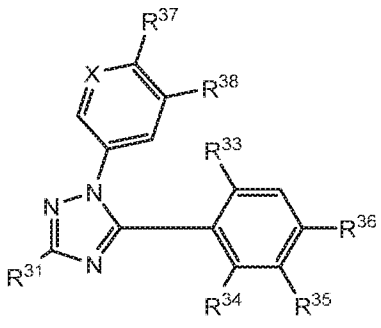
R^{28} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[00157] Aspect 35: The method of aspect 34, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

[00158] Aspect 36: A method of treating a neurodegenerative disease in a subject comprising administering to the subject a compound of Formula (**III**):



(III)

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^{31} is H, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^{33} is H, F, Cl, or Br;

R^{34} is H, F, Cl, or Br;

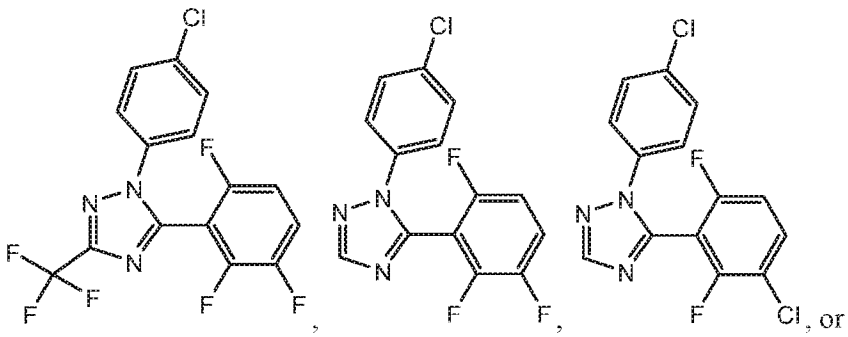
R^{35} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

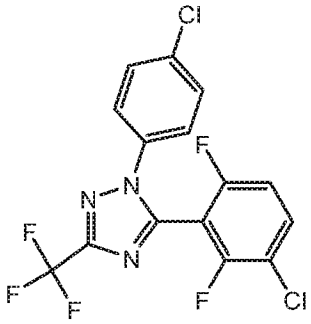
R^{36} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{37} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

R^{38} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

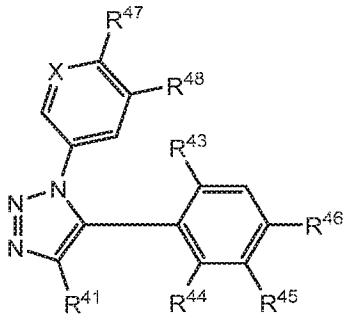
[00159] Aspect 37: The method of aspect 36, wherein the compound is





or a pharmaceutically acceptable salt thereof.

[00160] Aspect 38: A method of treating a neurodegenerative disease in a subject comprising administering to the subject a compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^{41} is H or C_{1-6}alkyl;

R^{43} is H, F, Cl, or Br;

R^{44} is H, F, Cl, or Br;

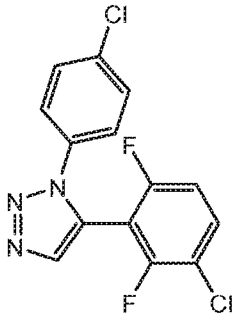
R^{45} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{46} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{47} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

R^{48} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

[00161] Aspect 39: The method of aspect 38, wherein the compound is



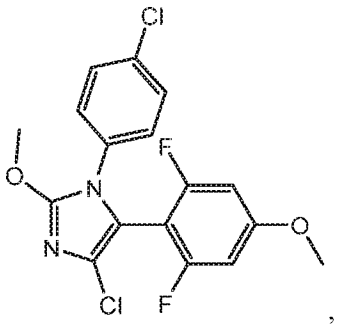
or a pharmaceutically acceptable salt thereof.

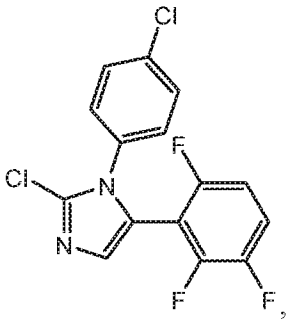
[00162] Aspect 40: The method of any one of the preceding aspects, wherein the neurodegenerative disease is characterized by a tauopathy or by compromised microtubule function in the brain of the subject.

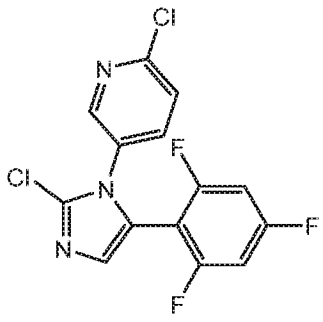
[00163] Aspect 41: The method of any one of the preceding aspects, wherein the neurodegenerative disease is Alzheimer's disease, frontotemporal lobar degeneration, Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration, Parkinson's disease (PD), PD with dementia, Lewy body disease with dementia, amyotrophic lateral sclerosis, argyrophilic grain disease, chronic traumatic encephalopathy, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, frontotemporal dementia, parkinsonism linked to chromosome 17, Gerstmann-Straussler-Scheinker disease, Guadeloupean parkinsonism, multiple sclerosis, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, or white matter tauopathy with globular glial inclusions.

[00164] Aspect 42: The method of any of the preceding aspects, wherein the neurodegenerative disease is traumatic brain injury, in particular, repetitive traumatic brain injury and chronic traumatic encephalopathy, or post-traumatic stress disorder.

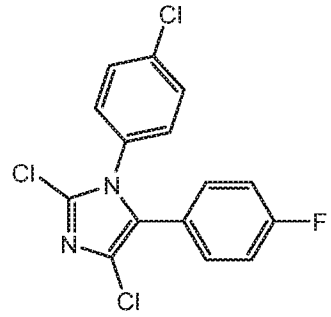
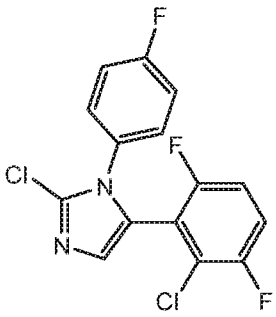
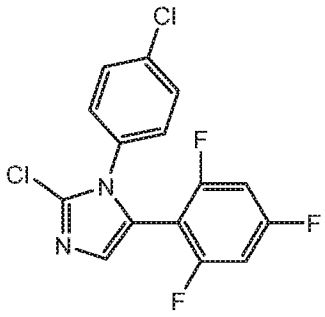
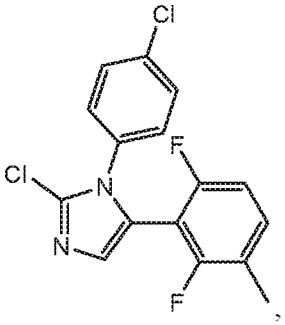
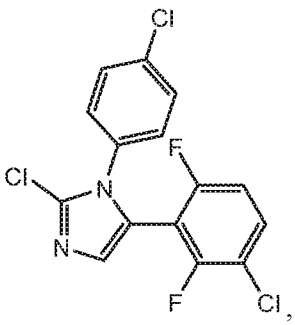
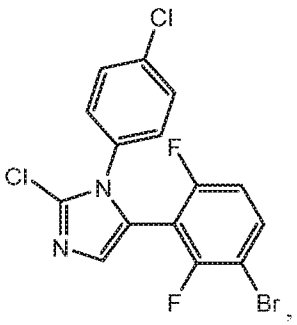
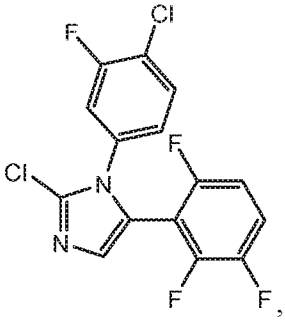
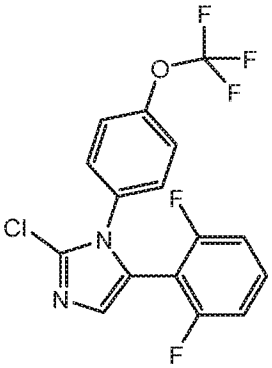
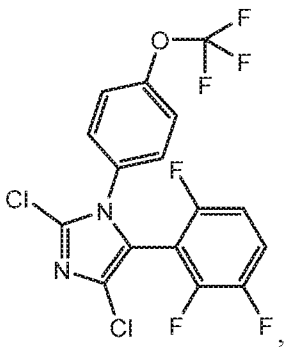
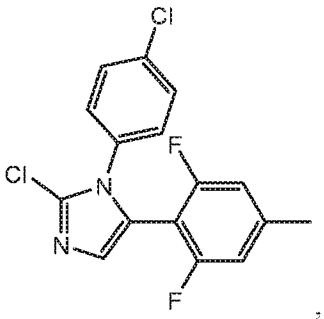
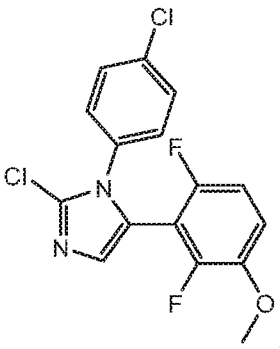
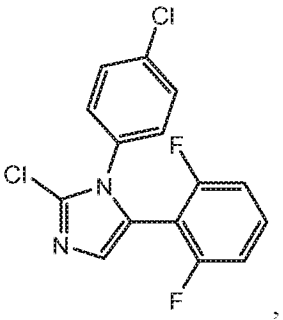
[00165] Aspect 43: A compound that is:

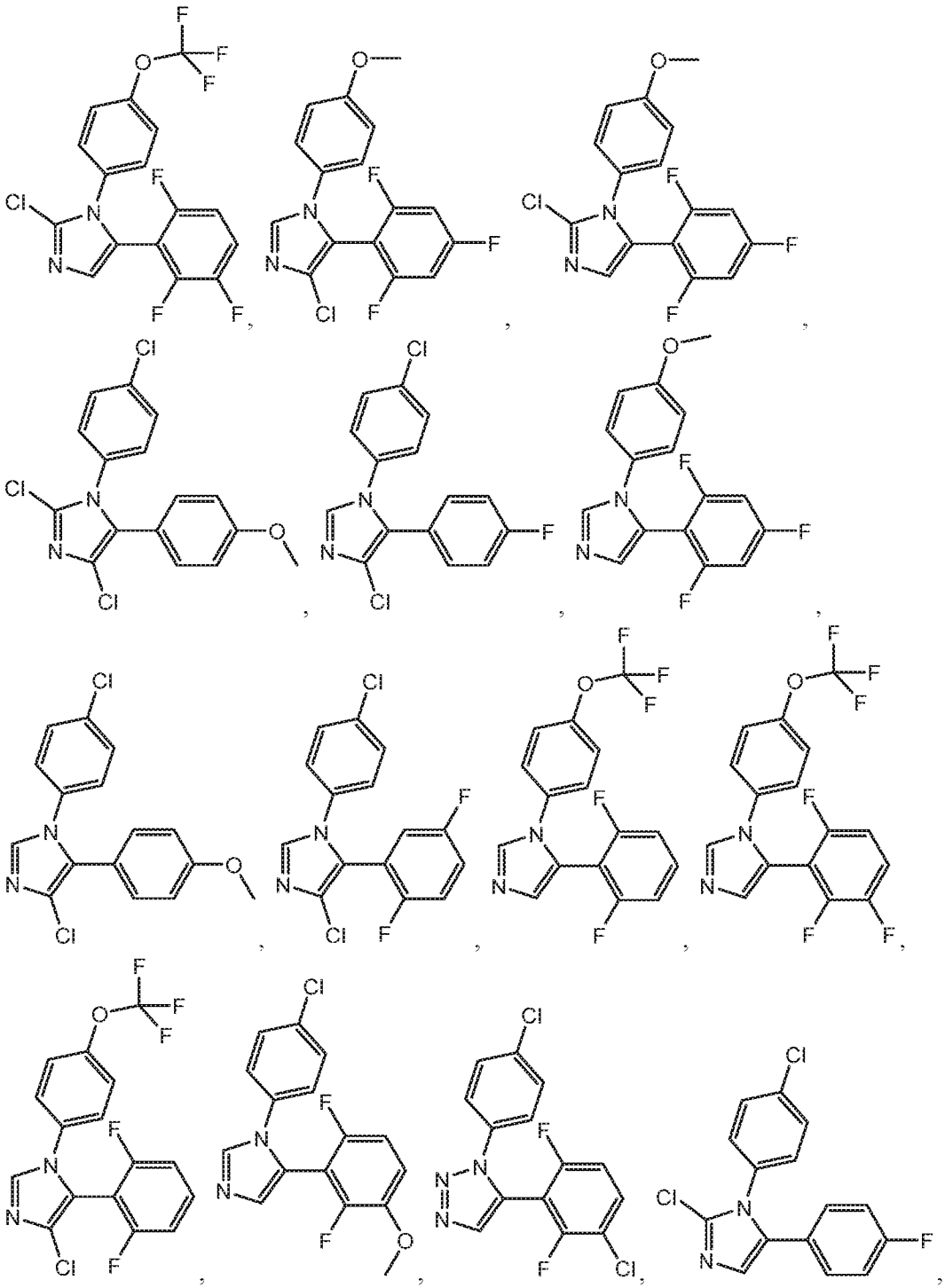


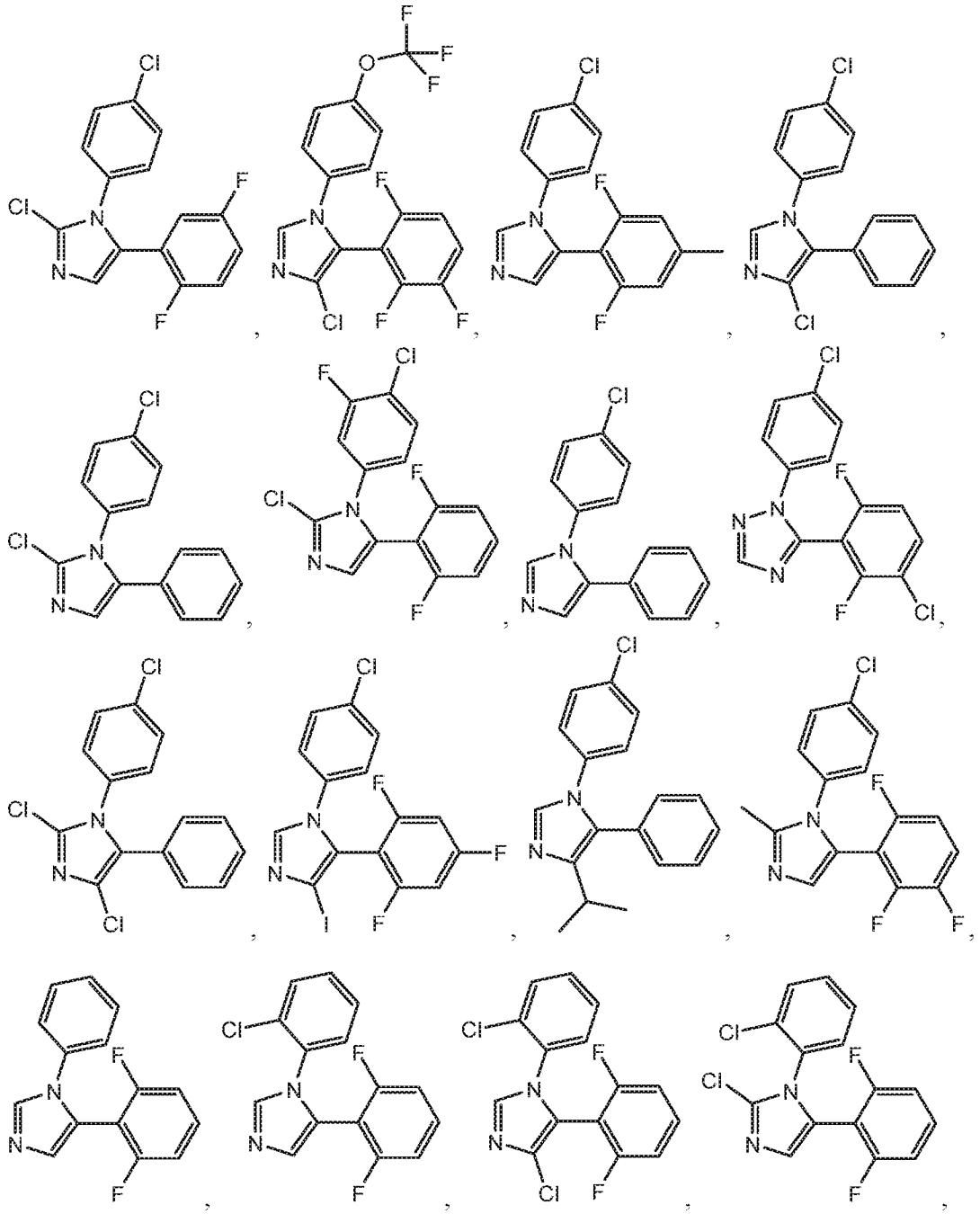
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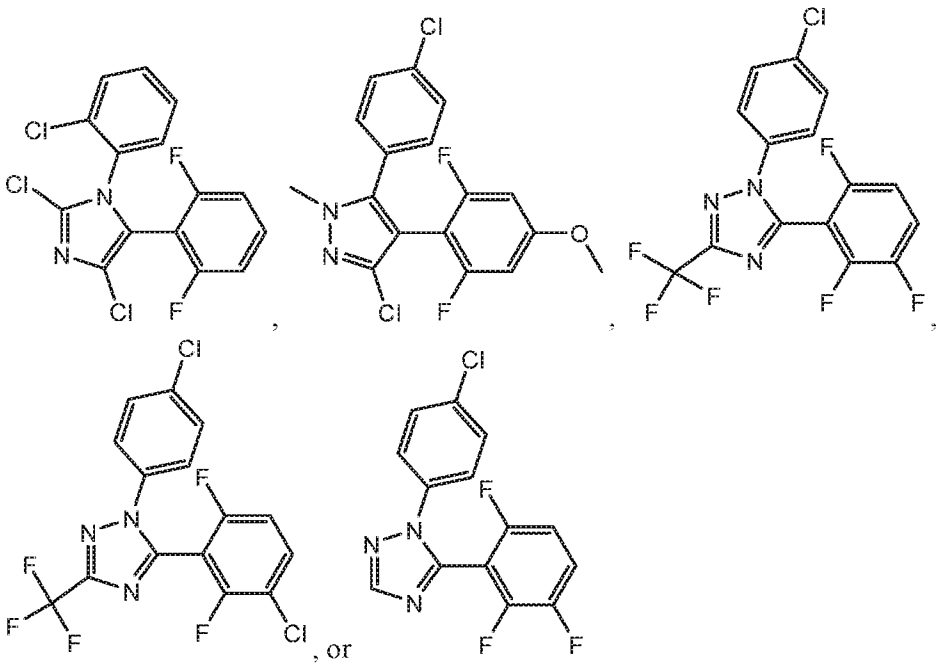
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or a pharmaceutically acceptable salt thereof.

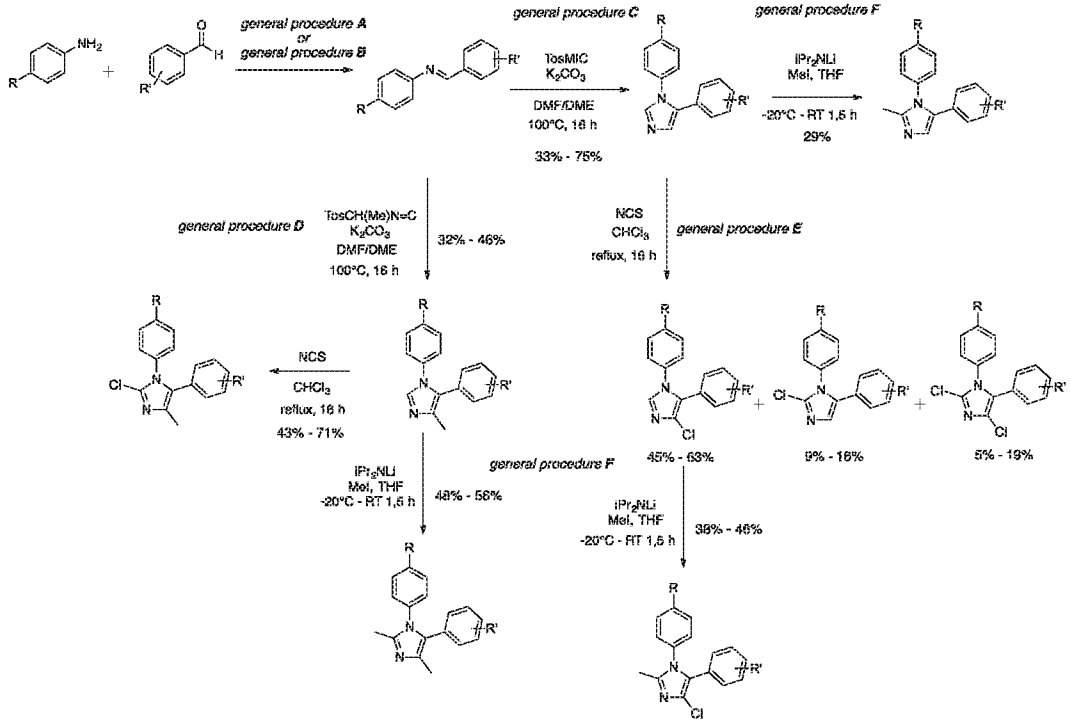
[00166] Aspect 44: A pharmaceutical composition comprising a compound of aspect 43, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00167] Aspect 44: A pharmaceutical composition comprising a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

EXAMPLES

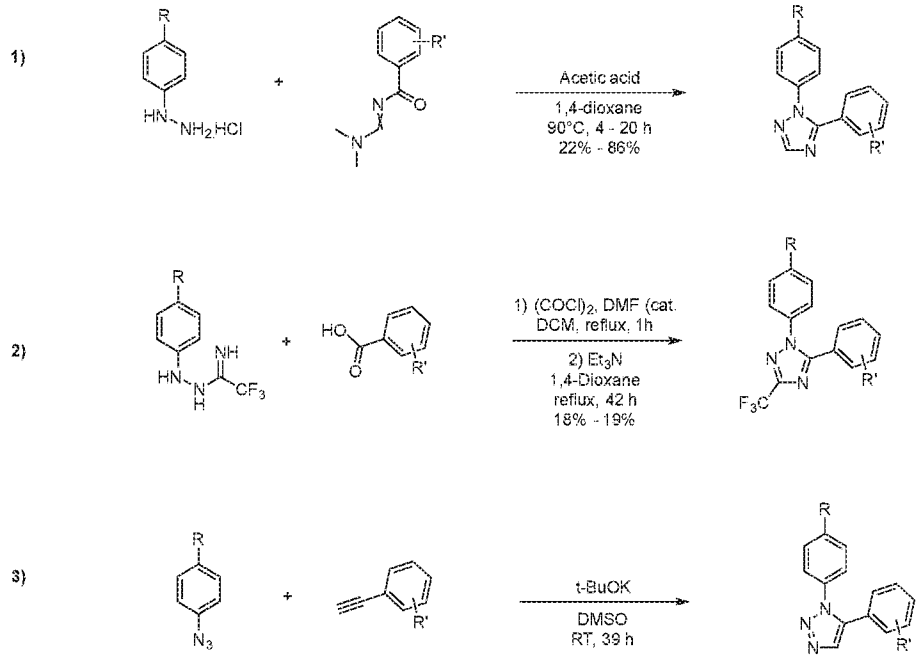
[00168] Exemplary compounds useful in methods of the disclosure will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I). Reactions may be performed between the melting point and the reflux temperature of the solvent, and preferably between 0 °C and the reflux temperature of the solvent. Reactions may be heated employing conventional heating or microwave heating. Reactions may also be conducted in sealed pressure vessels above the normal reflux temperature of the solvent.

[00169] Certain compounds of formula (**I**) can be prepared by reference to Scheme 1.



Scheme 1

[00170] Other compounds discussed herein may be prepared according to Scheme 2.



Scheme 2

[00171] **Material and methods**. All solvents were reagent grade. All chemical reagents were commercially available unless otherwise indicated. Thin layer chromatography (TLC) was performed by using 0.25 mm E. Merck pre-coated silica gel plates. Components were analyzed by using UV light. Flash chromatography was performed on silica gel 60 (particle size 0.040 – 0.062 mm) supplied by Silicycle and Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds. IR spectra were recorded on a Jasco Model FT/IR- 480 Plus spectrometer. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker AMX-500 spectrometer, using $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts were reported relative to solvents. High-resolution mass spectra (HRMS) were measured at the University of Pennsylvania Mass Spectrometry Service on a Waters LCT Premier XE LC/MS system. Analytical reversed-phased (Sunfire™ C18; 4.6x50 mm, 5 mL) high-performance liquid chromatography (HPLC) was performed with a Water binary gradient module 2525 equipped with Waters 2996 PDA and Water micromass ZQ. All samples were analyzed employing a linear gradient from 10% to 90% of acetonitrile in water over 8 minutes and flow rate of 1 mL/min. Preparative reverse phase HPLC purification was performed on a Gilson HPLC system equipped with Gilson 333 pumps, a 215 Liquid Handler, 845Z injection module, and UV detector, employing Waters SunFire™ prep C18 OBD™ columns (5 μm 19x50 or 19x100 mm). All samples were purified employing a linear gradient from 10% to 90% of acetonitrile in water over 15 minutes and flow rate of 20 mL/min. Unless otherwise stated, all final compounds were found to be >95% as determined by HPLC/MS and NMR.

Example 1: General procedure for the synthesis of imines (A) - Compounds LM-I-1, -4, -5, -20, -21, -24, -32, -38 and ASC-II-49, -97, -99, -102, -107, -109, -117, -121, -124, -126, -132, -146, -148, -150, -157, -161.

[00172] A solution of aniline (1 equiv.) and benzaldehyde (1 equiv.) in toluene (15 mL) was heated at reflux in a Dean-Stark apparatus for 4 days. Then the reaction mixture was cooled and evaporated under reduced pressure to obtain the title compound that was used in the next step without further purification.

Example 2: General procedure for the synthesis of imines (B): compounds LM-I-62, -63, -73, -104, -105.

[00173] To a solution of a primary amine (1 equiv.) in anhydrous Et_2O (20 mL) in the presence of molecular sieves (4 Å 1.6 mm pellets, 7 g) was added an aldehyde (1 equiv) according to the Taguchi's method. The mixture was heated and stirred at 30 °C for 48 h. Molecular sieves were then removed by filtration, and the solvent was removed in *vacuo* to afford the expected imine directly as pure product without further purification in quantitative yields.

Example 3: General procedure for the synthesis of imidazoles (C) - compounds LM-I-2, -6, -8, -25, -30, -33, -43, -82, -86, -106, -107 and ASC-II-53, -100, -105, -106, -112, -120, -122, -127, -129, -135, -153, -162.

[00174] To a solution of imine (1 equiv.) in a mixture of *N,N*-dimethylformamide (13 mL) and 1,2-dimethoxyethane (11 mL) were added toluenesulfonylmethyl isocyanide (1.5 equiv.) and anhydrous potassium carbonate (2.08 equiv.). The reaction mixture was heated for 16 h at 100 °C, then cooled to room temperature and filtered. The filtrate was evaporated, the residue was absorbed on Celite and purified by flash chromatography on silica gel to obtain the title compound.

Example 4: General procedure for the synthesis of 4-alkylated imidazoles (D) - compounds LM-I-76, -79, -80, -97.

[00175] To a solution of imine (1 equiv.) in a mixture of *N,N*- dimethylformamide (13 mL) and 1,2-dimethoxyethane (11 mL) were added mono-alkyl derivative of toluenesulfonylmethyl isocyanide (1.5 equiv.) and anhydrous potassium carbonate (2.08 equiv.) were added. The reaction mixture was heated for 16 h at 100 °C, then cooled to room temperature and filtered. The filtrate was evaporated, the residue was absorbed on Celite® 545 AW and purified by flash chromatography on silica gel to obtain the title compound.

Example 5: General procedure for the synthesis of mono and di-halogenated imidazoles (E) - compounds LM-I-10 B, -10 C, -10 D, -12 B, -12 C, -12 D, -14 B, -14 C, -14 D, -28 B, -28 C, -28 D, -34 B, -34 C, -34 D, -36 B, -36 C, -36 D, -46, -50 B, -50 C, -50 D, -67, -83, -84, -85, -90, -96, -108 B, -108 C, -109 and ASC-II-57, -67 f1, -67 f2, -103 f1, -103 f2, -108 f1, -108 f2, -110 f1, -110 f2, -116 f1, -116 f2, -123 f1, -123 f2, -138 f1, -138 f2, -139 f1, -139 f2, -159 f2, -159 f3, -160 f1, -160 f2, -160 f3, -166 f2, -166 f3.

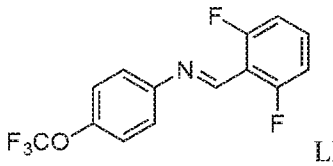
[00176] To a solution of imidazole (1 equiv.) in chloroform (7 mL) was added *N*-chlorosuccinimide or *N*-iodosuccinimide or *N*-bromosuccinimide (1.06 equiv). The reaction mixture was heated at 80 °C for 16 h, then cooled down and diluted with ethyl acetate. The organic layer was washed with brine (x3), dried over $MgSO_4$ and filtered. Removal of the solvent gave a residue that was purified by flash chromatography on silica gel.

Example 5B: General procedure for the synthesis of methylated imidazoles (F) - compounds LM-I-39, -41, -92, -98 and ASC-II-98.

[00177] To a solution of diisopropylamine (1.5 equiv.) in THF (2 mL) at -20 °C was added *n*BuLi (2.5M in hexanes, 1.5 equiv.), and the mixture was stirred for 10 min. A solution of imidazole (1 equiv.) in THF (0.15M) was added, and after stirring for 30 min, methyl iodide (3 equiv.) was added. The mixture was stirred for 30 min at -20 °C and for 30 min at room

temperature. H_2O was added to the reaction mixture, the aqueous phase was extracted with ethyl acetate, and the combined organic layers were washed with brine (x3), dried over MgSO4, filtered, and concentrated. The mixture was purified by flash chromatography on silica gel.

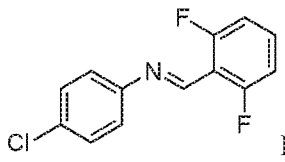
Example 6: (*E*)-1-(2,6-difluorophenyl)-*N*-(4-(trifluoromethoxy)phenyl)methanimine



LM-I-001

[00178] Following synthetic procedure A using 4-(trifluoromethoxy)aniline (0.531 g, 3.00 mmol) and 2,6-difluorobenzaldehyde (0.426 g, 3.00 mmol), the title compound was obtained as a brown liquid (1.034 g, 3.43 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (s, 1H), 7.43 (tt, J = 8.3, 6.1 Hz, 1H), 7.25 (d, J = 2.7 Hz, 4H), 7.00 (d, J = 8.7 Hz, 2H) ppm.

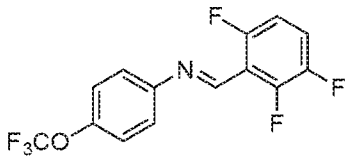
Example 7: (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluorophenyl)methanimine



LM-I-004

[00179] Following synthetic procedure A using 4-chloroaniline (0.829 g, 6.50 mmol) and 2,6-difluorobenzaldehyde (0.924 g, 6.50 mmol) the title compound was obtained as a brown liquid (1.62 g, 6.45 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.64 (s, 1H), 7.48–7.31 (m, 3H), 7.22–7.06 (m, 2H), 7.06–6.91 (m, 2H) ppm.

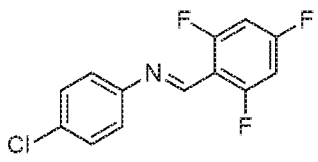
Example 8: (*E*)-*N*-(4-(trifluoromethoxy)phenyl)-1-(2,3,6-trifluorophenyl)methanimine



LM-I-005

[00180] Following synthetic procedure A using 4-(trifluoromethoxy)aniline (0.531 g, 3.00 mmol) and 2,3,6-trifluorobenzaldehyde (0.480 g, 3.00 mmol), the title compound was obtained as a brown solid (1.08 g, 3.47 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.62 (s, 1H), 7.37–7.27 (m, 2H), 7.25–7.10 (m, 1H), 7.00 – 6.92 (m, 1H) ppm.

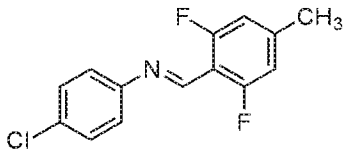
Example 9: (*E*)-*N*-(4-chlorophenyl)-1-(2,4,6-trifluorophenyl)methanimine



LM-I-020 (ASC-II-049)

[00181] Following synthetic procedure A using 4-chloroaniline (0.829 g, 6.50 mmol) and 2,4,6-trifluorobenzaldehyde (1.04 g, 6.50 mmol), the title compound was obtained as a brown solid (1.70 g, 6.30 mmol, 97% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.56 (s, 1H), 7.37 (dd, J = 8.6, 1.8 Hz, 2H), 7.18–7.12 (m, 2H), 6.83–6.74 (m, 2H) ppm.

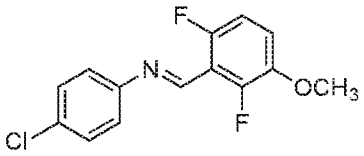
Example 10: (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-4-methylphenyl)methanimine



LM-I-021

[00182] Following synthetic procedure A using 4-chloroaniline (0.157 g, 1.23 mmol) and 2,6-difluoro-4-methylbenzaldehyde (0.192 g, 3 mmol), the title compound was obtained as a brown solid (0.183 g, 0.69 mmol, 56% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.59 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.82 (d, J = 10.1 Hz, 2H), 2.41 (d, J = 5.6 Hz, 3H) ppm.

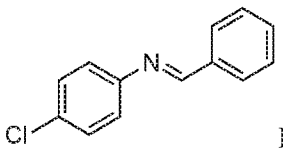
Example 11: (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-3-methoxyphenyl)methanimine



LM-I-024

[00183] Following synthetic procedure A using 4-chloroaniline (0.383 g, 3.00 mmol) and 2,6-difluoro-3-methoxybenzaldehyde (0.468 g, 3.00 mmol), the title compound was obtained as a brown solid (0.745 g, 2.64 mmol, 88% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.62 (s, 1H), 7.38–7.33 (m, 2H), 7.19–7.13 (m, 2H), 7.06–6.98 (m, 1H), 6.95–6.87 (m, 1H), 3.90 (s, 3H) ppm.

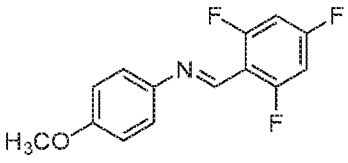
Example 12: (*E*)-*N*-(4-chlorophenyl)-1-phenylmethanimine



LM-I-032

[00184] Following synthetic procedure A using 4-chloroaniline (0.383 g, 3.00 mmol) and benzaldehyde (0.318 g, 3.00 mmol), the title compound was obtained as a brown solid (0.702 g, 3.25 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.44 (s, 1H), 7.97–7.86 (m, 2H), 7.58–7.44 (m, 3H), 7.36 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.3 Hz, 2H) ppm.

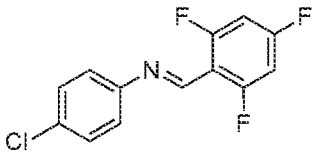
Example 13: (*E*)-*N*-(4-methoxyphenyl)-1-(2,4,6-trifluorophenyl)methanimine



LM-I-038

[00185] Following synthetic procedure A using 4-methoxyaniline (0.370 g, 3.00 mmol) and 2,4,6-trifluorobenzaldehyde (0.480 g, 3.00 mmol), the title compound was obtained as a brown solid (0.814 g, 3.07 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.59 (s, 1H), 7.25–7.22 (m, 2H), 6.96–6.91 (m, 2H), 6.79–6.73 (m, 2H), 3.84 (s, 3H) ppm.

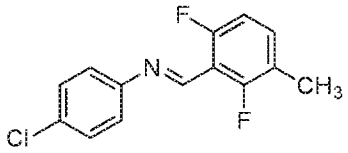
Example 14: (*E*)-*N*-(4-chlorophenyl)-1-(2,4,6-trifluorophenyl)methanimine



ASC-II-049

[00186] Following synthetic procedure A using 4-chloro-aniline (0.829 g, 6.5 mmol) and 2,4,6-trifluoro-benzaldehyde (1.041 g, 6.5 mmol), the title compound was obtained as a brown solid (1.750 g, 6.49 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.51 (s, 1H), 7.32 (d, J = 6.7 Hz, 2H), 7.12 (d, J = 6.8 Hz, 2H), 6.73 (m, 2H) ppm.

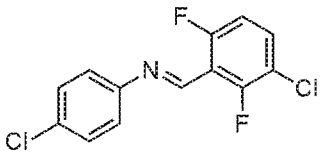
Example 15: (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-3-methylphenyl)methanimine



ASC-II-097

[00187] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,6-difluoro-3-methylbenzaldehyde (0.377 mL, 3 mmol), the title compound was obtained as a brown solid (0.781 g, 2.94 mmol, 98% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.63 (s, 1H), 7.36 (d, J = 8.2 Hz, 2H), 7.25 (q, J = 7.6 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 6.89 (t, J = 9.2 Hz, 1H), 2.28 (s, 3H) ppm.

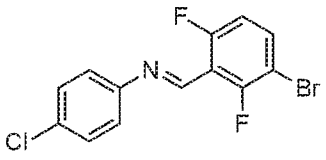
Example 16: (*E*)-1-(3-chloro-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine



ASC-II-099

[00188] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 3-chloro-2,6-difluorobenzaldehyde (0.530 g, 3 mmol), the title compound was obtained as a brown solid (0.850 g, 2.97 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.60 (s, 1H), 7.47 (td, J = 8.4, 5.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.00–6.96 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 159.87 (dd, J = 390.8, 5.6 Hz), 157.80 (dd, J = 393.2, 5.6 Hz), 150.87, 150.42, 132.72 (d, J = 10.3 Hz), 132.65, 129.47, 122.29, 117.77 (dd, J = 18.0, 3.9 Hz), 115.03 (t, J = 12.9 Hz), 112.80 (dd, J = 23.0, 4.4 Hz) ppm.

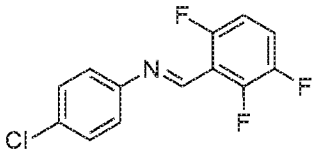
Example 17: (*E*)-1-(3-bromo-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine



ASC-II-102

[00189] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 3-bromo-2,6-difluorobenzaldehyde (0.663 g, 3 mmol), the title compound was obtained as a brown solid (0.971 g, 2.94 mmol, 98% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.59 (s, 1H), 7.61 (dd, J = 14.2, 7.6 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.93 (t, J = 9.2 Hz, 1H) ppm.

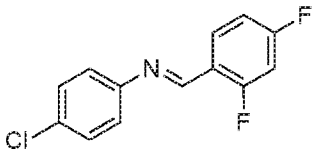
Example 18: (*E*)-*N*-(4-chlorophenyl)-1-(2,3,6-trifluorophenyl)methanimine



ASC-II-107

[00190] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,3,6-trifluorobenzaldehyde (0.337 mL, 3 mmol), the title compound was obtained as a brown solid (0.778 g, 2.88 mmol, 96% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.58 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.26–7.20 (m, 1H), 7.16 (d, J = 8.2 Hz, 2H), 6.92 (t, J = 9.0 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.28, 156.26, 150.76, 150.19, 148.36-148.23 (m), 146.34 (dd, J = 12.5, 3.6 Hz), 132.51, 129.30, 122.18, 119.33 (dd, J = 19.4, 10.4 Hz), 115.07 (dd, J = 14.2, 9.0 Hz), 111.42 (dt, J = 24.4, 5.3 Hz) ppm.

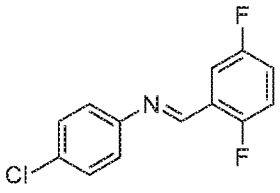
Example 19: (*E*)-*N*-(4-chlorophenyl)-1-(2,4-difluorophenyl)methanimine



ASC-II-109

[00191] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,4 difluorobenzaldehyde (0.328 mL, 3 mmol), the title compound was obtained as a brown solid (0.740 g, 2.94 mmol, 98% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (s, 1H), 7.50–7.45 (m, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.97 (t, J = 8.3 Hz, 1H), 6.89-6.85 (m, 1H) ppm.

