

BENZIMIDAZOLE COMPOUNDS AND USE THEREOF FOR TREATING ALZHEIMER'S DISEASE OR HUNTINGTON'S DISEASE

BACKGROUND

Alzheimer's disease (AD) and Huntington's disease (HD) are both incurable degenerative brain diseases.

More specifically, AD is the most common form of dementia and HD, on the other hand, causes uncontrolled movements of the arms, legs, head, face, and upper body. HD also causes a decline in thinking and reasoning skills, including memory, concentration, judgement, and ability to plan and organize.

Both AD and HD are caused by aberrant aggregation of proteins or peptide. Indeed, AD is triggered by a malfunction of aggregated mutant β -amyloid peptide (A β) and HD arises from a toxic function of aggregated mutant huntingtin protein (HTT).

Human glutaminyl cyclase (QC) catalyzes cyclization of N-terminal residues of glutamine or glutamate to form pyroglutamate (pGlu) on A β and HTT. The pGlu-modified A β and pGlu-modified HTT thus formed are aggregative, neurotoxic, and resistant to proteolysis. They can initiate pathological cascades, resulting in development of AD or HD.

Inhibition of human QC has been found to diminish aggregation of both A β and HTT in cultured macrophage cells and in *Drosophila* and mouse models. See *J. Pharmacol. Exp. Ther.* 2017, 362, 119-130; *J. Med. Chem.* 2017, 60, 2573-2590; *Nat. Med.* 2008, 14(10), 1106-1111; and *Nat. Chem. Bio.* 2015, 11, 347-354.

As such, human QC is an emerging drug target for the treatment of AD or HD.

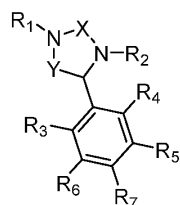
Currently, only a few drug candidates that inhibit QC are in clinical trials for treating AD or HD. There is a need to develop new QC inhibitors.

Earlier studies have shown that QC is a zinc-dependent enzyme. As such, compounds capable of chelating zinc at active sites of QC, e.g., benzimidazole compounds, are potential QC inhibitors.

SUMMARY

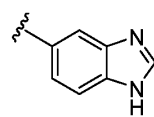
Certain benzimidazole compounds have been found to be QC inhibitors. Unexpectedly, the compounds demonstrate high potency in inhibiting QC and, as such, can be used for treating AD or HD.

In one aspect, this invention relates to the benzimidazole compounds of formula (I) below:



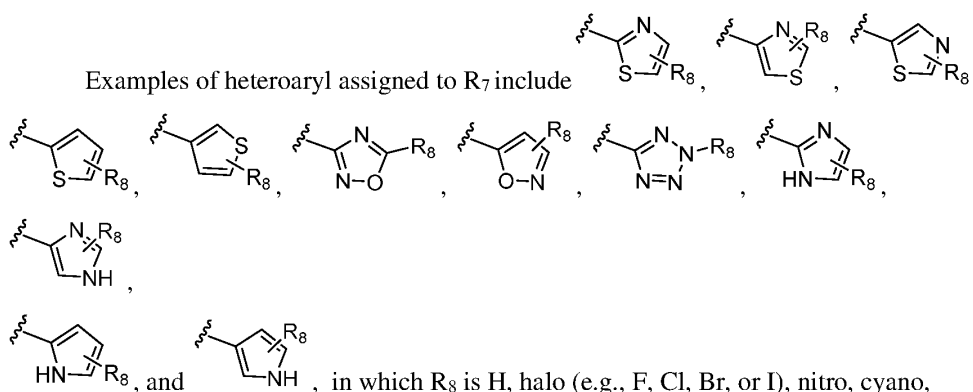
(I).

X and Y, independently, are CH₂ or C=O; R₁ is H or C₁₋₆ alkyl; R₂ is a moiety



containing a phenyl ring fused to a 5-membered heteroaryl ring (e.g., linked to N through the phenyl ring; R₃, R₄, R₅, R₆, and R₇, independently, are H, halo (e.g., F, Cl, Br, or I), nitro, cyano, amino, OH, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl that is optionally substituted by one or more substituents selected from halo (e.g., F, Cl, Br, or I), nitro, cyano, amino, OH, CF₃, -COOH, -COOC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, wherein at least one of R₃, R₄, R₅, R₆, and R₇ is heteroaryl and wherein each of C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, second or third occurrence, is optionally substituted with halo (e.g., F, Cl, Br, or I), nitro, cyano, amino, OH, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

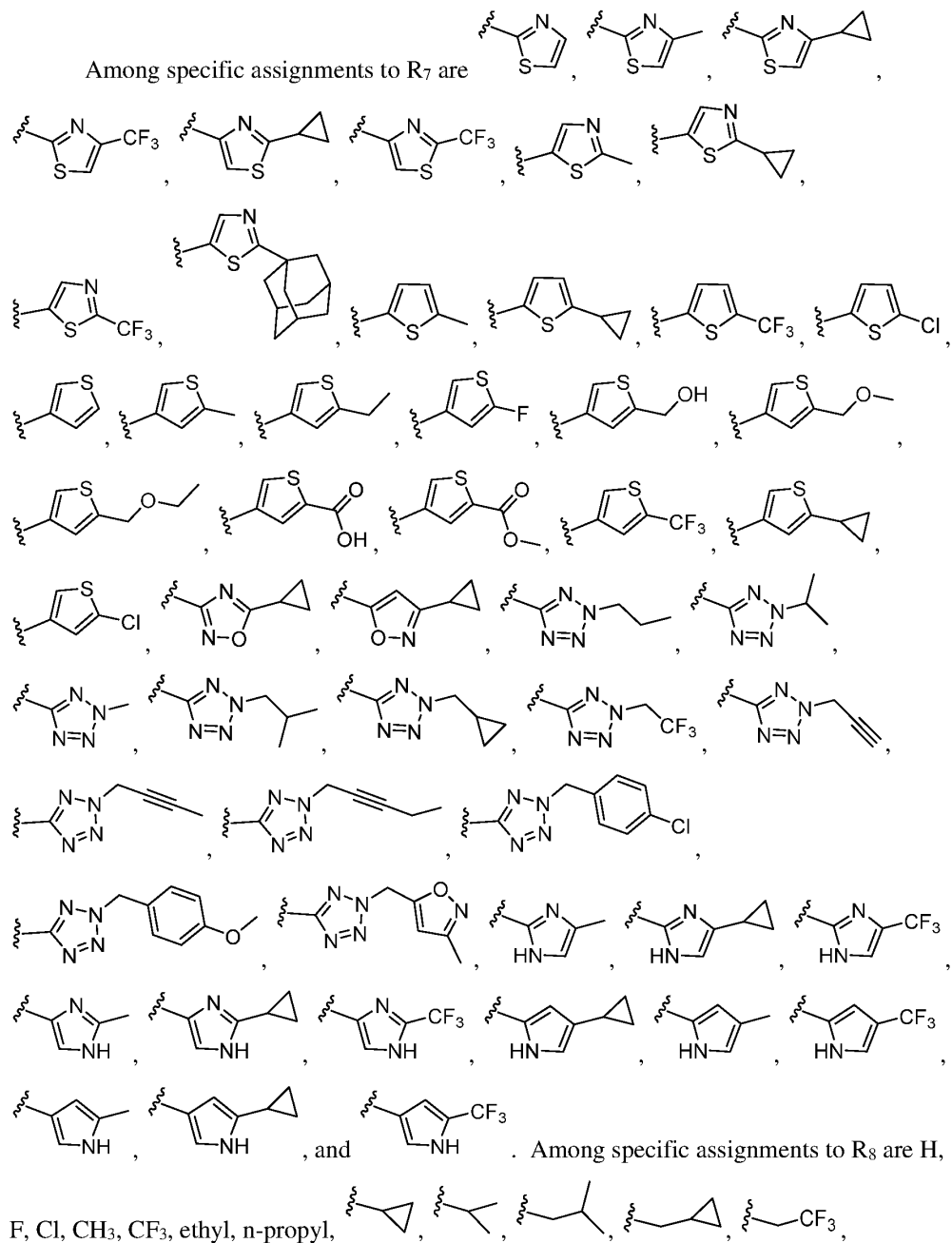
Examples of heteroaryl assigned to R₇ include

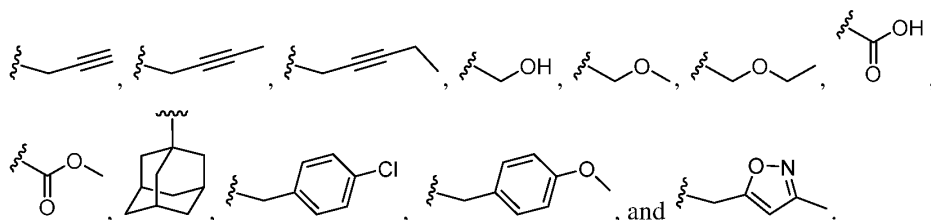


in which R₈ is H, halo (e.g., F, Cl, Br, or I), nitro, cyano, amino, OH, CF₃, -COOH, -COOC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, each of C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl being

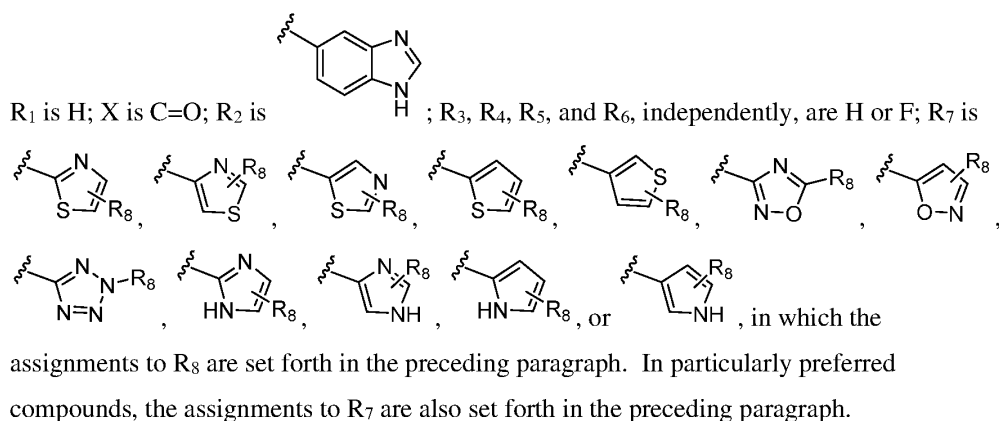
optionally substituted with halo (e.g., F, Cl, Br, or I), nitro, cyano, amino, OH, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

Among specific assignments to R₇ are





The above-described compounds can be classified into two subsets. In one subset, Y is CH₂ and, in the other subset, Y is C=O. Preferred compounds in each subset feature that



The term “alkyl” herein refers to a saturated, linear, or branched hydrocarbon moiety, e.g., –CH₃ or –CH(CH₃)₂. The term “alkoxy” refers to an –O(C₁₋₆ alkyl) radical, e.g., –OCH₃ and –OCH(CH₃)₂. The term “alkenyl” refers to a linear or branched hydrocarbon moiety that contains at least one double bond, e.g., –CH=CH–CH₃. The term “alkynyl” refers to a linear or branched hydrocarbon moiety that contains at least one triple bond, e.g., –C≡C–CH₃. The term “cycloalkyl” refers to a saturated mono-, di-, or tri-cyclic hydrocarbon moiety, e.g., cyclohexyl. The term “heterocycloalkyl” refers to a saturated mono-, di-, or tri-cyclic moiety having at least one ring heteroatom (e.g., N, O, and S), e.g., 4-tetrahydropyranyl. The term “aryl” refers to a hydrocarbon moiety having one or more aromatic rings. Examples of aryl include phenyl, phenylene, naphthyl, naphthylene, pyrenyl, anthryl, and phenanthryl. The term “heteroaryl” refers to a moiety having one or more aromatic rings that contain at least one heteroatom (e.g., N, O, and S). Examples of heteroaryl include furyl, furylene, fluorenyl, pyrrolyl, thienyl, oxazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidinyl, quinazolinyl, quinolyl, isoquinolyl, and indolyl. The term “amino” refers to a radical of –NH₂, –NH(C₁₋₆ alkyl), or –N(C₁₋₆ alkyl)₂, e.g., –NHCH₃ and –NHCH(CH₃)₂.

Alkoxy, Alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl mentioned herein include both substituted and unsubstituted moieties, unless specified

otherwise. Substituents on alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl include, but are not limited to, halo, nitro, cyano, amino, OH, CF₃, -COOH, -COOC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

The compounds described above include the compounds themselves, as well as their salts, prodrugs, stereoisomers, and tautomers, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a compound of formula (I). Suitable anions include chloride, bromide, iodide, sulfate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, acetate, malate, tosylate, tartrate, fumurate, glutamate, glucuronate, lactate, glutarate, and maleate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a compound of formula (I). Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The compounds also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives, which, upon administration to a subject, are capable of providing active compounds. Stereoisomers of the compounds of formula (I) can include *cis* and *trans* isomers, optical isomers such as (*R*) and (*S*) enantiomers, diastereomers, geometric isomers, rotational isomers, atropisomers, conformational isomers, and mixtures thereof. Tautomers of the compounds include those exhibiting more than one type of isomerism.

In another aspect, this invention relates to a pharmaceutical composition containing a compound of formula (I) and a pharmaceutical acceptable carrier.

The carrier in the pharmaceutical composition must be “acceptable” in the sense that it is compatible with the active ingredient of the composition (and preferably, capable of stabilizing the active ingredient) and not deleterious to the subject to be treated. Examples of carriers include colloidal silicon oxide, magnesium stearate, cellulose, sodium lauryl sulfate, and D&C Yellow 10.

Also within the scope of this invention is a method of treating AD or HD. The method includes administering to a subject in need thereof an effective amount of a compound of formula (I).

The term “treating” refers to application or administration of the compound or its salt, prodrug, stereoisomer, or tautomer to a subject with the purpose to confer a therapeutic effect, i.e., to cure, relieve, alter, affect, ameliorate, or prevent AD or HD, the symptom of AD or HD, or the predisposition toward AD or HD.

“An effective amount” is the amount of the compound or its salt, prodrug, stereoisomer, or tautomer, which is required to confer the desired effect on the subject. Effective amounts vary, as recognized by those skilled in the art, depending on route of administration, excipient usage, and the possibility of co-usage with other therapeutic treatments such as use of other active agents.

A composition having a compound of formula (I) or its salt, prodrug, stereoisomer, or tautomer can be administered parenterally or orally. The term “parenteral” as used herein refers to subcutaneous, intracutaneous, intravenous, intraperitoneal, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection, as well as any suitable infusion technique.

A composition for oral administration can be any orally acceptable dosage form, e.g., capsules, tablets, emulsions and aqueous suspensions, dispersions, and solutions. In the case of tablets, commonly used carriers include, among others, lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with an emulsifying or suspending agent. If desired, a sweetening, flavoring, or coloring agent can be added.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

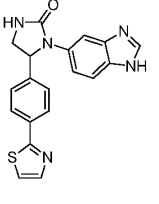
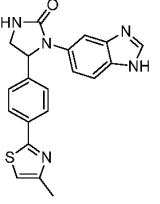
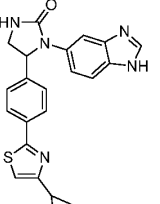
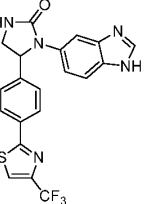
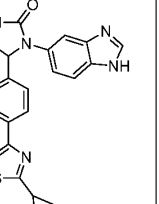
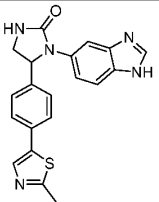
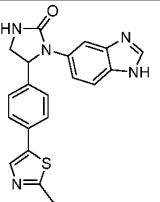
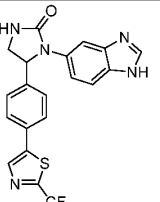
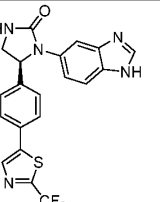
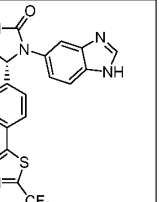
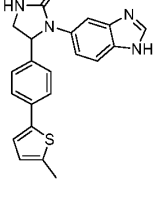
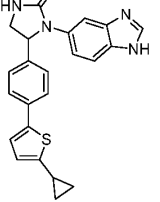
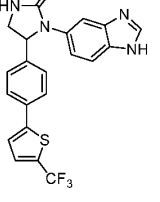
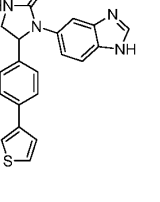
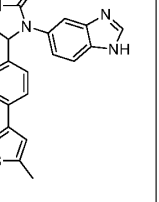
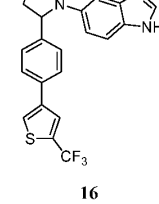
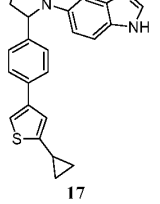
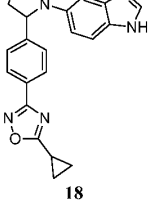
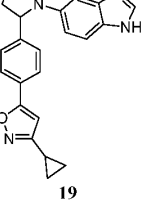
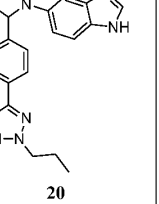
Disclosed in detail hereinafter are the benzimidazole compounds of formula (I) shown above.

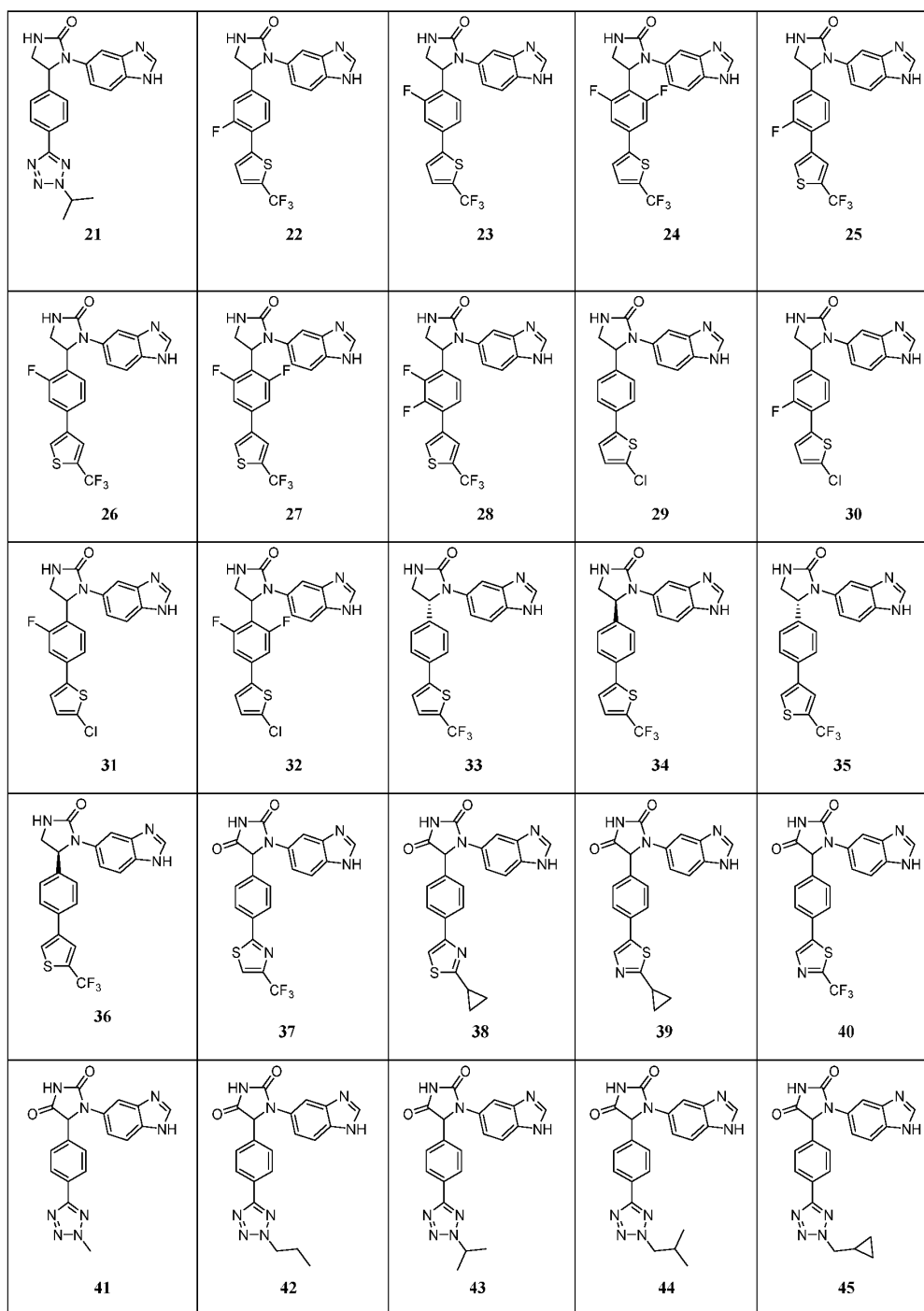
Compounds of this invention that have chiral centers may exist as stereoisomers. Stereoisomers of the compounds of formula (I) can include *cis* and *trans* isomers, optical isomers such as (*R*) and (*S*) enantiomers, diastereomers, geometric isomers, rotational isomers, atropisomers, conformational isomers, and tautomers of the compounds, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomers). All such isomeric forms are contemplated. In addition, the compounds of formula (I) in the present invention may exhibit the phenomena of tautomerism.

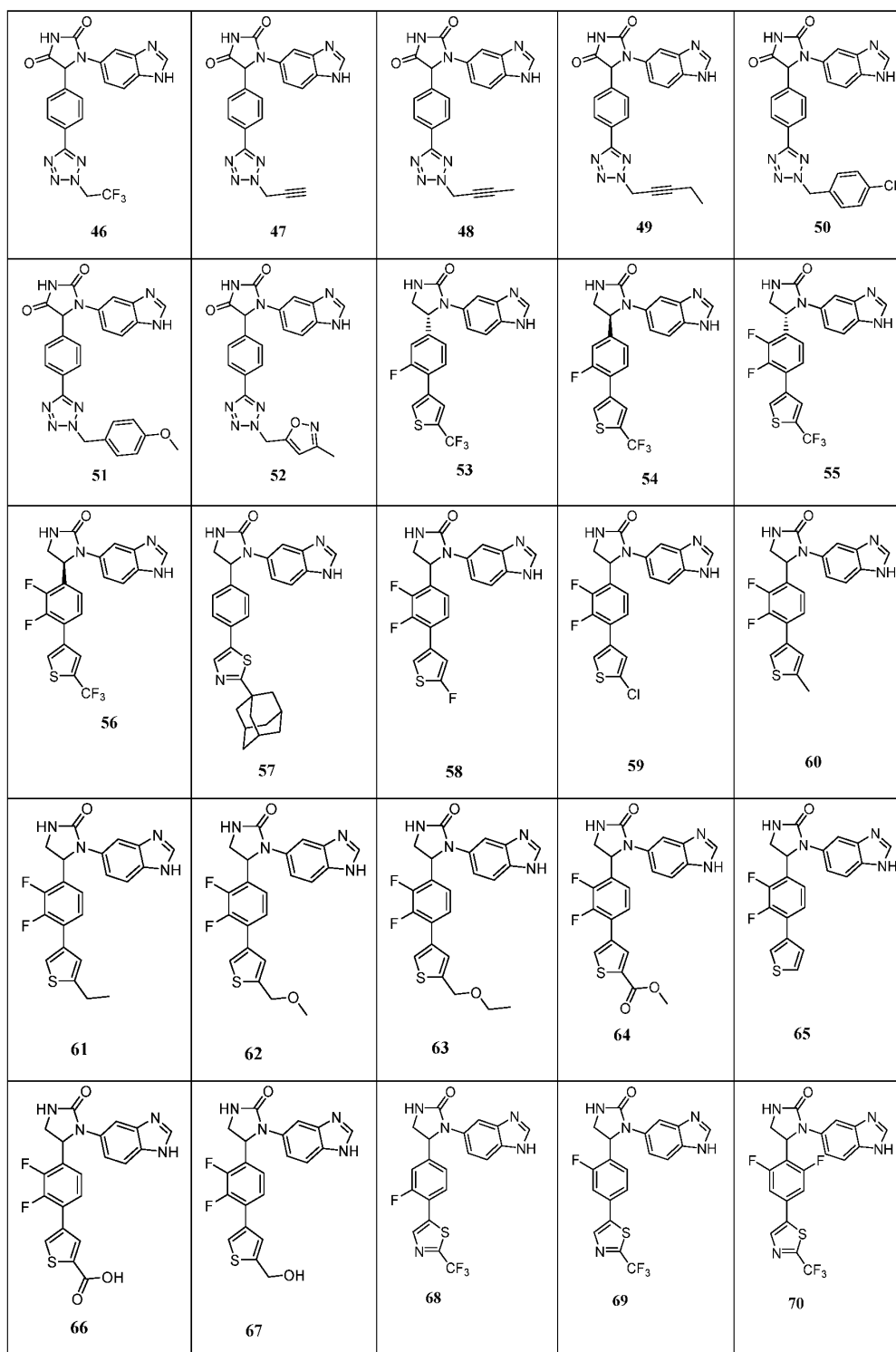
Of note, the compounds of formula (I) can have an enantiomeric excess of 90% or higher (e.g., $\geq 95\%$ and $\geq 99\%$).

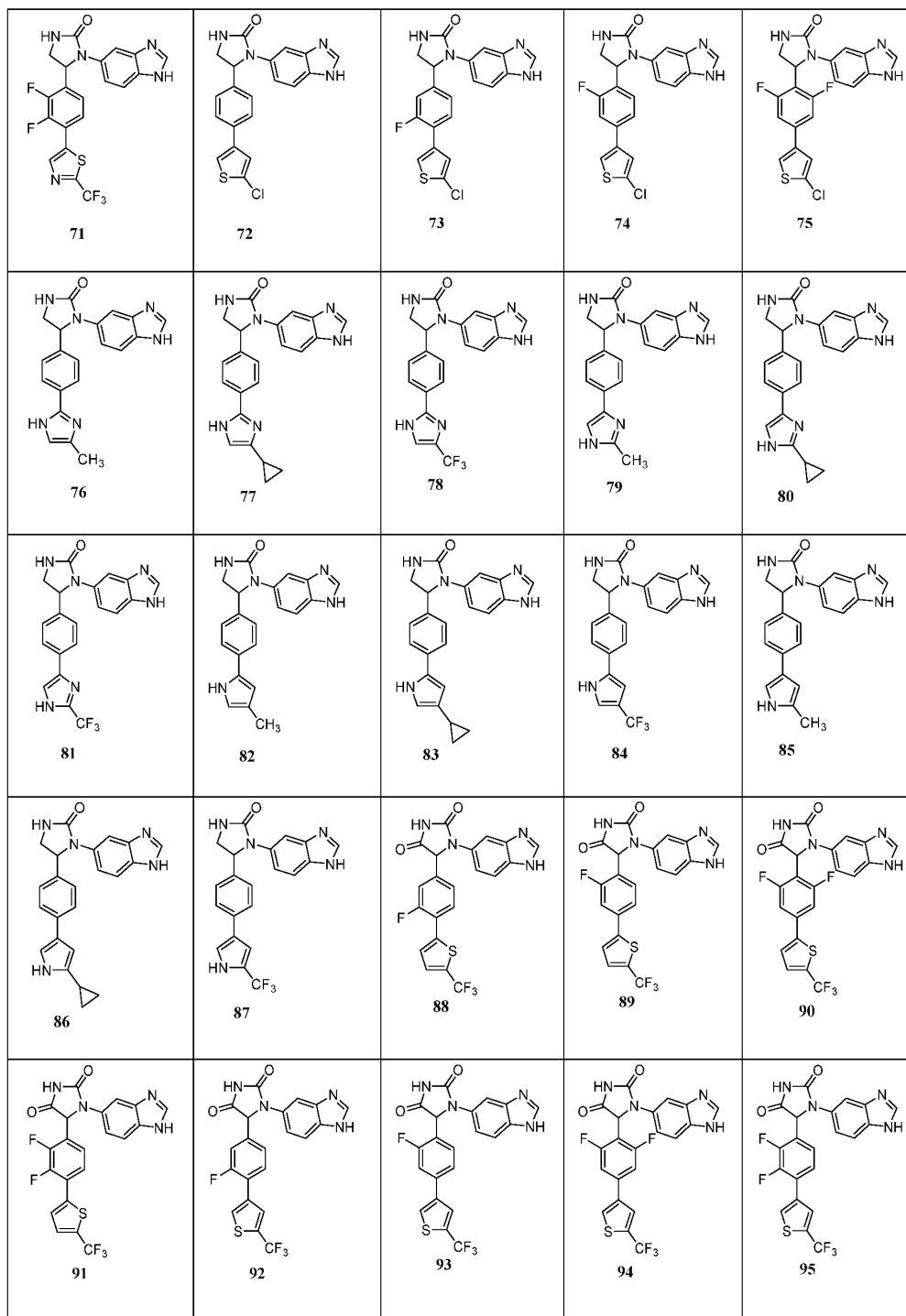
117 exemplary compounds of formula (I) are shown in Table 1 below:

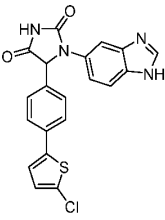
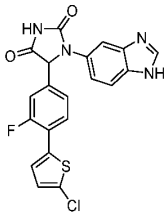
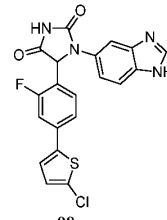
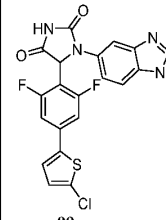
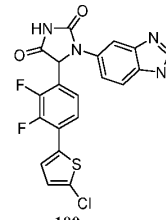
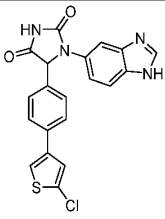
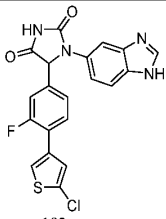
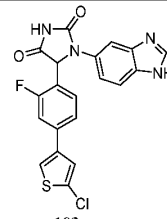
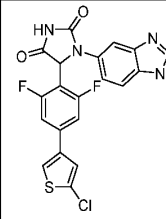
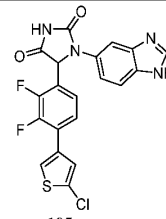
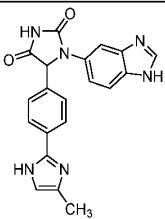
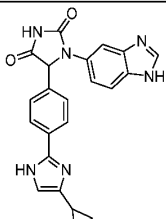
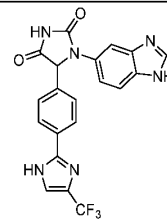
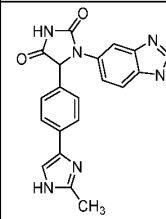
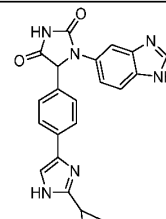
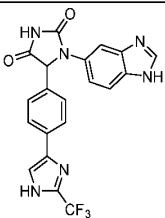
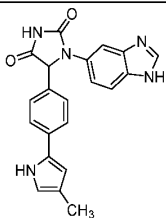
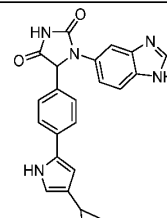
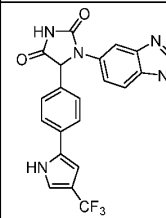
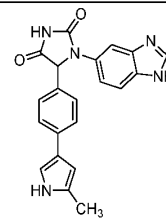
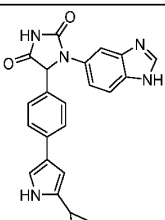
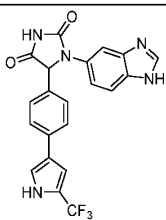
Table 1

 1	 2	 3	 4	 5
 6	 7	 8	 9	 10
 11	 12	 13	 14	 15
 16	 17	 18	 19	 20







 96	 97	 98	 99	 100
 101	 102	 103	 104	 105
 106	 107	 108	 109	 110
 111	 112	 113	 114	 115
 116	 117			

Among the 117 compounds listed above, Compounds **9** and **10** are the two enantiomers of Compound **8**; Compounds **33** and **34** are the two enantiomers of Compound **13**; Compounds **35** and **36** are the two enantiomers of Compound **16**; Compounds **53** and **54** are the two enantiomers of Compound **25**; and Compounds **55** and **56** are the two enantiomers of Compound **28**.

Compounds **9**, **34**, **36**, **54**, and **56** are preferred.

Methods for synthesizing the compounds of formula (I) are well known in the field. Note that the procedures for preparing as many as 67 compounds, i.e., Compounds **1-67**, are set forth in EXAMPLE 1 below.

The compounds thus prepared can be initially screened using *in vitro* assays for their potency in inhibiting the activity of glutamyl cyclase (QC). The *in vitro* assays are set forth in EXAMPLE 2 below. Further, the prepared compounds can be subsequently evaluated using *in vivo* assays. The *in vivo* assays are set forth in EXAMPLE 3 below. The selected compounds can be further tested to verify their efficacy in treating AD or HD. Based on the results, appropriate dosage ranges and administration routes can be investigated and determined.

All reagents and solvents were purchased from commercial suppliers and used without further purification unless otherwise noted. All anhydrous reactions were performed under a nitrogen atmosphere using dry solvents. All reactions were monitored by thin layer chromatography using Merck Silica gel 60 F₂₅₄ glass-backed plate. Column chromatography was performed by Merck silica gel 60 (0.040–0.063 mm, 230–400 mesh). Purity of the final compounds was determined on a Hitachi 2000 series HPLC system with a reverse phase C₁₈ column (Agilent ZORBAX Eclipse XDB-C18 5 µm, 4.6 mm x 150 mm), operating at 25 °C. Mobile phase A was acetonitrile. Mobile phase B was 10 mM NH₄OAc aqueous solution containing 0.1% formic acid. The gradient system started from A/B (10%/90%) at 0 min to A/B (90%/10%) at 45 min. The flow rate of the mobile phase was 0.5 mL/min, and the injection volume of the sample was 5 µL. Peaks were detected at 254 nm. The purity of all tested compounds is >95%. LC/MS data were measured on an Agilent MSD-1100 ESI-MS/MS System. All tested compounds were detected at UV 254 nm unless otherwise stated. ¹H NMR spectra were measured by Varian Mercury-300 and Varian Mercury-400 spectrometers, and the chemical shifts (δ) were reported in parts per million (ppm) relative to the resonance of the solvent peak. Multiplicities are reported with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), or br (broad).

Without further elaboration, it is believed that one skilled in the art can, based on the above description, utilize the present invention to its fullest extent. The specific embodiments described in EXAMPLES 1-3 below are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All publications cited herein are incorporated by reference.

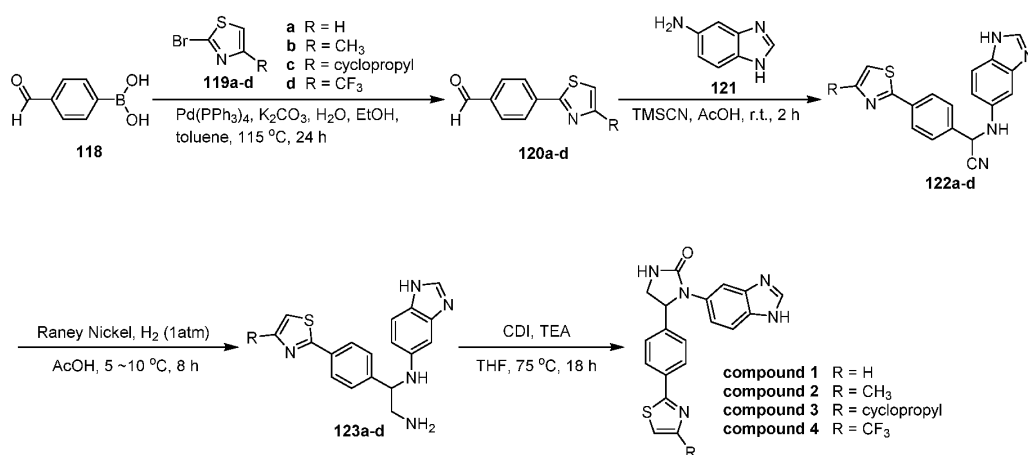
EXAMPLE 1: Preparation and Characterization of Compounds

Compounds **1-67** were prepared by Synthetic Methods 1-18 respectively shown in Schemes 1-18 below.

Synthetic Method 1

Compounds **1-4**, each having a 1,3-thiazol-2-yl ring, were prepared according to the synthetic procedures shown in Scheme 1 below. (4-Formylphenyl)boronic acid **118** was coupled with 2-bromothiazole derivatives **119a-d** under a Suzuki-coupling condition to afford 4-(1,3-thiazol-2-yl)benzaldehyde derivatives **120a-d**. The core structure of imidazolidinone ring was built in the following three steps. TMSCN was added to a solution of benzaldehydes **120a-d** and 1*H*-benzimidazol-5-amine **121** in acetic acid. The reaction mixture was stirred at room temperature for 2 hours and then worked up to yield amino acetonitriles **122a-d**, which were hydrogenated using Raney Nickel catalyst in acetic acid at 5~10 °C to afford diamines **123a-d**. In the final step, 1,1'-carbonyldiimidazole (CDI) was added to a solution of diamines **123a-d** in THF and then stirred at 75 °C for 18 hours. Compounds **1-4** were obtained after purification by column chromatography.

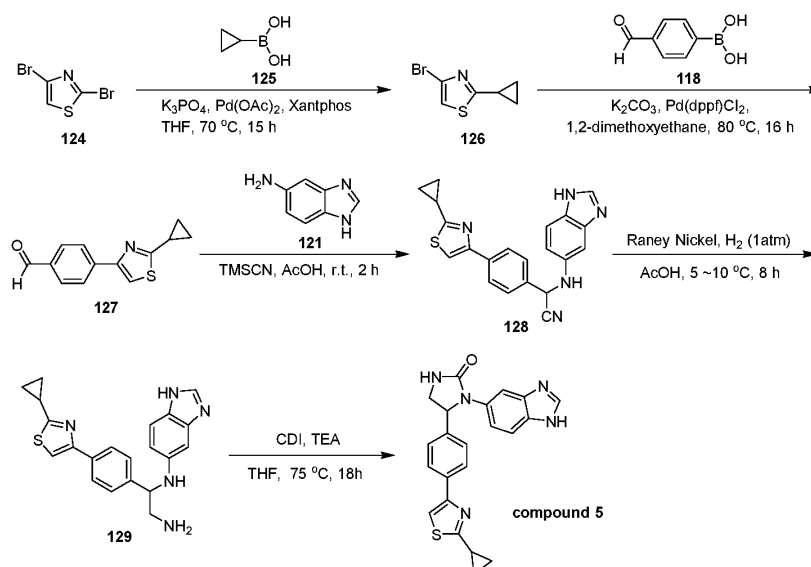
Scheme 1



Synthetic Method 2

4-(2-Cyclopropyl-1,3-thiazol-4-yl)benzaldehyde **127**, a precursor, was synthesized under two different Suzuki-coupling conditions shown in Scheme 2 below. 2,4-Dibromo-1,3-thiazole **124**, a starting material, was selectively coupled at 2-position with cyclopropylboronic acid **125** using $\text{Pd}(\text{OAc})_2$ as a catalyst. The resultant product **126** was coupled at 4-position with (4-formylphenyl)boronic acid **118** using $\text{Pd}(\text{dppf})\text{Cl}_2$ as a catalyst to afford precursor **127** having a 1,3-thiazol-4-yl ring. This precursor was then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain the final compound (Compound **5**).

Scheme 2

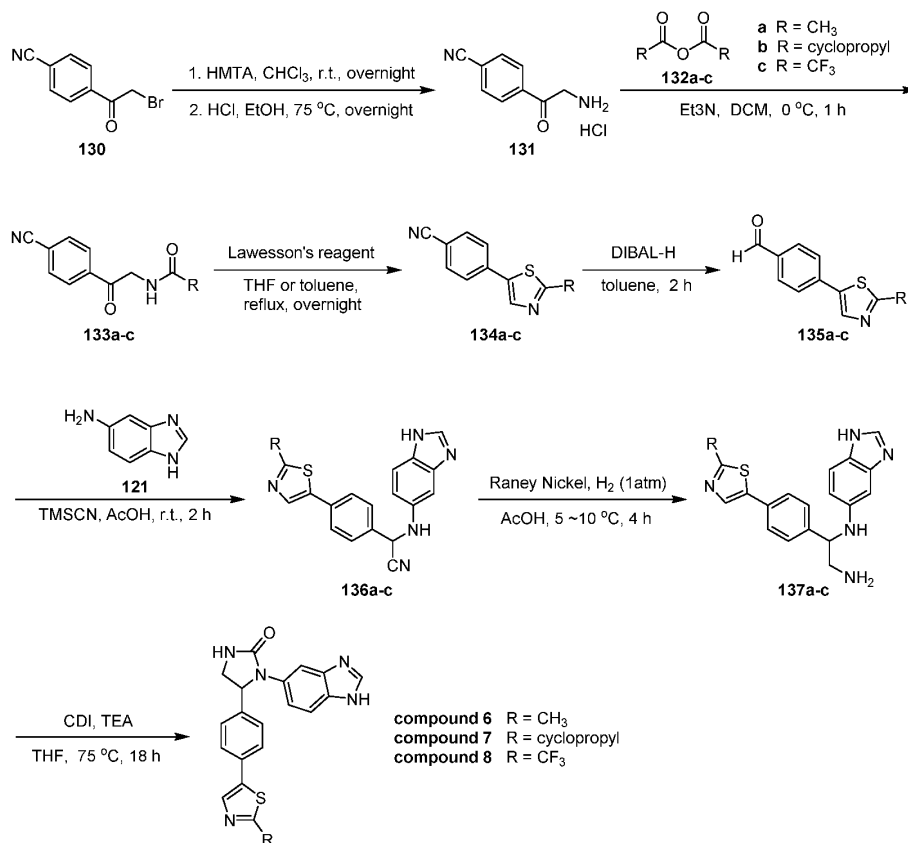


Synthetic Method 3

Compounds **6-8**, each having a 3-thiazol-5-yl ring, were prepared in eight steps as shown in Scheme 3 below. Commercially available starting material 4-(bromoacetyl)benzonitrile **130** was transformed into 4-(aminoacetyl)benzonitrile hydrochloride **131** after a substitution reaction using HMTA followed by refluxing in a solution of hydrochloride acid in ethanol. Compound **131** was then acetylated with variable anhydrides **132a-c** to obtain amides **133a-c**, which were subsequently treated with the Lawesson's reagent in THF or toluene under reflux to afford (1,3-thiazol-5-yl)benzonitrile analogs **134a-c**. The benzonitrile analogs **134a-c** were reduced by DIBAL-H to form benzaldehyde precursors **135a-c**. These

precursors were then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compounds **6-8**.

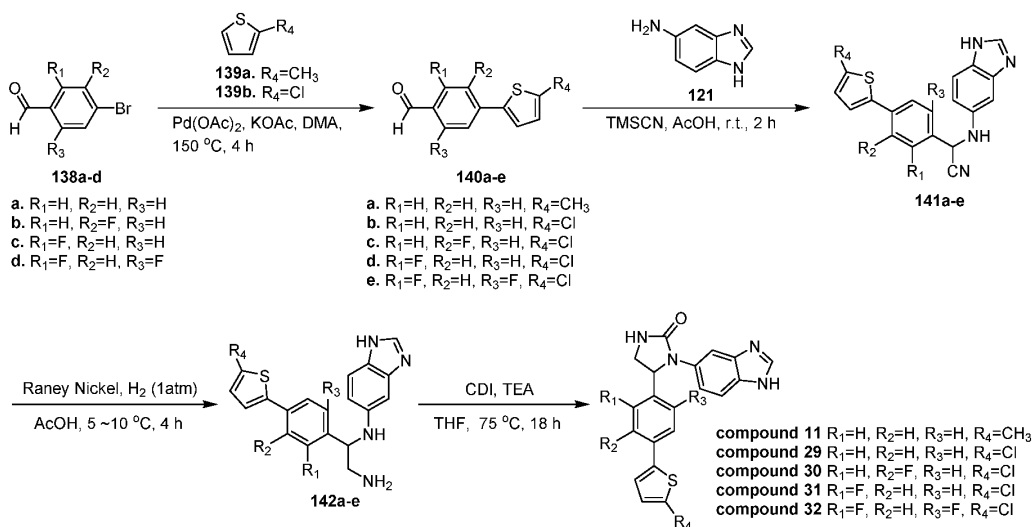
Scheme 3



Synthetic Method 4

Compounds **11** and **29-32**, each having a thiophen-2-yl ring, were prepared by the synthetic procedures shown in Scheme 4 below. 4-Bromobenzaldehydes **138a-d** were each coupled with 2-substituted thiophene **139a** or **139b** under a Suzuki-coupling condition to afford benzaldehyde precursors **140a-e**. These precursors were then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compounds **11** and **29-32**.

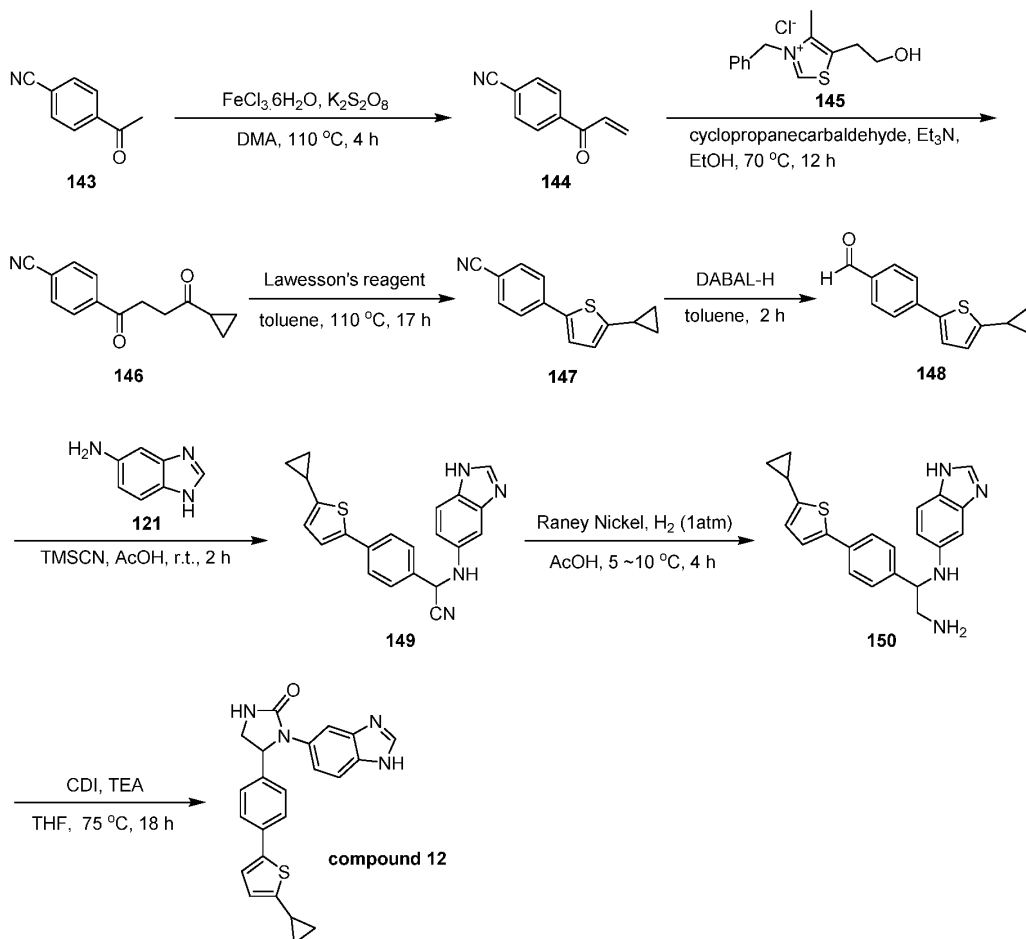
Scheme 4



Synthetic Method 5

Compound **12**, having a thiophen-2-yl ring, was prepared by the synthetic procedures shown in Scheme 5. 4-Acetyl benzonitrile **143** was α -methylenated using $FeCl_3 \cdot 6H_2O$ and $K_2S_2O_8$ in dimethylacetamide (DMA). The resultant α -methylene product **144** reacted with cyclopropanecarbaldehyde under a Stetter condition to form 1,4-dicarbonyl compound **146**. This dicarbonyl compound was then treated with the Lawesson's reagent under refluxing in toluene to afford 4-(5-cyclopropylthiophen-2-yl) benzonitrile **147**, which was reduced by DABAL-H to form benzaldehyde precursor **148**. This precursor was then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compound **12**.

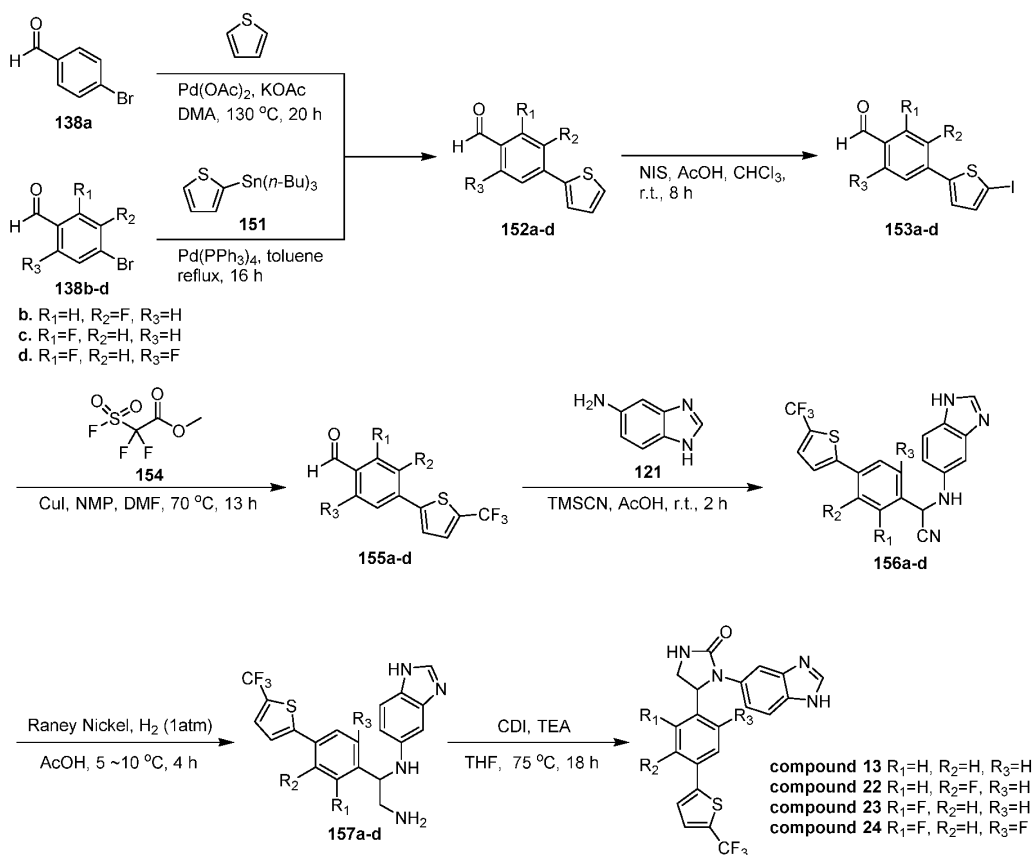
Scheme 5



Synthetic Method 6

Compounds **13** and **22-24**, each having a thiophen-2-yl ring, were prepared by the synthetic procedures shown in Scheme 6. 4-Bromobenzaldehydes **138a-d** were each coupled with thiophene under two different Suzuki-coupling conditions to form 4-(thiophen-2-yl)-benzaldehydes **152a-d**. The benzaldehydes were iodinated by *N*-iodosuccinimide (NIS) to produce iodinated products **153a-d**, which were trifluoromethylated using methyl difluoro-(fluoro-sulfonyl) acetate **154** and copper iodide to afford precursors **155a-d**. These precursors were then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compounds **13** and **22-24**.

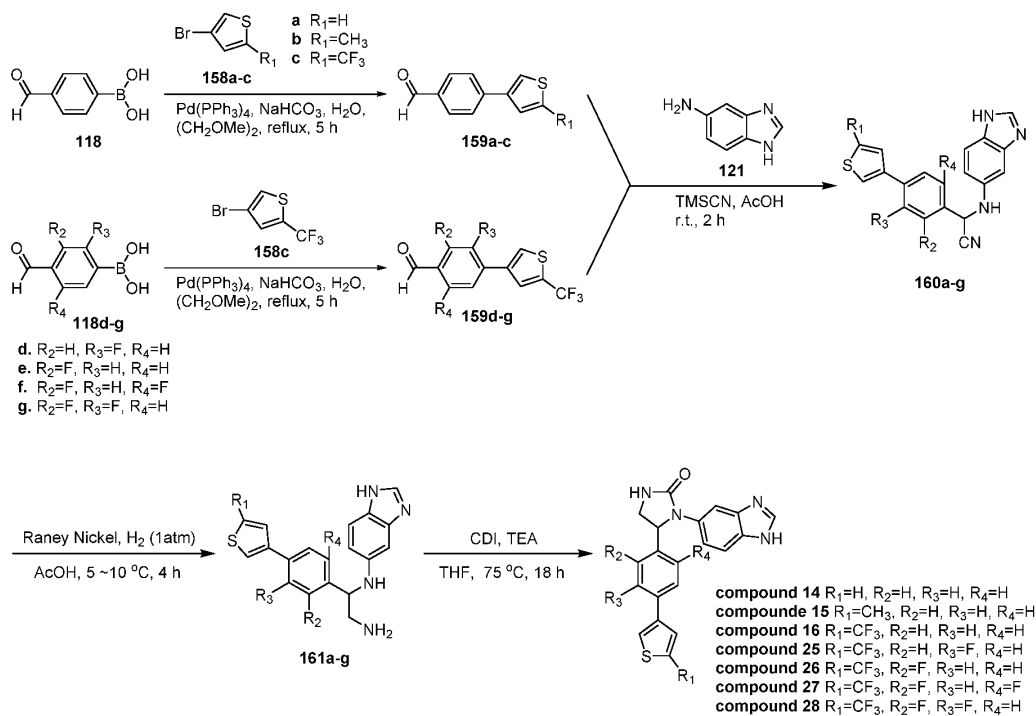
Scheme 6



Synthetic Method 7

Compounds **14-16** and **25-28**, each having a thiophen-3-yl ring, were prepared by the synthetic procedures shown in Scheme 7. Various (4-formylphenyl) boronic acids were coupled with 3-bromothiophene derivatives **158a-c** under a Suzuki-Miyaura coupling condition. The resultant products **159a-g** were then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compounds **14-16** and **25-28**.

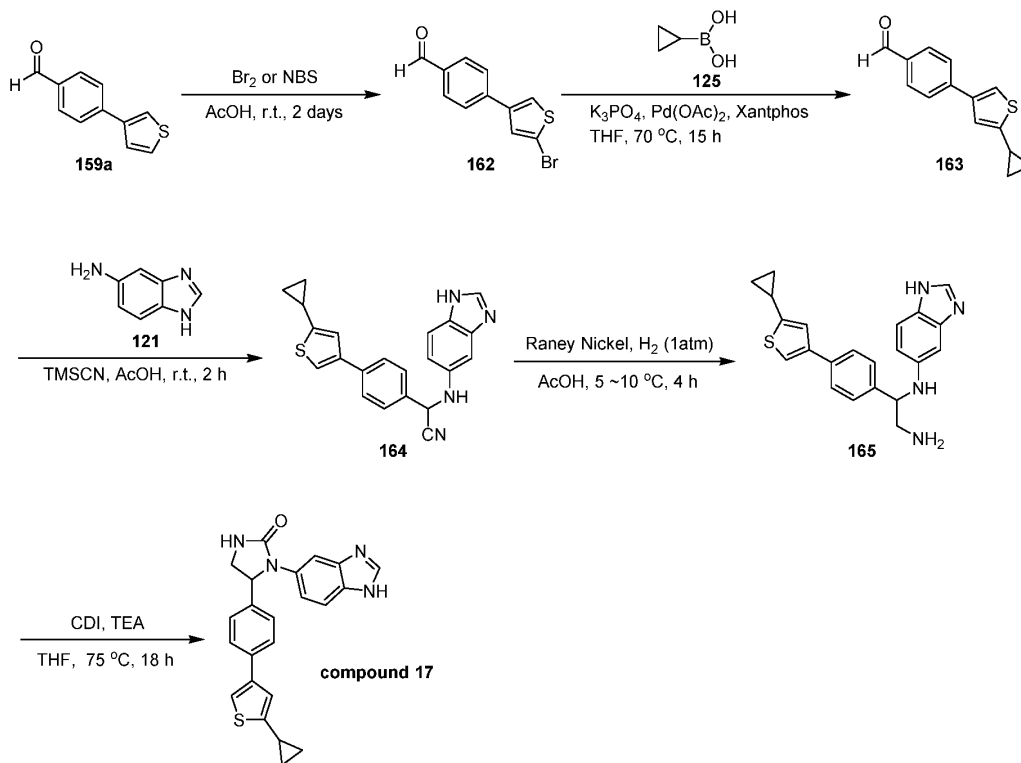
Scheme 7



Synthetic Method 8

Compound **17**, having a thiophen-3-yl ring, was prepared by the synthetic procedures shown in Scheme 8 below. Starting material **159a** was selectively brominated by bromine or NBS in acetic acid to afford 2-brominated thiophene product **162**, which was coupled with cyclopropyl-boronic acid under a Suzuki-coupling condition to form 4-(2-cyclopropylthiophen-3-yl)benzaldehyde **163**. This benzaldehyde was then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compound **17**.