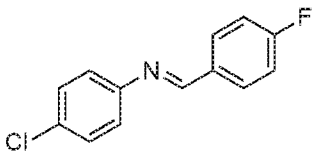
Example 20: (*E*)-*N*-(4-chlorophenyl)-1-(2,5-difluorophenyl)methanimine



SC-II-117

[00192] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2,5-difluorobenzaldehyde (0.326 mL, 3 mmol), the title compound was obtained as a brown solid (0.698 g, 2.77 mmol, 93% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.66 (s, 1H), 7.84 (dt, J = 7.6, 4.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.14–7.06 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 159.88, 157.92 (dd, J = 7.7, 1.9 Hz), 152.39 (d, J = 1.2 Hz), 149.67, 132.37, 131.65 (d, J = 16.8 Hz), 129.36, 129.11 (dd, J = 51.2, 13.4 Hz), 125.04 (dd, J = 11.3, 7.8 Hz), 122.40 (d, J = 19.7 Hz), 119.85 (dd, J = 24.9, 9.0 Hz), 117.27 (dd, J = 24.0, 8.3 Hz), 113.64 (dd, J = 25.1, 2.9 Hz) ppm.

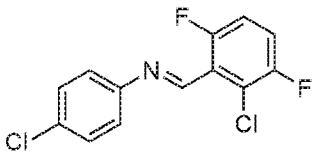
Example 21: (*E*)-*N*-(4-chlorophenyl)-1-(4-fluorophenyl)methanimine



ASC-II-121

[00193] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 4-fluorobenzaldehyde (0.322 mL, 3 mmol), the title compound was obtained as a brown solid (0.687 g, 2.94 mmol, 98% yield).

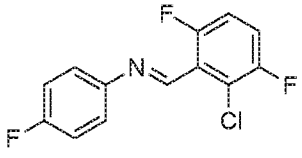
Example 22: (*E*)-1-(2-chloro-3,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine



ASC-II-124

[00194] Following synthetic procedure A using 4-chloro-aniline (0.383 g, 3 mmol) and 2-chloro-3,6-difluorobenzaldehyde (0.530 g, 3 mmol), the title compound was obtained as a brown solid (0.840 g, 2.94 mmol, 98% yield).

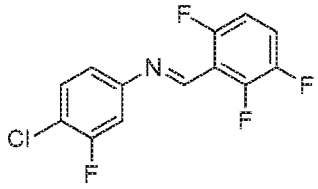
Example 23: (*E*)-1-(2-chloro-3,6-difluorophenyl)-*N*-(4-fluorophenyl)methanimine



ASC-II-126

[00195] Following synthetic procedure A using 4-fluoro-aniline (0.237 mL, 2.5 mmol) and 2-chloro-3,6-difluorobenzaldehyde (0.441 g, 2.5 mmol), the title compound was obtained as a brown (0.673 g, 2.50 mmol, 99% yield).

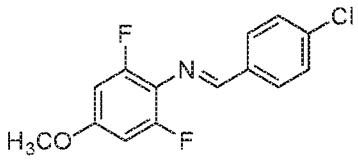
Example 24: (*E*)-*N*-(4-chloro-3-fluorophenyl)-1-(2,3,6-trifluorophenyl)methanimine



ASC-II-132

[00196] Following synthetic procedure A using 4-chloro-3-fluoroaniline (0.437 g, 3 mmol) and 2,3,6-trifluorobenzaldehyde (0.337 mL, 3 mmol), the title compound was obtained as a brown solid (0.846 g, 2.94 mmol, 98% yield).

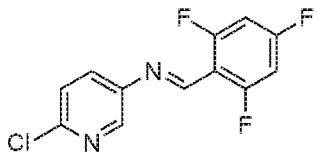
Example 25: (*E*)-1-(4-chlorophenyl)-*N*-(2,6-difluoro-4-methoxyphenyl)methanimine



ASC-II-146

[00197] Following synthetic procedure A using 2,6-difluoro-4-methoxyaniline (0.477 g, 3 mmol) and 4-chlorobenzaldehyde (0.421 g, 3 mmol), the title compound was obtained as a black solid (0.833 g, 2.96 mmol, 99% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.52 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 6.55–6.47 (m, 2H), 3.79 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 164.27 (d, J = 2.0 Hz), 159.94 (dd, J = 245.0, 15.6 Hz), 154.45 (dd, J = 251.1, 10.8 Hz), 153.53 (dt, J = 12.3, 6.4 Hz), 137.60 (s), 134.67 (s), 129.91 (s), 128.94 (s), 96.59 (t, J = 26.0 Hz), 95.77 (dd, J = 26.5, 3.0 Hz), 56.33 (s) ppm.

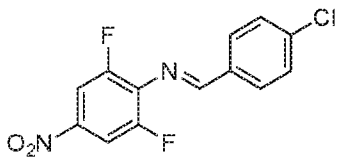
Example 26: (*E*)-*N*-(6-chloropyridin-3-yl)-1-(2,4,6-trifluorophenyl)methanimine



ASC-II-148

[00198] Following synthetic procedure A using 6-chloropyridin-3-amine (0.385 g, 3 mmol) and 2,4,6-trifluorobenzaldehyde (0.480 g, 3 mmol), the title compound was obtained as a brown solid (0.786 g, 2.90 mmol, 97% yield).

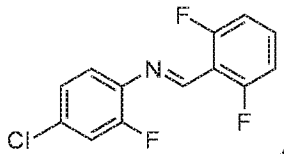
Example 27: (*E*)-1-(4-chlorophenyl)-*N*-(2,6-difluoro-4-nitrophenyl)methanimine



ASC-II-150

[00199] Following synthetic procedure A using 2,6-difluoro-4-nitroaniline (0.348 g, 2 mmol) and 4-chlorobenzaldehyde (0.281 g, 2 mmol), the title compound was obtained as a brown solid (0.500 g, 1.68 mmol, 84% yield).

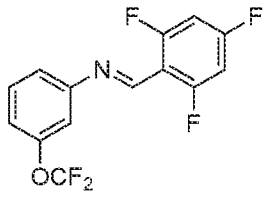
Example 28: (*E*)-*N*-(4-chloro-2-fluorophenyl)-1-(2,6-difluorophenyl)methanimine



ASC-II-157

[00200] Following synthetic procedure A using 4-chloro-2-fluoroaniline (0.437 g, 3 mmol) and 2,6-difluorobenzaldehyde (0.426 g, 3 mmol), the title compound was obtained as a brown solid (0.768 g, 2.85 mmol, 95% yield).

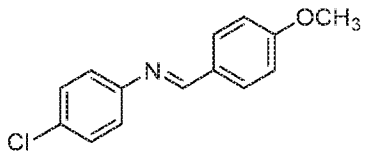
Example 29: (*E*)-*N*-(3-(difluoromethoxy)phenyl)-1-(2,4,6-trifluorophenyl)methanimine



ASC-II-161

[00201] Following synthetic procedure A using 3-(difluoromethoxy)aniline (0.477 g, 3 mmol) and 2,4,6-trifluorobenzaldehyde (0.480 g, 3 mmol), the title compound was obtained as a brown solid (0.885 g, 2.95 mmol, 98% yield).

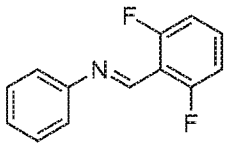
Example 30: (*E*)-*N*-(4-chlorophenyl)-1-(4-methoxyphenyl)methanimine



LM-I-073

[00202] Following synthetic procedure B using 4-chloroaniline (0.765 g, 6.00 mmol) and 4-methoxybenzaldehyde (0.817 g, 6.00 mmol), the title compound was obtained as a yellow solid (1.370 g, 5.58 mmol, 93% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.35 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 3.87 (s, 3H) ppm.

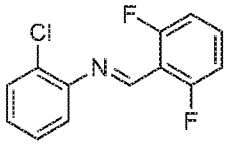
Example 31: (*E*)-1-(2,6-difluorophenyl)-*N*-phenylmethanimine



LM-I-104

[00203] Following synthetic procedure B using aniline (0.559 g, 6.00 mmol) and 2,6-difluorobenzaldehyde (0.853 g, 6.00 mmol), the title compound was obtained as a yellow liquid (0.637 g, 2.93 mmol, 49% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (d, J = 3.1 Hz, 1H), 7.39 (t, J = 7.6 Hz, 3H), 7.25–7.19 (m, 3H), 7.03–6.93 (m, 2H) ppm.

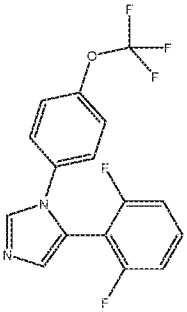
Example 32: (*E*)-*N*-(2-chlorophenyl)-1-(2,6-difluorophenyl)methanimine



LM-I-105

[00204] Following synthetic procedure B using 2-chloroaniline (0.765 g, 6.00 mmol) and 2,6-difluorobenzaldehyde (0.853 g, 6.00 mmol), the title compound was obtained as a yellow liquid (1.41 g, 5.58 mmol, 93% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.62 (s, 1H), 7.49–7.39 (m, 2H), 7.29 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 7.8 Hz, 1H), 7.02 (q, J = 8.7, 8.1 Hz, 3H) ppm.

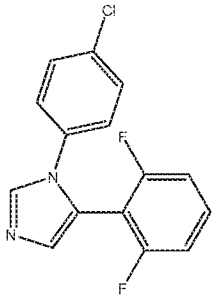
Example 33: 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole



LM-I-002

[00205] Following synthetic procedure C using (*E*)-1-(2,6-difluorophenyl)-*N*-(4-(trifluoromethoxy)phenyl)methanimine (1.03 g, 3.43 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as a white solid (0.644 g, 1.89 mmol, 55% yield). ^{1}H NMR (500 MHz; DMSO-d_6): δ 8.20 (s, 1H), 7.50 (m, 1H), 7.48–7.44 (m, 2H), 7.36–7.32 (m, 3H), 7.15 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{16}H_{10}F_5N_2O$ $[M + H]^+$ 341.0713, found 341.0719.

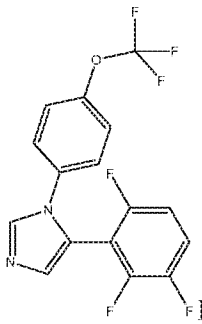
Example 34: 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



LM-I-006

[00206] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (1.62 g, 6.45 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as a yellow solid (1.18 g, 4.04 mmol, 63% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.86 (s, 1H), 7.60 (s, 1H), 7.49–7.39 (m, 3H), 7.22–7.16 (m, 2H), 6.96 (t, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_{10}ClF_2N_2$ $[M + H]^+$ 291.0501, found 291.0503.

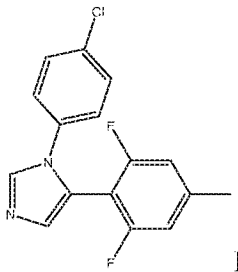
Example 35: 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



LM-I-008

[00207] Following synthetic procedure C using (*E*)-*N*-(4-(trifluoromethoxy)phenyl)-1-(2,3,6-trifluorophenyl)methanimine (1.08 g, 3.37 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as a brown solid (0.587 g, 1.64 mmol, 49% yield). ^{1}H NMR (500 MHz; DMSO-d_6): δ 7.83 (s, 1H), 7.36 (s, 1H), 7.24–7.19 (m, 4H), 7.17–7.11 (m, 1H), 6.84–6.79 (m, 1H) ppm; HRMS (ES^+) calculated for $C_{16}H_9F_6N_2O$ $[M + H]^+$ 359.0619, found 359.0621.

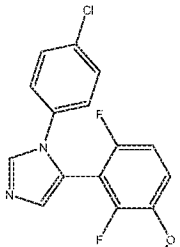
Example 36: 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1*H*-imidazole



LM-I-025

[00208] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-4-methylphenyl)methanimine (0.183 g, 0.689 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as a yellow solid (0.127 g, 0.417 mmol, 61% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.76 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.26 (s, 1H), 7.08 (d, J = 8.3 Hz, 2H), 6.67 (d, J = 8.2 Hz, 2H), 2.32 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_{12}ClF_2N_2$ $[M + H]^+$ 305.0657, found 305.0658.

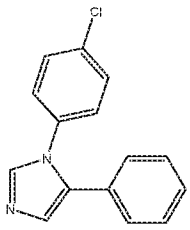
Example 37: 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1*H*-imidazole



LM-I-030

[00209] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-3-methoxyphenyl)methanimine (0.745 g, 2.64 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as a yellow solid (0.278 g, 0.867 mmol, 33% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.79 (s, 1H), 7.32 (d, J = 8.0 Hz, 3H), 7.10 (d, J = 8.2 Hz, 2H), 6.94–6.86 (m, 1H), 6.79 (t, J = 8.8 Hz, 1H), 3.84 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_{12}ClF_2N_2O$ $[M + H]^+$ 321.0606, found 321.0606.

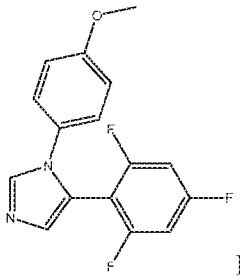
Example 38: 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole



LM-I-033

[00210] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-phenylmethanimine (0.702 g, 3.25 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as an orange solid (0.088 g, 0.345 mmol, 11% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.67 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.30–7.26 (m, 4H), 7.16–7.09 (m, 4H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_{12}ClN_2$ $[M + H]^+$ 255.0689, found 255.0690.

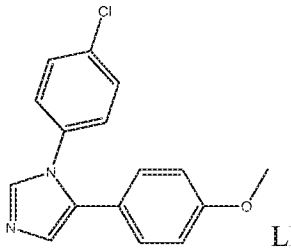
Example 39: 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole



LM-I-043

[00211] Following synthetic procedure C using (*E*)-*N*-(4-methoxyphenyl)-1-(2,4,6-trifluorophenyl)methanimine (0.814 g, 3.07 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as an orange solid (0.065 g, 0.214 mmol, 7% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.76 (s, 1H), 7.25 (s, 1H), 7.09–7.04 (m, 2H), 6.88–6.82 (m, 2H), 6.63 (dd, *J* = 8.7, 7.1 Hz, 2H), 3.79 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{12}F_3N_2O$ $[M + H]^+$ 309.0902, found 305.0908.

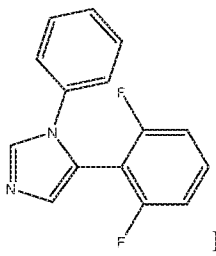
Example 40: 1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1*H*-imidazole



LM-I-082

[00212] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(4-methoxyphenyl)methanimine (0.100 g, 0.407 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as an orange solid (0.065 g, 0.228 mmol, 56% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.65 (s, 1H), 7.38–7.30 (m, 2H), 7.18 (s, 1H), 7.14–7.07 (m, 2H), 7.07–6.99 (m, 2H), 6.84–6.75 (m, 2H), 3.78 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{14}ClN_2O$ $[M + H]^+$ 285.0795, found 285.0798.

Example 41: 5-(2,6-difluorophenyl)-1-phenyl-1*H*-imidazole

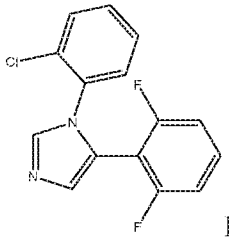


LM-I-106

[00213] Following synthetic procedure C using (*E*)-1-(2,6-difluorophenyl)-*N*-phenylmethanimine (0.600 g, 2.76 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as an orange solid (0.193 g, 0.753

mmol, 27% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.82 (s, 1H), 7.33 (dd, J = 9.3, 7.4 Hz, 4H), 7.30–7.26 (m, 1H), 7.18–7.13 (m, 2H), 6.86 (q, J = 7.8, 6.4 Hz, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_{11}F_2N_2$ $[M + H]^+$ 257.0890, found 257.0881.

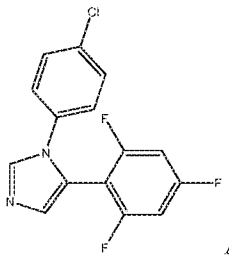
Example 42: 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



LM-I-107

[00214] Following synthetic procedure C using (*E*)-*N*-(2-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (0.600 g, 2.38 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as a yellow solid (0.478 g, 1.64 mmol, 69% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.77 (s, 1H), 7.47–7.42 (m, 1H), 7.36–7.30 (m, 2H), 6.83 (td, J = 8.1, 2.4 Hz, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_{10}ClF_2N_2$ $[M + H]^+$ 291.0501, found 291.0494.

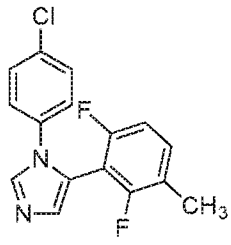
Example 43: 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole



ASC-II-053

[00215] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,4,6-trifluorophenyl)methanimine (0.865 g, 3.21 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a white powder (0.429 g, 1.39 mmol, 43% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.98 (s, 1H), 7.39–7.36 (m, 2H), 7.35 (s, 1H), 7.13–7.10 (m, 2H), 6.71–6.65 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.14 (dt, J = 252.4, 15.3 Hz), 160.75 (ddd, J = 251.5, 14.9, 8.7 Hz), 138.95 (s), 134.96 (s), 134.41 (s), 132.41 (s), 129.76 (s), 125.94 (s), 119.16 (s), 103.78 (td, J = 20.0, 4.6 Hz), 100.97-100.52 (m) ppm; HRMS (ES^+) calculated for $C_{15}H_9ClF_3N_2$ $[M + H]^+$ 309.04, found 309.06.

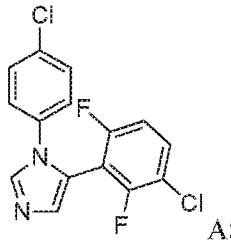
Example 44: 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole



ASC-II-100

[00216] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluoro-3-methylphenyl)methanimine (0.399 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 80:20 to 20:80) afforded the title compound as a yellow solid (0.327 g, 1.07 mmol, 72% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.81 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 3H), 7.15–7.08 (m, *J* = 15.1, 7.5 Hz, 3H), 6.75 (t, *J* = 8.6 Hz, 1H), 2.18 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_{11}ClF_2N_2$ [M + H]$^+$ 305.07, found 305.03.

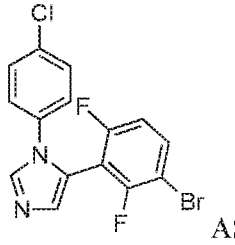
Example 45: 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole



ASC-II-105

[00217] Following synthetic procedure C using (*E*)-1-(3-chloro-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine (0.429 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a white solid (0.298 g, 0.916 mmol, 61% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.77 (d, *J* = 0.5 Hz, 1H), 7.29–7.27 (m, 2H), 7.27 (s, 1H), 7.06–7.04 (m, 2H), 6.78 (td, *J* = 8.7, 1.4 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.27 (dd, *J* = 251.2, 4.4 Hz), 155.38 (dd, *J* = 252.0, 6.3 Hz), 138.97 (s), 134.65 (s), 134.11 (s), 132.45 (s), 130.90 (s), 130.83 (s), 129.57 (s), 125.53 (s), 119.00 (s), 116.96 (dd, *J* = 18.6, 4.2 Hz), 112.05 (dd, *J* = 23.5, 4.1 Hz), 108.51 (t, *J* = 20.1 Hz) ppm; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ [M + H]$^+$ 325.01, found 324.93.

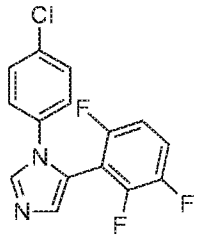
Example 46: 5-(3-bromo-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole



ASC-II-106

[00218] Following synthetic procedure C using (*E*)-1-(3-bromo-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine (0.495 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a yellow solid (0.450 g, 1.22 mmol, 82% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.83 (s, 1H), 7.53 (ddd, *J* = 8.8, 7.7, 5.8 Hz, 1H), 7.37–7.34 (m, 4H), 7.12–7.11 (m, 2H), 6.82 (td, *J* = 8.7, 1.4 Hz, 1H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_9BrClF_2N_2$ $[M + H]^+$ 368.96, found 370.98.

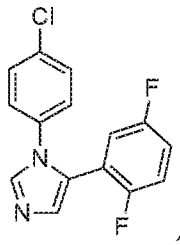
Example 47: 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



ASC-II-112

[00219] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (0.405 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a brown solid (0.350 g, 1.13 mmol, 76% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.80 (s, 1H), 7.34–7.31 (m, 4H), 7.15–7.11 (m, *J* = 9.0, 5.0 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.82–6.78 (m, 1H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_8ClF_3N_2$ $[M + H]^+$ 309.04, found 309.18.

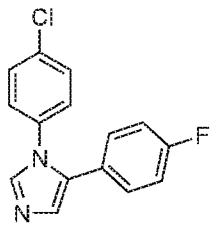
Example 48: 1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole



ASC-II-120

[00220] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(2,5-difluorophenyl)methanimine (0.378 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a yellow solid (0.392 g, 1.35 mmol, 90% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.09–7.07 (m, 2H), 6.86–6.83 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.35 (dd, *J* = 248.6, 7.2 Hz), 155.45 (d, *J* = 244.1 Hz), 139.09 (s), 135.05 (s), 134.29 (s), 131.29 (s), 129.80 (s), 126.02 (s), 118.66 (dd, *J* = 17.7, 8.8 Hz), 117.30 (dd, *J* = 24.8, 3.1 Hz), 117.18 (dd, *J* = 24.8, 8.9 Hz), 116.56 (dd, *J* = 23.8, 8.3 Hz) ppm; HRMS (ES$^+$) calculated for $C_{15}H_{10}ClF_2N_2$ $[M + H]^+$ 291.05, found 291.04.

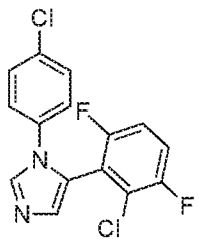
Example 49: 1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole



ASC-II-122

[00221] Following synthetic procedure C using (*E*)-*N*-(4-chlorophenyl)-1-(4-fluorophenyl)methanimine (0.350 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 90:10 to 60:40) afforded the title compound as a brown solid (0.260 g, 0.953 mmol, 64% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.67 (s, 1H), 7.39–7.36 (m, 2H), 7.22 (s, 1H), 7.12–7.08 (m, 4H), 7.00-6.96 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.48 (d, J = 248.1 Hz), 138.79 (s), 135.13 (s), 134.36 (s), 132.22 (s), 130.18 (d, J = 8.2 Hz), 129.92 (s), 129.20 (s), 126.92 (s), 125.39 (d, J = 3.2 Hz), 115.85 (d, J = 21.8 Hz) ppm; HRMS (ES^+) calculated for $C_{15}H_{11}ClFN_2$ $[M + H]^+$ 273.06, found 273.25.

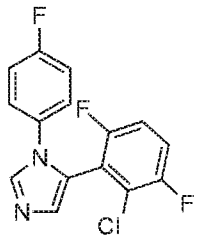
Example 50: 5-(2-chloro-3,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole



ASC-II-127

[00222] Following synthetic procedure C using (*E*)-1-(2-chloro-3,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine (0.429 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 50:50) afforded the title compound as an orange solid (0.364 g, 1.12 mmol, 75% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.75 (s, 1H), 7.24 (s, 1H), 7.21 (d, J = 5.7 Hz, 2H), 7.06 (td, J = 8.6, 4.7 Hz, 1H), 7.01 (d, J = 8.5 Hz, 2H), 6.86 (td, J = 8.6, 4.1 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 156.57 (dd, J = 227.8, 2.9 Hz), 154.61 (dd, J = 227.1, 2.7 Hz), 138.52 (s), 134.52 (s), 134.18 (s), 131.94 (s), 129.55 (s), 125.76 (s), 123.07 (dd, J = 19.2, 3.6 Hz), 122.09 (d, J = 1.4 Hz), 118.97 (s), 118.81 (s), 117.57 (dd, J = 23.7, 9.1 Hz), 114.55 (dd, J = 24.9, 7.9 Hz) ppm; HRMS (ES^+) calculated for $C_{15}H_9Cl_2F_2N_2$ $[M + H]^+$ 325.01, found 325.06.

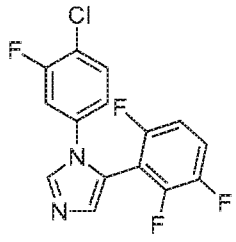
Example 51: 5-(2-chloro-3,6-difluorophenyl)-1-(4-fluorophenyl)-1*H*-imidazole



ASC-II-129

[00223] Following synthetic procedure C using (*E*)-1-(2-chloro-3,6-difluorophenyl)-*N*-(4-fluorophenyl)methanimine (0.405 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 50:50) afforded the title compound as an orange solid (0.357 g, 1.16 mmol, 77% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.76 (s, 1H), 7.20 (s, 1H), 7.07–7.03 (m, *J* = 3.4, 2.7 Hz, 3H), 6.95–6.91 (m, 2H), 6.84 (td, J = 8.6, 4.2 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.04 (d, *J* = 248.9 Hz), 156.57 (dd, *J* = 246.9, 2.6 Hz), 154.65 (dd, *J* = 246.4, 3.0 Hz), 138.72 (s), 131.97 (d, *J* = 3.2 Hz), 131.46 (s), 128.41 (d, *J* = 288.1 Hz), 126.49 (d, *J* = 8.8 Hz), 123.10 (dd, *J* = 19.2, 3.6 Hz), 122.37 (d, *J* = 1.8 Hz), 118.87 (d, *J* = 20.8 Hz), 117.61 (dd, *J* = 23.9, 9.2 Hz), 116.39 (s), 116.21 (s), 114.52 (dd, *J* = 25.0, 7.9 Hz) ppm; HRMS (ES$^+$) calculated for $C_{15}H_9ClF_3N_2$ $[M + H]^+$ 309.04, found 309.18.

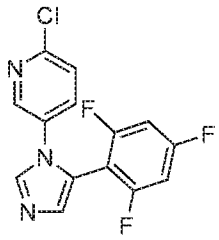
Example 52: 1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



ASC-II-135

[00224] Following synthetic procedure C using (*E*)-*N*-(4-chloro-3-fluorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (0.431 g, 1.5 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 50:50) afforded the title compound as an orange solid (0.385 g, 1.18 mmol, 79% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.77 (s, 1H), 7.34 (t, *J* = 8.2 Hz, 1H), 7.27 (s, 1H), 7.09 (qd, *J* = 9.1, 5.0 Hz, 1H), 6.95 (dd, *J* = 9.1, 2.4 Hz, 1H), 6.87 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.80–6.75 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.92 (s), 156.92 (s), 155.23 (dt, *J* = 247.6, 2.8 Hz), 147.79 (ddd, *J* = 252.4, 14.5, 6.4 Hz), 147.14 (ddd, *J* = 246.3, 13.0, 3.6 Hz), 139.06 (s), 135.89 (d, *J* = 8.8 Hz), 132.81 (s), 131.35 (s), 121.36 (s), 121.22 (s), 120.81 (d, *J* = 3.8 Hz), 119.00 (d, *J* = 1.6 Hz), 117.76 (dd, *J* = 19.6, 9.6 Hz), 113.15 (s), 112.96 (s), 111.14 (dt, *J* = 24.5, 5.4 Hz), 108.61 (dd, *J* = 21.6, 15.7 Hz) ppm; HRMS (ES$^+$) calculated for $C_{15}H_8ClF_4N_2$ $[M + H]^+$ 327.03, found 327.14.

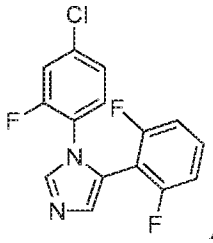
Example 53: 2-chloro-5-(5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine



ASC-II-153

[00225] Following synthetic procedure C (*E*)-*N*-(6-chloropyridin-3-yl)-1-(2,4,6-trifluorophenyl)methanimine (0.593 g, 2.2 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as an orange solid (0.304 g, 0.982 mmol, 45% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.21 (s, 1H), 7.78 (s, 1H), 7.45 (ddd, *J* = 8.4, 2.5, 1.2 Hz, 1H), 7.35–7.33 (m, 1H), 7.28 (s, 1H), 6.66–6.63 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.30 (dt, *J* = 253.2, 15.2 Hz), 160.50 (ddd, *J* = 251.6, 14.8, 8.5 Hz), 151.19 (s), 145.34 (s), 138.80 (s), 134.72 (s), 132.82 (s), 132.10 (s), 124.96 (s), 119.28 (s), 102.94 (td, *J* = 19.9, 4.7 Hz), 101.23–100.79 (m) ppm; HRMS (ES$^+$) calculated for $C_{14}H_8ClF_3N_3$ [M + H]$^+$ 310.04, found 310.13.

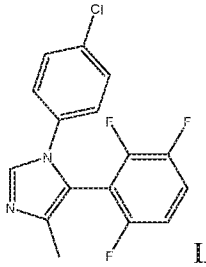
Example 54: 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



ASC-II-162

[00226] Following synthetic procedure C using (*E*)-*N*-(4-chloro-2-fluorophenyl)-1-(2,6-difluorophenyl)methanimine (0.539 g, 2 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 90:10 to 60:40) afforded the title compound as a yellow solid (0.351 g, 1.14 mmol, 57% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.77 (s, 1H), 7.35 (s, 1H), 7.31–7.27 (m, 1H), 7.21–7.19 (m, 1H), 7.15–7.10 (m, *J* = 6.6 Hz, 2H), 6.88 (quintet, *J* = 6.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 160.46 (dd, *J* = 250.9, 5.9 Hz), 156.39 (d, *J* = 256.0 Hz), 139.44 (d, *J* = 1.1 Hz), 135.42 (d, *J* = 9.2 Hz), 131.92 (s), 130.94 (t, *J* = 10.3 Hz), 128.57 (s), 125.17 (s), 125.14 (s), 123.30 (d, *J* = 12.7 Hz), 120.88 (s), 117.86 (s), 117.67 (s), 111.71 (dd, *J* = 20.5, 5.2 Hz), 106.96 (t, *J* = 19.5 Hz) ppm; HRMS (ES$^+$) calculated for $C_{15}H_9ClF_3N_2$ [M + H]$^+$ 309.04, found 309.12.

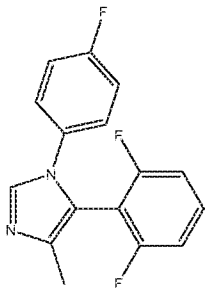
Example 55: 1-(4-chlorophenyl)-4-methyl-5-(2,3,6-trifluorophenyl)-1H-imidazole



LM-I-076

[00227] Following synthetic procedure D using (*E*)-*N*-(4-chlorophenyl)-1-(2,3,6-trifluorophenyl)methanimine (0.500 g, 1.85 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as an orange solid (0.190 g, 0.589 mmol, 32% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.33–7.29 (m, 2H), 7.15 (qd, J = 9.1, 5.0 Hz, 1H), 7.07–7.02 (m, 2H), 6.82 (tdd, J = 9.3, 3.8, 2.1 Hz, 1H), 2.22 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}ClF_3N_2$ $[M + H]^+$ 323.0563, found 323.0557.

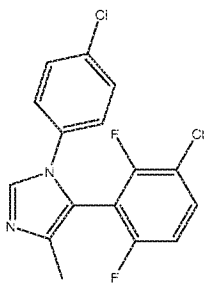
Example 56: 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1H-imidazole



LM-I-079

[00228] Following synthetic procedure D using (*E*)-*N*-(4-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (0.618 g, 2.46 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as an orange solid (0.292 g, 0.958 mmol, 39% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.34–7.27 (m, 3H), 7.06–7.02 (m, 2H), 6.91–6.85 (m, 2H), 2.21 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{12}ClF_2N_2$ $[M + H]^+$ 305.0657, found 305.0661.

Example 57: 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-1H-imidazole

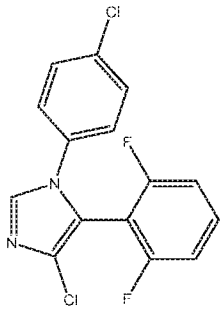


LM-I-080

[00229] Following synthetic procedure D using (*E*)-1-(3-chloro-2,6-difluorophenyl)-*N*-(4-chlorophenyl)methanimine (0.800 g, 2.80 mmol), purification by flash chromatography (silica

gel, hexanes/ethyl acetate 65:35) afforded the title compound as an orange solid (0.433 g, 1.28 mmol, 46% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.37 (ddd, J = 9.0, 8.0, 5.6 Hz, 1H), 7.33–7.29 (m, 2H), 7.07–7.01 (m, 2H), 6.84 (ddd, J = 9.0, 8.2, 1.8 Hz, 1H), 2.20 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_{11}Cl_2F_2N_2$ [M + H]$^+$ 339.0267, found 339.0273.

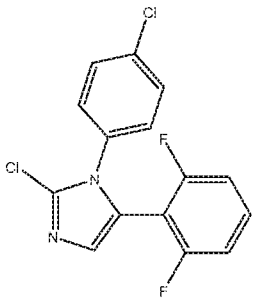
Example 58: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



LM-I-010 B

[00230] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.400 g, 1.38 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.265 g, 0.815 mmol, 59% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.69 (s, 1H), 7.40–7.30 (m, 3H), 7.08 (dd, J = 8.7, 2.7 Hz, 2H), 6.91 (t, J = 7.9 Hz, 2H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ [M + H]$^+$ 325.0111, found 325.0122.

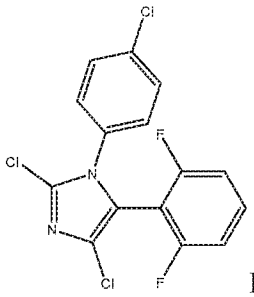
Example 59: 2-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



LM-I-010 C

[00231] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.400 g, 1.38 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.056 g, 0.172 mmol, 12% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.42–7.40 (m, 2H), 7.38–7.32 (m, 1H), 7.21–7.19 (m, 2H), 6.93–6.89 (m, 2H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_8Cl_2F_2N_2Na$ [M + Na]$^+$ 346.9930, found 346.9933.

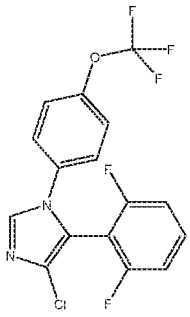
Example 60: 2,4-dichloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



LM-I-010 D

[00232] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.400 g, 1.38 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.026 g, 0.072 mmol, 5% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.35 (d, J = 7.9 Hz, 3H), 7.13 (d, J = 8.1 Hz, 2H), 6.88 (t, J = 8.0 Hz, 2H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_8Cl_3F_2N_2$ $[M + H]^+$ 358.9721, found 358.9725.

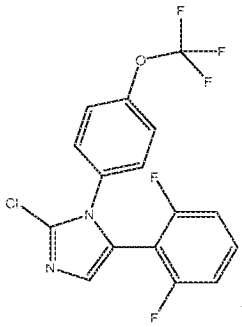
Example 61: 4-chloro-5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole



LM-I-012 B

[00233] Following synthetic procedure E using 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (0.400 g, 1.17 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.192 g, 0.512 mmol, 44% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.70 (s, 1H), 7.42–7.34 (m, 1H), 7.23–7.16 (m, 4H), 6.91 (t, J = 7.8 Hz, 2H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_9ClF_5N_2O$ $[M + H]^+$ 375.0325, found 375.0334.

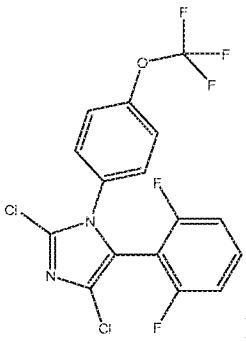
Example 62: 2-chloro-5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole



LM-I-012 C

[00234] Following synthetic procedure E using 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (0.400 g, 1.17 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.033 g, 0.088 mmol, 8% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.33–7.26 (m, 1H), 7.23 (d, J = 4.5 Hz, 4H), 7.20 (s, 1H), 6.88–6.81 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{16}H_9ClF_5N_2NaO$ $[M + Na]^+$ 397.0143, found 397.0149.

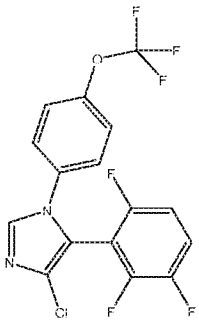
Example 63: 2,4-dichloro-5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole



LM-I-012 D

[00235] Following synthetic procedure E using 5-(2,6-difluorophenyl)-1-(4-(trifluoromethoxy)phenyl)-1*H*-imidazole (0.400 g, 1.17 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.028 g, 0.068 mmol, 6% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.39–7.31 (m, 1H), 7.25–7.19 (m, 4H), 6.92–6.84 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{16}H_8Cl_2F_5N_2O$ $[M + H]^+$ 408.9934, found 408.9940.

Example 64: 4-chloro-1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole

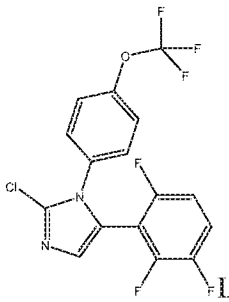


LM-I-014 B

[00236] Following synthetic procedure E using 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.500 g, 1.40 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow oil (0.198 g, 0.504 mmol, 36% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.25–7.17 (m, 5H), 6.88–

6.82 (m, 1H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_8ClF_6N_2NaO$ [M + Na]$^+$ 415.0049, found 415.0059.

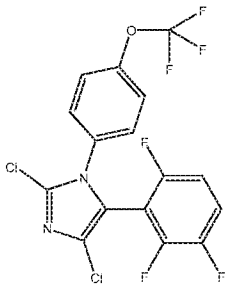
Example 65: 2-chloro-1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



LM-I-014 C

[00237] Following synthetic procedure E using 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.500 g, 1.40 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow solid (0.047 g, 0.120 mmol, 9% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.27–7.23 (m, 4H), 7.19–7.13 (m, 2H), 6.84–6.80 (m, 1H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_8ClF_6N_2O$ [M + H]$^+$ 393.0229, found 393.0232.

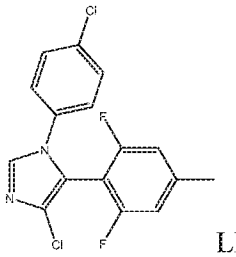
Example 66: 2,4-dichloro-1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1H-imidazole



LM-I-014 D

[00238] Following synthetic procedure E using 1-(4-(trifluoromethoxy)phenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.500 g, 1.40 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow solid (0.010 g, 0.023 mmol, 2% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.24 (dd, 4H), 7.22–7.16 (m, 1H), 6.87–6.78 (m, 1H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_7Cl_2F_6N_2O$ [M + H]$^+$ 426.9840, found 426.9850.

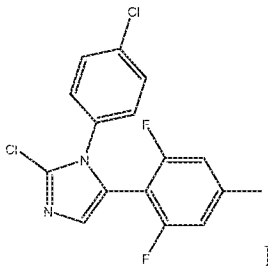
Example 67: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-imidazole



LM-I-028 B

[00239] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1*H*-imidazole (0.100 g, 0.328 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow solid (0.070 g, 0.206 mmol, 63% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.67 (s, 1H), 7.33 (dd, J = 8.8, 2.7 Hz, 2H), 7.11–7.05 (m, 2H), 6.71 (d, J = 8.5 Hz, 2H), 2.35 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2$ $[M + H]^+$ 339.0267, found 339.0259.

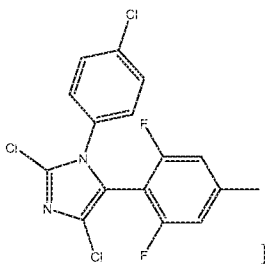
Example 68: 2-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-imidazole



LM-I-028 C

[00240] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1*H*-imidazole (0.100 g, 0.328 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow solid (0.009 g, 0.026 mmol, 8% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36–7.34 (m, 2H), 7.15–7.12 (m, 3H), 6.67–6.64 (m, 2H), 2.31 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2$ $[M + H]^+$ 339.0267, found 339.0263.