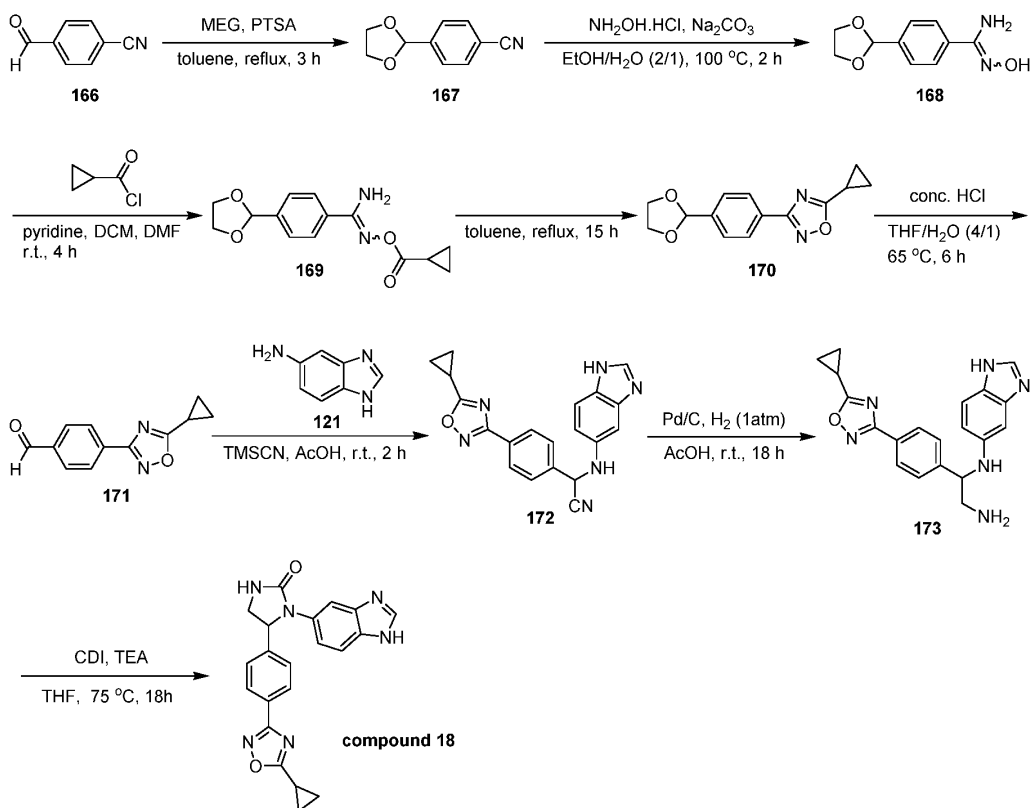
Scheme 8



Synthetic Method 9

Compound **18**, having a 1,2,4-oxadiazol-3-yl ring, was prepared by the synthetic procedures shown in Scheme 9. 4-Formylbenzonitrile **166**, a starting material, was protected by monoethyleneglycol (MEG) to form acetal **167**, which reacted with hydroxylamine hydrochloride to afford amidoxime **168**. The amidoxime was acetylated by cyclopropanecarbonyl chloride and then refluxed in toluene to form 1,2,4-oxadiazole **170**, which was deprotected under acidic condition. The resultant product **171** reacted with TMSCN and 1*H*-benzimidazol-5-amine **121** in acetic acid at room temperature for 2 hours and was then worked up to yield amino acetonitrile **172**. The amino acetonitrile was hydrogenated with a Pd/C catalyst in acetic acid at room temperature overnight to afford diamine **173**. In the final step, 1,1'-carbonyldiimidazole was added to a solution of diamine **173** in THF and then stirred at 75 °C for 18 hours. Compound **18** was finally obtained after purification by column chromatography.

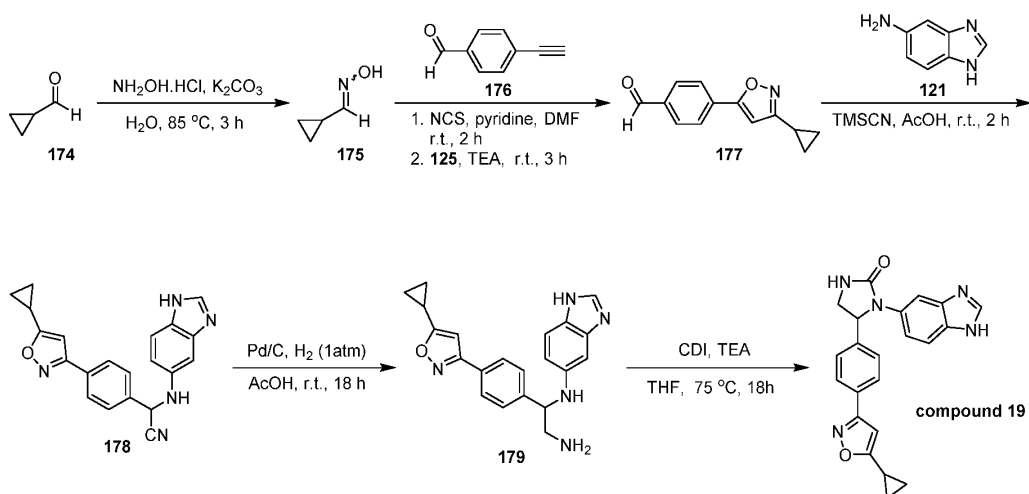
Scheme 9



Synthetic Method 10

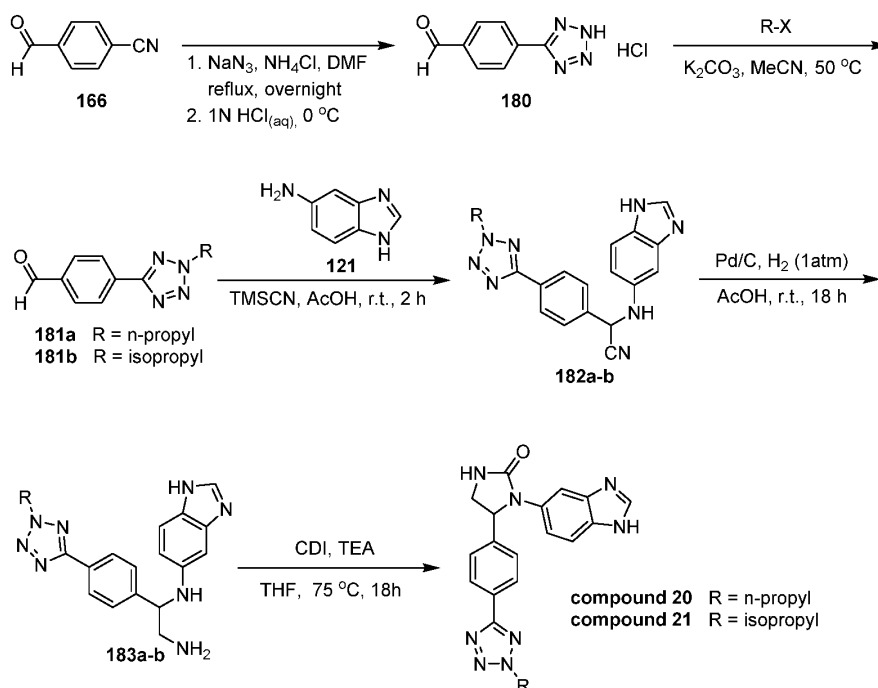
Compound **19**, having a 1,2-oxazol-3-yl ring, was prepared by the synthetic procedures shown in Scheme 10. Cyclopropanecarbaldehyde **174**, the starting material, reacted with hydroxylamine hydrochloride to afford oxime **175**, which was treated first with *N*-chlorosuccinimide (NCS) and then with 4-ethynylbenzaldehyde **176** in DMF at room temperature to form 1,2-oxazole precursor **177**. This precursor was then applied to the procedures shown in Synthetic Method 9 for forming imidazolidinone to obtain Compound **19**.

Scheme 10

Synthetic Method 11

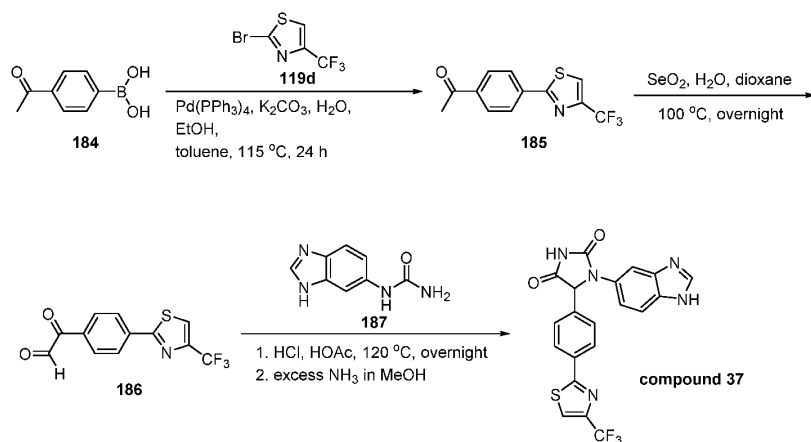
Compounds **20** and **21**, each having a 2*H*-tetrazol-5-yl ring, were prepared by the synthetic procedures shown in Scheme 11. 4-Formylbenzonitrile **166**, the starting material, reacted with sodium azide and ammonium chloride in DMF under refluxing to form tetrazole compound **180**, which was substituted by variable alkyl halides to afford precursors **181a-b**. These precursors were then applied to the procedures shown in Synthetic Method 9 for forming imidazolidinone to obtain Compounds **20** and **21**.

Scheme 11

Synthetic Method 12

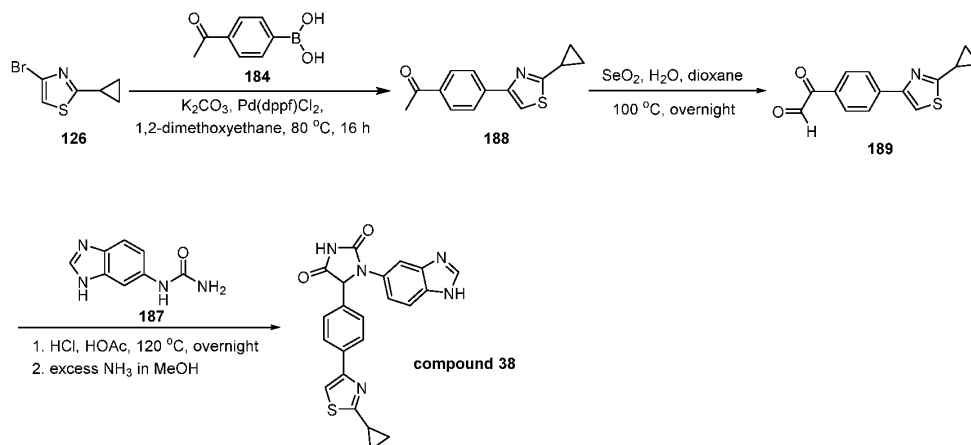
Compound **37**, having a 1,3-thiazol-2-yl ring, was prepared by the synthetic procedures shown in Scheme 12. (4-Acetylphenyl)boronic acid **184** was coupled with 2-bromo-4-(trifluoromethyl)-1,3-thiazole **119d** under a Suzuki-coupling condition. The resultant product **185** was oxidized by selenium dioxide to afford glyoxal **186**. The glyoxal was mixed with benzimidazolylurea **187** in HCl/AcOH (1/40 v/v) and then refluxed overnight. After removing the solvents under reduced pressure, the residue was treated with excess ammonia solution in methanol for several hours. The crude product was purified by column chromatography to yield Compound **37**.

Scheme 12

Synthetic Method 13

Compound **38**, having a 1,3-thiazol-4-yl ring, was prepared by the synthetic procedures shown in Scheme 13. 4-Bromo-2-cyclopropyl-1,3-thiazole **126**, an intermediate prepared following Synthetic Method 2, was coupled with (4-acetylphenyl)boronic acid **184** under a Suzuki-coupling condition. The resultant coupling product **188** was oxidized by selenium dioxide to glyoxal **189**. Compound **38** was formed from glyoxal **189** and benzimidazolylurea **187** via a cycloaddition reaction. The procedures were the same those shown in Synthetic Method 12.

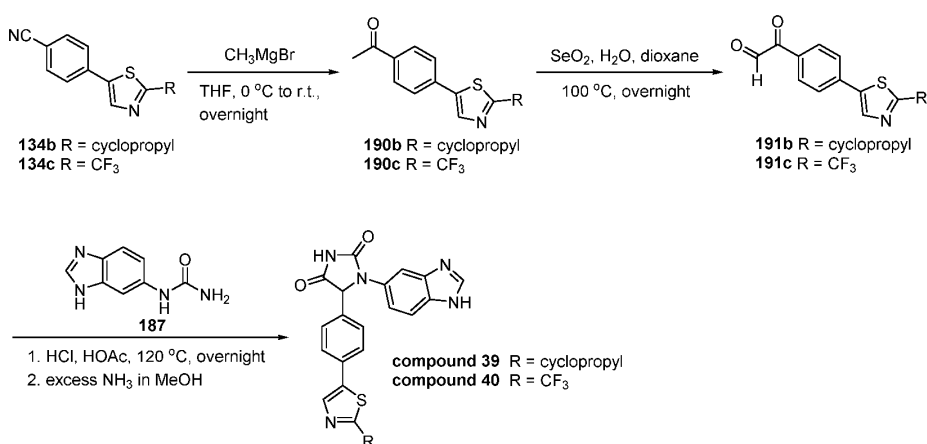
Scheme 13



Synthetic Method 14

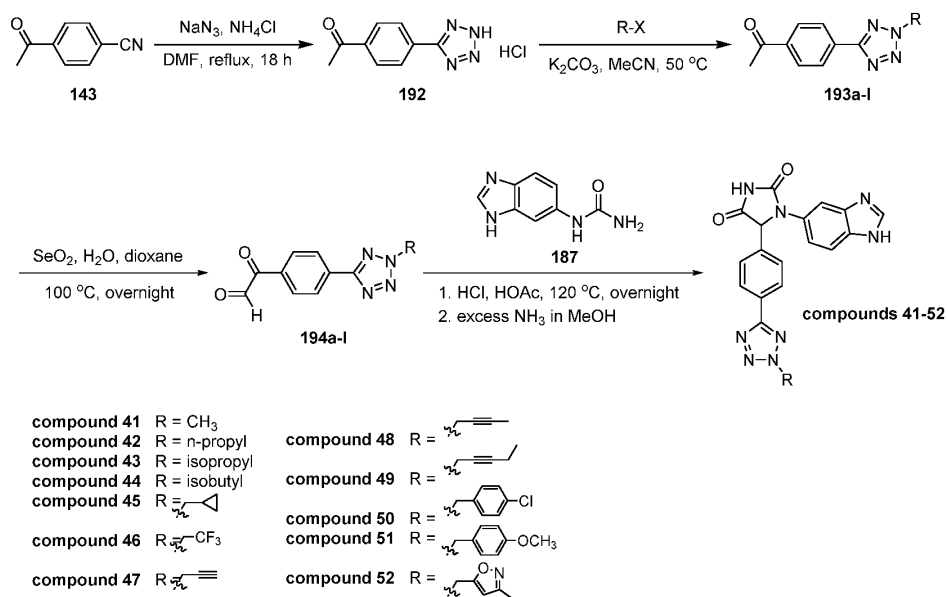
Compounds **39** and **40**, each having a 1,3-thiazol-5-yl ring, were prepared by the synthetic procedures shown in Scheme 14. 1,3-Thiazol-5-ylbenzonitriles **134b-c**, intermediates prepared following Synthetic Method 3, were acetylated by methylmagnesium bromide. The resultant acetyl products **190b-c** were oxidized by selenium dioxide to glyoxals **191b-c**. Compounds **39** and **40** were formed from glyoxals **191b-c** and benzimidazolylurea **187** via a cycloaddition reaction. The procedures were the same as those shown in Synthetic Method 12.

Scheme 14

Synthetic Method 15

Compounds **41-52**, each having a 2H-tetrazol-5-yl ring, were prepared by the synthetic procedures shown in Scheme 15. Starting material **143** reacted with sodium azide and ammonium chloride under refluxing in DMF to form tetrazole **192**, which was substituted with variable alkyl halides to give precursors **193a-l**. These precursors were then applied to the procedures shown in Synthetic Method 12 for forming hydantoin to yield Compounds **41-52**.

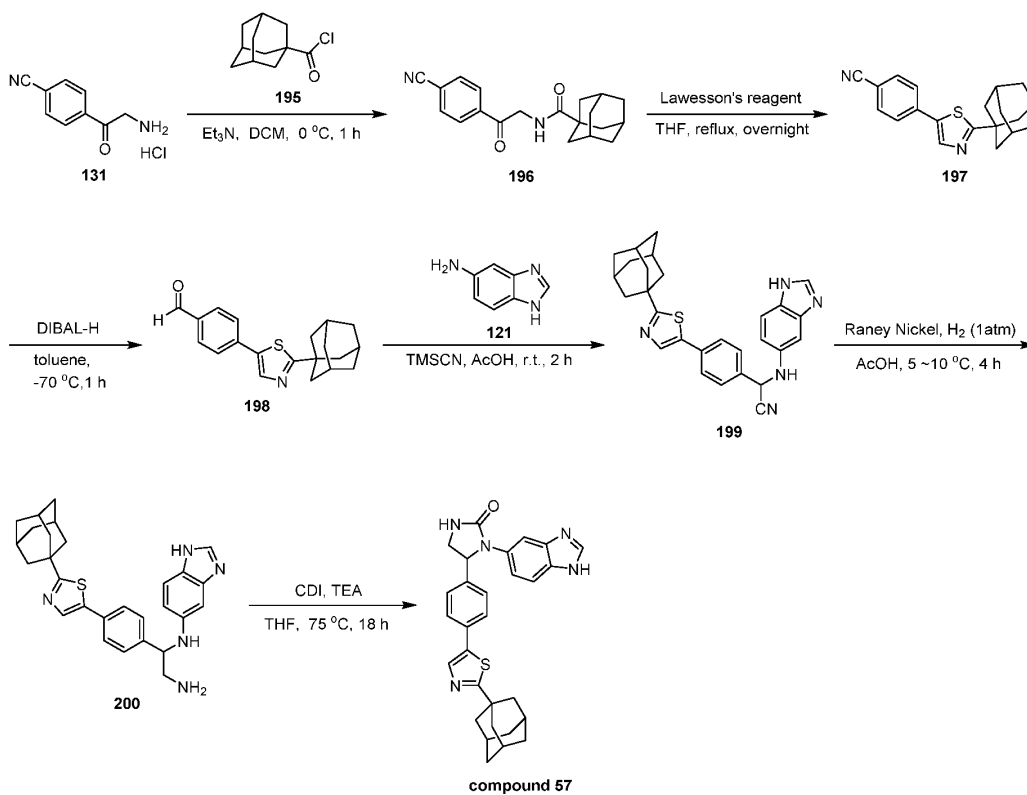
Scheme 15



Synthetic Method 16

Compound **57** having a 1,3-thiazol-5-yl ring was prepared by the synthetic procedures shown in the Scheme 16. Starting material **131** was acetylated with adamantane-1-carbonyl chloride **195** to obtain amide **196**. Subsequently, the amide **196** was mixed with the Lawesson's reagent under reflux in THF to afford (1,3-thiazol-5-yl)-benzonitrile **197**, which was reduced by DIBAL-H to form benzaldehyde **198**. The benzaldehyde **198** was then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compound **57**.

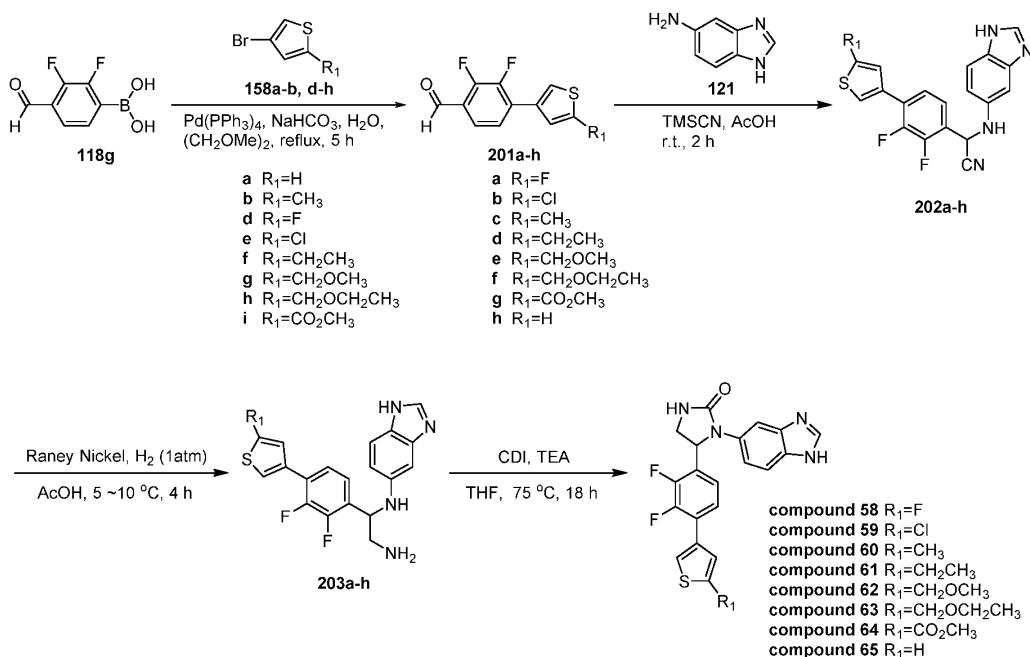
Scheme 16



Synthetic Method 17

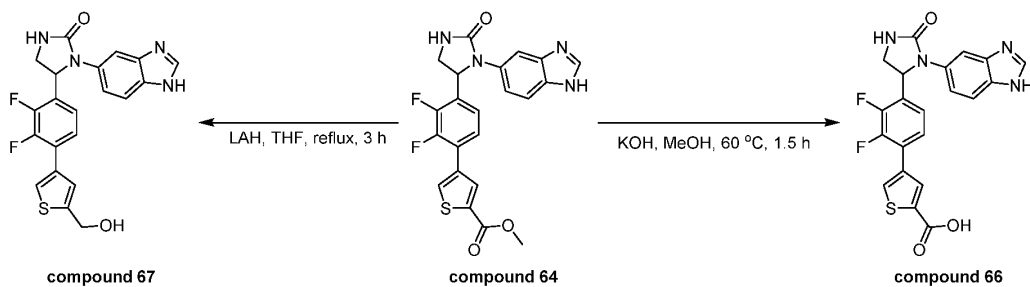
Compounds **58-65** each having a thiophen-3-yl ring were prepared by the synthetic procedures shown in Scheme 17. 2,3-Difluoro-4-formylphenylboronic acid **118g** was coupled with 3-bromothiophene derivatives **158a-b** and **158d-i** under a Suzuki-Miyaura coupling condition. The resulting products **201a-h** were then applied to the procedures shown in Synthetic Method 1 for forming imidazolidinone to obtain Compound **58-65**.

Scheme 17

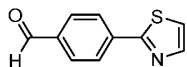
Synthetic Method 18

Compound **66** was prepared through hydrolysis reaction of compound **64** in a solution of potassium hydroxide in methanol shown in Scheme 18. Compound **67** was prepared through reduction of compound **64** by LAH in dry THF also shown in this scheme.

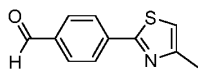
Scheme 18



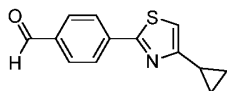
Below are the detailed procedures of preparing Compounds **1-67** following Synthetic Methods 1-18 set forth above and the analytical data of the intermediates and the final products generated in these procedures.

4-(1,3-thiazol-2-yl)benzaldehyde (Compound 120a)

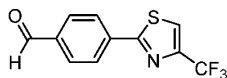
The (4-formylphenyl)boronic acid **118** (0.30 g, 2.0 mmol), 2-bromo-1,3-thiazole **119a** (0.33 g, 2.0 mmol), Pd(PPh₃)₄ (0.12 g, 0.1 mmol), aqueous solution of potassium carbonate (0.4 M, 5 mL), ethanol (5 mL) and toluene (2mL) were added to a 50 mL flask under nitrogen. The reaction mixture was stirred at 115 °C for 24 hours and then cooled to room temperature. After removing the solvent, the crude residue was purified by column chromatography on silica gel using EA/hexane (1/5) as eluent. The product **120a** was obtained as a white solid at a yield of 95%.

4-(4-methyl-1,3-thiazol-2-yl)benzaldehyde (Compound 120b)

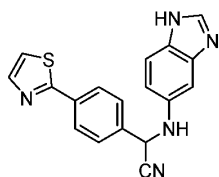
The 4-(4-methyl-1,3-thiazol-2-yl)benzaldehyde **120b** was prepared from the Suzuki-coupling of (4-formylphenyl)boronic acid **118** and 2-bromo-4-methyl-1,3-thiazole **119b**. The procedures were the same as the synthesis of Compound **120a**. The product **120b** was obtained as a white solid at a yield of 90%.

4-(4-cyclopropyl-1,3-thiazol-2-yl)benzaldehyde (Compound 120c)

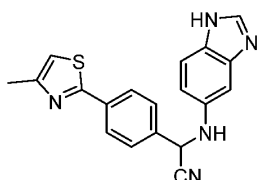
The 4-(4-cyclopropyl-1,3-thiazol-2-yl)benzaldehyde **120c** was prepared from the Suzuki-coupling of (4-formylphenyl)boronic acid **118** and 2-bromo-4-cyclopropyl-1,3-thiazole **119c**. The procedures were the same as the synthesis of Compound **120a**. The product **120c** was obtained as a white solid at a yield of 92%.

4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]benzaldehyde (Compound 120d)

The 4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]benzaldehyde **120d** was prepared from the Suzuki-coupling of (4-formylphenyl)boronic acid **118** and 2-bromo-4-(trifluoromethyl)-1,3-thiazole **119d**. The procedures were the same as the synthesis of Compound **120a**. The product **120d** was obtained as a white solid at a yield of 90%.

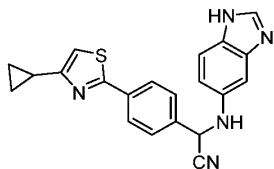
(1*H*-benzimidazol-5-ylamino)[4-(1,3-thiazol-2-yl)phenyl]acetonitrile (Compound 122a)

To the solution of 1*H*-benzimidazol-5-amine **121** (0.68 g, 5.11 mmol) in acetic acid (20 mL), the Compound **120a** (1.06 g, 5.62 mmol) was added and stirred at room temperature for 20 minutes. TMSCN (1 mL) was added dropwise to the reaction mixture and continuously stirred for 2 hours. After reaction completing, the reaction mixture was concentrated under reduced pressure to yield a viscous liquid. The viscous liquid was diluted with ethyl acetate (10 mL) and water. The diluted solution was adjusted to the pH 6~7 with ammonia at an ice-bath. The neutralized solution was extracted with ethyl acetate (20 mL x 4), dried over sodium sulfate, filtered and concentrated under reduced pressure to yield a viscous dark-yellow solid. The solid was dissolved in ethyl acetate (15 mL) and brine (15 mL). The mixture was stirred at room temperature for 2 minutes to form the pale-yellow precipitates. The pale-yellow precipitates was filtered and washed with water. The filtrate was dried over sodium sulfate and concentrated under reduced pressure to obtain the pale-yellow solid. Those pale-yellow solids were combined as the desired product **122a** at a yield of 96%.