Example 69: 2,4-dichloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1H-imidazole

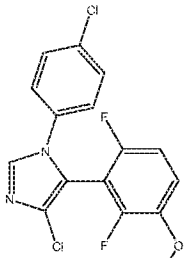


LM-I-028 D

[00241] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-4-methylphenyl)-1*H*-imidazole (0.100 g, 0.328 mmol), purification by flash chromatography

(silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow solid (0.024 g, 0.064 mmol, 20% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.35 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 2.33 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{10}Cl_3F_2N_2$ $[M + H]^+$ 372.9878, found 372.9869.

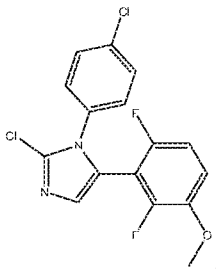
Example 70: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole



LM-I-034 B

[00242] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1*H*-imidazole (0.132 g, 0.412 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as white foam (0.065 g, 0.183 mmol, 45% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.68 (s, 1H), 7.32 (dd, J = 8.7, 2.8 Hz, 2H), 7.09 (d, J = 8.7 Hz, 2H), 7.00–6.92 (m, 1H), 6.85–6.77 (m, 1H), 3.83 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2O$ $[M + H]^+$ 355.0217, found 355.0203.

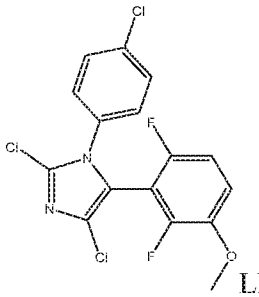
Example 71: 2-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole



LM-I-034 C

[00243] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1*H*-imidazole (0.132 g, 0.412 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.015 g, 0.042 mmol, 10% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37–7.32 (m, 2H), 7.18 (s, 1H), 7.16–7.11 (m, 2H), 6.92–6.85 (m, 1H), 6.79–6.73 (m, 1H), 3.82 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2O$ $[M + H]^+$ 355.0217, found 355.0219.

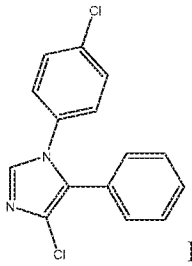
Example 72: 2,4-dichloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1H-imidazole



LM-I-034 D

[00244] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methoxyphenyl)-1*H*-imidazole (0.132 g, 0.412 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.009 g, 0.023 mmol, 6% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37–7.34 (m, 2H), 7.15–7.13 (m, 2H), 6.96–6.82 (m, 1H), 6.81–6.77 (m, 1H), 3.84 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{10}Cl_3F_2N_2O$ $[M + H]^+$ 388.9827, found 388.9832.

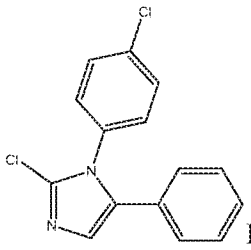
Example 73: 4-chloro-1-(4-chlorophenyl)-5-phenyl-1H-imidazole



LM-I-036 B

[00245] Following synthetic procedure E using 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (0.070 g, 0.275 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.061 g, 0.211 mmol, 77% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.58 (s, 1H), 7.36–7.28 (m, 5H), 7.21–7.17 (m, 2H), 7.08–7.04 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_{11}Cl_2N_2$ $[M + H]^+$ 289.0299, found 289.0300.

Example 74: 2-chloro-1-(4-chlorophenyl)-5-phenyl-1H-imidazole

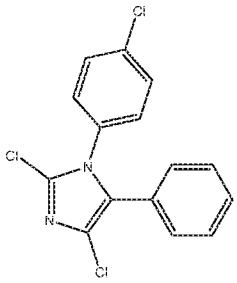


LM-I-036 C

[00246] Following synthetic procedure E using 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (0.070 g, 0.275 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.007 g, 0.025 mmol, 9% yield). ^{1}H NMR

(500 MHz; $CDCl_3$): δ 7.43–7.39 (m, 2H), 7.26–7.23 (m, 3H), 7.19–7.14 (m, 3H), 7.08–7.04 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_{11}Cl_2N_2$ $[M + H]^+$ 289.0299, found 289.0312.

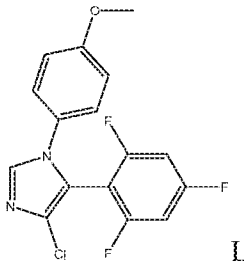
Example 75: 2,4-dichloro-1-(4-chlorophenyl)-5-phenyl-1H-imidazole



LM-I-036 D

[00247] Following synthetic procedure E using 1-(4-chlorophenyl)-5-phenyl-1*H*-imidazole (0.070 g, 0.275 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.008 g, 0.024 mmol, 9% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.41–7.36 (m, 2H), 7.31–7.27 (m, 3H), 7.17–7.12 (m, 2H), 7.12–7.08 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_{10}Cl_3N_2$ $[M + H]^+$ 322.9910, found 322.9906.

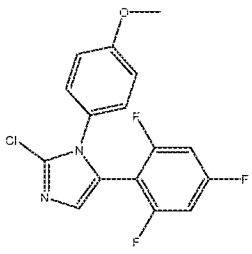
Example 76: 4-chloro-1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole



LM-I-050 B

[00248] Following synthetic procedure E using 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.086 g, 0.283 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.043 g, 0.127 mmol, 45% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.64 (s, 1H), 7.06 (d, J = 8.6 Hz, 2H), 6.88–6.82 (m, 2H), 6.66 (dd, J = 8.8, 7.2 Hz, 2H), 3.79 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}ClF_3N_2O$ $[M + H]^+$ 339.0512, found 339.0498.

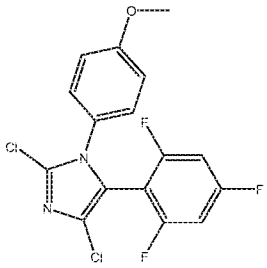
Example 77: 2-chloro-1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole



LM-I-050 C

[00249] Following synthetic procedure E using 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.086 g, 0.283 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.015 g, 0.044 mmol, 16% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.14 (s, 1H), 7.12–7.05 (m, 2H), 6.90–6.83 (m, 2H), 6.65–6.55 (m, 2H), 3.81 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}ClF_3N_2O$ $[M + H]^+$ 339.0512, found 339.0499.

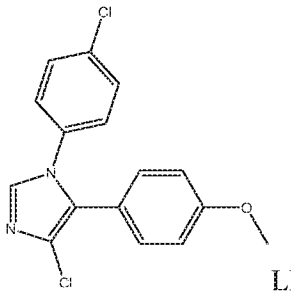
Example 78: 2,4-dichloro-1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole



LM-I-050 D

[00250] Following synthetic procedure E using 1-(4-methoxyphenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.086 g, 0.283 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.010 g, 0.027 mmol, 9% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.12–7.06 (m, 2H), 6.91–6.84 (m, 2H), 6.68–6.60 (m, 2H), 3.81 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{10}Cl_2F_3N_2O$ $[M + H]^+$ 373.0122, found 373.0112.

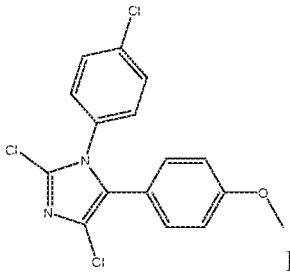
Example 79: 4-chloro-1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazole



LM-I-090

[00251] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1*H*-imidazole (0.220 g, 0.773 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow solid (0.159 g, 0.498 mmol, 65% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.55 (s, 1H), 7.36–7.31 (m, 2H), 7.13–7.08 (m, 2H), 7.08–7.03 (m, 2H), 6.84 (d, J = 8.3 Hz, 2H), 3.79 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{12}Cl_2N_2NaO$ $[M + Na]^+$ 341.0224, found 341.0229.

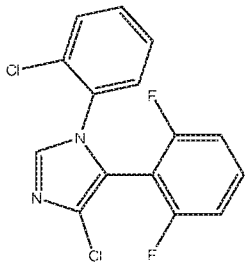
Example 80: 2,4-dichloro-1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1H-imidazole



LM-I-096

[00252] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-methoxyphenyl)-1*H*-imidazole (0.220 g, 0.773 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 90:10) afforded the title compound as a white solid (0.015 g, 0.047 mmol, 27% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40–7.36 (m, 2H), 7.11–7.08 (m, 2H), 7.08–7.03 (m, 2H), 6.82–6.79 (m, 2H), 3.78 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{12}Cl_3N_2O$ $[M + H]^+$ 353.0015, found 353.0012.

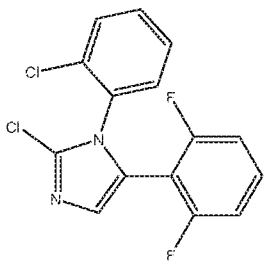
Example 81: 4-chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



LM-I-108 B

[00253] Following synthetic procedure E using 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.260 g, 0.894 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 75:25) afforded the title compound as a white solid (0.187 g, 0.575 mmol, 64% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.63 (d, J = 2.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.32 (ddt, *J* = 14.5, 7.8, 4.7 Hz, 2H), 7.27 (s, 1H), 6.84 (t, J = 8.5 Hz, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_9Cl_2F_2N_2$ $[M + H]^+$ 325.0111, found 325.0111.

Example 82: 2-chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole

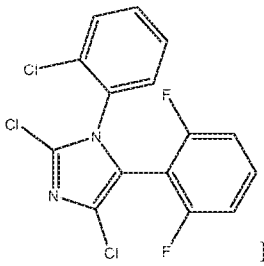


LM-I-108 C

[00254] Following synthetic procedure E using 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.260 g, 0.894 mmol), purification by flash chromatography (silica gel, hexanes/ethyl

acetate 75:25) afforded the title compound as a white solid (0.026 g, 0.080 mmol, 9% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.43 (d, J = 7.9 Hz, 1H), 7.38–7.28 (m, 3H), 7.23 (d, J = 14.4 Hz, 1H), 6.82 (t, J = 7.8 Hz, 2H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ [M + H]$^+$ 325.0111, found 325.0119.

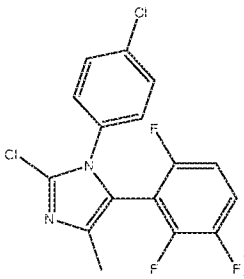
Example 83: 2,4-dichloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



LM-I-109

[00255] Following synthetic procedure E using 4-chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.060 g, 0.184 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a white solid (0.047 g, 0.131 mmol, 71% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.43 (d, J = 8.0 Hz, 1H), 7.40–7.27 (m, 3H), 6.88 (t, J = 8.5 Hz, 1H), 6.81 (t, J = 8.6 Hz, 1H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_8Cl_3F_2N_2$ [M + H]$^+$ 358.9721, found 358.9717.

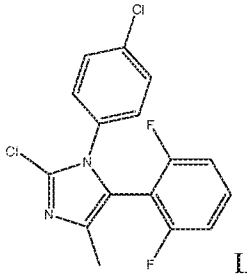
Example 84: 2-chloro-1-(4-chlorophenyl)-4-methyl-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



LM-I-083

[00256] Following synthetic procedure E using 1-(4-chlorophenyl)-4-methyl-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.310 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a white solid (0.079 g, 0.221 mmol, 71% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37–7.31 (m, 2H), 7.16–7.07 (m, 3H), 6.79 (tdd, J = 9.2, 3.8, 2.1 Hz, 1H), 2.17 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_{10}Cl_2F_3N_2$ [M + H]$^+$ 357.0173, found 357.0170.

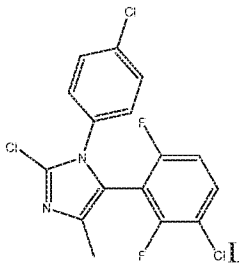
Example 85: 2-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole



LM-I-084

[00257] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole (0.150 g, 0.492 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a yellow oil (0.079 g, 0.232 mmol, 47% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.29 (t, J = 8.1 Hz, 3H), 7.12–7.06 (m, 2H), 6.87–6.81 (m, 2H), 2.15 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2$ $[M + H]^+$ 339.0267, found 339.0277.

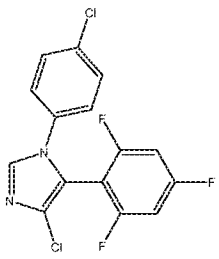
Example 86: 2-chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazole



LM-I-085

[00258] Following synthetic procedure E using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazole (0.150 g, 0.442 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a white solid (0.071 g, 0.190 mmol, 43% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.39–7.31 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 9.4 Hz, 1H), 2.17 (d, J = 4.8 Hz, 2H), 2.15 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{16}H_{10}Cl_3F_2N_2$ $[M + H]^+$ 372.9878, found 372.9874.

Example 87: 4-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole

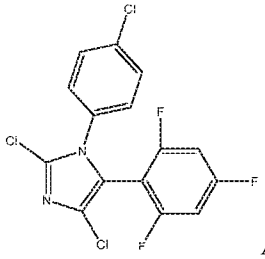


ASC-II-057

[00259] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.400 g, 1.3 mmol), purification by automated flash chromatography (silica gel,

hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a white solid (0.305 g, 0.889 mmol, 69% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.68 (s, 1H), 7.36–7.33 (m, 2H), 7.09–7.07 (m, 2H), 6.71–6.65 (m, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.93 (dt, J = 253.4, 15.3 Hz), 161.04 (ddd, J = 253.0, 15.1, 8.4 Hz), 136.90, 135.09, 134.44, 132.62, 129.98, 126.00, 115.23, 101.87 (td, J = 20.3, 4.8 Hz), 101.21–100.77 (m) ppm; IR: ν 3050, 2987, 2919, 2848, 1646, 1595, 1498, 1444, 1265, 1125, 1037, 908, 735 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_8Cl_2F_3N_2$ $[M + H]^+$ 343.0017, found 343.0008.

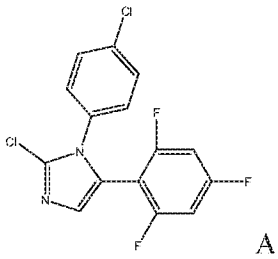
Example 88: 2,4-dichloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole



ASC-II-067 f1

[00260] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.400 g, 1.3 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a white solid (0.016 g, 0.042 mmol, 3% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.39–7.36 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.69-6.63 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 164.23 (dt, J = 254.2, 15.3 Hz), 161.26 (ddd, J = 253.1, 15.1, 8.3 Hz), 136.22, 132.94, 132.88, 130.83, 129.91, 128.57, 117.68, 101.61 (td, J = 20.2, 4.9 Hz), 101.23–100.78 (m) ppm; IR: ν 3100, 3067, 2962, 2928, 2857, 1645, 1599, 1495, 1446, 1121, 1038, 998 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_7Cl_3F_3N_2$ $[M + H]^+$ 376.9627, found 376.9627.

Example 89: 2-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole

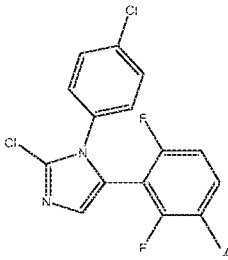


ASC-II-067 f2

[00261] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.400 g, 1.3 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a white solid (0.058 g, 0.169 mmol, 13% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37–7.34 (m, 2H), 7.16 (s, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.64–6.58 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.54 (dt, J =

253.0, 15.2 Hz, 1C), 161.05 (ddd, *J* = 251.8, 15.1, 8.4 Hz, 1C), 135.66 (s, 1C), 134.53 (s, 1C), 133.38 (s, 1C), 130.58 (s, 1C), 129.69 (s, 1C), 128.62 (s, 1C), 121.59 (s, 1C), 103.44 (td, *J* = 20.1, 4.6 Hz, 1C), 100.99–100.54 (m, 1C) ppm; IR: ν 3459, 1645, 1599, 1568, 1495, 1447, 1124, 1034 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8Cl_2F_3N_2$ $[M + H]^+$ 343.0017, found 343.0022.

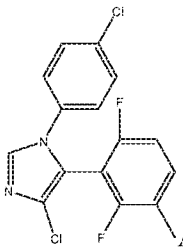
Example 90: 2-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole



ASC-II-103 f1

[00262] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole (0.326 g, 1.07 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a brown solid (0.030 g, 0.088 mmol, 8% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.35–7.32 (m, 2H), 7.16 (s, 1H), 7.14–7.08 (m, 3H), 6.71 (td, *J* = 8.5, 1.1 Hz, 1H), 2.15 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.66 (ddd, *J* = 248.9, 13.9, 5.4 Hz, 1C), 135.30 (s, 1C), 134.12 (s, 1C), 133.71 (s, 1C), 132.66 (t, *J* = 8.2 Hz, 1C), 130.33 (s, 1C), 129.48 (s, 1C), 128.68 (s, 1C), 123.01 (s, 1C), 120.95 (dd, *J* = 18.0, 4.0 Hz, 1C), 110.88 (dd, *J* = 21.7, 3.8 Hz, 1C), 106.33 (t, J = 20.1 Hz, 1C), 14.27 (d, *J* = 3.1 Hz, 1C) ppm; IR: ν 3445, 2919, 2848, 1496, 1478, 1443, 1093, 1042 cm^{-1}; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2$ $[M + H]^+$ 339.0267, found 339.0257.

Example 91: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole

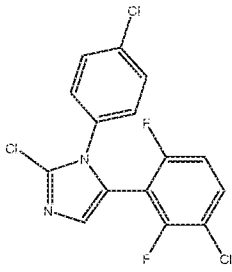


ASC-II-103 f2

[00263] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole (0.326 g, 1.07 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a beige solid (0.187 g, 0.551 mmol, 52% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.73 (s, 1H), 7.36–7.33 (m, 2H), 7.22 (q, *J* = 7.5 Hz, 1H), 7.14–7.11 (m, 2H), 6.81 (td, *J* = 8.5, 0.9 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.49 (ddd, *J* = 249.9, 12.8, 5.7 Hz, 1C), 136.49 (s, 1C), 134.57 (s, 1C), 134.56 (s, 1C), 133.20 (dd, *J* = 9.5, 7.1 Hz, 1C), 131.96 (s, 1C), 129.69 (s, 1C),

125.74 (s, 1C), 121.03 (dd, J = 17.6, 3.8 Hz, 1C), 116.38 (s, 1C), 110.95 (dd, J = 21.2, 3.9 Hz, 1C), 104.53 (t, J = 20.1 Hz, 1C), 14.10 (d, J = 3.2 Hz, 1C) ppm; IR: ν 3121, 3096, 2924, 2852, 1497, 1482, 1265, 1093, 958 cm^{-1}; HRMS (ES^+) calculated for $C_{16}H_{11}Cl_2F_2N_2$ $[M + H]^+$ 339.0267, found 339.0269.

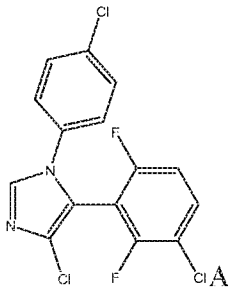
Example 92: 2-chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole



ASC-II-108 f1

[00264] Following synthetic procedure E using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.280 g, 0.861 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a yellow solid (0.050 g, 0.139 mmol, 16% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.37–7.32 (m, 3H), 7.14–7.11 (m, 2H), 6.80 (td, J = 8.6, 1.4 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.83 (dd, J = 251.3, 4.1 Hz), 155.97 (dd, J = 252.5, 6.2 Hz), 135.64 (s), 134.85 (s), 133.35 (s), 131.78 (s), 131.70 (s), 130.88 (s), 129.69 (s), 128.57 (s), 121.65 (s), 117.22 (dd, J = 18.6, 4.1 Hz), 112.19 (dd, J = 23.6, 4.3 Hz), 108.44 (t, J = 20.3 Hz) ppm; IR: ν 3100, 3071, 2928, 2857, 1683, 1652, 1635, 1558, 1538, 1495 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8Cl_3F_2N_2$ $[M + H]^+$ 358.9721, found 358.9717.

Example 93: 4-chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole

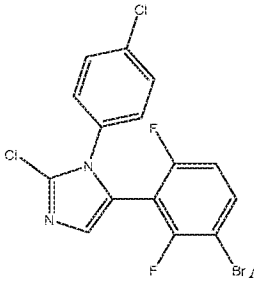


ASC-II-108 f2

[00265] Following synthetic procedure E using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.280 g, 0.434 mmol, 0.861 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a yellow solid (0.156 g, 50% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.69 (s, 1H), 7.41 (td, J = 8.6, 5.6 Hz, 1H), 7.34–7.31 (m, 2H), 7.09 7.06 (m, 2H), 6.88–6.84 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.79 (dd, J = 252.6, 4.4 Hz, 1C), 155.89 (dd, J = 253.6, 6.2 Hz, 1C), 137.09

(s, 1C), 135.05 (s, 1C), 134.27 (s, 1C), 132.65 (s, 1C), 132.28 (d, J = 9.6 Hz, 1C), 129.97 (s, 1C), 125.85 (s, 1C), 117.26 (dd, J = 18.4, 4.1 Hz, 1C), 115.25 (s, 1C), 112.37 (dd, J = 23.3, 4.2 Hz, 1C), 106.79 (t, J = 20.1 Hz, 1C) ppm; IR: ν 3121, 3104, 3075, 2932, 2848, 1558, 1497, 1472, 1453, 1267, 1092 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8Cl_3F_2N_2$ $[M + H]^+$ 358.9721, found 358.9724.

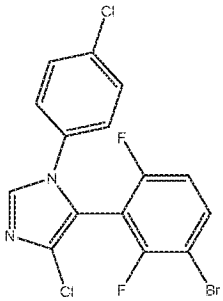
Example 94: 5-(3-bromo-2,6-difluorophenyl)-2-chloro-1-(4-chlorophenyl)-1*H*-imidazole



ASC-II-110 f1

[00266] Following synthetic procedure E using 5-(3-bromo-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.452 g, 1.223 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a brown solid (0.064 g, 0.158 mmol, 13% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.48 (ddd, J = 8.9, 7.7, 5.8 Hz, 1H), 7.37–7.34 (m, 2H), 7.19 (s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.76 (td, J = 8.6, 1.3 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 159.51 (dd, J = 251.7, 4.4 Hz, 1C), 156.89 (dd, J = 250.8, 6.2 Hz, 1C), 135.59 (s, 1C), 134.60 (s, 1C), 134.53 (d, J = 1.3 Hz, 1C), 133.27 (s, 1C), 130.76 (s, 1C), 129.67 (s, 1C), 128.53 (s, 1C), 121.69 (s, 1C), 112.75 (dd, J = 23.2, 4.1 Hz, 1C), 108.31 (t, J = 20.4 Hz, 1C), 104.38 (dd, J = 22.1, 4.1 Hz, 1C) ppm; IR: ν 3096, 3067, 2928, 2852, 1496, 1468, 1448, 1430, 1316, 1218, 1090, 1013 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8BrCl_2F_2N_2$ $[M + H]^+$ 402.9216, found 402.9216.

Example 95: 5-(3-bromo-2,6-difluorophenyl)-4-chloro-1-(4-chlorophenyl)-1*H*-imidazole

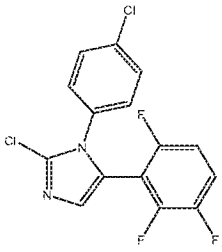


ASC-II-110 f2

[00267] Following synthetic procedure E using 5-(3-bromo-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.452 g, 1.223 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a brown

solid (0.224 g, 0.554 mmol, 45% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.68 (s, 1H), 7.55 (ddd, J = 8.9, 7.7, 5.8 Hz, 1H), 7.33–7.31 (m, 2H), 7.08–7.06 (m, 2H), 6.83–6.79 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 159.51 (dd, *J* = 252.8, 4.5 Hz, 1C), 156.83 (dd, *J* = 252.0, 6.2 Hz, 1C), 137.04 (s, 1C), 135.14 (s, 1C), 135.07 (s, 1C), 135.06 (d, *J* = 1.3 Hz, 1C), 135.06 (s, 1C), 135.00 (s, 1C), 134.23 (s, 1C), 132.59 (s, 1C), 129.93 (s, 1C), 125.81 (s, 1C), 115.25 (s, 1C), 112.89 (dd, *J* = 22.8, 4.2 Hz, 1C), 106.70 (t, *J* = 20.7 Hz, 1C), 104.44 (dd, *J* = 21.8, 4.3 Hz, 1C) ppm; IR: ν 3092, 2915, 2848, 1558, 1497, 1471, 1327, 1267, 1216, 1090, 1015, 999, 959 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_8BrCl_2F_2N_2$ [M + H]$^+$ 402.9216, found 402.9217.

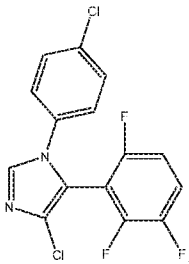
Example 96: 2-chloro-1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



ASC-II-116 f1

[00268] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.406 g, 1.316 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a brown solid (0.220 g, 0.641 mmol, 5% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 (d, *J* = 8.6 Hz, 2H), 7.22 (s, 1H), 7.16–7.08 (m, 3H), 6.81–6.76 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 155.76 (dt, *J* = 247.8, 3.0 Hz, 1C), 148.33 (ddd, *J* = 252.7, 14.5, 6.2 Hz, 1C), 147.14 (ddd, *J* = 246.7, 13.0, 3.7 Hz, 1C), 135.73 (s, 1C), 134.93 (s, 1C), 133.32 (s, 1C), 130.74 (s, 1C), 130.06 (s, 1C), 129.72 (s, 1C), 128.59 (s, 1C), 121.62 (s, 1C), 118.53–118.29 (m, 1C), 111.11 (ddd, *J* = 24.5, 6.5, 4.4 Hz, 1C), 108.71 (dd, *J* = 21.7, 15.9 Hz, 1C) ppm; IR: ν 3092, 3058, 2924, 2857, 1496, 1461, 1433, 1318, 1235, 1094 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_8Cl_2F_3N_2$ [M + H]$^+$ 343.0017, found 343.0007.

Example 97: 4-chloro-1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole

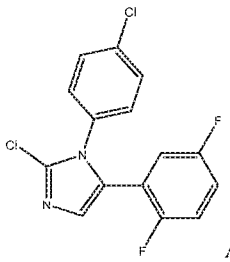


ASC-II-116 f2

[00269] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.406 g, 1.316 mmol), purification by automated flash chromatography

(hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a beige solid (0.244 g, 0.711 mmol, 55% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.69 (s, 1H), 7.33–7.31 (m, 2H), 7.18 (qd, J = 9.1, 5.0 Hz, 1H), 7.09–7.07 (m, 2H), 6.85-6.80 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 155.66 (dt, J = 248.9, 2.9 Hz, 1C), 148.20 (ddd, J = 253.9, 14.4, 6.4 Hz, 1C), 147.08 (ddd, J = 246.5, 12.7, 3.7 Hz, 1C), 137.12 (s, 1C), 135.02 (s, 1C), 134.27 (s, 1C), 132.63 (s, 1C), 129.92 (s, 1C), 125.83 (s, 1C), 118.88 (dd, J = 19.6, 9.5 Hz, 1C), 115.11 (d, J = 1.9 Hz, 1C), 111.25 (ddd, J = 24.1, 6.5, 4.4 Hz, 1C), 107.09 (dd, J = 21.5, 15.8 Hz, 1C) ppm; IR: ν 3054, 2987, 2924, 2852, 1499, 1265, 739, 704 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_8Cl_2F_3N_2$ [M + H]$^+$ 343.0017, found 343.0005.

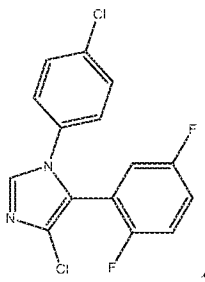
Example 98: 2-chloro-1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole



ASC-II-123 f1

[00270] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (0.300 g, 1.03 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 50:50) afforded the title compound as a yellow solid (0.010 g, 0.031 mmol, 3% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.41–7.38 (m, 2H), 7.22 (s, 1H), 7.15–7.12 (m, 2H), 6.98–6.94 (m, 2H), 6.81–6.77 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.39 (dd, J = 245.6, 4.0 Hz), 155.71 (dd, J = 247.1, 3.7 Hz), 135.57 (s), 134.62 (s), 133.73 (s), 129.79 (s), 129.68 (d, J = 2.8 Hz), 128.87 (s), 128.49 (s), 118.43 (dd, J = 16.0, 10.3 Hz), 117.45–116.90 (m) ppm; IR: ν 3071, 2932, 2857, 1495 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ [M + H]$^+$ 325.0111, found 325.0110.

Example 99: 4-chloro-1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole

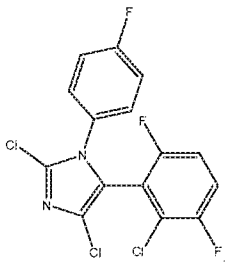


ASC-II-123 f2

[00271] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,5-difluorophenyl)-1*H*-imidazole (0.300 g, 1.03 mmol), purification by automated flash chromatography (hexanes/ethyl

acetate 100:0 to 50:50) afforded the title compound as a yellow solid (0.030 g, 0.092 mmol, 9% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.64 (s, 1H), 7.35–7.33 (m, 2H), 7.10–7.03 (m, 4H), 6.96 (td, J = 8.8, 4.5 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.48 (dd, J = 244.1, 2.0 Hz), 155.77 (dd, J = 246.1, 1.7 Hz), 144.02 (s), 136.41 (s), 134.84 (s), 134.79 (s), 131.12 (s), 129.97 (s), 129.80 (s), 129.45 (s), 127.34 (s), 125.83 (s), 123.07 (s), 121.05 (s), 118.61 (dd, J = 24.9, 2.7 Hz), 117.94 (dd, J = 24.0, 8.5 Hz), 117.36 (dd, J = 24.5, 8.9 Hz), 116.91 (dd, J = 18.1, 9.0 Hz) ppm; IR: ν 3126, 3100, 3067, 2924, 2857, 1733, 1683, 1652, 1558, 1539, 1497 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ $[M + H]^+$ 325.0111, found 325.0095.

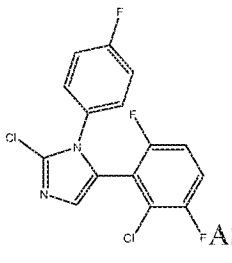
Example 100: 2,4-dichloro-5-(2-chloro-3,6-difluorophenyl)-1-(4-fluorophenyl)-1*H*-imidazole



ASC-II-138 f1

[00272] Following synthetic procedure E using 5-(2-chloro-3,6-difluorophenyl)-1-(4-fluorophenyl)-1*H*-imidazole (0.350 g, 1.13 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a yellow solid (0.015 g, 0.040 mmol, 4% yield). IR: ν 2925, 2853, 1733, 1683, 1652, 1595, 1558, 1538, 1506 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_7Cl_3F_3N_2$ $[M + H]^+$ 376.9627, found 376.9619.

Example 101: 2-chloro-5-(2-chloro-3,6-difluorophenyl)-1-(4-fluorophenyl)-1*H*-imidazole

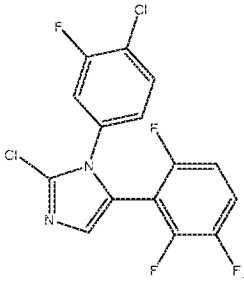


ASC-II-138 f2

[00273] Following synthetic procedure E using 5-(2-chloro-3,6-difluorophenyl)-1-(4-fluorophenyl)-1*H*-imidazole (0.350 g, 1.13 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a brown solid (0.023 g, 0.067 mmol, 6% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.19–7.15 (m, 3H), 7.11 (td, J = 8.6, 4.8 Hz, 1H), 7.05 (t, J = 8.1 Hz, 2H), 6.90 (td, J = 8.6, 4.1 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.83 (s), 161.84 (s), 156.99 (dd, J = 247.2, 2.7 Hz), 154.83 (dd, J = 246.9, 3.0 Hz), 134.50 (s), 130.69 (d, J = 3.2 Hz), 130.16 (s), 129.27 (s), 129.20 (s), 124.85 (s),

123.68 (dd, J = 19.1, 3.5 Hz), 118.86 (d, J = 20.8 Hz), 118.28 (dd, J = 23.9, 9.3 Hz), 116.56 (s), 116.38 (s), 114.63 (dd, J = 25.0, 7.8 Hz) ppm; IR: ν 3079, 2928, 2852, 1733, 1683, 1652, 1558, 1539, 1511 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8Cl_2F_3N_2$ $[M + H]^+$ 343.0017, found 343.0027.

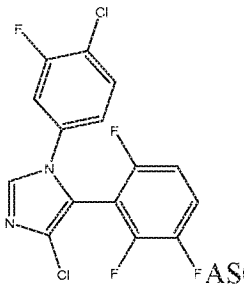
Example 102: 2-chloro-1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



ASC-II-139 f1

[00274] Following synthetic procedure E using 1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.370 g, 1.13 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a yellow solid (0.074 g, 0.205 mmol, 18% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.42 (t, J = 8.1 Hz, 1H), 7.21 (s, 1H), 7.14 (qd, J = 9.0, 5.0 Hz, 1H), 7.05 (dd, J = 8.8, 2.3 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.81 (tdd, J = 8.7, 3.3, 1.9 Hz, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 157.84 (d, J = 252.4 Hz), 155.60 (dt, J = 248.0, 2.9 Hz), 148.19 (ddd, J = 253.1, 14.6, 6.0 Hz), 147.11 (ddd, J = 247.0, 12.8, 3.6 Hz), 134.77 (s), 134.25 (d, J = 8.6 Hz), 131.23 (s), 131.08 (s), 123.87 (d, J = 3.8 Hz), 122.93 (s), 122.79 (s), 121.47 (d, J = 1.3 Hz), 118.53 (dd, J = 19.2, 9.9 Hz), 116.11 (d, J = 23.5 Hz), 111.23 (ddd, J = 24.4, 6.5, 4.4 Hz), 108.37 (dd, J = 21.6, 15.9 Hz) ppm; IR: ν 3094, 3058, 2932, 2860, 1587, 1494, 1459, 1426, 1313, 1238, 1074, 1009 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_7Cl_2F_4N_2$ $[M + H]^+$ 360.9922, found 360.9917.

Example 103: 4-chloro-1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole

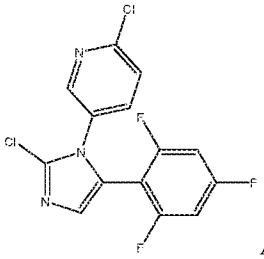


ASC-II-139 f2

[00275] Following synthetic procedure E using 1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.370 g, 1.13 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 60:40) afforded the title compound as a yellow solid (0.126 g, 0.349 mmol, 31% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.72 (s, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.22 (qd, J = 9.1, 5.0 Hz, 1H), 6.99 (dd, J = 8.8, 2.3 Hz, 1H), 6.91 (dd, J = 8.5, 1.0

Hz, 1H), 6.89–6.84 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.05 (d, J = 252.6 Hz), 155.63 (dt, J = 248.8, 2.8 Hz), 148.20 (ddd, J = 254.0, 14.4, 6.4 Hz), 147.17 (ddd, J = 246.9, 12.7, 3.7 Hz), 137.11 (s), 135.29 (d, J = 8.7 Hz), 133.06 (s), 131.69 (s), 122.28 (s), 122.14 (s), 121.01 (d, J = 3.8 Hz), 119.14 (dd, J = 19.9, 9.7 Hz), 115.09 (d, J = 1.5 Hz), 113.32 (d, J = 24.0 Hz), 111.42 (ddd, J = 24.1, 6.6, 4.3 Hz), 106.82 (dd, J = 21.5, 15.9 Hz) ppm; IR: ν 3126, 3096, 3058, 2915, 2848, 1497, 1266, 1225, 1197, 1004, 888, 863, 814, 738 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_7Cl_2F_4N_2$ $[M + H]^+$ 360.9922, found 360.9917.

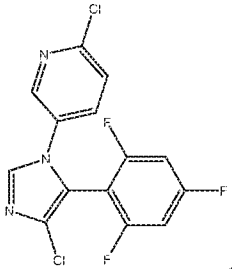
Example 104: 2-chloro-5-(2-chloro-5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine



ASC-II-159 f2

[00276] Following synthetic procedure E using 2-chloro-5-(5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (0.304 g, 0.98 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a brown solid (0.051 g, 0.148 mmol, 15% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.21 (d, J = 2.5 Hz, 1H), 7.53 (dd, J = 8.4, 2.6 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.19 (s, 1H), 6.64 (t, J = 7.9 Hz, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.70 (dt, J = 253.9, 15.3 Hz), 160.80 (ddd, J = 251.9, 14.9, 8.3 Hz), 152.31 (s), 147.86 (s), 137.38 (s), 134.63 (s), 131.22 (s), 130.82 (s), 124.92 (s), 121.67 (s), 102.82 (td, J = 19.9, 4.8 Hz), 101.26–100.82 (m) ppm; IR: ν 3100, 3057, 1683, 1646, 1595, 1575 cm^{-1}; HRMS (ES$^+$) calculated for $C_{14}H_7Cl_2F_3N_3$ $[M + H]^+$ 343.9969, found 343.9970.

Example 105: 2-chloro-5-(4-chloro-5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine

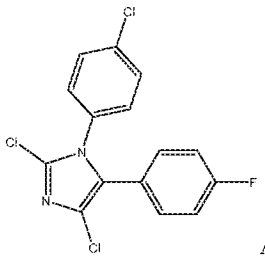


ASC-II-159 f3

[00277] Following synthetic procedure E using 2-chloro-5-(5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine (0.304 g, 0.98 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 70:30) afforded the title compound as a brown solid (0.172 g, 0.500 mmol, 51% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.24 (d, J = 2.7 Hz, 1H), 7.71 (s, 1H),

7.47 (dd, J = 8.4, 2.6 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 6.71 (t, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 164.22 (dt, J = 254.5, 15.2 Hz), 160.97 (ddd, J = 253.1, 15.1, 8.4 Hz), 151.97 (s), 145.53 (s), 136.91 (s), 134.87 (s), 133.36 (s), 131.72 (s), 125.18 (s), 115.41 (s), 101.48–101.04 (m) ppm; IR: ν 3100, 3058, 1646, 1599, 1575, 1558 cm^{-1}; HRMS (ES$^+$) calculated for $C_{14}H_7Cl_2F_3N_3$ [M + H]$^+$ 343.9969, found 343.9976.

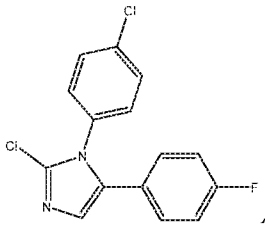
Example 106: 2,4-dichloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole



ASC-II-160 f1

[00278] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (0.124 g, 0.455 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a white solid (0.008 g, 0.023 mmol, 5% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.41–7.38 (m, 2H), 7.15–7.08 (m, 4H), 7.01–6.96 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.71 (d, J = 249.9 Hz), 135.88 (s), 133.44 (s), 131.61 (s), 131.55 (s), 131.46 (s), 130.02 (s), 129.20 (s), 128.98 (s), 127.34 (s), 123.20 (s), 123.17 (s), 116.05 (s), 115.87 (s) ppm; IR: ν 2924, 2852, 1683, 1652, 1558, 1496 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_3FN_2$ [M + H]$^+$ 340.9815, found 340.9803.

Example 107: 2-chloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole

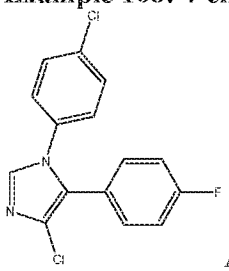


ASC-II-160 f2

[00279] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (0.124 g, 0.455 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a yellow solid (0.009 g, 0.029 mmol, 7% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.58 (s, 1H), 7.37–7.31 (m, 5H), 7.20–7.19 (m, 2H), 7.06 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.62 (d, J = 249.6 Hz), 135.75 (s), 135.01 (s), 134.79 (s), 134.58 (s), 131.70 (d, J = 8.3 Hz), 130.05 (s), 129.94 (s), 129.81 (s), 128.65 (s), 128.49 (s), 127.38 (s), 126.69 (s), 126.66 (s), 116.02 (s), 115.84 (s) ppm;

IR: ν 3067, 2924, 2852, 1562, 1496 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_{10}Cl_2FN_2$ $[M + H]^+$ 307.0205, found 307.0210.