(1*H*-benzimidazol-5-ylamino)[4-(4-methyl-1,3-thiazol-2-yl)phenyl]acetonitrile (Compound 122b)

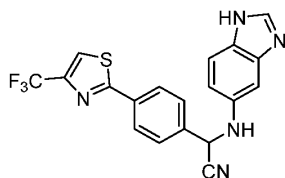
The (1*H*-benzimidazol-5-ylamino)[4-(4-methyl-1,3-thiazol-2-yl)phenyl]acetonitrile **122b** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **120b**. The procedures were the same as the synthesis of Compound **122a**. The product **122b** was obtained as a pale-yellow solid at a yield of 97%.

**(1*H*-benzimidazol-5-ylamino)[4-(4-cyclopropyl-1,3-thiazol-2-yl)phenyl]acetonitrile
(Compound 122c)**



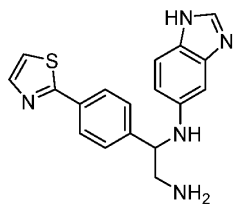
The (1*H*-benzimidazol-5-ylamino)[4-(4-cyclopropyl-1,3-thiazol-2-yl)phenyl]acetonitrile **122c** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **120c**. The procedures were the same as the synthesis of Compound **122a**. The product **122c** was obtained as a pale-yellow solid at a yield of 95%.

**(1*H*-benzimidazol-5-ylamino){4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl}acetonitrile
(Compound 122d)**



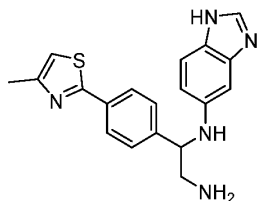
The (1*H*-benzimidazol-5-ylamino){4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl}-acetonitrile **122d** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **120d**. The procedures were the same as the synthesis of Compound **122a**. The product **122d** was obtained as a pale-yellow solid at a yield of 96%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(1,3-thiazol-2-yl)phenyl]ethane-1,2-diamine
(Compound 123a)**



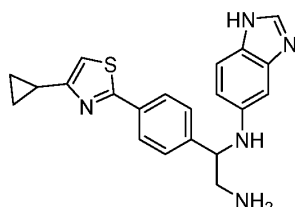
The Compound **122a** (5.0 g, 15.08 mmol) was dissolved in acetic acid (200 mL) and then stirred at 10 °C for 5 minutes. The Raney Nickel reagent was added to the stirring solution and refilled hydrogen three times. The reaction mixture was stirred under hydrogen at 10 °C for 8 hours. The catalyst was removed by filtration through celite. The filtrate was concentrated under reduced pressure to obtain the crude product. The crude product was purified by column chromatography on silica gel using methanol /dichloromethane (1/19) as eluent. The product **123a** was obtained as a yellow viscous liquid at a yield of 60%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(4-methyl-1,3-thiazol-2-yl)phenyl]ethane-1,2-diamine (Compound 123b)**



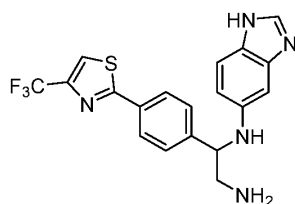
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(4-methyl-1,3-thiazol-2-yl)phenyl]ethane-1,2-diamine **123b** was prepared from the hydrogenation of Compound **122b** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **123b** was obtained as a yellow viscous liquid at a yield of 50%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(4-cyclopropyl-1,3-thiazol-2-yl)phenyl]ethane-1,2-diamine (Compound 123c)**

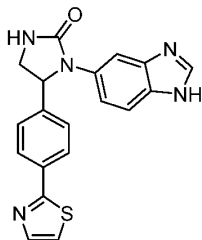


The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(4-cyclopropyl-1,3-thiazol-2-yl)phenyl]ethane-1,2-diamine **123c** was prepared from the hydrogenation of Compound **122c** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **123c** was obtained as a yellow viscous liquid at a yield of 54%.

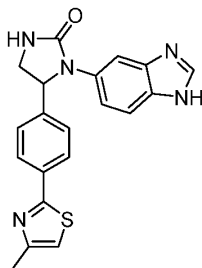
***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl]ethane-1,2-diamine (Compound 123d)**



The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl]ethane-1,2-diamine **123d** was prepared from the hydrogenation of Compound **122d** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **123d** was obtained as a yellow viscous liquid at a yield of 40%.

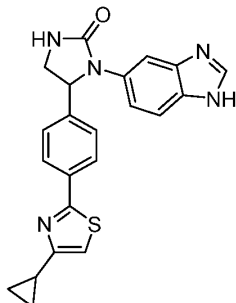
1-(1*H*-benzimidazol-5-yl)-5-[4-(1,3-thiazol-2-yl)phenyl]imidazolidin-2-one (Compound 1)

To the solution of 1,1'-carbonyl diimidazole (2.21 g, 20.5 mmol) and trimethylamine (7.5 mL) in anhydrous THF (100 mL), the solution of Compound **123a** (4.56 g, 13.6 mmol) in anhydrous THF (100 mL) was added dropwise by additional funnel at room temperature. The resulting mixture was heated to 75 °C and stirred for 18 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using methanol/dichloromethane (1/19) as eluent. The product (Compound **1**) was obtained as a white solid at a yield of 70%. ¹H NMR (400MHz, CD₃OD) δ 3.39 (dd, 1H, J = 7.0, 9.2 Hz), 4.02 (dd, 1H, J = 9.2, 9.2 Hz), 5.55 (dd, 1H, J = 7.0, 9.2 Hz), 7.31 (d, 1H, J = 8.8 Hz), 7.48 (d, 1H, J = 8.8 Hz), 7.52 (d, 2H, J = 8.2 Hz), 7.56 (s, 1H), 7.57 (s, 1H), 7.82 (d, 1H, J = 3.6 Hz), 7.88 (d, 2H, J = 8.2 Hz), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 362.1 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[4-(4-methyl-1,3-thiazol-2-yl)phenyl]imidazolidin-2-one (Compound 2)

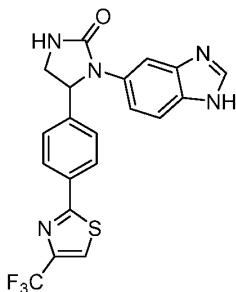
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(4-methyl-1,3-thiazol-2-yl)phenyl]imidazolidin-2-one (Compound **2**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **123b**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **2**) was obtained as a white solid at a yield of 66%. ¹H NMR (400MHz, DMSO-*d*₆) δ 2.37 (s, 3H), 3.13 (dd, 1H, J = 6.6, 8.8 Hz), 3.87 (dd, 1H, J = 8.8, 9.2 Hz), 5.58 (dd, 1H, J = 6.6, 9.2 Hz), 7.01 (s, 1H), 7.27 (s, 2H), 7.40 (s, 1H), 7.46 (d, 2H, J = 8.2 Hz), 7.57 (s, 1H), 7.83 (d, 2H, J = 8.2 Hz), 8.07 (s, 1H); LC/MS (ESI) *m/z*: 376.2 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[4-(4-cyclopropyl-1,3-thiazol-2-yl)phenyl]imidazolidin-2-one (Compound 3)

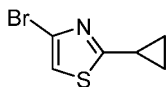


The 1-(1*H*-benzimidazol-5-yl)-5-[4-(4-cyclopropyl-1,3-thiazol-2-yl)phenyl]imidazolidin-2-one (Compound **3**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **123c**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **3**) was obtained as a white solid at a yield of 71%. ¹H NMR (400MHz, DMSO-*d*₆) δ 0.80-0.84 (m, 2H), 0.85-0.90 (m, 2H), 2.05-2.09 (m, 1H), 3.12 (dd, 1H, J = 6.4, 8.8 Hz), 3.87 (dd, 1H, J = 8.8, 9.2 Hz), 5.57 (dd, 1H, J = 6.4, 9.2 Hz), 7.02 (s, 1H), 7.26 (s, 2H), 7.39 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J = 7.8 Hz), 7.55 (s, 1H), 7.79 (d, 2H, J = 7.8 Hz), 8.07 (s, 1H), 12.27 (s, 1H); LC/MS (ESI) *m/z*: 402.2 [M + H]⁺.

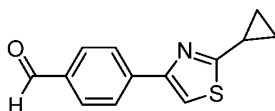
1-(1*H*-benzimidazol-5-yl)-5-[4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl]imidazolidin-2-one (Compound 4)



The 1-(1*H*-benzimidazol-5-yl)-5-[4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl]imidazolidin-2-one (Compound **4**) was prepared from the cycloaddition of carbonyl diimidazole and Compound **123d**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **4**) was obtained as a white solid at a yield of 67%. ¹H NMR (300MHz, DMSO-*d*₆) δ 3.14 (dd, 1H, J = 6.3, 8.7 Hz), 3.89 (dd, 1H, J = 8.7, 9.0 Hz), 5.62 (dd, 1H, J = 6.3, 9.0 Hz), 7.02 (d, 1H, J = 8.7 Hz), 7.28 (s, 1H), 7.40 (d, 1H, J = 8.7 Hz), 7.52 (d, 2H, J = 8.1 Hz), 7.57 (s, 1H), 7.92 (d, 2H, J = 8.1 Hz), 8.08 (s, 1H), 8.50 (s, 1H), 12.21 (s, 1H); LC/MS (ESI) *m/z*: 430.2 [M + H]⁺.

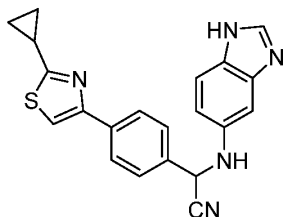
4-bromo-2-cyclopropyl-1,3-thiazole (Compound 126)

The palladium acetate (0.025 g, 0.11 mmol) and Xantphos (0.066 g, 0.11 mmol) were added in THF (22 mL) that degassed under argon. Then, the reaction mixture was stirred at room temperature for 5 minutes. The 2,4-dibromo-1,3-thiazole **124** (1.09 g, 4.50 mmol), cyclopropylboronic acid **125** (0.58 g, 6.70 mmol) and potassium phosphate (2.86 g) were added to the reaction mixture and flushed with argon. The reaction mixture was stirred at 70 °C for 15 hours. After cooling to room temperature, the reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel using hexane as eluent. The product **126** was obtained as a colorless oil at a yield of 81%.

4-(2-cyclopropyl-1,3-thiazol-4-yl)benzaldehyde (Compound 127)

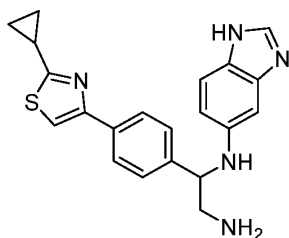
The (4-formylphenyl)boronic acid **118** (0.33 g, 2.2 mmol), 4-bromo-2-cyclopropyl-1,3-thiazole **126** (0.41 g, 2.0 mmol), Pd(dppf)Cl₂ (0.08 g, 0.1 mmol), potassium carbonate (0.41 g) and 1,2-dimethoxyethane (20 mL) were added to a 50 mL round-bottom flask under nitrogen. The reaction mixture was stirred at 80 °C for 16 hours and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic layers were collected, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/ether (10/1) as eluent. The product **127** was obtained as a white solid at a yield of 55%. ¹H NMR (300 MHz, CDCl₃) δ 1.10-1.16 (m, 4H), 2.32-2.39 (m, 1H), 7.40 (s, 1H), 7.89 (d, 2H, J = 8.4 Hz), 8.03 (d, 2H, J = 8.4 Hz), 10.01 (s, 1H); LC/MS (ESI) *m/z*: 230.1 [M + H]⁺.

**(1*H*-benzimidazol-5-ylamino)[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]acetonitrile
(Compound 128)**



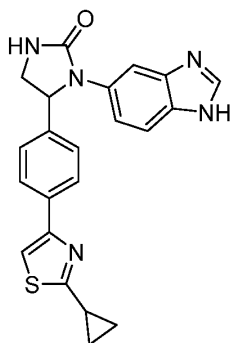
The (1*H*-benzimidazol-5-ylamino)[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]acetonitrile **128** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **127**. The procedures were the same as the synthesis of Compound **122a**. The product **128** was obtained as a pale-yellow solid at a yield of 93%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]ethane-1,2-diamine (Compound 129)**



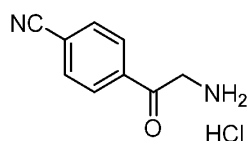
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]ethane-1,2-diamine **129** was prepared from the hydrogenation of Compound **128** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **129** was obtained as a yellow viscous liquid at a yield of 52%.

**1-(1*H*-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]imidazolidin-2-one
(Compound 5)**



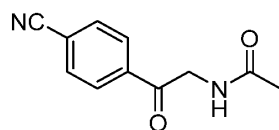
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]imidazolidin-2-one (Compound **5**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and product (**129**). The procedures were the same as the synthesis of Compound **1**. The product (Compound **5**) was obtained as a white solid at a yield of 73%. ¹H NMR (300MHz, DMSO-*d*₆) δ 0.93-0.98 (m, 2H), 1.08-1.16 (m, 2H), 2.34-2.42 (m, 1H), 3.13 (dd, 1H, J = 6.6, 9.0 Hz), 3.85 (dd, 1H, J = 8.7, 9.0 Hz), 5.52 (dd, 1H, J = 6.6, 8.7 Hz), 6.98 (s, 1H), 7.25 (d, 1H, J = 8.1 Hz), 7.37-7.40 (m, 3H), 7.54 (s, 1H), 7.72 (s, 1H), 7.80 (d, 2H, J = 8.1 Hz), 8.07 (s, 1H), 12.24 (s, 1H); LC/MS (ESI) *m/z*: 402.2 [M + H]⁺.

4-Glycylbenzonitrile hydrochloride (Compound **131**)



The 4-(bromoacetyl)benzonitrile **130** (22.4 g, 100 mmol) and hexamethylenetetramine (HMTA, 15.4 g, 110 mmol) were dissolved in chloroform (900 mL). The reaction mixture was stirred at room temperature overnight. The precipitates were filtered and washed with ethanol and ether. The resulting solids were suspended in the mixture of HCl/ethanol (48 mL/240 mL) and then stirred at 75 °C overnight. The precipitates were filtered when the solution was still warm. The filtrate was concentrated to remove solvents. Some acetone (100 mL) was added and stirred for an hour. The precipitates were filtered and washed with acetone and ether. The product **131** was obtained as an off-white solid in a quantum yield and without further purification. ¹H NMR (300MHz, DMSO-*d*₆) δ 4.62 (s, 2H), 8.06 (d, 2H, J = 8.4 Hz), 8.16 (d, 2H, J = 8.4 Hz), 8.59 (s, 2H); LC/MS (ESI) *m/z*: 161.1 [M + H]⁺.

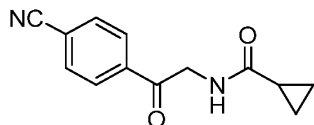
N-[2-(4-cyanophenyl)-2-oxoethyl]acetamide (Compound **133a**)



The triethylamine (21 mL) was added to the suspending solution of Compound **131** (10 g, 50.85 mmol) in dichloromethane (330 mL) and stirred at room temperature for 10 minutes. The acetic anhydride (7.79 g, 76.28 mmol) was diluted in dichloromethane (20 mL) and then added to the reaction solution during 30 minutes by additional funnel at an ice-bath. The resulting mixture was continuously stirred at room temperature for an hour. The reaction was quenched by water and extracted with dichloromethane. The organic layers were collected, dried over sodium sulfate, filtered and concentrated under reduced pressure. The

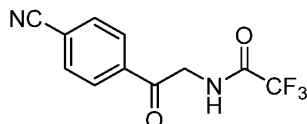
crude residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1/2) as eluent. The product **133a** was obtained as a yellow solid at a yield of 70%.

***N*-[2-(4-cyanophenyl)-2-oxoethyl]cyclopropanecarboxamide (Compound 133b)**



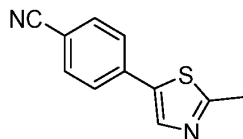
The *N*-[2-(4-cyanophenyl)-2-oxoethyl]cyclopropanecarboxamide **133b** was prepared from the acetylation of Compound **131** with cyclopropanecarboxylic anhydride **132b**. The procedures were the same as the synthesis of Compound **133a**. The product **133b** was obtained as a yellow solid at a yield of 73%. ¹H NMR (400MHz, DMSO-*d*₆) δ 0.65-0.68 (m, 4H), 1.70 (m, 1H), 4.64 (d, 2H, *J* = 5.4 Hz), 8.01 (d, 2H, *J* = 8.4 Hz), 8.10 (d, 2H, *J* = 8.4 Hz), 8.51 (t, 1H, d, *J* = 5.4 Hz); LC/MS (ESI) *m/z*: 229.1 [M + H]⁺.

***N*-[2-(4-cyanophenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide (Compound 133c)**

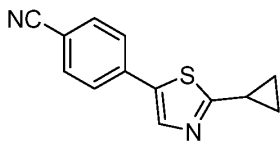


The *N*-[2-(4-cyanophenyl)-2-oxoethyl]-2,2,2-trifluoroacetamide **133c** was prepared from the acetylation of Compound **131** with trifluoroacetic anhydride **132c**. The procedures were the same as the synthesis of Compound **133a**. The product **133c** was obtained as a yellow solid at a yield of 73%.

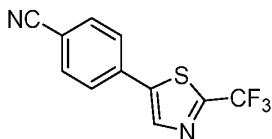
4-(2-methyl-1,3-thiazol-5-yl)benzonitrile (Compound 134a)



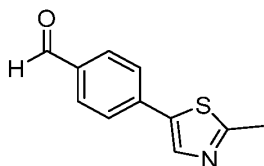
The Compound **133a** (0.3 g, 1.48 mmol) and Lawesson's reagent (0.9 g, 2.22 mmol) were dissolved in THF (20 mL). The reaction mixture was refluxed and stirred for 17 hours. After removing the solvent, the crude residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1/10) as eluent. The product **134a** was obtained as a yellow solid at a yield of 70%.

4-(2-cyclopropyl-1,3-thiazol-5-yl)benzonitrile (Compound 134b)

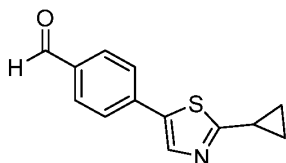
The 4-(2-cyclopropyl-1,3-thiazol-5-yl)benzonitrile **134b** was prepared from the cyclization of Compound **133b** with the Lawesson's reagent in THF. The procedures were the same as the synthesis of Compound **134a**. The product **134b** was obtained as a yellow solid at a yield of 67%. ¹H NMR (300MHz, CDCl₃) δ 1.10-1.21 (m, 4H), 2.31-2.35 (m, 1H), 7.59 (d, 2H, J = 8.4 Hz), 7.66 (d, 2H, J = 8.4 Hz), 7.84 (s, 1H); LC/MS (ESI) *m/z*: 227.1 [M + H]⁺.

4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]benzonitrile (Compound 134c)

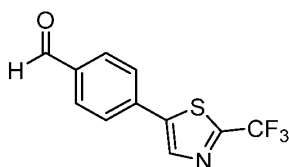
The 4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]benzonitrile **134c** was prepared from the cyclization of Compound **133c** with the Lawesson's reagent in toluene. The procedures were the same as the synthesis of Compound **134a**. The product **134c** was obtained as a yellow solid at a yield of 65%. ¹H NMR (400MHz, CDCl₃) δ 7.68 (d, 2H, J = 8.8 Hz), 7.74 (d, 2H, J = 8.8 Hz), 8.15 (s, 1H); LC/MS (ESI) *m/z*: 255.1 [M + H]⁺.

4-(2-methyl-1,3-thiazol-5-yl)benzaldehyde (Compound 135a)

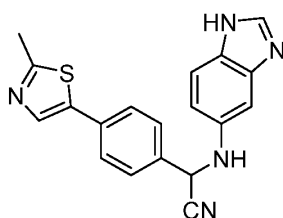
To a solution of Compound **134a** (1.57 g, 7.86 mmol) in anhydrous toluene (100 mL) that cooled at -70 °C, the solution of DIBAL-H in toluene (1.2M, 13.1 mL) was added dropwise by using additional funnel. The reaction mixture was stirred at -70 °C under argon for an hour and then quenched with 1N HCl_(aq) (20 mL). The reaction mixture was stirred continuously at room temperature overnight. The reaction mixture was partition between ethyl acetate and water. The organic layers were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1/5) as eluent. The product **135a** was obtained as a yellow solid at a yield of 63%.

4-(2-cyclopropyl-1,3-thiazol-5-yl)benzaldehyde (Compound 135b)

The 4-(2-cyclopropyl-1,3-thiazol-5-yl)benzaldehyde **135b** was prepared from the reduction of Compound **134b** with the DIBAL-H reagent. The procedures were the same as the synthesis of Compound **135a**. The product **135b** was obtained as a yellow solid at a yield of 66%. ¹H NMR (300MHz, CDCl₃) δ 1.13-1.20 (m, 4H), 2.31-2.35 (m, 1H), 7.65 (d, 2H, J = 6.9 Hz), 7.87-7.89 (m, 3H), 9.99 (s, 1H); LC/MS (ESI) *m/z*: 230.1 [M + H]⁺.

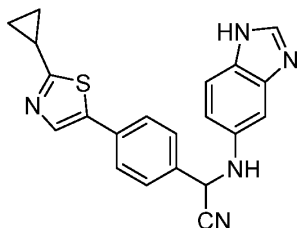
4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]benzaldehyde (Compound 135c)

The 4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]benzaldehyde **135c** was prepared from the reduction of Compound **134c** with the DIBAL-H reagent. The procedures were the same as the synthesis of Compound **135a**. The product **135c** was obtained as a yellow solid at a yield of 65%.

(1H-benzimidazol-5-ylamino)[4-(2-methyl-1,3-thiazol-5-yl)phenyl]acetonitrile (Compound 136a)

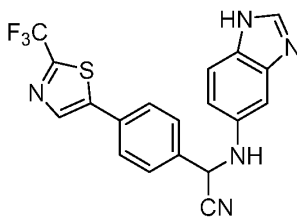
The (1H-benzimidazol-5-ylamino)[4-(2-methyl-1,3-thiazol-5-yl)phenyl]acetonitrile **136a** was prepared from the addition of 1H-benzimidazol-5-amine **121**, TMSCN and Compound **135a**. The procedures were the same as the synthesis of Compound **122a**. The product **136a** was obtained as a pale-yellow solid at a yield of 90%.

**(1*H*-benzimidazol-5-ylamino)[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]acetonitrile
(Compound 136b)**



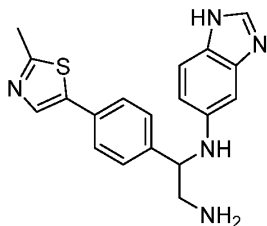
The (1*H*-benzimidazol-5-ylamino)[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]acetonitrile **136b** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **135b**. The procedures were the same as the synthesis of Compound **122a**. The product **136b** was obtained as a pale-yellow solid at a yield of 92%.

**(1*H*-benzimidazol-5-ylamino){4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}acetonitrile
(Compound 136c)**



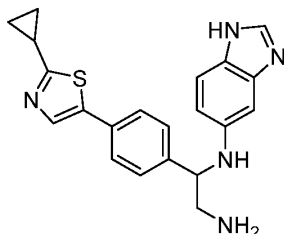
The (1*H*-benzimidazol-5-ylamino){4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}-acetonitrile **136c** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **135c**. The procedures were the same as the synthesis of Compound **122a**. The product **136c** was obtained as a pale-yellow solid at a yield of 90%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-methyl-1,3-thiazol-5-yl)phenyl]ethane-1,2-diamine
(Compound 137a)**



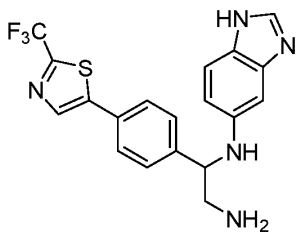
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-methyl-1,3-thiazol-5-yl)phenyl]ethane-1,2-diamine **137a** was prepared from the hydrogenation of Compound **136a** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **137a** was obtained as a yellow viscous liquid at a yield of 50%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]ethane-1,2-diamine (Compound 137b)**



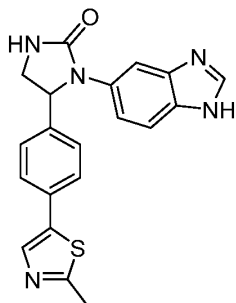
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]ethane-1,2-diamine **137b** was prepared from the hydrogenation of Compound **136b** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **137b** was obtained as a yellow viscous liquid at a yield of 54%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}ethane-1,2-diamine (Compound 137c)**



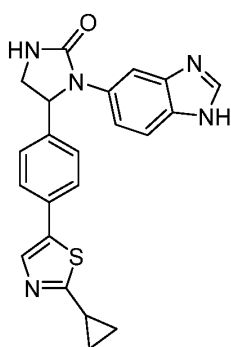
The *N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}ethane-1,2-diamine **137c** was prepared from the hydrogenation of Compound **136c** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **137c** was obtained as a yellow viscous liquid at a yield of 50%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(2-methyl-1,3-thiazol-5-yl)phenyl]imidazolidin-2-one (Compound 6)



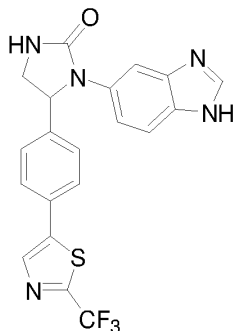
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(2-methyl-1,3-thiazol-5-yl)phenyl]imidazolidin-2-one (Compound **6**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **137a**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **6**) was obtained as a white solid at a yield of 71%. ¹H NMR (400MHz, CD₃OD) δ 2.64 (s, 3H), 3.30-3.36 (m, 1H), 3.97 (dd, 1H, J = 8.6, 9.2 Hz), 5.48 (dd, 1H, J = 7.6, 8.6 Hz), 7.29 (d, 1H, J = 8.8 Hz), 7.39 (d, 2H, J = 8.0 Hz), 7.45-7.46 (m, 3H), 7.55 (s, 1H), 7.76 (s, 1H), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 376.3 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]imidazolidin-2-one (Compound **7)**



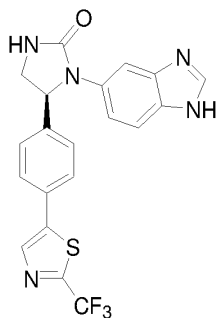
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]imidazolidin-2-one (Compound **7**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **137b**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **7**) was obtained as a white solid at a yield of 74%. ¹H NMR (400MHz, DMSO-*d*₆) δ 0.92-0.95 (m, 2H), 1.06-1.11 (m, 2H), 2.32-2.39 (m, 1H), 3.10 (dd, 1H, J = 6.4, 9.2 Hz), 3.84 (dd, 1H, J = 8.4, 9.2 Hz), 5.53 (dd, 1H, J = 6.4, 8.4 Hz), 6.99 (s, 1H), 7.26 (s, 1H), 7.37-7.39 (m, 3H), 7.50 (d, 2H, J = 8.0 Hz), 7.54 (s, 1H), 7.88 (s, 1H), 8.07 (s, 1H), 12.23 (s, 1H); LC/MS (ESI) *m/z*: 402.2 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}imidazolidin-2-one (Compound 8)

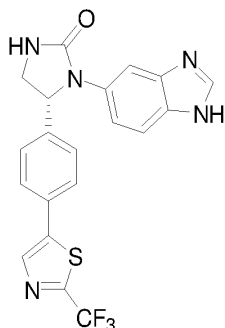


The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}imidazolidin-2-one (Compound **8**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **137c**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **8**) was obtained as a white solid at a yield of 70%. ¹H NMR (400MHz, CD₃OD) δ 3.37 (dd, 1H, J = 7.2, 8.8 Hz), 4.01 (dd, 1H, J = 8.8, 9.2 Hz), 5.56 (dd, 1H, J = 7.2, 9.2 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 8.0 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.58 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 8.07 (s, 1H), 8.18 (s, 1H); LC/MS (ESI) *m/z*: 430.2 [M + H]⁺.

(5*S*)-1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}imidazolidin-2-one (Compound 9)

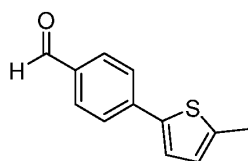


(5*R*)-1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}-imidazolidin-2-one (Compound 10)



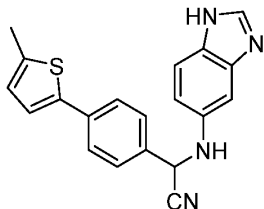
The enantiomers (Compounds **9** and **10**) were separated from Compound **8** by HPLC using CHIRALPAK IC. The isomer fractions were respectively collected and the optical pure isomers (Compounds **9** and **10**) were thus obtained by removing the solvent under reduced pressure. ¹H NMR (400MHz, CD₃OD) δ 3.37 (dd, 1H, J = 7.2, 8.8 Hz), 4.01 (dd, 1H, J = 8.8, 9.2 Hz), 5.56 (dd, 1H, J = 7.2, 9.2 Hz), 7.31 (d, 1H, J = 8.0 Hz), 7.47 (d, 1H, J = 8.0 Hz), 7.50 (d, 2H, J = 8.4 Hz), 7.58 (s, 1H), 7.63 (d, 2H, J = 8.4 Hz), 8.07 (s, 1H), 8.18 (s, 1H); LC/MS (ESI) *m/z*: 430.2 [M + H]⁺.

4-(5-methylthiophen-2-yl)benzaldehyde (Compound 140a)



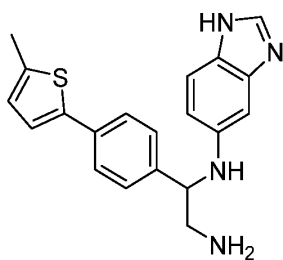
The 4-bromobenzaldehyde **138a** (1.85 g, 10.0 mmol), 2-methylthiophene **139a** (1.96 g, 20.0 mmol), potassium acetate (1.96 g, 20.0 mmol) and palladium acetate (0.002 g, 0.01 mmol) were dissolved in dimethylacetamide (DMA). The reaction mixture was purged with argon and stirred at 150 °C for 4 hours. The reaction mixture was cooled to room temperature and extracted with dichloromethane. The organic layers were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using pentane/ether (1/4) as eluent. The product **140a** was obtained as a white solid at a yield of 92%.

(1*H*-benzimidazol-5-ylamino)[4-(5-methylthiophen-2-yl)phenyl]acetonitrile (Compound 141a)



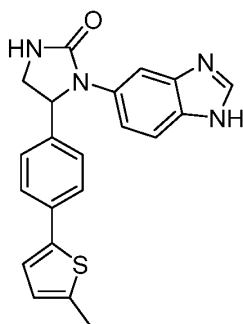
The (1*H*-benzimidazol-5-ylamino)[4-(5-methylthiophen-2-yl)phenyl]acetonitrile **141a** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **140a**. The procedures were the same as the synthesis of Compound **122a**. The product **141a** was obtained as a pale-yellow solid at a yield of 90%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-methylthiophen-2-yl)phenyl]ethane-1,2-diamine (Compound 142a)**



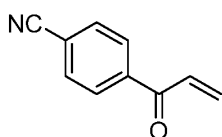
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-methylthiophen-2-yl)phenyl]ethane-1,2-diamine **142a** was prepared from the hydrogenation of Compound **141a** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **142a** was obtained as a yellow viscous liquid at a yield of 55%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-methylthiophen-2-yl)phenyl]imidazolidin-2-one (Compound 11)



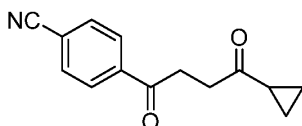
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-methylthiophen-2-yl)phenyl]imidazolidin-2-one (Compound **11**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **142a**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **11**) was obtained as a white solid at a yield of 63%. ¹H NMR (400MHz, CD₃OD) δ 2.44 (s, 3H), 3.39 (dd, 1H, *J* = 7.6, 8.8 Hz), 3.97 (dd, 1H, *J* = 8.8, 9.2 Hz), 5.40 (dd, 1H, *J* = 7.6, 9.2 Hz), 6.67 (d, 1H, *J* = 3.0 Hz), 7.05 (d, 1H, *J* = 3.0 Hz), 7.26 (d, 1H, *J* = 8.8 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 7.45-7.47 (m, 3H), 7.52 (s, 1H), 7.99 (s, 1H); LC/MS (ESI) *m/z*: 375.3 [M + H]⁺.

4-acryloylbenzonitrile (Compound 144)

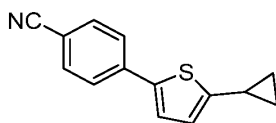


The 4-acetylbenzonitrile **143** (0.73 g, 5.0 mmol), FeCl₃·6H₂O (0.14 g, 0.5 mmol), K₂S₂O₈ (2.7 g, 10.0 mmol) and DMA (20 mL) were sequentially added to the round-bottle flask. The reaction mixture was stirred at 110 °C for 4 hours. Upon completion of the reaction (monitored by TLC), the resulting mixture was diluted with ether and washed with brine. The organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using ethyl acetate/ether (1/4) as eluent. The product **144** was obtained as an off-white solid at a yield of 40%.

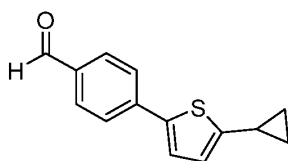
4-(4-oxopentanoyl)benzonitrile (Compound 146)



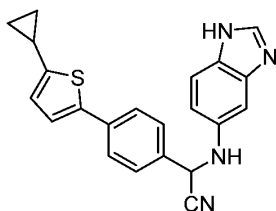
The product **144** (2.0 g, 12.7 mmol), cyclopropanecarbaldehyde (1.2 mL, 15.3 mmol), triethylamine (1.2 mL, 8.6 mmol) and 2-(2-hydroxyethyl)-3-methyl-4-benzylthiazolium chloride **145** (0.65 g, 15.2 mmol) were sequentially added to the round-bottle flask. The reaction mixture was stirred at 70 °C overnight. Upon completion of the reaction (monitored by TLC), the resulting mixture was partitioned between ether and water. The organic layers were washed with water, 2 M HCl and brine. After drying over sodium sulfate, filtering and concentrating in vacuo, the crude residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1/3) as eluent. The product **146** was obtained as a yellow liquid at a yield of 50%.

4-(5-cyclopropylthiophen-2-yl)benzonitrile (Compound 147)

The 4-(5-cyclopropylthiophen-2-yl)benzonitrile **147** was prepared from the cyclization of product **146** with the Lawesson's reagent in THF. The procedures were the same as the synthesis of Compound **134a**. The product **147** was obtained as a yellow solid at a yield of 75%.

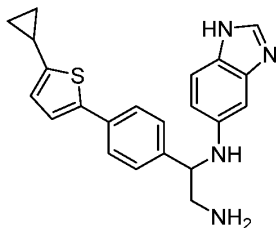
4-(5-cyclopropylthiophen-2-yl)benzaldehyde (Compound 148)

The 4-(5-cyclopropylthiophen-2-yl)benzaldehyde **148** was prepared from the reduction of Compound **147** with the DIBAL-H reagent. The procedures were the same as the synthesis of Compound **135a**. The product **148** was obtained as a yellow solid at a yield of 64%.

(1H-benzimidazol-5-ylamino)[4-(5-cyclopropylthiophen-2-yl)phenyl]acetonitrile (Compound 149)

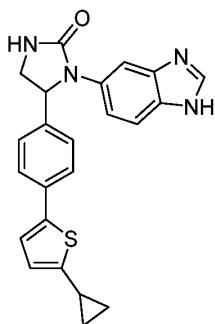
The (1H-benzimidazol-5-ylamino)[4-(5-cyclopropylthiophen-2-yl)phenyl]acetonitrile **149** was prepared from the addition of 1H-benzimidazol-5-amine **121**, TMSCN and Compound **148**. The procedures were the same as the synthesis of Compound **122a**. The product **149** was obtained as a pale-yellow solid at a yield of 91%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropylthiophen-2-yl)phenyl]ethane-1,2-diamine
(Compound 150)**



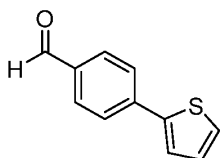
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropylthiophen-2-yl)phenyl]ethane-1,2-diamine **150** was prepared from the hydrogenation of Compound **149** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **150** was obtained as a yellow viscous liquid at a yield of 53%.

**1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropylthiophen-2-yl)phenyl]imidazolidin-2-one
(Compound 12)**

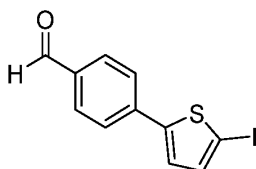


The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropylthiophen-2-yl)phenyl]imidazolidin-2-one (Compound **12**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and product **150**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **12**) was obtained as a white solid at a yield of 69%.

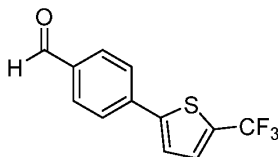
¹H NMR (400MHz, CD₃OD) δ 0.67-0.71 (m, 2H), 0.96-1.01 (m, 2H), 2.03-2.09 (m, 1H), 3.36 (dd, 1H, *J* = 6.8, 8.8 Hz), 3.97 (dd, 1H, *J* = 8.8, 9.2 Hz), 5.45 (dd, 1H, *J* = 6.8, 9.2 Hz), 6.69 (d, 1H, *J* = 3.6 Hz), 7.08 (d, 1H, *J* = 3.6 Hz), 7.29 (d, 1H, *J* = 8.8 Hz), 7.36 (d, 2H, *J* = 8.4 Hz), 7.46-7.49 (m, 3H), 7.54 (s, 1H), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 401.3 [M + H]⁺.

4-(thiophen-2-yl)benzaldehyde (Compound 152a)

The 4-bromobenzaldehyde **138a** (1.85 g, 10.0 mmol), thiophene (6.72 g, 80.0 mmol), potassium acetate (1.96 g, 20.0 mmol) and palladium acetate (0.002 g, 0.01 mmol) were dissolved in DMA (50 mL). The reaction mixture was purged with argon and stirred at 130 °C for 20 hours. The reaction mixture was cooled to room temperature and removed the solvent in vacuo. The crude residue was purified by column chromatography on silica gel using pentane/ether (1/4) as eluent. The product **152a** was obtained as a light-yellow solid at a yield of 60%.

4-(5-iodothiophen-2-yl)benzaldehyde (Compound 153a)

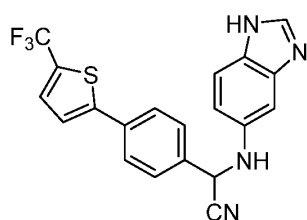
The Compound **152a** (0.94 g, 5.0 mmol) and *N*-iodosuccinimide (2.81 g, 12.5 mmol) were added to the 500 mL flask. The flask was flushed with nitrogen and then added chloroform (200 mL) and acetic acid (16 mL). The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was washed with saturated sodium thiosulfate solution (75 mL), saturated sodium bicarbonate solution (75 mL), and water (75 mL). The organic layers were collected, dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using dichloromethane/hexane (1/1) as eluent. The product **153a** was obtained as a yellow solid at a yield of 75%.

4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde (Compound 155a)

A mixture of Compound **153a** (0.31 g, 1.0 mmol), methyl difluoro(fluorosulfonyl)acetate **154** (0.96 g, 5.0 mmol), copper iodide (0.23 g, 1.2 mmol), *N*-methylpyrrolidine (NMP, 1.2 mL) and DMF (10 mL) was stirred at 70 °C for 13 hours. The

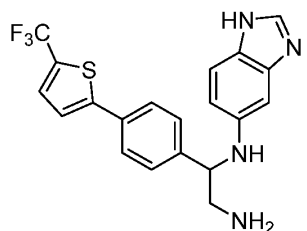
reaction mixture was quenched with saturated aqueous ammonium chloride (15 mL), diluted with water (10 mL), filtered through celite, and extracted with ethyl acetate. The organic layers were collected, dried over sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1/6) as eluent. The product **155a** was obtained as a yellow solid at a yield of 70%.

(1*H*-benzimidazol-5-ylamino){4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}acetonitrile (Compound 156a)



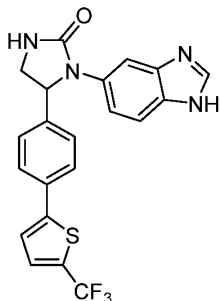
The (1*H*-benzimidazol-5-ylamino){4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-acetonitrile **156a** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **155a**. The procedures were the same as the synthesis of Compound **122a**. The product **156a** was obtained as a pale-yellow solid at a yield of 88%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}ethane-1,2-diamine (Compound 157a)**



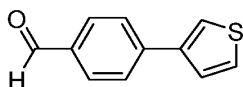
The *N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}ethane-1,2-diamine **157a** was prepared from the hydrogenation of Compound **156a** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **157a** was obtained as a yellow viscous liquid at a yield of 49%.

1-(1*H*-benzimidazol-5-yl)-5-{4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}imidazolidin-2-one (Compound 13)



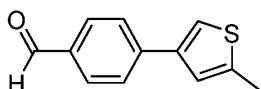
The 1-(1*H*-benzimidazol-5-yl)-5-{4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-imidazolidin-2-one (Compound **13**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **157a**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **13**) was obtained as a white solid at a yield of 67%. ¹H NMR (300MHz, CD₃OD) δ 3.36 (dd, 1H, J = 6.9, 9.3 Hz), 3.99 (dd, 1H, J = 9.3, 9.3 Hz), 5.51 (dd, 1H, J = 6.9, 9.3 Hz), 7.29-7.32 (m, 2H), 7.43-7.48 (m, 4H), 7.55-7.60 (m, 3H), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 429.2 [M + H]⁺.

4-(thiophen-3-yl)benzaldehyde (Compound 159a)



The 3-bromothiophene **158a** (1.96 g, 12.0 mmol), (4-formylphenyl)boronic acid **118** (2.70 g, 18.0 mmol), ethylene glycol dimethyl ether (17 mL), water (10 mL) and sodium bicarbonate (3.02 g, 36.0 mmol) were placed in a 50 mL round-bottom flask. After adding Pd(PPh₃)₄ (0.69 g, 0.6 mmol) at room temperature, the reaction mixture was refluxed for 5 hours. The resulting mixture was extracted with ethyl acetate and water. The organic layers were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using toluene/hexane (2/1) as eluent. The product **159a** was obtained as a pale yellow oil at a yield of 95%.

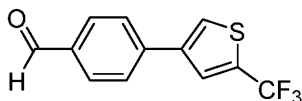
4-(5-methylthiophen-3-yl)benzaldehyde (Compound 159b)



The 4-(5-methylthiophen-3-yl)benzaldehyde **159b** was prepared from the Suzuki-Miyaura coupling of (4-formylphenyl)boronic acid **118** and 3-bromo-5-methylthiophene

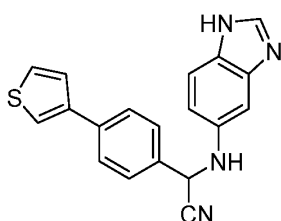
158b. The procedures were the same as the synthesis of Compound **159a**. The product **159b** was obtained as a pale-yellow oil at a yield of 92%.

4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde (Compound 159c)



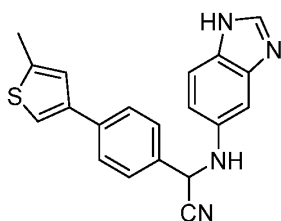
The 4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde **159c** was prepared from the Suzuki-Miyaura coupling of (4-formylphenyl)boronic acid **118** and 3-bromo-(5-trifluoromethyl)-thiophene **158c**. The procedures were the same as the synthesis of Compound **159a**. The product **159c** was obtained as a pale-yellow oil at a yield of 85%.

(1H-benzimidazol-5-ylamino)[4-(thiophen-3-yl)phenyl]acetonitrile (Compound 160a)



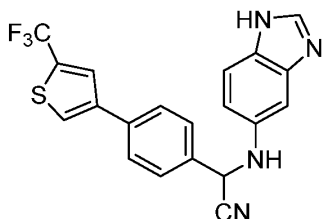
The (1H-benzimidazol-5-ylamino)[4-(thiophen-3-yl)phenyl]acetonitrile **160a** was prepared from the addition of 1H-benzimidazol-5-amine **121**, TMSCN and Compound **159a**. The procedures were the same as the synthesis of Compound **122a**. The product **160a** was obtained as a pale-yellow solid at a yield of 92%.

(1H-benzimidazol-5-ylamino)[4-(5-methylthiophen-3-yl)phenyl]acetonitrile (Compound 160b)



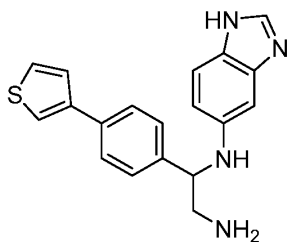
The (1H-benzimidazol-5-ylamino)[4-(5-methylthiophen-3-yl)phenyl]acetonitrile **160b** was prepared from the addition of 1H-benzimidazol-5-amine **121**, TMSCN and Compound **159b**. The procedures were the same as the synthesis of Compound **122a**. The product **160b** was obtained as a pale-yellow solid at a yield of 90%.

**(1*H*-benzimidazol-5-ylamino){4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}acetonitrile
(Compound 160c)**



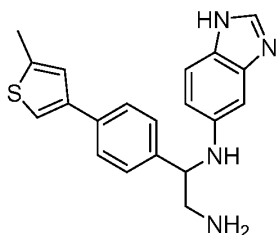
The (1*H*-benzimidazol-5-ylamino){4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}-acetonitrile **160c** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **159c**. The procedures were the same as the synthesis of Compound **122a**. The product **160c** was obtained as a pale-yellow solid at a yield of 85%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(thiophen-3-yl)phenyl]ethane-1,2-diamine (Compound 161a)**



The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(thiophen-3-yl)phenyl]ethane-1,2-diamine **161a** was prepared from the hydrogenation of Compound **160a** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product was obtained as a yellow viscous liquid at a yield of 53%.

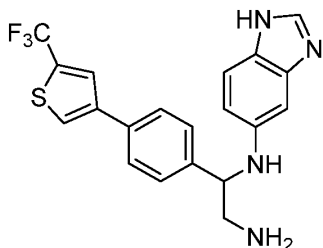
***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-methylthiophen-3-yl)phenyl]ethane-1,2-diamine
(Compound 161b)**



The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-methylthiophen-3-yl)phenyl]ethane-1,2-diamine **161b** was prepared from the hydrogenation of Compound **160b** with the Raney

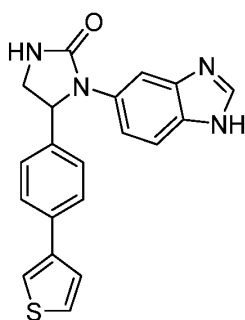
Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **161b** was obtained as a yellow viscous liquid at a yield of 50%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}ethane-1,2-diamine (Compound 161c)**



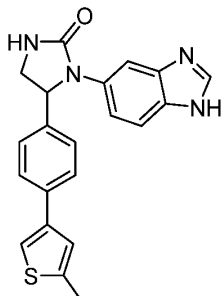
The *N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}ethane-1,2-diamine **161c** was prepared from the hydrogenation of Compound **160c** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **161c** was obtained as a yellow viscous liquid at a yield of 51%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(thiophen-3-yl)phenyl]imidazolidin-2-one (Compound 14)



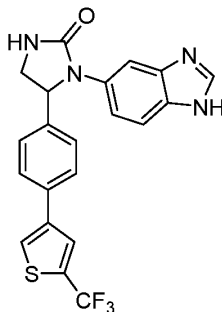
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(thiophen-3-yl)phenyl]imidazolidin-2-one (Compound **14**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **161a**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **14**) was obtained as a white solid at a yield of 73%. ¹H NMR (300MHz, CD₃OD) δ 3.38 (dd, 1H, J = 6.9, 9.0 Hz), 3.99 (dd, 1H, J = 9.0, 9.3 Hz), 5.48 (dd, 1H, J = 6.9, 9.3 Hz), 7.05 (s, 1H), 7.30 (d, 1H, J = 8.4 Hz), 7.37-7.48 (m, 4H), 7.54-7.60 (m, 3H), 7.68 (s, 1H), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 361.3 [M + H]⁺.

**1-(1*H*-benzimidazol-5-yl)-5-[4-(5-methylthiophen-3-yl)phenyl]imidazolidin-2-one
(Compound 15)**

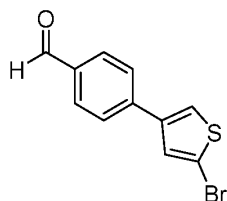


The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-methylthiophen-3-yl)phenyl]imidazolidin-2-one (Compound **15**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **161b**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **15**) was obtained as a white solid at a yield of 75%. ¹H NMR (300MHz, CD₃OD) δ 2.40 (s, 3H), 3.30 (dd, 1H, J = 7.5, 9.0 Hz), 3.90 (dd, 1H, J = 9.0, 9.0 Hz), 5.38 (dd, 1H, J = 7.5, 9.0 Hz), 6.95 (s, 1H), 7.17 (s, 1H), 7.26-7.31 (m, 3H), 7.42-7.45 (m, 3H), 7.55 (s, 1H), 8.03 (s, 1H); LC/MS (ESI) *m/z*: 375.1 [M + H]⁺.

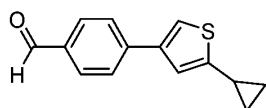
1-(1*H*-benzimidazol-5-yl)-5-[4-[5-(trifluoromethyl)thiophen-3-yl]phenyl]imidazolidin-2-one (Compound 16)



The 1-(1*H*-benzimidazol-5-yl)-5-[4-[5-(trifluoromethyl)thiophen-3-yl]phenyl]imidazolidin-2-one (Compound **16**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **161c**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **16**) was obtained as a white solid at a yield of 67%. ¹H NMR (300MHz, CD₃OD) δ 3.36 (dd, 1H, J = 6.9, 9.0 Hz), 3.99 (dd, 1H, J = 9.0, 9.3 Hz), 5.50 (dd, 1H, J = 6.9, 9.3 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.41-7.47 (m, 3H), 7.56-7.58 (m, 3H), 7.81 (s, 2H), 8.05 (s, 1H); LC/MS (ESI) *m/z*: 429.1 [M + H]⁺.

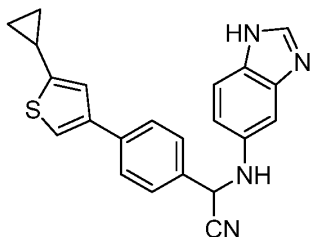
4-(5-bromothiophen-3-yl)benzaldehyde (Compound 162)

Bromine (5.0 g, 32.0 mmol) in 50 mL of glacial acetic acid was added dropwise to a solution of Compound **159a** (6.0 g, 32.0 mmol) in 65 mL of glacial acetic acid. The resulting yellow solution was stirred at room temperature for 2 days. The reaction mixture was diluted with 300 mL of water and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using ethyl acetate /hexane (1/9) as eluent. The product **162** was obtained as a yellow solid at a yield of 73%.

4-(5-cyclopropylthiophen-3-yl)benzaldehyde (Compound 163)

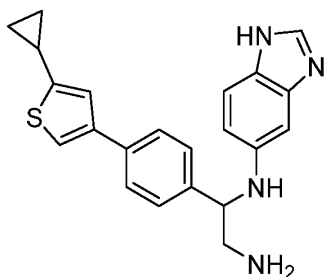
The palladium acetate (0.025 g, 0.11 mmol) and Xantphos (0.066 g, 0.11 mmol) were added in THF (22 mL) that degassed under argon. Then, the reaction mixture was stirred at room temperature for 5 minutes. The 4-(5-bromothiophen-3-yl)benzaldehyde **162** (0.73 g, 3.0 mmol), cyclopropylboronic acid **125** (0.58 g, 6.70 mmol) and potassium phosphate (2.86 g) were added to the reaction mixture and flushed with argon. The reaction mixture was stirred at 70 °C for 15 hours. After cooling to room temperature, the reaction mixture was filtered and washed with dichloromethane. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel using hexane as eluent. The product **163** was obtained as a yellow solid at a yield of 84%.

**(1*H*-benzimidazol-5-ylamino)[4-(5-cyclopropylthiophen-3-yl)phenyl]acetonitrile
(Compound 164)**



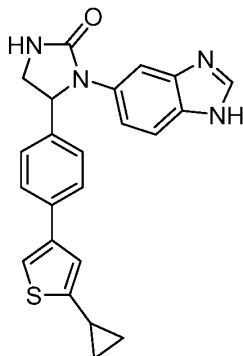
The (1*H*-benzimidazol-5-ylamino)[4-(5-cyclopropylthiophen-3-yl)phenyl]acetonitrile **164** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **163**. The procedures were the same as the synthesis of Compound **122a**. The product **164** was obtained as a pale-yellow solid at a yield of 81%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropylthiophen-3-yl)phenyl]ethane-1,2-diamine
(Compound 165)**



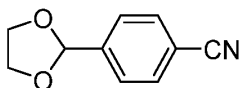
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropylthiophen-3-yl)phenyl]ethane-1,2-diamine **165** was prepared from the hydrogenation of Compound **164** with the Raney Nickel reagent as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **165** was obtained as a yellow viscous liquid at a yield of 49%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropylthiophen-3-yl)phenyl]imidazolidin-2-one (Compound 17)

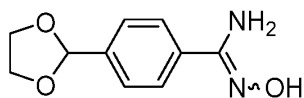


The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropylthiophen-3-yl)phenyl]imidazolidin-2-one (Compound **17**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **165**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **17**) was obtained as a white solid at a yield of 65%. ¹H NMR (300MHz, CD₃OD) δ 0.59-0.63 (m, 2H), 0.91-0.96 (m, 2H), 2.00-2.09 (m, 1H), 3.39 (dd, 1H, *J* = 6.9, 9.0 Hz), 4.00 (dd, 1H, *J* = 9.0, 9.3 Hz), 5.50 (dd, 1H, *J* = 6.9, 9.3 Hz), 6.69 (d, 1H, *J* = 5.4 Hz), 7.05 (d, 1H, *J* = 5.4 Hz), 7.32 (dd, 1H, *J* = 1.8, 8.7 Hz), 7.41-7.45 (m, 3H), 7.46 (d, 2H, *J* = 8.1 Hz), 7.58 (d, 1H, *J* = 1.8 Hz), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 401.2 [M + H]⁺.

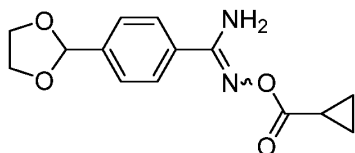
4-(1,3-dioxolan-2-yl)benzonitrile (Compound 167)



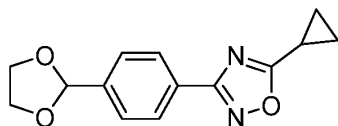
To a round-bottom flask equipped with a Dean-Stark trap was successively added 4-formylbenzonitrile **166** (7.68 g, 58.6 mmol), a catalytic amount of *p*-TsOH (PTSA) and toluene (150 mL). After stirring 5 minutes at room temperature, the monoethyleneglycol (MEG) (13 mL, 234.3 mmol) was added dropwise. The reaction mixture was refluxed for 3 hours and cooled to room temperature. After removing toluene under reduced pressure, sat. Na₂CO_{3(aq)} was added to quench the reaction and partitioned between DCM and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The viscous residue was treated with hexane at ice-bath to form the product **167** as a yellow solid in a quantum yield.

4-(1,3-dioxolan-2-yl)-N'-hydroxybenzenecarboximidamide (Compound 168)

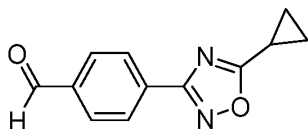
To the solution of the Compound **167** (7.6 g, 43.4 mmol) in ethanol/water (2/1, 75 mL), hydroxylamine hydrochloride (10.6 g, 151.8 mmol) and sodium carbonate (9.2 g, 86.8 mmol) were added at room temperature. The reaction mixture was stirred at 100 °C for 2 hours. After concentrating under reduced pressure, the residue was poured into water (50 mL) and stirred for 30 minutes. The precipitates were filtered and washed with cold water to give the product **168** as a white solid at a yield of 83%.

N'-[(cyclopropylcarbonyl)oxy]-4-(1,3-dioxolan-2-yl)benzenecarboximidamide (Compound 169)

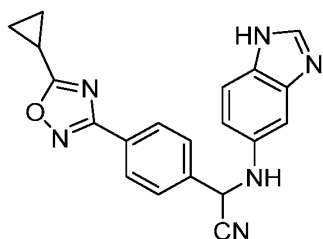
To the suspension of the Compound **168** (1.8 g, 8.65 mmol) in DCM (100 mL), pyridine (1.4 mL, 17.30 mmol) and cyclopropanecarbonyl chloride (0.02 mL, 11.20 mmol) were added dropwise under nitrogen at room temperature. The reaction mixture was stirred at room temperature for 4 hours and then partitioned between DCM and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using DCM/methanol (9/1) as eluent to give the product **169** as a white solid at a yield of 60%.

5-cyclopropyl-3-[4-(1,3-dioxolan-2-yl)phenyl]-1,2,4-oxadiazole (Compound 170)

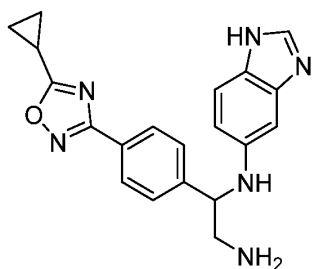
The starting material **169** (1.1 g, 3.98 mmol) was dissolved in toluene (40 mL). The reaction mixture was refluxed for 15 hours and then cooled to room temperature. After removing the solvent under reduced pressure, the crude residue was purified by column chromatography on silica gel using EA/hexane (1/4) as eluent to give the product **170** as a white solid at a yield of 70%.