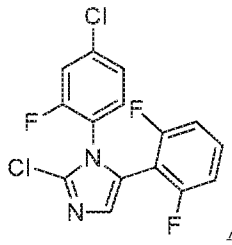
Example 108: 4-chloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole



ASC-II-160 f3

[00280] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (0.124 g, 0.455 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a white solid (0.060 g, 0.195 mmol, 43% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.57 (s, 1H), 7.36–7.33 (m, 2H), 7.18–7.15 (m, 2H), 7.06–6.99 (m, 4H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.58 (d, J = 249.6 Hz), 135.74 (s), 134.73 (d, J = 3.7 Hz), 131.66 (d, J = 8.2 Hz), 129.99 (s), 129.33 (s), 126.66 (s), 126.23 (s), 123.39 (d, J = 3.4 Hz), 115.96 (s), 115.78 (s) ppm; IR: ν 3117, 3062, 2962, 2916, 2848, 1683, 1652, 1599, 1575, 1558, 1497 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_{10}Cl_2FN_2$ $[M + H]^+$ 307.0205, found 307.0206.

Example 109: 2-chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole

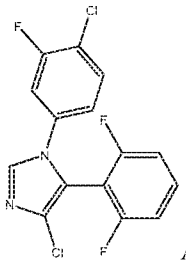


ASC-II-166 f2

[00281] Following synthetic procedure E using 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.351 g, 1.14 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a yellow solid (0.025 g, 0.073 mmol, 6% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.58 (s, 1H), 7.37–7.31 (m, 5H), 7.20–7.19 (m, 2H), 7.06 (d, J = 8.0 Hz, 2H) ppm; ^1H NMR (500 MHz; $CDCl_3$): δ 7.31–7.26 (m, 1H), 7.22 (s, 1H), 7.19 (d, J = 9.3 Hz, 1H), 7.15 (d, J = 3.1 Hz, 2H), 6.85 (t, J = 7.6 Hz, 2H) ppm; ^{13}C NMR (126 MHz; CDCl3): δ 160.60 (dd, J = 251.4, 5.9 Hz), 157.37 (d, J = 257.9 Hz), 136.78 (d, J = 9.2 Hz), 134.86 (s), 131.52 (t, J = 10.3 Hz), 130.78 (s), 130.32 (s), 125.13 (s), 125.10 (s), 122.95 (s), 121.74 (d, J = 13.0 Hz), 117.73 (d, J = 23.1 Hz), 111.69 (dd, J = 20.5, 5.0

Hz), 106.50 (t, J = 19.5 Hz) ppm; IR: ν 3104, 3071, 2936, 2860, 1683, 1652, 1634, 1587, 1558, 1538, 1505 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8Cl_2F_3N_2$ $[M + H]^+$ 343.0017, found 343.0013.

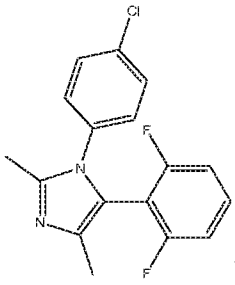
Example 110: 4-chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole



ASC-II-166 f3

[00282] Following synthetic procedure E using 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.351 g, 1.14 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a yellow solid (0.126 g, 0.367 mmol, 32% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.65 (s, 1H), 7.38–7.33 (m, 1H), 7.19–7.17 (m, 1H), 7.13 (q, J = 6.4 Hz, 2H), 6.90 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 160.74 (dd, J = 252.5, 5.9 Hz), 156.36 (d, J = 256.9 Hz), 137.49 (s), 136.16 (d, J = 9.2 Hz), 132.18 (s), 132.13 (t, J = 10.1 Hz), 128.61 (s), 125.34 (d, J = 3.7 Hz), 122.69 (d, J = 12.6 Hz), 117.87 (d, J = 22.8 Hz), 116.88 (s), 111.80 (dd, J = 20.6, 4.5 Hz), 105.04 (t, J = 19.6 Hz) ppm; IR: ν 3105, 2932, 1683, 1652, 1634, 1590, 1568, 1506 cm^{-1}; HRMS (ES^+) calculated for $C_{15}H_8Cl_2F_3N_2$ $[M + H]^+$ 343.0017, found 343.0018.

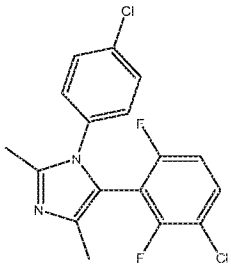
Example 111: 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-2,4-dimethyl-1H-imidazole



LM-I-092

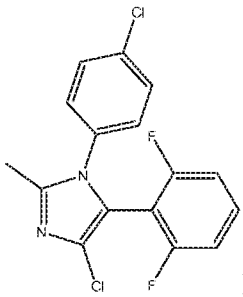
[00283] Following synthetic procedure F using 1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1*H*-imidazole (0.050 g, 0.164 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 65:35) afforded the title compound as a colorless liquid (0.025 g, 0.078 mmol, 48% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.31–7.27 (m, 2H), 7.25–7.19 (m, 1H), 7.06–7.01 (m, 2H), 6.81 (t, J = 7.7 Hz, 2H), 2.29 (s, 3H), 2.14 (s, 3H) ppm; HRMS (ES^+) calculated for $C_{17}H_{14}ClF_2N_2$ $[M + H]^+$ 319.0814, found 319.0807.

Example 112: 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-2,4-dimethyl-1H-imidazole


LM-I-098

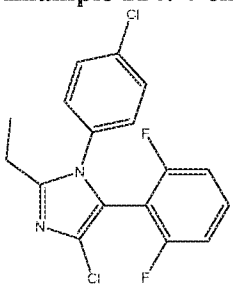
[00284] Following synthetic procedure F using 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-4-methyl-1*H*-imidazole (0.050 g, 0.147 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 60:40) afforded the title compound as an orange solid (0.029 g, 0.082 mmol, 56% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.31 (dd, J = 8.7, 6.6 Hz, 3H), 7.03 (d, J = 8.4 Hz, 2H), 6.78 (td, J = 8.6, 1.7 Hz, 1H), 2.29 (s, 3H), 2.14 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{17}H_{13}Cl_2F_2N_2$ $[M + H]^+$ 353.0424, found 353.0413.

Example 113: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-2-methyl-1H-imidazole


LM-I-039

[00285] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.050 g, 0.154 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 80:20) afforded the title compound as a white solid (0.020 g, 0.059 mmol, 38% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36–7.28 (m, 3H), 7.08 (d, J = 8.5 Hz, 2H), 6.89–6.81 (m, 2H), 2.31 (s, 3H) ppm; HRMS (ES$^+$) calculated for $C_{16}H_{11}Cl_2F_2N_2$ $[M + H]^+$ 339.0267, found 339.0265.

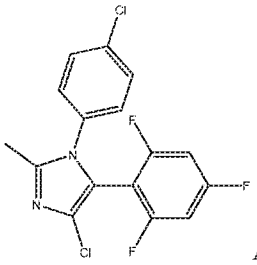
Example 114: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-2-ethyl-1H-imidazole


LM-I-041

[00286] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.040 g, 0.123 mmol), purification by flash chromatography

(silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a white solid (0.015 g, 0.042 mmol, 35% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.38–7.29 (m, 2H), 7.09 (d, J = 8.5 Hz, 2H), 6.89–6.79 (m, 2H), 2.58 (q, J = 7.5 Hz, 2H), 1.31–1.21 (m, 3H) ppm; HRMS (ES$^+$) calculated for $C_{17}H_{13}Cl_2F_2N_2$ [M + H]$^+$ 353.0424, found 353.0429.

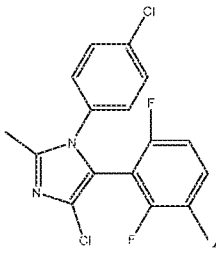
Example 115: 4-chloro-1-(4-chlorophenyl)-2-methyl-5-(2,4,6-trifluorophenyl)-1*H*-imidazole



ASC-II-098

[00287] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.290 mmol), purification by automated flash chromatography (silica gel, hexanes/ethyl acetate 90:10 to 70:30) afforded the title compound as a white solid (9 mg, 9% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.81 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.66 (t, J = 9.0 Hz, 1H), 2.12 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.87 (dt, J = 253.2, 15.3 Hz, 1C), 161.27 (ddd, J = 252.3, 15.1, 8.5 Hz, 1C), 145.85 (s, 1C), 135.65 (s, 1C), 134.21 (s, 1C), 130.25 (s, 1C), 129.96 (s, 1C), 128.37 (s, 1C), 115.30 (s, 1C), 102.36 (td, J = 20.6, 4.2 Hz, 1C), 101.05–100.60 (m, 1C), 14.02 (s, 1C) ppm; IR: ν 2962, 2927, 2852, 1644, 1585, 1495, 1442, 1400, 1122, 1038, 999 cm^{-1}. HRMS (ES$^+$) calculated for $C_{16}H_{10}Cl_2F_3N_2$ [M + H]$^+$ 357.0173, found 357.0171.

Example 116: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-2-methyl-1*H*-imidazole

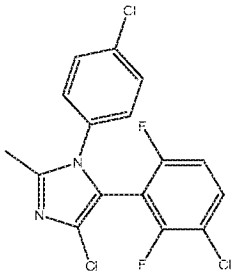


ASC-II-111

[00288] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-3-methylphenyl)-1*H*-imidazole (0.094 g, 0.276 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a brown solid (0.034 g, 0.096 mmol, 45% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.34–7.31 (m, 2H), 7.14–7.09 (m, 1H), 7.09–7.06 (m, 2H), 6.72 (td, J = 8.5, 1.2 Hz, 1H), 2.29 (s, 3H), 2.16 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.79 (ddd, J = 249.3, 13.3, 5.5 Hz, 1C), 145.40 (s, 1C),

135.13 (s, 1C), 134.50 (s, 1C), 133.00 (dd, J = 9.6, 7.1 Hz, 1C), 129.90 (s, 1C), 129.69 (s, 1C), 128.37 (s, 1C), 120.86 (dd, J = 17.9, 3.8 Hz, 1C), 116.50 (s, 1C), 110.84 (dd, J = 21.6, 4.1 Hz, 1C), 105.24 (t, J = 20.3 Hz, 1C), 14.26 (d, J = 2.9 Hz, 1C), 14.10 (s, 1C) ppm; IR: ν 3096, 3054, 2929, 2865, 1635, 1568, 1495, 1398, 1251, 1239, 1091, 1071, 1012, 998 cm-1; HRMS (ES^+) calculated for $C_{17}H_{12}Cl_2F_2N_2Na$ $[M + Na]^+$ 375.0243, found 375.0247.

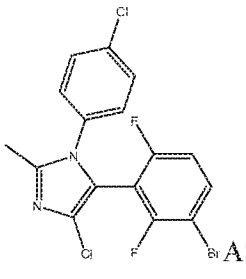
Example 117: 4-chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-2-methyl-1*H*-imidazole



ASC-II-114

[00289] Following synthetic procedure F using 4-chloro-5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1*H*-imidazole (0.078 g, 0.216 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 80:20) afforded the title compound as a brown solid (0.039 g, 0.104 mmol, 48% yield). ^1H NMR (500 MHz; $CDCl_3$): δ 7.38–7.33 (m, 3H), 7.07 (d, J = 8.6 Hz, 2H), 6.83–6.79 (m, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 159.02 (dd, J = 251.5, 4.4 Hz, 1C), 156.10 (dd, J = 252.9, 6.3 Hz, 1C), 146.08 (s, 1C), 135.50 (s, 1C), 134.14 (s, 1C), 132.05 (d, J = 9.6 Hz, 1C), 130.54 (s, 1C), 129.91 (s, 1C), 128.29 (s, 1C), 117.08 (dd, J = 18.5, 4.1 Hz, 1C), 115.24 (s, 1C), 112.19 (dd, J = 23.5, 4.4 Hz, 1C), 107.42 (t, J = 20.5 Hz, 1C), 14.06 (s, 1C) ppm; IR: ν 3100, 3071, 2928, 2848, 1558, 1495, 1465, 1399, 1495, 1465, 1399, 1338, 1287, 1242, 1219, 1092, 1011, 997 cm^{-1}; HRMS (ES^+) calculated for $C_{16}H_{10}Cl_3F_2N_2$ $[M + H]^+$ 372.9878, found 372.9864.

Example 118: 5-(3-bromo-2,6-difluorophenyl)-4-chloro-1-(4-chlorophenyl)-2-methyl-1*H*-imidazole

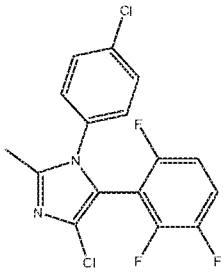


ASC-II-119

[00290] Following synthetic procedure F using 5-(3-bromo-2,6-difluorophenyl)-4-chloro-1-(4-chlorophenyl)-1*H*-imidazole (0.112 g, 0.277 mmol), purification by preparative reverse phase

HPLC afforded the title compound as a white solid (0.006 g, 0.014 mmol, 5% yield) ppm; ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.53 (ddd, J = 9.0, 7.7, 5.8 Hz, 1H), 7.39–7.36 (m, 2H), 7.09 (d, J = 8.6 Hz, 2H), 6.81-6.77 (m, 1H), 2.34 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 159.87 (dd, J = 252.4, 4.3 Hz, 1C), 157.21 (dd, J = 251.6, 6.1 Hz, 1C), 146.19 (s, 1C), 135.94 (s, 1C), 135.26 (d, J = 8.7 Hz, 1C), 133.78 (s, 1C), 130.09 (s, 1C), 128.32 (s, 1C), 115.75 (s, 1C), 112.84 (dd, J = 23.0, 3.8 Hz, 1C), 106.96 (t, J = 20.8 Hz, 1C), 104.43 (dd, J = 21.9, 4.2 Hz, 1C), 13.82 (s, 1C); IR: ν 3394, 2962, 2924, 2852, 1494, 1462, 1398, 1239, 1091 cm^{-1}; HRMS (ES$^+$) calculated for $C_{16}H_{10}BrCl_2F_2N_2$ [M + H]$^+$ 416.9372, found 416.9374.

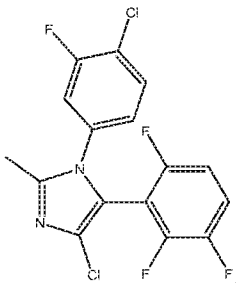
Example 119: 4-chloro-1-(4-chlorophenyl)-2-methyl-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



ASC-II-147

[00291] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.112 g, 0.277 mmol), reverse-phase HPLC purification afforded the title compound as a white solid (0.006 g, 0.017 mmol, 5% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 (d, J = 8.6 Hz, 2H), 7.22 (s, 1H), 7.16–7.08 (m, 3H), 6.81–6.76 (m, 1H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 160.09 (q, J = 39.8 Hz, 1C), 155.98 (dt, J = 248.9, 2.9 Hz, 1C), 148.56 (ddd, J = 254.2, 14.4, 6.1 Hz, 1C), 147.13 (ddd, J = 247.3, 12.7, 3.8 Hz, 1C), 146.57 (s, 1C), 136.41 (s, 1C), 133.18 (s, 1C), 130.25 (s, 1C), 128.60 (s, 1C), 128.30 (s, 1C), 119.47 (dd, J = 19.5, 9.7 Hz, 1C), 116.11 (s, 1C), 111.32 (ddd, J = 23.9, 6.3, 4.5 Hz, 1C), 106.65 (dd, J = 22.3, 15.9 Hz, 1C), 13.24 (s, 1C) ppm; IR: ν 3449, 3096, 2936, 2848, 1494, 1402, 1250, 1093, 1012, 995 cm^{-1}; HRMS (ES$^+$) calculated for $C_{16}H_{10}Cl_2F_3N_2$ [M + H]$^+$ 357.0173, found 357.0176.

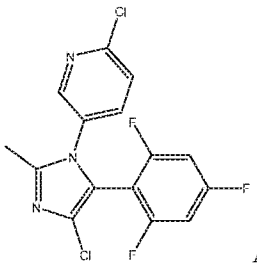
Example 120: 4-chloro-1-(4-chloro-3-fluorophenyl)-2-methyl-5-(2,3,6-trifluorophenyl)-1*H*-imidazole



ASC-II-149

[00292] Following synthetic procedure F using 4-chloro-1-(4-chloro-3-fluorophenyl)-5-(2,3,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.277 mmol), purification by automated flash chromatography (hexanes/ethyl acetate 100:0 to 90:10) afforded the title compound as a white solid (0.014 g, 0.037 mmol, 13% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.43 (t, *J* = 8.1 Hz, 1H), 7.17 (qd, *J* = 9.1, 5.0 Hz, 1H), 6.99 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.84–6.80 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 158.00 (d, *J* = 253.0 Hz), 155.94 (dt, *J* = 248.2, 3.0 Hz), 148.48 (ddd, *J* = 253.4, 14.4, 6.3 Hz), 147.17 (ddd, *J* = 244.4, 12.9, 3.8 Hz), 146.11 (s), 135.15 (d, *J* = 8.6 Hz), 131.59 (s), 130.83 (s), 123.69 (d, *J* = 3.8 Hz), 122.96 (d, *J* = 17.4 Hz), 118.97 (dd, *J* = 19.6, 9.8 Hz), 115.86 (d, *J* = 23.1 Hz), 115.23 (d, *J* = 2.1 Hz), 111.22 (ddd, *J* = 24.3, 6.7, 4.3 Hz), 107.44 (dd, *J* = 21.9, 16.1 Hz), 14.05 (s); IR: ν 1493, 1435, 1394, 1249, 1234, 1222, 1077, 1058, 997 cm^{-1}; HRMS (ES$^+$) calculated for $C_{16}H_9Cl_2F_4N_2$ [M + H]$^+$ 375.0079, found 375.0070.

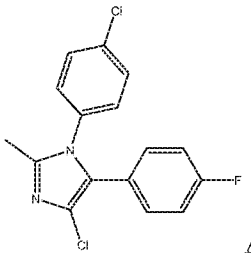
Example 121: 2-chloro-5-(4-chloro-2-methyl-5-(2,4,6-trifluorophenyl)-1*H*-imidazol-1-yl)pyridine



ASC-II-165

[00293] Following synthetic procedure F using 2-chloro-5-(4-chloro-5-(2,4,6-trifluorophenyl)-1*H*-imidazol- 1-yl)pyridine (0.120 g, 0.349 mmol), purification by reverse-phase HPLC afforded the title compound as a white solid (0.003 g, 0.008 mmol, 2% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.24 (d, *J* = 2.6 Hz, 1H), 7.48 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 6.68 (t, *J* = 8.0 Hz, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 164.28 (dt, *J* = 254.7, 15.4 Hz), 161.13 (ddd, *J* = 252.8, 15.0, 8.4 Hz), 152.78 (s), 152.31 (s), 147.82 (s), 146.34 (s), 145.63 (s), 137.11 (s), 134.97 (s), 131.20 (s), 130.32 (s), 125.31 (s), 115.88 (s), 101.21 (td, *J* = 26.1, 3.8 Hz), 13.68 (s) ppm; IR: ν 3067, 2962, 2924, 1733, 1683, 1646, 1558, 1539, 1506 cm^{-1}; HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_3N_3$ [M + H]$^+$ 358.0126, found 358.0123.

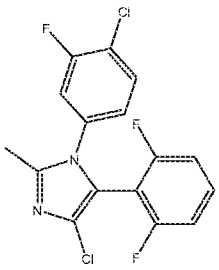
Example 122: 4-chloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-2-methyl-1*H*-imidazole



ASC-II-170

[00294] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(4-fluorophenyl)-1*H*-imidazole (0.100 g, 0.325 mmol), purification by reverse-phase HPLC afforded the title compound as a white solid (0.028 g, 0.087 mmol, 26% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.44–7.41 (m, 2H), 7.13–7.06 (m, 4H), 7.01–6.97 (m, 2H), 2.39 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.89 (d, J = 250.3 Hz), 144.67 (s), 136.16 (s), 133.60 (s), 131.66 (d, J = 8.7 Hz), 130.41 (s), 128.86 (s), 127.47 (s), 124.49 (s), 122.69 (d, J = 3.4 Hz), 116.16 (s), 115.99 (s), 13.14 (s) ppm; IR: ν 3067, 1683, 1652, 1558, 1539, 1496 cm^{-1}; HRMS (ES^+) calculated for $C_{16}H_{12}Cl_2FN_2$ $[M + H]^+$ 321.0362, found 321.0367.

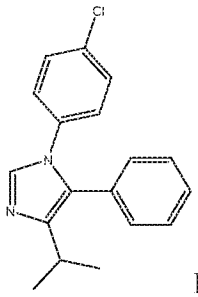
Example 123: 4-chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-2-methyl-1*H*-imidazole



ASC-II-172

[00295] Following synthetic procedure F using 4-chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1*H*-imidazole (0.100 g, 0.291 mmol), purification by preparative reverse phase HPLC afforded the title compound as a white solid (0.012 g, 0.034 mmol, 12% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.34–7.28 (m, 1H), 7.20 (dd, J = 9.3, 2.1 Hz, 1H), 7.14–7.06 (m, 2H), 6.90–6.82 (m, 2H), 2.30 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 161.91–159.82 (m), 158.30 (s), 156.25 (s), 146.33 (s), 136.66 (s), 136.59 (s), 131.93 (t, J = 10.2 Hz), 130.41 (s), 130.00 (s), 125.33 (d, J = 4.1 Hz), 122.40 (d, J = 13.1 Hz), 117.98 (s), 117.79 (s), 116.45 (s), 111.70 (ddd, J = 21.8, 18.3, 3.5 Hz), 105.46 (t, J = 19.8 Hz), 13.61 (s) ppm; IR: ν 3079, 2932, 1683, 1652, 1634, 1591, 1558, 1539, 1505 cm^{-1}; HRMS (ES^+) calculated for $C_{16}H_{10}Cl_2F_3N_2$ $[M + H]^+$ 357.0173, found 357.0175.

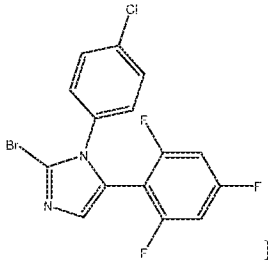
Example 124: 1-(4-chlorophenyl)-4-isopropyl-5-phenyl-1H-imidazole



LM-I-097

[00296] Following synthetic procedure D using (E)-*N*-(4-chlorophenyl)-1-phenylmethanimine (0.100 g, 0.464 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 70:30) afforded the title compound as a yellow oil (0.017 g, 0.057 mmol, 12% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.65 (s, 1H), 7.34–7.30 (m, 1H), 7.29 (q, J = 2.5, 2.0 Hz, 2H), 7.27 (s, 1H), 7.08 (dd, J = 7.5, 2.0 Hz, 2H), 7.04–6.99 (m, 2H), 2.99 (dq, J = 16.3, 9.1, 8.0 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.25 (s, 1H) ppm; HRMS (ES^+) calculated for $C_{18}H_{17}ClN_2Na$ $[M + Na]^+$ 319.0978, found 319.0971.

Example 125: 2-bromo-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole

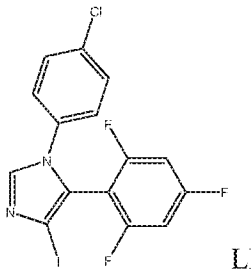


LM-I-046

[00297] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.464 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as a yellow wax (0.077 g, 0.020 mmol, 31% yield).

^{1}H NMR (500 MHz; $CDCl_3$): δ 7.39–7.33 (m, 2H), 7.21 (s, 1H), 7.14–7.09 (m, 2H), 6.65–6.57 (m, 2H) ppm; HRMS (ES^+) calculated for $C_{15}H_8BrClF_3N_2$ $[M + H]^+$ 386.9511, found 386.9504.

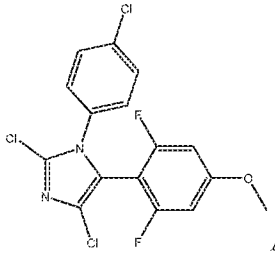
Example 126: 1-(4-chlorophenyl)-4-iodo-5-(2,4,6-trifluorophenyl)-1H-imidazole



LM-I-067

[00298] Following synthetic procedure E using 1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.100 g, 0.464 mmol), purification by flash chromatography (silica gel, hexanes/ethyl acetate 85:15) afforded the title compound as an orange solid (0.117 g, 0.269 mmol, 25% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40–7.34 (m, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.66–6.57 (m, 1H) ppm; HRMS (ES$^+$) calculated for $C_{15}H_8ClF_3IN_2$ $[M + H]^+$ 434.9373, found 434.9364.

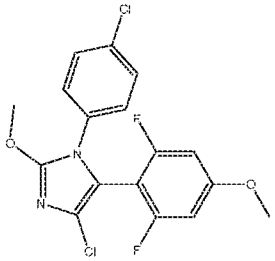
Example 127: 2,4-dichloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methoxyphenyl)-1*H*-imidazole



ASC-II-092 f2

[00299] To a solution of 2,4-dichloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.032 g, 0.085 mmol) in THF (0.53 mL) at 0 °C was added a 30% sodium methoxide solution in methanol (0.031 mL). The reaction mixture was stirred for 16 h at room temperature, then quenched with an aqueous ammonium chloride solution and extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude products were purified by preparative reverse phase HPLC to obtain the title compound as a white solid (0.011 g, 0.028 mmol, 33% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.38–7.35 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 6.41 (q, J = 7.3 Hz, 2H), 3.78 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.97 (t, J = 14.0 Hz, 1C), 161.59 (dd, J = 249.7, 9.1 Hz, 1C), 135.90 (s, 1C), 133.24 (s, 1C), 132.20 (s, 1C), 130.42 (s, 1C), 129.75 (s, 1C), 118.83 (s, 1C), 101.00 (td, J = 26.4, 3.1 Hz, 1C), 98.46–98.24 (m, 1C), 97.03 (t, J = 20.6 Hz, 1C), 56.07 (s, 1C) ppm; IR: ν 3390, 2965, 2924, 2848, 1644, 1574, 1495, 1445, 1384, 1352, 1150 cm^{-1}; HRMS (ES$^+$) calculated for $C_{16}H_{10}Cl_3F_2N_2O$ $[M + H]^+$ 388.9827, found 388.9830.

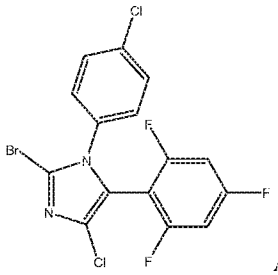
Example 128: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methoxyphenyl)-2-methoxy-1*H*-imidazole



ASC-II-092 f1

[00300] To a solution of 2,4-dichloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.032 g, 0.085 mmol) in THF (0.53 mL) at 0 °C was added a 30% sodium methoxide solution in methanol (0.031 mL). The reaction mixture was stirred for 16 h at room temperature, then quenched with an aqueous ammonium chloride solution and extracted with ethyl acetate (3x). The combined organic layers were dried (Na_2SO4), filtered, and concentrated. The crude products were purified by preparative reverse phase HPLC to obtain the title compound as a white solid (0.007 g, 0.018 mmol, 23% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.32–7.29 (m, 2H), 7.08-7.05 (m, 2H), 6.43–6.39 (m, 2H), 4.07 (s, 3H), 3.78 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.33 (t, J = 13.9 Hz, 1C), 161.65 (dd, J = 249.5, 10.1 Hz, 1C), 134.27 (s, 1C), 133.01 (s, 1C), 129.38 (s, 1C), 127.77 (s, 1C), 126.43 (s, 1C), 98.40–98.17 (m, 1C), 57.48 (s, 1C), 56.00 (s, 1C) ppm; IR: ν 2940, 2919, 2848, 1646, 1579, 1554, 1496, 1143 cm^{-1}; HRMS (ES$^+$) calculated for $C_{17}H_{13}Cl_2F_2N_2O_2$ $[M + H]^+$ 385.0322, found 385.0321.

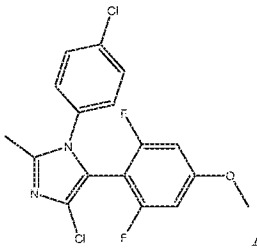
Example 129: 2-bromo-4-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole



ASC-II-095

[00301] To a solution of 4-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.050 g, 0.146 mmol) in acetonitrile (0.6 mL) was added N-bromosuccinimide (0.337 g, 0.189 mmol). The reaction mixture was heated at 80 °C for 48 h, then cooled down before dilution with ethyl acetate. The organic layer was washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The products were purified by preparative reverse phase HPLC to obtain the title compound as a white solid (0.044 g, 0.104 mmol, 71% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.37 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.67–6.62 (m, 2H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 164.22 (dt, J = 254.1, 15.2 Hz), 161.20 (ddd, J = 253.1, 15.2, 8.3 Hz), 136.26 (s), 133.81 (s), 132.00 (s), 129.84 (s), 128.84 (s), 120.41 (s), 118.81 (s), 101.66 (td, J = 20.2, 4.6 Hz), 101.18–100.73 (m) ppm; IR: ν 3100, 3062, 1683, 1645, 1597, 1575, 1558, 1539, 1494 cm^{-1}; HRMS (ES$^+$) calculated $C_{15}H_7BrCl_2F_3N_2$ $[M + H]^+$ 420.9122, found 420.9117.

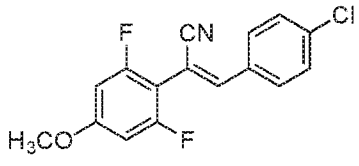
Example 130: 4-chloro-1-(4-chlorophenyl)-5-(2,6-difluoro-4-methoxyphenyl)-2-methyl-1*H*-imidazole



ASC-II-104

[00302] To a solution of 4-chloro-1-(4-chlorophenyl)-2-methyl-5-(2,4,6-trifluorophenyl)-1*H*-imidazole (0.004 g, 0.011 mmol) in THF (0.011 mL) at 0 °C was added a 30% sodium methoxide solution in methanol (0.007 mL). The reaction mixture was stirred for 19 h at room temperature, then quenched with an aqueous ammonium chloride solution and extracted with ethyl acetate (3x). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude products were purified by preparative reverse phase HPLC to obtain the title compound as a white solid (0.004 g, 0.011 mmol, 97% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 6.41 (d, J = 9.1 Hz, 2H), 3.78 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 163.04 (t, J = 14.0 Hz), 161.61 (dd, J = 249.5, 8.9 Hz), 145.57 (s), 136.11 (s), 133.46 (s), 130.11 (s), 129.90 (s), 128.65 (s), 128.38 (s), 127.63 (s), 117.32 (s), 98.38 (d, J = 28.0 Hz), 96.57 (t, J = 20.8 Hz), 56.09 (s), 13.37 (s) ppm; IR: ν 2962, 2928, 2852, 1646, 1575, 1494, 1448, 1152 cm^{-1}; HRMS (ES$^+$) calculated for $C_{17}H_{13}Cl_2F_2N_2O$ [M + H]$^+$ 369.0373, found 369.0374.

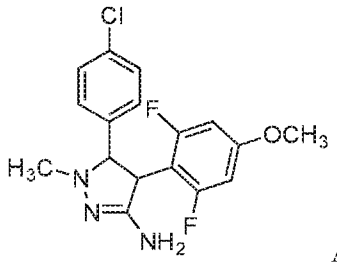
Example 131: 3-(4-chlorophenyl)-2-(2,6-difluoro-4-methoxyphenyl)acrylonitrile



ASC-II-062

[00303] In a microwave vial, potassium carbonate (0.546 g, 3.95 mmol) was added to a solution of (2,4,6-trifluorophenyl)-acetonitrile (0.558 g, 3.26 mmol) and 4-chlorobenzaldehyde (0.457 g, 3.26 mmol) in methanol (7 mL). The reaction mixture was heated to reflux for 16 h, cooled, poured into H_2O and filtered. The solid was washed twice with H_2O and twice with hexane, and dried under vacuum to obtain the mixture of E and Z isomers of the title compound as a solid (0.644 g, 2.11 mmol, 65% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.83–7.81 (m, J = 8.6, 1.8 Hz, 2H), 7.45–7.43 (m, 2H), 7.22 (s, 0.8H), 7.13 (s, 0.2H), 6.58–6.53 (m, 2H), 3.90 (s, 0.8H), 3.84 (s, 2.2H) ppm.

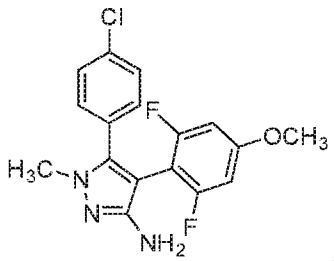
Example 132: 5-(4-chlorophenyl)-4-(2,6-difluoro-4-methoxyphenyl)-1-methyl-4,5-dihydro-1H-pyrazol-3-amine



ASC-II-063

[00304] To a solution of 3-(4-chlorophenyl)-2-(2,6-difluoro-4-methoxyphenyl)acrylonitrile (0.08 g, 0.26 mmol) in methanol (1.6 mL), triethylamine (0.036 mL, 0.26 mmol) and methylhydrazine (0.137 mL, 2.6 mmol) were added consecutively. The reaction mixture was heated to reflux for 72 h, then cooled and concentrated under reduced pressure to obtain the title compound as a crude mixture.

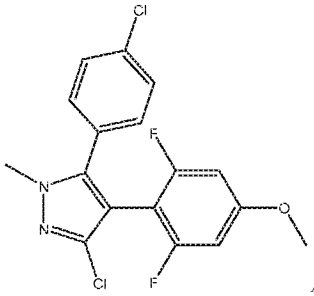
Example 133: 5-(4-chlorophenyl)-4-(2,6-difluoro-4-methoxyphenyl)-1-methyl-1H-pyrazol-3-amine



ASC-II-065

[00305] To a solution of 5-(4-chlorophenyl)-4-(2,6-difluoro-4-methoxyphenyl)-1-methyl-4,5-dihydro-1H-pyrazol-3-amine (0.114 g, 0.325 mmol) in chloroform (2.5 mL) at 0°C, was added MnO_2 (0.141 g, 1.625 mmol). The reaction mixture was stirred at 0 °C for 30 minutes, then at room temperature for 4h, and subsequently diluted with ethyl acetate and filtered over Celite. The filtrate was concentrated under reduced pressure and the residue was purified by preparative reverse phase HPLC to obtain the title compound as a white solid (0.008 g, 0.023 mmol, 8% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 9.3 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H) ppm.

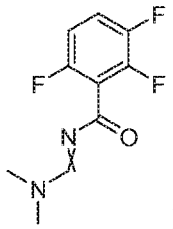
Example 134: 3-chloro-5-(4-chlorophenyl)-4-(2,6-difluoro-4-methoxyphenyl)-1-methyl-1*H*-pyrazole



ASC-II-091

[00306] 5-(4-chlorophenyl)-4-(2,6-difluoro-4-methoxyphenyl)-1-methyl-1*H*-pyrazol-3-amine (0.019 g, 0.05 mmol) was dissolved in concentrated HCl (0.16 mL) and cooled to 0 °C. A solution of $NaNO_2$ (3.45 mg, 0.05 mmol) in H_2O (0.029 mL) was then added dropwise. A solution of CuCl (4.95 mg, 0.05 mmol) in concentrated HCl (0.087 mL) was added and the reaction mixture was heated to 60 °C for 30 minutes, then the reaction mixture was cooled down and neutralized by the addition of 2N NaOH and diluted with ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate (3x) and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by preparative reverse phase HPLC to obtain the title compound as a white solid (0.001 g, 0.003 mmol, 6% yield). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.36 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.45–6.42 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H) ppm; ^{13}C NMR (126 MHz; $CDCl_3$): δ 162.53–160.49 (dd, J = 248.2, 8.8 Hz, 1C), 161.28 (t, J = 14.0 Hz, 1C), 143.41 (s, 1C), 139.44 (s, 1C), 135.64 (s, 1C), 130.66 (s, 1C), 129.25 (s, 1C), 127.62 (s, 1C), 106.78 (s, 1C), 98.28–98.05 (m, 1C), 55.92 (s, 1C), 37.91 (s, 1C) ppm; IR: ν 2922, 2848, 1646, 1575, 1558, 1390, 1196, 1145 cm^{-1}. HRMS (ES^+) calculated for $C_{17}H_{13}Cl_2F_2N_2O$ $[M + H]^+$ 369.04, found 368.96.

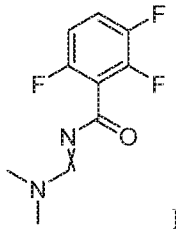
Example 135: N-((dimethylamino)methylene)-2,3,6-trifluorobenzamide



KO-I-061

[00307] To a solution of 2,3,6-trifluorobenzamide (450 mg, 2.57 mmol, 1.00 equiv.) in toluene (3.10 mL) was added DMA-DMF (1.02 mL, 7.71 mmol, 3.00 equiv.). The reaction was heated at reflux for 2 h. Then, the reaction was concentrated under reduce pressure to give without further purification the title compound as brown oil (592 mg, 2.57 mmol, 100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.06 – 7.00 (m, 1H), 6.78 – 6.73 (m, 1H), 3.12 (s, 3H), 3.04 (s, 3H).

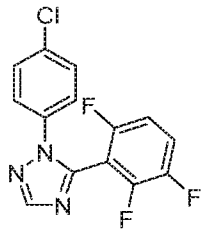
Example 136: 3-chloro-N-((dimethylamino)methylene)-2,6-difluorobenzamide



KO-I-102

[00308] To a solution of 2,3,6-trifluorobenzamide (450 mg, 2.34 mmol, 1.00 equiv.) in toluene (3.00 mL) was added DMA-DMF (0.936 mL, 7.05 mmol, 3.00 equiv.). The reaction was heated at reflux for 2 h. Then, the reaction was concentrated under reduce pressure. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 30:70) to obtain the title compound as white solid (402 mg, 1.630 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.32 – 7.27 (m, 1H), 6.85 – 6.81 (m, 1H), 3.16 (s, 3H), 3.09 (s, 3H).

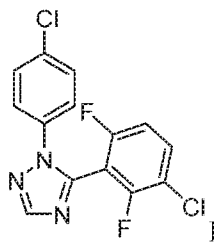
Example 137: 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)-1H-1,2,4-triazole



KO-I-062

[00309] To a solution of N-((dimethylamino)methylene)-2,3,6-trifluorobenzamide (250 mg, 1.43 mmol, 1.00 equiv.) in 1,4-dioxane (1.20 mL) and acetic acid (2.38 mL) was added (4-chlorophenyl)hydrazine hydrochloride (255 mg, 1.43 mmol, 1.00 equiv.) and stirred for 20 h at 90 °C. The mixture was concentrated under reduced pressure. Water was added and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 85:15) to obtain the title compound as orange solid (98 mg, 0.317 mmol, 22%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.30 – 7.23 (m, 3H), 6.89 (t, J = 8.1 Hz, 1H). HRMS (ES^+) calculated for $C_{14}H_8ClF_3N_3$ $[M + H]^+$ 310.0353, found 310.0367.

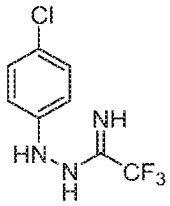
Example 138: 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1H-1,2,4-triazole



KO-I-106

[00310] To a solution of 3-chloro-N-((dimethylamino)methylene)-2,6-difluorobenzamide (300 mg, 1.22 mmol, 1.00 equiv.) in 1,4-dioxane (1.02 mL) and acetic acid (2.03 mL) was added (4-chlorophenyl)hydrazine hydrochloride (218 mg, 1.22 mmol, 1.00 equiv.) and stirred for 4 h at 90 °C. The mixture was concentrated under reduced pressure. Water was added and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 85:15) to obtain the title compound as orange solid (343 mg, 1.051 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.49 – 7.45 (m, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 6.89 (dt, J = 10.0, 9.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.51 (dd, J = 254.4, 4.3 Hz), 155.72 (dd, J = 256.0, 6.2 Hz), 152.47, 143.35, 135.57, 135.07, 133.27 (d, J = 9.6 Hz), 129.64, 124.98, 117.62 (dd, J = 17.8, 4.3 Hz), 112.65 (dd, J = 22.5, 4.2 Hz), 108.03 (t, J = 19.7 Hz). MS (ES^+): m/z = 326, 328.

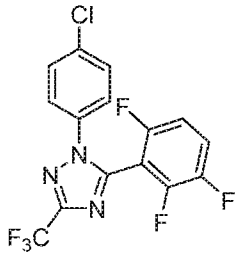
Example 139: N'-(4-chlorophenyl)-2,2,2-trifluoroacetimidohydrazide



KO-I-077

[00311] To a solution (4-chlorophenyl)hydrazine hydrochloride (1 g, 5.59 mmol, 1.00 equiv.) in MeOH/THF (1:1, 20 mL/20 mL) was added triethylamine (0.587 mL, 6.15 mmol, 1.10 equiv.). The reaction was stirred at room temperature for 30 min. Then, 2,2,2-trifluoroacetamide was added and the reaction was stirred at room temperature for 24 h. Water was added and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 80:20) to obtain the title compound as brown oil (887 mg, 3.74 mmol, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.51 (bs, 1H), 4.54 (bs, 2H).

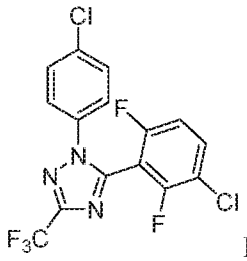
Example 140: 1-(4-chlorophenyl)-3-(trifluoromethyl)-5-(2,3,6-trifluorophenyl)-1H-1,2,4-triazole



KO-I-090

[00312] To a suspension of 2,3,6-trifluorobenzoic acid (200 mg, 1.14 mmol, 1.00 equiv.) in anhydrous dichloromethane (1.43 mL) was added oxalyl chloride (0.10 mL, 1.14 mmol, 1.00 equiv.) and a catalytic amount of dimethylformamide (9 µL, 0.114 mmol, 0.10 equiv). The reaction was stirred at reflux for 1 h. Then, the reaction was concentrated under reduce pressure. 1,4-dioxane (2.21 mL) was added, followed by the addition of triethylamine (0.160 mL, 1.14 mmol, 1.00 equiv.) and N'-(4-chlorophenyl)-2,2,2-trifluoroacetimidohydrazide (225 mg, 0.95 mmol, 0.83 equiv.). The reaction was stirred at reflux for 42 h. After that, the reaction was concentrated under reduce pressure, water was added and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 92:8) to obtain the title compound as brown oil (69 mg, 0.183 mmol, 19%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.6 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.30 (d, J = 8.6 Hz, 2H), 6.95 (dt, J = 9.0, 3.0 Hz, 1H). HRMS (ES^+) calculated for $C_{15}H_7ClF_6N_3$ [M + H] 378.0227, found 378.0239.

Example 141: 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-3-(trifluoromethyl)-1H-1,2,4-triazole



KO-I-104

[00313] To a suspension of 3-chloro-2,6-difluorobenzoic acid (300 mg, 1.56 mmol, 1.00 equiv.) in anhydrous dichloromethane (1.95 mL) was added oxalyl chloride (0.140 mL, 1.56 mmol, 1.00 equiv.) and a catalytic amount of dimethylformamide (12 µL, 0.156 mmol, 0.10 equiv). The reaction was stirred at reflux for 1 h. Then, the reaction was concentrated under reduce pressure. 1,4-dioxane (3.0 mL) was added, followed by the addition of triethylamine (0.217 mL, 1.56 mmol, 1.00 equiv.) and N'-(4-chlorophenyl)-2,2,2-trifluoroacetimidohydrazide (308 mg, 1.30 mmol, 0.83 equiv.). The reaction was stirred at reflux for 42 h. After that, the

reaction was concentrated under reduce pressure, water was added and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 95:5) to obtain the title compound as brown oil (90 mg, 0.228 mmol, 18%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.5 – 7.54 (m, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.97 (t, J = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.58 (dd, J = 255.5, 4.1 Hz), 155.86 (dd, J = 257.0, 5.9 Hz), 154.93 (q, J = 40.3 Hz), 145.39, 136.30, 134.86, 134.21 (d, J = 9.6 Hz), 130.05 , 125.31, 118.98 (q, J = 270.7 Hz), 118.00 (dd, J = 18.1, 4.9 Hz), 112.94 (dd, J = 22.3, 4.3 Hz), 106.89 (t, J = 19.5 Hz). MS (ES^+): m/z = 394

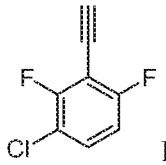
Example 142: 1-azido-4-chlorobenzene



KO-I-046

[00314] To a solution of 4-chloroaniline (1.00 g, 7.80 mmol, 1.00 equiv.) in water/Acetonitrile (1:10, 1.56 mL/ 12.48 mL) was added aqueous solution (12 M) of HCl (3.9 mL). The solution was stirred at room temperature for 10 min. Then, $NaNO_2$ (1.08 g, 15.6 mmol, 2.00 equiv) was added portion wise and the mixture was stirred at room temperature for 1h. After that, at 0°C NaN_3 was added portion wise and the reaction was stirred at 0°C for 1 h and at room temperature for 1 h. Water was added and the reaction was concentrated under reduce pressure to eliminate acetonitrile. The remaining aqueous solution was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated to give without further purification the title compound as brown solid (874 mg, 5.69 mmol, 73%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H).

Example 143: 1-chloro-3-ethynyl-2,4-difluorobenzene

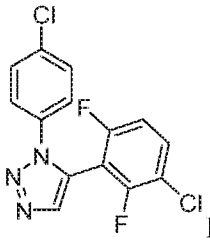


KO-I-056

[00315] To a solution of 3-chloro-2,6-difluorobenzaldehyde (301 mg, 1.71 mmol, 1.00 equiv.) and K_2CO_3 (473 mg, 3.42 mmol, 2.00 equiv.) in anhydrous MeOH (20 mL) was added dimethyl (1-diazo-2-oxopropyl)phosphonate (496 mg, 2.60 mmol, 1.5 equiv.). The reaction was stirred at room temperature for 2 h. Et_2O (40 mL) and a solution (1 M) of $NaHCO_3$ (40 mL) were added. The aqueous was extracted with Et_2O (3x). The combined organic layers were washed with

brine, dried ($MgSO_4$), filtered, and concentrated to give without further purification the title compound as white solid (281 mg, 1.63 mmol, 95%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 1H), 6.90 – 6.84 (m, 1H), 3.57 (s, 1H).

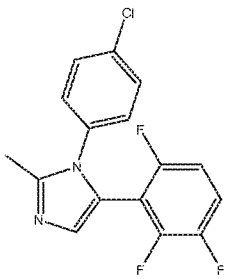
Example 144: 5-(3-chloro-2,6-difluorophenyl)-1-(4-chlorophenyl)-1H-1,2,3-triazole



KO-I-139

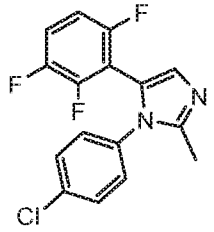
[00316] To a solution of 1-chloro-3-ethynyl-2,4-difluorobenzene (100 mg, 0.580 mmol, 1.00 equiv.) and 1-azido-4-chlorobenzene (98 mg, 0.637 mmol, 1.10 equiv.) in anhydrous DMSO (2.10 mL) was added potassium *tert*-butoxide (13 mg, 0.116, 0.20 equiv.). The reaction was stirred at room temperature for 39 h. Water was added and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (hexanes/ethyl acetate 85:15) to obtain the title compound as orange solid (47.6 mg, 0.147 mmol, 25%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.52 – 7.44 (m, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.7 Hz, 2H), 6.95 – 6.91 (m, 1H). HRMS (ES^+) calculated for $C_{14}H_8Cl_2F_2N_3$ $[M+H]^+$ 326.0058, found 326.0073.

Example 145: 1-(4-chlorophenyl)-2-methyl-5-(2,3,6-trifluorophenyl)-4H-1λ⁴-imidazole



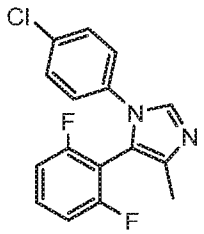
[00317] This compound was prepared using the schemes and reactions described herein.

Example 146: 1-(4-Chlorophenyl)-2-methyl-5-(2,3,6-trifluorophenyl)-1H-imidazole



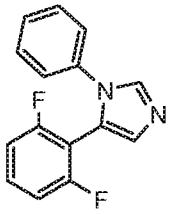
[00318] To a solution of diisopropylamine (0.02 mL, 0.146 mmol, 1.5 equiv) in THF (0.3 M) at −20 °C was added n-BuLi (2.5 M in hexanes, 0.06 mL, 0.146 mmol, 1.5 equiv), and the mixture was stirred for 10 min. A solution of 1-(4-chlorophenyl)-5-(2,3,6-trifluorophenyl)- 1H-imidazole (0.030 g, 0.097 mmol, 1 equiv) in THF (1 mL) was added, and after stirring for 30 min, methyl iodide (0.009 mL, 0.146 mmol, 1.5 equiv) was added. The mixture was stirred for 30 min at −20 °C and for 30 min at rt. H2O was added to the reaction mixture, the aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine (×3), dried over $MgSO_4$, filtered, and concentrated. The mixture was purified by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title com-pound as a yellow solid (0.009 g, 0.028 mmol, 29% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 7.19 (s, 1H), 7.11−7.04 (m, 3H), 6.78−6.73 (m, 1H), 2.34 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.73 (dt, J = 246.7, 3.2 Hz), 148.24 (ddd, J = 251.2, 14.2, 6.5 Hz), 147.45, 147.13 (ddd, J = 245.9, 13.2, 3.6 Hz), 134.95, 134.80, 130.14, 129.73, 128.32, 125.88, 119.63, 117.77−117.37 (m), 110.88 (ddd, J = 24.7, 6.9, 4.3 Hz), 109.67 (dd, J = 21.8, 16.1 Hz), 14.24 ppm. IR (KBr) ν 3098, 3061, 2961, 2924, 2850, 1641, 1494, 1402, 1237, 1093 cm^{-1}. HRMS (ES$^+$) calculated for $C_{16}H_{11}F_3N_2Cl$ $[M + H]^+$ 323.0563, found 323.0568.

Example 147: 1-(4-Chlorophenyl)-5-(2,6-difluorophenyl)-4-methyl-1H-imidazole



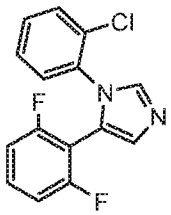
[00319] Following synthetic procedure D using (E)-N-(4-chlorophen-yl)-1-(2,6-difluorophenyl)methanimine (0.618 g, 2.46 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as an orange solid (0.292 g, 0.958 mmol, 39% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.36−7.28 (m, 1H), 7.32−7.25 (m, 2H), 7.08−7.01 (m, 2H), 6.93−6.83 (m, 2H), 2.21 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.61 (dd, J = 250.3, 6.3 Hz), 140.19, 137.61, 135.40, 133.91, 131.00 (t, J = 10.2 Hz), 129.63, 125.7, 116.13, 111.74 (dd, J = 20.1, 5.3 Hz), 107.53 (t, J = 20.0 Hz), 13.44 ppm. IR (KBr) ν 3105, 2921, 2851, 1692, 1630, 1590, 1569, 1498, 1479, 1461, 1274, 1235, 1091, 997 cm^{-1}. HRMS (ES$^+$) calculated for $C_{16}H_{12}ClF_2N_2$ $[M + H]^+$ 305.0657, found 305.0661.

Example 148: 5-(2,6-Difluorophenyl)-1-phenyl-1H-imidazole



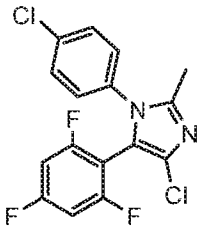
[00320] Following synthetic procedure C using (E)-1-(2,6-difluorophenyl)-N-phenyl-methanimine (0.600 g, 2.76 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as an orange solid (0.193 g, 0.753 mmol, 27% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.41−7.34 (m, 3H), 7.34 (s, 1H), 7.34−7.25 (m, 1H), 7.21−7.15 (m, 2H), 6.91−6.83 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.55 (dd, J = 250.5, 6.2 Hz), 138.99, 136.71, 132.15, 130.67 (t, J = 10.2 Hz), 129.46, 128.25, 124.59, 120.06, 111.61 (dd, J = 20.4, 5.0 Hz), 107.65 (t, J = 19.7 Hz) ppm. IR (KBr) ν 3103, 3070, 3045, 2916, 2848, 1631, 1597, 1563, 1498, 1470, 1447, 1278, 1255, 1236, 1216, 1116, 1077, 998 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_{11}F_2N_2$ $[M + H]^+$ 257.0890, found 257.0881.

Example 149: 1-(2-Chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



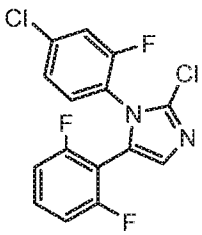
[00321] Following synthetic procedure C using (E)-N-(2-chlorophenyl)-1-(2,6-difluorophenyl)methanimine (0.600 g, 2.38 mmol), purification by silica gel column chromatography (hexanes/EtOAc 65:35) afforded the title compound as a yellow solid (0.478 g, 1.64 mmol, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.41−7.37 (m, 1H), 7.32−7.24 (m, 2H), 7.25−7.14 (m, 3H), 6.82−6.74 (m, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.49 (dd, J = 250.9, 6.1 Hz), 139.5, 134.11, 131.55, 131.53, 130.68 (t, J = 10.2 Hz), 130.54, 130.13, 129.00, 127.44, 121.01, 111.52 (dd, J = 20.3, 5.0 Hz), 107.32 (t, J = 19.4 Hz) ppm. IR (KBr) ν 3104, 3062, 1632, 1587, 1566, 1491, 1467, 1444, 1275, 1235, 1213, 1110, 1089, 1045, 999 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_{10}ClF_2N_2$ $[M + H]$+ 291.0501, found 291.0494.

Example 150: 4-Chloro-1-(4-chlorophenyl)-2-methyl-5-(2,4,6-trifluorophenyl)-1H-imidazole



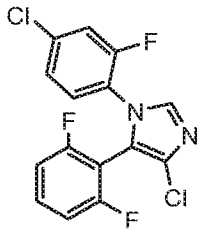
[00322] Following synthetic procedure F using 4-chloro-1-(4-chlorophenyl)-5-(2,4,6-trifluorophenyl)-1H-imidazole (0.100 g, 0.290 mmol), purification by silica gel column chromatography (hexanes/EtOAc 90:10 to 70:30) afforded the title compound as a white solid (9 mg, 9% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.66 (t, J = 9.0 Hz, 1H), 2.12 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.87 (dt, J = 253.2, 15.3 Hz, 1C), 161.27 (ddd, J = 252.3, 15.1, 8.5 Hz), 145.85, 135.65, 134.21, 130.25, 129.96, 128.37, 115.30, 102.36 (td, J = 20.6, 4.2 Hz), 101.05−100.60 (m), 14.02 ppm. IR (KBr) ν 2962, 2927, 2852, 1644, 1585, 1495, 1442, 1400, 1122, 1038, 999 cm^{-1}. HRMS (ES$^+$) calculated for $C_{16}H_{10}Cl_2F_3N_2$ $[M + H]^+$ 357.0173, found 357.0171.

Example 151: 2-Chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



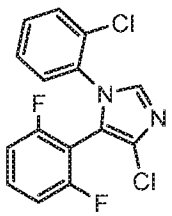
[00323] Following synthetic procedure E using 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.351 g, 1.14 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.025 g, 0.073 mmol, 6% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.26 (m, 1H), 7.22 (s, 1H), 7.19 (d, J = 9.3 Hz, 1H), 7.15 (d, J = 3.1 Hz, 2H), 6.85 (t, J =7.6 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.60 (dd, J = 251.4, 5.9 Hz), 157.37 (d, J = 257.9 Hz), 136.78 (d, J = 9.2 Hz), 134.86, 131.52 (t, J = 10.3 Hz), 130.78, 130.32, 125.13, 125.10, 122.95, 121.74 (d, J = 13.0 Hz), 117.73 (d, J = 23.1 Hz), 111.69 (dd, J = 20.5, 5.0 Hz), 106.50 (t, J = 19.5 Hz) ppm. IR (KBr) ν 3104, 3071, 2936, 2860, 1683, 1652, 1634, 1587, 1558, 1538, 1505 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_8Cl_2F_3N_2$ $[M + H]^+$ 343.0017, found 343.0013.

Example 152: 4-Chloro-1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



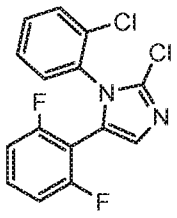
[00324] Following synthetic procedure E using 1-(4-chloro-2-fluorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.351 g, 1.14 mmol), purification by silica gel column chromatography (hexanes/EtOAc 100:0 to 80:20) afforded the title compound as a yellow solid (0.126 g, 0.367 mmol, 32% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.38−7.33 (m, 1H), 7.19−7.17 (m, 1H), 7.13 (q, J = 6.4 Hz, 2H), 6.90 (t, J = 7.8 Hz, 2H) ppm. ^{13}C NMR (126 MHz, CDCl3) δ 160.74 (dd, J = 252.5, 5.9 Hz), 156.36 (d, J = 256.9 Hz), 137.49, 136.16 (d, J =9.2 Hz), 132.18, 132.13 (t, J = 10.1 Hz), 128.61, 125.34 (d, J = 3.7 Hz), 122.69 (d, J = 12.6 Hz), 117.87 (d, J = 22.8 Hz), 116.88, 111.80 (dd, J =20.6, 4.5 Hz), 105.04 (t, J = 19.6 Hz) ppm. IR (KBr) ν 3105, 2932, 1683, 1652, 1634, 1590, 1568, 1506 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_8Cl_2F_3N_2$ [M + H]$^+$ 343.0017, found 343.0018.

Example 153: 4-Chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



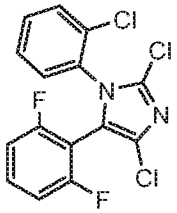
[00325] Following synthetic procedure E using 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.260 g, 0.894 mmol), purification by silica gel column chromatography (hexanes/EtOAc 75:25) afforded the title compound as a white solid (0.187 g, 0.575 mmol, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.36−7.29 (m, 2H), 7.29−7.26 (m, 2H), 6.85 (t, J = 8.6 Hz, 2H) ppm. ^{13}C NMR (126 MHz, CDCl3) δ 160.77 (dd, J = 252.5, 5.9 Hz), 137.58, 133.55, 131.88 (t, J = 10.2 Hz), 131.70, 131.67, 130.73, 130.61, 129.10, 127.60, 117.02, 111.64 (dd, J = 21.8, 3.6 Hz), 105.35 (t, J = 19.5 Hz) ppm. IR (KBr) ν 3129, 3052, 2988, 2922, 2846, 1633, 1589, 1568, 1492, 1471, 1455, 1266, 1238, 1003 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ [M + H]$^+$ 325.0111, found 325.0111.

Example 154: 2-Chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



[00326] Following synthetic procedure E using 1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.260 g, 0.894 mmol), purification by silica gel column chromatography (hexanes/EtOAc 75:25) afforded the title compound as a white solid (0.026 g, 0.080 mmol, 9% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 1H), 7.36−7.27 (m, 3H), 7.25−7.16 (m, 2H), 6.79 (t, J = 7.7 Hz, 2H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.72 (dd, J = 251.5, 5.8 Hz), 134.75, 133.21, 132.81, 131.34 (t, J = 10.2 Hz), 131.06, 130.51, 130.44, 130.32, 127.44, 122.84, 111.53 (dd, J = 20.6, 5.1 Hz), 106.87 (t, J = 19.5 Hz) ppm. IR (KBr) ν 2916, 2852, 1633, 1587, 1487, 1468, 1435, 1383, 1313, 1277, 1235, 1000 cm^{-1}. HRMS (ES$^+$) calculated for $C_{15}H_9Cl_2F_2N_2$ $[M + H]^+$ 325.0111, found 325.0119.

Example 155: 2,4-Dichloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole



[00327] Following synthetic procedure E using 4-chloro-1-(2-chlorophenyl)-5-(2,6-difluorophenyl)-1H-imidazole (0.060 g, 0.184 mmol), purification by silica gel column chromatography (hexanes/EtOAc 80:20) afforded the title compound as a white solid (0.047 g, 0.131 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 7.9 Hz, 1H), 7.40−7.27 (m, 4H), 6.88 (t, J = 8.5 Hz, 1H), 6.82 (t, J = 8.6 Hz, 1H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.07 (dd, J = 254.4, 5.9 Hz), 133.11, 133.08, 132.37 (t, J = 11.2 Hz), 131.53, 130.56, 130.39, 130.24, 130.22, 127.62, 118.89, 111.95 (dd, J = 21.7, 3.5 Hz), 111.41 (dd, J = 21.8, 3.7 Hz), 104.92 (t, J = 19.8 Hz) ppm. IR (KBr) ν 3073, 2918, 2853, 1633, 1588, 1487, 1466, 1439, 1384, 1278, 1237, 1002 cm^{-1}. HRMS (ES+) calculated for $C_{15}H_8Cl_3F_2N_2$ $[M + H]$+ 358.9721, found 358.9717.

Example 156

[00328] Compounds discussed herein were tested for microtubule activity, inhibition of cyclooxygenase-derived eicosanoid production and inhibition of 5-lipoxygenase-derived eicosanoid production activity.

[00329] QBI-293 Cell Culture

[00330] QBI-293 cells, a derivative of HEK-293 cells, were maintained in Dulbecco's Modified Eagle's Medium (Mediatech Inc, Manassas, VA, USA) containing 10% fetal bovine serum (FBS) (Atlanta Biologicals, Lawrenceville, GA, USA), 2 mM L-glutamine (Mediatech), 50 units/ml penicillin, and 50 µg/ml streptomycin (1% penicillin/streptomycin; Thermo Fisher Scientific, Waltham, MA, USA). For compound testing, cells were dissociated with trypsin/EDTA (Thermo Fisher Scientific) and plated at a density of 6 x 10^5 cells/well in 6-well plates. After overnight incubation, the medium was aspirated and fresh medium containing vehicle (DMSO) or test compound was added. Cells were maintained at 37°C in a humidified atmosphere (5% CO_2) for all experiments.

[00331] Extraction of Whole-Cell Lysates

[00332] To obtain whole-cell extracts from QBI-293 cells, cells were washed once with 1X phosphate-buffered saline (PBS), (pH 7.4) and then lysed in 200 µl RIPA buffer containing protease inhibitor cocktail (Sigma-Aldrich, St. Louis, MO), 1 mM phenylmethylsulfonyl fluoride (Sigma-Aldrich), and 1 µM Trichostatin A (Sigma-Aldrich). Lysed cells were scraped into 1.5 ml Beckman ultracentrifuge tubes (Beckman, Brea, CA, USA), briefly sonicated, and centrifuged at 100,000 x g for 30 min at 4°C. Following centrifugation, the supernatant from each sample was collected and analyzed for protein content by BCA assay.

[00333] Acetyl- and Alpha-Tubulin ELISA

[00334] For sandwich ELISA analysis of acetyl- and alpha-tubulin levels, 384-well plates were coated with 12G10 α-tubulin antibody (10 µg/ml; Covance, Princeton, NJ, USA) in 30 µl of cold 0.1 M bicarbonate buffer. 12G10 anti-α-tubulin antibody was originally deposited to the Developmental Studies Hybridoma Bank. After overnight incubation at 4°C, the plates were blocked in Block Ace solution (Bio-Rad, Hercules, CA, USA) for a minimum of 24 hours at 4°C. QBI-293 cell homogenates were diluted in C buffer (0.02 M sodium phosphate, 2 mM EDTA, 0.4 M NaCl, 1% BSA, 0.005% Thimerosal, pH 7.0). Typically two-fold dilutions from 266 ng/µl to 22.2 ng/µl total protein were prepared and 30 µl of sample were added to wells in duplicate. Plates were sealed, centrifuged, and incubated overnight at 4°C. Following incubation with antigen, wells were aspirated and washed with PBS containing 0.05% Tween-20 and 0.005% thimerosal (PBS-Tween buffer). A horseradish peroxidase (HRP)-acetyl-tubulin reporter antibody was prepared by conjugating acetyl-tubulin primary antibody (Sigma Aldrich; clone 6-11B-1) to HRP using a commercially available peroxidase labeling kit (Roche Applied Science, Indianapolis, IN, USA). The HRP-acetyl-tubulin reporter antibody (1:1,000 v/v) or pre-

conjugated HRP-alpha-tubulin (1:5,000 v/v; ProteinTech Group, Chicago, IL, USA) diluted in C buffer was added to appropriate wells (30 µl per well). The plates were sealed and incubated at room temperature for 4 hours on a platform rocker, followed by washing with PBS-Tween buffer. Peroxidase substrate solution (KPL, Gaithersburg, MD, USA) was added to each well and the reaction was quenched after 10 min with 10% phosphoric acid. Plates were read on a SpectraMax M5 plate reader at an absorbance of 450 nm. The amount of acetyl- and alpha-tubulin protein in each sample was interpolated using standard curves generated from serial dilutions of known protein standard (acetyl- or alpha-tubulin) concentrations.

[00335] Eicosanoid Measurements

[00336] Determination of 5-LOX and COX-1 inhibition by test compounds was via the utilization of an established RBL-1 cell assay (Tries et al., Inflammation research 51, 135-143, 2002). Briefly, rat basophilic leukemia (RBL-1) cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS), 50 U/mL penicillin, 0.05 mg/mL streptomycin, and 1 mM L-glutamine. For COX/LOX activity assays, RBL-1 cells were plated into 24-well plate at ~ 9 x 105 cells / well in growth media. After 2 h, cells were incubated with the test compounds at indicated concentrations at 37°C for 2 h. Following pre-incubation with the test compounds, COX/LOX product formation was induced by incubating cells with 12 µM calcium ionophore, A23187, at 37 °C for 15 min. Cell culture supernatants (200 µL/well) were then collected and extracted by adding 600 µL methanol containing 0.01% BHT (butylated hydroxytoluene). Samples were vortexed and centrifuged at 17,000 x g for 10 min. Supernatants were collected and dried under vacuum. Dried samples were dissolved in 50% acetonitrile and analyzed by LC-MS/MS. Reverse-phase HPLC was performed with a C18 column (Waters Acquity UPLC BEH, C18, 1.7 um, 2.1 x 50 mm, Milford, MA) using a gradient elution on a Waters Acquity UPLC system (Waters Corporation, Milford, MA). The mobile phase consisted of solvent A: 10 mM ammonium formate and solvent B: acetonitrile. The samples were injected using an autosampler with injection volumes of 10 µL. The flow rate was maintained at 0.6 mL/min. The column was eluted using a gradient of 5-95% solvent B over 2 min. The HPLC eluent was directly introduced into a Waters triple quadruple mass spectrometer (Waters Corporation, Milford, MA). The parent (PGD_2: 351.212 and LTB_4: 335.154) and daughter (PGD_2: 315.251 and LTB_4: 195.156) ions were detected in the multiple reaction monitoring (MRM) mode. Data for PGD_2 and LTB_4 were acquired simultaneously from a single injection. Chromatographic data were analyzed by MassLynx software (Waters corporation, Milford MA) to integrate each MRM chromatogram. The amounts of PGD_2 and LTB_4 products were

quantified using the slope intercept equation from linear standard curves of PGD_2 and LTB_4, respectively.

[00337] *Determination of Plasma and Brain Compound Concentrations*

[00338] Mouse brains were homogenized in 10 mM ammonium acetate, pH 5.7 (1:2; w/v) using a handheld sonic homogenizer. Mouse plasma was obtained from blood that was collected into a 1.5 ml tube containing 0.5M EDTA solution and which was centrifuged for 10 minutes at 4500g at 4°C. Aliquots (50 µl) of brain homogenates or plasma were mixed with 0.2 ml of acetonitrile, centrifuged at 15,000g, and the resulting supernatant was used for subsequent LC-MS/MS analysis. The LC-MS/MS system was comprised of an Aquity UPLC and a TQ MS that was controlled using MassLynx software (Waters Corporation, Milford, MA, USA). Compounds were detected using multiple reaction monitoring (MRM) of their specific collision-induced ion transitions. Samples were separated on an Aquity BEH C18 column (1.7 µm, 2.1 x 50 mm) at 35°C. Operation was in positive electrospray ionization mode, with mobile phase A of 0.1% (v/v) formic acid, and B of either acetonitrile or methanol with 0.1% (v/v) formic acid. Injections of 5 µl were separated at a flow rate of 0.6 mL/min using a gradient from 5% to 95% B over two minutes, followed by wash and re-equilibration steps. The MS was operated with a desolvation temperature of 450°C and a source temperature of 150°C. Desolvation and source nitrogen gas flows were 900 L/hr and 50 L/hr, respectively. Source and MS/MS voltages were optimized for each compound using the MassLynx auto tune utility. To account for possible matrix effects on analytes, standard curves were generated for each compound from brain homogenate and plasma samples that had compound added at 4, 40, 400 and 4000 ng/mL. The standard curve samples were extracted and analyzed in an identical fashion as the corresponding tissue-derived samples, and peak areas were plotted against concentration and a 1/x weighted linear regression curve was used to obtain estimated concentrations of the tissue-derived samples using the average peak area from triplicate injections. In all cases, the tissue-derived sample peak areas fell within the linear portion of standard curves that were prepared and analyzed concurrently with the samples.

[00339] The compounds of Examples 1-32, 132, and 133 are synthetic intermediates. The results for certain of the other compounds are set forth in Table 10.

Table 10

Example	Structure	Active Dose(s) in Acetyl-Tubulin Assay	Active Dose(s) in Alpha-Tubulin Assay	Cox/Lox % Inhibition at 10 µM

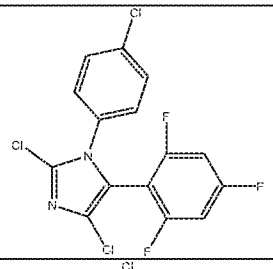
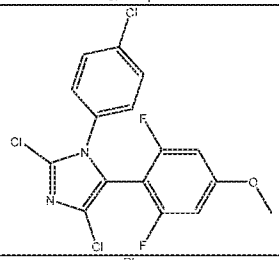
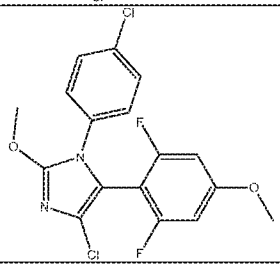
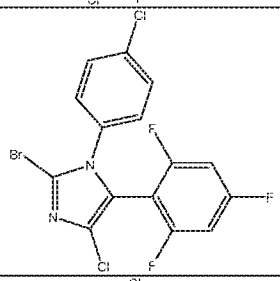
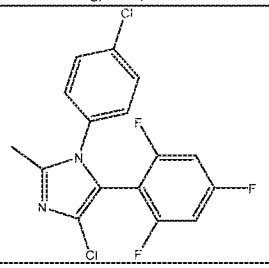
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
88		10 μM (4.2X)	< 10%	-7/48
127		1 μM (3.3X) 10 μM (2.5X)	1 μM (0.60X) 10 μM (0.26X)	12/38
128		1 μM (1.7X) 10 μM (5.2X)	10 μM (0.41X)	-25/30
129		10 μM (4.3X)	10 μM (0.76X)	-107/-34
115		10 μM (5.7X)	10 μM (0.8X)	-3/2

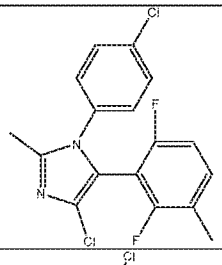
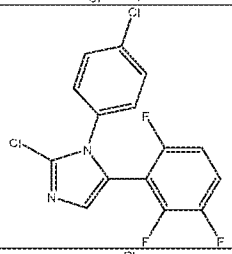
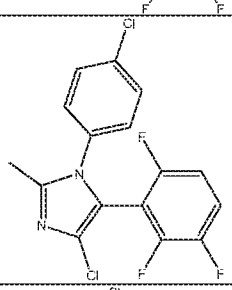
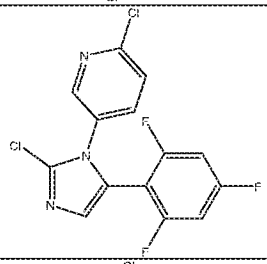
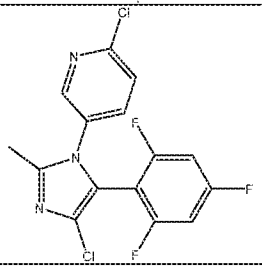
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
116		10 μM (8.5X)	10 μM (0.57X)	-29/42
96		10 μM (2.4X)	< 10%	26/24
119		1 μM (2.9X) 10 μM (5.5X)	10 μM (0.71X)	-27/47
104		10 μM (1.8X)	10 μM (0.84X)	-80/-6
121		10 μM (4.4X)	< 10%	5/26

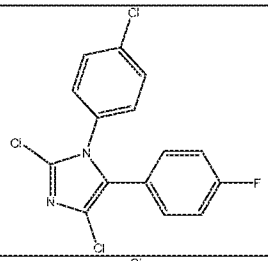
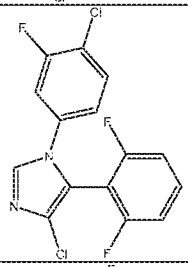
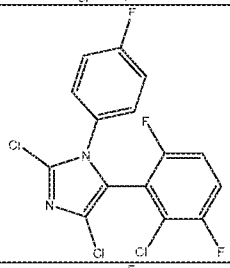
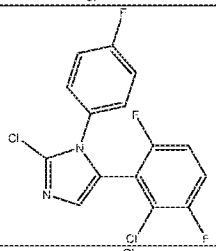
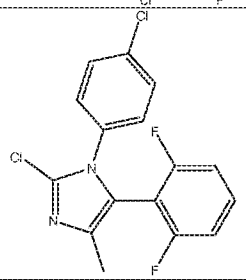
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
106		10 μM (1.6X)	< 10%	-238/-396
110		10 μM (2.6X)	< 10%	36/14
100		10 μM (2.0X)	< 10%	-136/7
101		10 μM (1.5X)	< 10%	-70/5
85		10 μM (4.11X)	-	-10/42

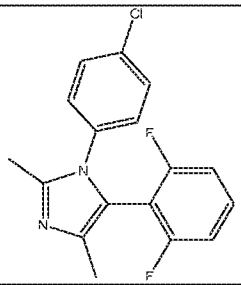
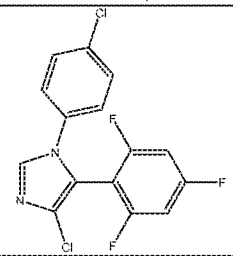
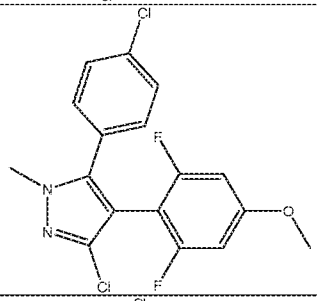
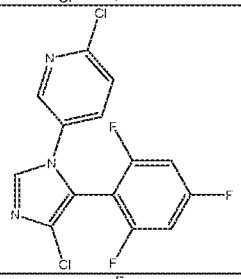
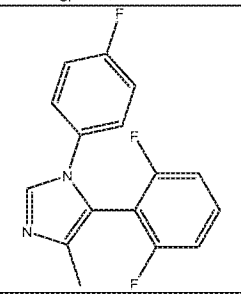
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
111		10 μM (8.30X)	1 μM (1.16X)	-1/40
87		10 μM (3.3X)	< 10%	91/46
134		10 μM (6.55X)	1 μM (0.68X) 10 μM (0.43X)	75/47
105		10 μM (1.9X)	10 μM (0.84X)	65/2
56		10 μM (1.60X)	< 10%	72/44

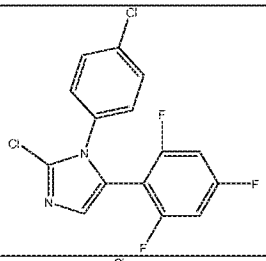
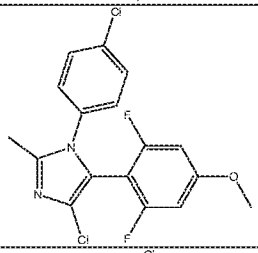
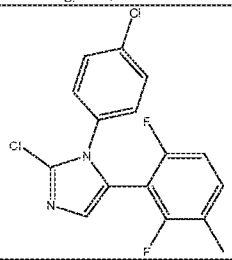
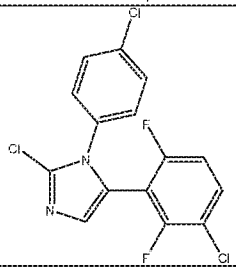
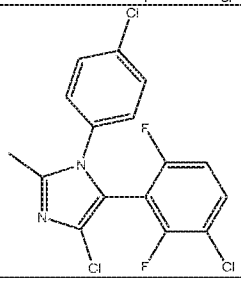
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
89		10 μM (3.1X)	100 nM (1.16X)	34/61
130		1 μM (7.1X) 10 μM (2.9X)	1 μM (0.64X) 10 μM (0.33X)	39/88
90		10 μM (2.3X)	1 μM (0.83X) 10 μM (0.85X)	0/69
92		10 μM (2.2X)	10 μM (0.77X)	-23/88
117		1 μM (1.7X) 10 μM (9.7X)	10 μM (0.58X)	34/84

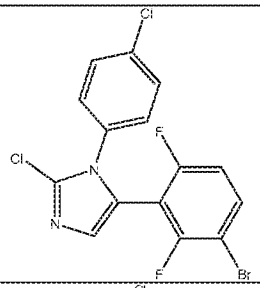
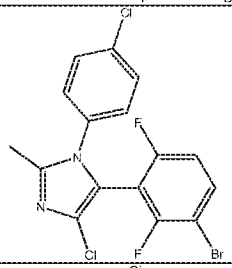
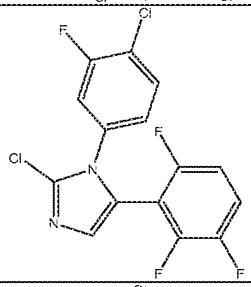
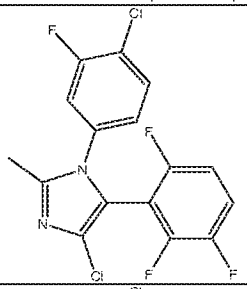
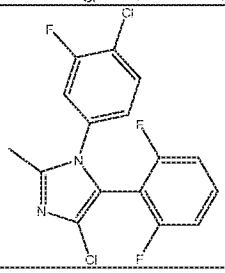
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
94		10 μM (2.0X)	< 10%	-27/65
118		10 μM (5.3X)	10 μM (0.80X)	-45/68
102		10 μM (3.2X)	< 10%	32/58
120		1 μM (3.9X) 10 μM (2.4X)	1 μM (0.83X) 10 μM (0.70X)	-3/75
123		10 μM (4.1X)	< 10%	-30/55

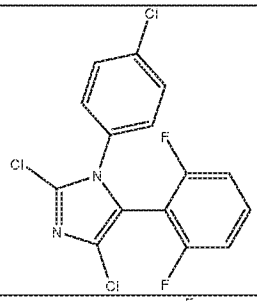
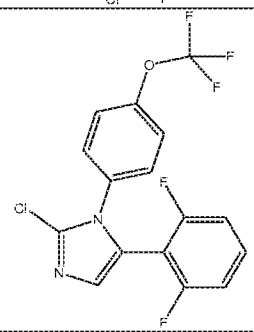
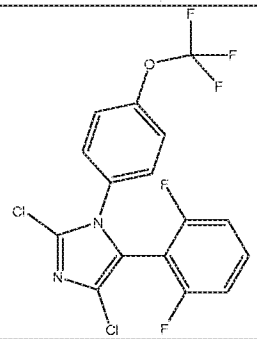
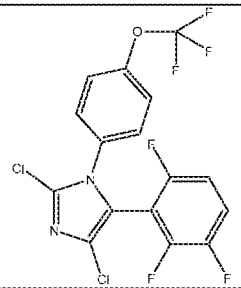
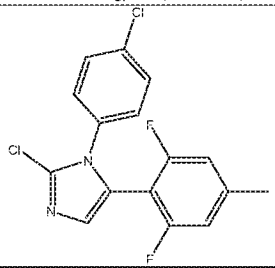
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
60		10 μM (7.7X)	10 μM (0.85X)	17/90
62		10 μM (2.15X)	< 10%	19/61
63		10 μM (6.09X)	< 10%	19/81
66		10 μM (6.31X)	< 10%	40/56
68		10 μM (5.72X)	< 10%	42/73