4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)benzaldehyde (Compound 171)

To the solution of the Compound **170** (1.2 g, 4.64 mmol) in THF/H₂O (4/1, 30 mL), the con. HCl was added dropwise. The reaction mixture was stirred at 65 °C for 6 hours and then cooled to room temperature. The reaction mixture was partitioned between DCM and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using EA/hexane (1/9) as eluent to give the product **171** as a white solid at a yield of 97%.

(1*H*-benzimidazol-5-ylamino)[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]acetonitrile (Compound 172)

The (1*H*-benzimidazol-5-ylamino)[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]-acetonitrile **172** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **171**. The procedures were the same as the synthesis of Compound **122a**. The product **172** was obtained as a pale-yellow solid at a yield of 86%.

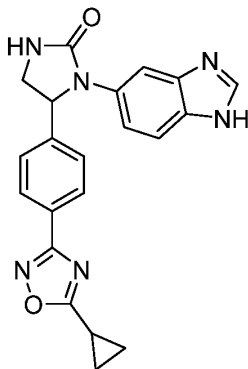
***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]ethane-1,2-diamine (Compound 173)**

The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]ethane-1,2-diamine **173** was prepared from the hydrogenation of Compound **172**

with Pd/C as catalyst. The procedures were the same as the synthesis of Compound **123a**.

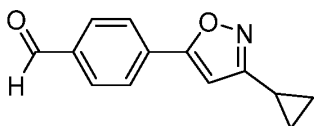
The product **173** was obtained as a yellow viscous liquid at a yield of 55%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]imidazolidin-2-one (Compound **18)**



The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]imidazolidin-2-one (Compound **18**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **173**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **18**) was obtained as a white solid at a yield of 68%. ¹H NMR (300MHz, DMSO- *d*₆) δ 1.12-1.19 (m, 2H), 1.21-1.28 (m, 2H), 2.31-2.38 (m, 1H), 3.13 (dd, 1H, *J* = 6.3, 8.7 Hz), 3.89 (dd, 1H, *J* = 8.7, 9.0 Hz), 5.60 (dd, 1H, *J* = 6.3, 9.0 Hz), 6.98-7.03 (m, 1H), 7.19 (br. s, 1H), 7.35-7.59 (m, 4H), 7.88 (d, 2H, *J* = 7.8 Hz), 8.07 (s, 1H), 12.23 (s, 1H); LC/MS (ESI) *m/z*: 387.1 [*M* + *H*]⁺.

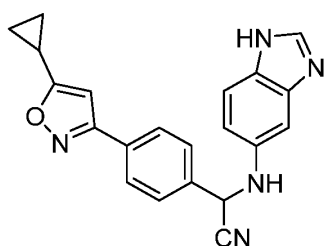
4-(3-cyclopropyl-1,2-oxazol-5-yl)benzaldehyde (Compound **177)**



The cyclopropanecarboxaldehyde **174** (1.0 g, 14.26 mmol), hydroxylamine hydrochloride (0.99 g, 14.26 mmol) and potassium carbonate (2.17 g, 15.68 mmol) were dissolved in H₂O (25 mL). The reaction mixture was stirred at 85 °C for 3 hours and then cooled to room temperature. The reaction mixture was partitioned between ether and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product **175** was used in next step without any further purification. To the solution of Compound **175** and NCS (1.9 g, 14.26 mmol) in DMF (30 mL), the catalytic amount of pyridine was added under argon. The reaction mixture was stirred at room temperature for 2 hours. After cooling to 0 °C, 4-

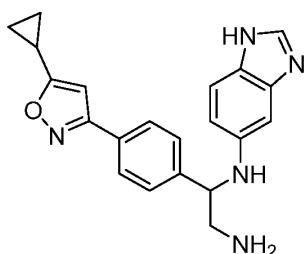
ethynylbenzaldehyde **176** (1.9 g, 14.26 mmol) and triethylamine (3 mL) were added. The reaction mixture was continuously stirred at room temperature for 3 hours. The reaction mixture was partitioned between EA and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using EA/hexane (1/8) as eluent to give the product **177** as a yellow solid at overall yield of 54%.

(1*H*-benzimidazol-5-ylamino)[4-(5-cyclopropyl-1,2-oxazol-3-yl)phenyl]acetonitrile (Compound 178)



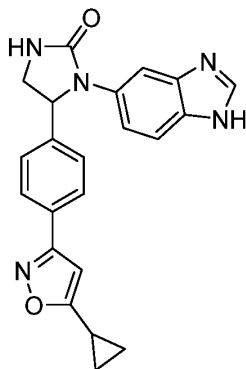
The (1*H*-benzimidazol-5-ylamino)[4-(5-cyclopropyl-1,2-oxazol-3-yl)phenyl]acetonitrile **178** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **177**. The procedures were the same as the synthesis of Compound **122a**. The product **178** was obtained as a pale-yellow solid at a yield of 83%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropyl-1,2-oxazol-3-yl)phenyl]ethane-1,2-diamine (Compound 179)**



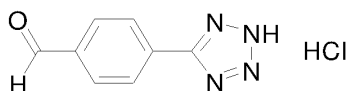
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-cyclopropyl-1,2-oxazol-3-yl)phenyl]ethane-1,2-diamine **179** was prepared from the hydrogenation of Compound **178** with Pd/C as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **179** was obtained as a yellow viscous liquid at a yield of 49%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropyl-1,2-oxazol-3-yl)phenyl]imidazolidin-2-one (Compound 19)



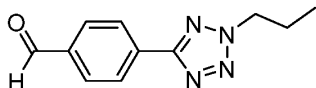
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-cyclopropyl-1,2-oxazol-3-yl)phenyl]imidazolidin-2-one (Compound **19**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **179**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **19**) was obtained as a white solid at a yield of 58%. ¹H NMR (400MHz, DMSO- *d*₆) δ 0.75-0.79 (m, 2H), 0.99-1.04 (m, 2H), 1.98-2.02 (m, 1H), 3.13 (dd, 1H, *J* = 6.3, 9.0 Hz), 3.88 (dd, 1H, *J* = 8.7, 9.0 Hz), 5.59 (dd, 1H, *J* = 6.3, 8.7 Hz), 6.68 (s, 1H), 7.01 (s, 1H), 7.26 (d, 1H, *J* = 8.4 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.49 (d, 2H, *J* = 7.8 Hz), 7.56 (s, 1H), 7.72 (d, 2H, *J* = 7.8 Hz), 7.79 (s, 1H), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 386.2 [M + H]⁺.

4-(2*H*-tetrazol-5-yl)benzaldehyde hydrochloride (Compound 180)



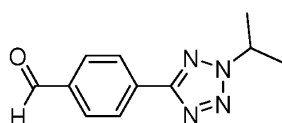
To the solution of 4-formylbenzonitrile **166** (1.31 g, 10.0 mmol) in DMF (10 mL), sodium azide (0.72 g, 11 mmol) and ammonium chloride (0.14 g, 2.5 mmol) were added under nitrogen. The reaction mixture was refluxed overnight and then cooled to room temperature. The reaction mixture was diluted with water and extracted with DCM. The aqueous phase was chilled in ice and acidified by adding 1N HCl_(aq). After filtering, the precipitates were washed with water and ether to obtain the product **180** as a yellow solid at a yield of 94%.

4-(2-propyl-2*H*-tetrazol-5-yl)benzaldehyde (Compound 181a)



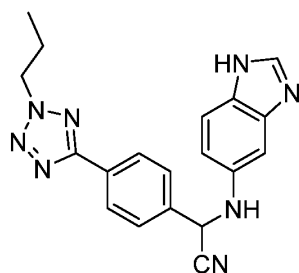
To the suspension of the Compound **180** (2.1 g, 10.0 mmol) in acetonitrile (20 mL), potassium carbonate (2.76 g, 20 mmol) and 1-bromopropane (2.46 g, 20 mmol) were added under nitrogen. The reaction mixture was stirred at 50 °C overnight and then cooled to room temperature. The reaction mixture was partitioned between EA and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using EA/hexane (1/4) as eluent to give the product **181a** as a yellow solid at a yield of 76%.

4-[2-(propan-2-yl)-2H-tetrazol-5-yl]benzaldehyde (Compound 181b)



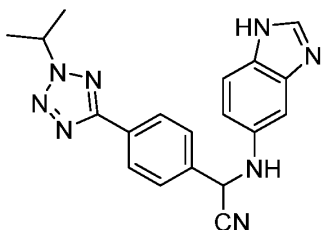
Isopropanol (1.2 g, 20.0 mmol) was added to the solution of the Compound **180** (2.1 g, 10.0 mmol) in trifluoromethanesulfonic acid (20 mL) under nitrogen. The reaction mixture was stirred at room temperature for an hour. The reaction mixture was poured into water and treated with sat. NaHCO_{3(aq)} until pH = 8~9. The mixture was partitioned between DCM and water. The organic phases were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using EA/hexane (1/4) as eluent to give the product **181b** as a yellow solid at a yield of 54%.

(1H-benzimidazol-5-ylamino)[4-(2-propyl-2H-tetrazol-5-yl)phenyl]acetonitrile (Compound 182a)



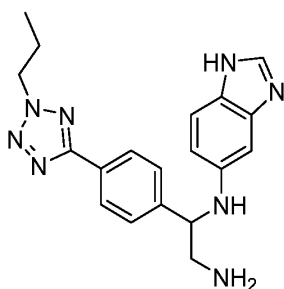
The (1H-benzimidazol-5-ylamino)[4-(2-propyl-2H-tetrazol-5-yl)phenyl]acetonitrile **182a** was prepared from the addition of 1H-benzimidazol-5-amine **121**, TMSCN and Compound **181a**. The procedures were the same as the synthesis of Compound **122a**. The product **182a** was obtained as a pale-yellow solid at a yield of 86%.

(1*H*-benzimidazol-5-ylamino){4-[2-(propan-2-yl)-2*H*-tetrazol-5-yl]phenyl}acetonitrile
(Compound **182b**)



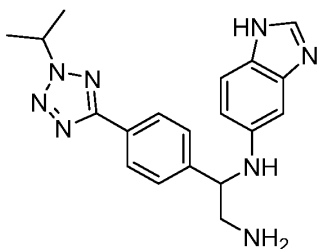
The (1*H*-benzimidazol-5-ylamino){4-[2-(propan-2-yl)-2*H*-tetrazol-5-yl]phenyl}-acetonitrile **182b** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and Compound **181b**. The procedures were the same as the synthesis of Compound **122a**. The product **182b** was obtained as a pale-yellow solid at a yield of 81%.

*N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-propyl-2*H*-tetrazol-5-yl)phenyl]ethane-1,2-diamine
(Compound **183a**)



The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(2-propyl-2*H*-tetrazol-5-yl)phenyl]ethane-1,2-diamine **183a** was prepared from the hydrogenation of Compound **182a** with Pd/C as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **183a** was obtained as a yellow viscous liquid at a yield of 50%.

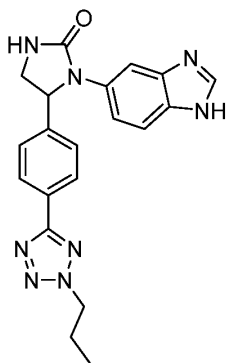
*N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[2-(propan-2-yl)-2*H*-tetrazol-5-yl]phenyl}ethane-1,2-diamine (Compound **183b**)



The *N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[2-(propan-2-yl)-2*H*-tetrazol-5-yl]phenyl}ethane-1,2-diamine **183b** was prepared from the hydrogenation of Compound

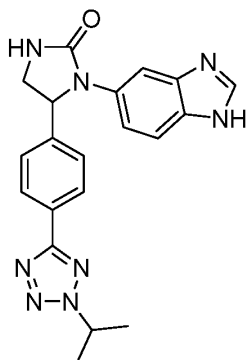
182b with Pd/C as catalyst. The procedures were the same as the synthesis of Compound **123a**. The product **183b** was obtained as a yellow viscous liquid at a yield of 45%.

1-(1H-benzimidazol-5-yl)-5-[4-(2-propyl-2H-tetrazol-5-yl)phenyl]imidazolidin-2-one
(Compound **20**)



The 1-(1H-benzimidazol-5-yl)-5-[4-(2-propyl-2H-tetrazol-5-yl)phenyl]imidazolidin-2-one (Compound **20**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **183a**. The procedures were the same as the synthesis of Compound **1**. The product (Compound **20**) was obtained as a white solid at a yield of 60%. ¹H NMR (300MHz, DMSO- *d*₆) δ 0.83 (t, 3H, J = 7.2 Hz), 1.87-1.99 (m, 2H), 3.14 (dd, 1H, J = 6.3, 8.7 Hz), 3.89 (dd, 1H, J = 8.7, 9.0 Hz), 4.64 (t, 2H, J = 7.2 Hz), 5.60 (dd, 1H, J = 6.3, 9.0 Hz), 7.01 (s, 1H), 7.26 (d, 1H, J = 8.9 Hz), 7.39 (d, 1H, J = 8.9 Hz), 7.52-7.57 (m, 3H), 7.98 (d, 2H, J = 8.4 Hz), 8.07 (s, 1H), 12.21 (s, 1H); LC/MS (ESI) *m/z*: 389.2 [M + H]⁺.

1-(1H-benzimidazol-5-yl)-5-[4-[2-(propan-2-yl)-2H-tetrazol-5-yl]phenyl]imidazolidin-2-one
(Compound **21**)

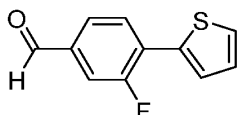


The 1-(1H-benzimidazol-5-yl)-5-[4-[2-(propan-2-yl)-2H-tetrazol-5-yl]phenyl]-imidazolidin-2-one (Compound **21**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and Compound **183b**. The procedures were the same as the synthesis of

Compound **1**. The product (Compound **21**) was obtained as a white solid at a yield of 62%.

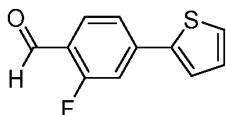
^1H NMR (400MHz, DMSO- d_6) δ 1.56 (d, 6H, J = 6.4 Hz), 3.14 (dd, 1H, J = 6.4, 8.8 Hz), 3.89 (dd, 1H, J = 8.8, 9.2 Hz), 5.09-5.15 (m, 1H), 5.60 (dd, 1H, J = 6.4, 9.2 Hz), 7.04 (s, 1H), 7.26 (d, 1H, J = 7.6 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.52-7.57 (m, 3H), 7.97 (d, 2H, J = 8.4 Hz), 8.07 (s, 1H), 12.25 (s, 1H); LC/MS (ESI) m/z : 389.2 $[\text{M} + \text{H}]^+$.

3-fluoro-4-(thiophen-2-yl)benzaldehyde (Compound 152b)



A mixture of tributyl(thiophen-2-yl)stannane **151** (6.62 g, 17.7 mmol), 4-bromo-3-fluorobenzaldehyde **138b** (3.0 g, 14.8 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.51 g, 0.43 mmol) in toluene (160 mL) was refluxed for 16 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was diluted with dichloromethane and filtered through celite. The organic phase was washed with water, dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography on silica gel using dichloromethane/hexane (1/9) as eluent. The product **152b** was obtained as a pale-yellow solid at a yield of 70%.

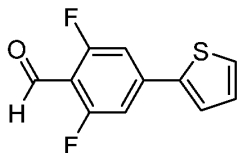
2-fluoro-4-(thiophen-2-yl)benzaldehyde (Compound 152c)



The 2-fluoro-4-(thiophen-2-yl)benzaldehyde **152c** was prepared from the Suzuki-coupling of 4-bromo-2-fluorobenzaldehyde **138c** and tributyl(thiophen-2-yl)stannane **151** using $\text{Pd}(\text{PPh}_3)_4$ as a catalyst. The procedures were the same as the synthesis of the Compound **152b**.

The product **152c** was obtained as a pale-yellow solid at a yield of 68%.

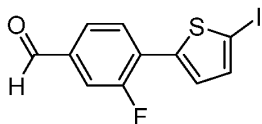
2,6-difluoro-4-(thiophen-2-yl)benzaldehyde (Compound 152d)



The 2,6-difluoro-4-(thiophen-2-yl)benzaldehyde **152d** was prepared from the Suzuki-coupling of 4-bromo-2,6-difluorobenzaldehyde **138d** and tributyl(thiophen-2-yl)stannane **151**

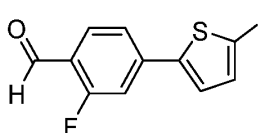
using $\text{Pd}(\text{PPh}_3)_4$ as a catalyst. The procedures were the same as the synthesis of the Compound **152b**. The product **152d** was obtained as a pale-yellow solid at a yield of 56%.

3-fluoro-4-(5-iodothiophen-2-yl)benzaldehyde (Compound 153b)



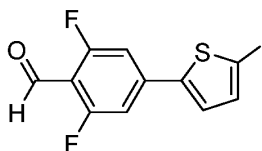
The 3-fluoro-4-(5-iodothiophen-2-yl)benzaldehyde **153b** was prepared from the selective iodination of the Compound **152b** using *N*-iodosuccinimide. The procedures were the same as the synthesis of the Compound **153a**. The product **153b** was obtained as a yellow-green solid at a yield of 77%.

2-fluoro-4-(5-iodothiophen-2-yl)benzaldehyde (Compound 153c)



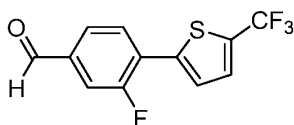
The 2-fluoro-4-(5-iodothiophen-2-yl)benzaldehyde **153c** was prepared from the selective iodination of the Compound **152c** using *N*-iodosuccinimide. The procedures were the same as the synthesis of the Compound **153a**. The product **153c** was obtained as a yellow-green solid at a yield of 75%.

2,6-difluoro-4-(5-iodothiophen-2-yl)benzaldehyde (Compound 153d)



The 2,6-difluoro-4-(5-iodothiophen-2-yl)benzaldehyde **153d** was prepared from the selective iodination of the Compound **152d** using *N*-iodosuccinimide. The procedures were the same as the synthesis of the Compound **153a**. The product **153d** was obtained as a yellow-green solid at a yield of 71%.

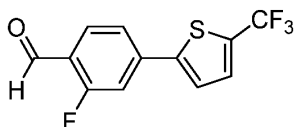
3-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde (Compound 155b)



The 3-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde **155b** was prepared from the trifluoromethylation of the Compound **153b** that treated with methyl

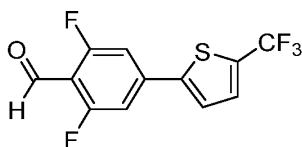
difluoro(fluorosulfonyl)acetate **154** and copper iodide. The procedures were the same as the synthesis of the Compound **155a**. The product **155b** was obtained as a yellow solid at a yield of 70%.

2-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde (Compound 155c)



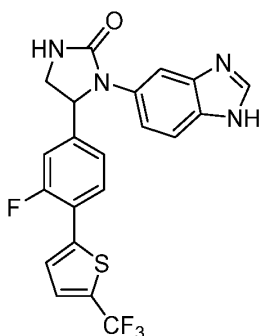
The 2-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde **155c** was prepared from the trifluoromethylation of the Compound **153c** that treated with methyl difluoro(fluorosulfonyl)acetate **154** and copper iodide. The procedures were the same as the synthesis of the Compound **155a**. The product **155c** was obtained as a yellow solid at a yield of 72%.

2,6-difluoro-4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde (Compound 155d)



The 2,6-difluoro-4-[5-(trifluoromethyl)thiophen-2-yl]benzaldehyde **155d** was prepared from the trifluoromethylation of the Compound **153d** that treated with methyl difluoro(fluorosulfonyl)acetate **154** and copper iodide. The procedures were the same as the synthesis of the Compound **155a**. The product **155d** was obtained as a yellow solid at a yield of 67%.

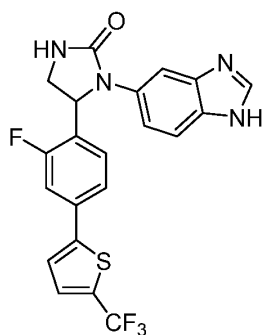
1-(1H-benzimidazol-5-yl)-5-{3-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-imidazolidin-2-one (Compound 22)



The 1-(1H-benzimidazol-5-yl)-5-{3-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-imidazolidin-2-one (Compound **22**) was prepared from the Compound **155b** in

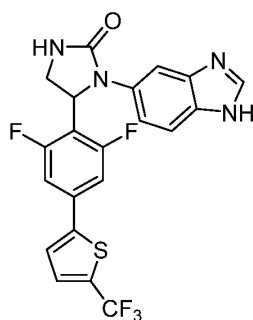
three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **22**) was obtained as a white solid at an overall yield of 27%. ¹H NMR (300MHz, CD₃OD) δ 3.36 (dd, 1H, J = 6.9, 9.0 Hz), 4.01 (dd, 1H, J = 9.0, 9.6 Hz), 5.54 (dd, 1H, J = 6.9, 9.6 Hz), 7.27-7.34 (m, 3H), 7.41 (d, 1H, J = 3.9 Hz), 7.48-7.51 (m, 2H), 7.59-7.67 (m, 2H), 8.07 (s, 1H); LC/MS (ESI) *m/z*: 447.0 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{2-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-imidazolidin-2-one (Compound 23)



The 1-(1*H*-benzimidazol-5-yl)-5-{2-fluoro-4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-imidazolidin-2-one (Compound **23**) was prepared from the Compound **155c** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **23**) was obtained as a white solid at an overall yield of 25%. ¹H NMR (300MHz, CD₃OD) δ 3.44 (dd, 1H, J = 6.0, 9.0 Hz), 4.05 (dd, 1H, J = 9.0, 9.3 Hz), 5.83 (dd, 1H, J = 6.0, 9.3 Hz), 7.31-7.51 (m, 7H), 7.60 (d, 1H, J = 2.1 Hz), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 447.1 [M + H]⁺.

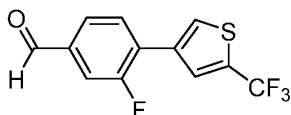
1-(1*H*-benzimidazol-5-yl)-5-{2,6-difluoro-4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}-imidazolidin-2-one (Compound 24)



The 1-(1*H*-benzimidazol-5-yl)-5-{2,6-difluoro-4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}imidazolidin-2-one (Compound **24**) was prepared from the Compound **155d** in

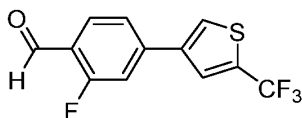
three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **24**) was obtained as a white solid at an overall yield of 21%. ¹H NMR (300MHz, CD₃OD) δ 3.65 (dd, 1H, J = 7.2, 9.3 Hz), 4.05 (dd, 1H, J = 9.3, 10.5 Hz), 6.01 (dd, 1H, J = 7.2, 10.5 Hz), 7.23-7.28 (m, 3H), 7.39-7.41 (m, 1H), 7.46-7.50 (m, 2H), 7.57 (d, 1H, J = 1.8 Hz), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 465.1 [M + H]⁺.

3-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde (Compound 159d)



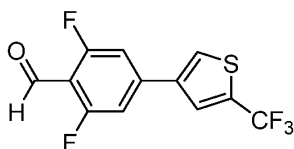
The 3-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde **159d** was prepared from the Suzuki-Miyaura coupling of (2-fluoro-4-formylphenyl)boronic acid **118d** and 3-bromo-(5-trifluoromethyl)thiophene **158c**. The procedures were the same as the synthesis of Compound **159a**. The product **159d** was obtained as a pale-yellow solid at a yield of 60%.

2-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde (Compound 159e)

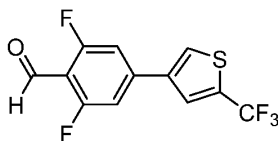


The 2-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde **159e** was prepared from the Suzuki-Miyaura coupling of (3-fluoro-4-formylphenyl)boronic acid **118e** and 3-bromo-(5-trifluoromethyl)thiophene **158c**. The procedures were the same as the synthesis of Compound **159a**. The product **159e** was obtained as a pale-yellow solid at a yield of 53%.

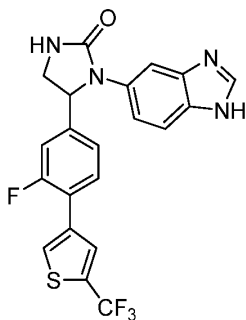
2,6-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde (Compound 159f)



The 2,6-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde **159f** was prepared from the Suzuki-Miyaura coupling of (3,5-difluoro-4-formylphenyl)boronic acid **118f** and 3-bromo-(5-trifluoromethyl)thiophene **158c**. The procedures were the same as the synthesis of Compound **159a**. The product **159f** was obtained as a pale-yellow solid at a yield of 33%.

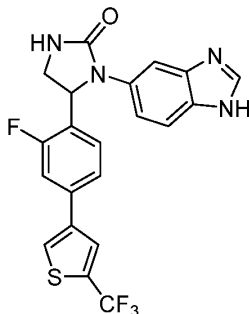
2,3-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde (Compound 159g)

The 2,3-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]benzaldehyde **159g** was prepared from the Suzuki-Miyaura coupling of (2,3-difluoro-4-formylphenyl)boronic acid **118g** and 3-bromo-(5-trifluoromethyl)thiophene **158c**. The procedures were the same as the synthesis of Compound **159a**. The product **159g** was obtained as a pale-yellow solid at a yield of 29%.

1-(1*H*-benzimidazol-5-yl)-5-{3-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}-imidazolidin-2-one (Compound 25)

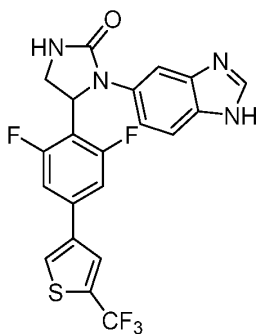
The 1-(1*H*-benzimidazol-5-yl)-5-{3-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}-imidazolidin-2-one (Compound **25**) was prepared from the Compound **159d** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **25**) was obtained as a white solid at an overall yield of 25%. ¹H NMR (300MHz, CD₃OD) δ 3.37 (dd, 1H, J = 6.9, 9.0 Hz), 4.01 (dd, 1H, J = 9.0, 9.3 Hz), 5.54 (dd, 1H, J = 6.9, 9.3 Hz), 7.24-7.34 (m, 3H), 7.49 (d, 1H, J = 8.7 Hz), 7.56-7.61 (m, 2H), 7.80 (d, 1H, J = 0.9 Hz), 7.90 (s, 1H), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 447.0 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{2-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}-imidazolidin-2-one (Compound 26)



The 1-(1*H*-benzimidazol-5-yl)-5-{2-fluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound **26**) was prepared from the Compound **159e** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **26**) was obtained as a white solid at an overall yield of 27%. ¹H NMR (300MHz, CD₃OD) δ 3.44 (dd, 1H, J = 6.3, 9.0 Hz), 4.05 (dd, 1H, J = 9.0, 9.6 Hz), 5.82 (dd, 1H, J = 6.3, 9.6 Hz), 7.33 (dd, 1H, J = 1.2, 8.7 Hz), 7.42-7.50 (m, 4H), 7.60 (d, 1H, J = 2.0 Hz), 7.86 (d, 1H, J = 1.2 Hz), 7.93 (d, 1H, J = 2.0 Hz), 8.07 (s, 1H); LC/MS (ESI) *m/z*: 447.0 [M + H]⁺.