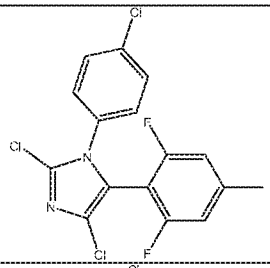
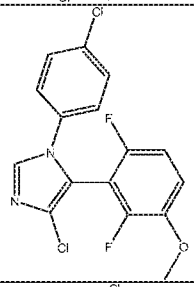
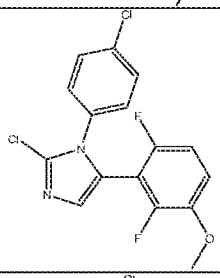
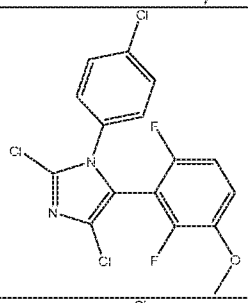
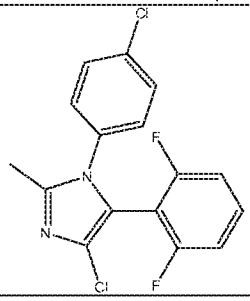
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
69		10 μM (18.25X)	10 μM (0.72X)	-10/63
70		10 μM (4.05X)	10 μM (0.80X)	48/91
71		10 μM (8.20X)	10 μM (0.62X)	-15/68
72		1 μM (5.09X) 10 μM (10.06)	1 μM (0.88X) 10 μM (0.43X)	17/88
113		1 μM (2.47X) 10 μM (15.71)	10 μM (0.84X)	45/87

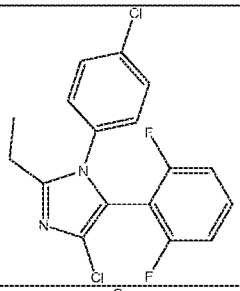
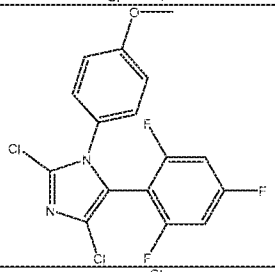
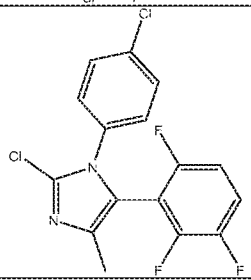
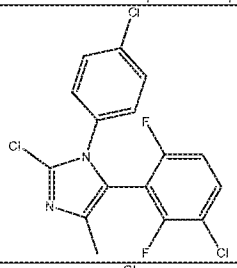
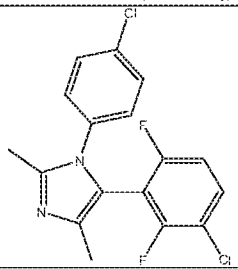
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
114		1 μM (1.75X) 10 μM (5.01)	< 10%	30/81
78		1 μM (1.95X) 10 μM (6.37X)	< 10%	31/77
84		10 μM (14.3X)	10 μM < 15%	6/58
86		10 μM (9.16X)	10 μM (0.55X)	-21/54
112		10 μM (14.18X)	< 10%	-9/51

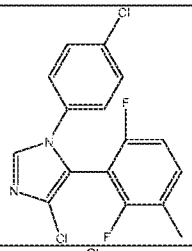
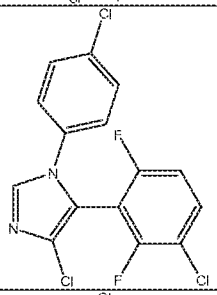
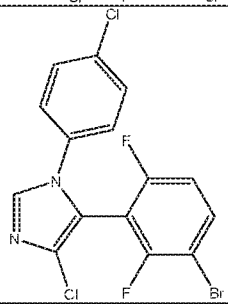
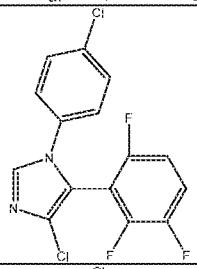
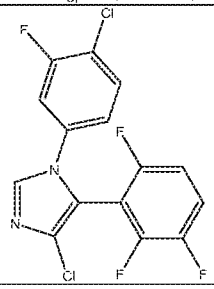
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
91		10 μM (2.2X)	10 μM (0.84X)	79/78
93		10 μM (2.4X)	< 10%	71/63
95		10 μM (2.1X)	< 10%	54/78
97		10 μM (2.0X)	< 10%	82/69
103		10 μM (1.9X)	< 10%	74/66

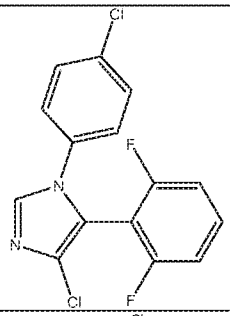
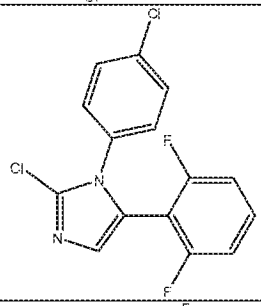
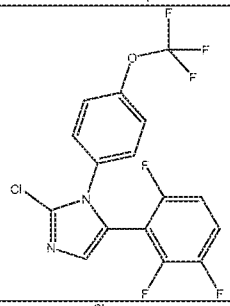
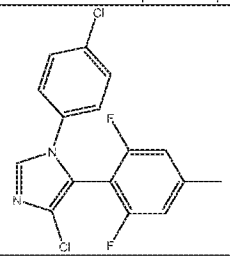
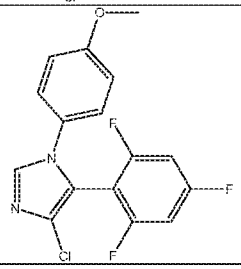
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
58		10 μM (4.0X)	< 10%	94/76
59		10 μM (4.8X)	< 10%	50/92
65		10 μM (3.43X)	< 10%	58/80
67		10 μM (3.6X)	< 10%	90/75
76		10 μM (4.13X)	< 10%	93/86

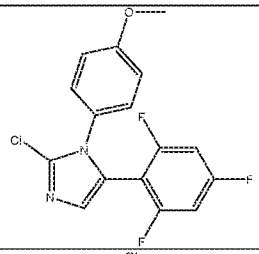
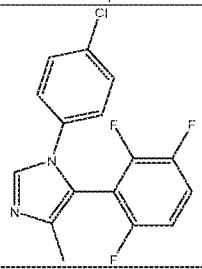
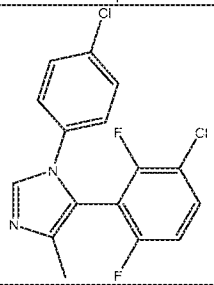
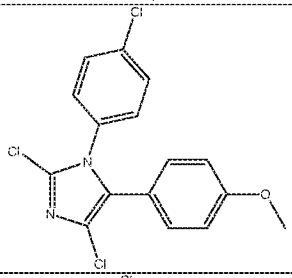
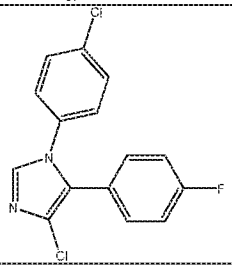
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
77		10 μM (3.44X)	< 10%	85/75
55		10 μM (3.37X)	1 μM (1.21X)	74/74
57		10 μM (3.48X)	< 10%	59/71
80		10 μM (3.21X)	< 10%	63/63
108		< 10%	< 10%	85/-59

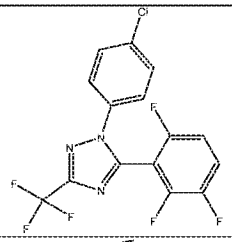
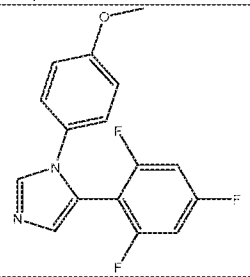
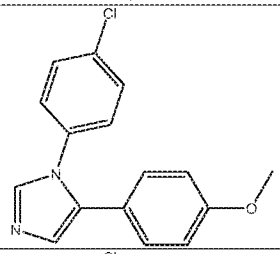
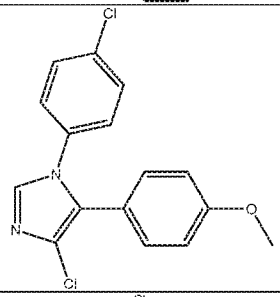
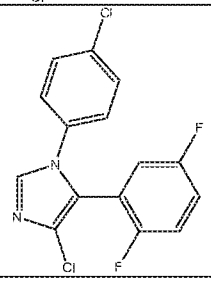
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
140		< 10%	< 10%	68/46
39		< 10%	< 10%	65/25
40		< 10%	< 10%	94/-5
79		< 10%	< 10%	95/6
99		< 10%	< 10%	46/69

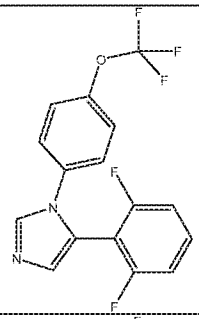
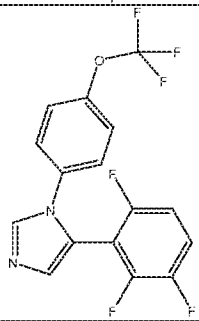
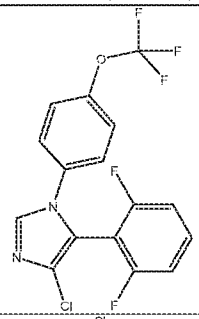
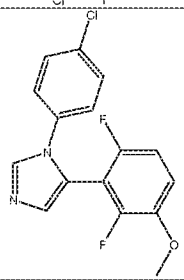
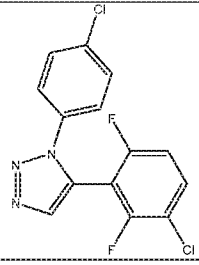
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
33		< 10%	< 10%	38/55
35		< 10%	10 μM (1.16X)	31/52
61		< 10%	< 10%	46/78
37		< 10%	< 10%	9/78
144		< 10%	< 10%	-22/64

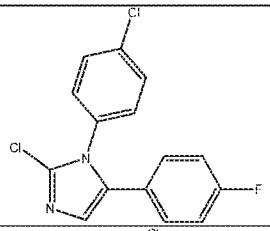
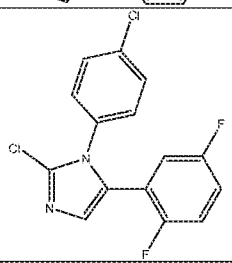
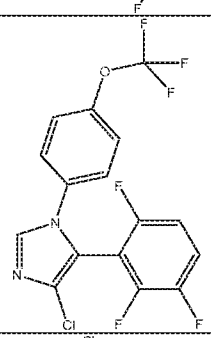
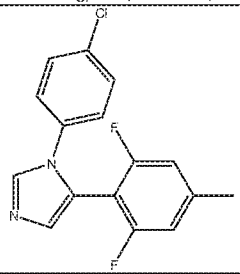
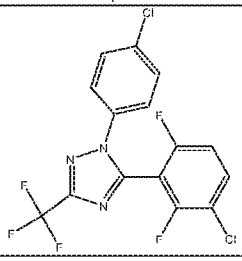
Table 10				
Example	Structure	Active Dose(s) in Acetyl-Tubulin Assay	Active Dose(s) in Alpha-Tubulin Assay	Cox/Lox % Inhibition at 10 μM
107		< 10%	< 10%	87/57
98		< 10%	< 10%	76/96
64		< 10%	< 10%	54/85
36		< 10%	< 10%	66/84
141		< 10%	< 10%	56/72

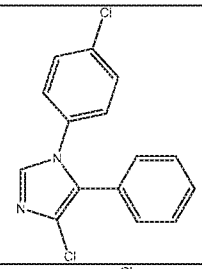
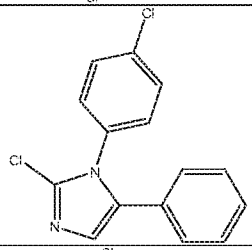
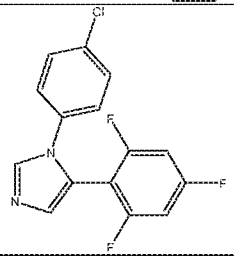
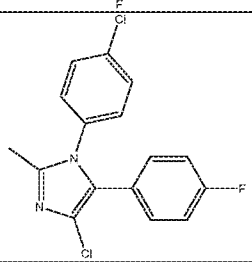
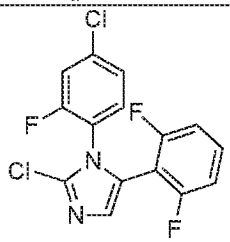
Table 10				
Example	**Structure**	**Active Dose(s) in Acetyl-Tubulin Assay**	**Active Dose(s) in Alpha-Tubulin Assay**	**Cox/Lox % Inhibition at 10 μM**
73		< 10%	< 10%	94/71
74		< 10%	10 μM (1.17X)	75/52
43		< 10%	< 10%	44/24
122		< 10%	10 μM (0.78X)	-100/-87
109		< 10%	< 10%	4/49

Table 10

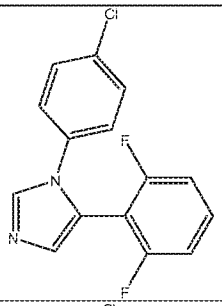
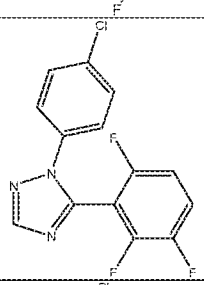
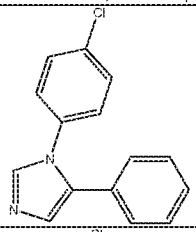
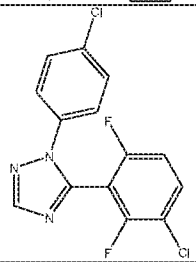
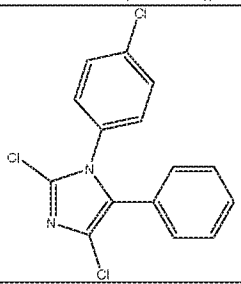
Example	Structure	Active Dose(s) in Acetyl-Tubulin Assay	Active Dose(s) in Alpha-Tubulin Assay	Cox/Lox % Inhibition at 10 μM
34		< 10%	1 μM (1.2X)	15/46
137		< 10%	< 10%	35/6
38		< 10%	< 10%	40/16
138		< 10%	< 10%	-52/-54
75		< 10%	< 10%	14/8

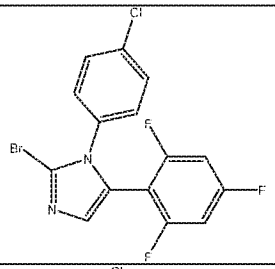
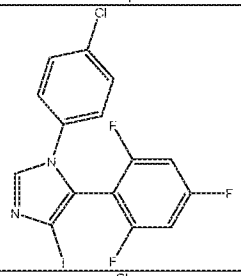
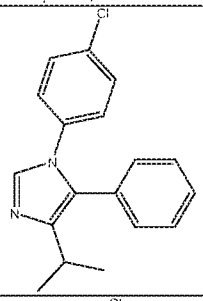
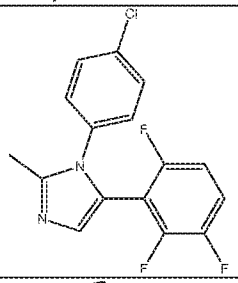
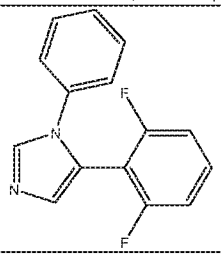
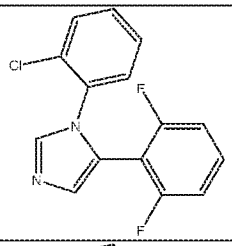
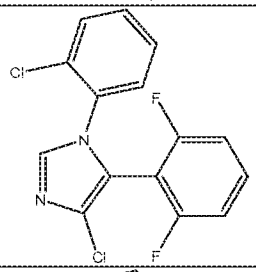
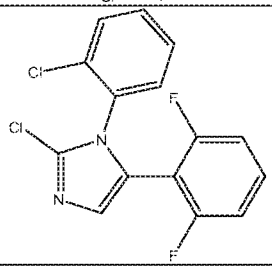
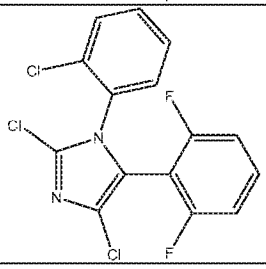
Table 10				
Example	Structure	Active Dose(s) in Acetyl-Tubulin Assay	Active Dose(s) in Alpha-Tubulin Assay	Cox/Lox % Inhibition at 10 μM
125		10 μM (2.42X)	< 10%	-
126		10 μM (1.79X)	10 μM (1.19X)	-
124		< 10%	< 10%	-
145		10 μM (4.67X)	10 μM < 15%	-
41		< 10%	< 10%	-

Table 10				
Example	Structure	Active Dose(s) in Acetyl-Tubulin Assay	Active Dose(s) in Alpha-Tubulin Assay	Cox/Lox % Inhibition at 10 μM
42		< 10%	< 10%	-
81		10 μM (3.51X)	< 10%	-
82		< 10%	< 10%	-
83		10 μM (3.75X)	< 10%	-

Example 156

[00340] (i) Chemistry

[00341] A library of imidazoles was synthesized, including 36 known compounds (compounds 2, 25, 29–31, 35, 36, 38, 43–46, 51, 54, 55, 57, 58, 61, 62, 64, 65, 67, 68, 70, 71, 73, 74, 83–86, 88, 92, 94, 95, and 97 of Table 11), most with reported antifungal activity (Lamberth, Synthesis and fungicidal activity of tubulin polymerisation promoters. Part 3: imidazoles. Bioorg. Med. Chem. 2013, 21, 127–134) or antimicrobial activity, as well as 45 new compounds (compounds 26–28, 32–34, 37, 39–42, 47–50, 52, 53, 56, 59, 60, 63, 66, 69, 72, 75–82, 87, 89–91, 93, 96, 98–104 of Table 11). In general, the synthesis of the 1,5-diarylimidazoles was conducted

following the Van Leusen imidazole synthesis. See, Van Leusen, Chemistry of sulfonylmethyl isocyanides. 12.

[00342] Base-induced cycloaddition of sulfonylmethyl isocyanides to carbon, nitrogen double bonds. Synthesis of 1,5-disubstituted and 1,4,5-trisubstituted imidazoles from aldimines and imidoyl chlorides. J. Org. Chem. 1977, 42, 1153−1159. Thus, after condensation of the appropriate aryl-amine and benzaldehyde, the resulting Schiff base (compounds 5−24 of Scheme 3) was cyclized in the presence of toluenesulfonylmethyl isocyanide (TosMIC) to form the 1,5-diarylimidazole (cmpounds 25−28, 32, 33, 37−43, and 47−53 of Scheme 3). Further derivatizations of the imidazole ring included the introduction of small alkyl groups and/or halogens in position 2 and/or 4 (compounds 29−31, 34−36, and 44−46 in Scheme 3 and compounds 54−104 in Scheme 4). Imidazole derivatives bearing a methyl substituent at C4 were accessed by employing the appropriately C-substituted TosMIC reagent during the cyclization step (compounds 29, 35, and 44), while alkylated derivatives at C2 (compounds 34 and 86) were obtained by treating the appropriate 1,5-diarylimidazole with LDA followed by addition of the desired alkyl iodide. Finally, halogenation of the imidazole ring was accomplished upon treatment with N-chlorosuccinimide. When the halogenation was carried out on imidazoles that were not substituted at C2 and C4, the reaction typically proceeded with the generation of separable mixtures of mono- and dichlorinated imidazoles.

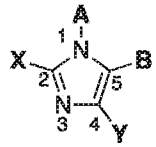


Table 11

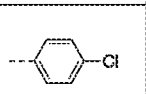
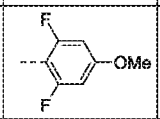
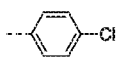
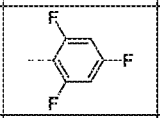
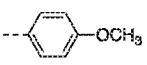
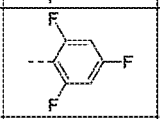
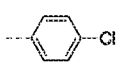
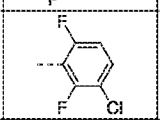
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2	Me	Cl			39	88	×7.1 (1 μM)** ×2.9 (10 μM)**	×0.6 (1 μM)** ×0.3 (10 μM)**
25	H	H			44	24	NS	NS
26	H	H			65	25	NS	NS
29	H	Me			59	71	×3.5 (10 μM)**	NS

Table 11

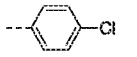
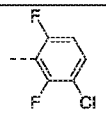
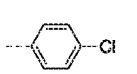
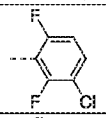
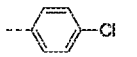
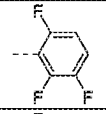
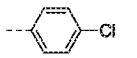
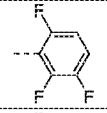
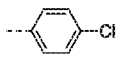
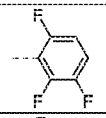
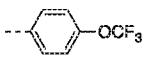
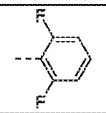
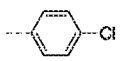
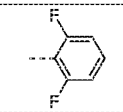
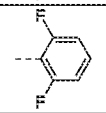
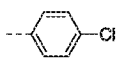
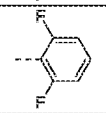
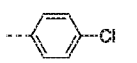
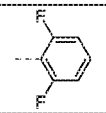
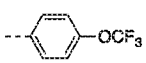
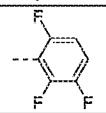
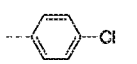
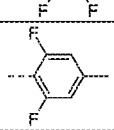
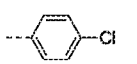
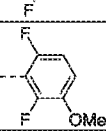
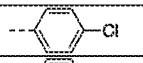
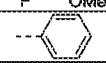
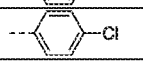
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30	Cl	Me			<10	54	×9.2 (10 μM)**	×0.5 (10 μM)**
31	Me	Me			<10	51	×14.2 (10 μM)**	NS
34	Me	H			49	45	×4.7 (10 μM)**	×0.9 (10 μM)**
35	H	Me			74	74	×3.4 (10 μM)**	×1.2 (1 μM)**
36	Cl	Me			<10	58	×14.3 (10 μM)**	NS
42	H	H			38	55	NS	NS
43	H	H			15	46	NS	×1.2 (1 μM)*
44	H	Me			72	44	×1.6 (10 μM)**	NS
45	Cl	Me			<10	42	×4.1 (10 μM)**	NS
46	Me	Me			<10	40	×8.3 (10 μM)**	×1.2 (1 μM)*
47	H	H			31	52	NS	×1.2 (10 μM)*
48	H	H			66	84	NS	NS
49	H	H			<10	78	NS	NS
50	H	H			40	16	NS	NS
51	H	H			94	<10	NS	NS

Table 11

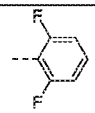
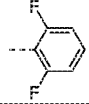
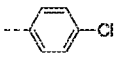
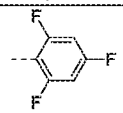
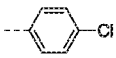
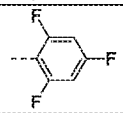
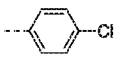
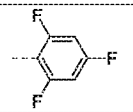
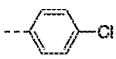
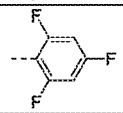
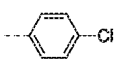
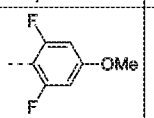
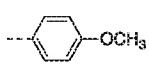
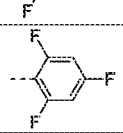
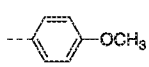
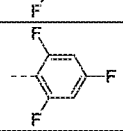
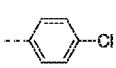
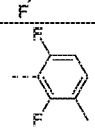
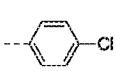
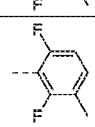
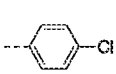
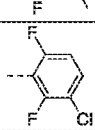
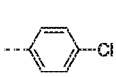
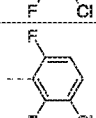
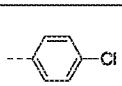
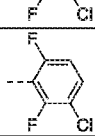
Cpd #	X	Y	Ring A	Ring B	PGD_2/E_2 % Inhibition at 10 μM[a]	LTB_4 % Inhibition at 10 μM[b]	Relative Change in AcTub[c]	Relative Change in α-Tubulin[d]
52	H	H			19	<10	NS	NS
53	H	H			24	<10	NS	NS
54	H	Cl			91	46	×3.3 (10 μM)**	NS
55	Me	Cl			<10	<10	×5.7 (10μM)**	NS
56	Cl	H			34	61	×3.1 (10 μM)**	NS
57	Cl	Cl			<10	48	×4.2 (10 μM)**	NS
58	Cl	Cl			12	38	×3.3 (1 μM)** ×2.5 (10 μM)**	×0.6 (1 μM)** ×0.3 (10 μM)**
59	H	Cl			93	86	×4.1 (10 μM)**	NS
60	Cl	H			85	75	×3.4 (10 μM)**	NS
62	H	Cl			79	78	×2.2 (10 μM)**	×0.8 (10 μM)**
63	Cl	H			<10	69	×2.3 (10 μM)**	×0.8 (1 μM)** ×0.9 (10 μM)**
64	H	Cl			71	63	×2.4 (10 μM)**	NS
65	Me	Cl			34	84	×1.7 (1 μM)** ×9.7 (10 μM)**	×0.6 (10 μM)**
66	Cl	H			<10	88	×2.2 (10 μM)**	×0.8 (10 μM)**

Table 11

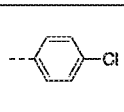
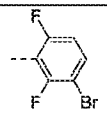
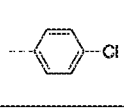
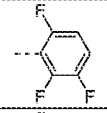
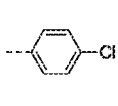
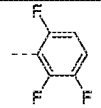
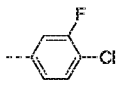
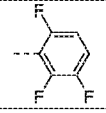
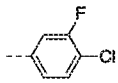
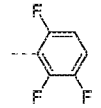
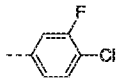
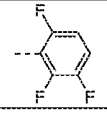
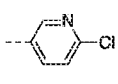
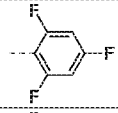
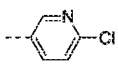
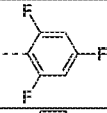
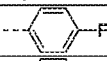
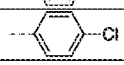
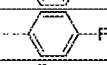
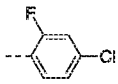
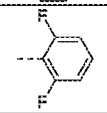
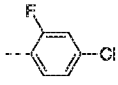
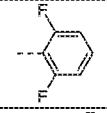
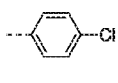
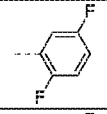
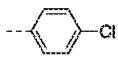
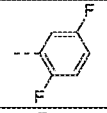
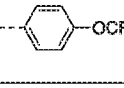
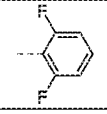
Cpd #	X	Y	Ring A	Ring B	PGD_2/E_2 % Inhibition at 10 μM[a]	LTB_4 % Inhibition at 10 μM[b]	Relative Change in AcTub[c]	Relative Change in α-Tubulin[d]
67	H	Cl			54	78	×2.1 (10 μM)**	NS
68	H	Cl			82	69	×2.0 (10 μM)**	NS
69	Cl	H			26	24	×2.4 (10 μM)**	NS
70	H	Cl			74	66	×1.9 (10 μM)**	NS
71	Me	Cl			<10	75	×3.9 (1 μM)** ×2.4 (10 μM)**	×0.8 (1 μM)** ×0.7 (10 μM)**
72	Cl	H			32	58	×3.2 (10 μM)**	NS
73	H	Cl			65	<10	×1.9 (10 μM)**	×0.8 (10 μM)**
74	Me	Cl			<10	26	×4.4 (10 μM)**	NS
75	Cl	H			87	57	NS	NS
76	H	Cl			85	59	NS	NS
77	Cl	H			<10	49	NS	NS
78	H	Cl			36	14	×2.6 (10 μM)**	NS
79	Cl	H			76	96	NS	NS
80	H	Cl			46	69	NS	NS
81	H	Cl			46	78	NS	NS

Table 11

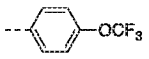
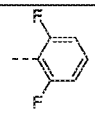
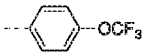
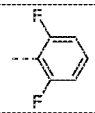
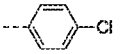
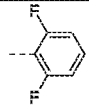
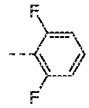
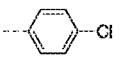
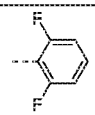
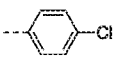
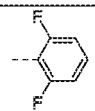
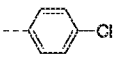
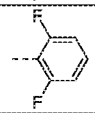
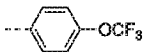
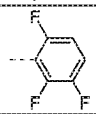
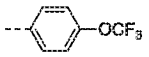
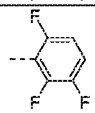
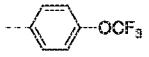
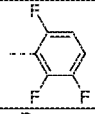
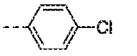
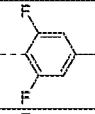
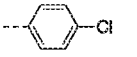
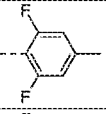
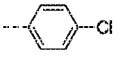
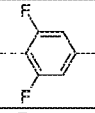
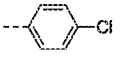
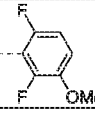
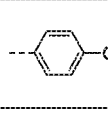
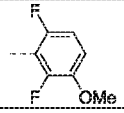
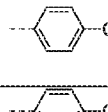
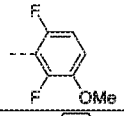
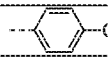
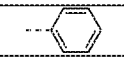
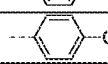
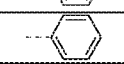
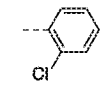
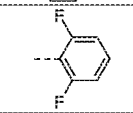
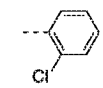
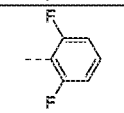
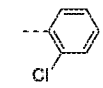
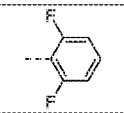
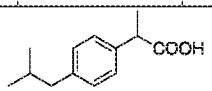
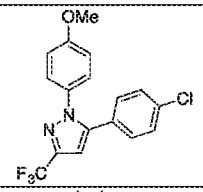
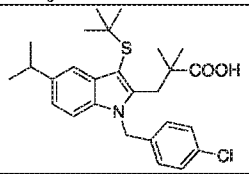
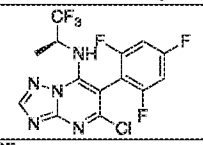
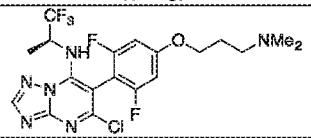
Cpd #	X	Y	Ring A	Ring B	PGD_2/E_2 % Inhibition at 10 μM[a]	LTB_4 % Inhibition at 10 μM[b]	Relative Change in AcTub[c]	Relative Change in α-Tubulin[d]
82	Cl	H			19	61	×2.2 (10 μM)**	NS
83	Cl	Cl			19	81	×6.1 (10 μM)**	NS
84	H	Cl			94	76	×4.0 (10 μM)**	NS
85	Me	Cl			45	87	×2.5 (1 μM)* ×15.7 (10 μM)**	×0.8 (10 μM)**
86	Et	Cl			30	81	×1.8 (1 μM)** ×5.0 (10 μM)**	NS
87	Cl	H			50	92	×4.8 (10 μM)**	NS
88	Cl	Cl			17	90	×7.7 (10 μM)**	NS
89	H	Cl			54	85	NS	NS
90	Cl	H			58	80	×3.4 (10 μM)**	NS
91	Cl	Cl			40	56	×6.3 (10 μM)**	NS
92	H	Cl			90	75	×3.6 (10 μM)**	NS
93	Cl	H			42	73	×5.7 (10 μM)**	NS
94	Cl	Cl			<10	63	×18.2 (10 μM)**	×0.7 (10 μM)**
95	H	Cl			48	91	×4.0 (10 μM)**	×0.8 (10 μM)**

Table 11

Cpd #	X	Y	Ring A	Ring B	PGD_2/E_2 % Inhibition at 10 μM[a]	LTB_4 % Inhibition at 10 μM[b]	Relative Change in AcTub[c]	Relative Change in α-Tubulin[d]
96	Cl	H			<10	68	×8.2 (10 μM)**	×0.6 (10 μM)**
97	Cl	Cl			17	88	×5.1 (1 μM)** ×10.1 (10 μM)**	×0.9 (1 μM)** ×0.4 (10 μM)**
98	H	Cl			94	71	NS	NS
99	Cl	H			75	52	NS	×1.2 (10 μM)**
100	Cl	Cl			14	<10	NS	NS
101	H	Cl			95	<10	NS	NS
102	H	Cl			44	56	×3.5 (10 μM)**	NS
103	Cl	H			28	38	NS	NS
104	Cl	Cl			66	21	×3.8 (10 μM)**	NS
Ibuprofen (105)					95	<10	NS	NS
3					79[§]	<10[§]	NS	NS
MK866 (106)					<10[§]	70[§]	ND	ND
Triazolopyrimidine (107)					ND	ND	×2.5 (1 μM) ×4.9 (10 μM)	NS
Triazolopyrimidine (108)					ND	ND	×6.0 (1 μM) ×0.5 (10 μM)	×0.7 (1 μM) ×0.4 (10 μM)

[a] Inhibition of COX pathway was determined by monitoring via LC/MS/MS analyses the combined production of COX-derived PGD_2 and PGE_2 in RBL-1 upon stimulation with

arachidonic acid in the presence or absence of test compounds, with all samples run in at least triplicate.

[b] Inhibition of 5-LOX pathway was determined by monitoring via LC/MS/MS analyses the production of 5-LOX-derived LTB_4 in RBL-1 upon stimulation with arachidonic acid in the presence or absence of test compounds, with all samples run in at least triplicate.

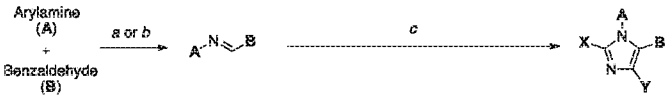
[c] MT-stabilizing activity in QBI-293 cells was determined by monitoring via ELISA the relative changes in acetylated α-tubulin levels in response to 4-hour treatment with test compounds, with all samples run in at least triplicate.

[d] Relative changes in total α-tubulin, as determined by tubulin ELISA, in response to compound treatment, with all samples run in at least triplicate.

[§] compound tested at 10 nM.

*$P < 0.05$; **$P < 0.01$ compared with vehicle (DMSO)–treated controls as determined using an two-tailed unpaired t-test; NS: not significant; ND: not determined.

Scheme 3*

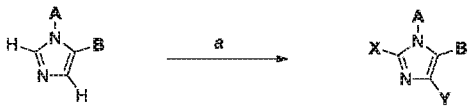


A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (5)
A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (6)
A = 4-chlorophenyl; B = 2,6-difluoro-3-methylphenyl (7)
A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (8)
A = 4-chlorophenyl; B = 3-bromo-2,6-difluorophenyl (9)
A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (10)
A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (11)
A = 6-chloropyridin-3-yl; B = 2,4,6-trifluorophenyl (12)
A = 4-chlorophenyl; B = 4-fluorophenyl (13)
A = 4-chloro-2-fluorophenyl; B = 2,6-difluorophenyl (14)
A = 4-chlorophenyl; B = 2,5-difluorophenyl (15)
A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (16)
A = 4-chlorophenyl; B = 2,6-difluorophenyl (17)
A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (18)
A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (19)
A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (20)
A = 4-chlorophenyl; B = phenyl (21)
A = 4-chlorophenyl; B = 4-methoxyphenyl (22)
A = phenyl; B = 2,6-difluorophenyl (23)
A = 2-chlorophenyl; B = 2,6-difluorophenyl (24)

X = H; Y = H; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (25)
X = H; Y = H; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (26)
X = H; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-3-methylphenyl (27)
X = H; Y = H; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (28)
X = H; Y = Me; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (29) ← d
X = Cl; Y = Me; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (30) ← d
X = Me; Y = Me; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (31) ← e
X = H; Y = H; A = 4-chlorophenyl; B = 3-bromo-2,6-difluorophenyl (32)
X = H; Y = H; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (33)
X = Me; Y = H; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (34) ← e
X = H; Y = Me; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (35) ← d
X = Cl; Y = Me; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (36) ← d
X = H; Y = H; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (37)
X = H; Y = H; A = 6-chloropyridin-3-yl; B = 2,4,6-trifluorophenyl (38)
X = H; Y = H; A = 4-chlorophenyl; B = 4-fluorophenyl (39)
X = H; Y = H; A = 4-chloro-2-fluorophenyl; B = 2,6-difluorophenyl (40)
X = H; Y = H; A = 4-chlorophenyl; B = 2,5-difluorophenyl (41)
X = H; Y = H; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (42)
X = H; Y = H; A = 4-chlorophenyl; B = 2,6-difluorophenyl (43)
X = H; Y = Me; A = 4-chlorophenyl; B = 2,6-difluorophenyl (44) ← d
X = Cl; Y = Me; A = 4-chlorophenyl; B = 2,6-difluorophenyl (45) ← d
X = Me; Y = Me; A = 4-chlorophenyl; B = 2,6-difluorophenyl (46) ← e
X = H; Y = H; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (47)
X = H; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (48)
X = H; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (49)
X = H; Y = H; A = 4-chlorophenyl; B = phenyl (50)
X = H; Y = H; A = 4-chlorophenyl; B = 4-methoxyphenyl (51)
X = H; Y = H; A = phenyl; B = 2,6-difluorophenyl (52)
X = H; Y = H; A = 2-chlorophenyl; B = 2,6-difluorophenyl (53)

*Reagents and reaction conditions: (a) Dean–Stark apparatus, toluene, 110 °C, 4 days, 99%; (b) 4 Å molecular sieves, Et_2O, 30 °C, 48 h, 99%; (c) appropriate TosMIC reagent, K_2CO_3, DMF/1,2-dimethoxyethane, 100 °C, 16 h, 7–90%; (d) N-chlorosuccinimide, $CHCl_3$,60 °C, 16 h, 43–71%; (e) LDA, methyliodide, THF, −20 °C to rt, 1.5 h, 29–56%.