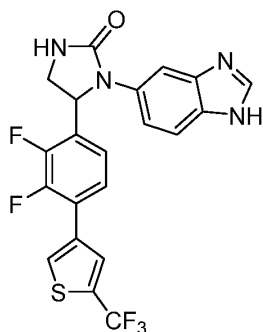
1-(1*H*-benzimidazol-5-yl)-5-{2,6-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}-imidazolidin-2-one (Compound 27)



The 1-(1*H*-benzimidazol-5-yl)-5-{2,6-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound **27**) was prepared from the Compound **159f** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **27**) was obtained as a white solid at an overall yield of 21%. ¹H NMR (300MHz, CD₃OD) δ 3.65 (dd, 1H, J = 7.2, 9.3 Hz), 4.04 (dd, 1H, J = 9.3, 10.2 Hz), 6.00 (dd, 1H, J = 7.2, 10.2 Hz), 7.24-7.28 (m, 3H), 7.48 (d, 1H, J = 8.7

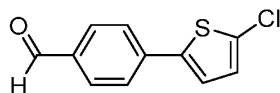
Hz), 7.56 (d, 1H, J = 1.8 Hz), 7.84 (s, 1H), 7.95 (d, 1H, J = 1.8 Hz), 8.07 (s, 1H); LC/MS (ESI) m/z : 465.1 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{2,3-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}-imidazolidin-2-one (Compound 28)



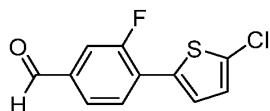
The 1-(1*H*-benzimidazol-5-yl)-5-{2,3-difluoro-4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound **28**) was prepared from the Compound **159g** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **28**) was obtained as a white solid at an overall yield of 20%. ¹H NMR (300MHz, CD₃OD) δ 3.46 (dd, 1H, J = 6.3, 9.0 Hz), 4.07 (dd, 1H, J = 9.0, 9.6 Hz), 5.87 (dd, 1H, J = 6.3, 9.6 Hz), 7.23-7.40 (m, 3H), 7.50 (d, 1H, J = 8.4 Hz), 7.61 (d, 1H, J = 1.8 Hz), 7.82 (s, 1H), 7.97 (s, 1H), 8.09 (s, 1H); LC/MS (ESI) m/z : 465.1 [M + H]⁺.

4-(5-chlorothiophen-2-yl)benzaldehyde (Compound 140b)



The 4-(5-chlorothiophen-2-yl)benzaldehyde **140b** was prepared from the Suzuki-coupling of 4-bromobenzaldehyde **138a** and 2-chlorothiophene **139b**. The procedures were the same as the synthesis of Compound **140a**. The product **140b** was obtained as a yellow solid at a yield of 74%.

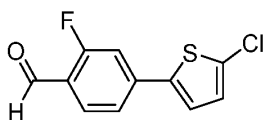
4-(5-chlorothiophen-2-yl)-3-fluorobenzaldehyde (Compound 140c)



The 4-(5-chlorothiophen-2-yl)-3-fluorobenzaldehyde **140c** was prepared from the Suzuki-coupling of 4-bromo-3-fluorobenzaldehyde **138b** and 2-chlorothiophene **139b**. The

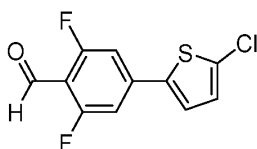
procedures were the same as the synthesis of Compound **140a**. The product **140c** was obtained as a yellow solid at a yield of 69%.

4-(5-chlorothiophen-2-yl)-2-fluorobenzaldehyde (Compound 140d)



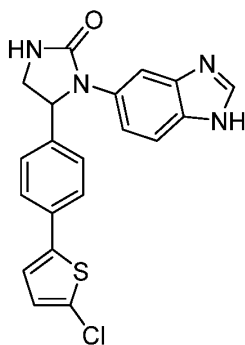
The 4-(5-chlorothiophen-2-yl)-2-fluorobenzaldehyde **140d** was prepared from the Suzuki-coupling of 4-bromo-2-fluorobenzaldehyde **138c** and 2-chlorothiophene **139b**. The procedures were the same as the synthesis of Compound **140a**. The product **140d** was obtained as a yellow solid at a yield of 67%.

4-(5-chlorothiophen-2-yl)-2,6-difluorobenzaldehyde (Compound 140e)



The 4-(5-chlorothiophen-2-yl)-2,6-difluorobenzaldehyde **140e** was prepared from the Suzuki-coupling of 4-bromo-2,6-difluorobenzaldehyde **138d** and 2-chlorothiophene **139b**. The procedures were the same as the synthesis of Compound **140a**. The product **140e** was obtained as a yellow solid at a yield of 60%.

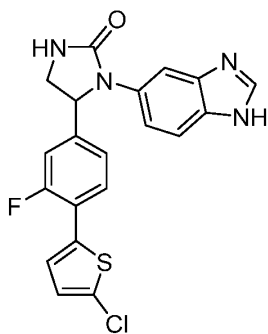
1-(1H-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)phenyl]imidazolidin-2-one (Compound 29)



The 1-(1H-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)phenyl]imidazolidin-2-one (Compound **29**) was prepared from the Compound **140b** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **29**) was obtained as a white solid at an overall yield of 28%. ¹H NMR (300MHz, CD₃OD) δ 3.36 (dd, 1H, J = 6.9, 9.0 Hz), 3.99 (dd, 1H, J = 9.0, 9.3 Hz),

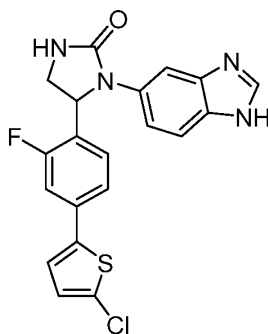
5.48 (dd, 1H, J = 6.9, 9.3 Hz), 6.90 (d, 1H, J = 3.9 Hz), 7.12 (d, 1H, J = 3.9 Hz), 7.30 (d, 1H, J = 9.0 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.45-7.49 (m, 3H), 7.54 (d, 1H, J = 2.1 Hz), 8.06 (s, 1H); LC/MS (ESI) m/z : 395.0 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)-3-fluorophenyl]imidazolidin-2-one (Compound 30)



The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)-3-fluorophenyl]imidazolidin-2-one (Compound **30**) was prepared from the Compound **140c** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **30**) was obtained as a white solid at an overall yield of 24%. ¹H NMR (400MHz, CD₃OD) δ 3.36 (dd, 1H, J = 6.8, 9.2 Hz), 4.00 (dd, 1H, J = 9.2, 9.2 Hz), 5.52 (dd, 1H, J = 6.8, 9.2 Hz), 6.95 (d, 1H, J = 4.0 Hz), 7.23-7.26 (m, 3H), 7.31 (d, 1H, J = 8.0 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.56-7.59 (m, 2H), 8.08 (s, 1H); LC/MS (ESI) m/z : 413.0 [M + H]⁺.

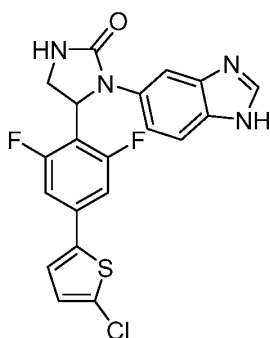
1-(1*H*-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)-2-fluorophenyl]imidazolidin-2-one (Compound 31)



The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)-2-fluorophenyl]imidazolidin-2-one (Compound **31**) was prepared from the Compound **140d** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of

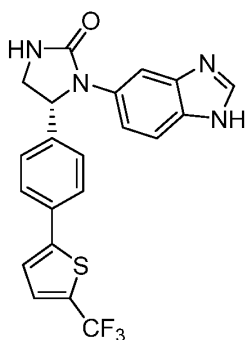
Compound **1**. The product (Compound **31**) was obtained as a white solid at an overall yield of 25%. ^1H NMR (300MHz, CD_3OD) δ 3.42 (dd, 1H, $J = 6.6, 9.0$ Hz), 4.03 (dd, 1H, $J = 9.0, 9.6$ Hz), 5.78 (dd, 1H, $J = 6.6, 9.6$ Hz), 6.91 (d, 1H, $J = 4.2$ Hz), 7.17 (d, 1H, $J = 4.2$ Hz), 7.24-7.42 (m, 4H), 7.48 (d, 1H, $J = 8.4$ Hz), 7.58 (d, 1H, $J = 1.8$ Hz), 8.07 (s, 1H); LC/MS (ESI) m/z : 413.0 $[\text{M} + \text{H}]^+$.

1-(1H-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)-2,6-difluorophenyl]imidazolidin-2-one (Compound 32)

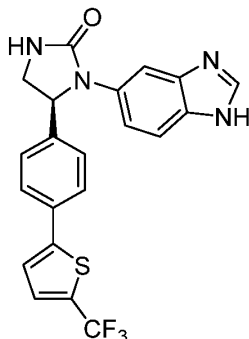


The 1-(1H-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-2-yl)-2,6-difluorophenyl]-imidazolidin-2-one (Compound **32**) was prepared from the Compound **140e** in three-steps synthesis of imidazolidinone formation. The procedures were the same as the synthesis of Compound **1**. The product (Compound **32**) was obtained as a white solid at an overall yield of 20%.

(5R)-1-(1H-benzimidazol-5-yl)-5-{4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}imidazolidin-2-one (Compound 33)

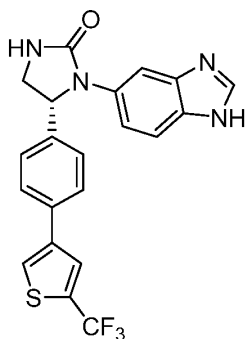


(5S)-1-(1H-benzimidazol-5-yl)-5-{4-[5-(trifluoromethyl)thiophen-2-yl]phenyl}imidazolidin-2-one (Compound 34)

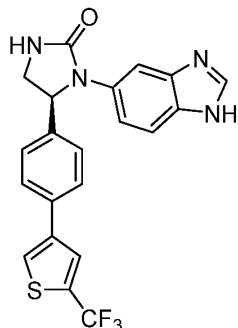


The enantiomers (Compounds **33** and **34**) were separated from Compound **13** by HPLC using CHIRALPAK AD-H. The isomer fractions were respectively collected and the optical pure isomers (Compounds **33** and **34**) were thus obtained by removing the solvent under reduced pressure. ^1H NMR (300MHz, CD_3OD) δ 3.36 (dd, 1H, $J = 6.9, 9.3$ Hz), 3.99 (dd, 1H, $J = 9.3, 9.3$ Hz), 5.51 (dd, 1H, $J = 6.9, 9.3$ Hz), 7.29-7.32 (m, 2H), 7.43-7.48 (m, 4H), 7.55-7.60 (m, 3H), 8.06 (s, 1H); LC/MS (ESI) m/z : 429.2 $[\text{M} + \text{H}]^+$.

(5R)-1-(1H-benzimidazol-5-yl)-5-{4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound 35)

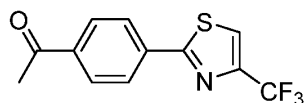


(5S)-1-(1H-benzimidazol-5-yl)-5-{4-[5-(trifluoromethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound 36)



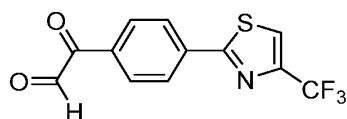
The enantiomers (Compounds **35** and **36**) were separated from Compound **16** by HPLC using CHIRALPAK AD-H. The isomer fractions were respectively collected and the optical pure isomers (Compounds **35** and **36**) were thus obtained by removing the solvent under reduced pressure. ¹H NMR (300MHz, CD₃OD) δ 3.36 (dd, 1H, J = 6.9, 9.0 Hz), 3.99 (dd, 1H, J = 9.0, 9.3 Hz), 5.50 (dd, 1H, J = 6.9, 9.3 Hz), 7.30 (d, 1H, J = 8.1 Hz), 7.41-7.47 (m, 3H), 7.56-7.58 (m, 3H), 7.81 (s, 2H), 8.05 (s, 1H); LC/MS (ESI) *m/z*: 429.1 [M + H]⁺.

1-{4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl}ethanone (Compound 185)



The 1-{4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl}ethanone **185** was prepared from the Suzuki-coupling of (4-acetylphenyl)boronic acid **184** and Compound **119d**. The procedures were the same as the synthesis of Compound **120a**. The product **185** was obtained as a white solid at a yield of 83%. ¹H NMR (400MHz, CDCl₃) δ 2.65 (s, 3H), 7.82 (s, 1H), 8.05 (d, 2H, J = 8.6 Hz), 8.09 (d, 2H, J = 8.6 Hz); LC/MS (ESI) *m/z*: 271.7 [M + H]⁺.

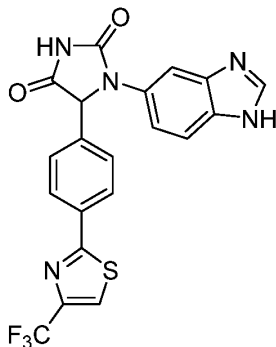
oxo{4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl}acetaldehyde (Compound 186)



The Compound **185** (10.0 g, 36.86 mmol) and selenium dioxide (6.95 g, 62.67 mmol) were dissolved in H₂O/1,4-dioxane (8 mL/160 mL). The reaction mixture was stirred at 100 °C overnight. The black solid was filtered through celite and washed with ethyl acetate. The filtrate was concentrated under the reduced pressure. The residue was purified by column

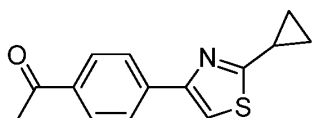
chromatography on silica gel using ethyl acetate/hexane (1/1) as eluent. The product **186** was obtained as a yellow solid at a yield of 100%.

1-(1*H*-benzimidazol-5-yl)-5-{4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]phenyl}imidazolidine-2,4-dione (Compound 37)

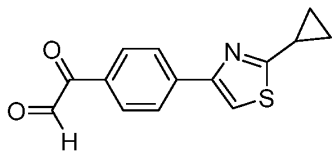


The Compound **186** (9.0 g, 31.55 mmol) and 1-(1*H*-benzimidazol-6-yl)urea **187** (5.56 g, 31.55 mmol) were dissolved in HCl/AcOH (3 mL/120 mL). The reaction mixture was stirred at 120 °C overnight. After removing the solvents, the residue was treated with the excess ammonia in methanol at an ice-bath and stirred at room temperature for an hour. The precipitates were filtered and washed with ethyl acetate and water to get the pure product. The filtrate was concentrated and recrystallized in ethyl acetate. The white solids were collected as the product (Compound **37**) at a yield of 45%. ¹H NMR (300MHz, DMSO-*d*₆) δ 6.13 (s, 1H), 7.27 (s, 1H), 7.43 (s, 1H), 7.55 (d, 2H, J = 8.4 Hz), 7.71 (s, 1H), 7.94 (d, 2H, J = 8.4 Hz), 8.16 (s, 1H), 8.52 (s, 1H), 11.43 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) *m/z*: 444.2 [M + H]⁺.

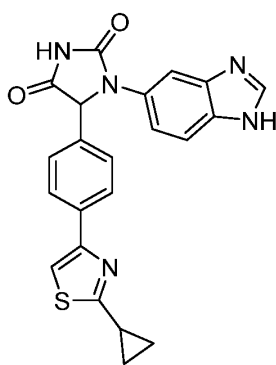
1-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]ethanone (Compound 188)



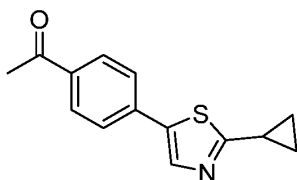
The 1-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]ethanone **188** was prepared from the Suzuki-coupling of (4-acetylphenyl)boronic acid **184** and Compound **126** with Pd(dppf)Cl₂ as catalyst. The procedures were the same as the synthesis of Compound **127**. The product **188** was obtained as a white solid at a yield of 57%. ¹H NMR (400MHz, CDCl₃) δ 1.09-1.16 (m, 4H), 2.32-2.37 (m, 1H), 2.60 (s, 3H), 7.35 (s, 1H), 7.94 (d, 2H, J = 8.8 Hz), 7.97 (d, 2H, J = 8.8 Hz); LC/MS (ESI) *m/z*: 244.1 [M + H]⁺.

[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl](oxo)acetaldehyde (Compound 189)

The [4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl](oxo)acetaldehyde **189** was prepared from the oxidation of Compound **188** by selenium dioxide. The procedures were the same as the synthesis of Compound **186**. The product **189** was obtained as a yellow solid at a yield of 100%.

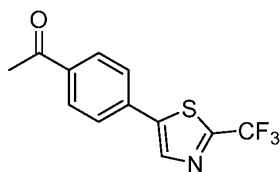
1-(1H-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]imidazolidine-2,4-dione (Compound 38)

The 1-(1H-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-4-yl)phenyl]imidazolidine-2,4-dione (Compound **38**) was prepared from the cycloaddition of 1-(1H-benzimidazol-6-yl)urea **187** and Compound **189**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **38**) was obtained as a white solid at a yield of 49%. ¹H NMR (400MHz, DMSO-*d*₆) δ 1.00-1.03 (m, 2H), 1.08-1.11 (m, 2H), 2.36-2.42 (m, 1H), 6.03 (s, 1H), 7.28 (s, 1H), 7.41 (d, 2H, J = 8.0 Hz), 7.48 (s, 1H), 7.69 (s, 1H), 7.77 (s, 1H), 7.83 (d, 2H, J = 8.0 Hz), 8.15 (s, 1H), 11.38 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) *m/z*: 416.2 [M + H]⁺.

1-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]ethanone (Compound 190b)

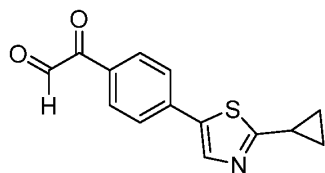
To the solution of Compound **134b** (0.23 g, 1.0 mmol) in anhydrous THF (4 mL), the methylmagnesium bromide in THF (1M, 2 mL) was added dropwise at 0 °C. Then, the reaction mixture was stirred at room temperature overnight. The saturated aqueous solution of ammonium chloride was added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The organic layers were collected, washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane (1/4) as eluent. The product **190b** was obtained as a yellow solid at a yield of 48%. ¹H NMR (300MHz, CDCl₃) δ 1.13-1.19 (m, 4H), 2.30-2.35 (m, 1H), 2.61 (s, 3H), 7.58 (d, 2H, J = 8.0 Hz), 7.85 (s, 1H), 7.96 (d, 2H, J = 8.0 Hz); LC/MS (ESI) *m/z*: 244.1 [M + H]⁺.

1-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}ethanone (Compound 190c)

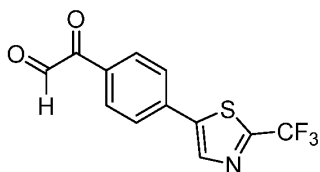


The 1-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}ethanone **190c** was prepared from the methylation of Compound **134c**. The procedures were the same as the synthesis of Compound **190b**. The product **190c** was obtained as a yellow solid at a yield of 49%. ¹H NMR (400MHz, CDCl₃) δ 2.64 (s, 3H), 7.69 (d, 2H, J = 8.0 Hz), 8.04 (d, 2H, J = 8.0 Hz), 8.17 (s, 1H); LC/MS (ESI) *m/z*: 271.7 [M + H]⁺.

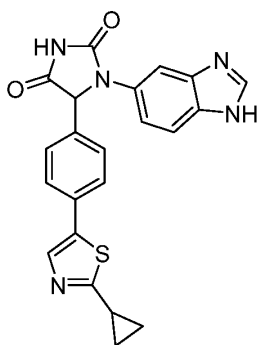
[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl](oxo)acetaldehyde (Compound 191b)



The [4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl](oxo)acetaldehyde **191b** was prepared from the oxidation of Compound **190b** by selenium dioxide. The procedures were the same as the synthesis of Compound **186**. The product **191b** was obtained as a yellow solid at a yield of 100%.

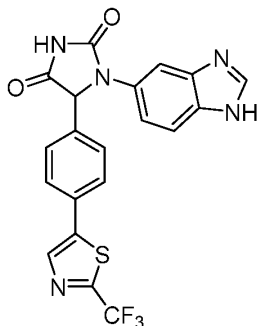
oxo{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}acetaldehyde (Compound 191c)

The oxo{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}acetaldehyde **191c** was prepared from the oxidation of Compound **190c** by selenium dioxide. The procedures were the same as the synthesis of Compound **186**. The product **191c** was obtained as a yellow solid at a yield of 100%.

1-(1H-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]imidazolidine-2,4-dione (Compound 39)

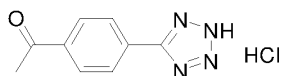
The 1-(1H-benzimidazol-5-yl)-5-[4-(2-cyclopropyl-1,3-thiazol-5-yl)phenyl]imidazolidine-2,4-dione (Compound **39**) was prepared from the cycloaddition of 1-(1H-benzimidazol-6-yl)urea **187** and Compound **191b**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **39**) was obtained as a white solid at a yield of 57%. ¹H NMR (400MHz, DMSO-*d*₆) δ 0.93-0.99 (m, 2H), 1.01-1.11 (m, 2H), 2.33-2.39 (m, 1H), 6.05 (s, 1H), 7.33 (d, 1H, J = 8.6 Hz), 7.41 (d, 2H, J = 8.0 Hz), 7.48 (d, 1H, J = 8.6 Hz), 7.53 (d, 2H, J = 8.0 Hz), 7.70 (d, 1H, J = 1.2 Hz), 7.91 (s, 1H), 8.18 (s, 1H), 11.39 (s, 1H), 12.47 (s, 1H); LC/MS (ESI) *m/z*: 416.2 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound 40)



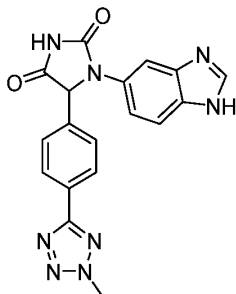
The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(trifluoromethyl)-1,3-thiazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **40**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **191c**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **40**) was obtained as a white solid at a yield of 30%. ¹H NMR (400MHz, DMSO-*d*₆) δ 6.12 (s, 1H), 7.35 (s, 1H), 7.47-7.52 (m, 3H), 7.71-7.75 (m, 3H), 8.16 (s, 1H), 8.48 (s, 1H), 11.44 (s, 1H), 12.43 (s, 1H); LC/MS (ESI) *m/z*: 444.2 [M + H]⁺.

1-[4-(2*H*-tetrazol-5-yl)phenyl]ethanone (Compound 192)



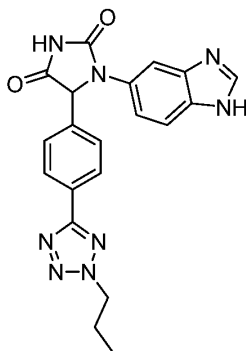
To the solution of 4-acetylbenzonitrile **143** (4.35 g, 30.0 mmol) in DMF (30 mL), sodium azide (2.15 g, 33 mmol) and ammonium chloride (0.40 g, 7.5 mmol) were added under nitrogen. The reaction mixture was refluxed overnight and then cooled to room temperature. The reaction mixture was diluted with water and extracted with DCM. The aqueous phase was chilled in ice and acidified by adding 1N HCl_(aq). After filtering, the precipitates were washed with water and ether to obtain the product **192** as a yellow solid at a yield of 94%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(2-methyl-2*H*-tetrazol-5-yl)phenyl]imidazolidine-2,4-dione (Compound 41)



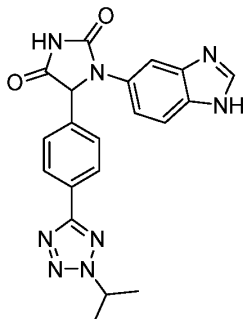
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(2-methyl-2*H*-tetrazol-5-yl)phenyl]imidazolidine-2,4-dione (Compound **41**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194a**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **41**) was obtained as a white solid at a yield of 17%. ¹H NMR (400MHz, DMSO-*d*₆) δ 4.38 (s, 3H), 6.12 (s, 1H), 7.28 (br s, 1H), 7.47 (br s, 1H), 7.57 (d, 2H, J = 8.4 Hz), 7.72 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 8.16 (s, 1H), 11.46 (br s, 1H), 12.44 (br s, 1H); LC/MS (ESI) *m/z*: 375.1 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[4-(2-propyl-2*H*-tetrazol-5-yl)phenyl]imidazolidine-2,4-dione (Compound 42)



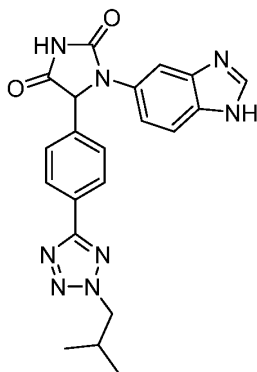
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(2-propyl-2*H*-tetrazol-5-yl)phenyl]imidazolidine-2,4-dione (Compound **42**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194b**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **42**) was obtained as a white solid at a yield of 33%. ¹H NMR (300MHz, DMSO-*d*₆) δ 0.84 (t, 3H, J = 7.5 Hz), 1.87-1.99 (m, 2H), 4.65 (t, 2H, J = 6.8 Hz), 6.12 (s, 1H), 7.34 (br s, 1H), 7.47 (br s, 1H), 7.57 (d, 2H, J = 8.4 Hz), 7.71 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 8.15 (s, 1H), 11.43 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) *m/z*: 403.2 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(propan-2-yl)-2*H*-tetrazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound 43)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(propan-2-yl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **43**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194c**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **43**) was obtained as a white solid at a yield of 28%. ¹H NMR (400MHz, DMSO-*d*₆) δ 1.57 (d, 6H, J = 6.4 Hz), 5.09-5.16 (m, 1H), 6.11 (s, 1H), 7.27 (br s, 1H), 7.42 (br s, 1H), 7.57 (d, 2H, J = 8.4 Hz), 7.71 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 8.15 (s, 1H), 11.43 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) *m/z*: 403.2 [M + H]⁺.

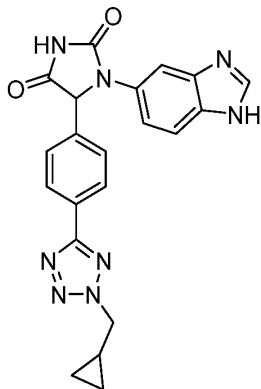
1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(2-methylpropyl)-2*H*-tetrazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound 44)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(2-methylpropyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **44**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194d**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **44**) was obtained as a white solid at a yield of 34%. ¹H NMR (400MHz, DMSO-*d*₆) δ 0.86 (d, 6H, J = 6.4 Hz), 2.22-2.29 (m, 1H), 4.53 (d, 2H, J = 6.8 Hz), 6.12 (s, 1H), 7.28 (br s, 1H), 7.47 (br s, 1H), 7.57 (d, 2H, J = 8.0

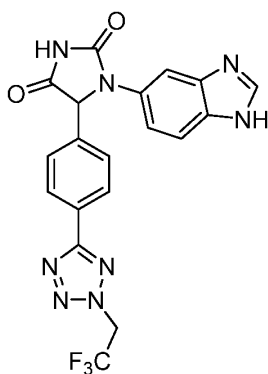
Hz), 7.72 (s, 1H), 8.01 (d, 2H, J = 8.0 Hz), 8.16 (s, 1H), 11.45 (s, 1H), 12.42 (s, 1H); LC/MS (ESI) m/z : 417.2 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(cyclopropylmethyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound 45)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(cyclopropylmethyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **45**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194e**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **45**) was obtained as a white solid at a yield of 31%. ¹H NMR (300MHz, DMSO-*d*₆) δ 0.42-0.45 (m, 2H), 0.54-0.58 (m, 2H), 1.33-1.41 (m, 1H), 4.57 (d, 2H, J = 7.2 Hz), 6.12 (s, 1H), 7.29 (br s, 1H), 7.46 (br s, 1H), 7.58 (d, 2H, J = 8.4 Hz), 7.72 (s, 1H), 8.01 (d, 2H, J = 8.4 Hz), 8.15 (s, 1H), 11.43 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) m/z : 415.1 [M + H]⁺.

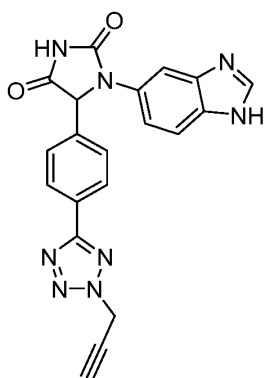
1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(2,2,2-trifluoroethyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound 46)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(2,2,2-trifluoroethyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **46**) was prepared from the cycloaddition of

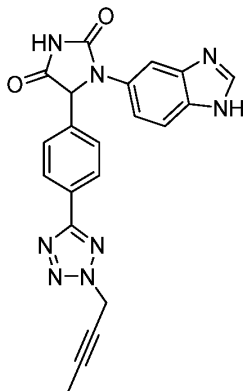
1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194f**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **46**) was obtained as a white solid at a yield of 36%. ¹H NMR (300MHz, DMSO-*d*₆) δ 6.01 (q, 2H, J = 8.7 Hz), 6.15 (s, 1H), 7.36 (br s, 1H), 7.48 (br s, 1H), 7.61 (d, 2H, J = 8.4 Hz), 7.73 (s, 1H), 8.04 (d, 2H, J = 8.4 Hz), 8.17 (s, 1H), 11.49 (br s, 1H), 12.41 (br s, 1H); LC/MS (ESI) *m/z*: 443.2 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(prop-2-yn-1-yl)-2*H*-tetrazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound **47)**



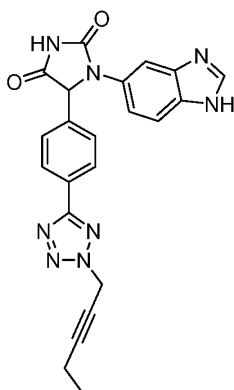
The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(prop-2-yn-1-yl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **47**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194g**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **47**) was obtained as a white solid at a yield of 36%. ¹H NMR (300MHz, DMSO-*d*₆) δ 5.75 (d, 1H, J = 1.5 Hz), 6.07 (d, 1H, J = 6.6 Hz), 6.14 (s, 1H), 7.29 (br s, 1H), 7.47 (br s, 1H), 7.59 (d, 2H, J = 8.0 Hz), 7.72 (s, 1H), 8.02 (d, 2H, J = 8.0 Hz), 8.16 (s, 1H), 8.24 (dd, 1H, J = 1.5, 6.6 Hz), 11.47 (br s, 1H), 12.44 (s, 1H); LC/MS (ESI) *m/z*: 399.1 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(but-2-yn-1-yl)-2*H*-tetrazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound 48)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(but-2-yn-1-yl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **48**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194h**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **48**) was obtained as a white solid at a yield of 34%. ¹H NMR (300MHz, DMSO-*d*₆) δ 1.83 (s, 3H), 5.65 (d, 2H, *J* = 1.8 Hz), 6.13 (s, 1H), 7.34 (d, 1H, *J* = 6.6 Hz), 7.48 (d, 1H, *J* = 8.7 Hz), 7.58 (d, 2H, *J* = 7.8 Hz), 7.72 (s, 1H), 8.02 (d, 2H, *J* = 7.8 Hz), 8.16 (s, 1H), 11.44 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) *m/z*: 413.1 [M + H]⁺.