Scheme 4*



X = H; Y = Cl; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (54) — b
X = Me; Y = Cl; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (55) — b
X = Me; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methoxyphenyl (2) — c
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (56)
X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,4,6-trifluorophenyl (57)
X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methoxyphenyl (58) — c
X = H; Y = Cl; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (59)
X = Cl; Y = H; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (60)
X = Cl; Y = Cl; A = 4-methoxyphenyl; B = 2,4,6-trifluorophenyl (61)
X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-3-methylphenyl (62)
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-3-methylphenyl (63)
X = H; Y = Cl; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (64)
X = Me; Y = Cl; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (65) — b
X = Cl; Y = H; A = 4-chlorophenyl; B = 3-chloro-2,6-difluorophenyl (66)
X = H; Y = Cl; A = 4-chlorophenyl; B = 3-bromo-2,6-difluorophenyl (67)
X = H; Y = Cl; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (68)
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,3,6-trifluorophenyl (69)
X = H; Y = Cl; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (70)
X = Me; Y = Cl; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (71) — b
X = Cl; Y =H; A = 4-chloro-3-fluorophenyl; B = 2,3,6-trifluorophenyl (72)
X = H; Y = Cl; A = 6-chloropyridin-3-yl; B = 2,4,6-trifluorophenyl (73)
X = Me; Y = Cl; A = 6-chloropyridin-3-yl; B = 2,4,6-trifluorophenyl (74) — b
X = Cl; Y = H; A = 4-chlorophenyl; B = 4-fluorophenyl (75)
X = H; Y = Cl; A = 4-chlorophenyl; B = 4-fluorophenyl (76)
X = Cl; Y = H; A = 4-chloro-2-fluorophenyl; B = 2,6-difluorophenyl (77)
X = H; Y = Cl; A = 4-chloro-2-fluorophenyl; B = 2,6-difluorophenyl (78)
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,5-difluorophenyl (79)
X = H; Y = Cl; A = 4-chlorophenyl; B = 2,5-difluorophenyl (80)
X = H; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (81)
X = Cl; Y = H; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (82)
X = Cl; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,6-difluorophenyl (83)
X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (84)
X = Me; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (85) — b
X = Et; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (86) — d
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluorophenyl (87)
X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluorophenyl (88)
X = H; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (89)
X = Cl; Y = H; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (90)
X = Cl; Y = Cl; A = 4-(trifluoromethoxy)phenyl; B = 2,3,6-trifluorophenyl (91)
X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (92)
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (93)
X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-4-methylphenyl (94)
X = H; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (95)
X = Cl; Y = H; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (96)
X = Cl; Y = Cl; A = 4-chlorophenyl; B = 2,6-difluoro-3-methoxyphenyl (97)
X = H; Y = Cl; A = 4-chlorophenyl; B = phenyl (98)
X = Cl; Y = H; A = 4-chlorophenyl; B = phenyl (99)
X = Cl; Y = Cl; A = 4-chlorophenyl; B = phenyl (100)
X = H; Y = Cl; A = 4-chlorophenyl; B = 4-methoxyphenyl (101)
X = H; Y = Cl; A = 2-chlorophenyl; B = 2,6-difluorophenyl (102)
X = Cl; Y = H; A = 2-chlorophenyl; B = 2,6-difluorophenyl (103)
X = Cl; Y = Cl; A = 2-chlorophenyl; B = 2,6-difluorophenyl (104) — a

[00343] *Reagents and reaction conditions: (a) N-chlorosuccinimide, $CHCl_3$, 60 °C, 16 h, 9−77% for monohalogenation at C4, 3−18% for mono-halogenation at C2, and 2−20% for dihalogenation at C2/C4;(b) LDA, methyliodide, THF, −20 °C to rt,1.5h, 2−48%; (c) NaOMe, MeOH, THF, rt, 19 h, 33−97%; (d) LDA, ethyliodide, THF, −20 °C to rt, 1.5 h, 35%.

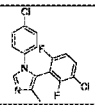
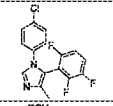
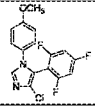
[00344] (ii) Structure−Activity Relationships

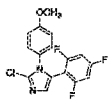
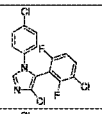
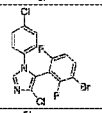
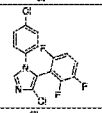
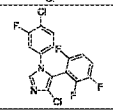
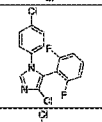
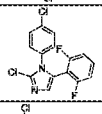
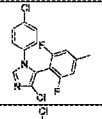
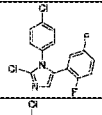
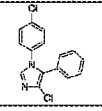
[00345] The MT-stabilizing activity of test compounds was determined in QBI-293 cells by monitoring compound-induced elevation in acetylated α-tubulin (AcTub), which is a known

marker of stable MTs. See, Lou, Brain-penetrant, orally bioavailable microtubule-stabilizing small molecules are potential candidate therapeutics for Alzheimer's disease and related tauopathies. J. Med. Chem. 2014, 57, 6116−6127 and Fukushima, Post-translational modifications of tubulin in the nervous system. J. Neurochem. 2009, 109, 683−693. The effect of compound treatment on total α-tubulin was also monitored. Evaluation of compound inhibition of the biosynthesis of COX- and 5-LOX-derived eicosanoids was conducted in a modified rat basophilic leukemia (RBL-1) cell assay that has previously been described for the evaluation of 5-LOX. See, Tries, The mechanism of action of the new antiinflammatory compound ML3000: inhibition of 5-LOX and COX-1/2. Inflammation Res. 2002, 51, 135−143. It was found herein that it could be used to assess both COX-derived prostaglandins (PGs) and 5-LOX-derived leukotrienes (LTs) formed in the presence or absence of test compounds.

[00346] All compounds were initially screened at 1 and 10 μM concentration in the QBI cell MT assay and at 10 μM in the RBL-1 cell assay (Table 11). In this initial RBL-1 cell analysis, 5-LOX-derived LTB_4 and COX-derived PGD_2 and PGE_2, which coeluted during LC/MS/MS, were quantified. Selected compounds (Table 12) exhibiting evidence of multitargeted activity underwent further confirmatory studies in the RBL-1 cell assay, which included concentration−response testing, and further LC/MS/MS analyses using a refined protocol to individually detect and quantitate PGD_2 and PGE_2, as well as both LTB_4 and LTC_4. Concurrent analysis of all four of these eicosanoids provides a convenient and reliable method to evaluate the overall effect of test compounds on COX and 5-LOX pathways in a cellular milieu.Several compounds in Table 12 were also assessed for their relative brain-to-plasma exposure levels after administration to mice.

Table 12
Further evaluation of test compounds with multi-targeted activity as MT-stabilizing agents and/or inhibitors of COX and 5-LOX pathways.

	Cpd#	Structure	PGD_2/E_2 Inhibition IC_{50} (μM)	LTB_4 Inhibition IC_{50} (μM)	Acetyl-Tubulin Assay	Brain (nM)	Plasma (nM)	B/P
Multi-targeted Compounds with Activity as MT-Stabilizing Agents and	29		12.1	13.4	× 3.5 (10 μM)	600^ ± 200	500^ ± 300	1.4 ± 0.3
	35		4.7	23.7	× 3.4 (10 μM)	400^ ± 200	200^ ± 100	1.9 ± 0.2
	59		2.4	9.7	× 4.1 (10 μM)	ND	ND	ND

Inhibitors of COX and 5-LOX Pathways	**60**		9.8	20.8	× 3.4 (10 μM)	210^ ± 90	210^ ± 80	0.9 ± 0.1
	64		2.2	9.5	× 2.4 (10 μM)	400# ± 200	190# ± 90	2.1 ± 0.5
	67		6.5	7.8	× 2.1 (10 μM)	240# ± 100	260# ± 90	0.9# ± 0.2
	68		2.9	2.4	× 2.0 (10 μM)	700# ± 500	300# ± 200	2.8 ± 0.8
	70		4.6	6.0	× 1.9 (10 μM)	700# ± 200	240# ± 50	3.0 ± 1.0
	84		2.4	13.8	× 4.0 (10 μM)	700^ ± 400	400^ ± 200	1.9 ± 0.2
	87		15.0	10.7	× 4.8 (10 μM)	900# ± 300	480# ± 60	1.9 ± 0.4
	92		1.8	11.7	× 3.6 (10 μM)	300^ ± 100	110^ ± 60	2.5 ± 0.1
Dual Inhibitors of COX/5-LOX Pathways	**79**		2.2	2.5	Inactive	200^ ± 80	60^ ± 30	3.3 ± 0.1
	98		1.0	12.5	Inactive	200^ ± 60	80^ ± 20	2.4 ± 0.1

[00347] All concentration-response analyses were conducted at multiple concentrations with triplicate samples per concentration.

[00348] # Study conducted after a 5 mg/kg i.p. injection of test compound.

[00349] ^ Study conducted after a 2 mg/kg i.p. injection of test compound with drug concentrations adjusted proportionally upward to allow comparison to 5 mg/kg doses.

[00350] ND: not determined.

[00351] +/- errors represent standard deviations; all analyses were conducted with groups of 3 mice.

[00352] (iii) MT-Stabilizing Activity

[00353] Evaluation of compounds in the QBI-293 cell MT assay revealed that out of 71 tested compounds, 48 compounds exhibited activity on MTs as revealed by statistically significant changes in AcTub levels. Among MT-active compounds, seven compounds (compounds 2, 58, 65, 71, 85, 86, and 97) were found to be active at 1 μM compound

concentration, whereas the remaining 41 compounds were active only at 10 μM. Consistent with the notion that the MT-stabilizing 1,5-diarylimidazoles may be acting on MTs in a similar manner as the triazolopyrimidines, the data presented in Table 11 reveal these imidazoles can be broadly divided into two subsets: one group which causes a significant reduction in total α-tubulin levels at doses typically required to induce an elevation in AcTub (see, e.g., compounds 2, 30, 34, 58, 62, 63, 65, 66, 71, 73, 85, and 94–97) and a second group that produces an elevation in AcTub at 1 or 10 μM without decreasing α-tubulin level (see, e.g., compounds 29, 31, 35, 36, 44–46, 54, 55–57, 59, 60, 64, 67–70, 72, 74, 78, 82–84, 86–88, 90–93, 102, and 104). A comparison of the activities of compounds in the AcTub assay at 1 and 10 μM suggest that selected entries, such as compounds 2, 58, and 71, may exhibit a bell-shaped concentration–response relationship, and additional examples would likely show a similar concentration–response if tested at higher concentrations. This phenomenon was observed in the case of the triazolopyrimidines that reduce α-tubulin level, such as compound 108. See, Kovalevich. Irrespective of whether or not test compounds cause a reduction in total α-tubulin, the AcTub SAR emerging from the data shown in Table 11 appear to be in general agreement with SAR from prior studies in which MT-stabilizing 1,5-diarylimidazoles were evaluated for antifungal activity.

[00354] In light of the observed elements of SAR for the three biological targets, the particular substitution pattern decorating the 1,5-diarylimidazole scaffold can result in compounds with different activity profiles, including multitargeted activity on MTs and/or eicosanoid biosynthesis (FIG. 1). Selected representative examples of multitargeted compounds were evaluated further to determine the IC_{50} values in the RBL-1 cell assays and brain penetration (see FIG. 2 and Table 12). Moreover, the compounds in Table 12 were also examined with improved LC/MS/MS methodologies for their ability to inhibit the individual COX-derived products PGE_2 and PGD_2 as well as a second 5-LOX-derived product, LTC_4 (FIG. 3). Example compounds underwent full concentration–response analyses in the AcTub assay (FIG. 4).These studies confirmed that all Table 12 compounds effectively inhibited both COX and 5-LOX biosynthetic pathways with multiple compounds exhibiting balanced multitargeted activity in the low μM range.Consistent with the relatively small size of these molecules, these compounds appeared to be generally brain-penetrant.

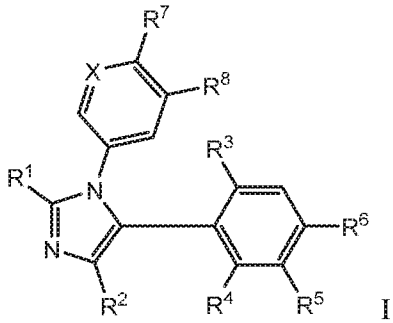
[00355] It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description and the examples that follow are intended to illustrate and not limit the scope of the invention. It will be understood by those skilled in the art that various changes may be made and equivalents may be substituted

without departing from the scope of the invention, and further that other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. In addition to the embodiments described herein, the present invention contemplates and claims those inventions resulting from the combination of features of the invention cited herein and those of the cited prior art references which complement the features of the present invention. Similarly, it will be appreciated that any described material, feature, or article may be used in combination with any other material, feature, or article, and such combinations are considered within the scope of this invention.

[00356] The disclosures of each patent, patent application, and publication cited or described in this document and Cornec, et al., Multitargeted Imidazoles: Potential Therapetuic Leads for Alzheimer's and Other Neurodegenerative Diseases," J. Med. Chem., 2017, 60, 5120-5145 are hereby incorporated herein by reference, each in its entirety, for all purposes.

What is Claimed:

1. A method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^1 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^2 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^3 is H, F, Cl, or Br;

R^4 is H, F, Cl, or Br;

R^5 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^6 is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^7 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

R^8 is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

2. The method of claim 1, wherein X is CH.

3. The method of claim 1, wherein X is N.

4. The method of claim 1, wherein R^1 is H.

5. The method of claim 1, wherein R^1 is F, Cl, or Br.

6. The method of claim 1, wherein R^1 is C_{1-6}alkyl or OC_{1-6}alkyl.

7. The method of claim 1, wherein R^2 is H.

8. The method of claim 1, wherein R^2 is F, Cl, or Br.

9. The method of claim 1, wherein R^2 is C_{1-6}alkyl or OC_{1-6}alkyl.

10. The method of claim 1, wherein R^3 is H.

11. The method of claim 1, wherein R^3 is F, Cl, or Br.

12. The method of claim 1, wherein R^4 is H.

13. The method of claim 1, wherein R^4 is F, Cl, or Br.

14. The method of claim 1, wherein R^5 is H.

15. The method of claim 1, wherein R^5 is F, Cl, or Br.

16. The method of claim 1, wherein R^5 is C_{1-6}alkyl or OC_{1-6}alkyl.

17. The method of claim 1, wherein R^6 is H.

18. The method of claim 1, wherein R^6 is F, Cl, or Br.

19. The method of claim 1, wherein R^6 is C_{1-6}alkyl or OC_{1-6}alkyl.

20. The method of claim 1, wherein R^7 is H.

21. The method of claim 1, wherein R^7 is F, Cl, or Br.

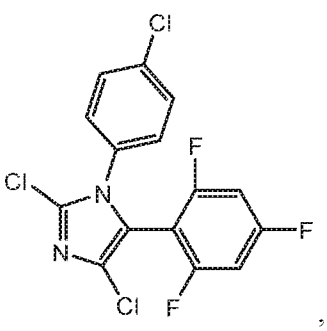
22. The method of claim 1, wherein R^7 is C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

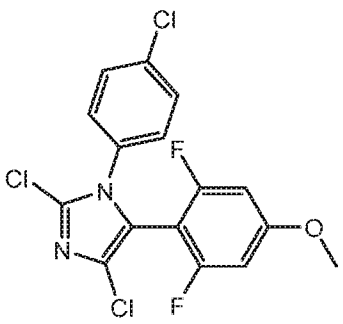
23. The method of claim 1, wherein R^8 is H.

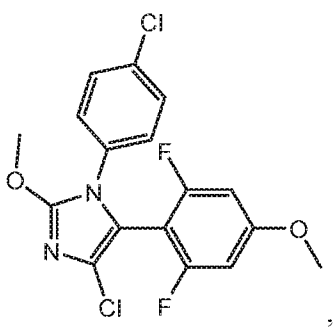
24. The method of claim 1, wherein R^8 is F, Cl, or Br.

25. The method of claim 1, wherein R^8 is C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

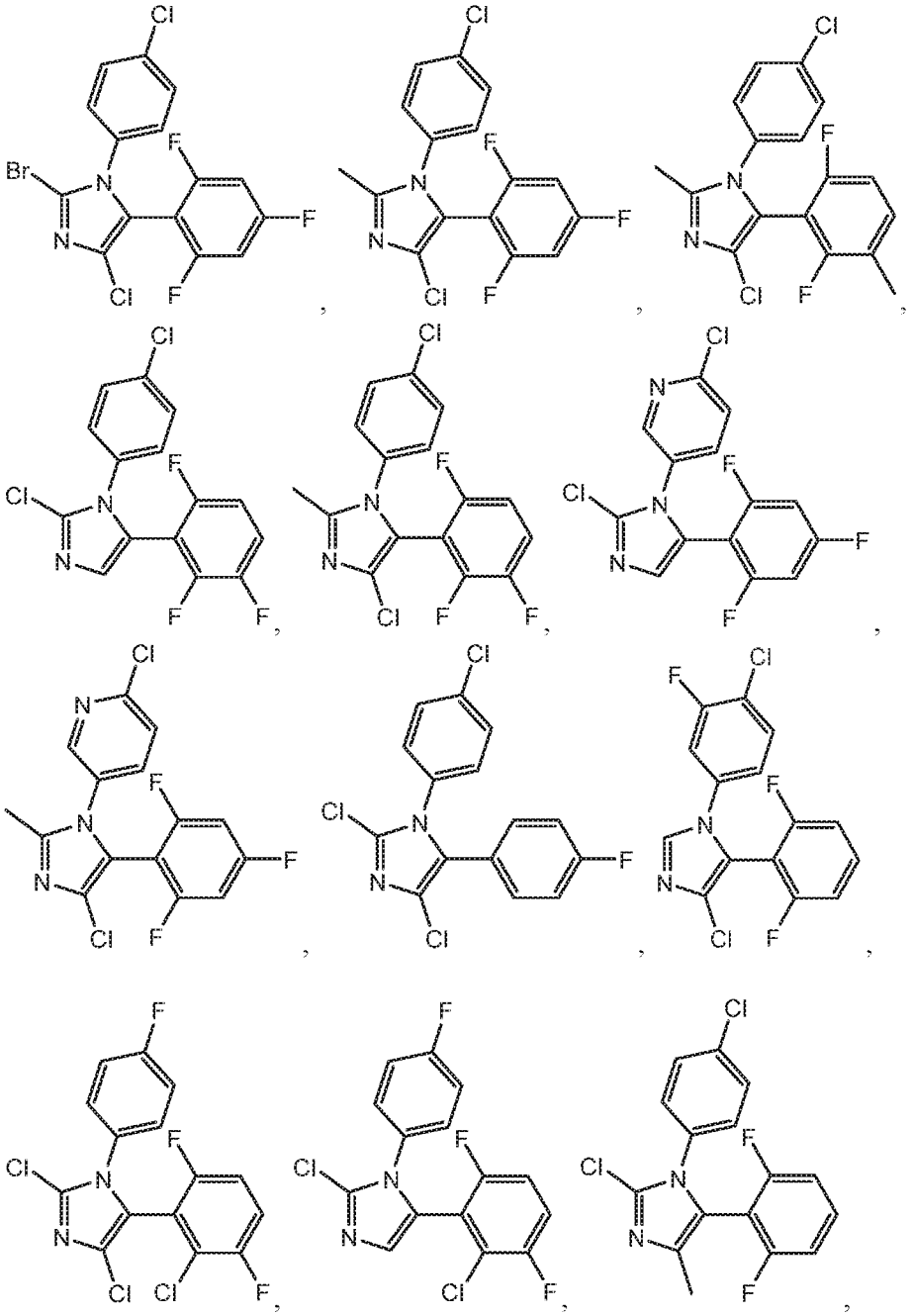
26. The method of claim 1, wherein the compound of formula (**I**) is:

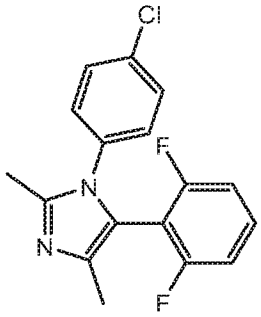
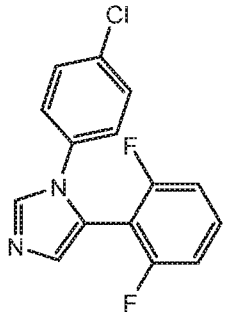
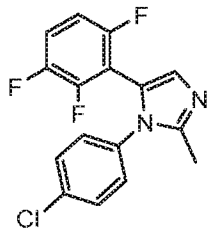
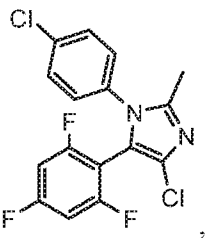
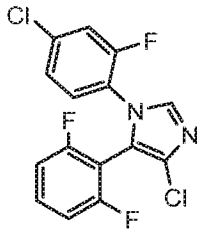
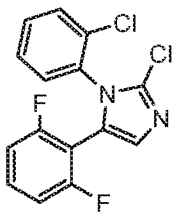


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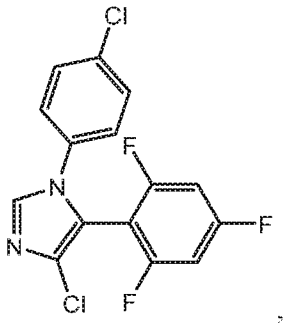
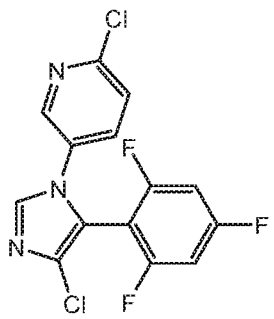
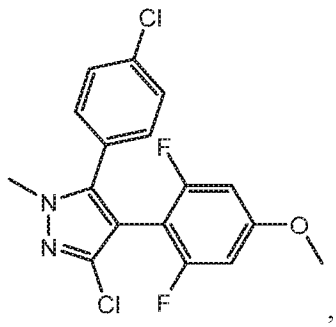
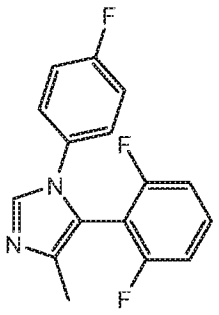
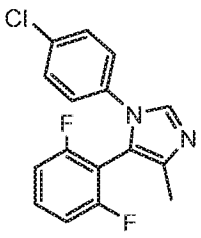
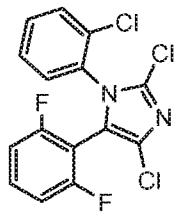
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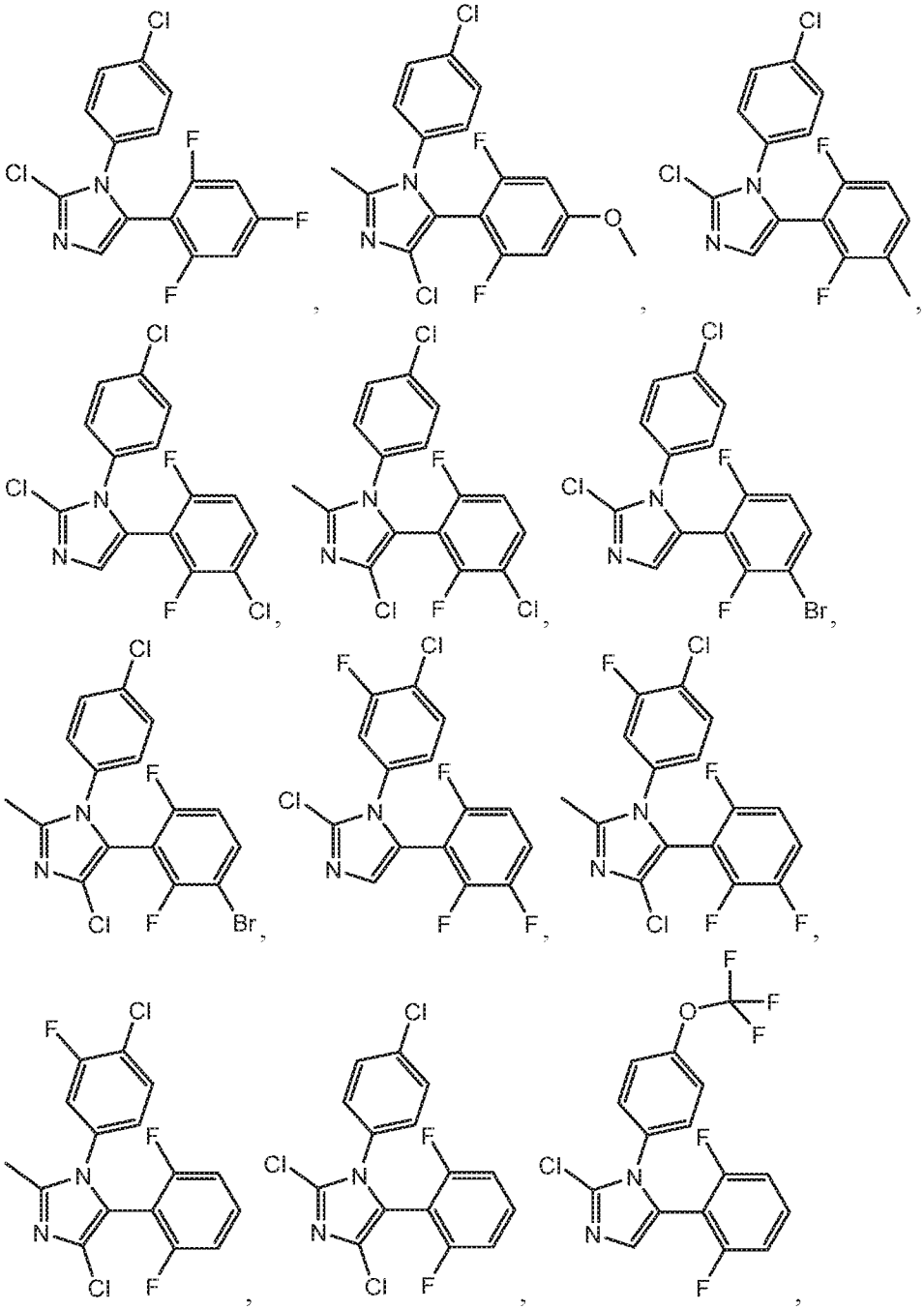

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, or a pharmaceutically acceptable salt thereof.

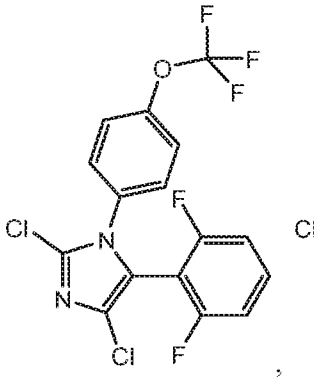
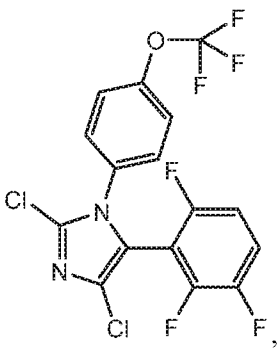
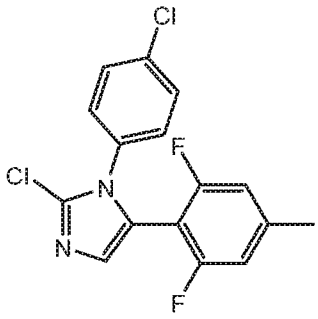
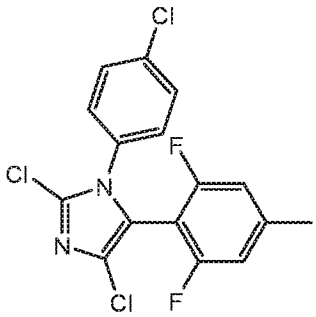
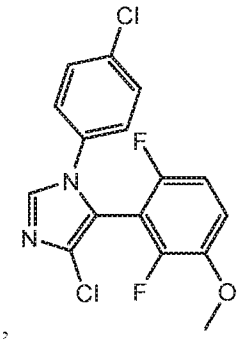
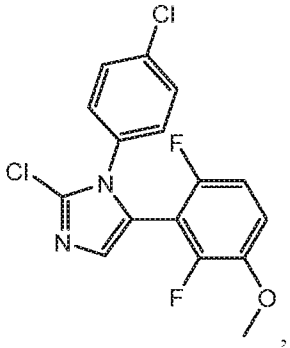
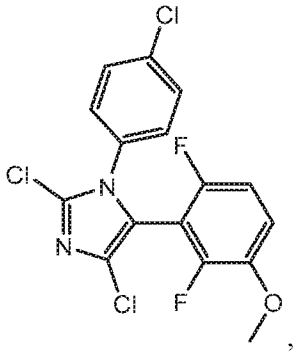
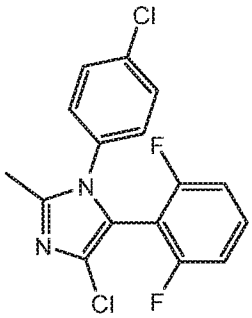
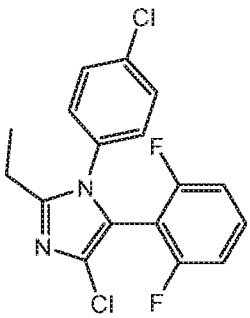
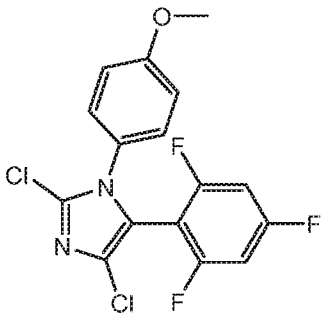
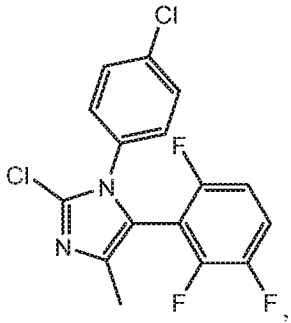
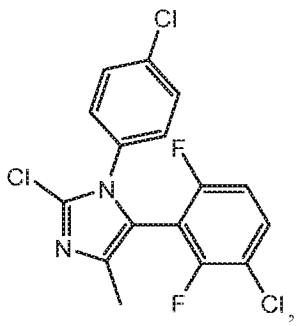
27. The method of claim 1, wherein the compound of formula (**I**) is:

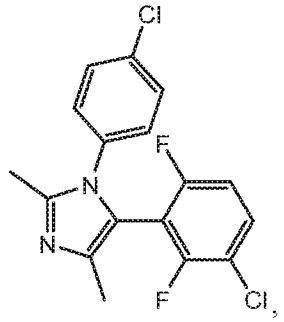

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or a pharmaceutically acceptable salt thereof.

28. The method of claim 1, wherein the compound of formula (**I**) is:

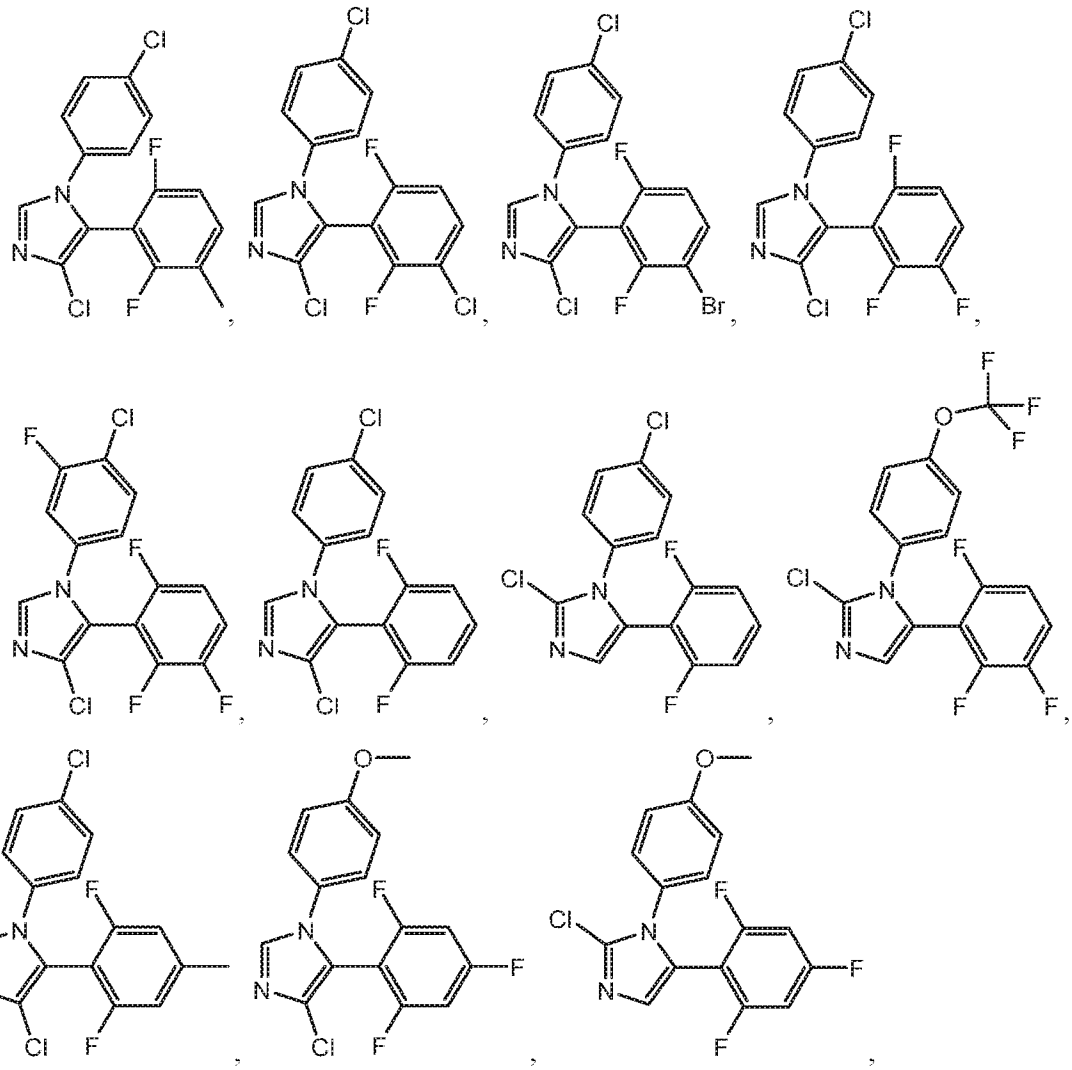


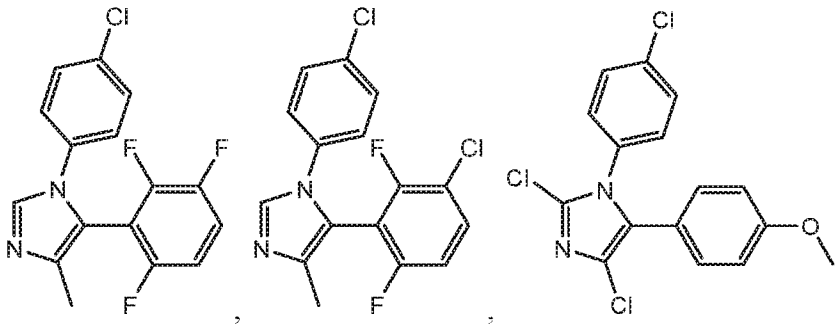

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or a pharmaceutically acceptable salt thereof.

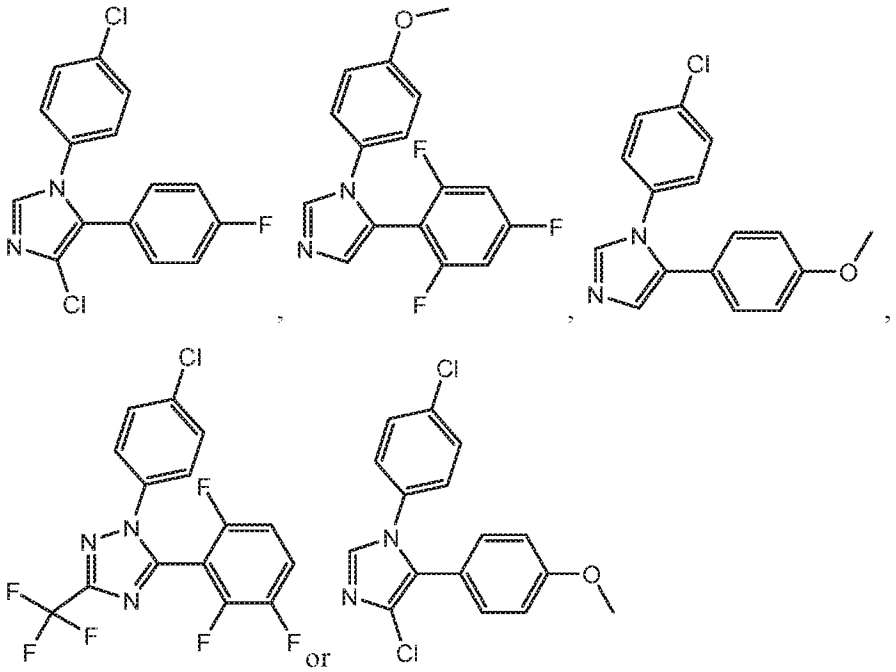
29. The method of claim 1, wherein the compound of formula (I) is:





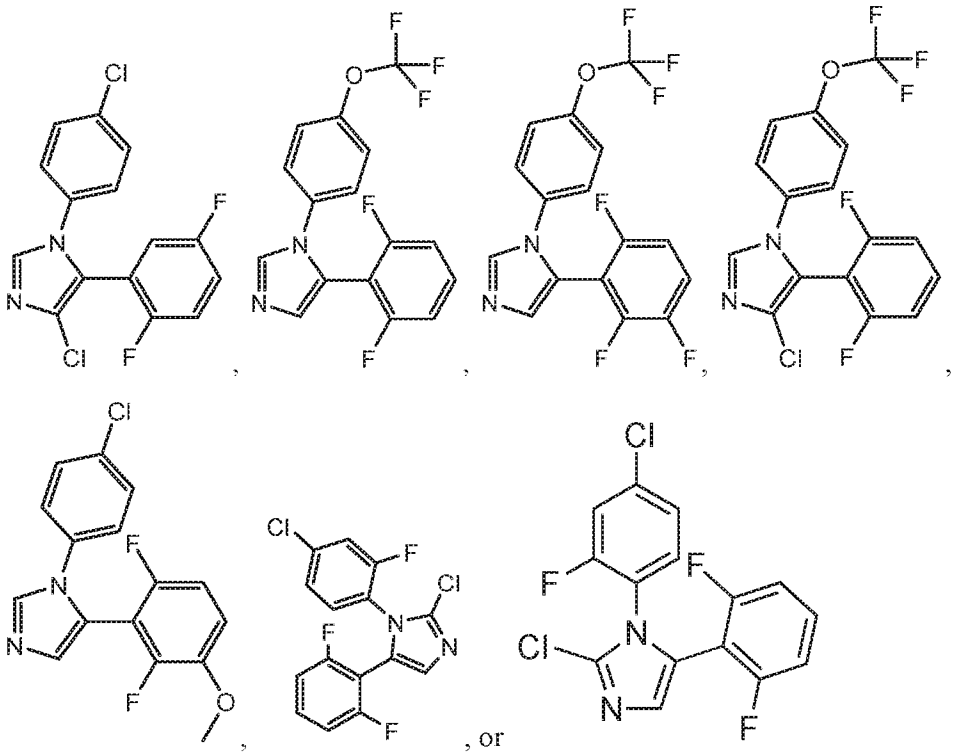
or a pharmaceutically acceptable salt thereof.

30. The method of claim 1, wherein the compound of formula (**I**) is:



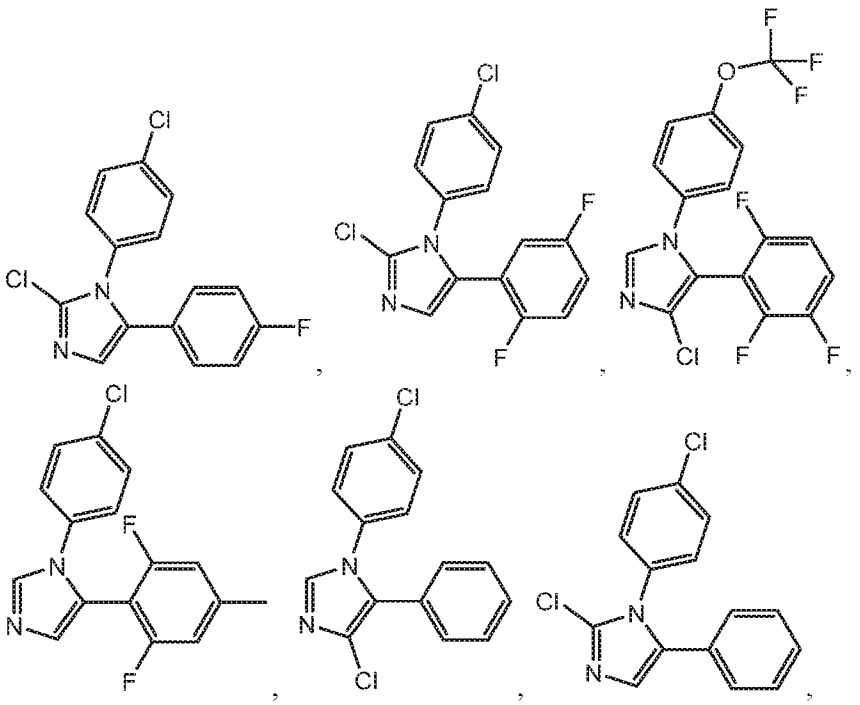
or a pharmaceutically acceptable salt thereof.

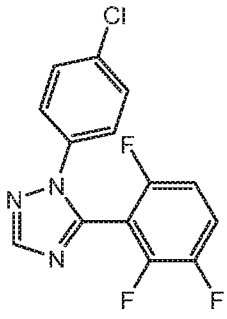
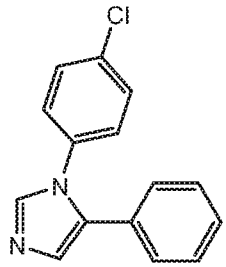
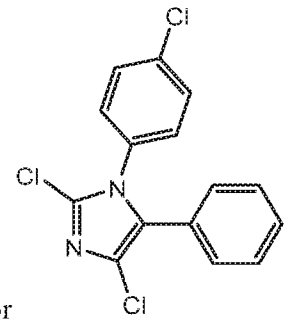
31. The method of claim 1, wherein the compound of formula (**I**) is:



or a pharmaceutically acceptable salt thereof.

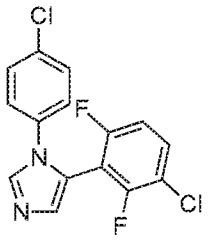
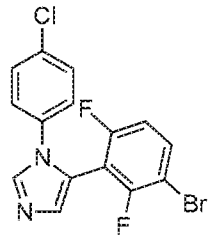
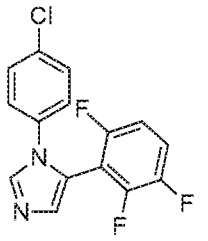
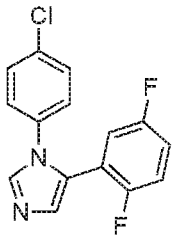
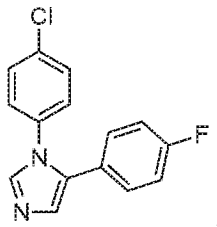
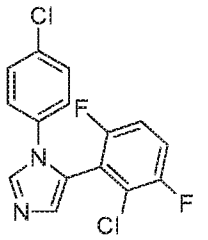
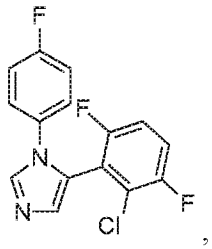
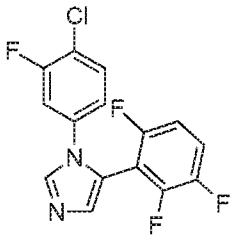
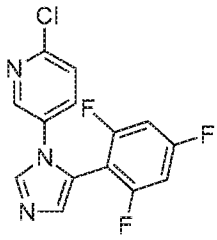
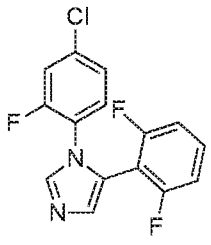
32. The method of claim 1, wherein the compound of formula (**I**) is:





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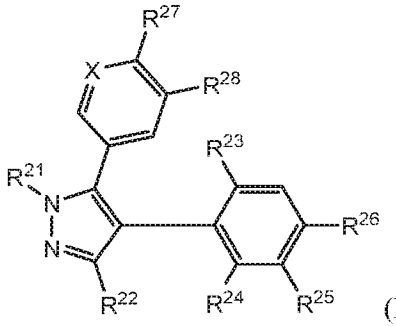
or a pharmaceutically acceptable salt thereof.

33. The method of claim 1, wherein the compound of formula (**I**) is:


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or a pharmaceutically acceptable salt thereof.

34. A method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound of Formula (**II**):



(II)

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^{21} is H or C_{1-6}alkyl;

R^{22} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{23} is H, F, Cl, or Br;

R^{24} is H, F, Cl, or Br;

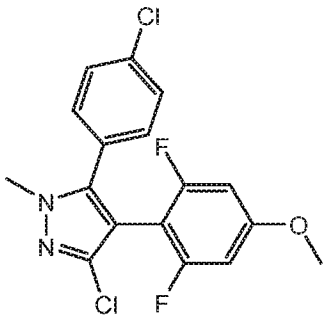
R^{25} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{26} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{27} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

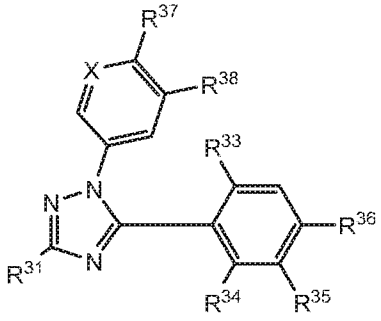
R^{28} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

35. The method of claim 34, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

36. A method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound of Formula (**III**):



(III)

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^{31} is H, C_{1-6}alkyl, or C_{1-6}haloalkyl;

R^{33} is H, F, Cl, or Br;

R^{34} is H, F, Cl, or Br;

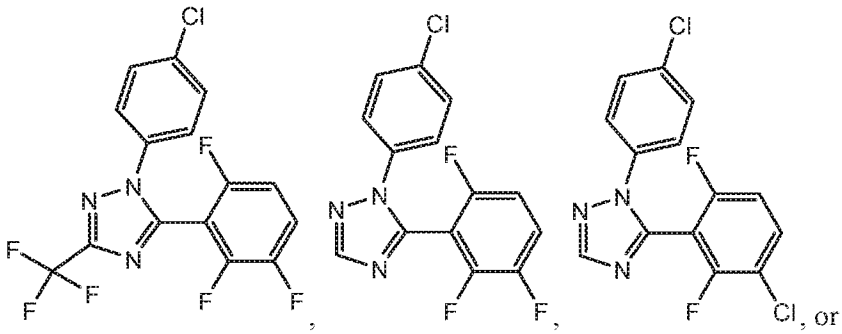
R^{35} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

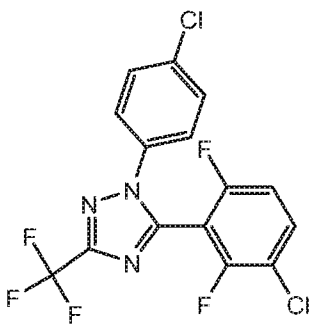
R^{36} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{37} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

R^{38} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

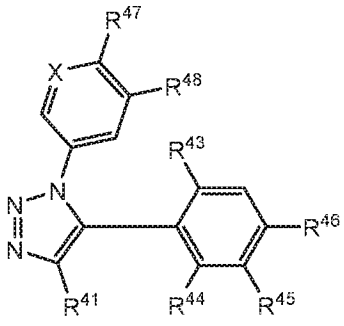
37. The method of claim 36, wherein the compound is





or a pharmaceutically acceptable salt thereof.

38. A method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof, wherein

X is CH or N;

R^{41} is H or C_{1-6}alkyl;

R^{43} is H, F, Cl, or Br;

R^{44} is H, F, Cl, or Br;

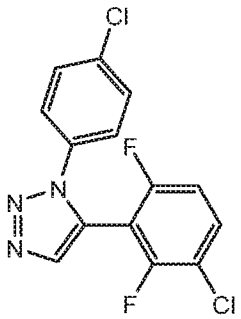
R^{45} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{46} is H, F, Cl, Br, C_{1-6}alkyl, or OC_{1-6}alkyl;

R^{47} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl; and

R^{48} is H, F, Cl, Br, C_{1-6}alkyl, C_{1-6}haloalkyl or OC_{1-6}alkyl.

39. The method of claim 38, wherein the compound is



or a pharmaceutically acceptable salt thereof.

40. The method of any one of the preceding claims, for treating a neurodegenerative disease that is characterized by a tauopathy or by compromised microtubule function in the brain of the subject.

41. The method of claim 40, wherein the neurodegenerative disease is Alzheimer's disease, frontotemporal lobar degeneration, Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration, Parkinson's disease (PD), PD with dementia, Lewy body disease with dementia, amyotrophic lateral sclerosis, argyrophilic grain disease, chronic traumatic encephalopathy, diffuse neurofibrillary tangles with calcification, Down's syndrome, Familial British dementia, Familial Danish dementia, frontotemporal dementia, parkinsonism linked to chromosome 17, Gerstmann-Straussler-Scheinker disease, Guadeloupean parkinsonism, multiple sclerosis, myotonic dystrophy, neurodegeneration with brain iron accumulation, Niemann-Pick disease, type C, non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, SLC9A6-related mental retardation, subacute sclerosing panencephalitis, tangle-only dementia, or white matter tauopathy with globular glial inclusions.

42. The method of claim 40, wherein the neurodegenerative disease is traumatic brain injury, in particular, repetitive traumatic brain injury and chronic traumatic encephalopathy, or post-traumatic stress disorder.

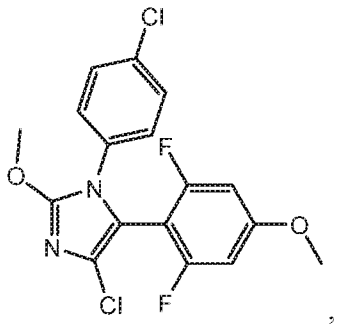
43. The method of any one of claims 1 to 39, for treating a peripheral inflammatory condition.

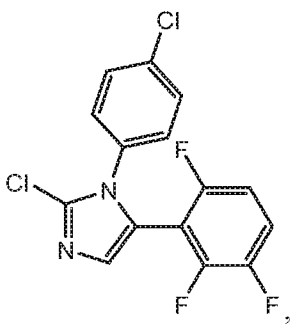
44. The method of any one of claims 1 to 39, wherein the peripheral inflammatory condition is rheumatoid arthritis or Crohn's disease.

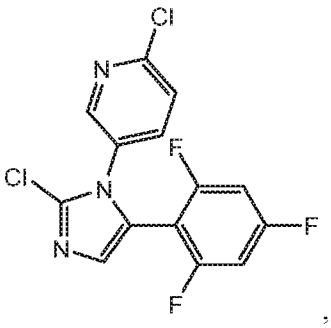
45. The method of any one of claims 1 to 39, for treating a cancer.

46. The method of any one of claims 1 to 39, for treating a parasitic disease.

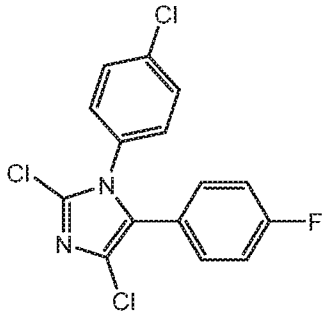
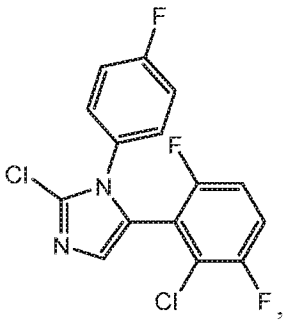
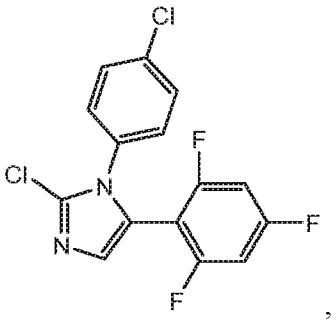
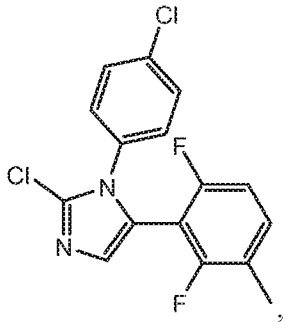
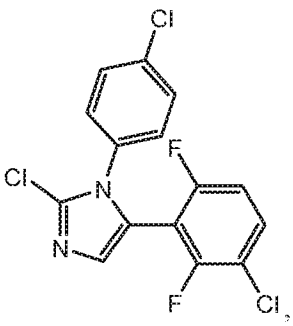
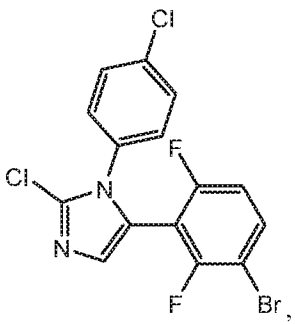
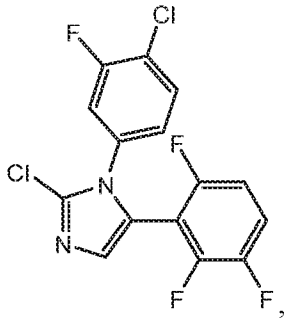
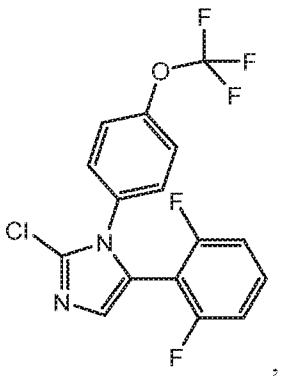
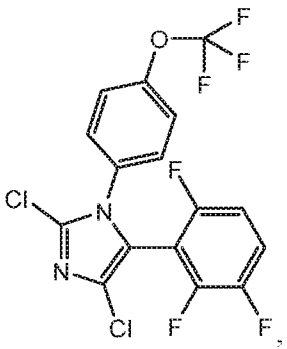
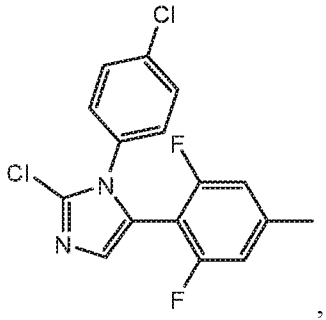
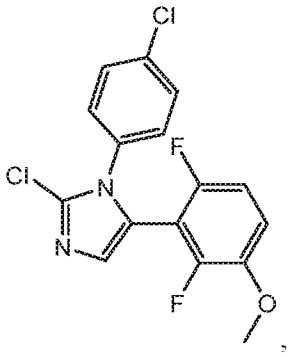
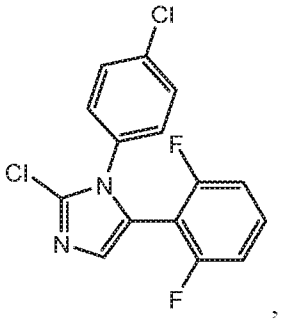
47. A compound that is:

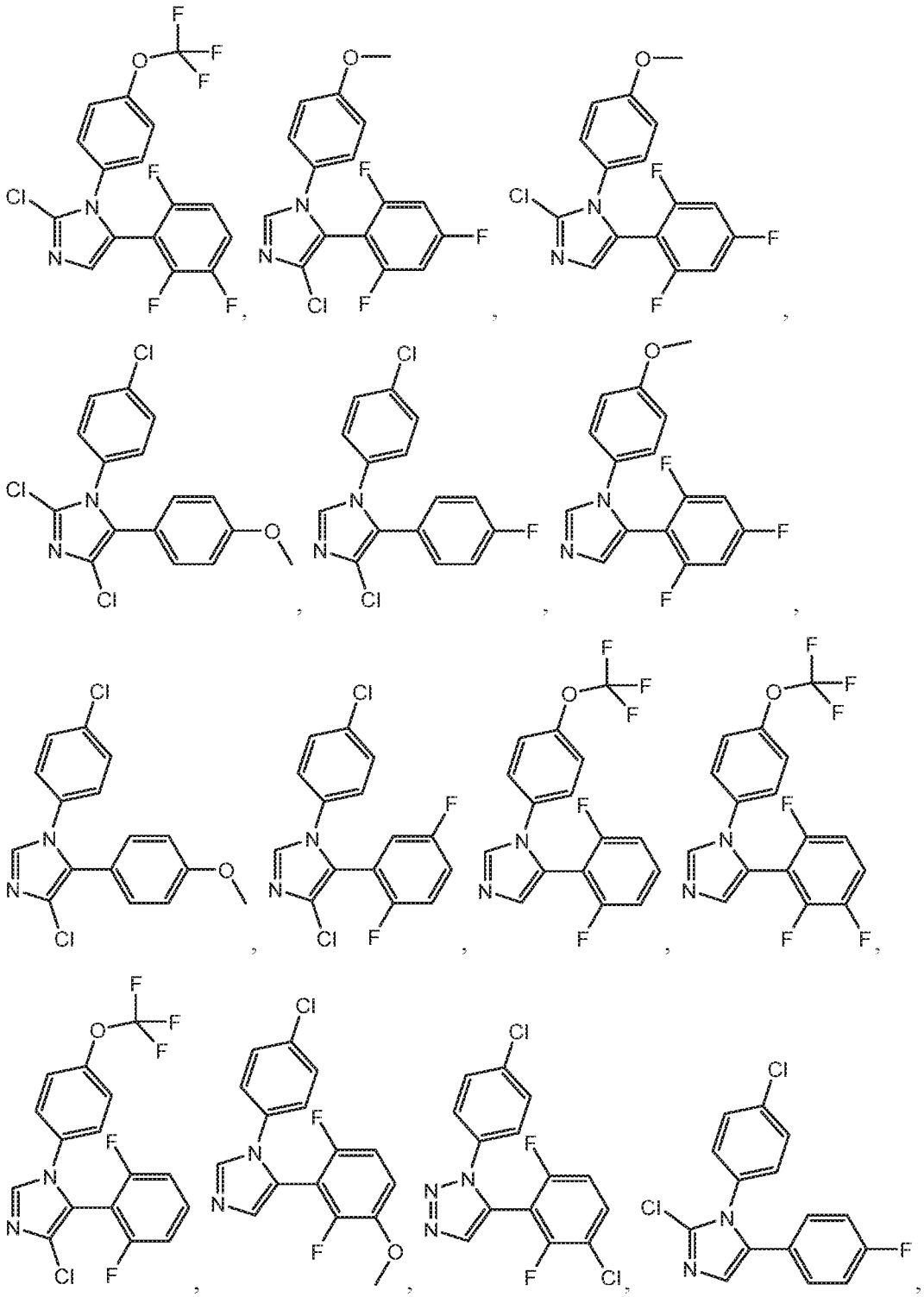


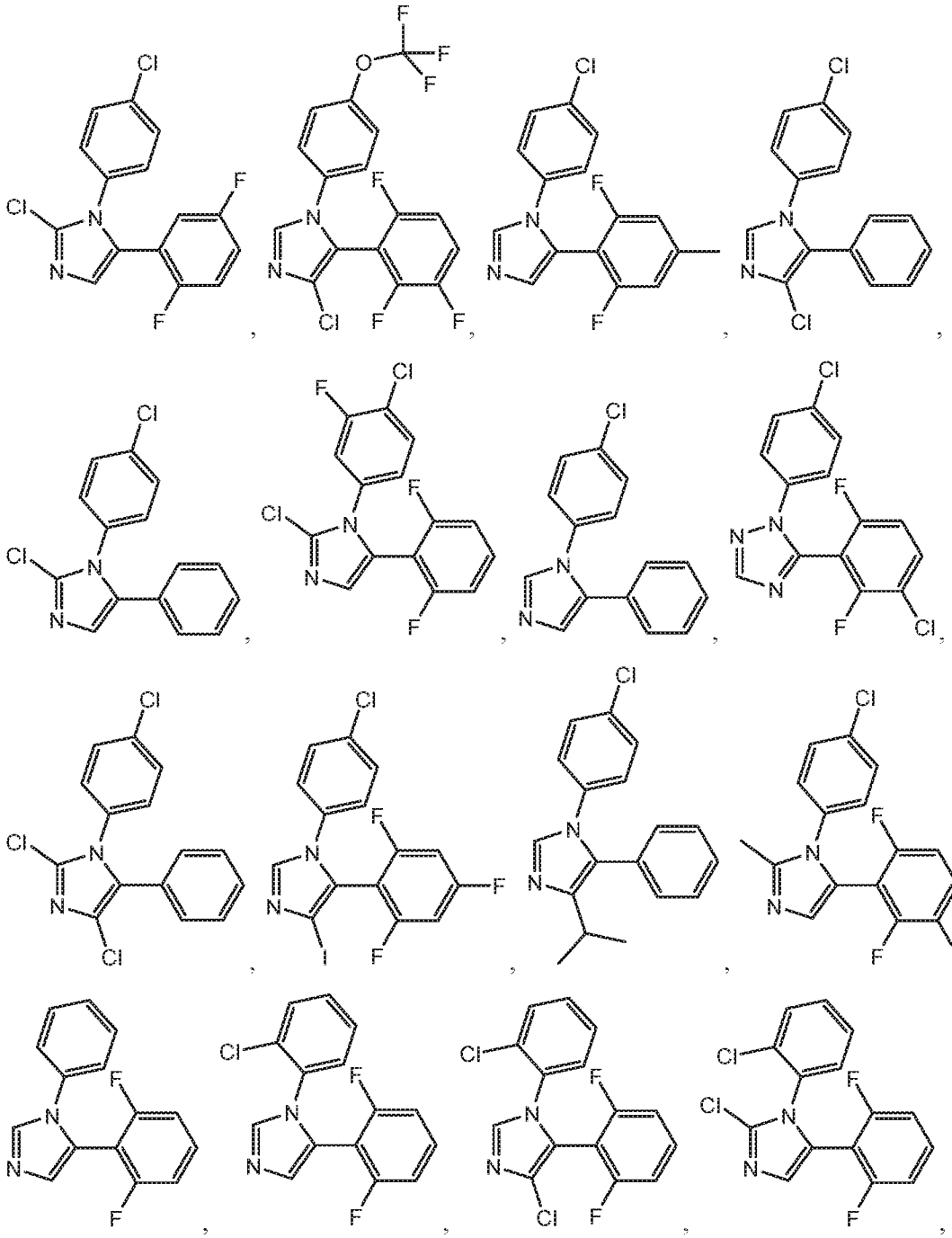
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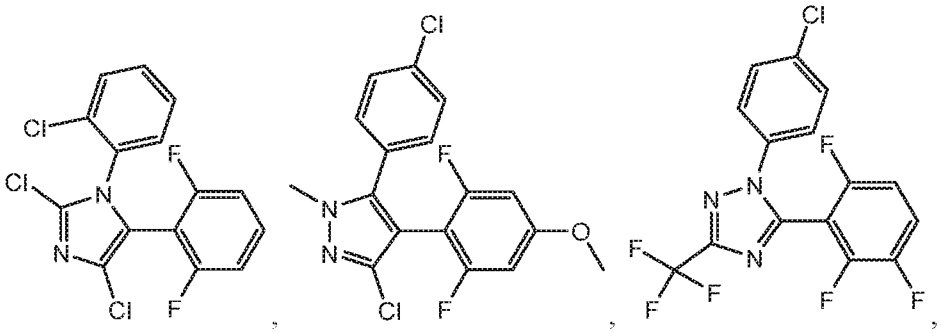
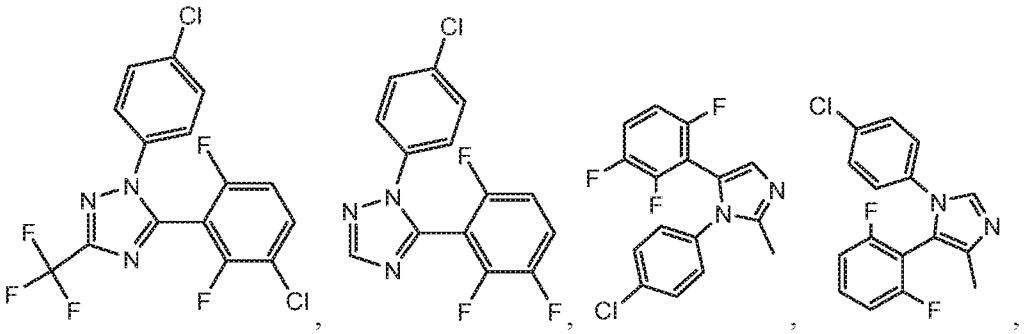
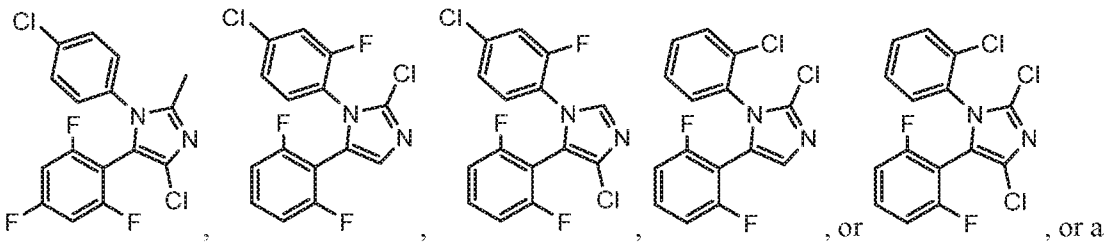
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pharmaceutically acceptable salt thereof.

48. A pharmaceutical composition comprising a compound of claim 47, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

49. A pharmaceutical composition comprising a compound of Formula I, II, III, or IV, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

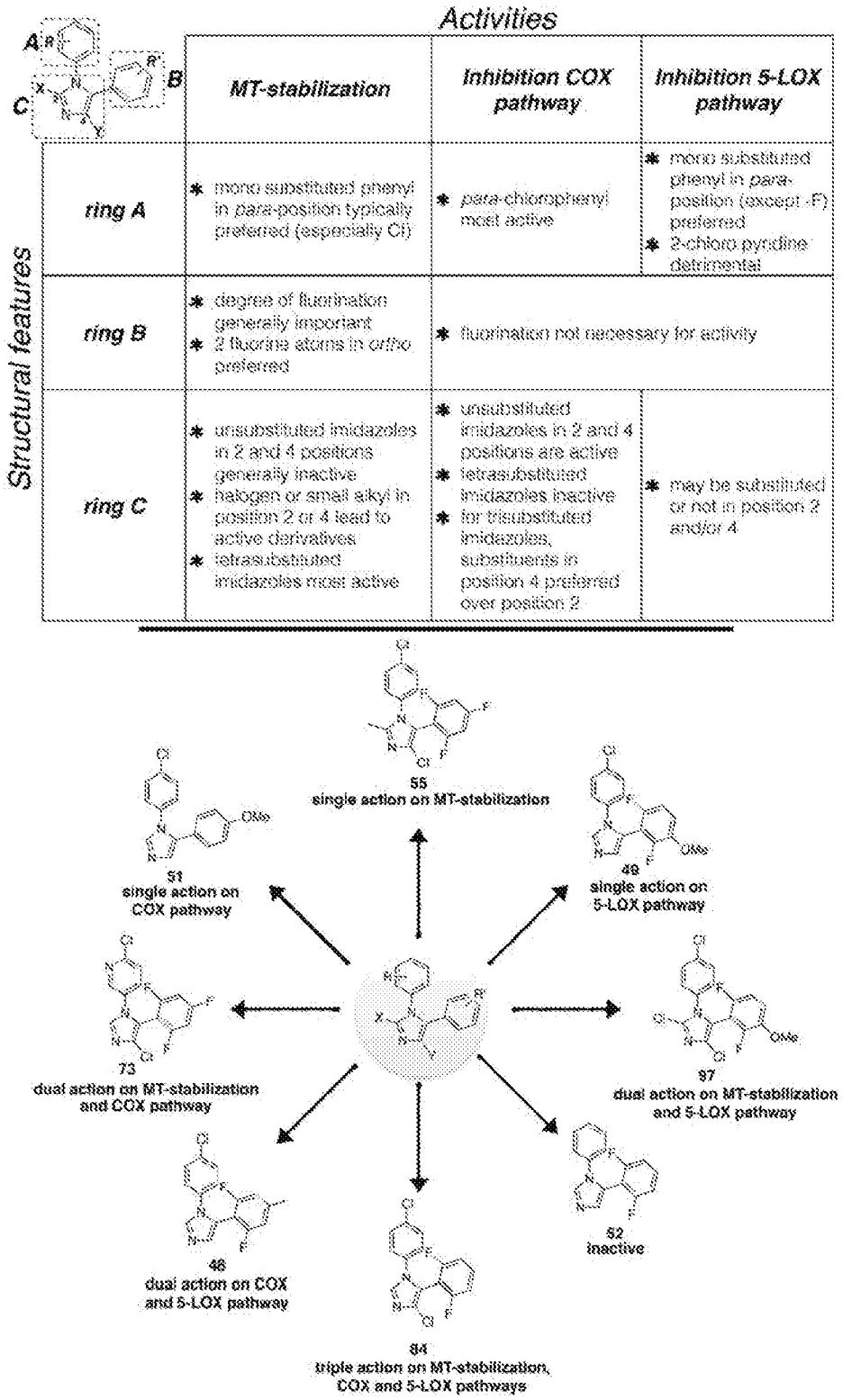

Activities
MT-stabilization
Inhibition COX pathway
Inhibition 5-LOX pathway
Structural features
ring A
mono substituted phenyl in para-position typically preferred (especially Cl)
para-chlorophenyl most active
mono substituted phenyl in para-position (except -F) preferred
2-chloro pyridine detrimental
ring B
degree of fluorination generally important
2 fluorine atoms in ortho preferred
fluorination not necessary for activity
ring C
unsubstituted imidazoles in 2 and 4 positions generally inactive
halogen or small alkyl in position 2 or 4 lead to active derivatives
tetrasubstituted imidazoles most active
unsubstituted imidazoles in 2 and 4 positions are active
tetrasubstituted imidazoles inactive
for trisubstituted imidazoles, substituents in position 4 preferred over position 2
may be substituted or not in position 2 and/or 4
55
single action on MT-stabilization
51
single action on COX pathway
49
single action on 5-LOX pathway
73
dual action on MT-stabilization and COX pathway
97
dual action on MT-stabilization and 5-LOX pathway
52
inactive
48
dual action on COX and 5-LOX pathway
84
triple action on MT-stabilization, COX and 5-LOX pathways

FIG. 1

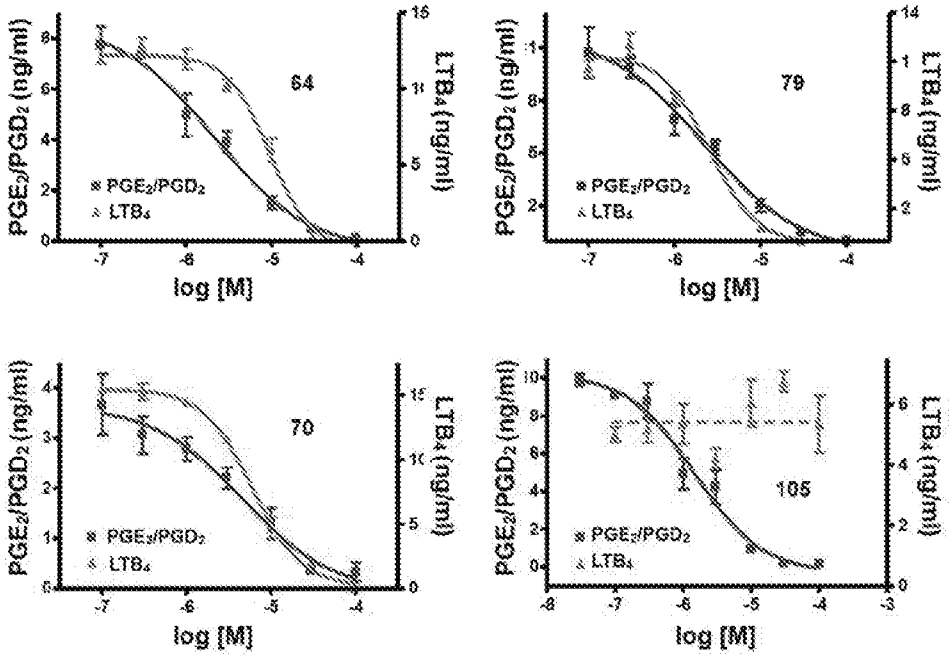

64
79
70
105
PGE2/PGD2 (ng/ml)
LTB4 (ng/ml)
log [M]
PGE2/PGD2
LTB4

FIG. 2


Relative Values
PGE2
PGD2
LTB4
LTC4
Vehicle
29
35
59
60
64
67
68
70
84
87
92
79
98

FIG. 3

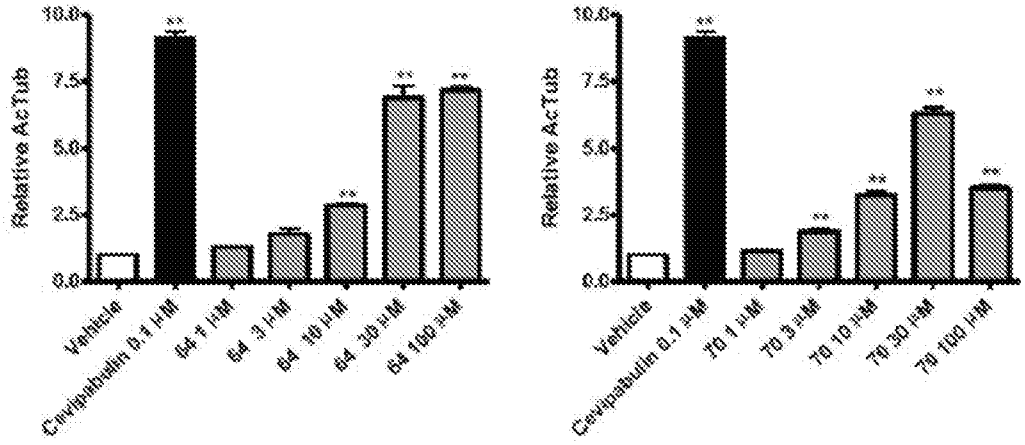

Relative AcTub
10.0
7.5
5.0
2.5
0.0
**
Vehicle
Cevipabulin 0.1 nM
64 1 nM
64 3 nM
64 10 nM
64 30 nM
64 100 nM
Relative AcTub
10.0
7.5
5.0
2.5
0.0
**
Vehicle
Cevipabulin 0.1 nM
TO 1 nM
TO 3 nM
TO 10 nM
TO 30 nM
TO 100 nM

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/50379

A. CLASSIFICATION OF SUBJECT MATTER
IPC - A61K 31/4164; C07D 233/64 (2017.01)
CPC - A61K 31/4164; C07D 233/64

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2012/0277217 A1 (MAUTINO, MR et al.) 01 November 2012; paragraphs [0014], [0124], [0402]-[0404], [0456], [0464]	1-2, 4, 7, 10, 12, 14, 17, 20, 23, 45/1-2, 45/4, 45/7, 45/10, 45/12, 45/14, 45/17, 45/20, 45/23, 49 --- 40/1-2, 40/4, 40/7, 40/10, 40/12, 40/14, 40/17, 40/20, 40/23, 41/40/1-2, 41/40/4, 41/40/7, 41/40/10, 41/40/12, 41/40/14, 41/40/17, 41/40/20, 41/40/23, 42/40/1-2, 42/40/4, 42/40/7, 42/40/10, 42/40/12, 42/40/14, 42/40/17, 42/40/20, 42/40/23, 43/1-2, 43/4, 43/7, 43/10, 43/12, 43/14, 43/17, 43/20, 43/23, 44/1-2, 44/4, 44/7, 44/10, 44/12, 44/14, 44/17, 44/20, 44/23, 46/1-2, 46/4, 46/7, 46/10, 46/12, 46/14, 46/17, 46/20, 46/23

☒ 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
"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

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2017 (11.10.2017)	02 JAN 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/50379

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/089349 A1 (TABACZYNSKI, DA) 18 June 2015; paragraphs [0016], [0033]; claim 79	40/1-2, 40/4, 40/7, 40/10, 40/12, 40/14, 40/17, 40/20, 40/23, 41/40/1-2, 41/40/4, 41/40/7, 41/40/10, 41/40/12, 41/40/14, 41/40/17, 41/40/20, 41/40/23, 42/40/1-2, 42/40/4, 42/40/7, 42/40/10, 42/40/12, 42/40/14, 42/40/17, 42/40/20, 42/40/23
Y	US 2010/0041756 A1 (SELLEY, ML et al.) 18 February 2010; abstract	43/1-2, 43/4, 43/7, 43/10, 43/12, 43/14, 43/17, 43/20, 43/23, 44/1-2, 44/4, 44/7, 44/10, 44/12, 44/14, 44/17, 44/20, 44/23
Y	WO 2011/100295 A2 (MEDICAL COLLEGE OF GEORGIA RESEARCH INSTITUTE, INC.) 18 August 2011; claims 1, 9, 37	46/1-2, 46/4, 46/7, 46/10, 46/12, 46/14, 46/17, 46/20, 46/23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US17/50379

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

-***-Continued Within the Next Supplemental Box-***-

Claims 1-2, 4, 7, 10, 12, 14, 17, 20, 23, 40/1-2, 40/4, 40/7, 40/10, 40/12, 40/14, 40/17, 40/20, 40/23, 41/40/1-2, 41/40/4, 41/40/7, 41/40/10, 41/40/12, 41/40/14, 41/40/17, 41/40/20, 41/40/23, 42/40/1-2, 42/40/4, 42/40/7, 42/40/10, 42/40/12, 42/40/14, 42/40/17, 42/40/20, 42/40/23, 43/1-2, 43/4, 43/7, 43/10, 43/12, 43/14, 43/17, 43/20, 43/23, 44/1-2, 44/4, 44/7, 44/10, 44/12, 44/14, 44/17, 44/20, 44/23, 45/1-2, 45/4, 45/7, 45/10, 45/12, 45/14, 45/17, 45/20, 45/23, 46/1-2, 46/4, 46/7, 46/10, 46/12, 46/14, 46/17, 46/20, 46/23, 49

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
SEE ABOVE

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

-***-Continued from Box No. III Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.
Groups I+, Claims 1-33 and 40-49 (in-part) a method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound of Formula I wherein X is CH; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H (first exemplary compound structure).
The compound, method and composition will be searched to the extent they encompass a compound of Formula I wherein X is CH; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H (first exemplary compound structure). Applicant is invited to elect additional compound(s), with specified structural formula(ae) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part), 2 (in-part), 4 (in-part), 7 (in-part), 10 (in-part), 12 (in-part), 14 (in-part), 17 (in-part), 20 (in-part), 23 (in-part), 40 (in-part), 41 (in-part), 42 (in-part), 43 (in-part), 44 (in-part), 45 (in-part), 46 (in-part), and 49 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula (I) wherein X is CH; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H (first exemplary compound structure). Applicants must specify the claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula I wherein X is N; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H (first exemplary elected compound structure).
Groups I+ share the technical features including a method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound of Formula I wherein X is CH; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H.
However, these shared technical features are previously disclosed by US 2012/0277217 A1 to Mautino, et al. (hereinafter 'Mautino').
Mautino discloses a method of treating cancer in a subject (method of treating cancer; paragraphs [0403]-[0404]) comprising administering to the subject a compound of Formula I wherein X is CH; R1 is H; R2 is H; R3 is H; R4 is H; R5 is H; R6 is H; R7 is H; and R8 is H (administering an effective amount of a compound of formula III, specifically 1,5-diphenyl-1H-imidazole shown on page 20 (R1-R8 are H); paragraphs [0014], [0124], [0403]).
Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Mautino reference, unity of invention is lacking.
Group II, Claims 34-35 and 40-49 (in-part) are directed toward a compound of Formula II, and methods associated therewith.
Group III, Claims 36-37 and 40-49 (in-part) are directed toward a compound of Formula III, and methods associated therewith.
Group IV, Claims 38-39 and 40-49 (in-part) are directed toward a compound of Formula IV, and methods associated therewith.
The inventions listed as Groups I+ and II-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Groups I+ include an imidazole core ring, which is not present in Groups II-IV; the special technical features of Group II include a core pyrazole ring, which is not present in Groups I+ and III-IV; the special technical features of Group III include a 1H-1,2,4-triazole core ring, which is not present in Groups I+, II and IV; and the special technical features of Group IV include a 1H-1,2,3-triazole core ring, which is not present in Groups I+ and II-III.
The common technical features of Groups I+ and II-IV are a method of treating a neurodegenerative disease, peripheral inflammatory condition, cancer, or parasitic disease in a subject comprising administering to the subject a compound, wherein said compound has an aromatic 5-membered ring comprising 1 to 3 nitrogen atoms and is ortho-substituted by two optionally substituted six-membered aromatic rings.
These common technical features are disclosed by Mautino.
Mautino discloses a method of treating cancer in a subject (method of treating cancer; paragraphs [0403]-[0404]) comprising administering to the subject a compound, wherein said compound has an aromatic 5-membered ring comprising 1 to 3 nitrogen atoms and is ortho-substituted by two optionally substituted six-membered aromatic rings (administering an effective amount of a compound of formula III, specifically 1,5-diphenyl-1H-imidazole shown on page 20; paragraphs [0014], [0124], [0403]).
Since the common technical features are previously disclosed by Mautino, these common features are not special and so Groups I+ and II-IV lack unity.