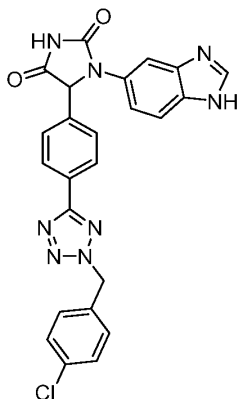
1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(pent-2-yn-1-yl)-2*H*-tetrazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound 49)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(pent-2-yn-1-yl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **49**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194i**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **49**) was obtained as a white solid at a

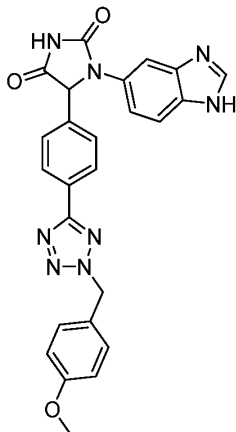
yield of 32%. ^1H NMR (300MHz, $\text{DMSO-}d_6$) δ 1.03 (t, 3H, $J = 7.5$ Hz), 2.17-2.26 (m, 2H), 5.65 (t, 2H, $J = 2.1$ Hz), 6.11 (s, 1H), 7.29 (br s, 1H), 7.46 (br s, 1H), 7.58 (d, 2H, $J = 8.4$ Hz), 7.71 (s, 1H), 8.01 (d, 2H, $J = 8.4$ Hz), 8.15 (s, 1H), 11.43 (br s, 1H), 12.42 (br s, 1H); LC/MS (ESI) m/z : 427.1 $[\text{M} + \text{H}]^+$.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(4-chlorobenzyl)-2*H*-tetrazol-5-yl]phenyl}imidazolidine-2,4-dione (Compound 50)



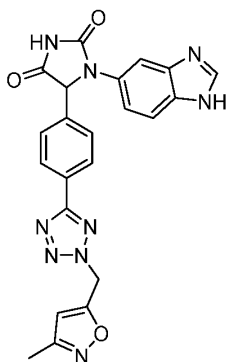
The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(4-chlorobenzyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **50**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194j**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **50**) was obtained as a white solid at a yield of 43%. ^1H NMR (300MHz, $\text{DMSO-}d_6$) δ 5.98 (s, 2H), 6.11 (s, 1H), 7.25 (d, 1H, $J = 8.1$ Hz), 7.36-7.50 (m, 5H), 7.56 (d, 2H, $J = 8.4$ Hz), 7.70 (s, 1H), 7.99 (d, 2H, $J = 8.4$ Hz), 8.15 (s, 1H), 11.44 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) m/z : 485.1 $[\text{M} + \text{H}]^+$.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(4-methoxybenzyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound 51)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(4-methoxybenzyl)-2*H*-tetrazol-5-yl]phenyl}-imidazolidine-2,4-dione (Compound **51**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194k**. The procedures were the same as the synthesis of Compound **37**. The product (Compound **51**) was obtained as a white solid at a yield of 22%. ¹H NMR (300MHz, DMSO-*d*₆) δ 3.71 (s, 3H), 5.86 (s, 2H), 6.15 (s, 1H), 6.91 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.42 (br s, 2H), 7.55 (d, 2H, J = 8.1 Hz), 7.70 (s, 1H), 7.98 (d, 2H, J = 8.1 Hz), 8.15 (s, 1H), 11.43 (s, 1H), 12.41 (s, 1H); LC/MS (ESI) *m/z*: 481.2 [M + H]⁺.

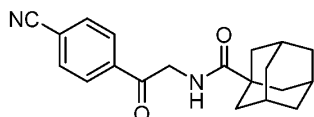
1-(1*H*-benzimidazol-5-yl)-5-(4-{2-[(3-methyl-1,2-oxazol-5-yl)methyl]-2*H*-tetrazol-5-yl}phenyl)imidazolidine-2,4-dione (Compound 52)



The 1-(1*H*-benzimidazol-5-yl)-5-(4-{2-[(3-methyl-1,2-oxazol-5-yl)methyl]-2*H*-tetrazol-5-yl}phenyl)imidazolidine-2,4-dione (Compound **52**) was prepared from the cycloaddition of 1-(1*H*-benzimidazol-6-yl)urea **187** and Compound **194l**. The procedures

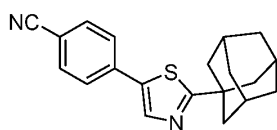
were the same as the synthesis of Compound **37**. The product (Compound **52**) was obtained as a white solid at a yield of 52%. ¹H NMR (400MHz, DMSO-*d*₆) δ 2.20 (s, 3H), 6.12 (s, 1H), 6.24 (s, 2H), 6.51 (s, 1H), 7.27 (br s, 1H), 7.46 (br s, 1H), 7.58 (d, 2H, J = 8.0 Hz), 7.71 (s, 1H), 8.00 (d, 2H, J = 8.0 Hz), 8.16 (s, 1H), 11.30 (br s, 1H), 12.42 (br s, 1H); LC/MS (ESI) *m/z*: 456.1 [M + H]⁺.

***N*-[2-(4-cyanophenyl)-2-oxoethyl]tricyclo[3.3.1.1^{3,7}]decane-1-carboxamide (Compound 196)**



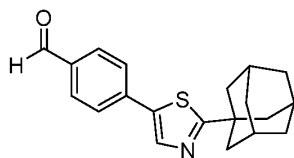
The *N*-[2-(4-cyanophenyl)-2-oxoethyl]tricyclo[3.3.1.1^{3,7}]decane-1-carboxamide **196** was prepared through the acetylation of compound **131** with adamantane-1-carbonyl chloride **195**. The experimental procedures were the same as the synthesis of compound **133a**. The product **196** was obtained as a yellow solid at a yield of 53%. ¹H NMR (400MHz, CDCl₃) δ 1.71-1.78 (m, 6H), 1.92 (s, 6H), 2.07 (s, 3H), 4.74 (d, 2H, J = 4.0 Hz), 6.65 (s, 1H), 7.81 (d, 2H, J = 8.6 Hz), 8.07 (d, 2H, J = 8.6 Hz); LC/MS (ESI) *m/z*: 323.3 [M + H]⁺.

4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]benzonitrile (Compound 197)



The 4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]benzonitrile **197** was prepared from the cyclization of compound **196** with the Lawesson's reagent in THF. The experimental procedures were the same as the synthesis of compound **134a**. The product **197** was obtained as a white solid at a yield of 49%. ¹H NMR (400MHz, CDCl₃) δ 1.80 (s, 6H), 2.08 (s, 6H), 2.13 (s, 3H), 7.61-7.67 (m, 4H), 7.94 (s, 1H); LC/MS (ESI) *m/z*: 321.3 [M + H]⁺.

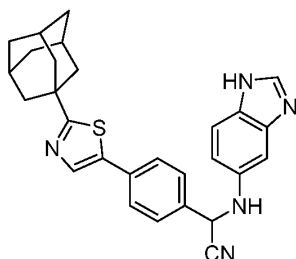
4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]benzaldehyde (Compound 198)



The 4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]benzaldehyde **198** was prepared from the reduction of compound **197** with the DIBAL-H reagent. The experimental procedures were the same as the synthesis of compound **135a**. The product **198** was obtained

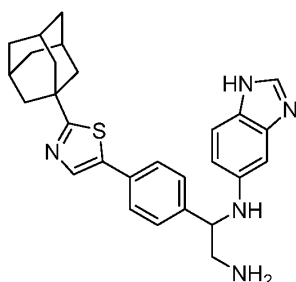
as a yellow solid at a yield of 83%. ^1H NMR (300MHz, CDCl_3) δ 1.81 (s, 6H), 2.10 (s, 6H), 2.14 (s, 3H), 7.70 (d, 2H, $J = 8.4$ Hz), 7.89 (d, 2H, $J = 8.4$ Hz), 7.98 (s, 1H), 10.00 (s, 1H); LC/MS (ESI) m/z : 324.3 $[\text{M} + \text{H}]^+$.

(1*H*-benzimidazol-5-ylamino){4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]phenyl}acetonitrile (Compound 199)



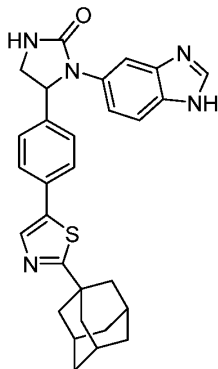
The (1*H*-benzimidazol-5-ylamino){4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]phenyl}acetonitrile **199** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **198**. The experimental procedures were the same as the synthesis of compound **122a**. The product **199** was obtained as a pale-yellow solid at a yield of 91%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]phenyl}ethane-1,2-diamine (Compound 200)**



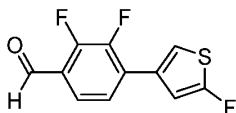
The *N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]phenyl}ethane-1,2-diamine **200** was prepared from the hydrogenation of compound **199** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **200** was obtained as a yellow viscous liquid at a yield of 60%.

1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]phenyl}imidazolidin-2-one (Compound 57)



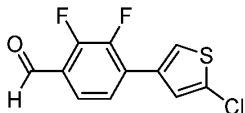
The 1-(1*H*-benzimidazol-5-yl)-5-{4-[2-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3-thiazol-5-yl]phenyl}imidazolidin-2-one (Compound **57**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **200**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **57**) was obtained as a yellow solid at a yield of 78%. ¹H NMR (400MHz, CD₃OD) δ 1.75 (s, 6H), 2.03 (s, 6H), 2.05 (s, 3H), 3.32-3.36 (m, 1H), 3.97 (dd, 1H, *J* = 9.2, 9.2 Hz), 5.49 (dd, 1H, *J* = 6.8, 9.2 Hz), 7.30 (d, 1H, *J* = 8.8 Hz), 7.40 (d, 2H, *J* = 8.4 Hz), 7.45-7.49 (m, 3H), 7.56 (s, 1H), 7.79 (s, 1H), 8.06 (s, 1H); LC/MS (ESI) *m/z*: 496.4 [M + H]⁺.

2,3-difluoro-4-(5-fluorothiophen-3-yl)benzaldehyde (Compound 201a)



The 2,3-difluoro-4-(5-fluorothiophen-3-yl)benzaldehyde **201a** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 4-bromo-2-fluorothiophene **158d**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201a** was obtained as a pale-yellow oil at a yield of 42%.

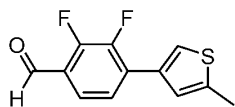
4-(5-chlorothiophen-3-yl)-2,3-difluorobenzaldehyde (Compound 201b)



The 4-(5-chlorothiophen-3-yl)-2,3-difluorobenzaldehyde **201b** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 4-bromo-2-

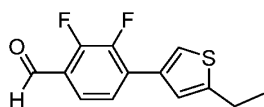
chlorothiophene **158e**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201b** was obtained as a pale-yellow oil at a yield of 45%.

2,3-difluoro-4-(5-methylthiophen-3-yl)benzaldehyde (Compound 201c)



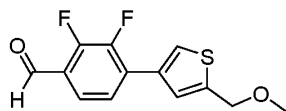
The 2,3-difluoro-4-(5-methylthiophen-3-yl)benzaldehyde **201c** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 4-bromo-2-methylthiophene **158b**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201c** was obtained as a pale-yellow oil at a yield of 53%.

4-(5-ethylthiophen-3-yl)-2,3-difluorobenzaldehyde (Compound 201d)



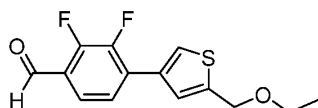
The 4-(5-ethylthiophen-3-yl)-2,3-difluorobenzaldehyde **201d** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 4-bromo-2-ethylthiophene **158f**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201d** was obtained as a pale-yellow oil at a yield of 56%.

2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]benzaldehyde (Compound 201e)



The 2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]benzaldehyde **201e** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 4-bromo-2-(methoxymethyl)thiophene **158g**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201e** was obtained as a pale-yellow oil at a yield of 49%.

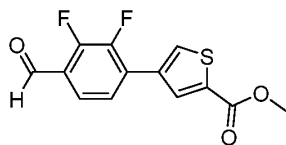
4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorobenzaldehyde (Compound 201f)



The 4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorobenzaldehyde **201f** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 4-bromo-2-(ethoxymethyl)thiophene **158h**. The experimental procedures were the same as the

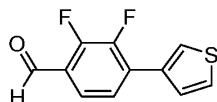
synthesis of compound **159a**. The product **201f** was obtained as a pale-yellow oil at a yield of 48%.

methyl 4-(2,3-difluoro-4-formylphenyl)thiophene-2-carboxylate (Compound 201g)



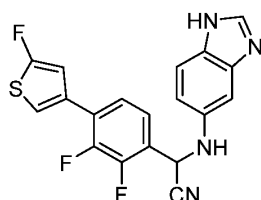
The methyl 4-(2,3-difluoro-4-formylphenyl)thiophene-2-carboxylate **201g** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and methyl 4-bromothiophene-2-carboxylate **158i**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201g** was obtained as a pale-yellow oil at a yield of 42%.

2,3-difluoro-4-(thiophen-3-yl)benzaldehyde (Compound 201h)



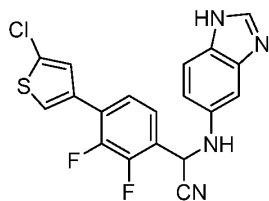
The 2,3-difluoro-4-(thiophen-3-yl)benzaldehyde **201h** was prepared from the Suzuki-Miyaura coupling of 2,3-difluoro-4-formylphenylboronic acid **118g** and 3-bromothiophene **158a**. The experimental procedures were the same as the synthesis of compound **159a**. The product **201h** was obtained as a pale-yellow oil at a yield of 54%.

(1H-benzimidazol-5-ylamino)[2,3-difluoro-4-(5-fluorothiophen-3-yl)phenyl]acetonitrile (Compound 202a)



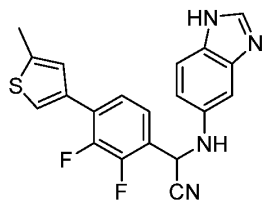
The (1H-benzimidazol-5-ylamino)[2,3-difluoro-4-(5-fluorothiophen-3-yl)phenyl]acetonitrile **202a** was prepared from the addition of 1H-benzimidazol-5-amine **121**, TMSCN and compound **201a**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202a** was obtained as a pale-yellow solid at a yield of 85%.

**(1*H*-benzimidazol-5-ylamino)[4-(5-chlorothiophen-3-yl)-2,3-difluorophenyl]acetonitrile
(Compound 202b)**



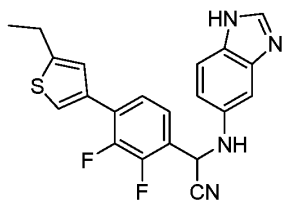
The (1*H*-benzimidazol-5-ylamino)[4-(5-chlorothiophen-3-yl)-2,3-difluorophenyl]acetonitrile **202b** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201b**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202b** was obtained as a pale-yellow solid at a yield of 79%.

**(1*H*-benzimidazol-5-ylamino)[2,3-difluoro-4-(5-methylthiophen-3-yl)phenyl]acetonitrile
(Compound 202c)**



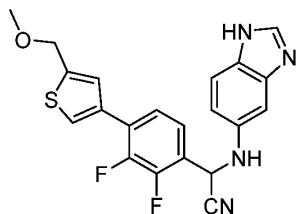
The (1*H*-benzimidazol-5-ylamino)[2,3-difluoro-4-(5-methylthiophen-3-yl)phenyl]acetonitrile **202c** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201c**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202c** was obtained as a pale-yellow solid at a yield of 88%.

**(1*H*-benzimidazol-5-ylamino)[4-(5-ethylthiophen-3-yl)-2,3-difluorophenyl]acetonitrile
(Compound 202d)**



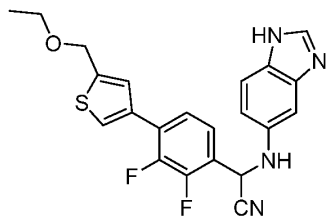
The (1*H*-benzimidazol-5-ylamino)[4-(5-ethylthiophen-3-yl)-2,3-difluorophenyl]acetonitrile **202d** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201d**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202d** was obtained as a pale-yellow solid at a yield of 81%.

(1*H*-benzimidazol-5-ylamino){2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]phenyl}acetonitrile (Compound 202e)



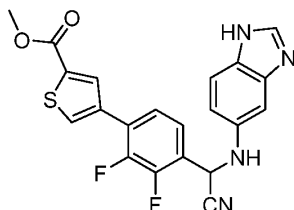
The (1*H*-benzimidazol-5-ylamino){2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]phenyl}acetonitrile **202e** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201e**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202e** was obtained as a pale-yellow solid at a yield of 84%.

(1*H*-benzimidazol-5-ylamino){4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorophenyl}acetonitrile (Compound 202f)



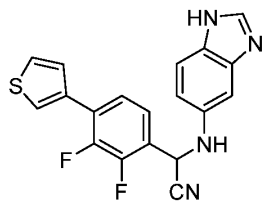
The (1*H*-benzimidazol-5-ylamino){4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorophenyl}acetonitrile **202f** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201f**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202f** was obtained as a pale-yellow solid at a yield of 90%.

Methyl 4-{4-[(1*H*-benzimidazol-5-ylamino)(cyano)methyl]-2,3-difluorophenyl}thiophene-2-carboxylate (Compound 202g)



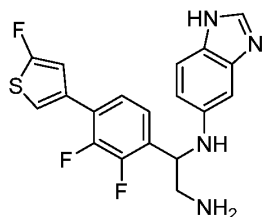
The methyl 4-{4-[(1*H*-benzimidazol-5-ylamino)(cyano)methyl]-2,3-difluorophenyl}thiophene-2-carboxylate **202g** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201g**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202g** was obtained as a pale-yellow solid at a yield of 81%.

(1*H*-benzimidazol-5-ylamino)[2,3-difluoro-4-(thiophen-3-yl)phenyl]acetonitrile (Compound 202h)



The (1*H*-benzimidazol-5-ylamino)[2,3-difluoro-4-(thiophen-3-yl)phenyl]acetonitrile **202h** was prepared from the addition of 1*H*-benzimidazol-5-amine **121**, TMSCN and compound **201h**. The experimental procedures were the same as the synthesis of compound **122a**. The product **202h** was obtained as a pale-yellow solid at a yield of 92%.

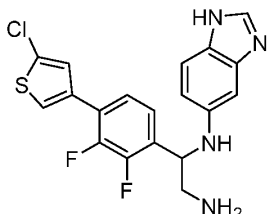
***N*¹-(1*H*-benzimidazol-5-yl)-1-[2,3-difluoro-4-(5-fluorothiophen-3-yl)phenyl]ethane-1,2-diamine (Compound 203a)**



The *N*¹-(1*H*-benzimidazol-5-yl)-1-[2,3-difluoro-4-(5-fluorothiophen-3-yl)phenyl]ethane-1,2-diamine **203a** was prepared from the hydrogenation of compound **202a** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the

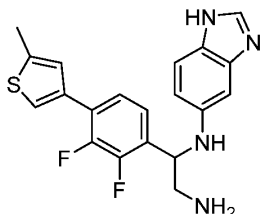
synthesis of compound **123a**. The product **203a** was obtained as a yellow viscous liquid at a yield of 43%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-chlorothiophen-3-yl)-2,3-difluorophenyl]ethane-1,2-diamine (Compound 203b)**



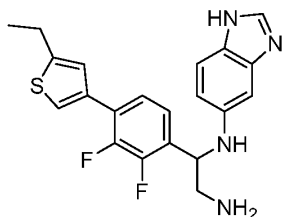
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-chlorothiophen-3-yl)-2,3-difluorophenyl]ethane-1,2-diamine **203b** was prepared from the hydrogenation of compound **202b** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203b** was obtained as a yellow viscous liquid at a yield of 40%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[2,3-difluoro-4-(5-methylthiophen-3-yl)phenyl]ethane-1,2-diamine (Compound 203c)**



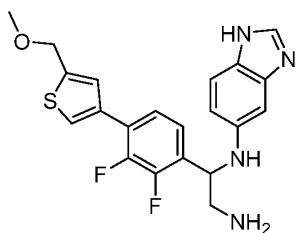
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[2,3-difluoro-4-(5-methylthiophen-3-yl)phenyl]ethane-1,2-diamine **203c** was prepared from the hydrogenation of compound **202c** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203c** was obtained as a yellow viscous liquid at a yield of 53%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-ethylthiophen-3-yl)-2,3-difluorophenyl]ethane-1,2-diamine (Compound 203d)**



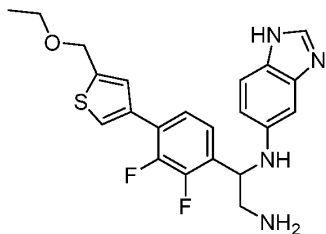
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[4-(5-ethylthiophen-3-yl)-2,3-difluorophenyl]ethane-1,2-diamine **203d** was prepared from the hydrogenation of compound **202d** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203d** was obtained as a yellow viscous liquid at a yield of 51%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-{2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]phenyl}ethane-1,2-diamine (Compound 203e)**



The *N*¹-(1*H*-benzimidazol-5-yl)-1-{2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]phenyl}ethane-1,2-diamine **203e** was prepared from the hydrogenation of compound **202e** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203e** was obtained as a yellow viscous liquid at a yield of 46%.

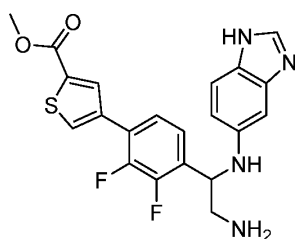
***N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorophenyl}ethane-1,2-diamine (Compound 203f)**



The *N*¹-(1*H*-benzimidazol-5-yl)-1-{4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorophenyl}ethane-1,2-diamine **203f** was prepared from the hydrogenation of compound

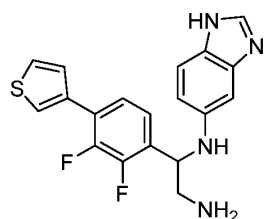
202f with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203f** was obtained as a yellow viscous liquid at a yield of 49%.

methyl 4-{4-[2-amino-1-(1*H*-benzimidazol-5-ylamino)ethyl]-2,3-difluorophenyl}thiophene-2-carboxylate (Compound 203g)



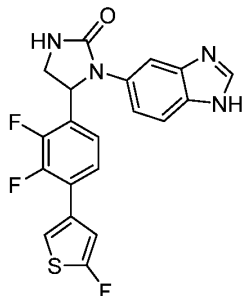
The methyl 4-{4-[2-amino-1-(1*H*-benzimidazol-5-ylamino)ethyl]-2,3-difluorophenyl}thiophene-2-carboxylate **203g** was prepared from the hydrogenation of compound **202g** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203g** was obtained as a yellow viscous liquid at a yield of 47%.

***N*¹-(1*H*-benzimidazol-5-yl)-1-[2,3-difluoro-4-(thiophen-3-yl)phenyl]ethane-1,2-diamine (Compound 203h)**



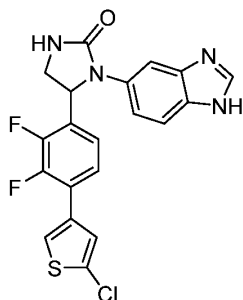
The *N*¹-(1*H*-benzimidazol-5-yl)-1-[2,3-difluoro-4-(thiophen-3-yl)phenyl]ethane-1,2-diamine **203h** was prepared from the hydrogenation of compound **202h** with the Raney Nickel reagent as catalyst. The experimental procedures were the same as the synthesis of compound **123a**. The product **203h** was obtained as a yellow viscous liquid at a yield of 58%.

1-(1*H*-benzimidazol-5-yl)-5-[2,3-difluoro-4-(5-fluorothiophen-3-yl)phenyl]imidazolidin-2-one (Compound 58)



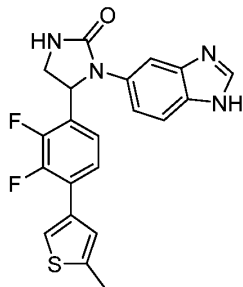
The 1-(1*H*-benzimidazol-5-yl)-5-[2,3-difluoro-4-(5-fluorothiophen-3-yl)phenyl]imidazolidin-2-one (Compound **58**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203a**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **58**) was obtained as a white solid at a yield of 71%.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-3-yl)-2,3-difluorophenyl]imidazolidin-2-one (Compound 59)



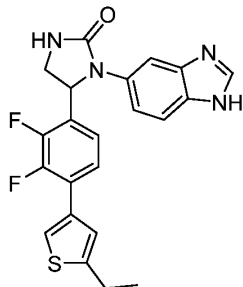
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-chlorothiophen-3-yl)-2,3-difluorophenyl]imidazolidin-2-one (Compound **59**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203b**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **59**) was obtained as a white solid at a yield of 74%. ¹H NMR (300MHz, CD₃OD) δ 3.44 (dd, 1H, J = 6.3, 9.3 Hz), 4.05 (dd, 1H, J = 9.3, 9.6 Hz), 5.83 (dd, 1H, J = 6.3, 9.6 Hz), 7.17-7.34 (m, 4H), 7.48-7.51 (m, 2H), 7.60 (d, 1H, J = 1.8 Hz), 8.07 (d, 1H, J = 3.9 Hz); LC/MS (ESI) *m/z*: 431.0 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[2,3-difluoro-4-(5-methylthiophen-3-yl)phenyl]imidazolidin-2-one (Compound 60)



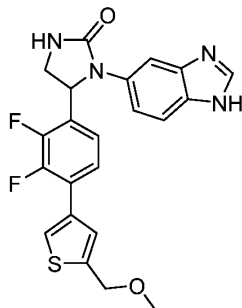
The 1-(1*H*-benzimidazol-5-yl)-5-[2,3-difluoro-4-(5-methylthiophen-3-yl)phenyl]imidazolidin-2-one (Compound **60**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203c**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **60**) was obtained as a white solid at a yield of 70%. ¹H NMR (300MHz, CD₃OD) δ 2.45 (s, 3H), 3.43 (dd, 1H, J = 6.3, 9.0 Hz), 4.04 (dd, 1H, J = 9.0, 9.3 Hz), 5.81 (dd, 1H, J = 6.3, 9.3 Hz), 7.02 (s, 1H), 7.18-7.38 (m, 4H), 7.49 (d, 1H, J = 8.4 Hz), 7.59 (s, 1H), 8.07 (s, 1H); LC/MS (ESI) *m/z*: 411.3 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-[4-(5-ethylthiophen-3-yl)-2,3-difluorophenyl]imidazolidin-2-one (Compound 61)



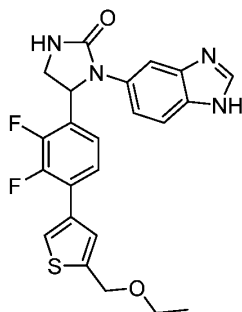
The 1-(1*H*-benzimidazol-5-yl)-5-[4-(5-ethylthiophen-3-yl)-2,3-difluorophenyl]imidazolidin-2-one (Compound **61**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203d**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **61**) was obtained as a white solid at a yield of 70%. ¹H NMR (400MHz, CD₃OD) δ 1.28 (t, 3H, J = 7.6 Hz), 2.83 (q, 2H, J = 7.6 Hz), 3.44 (dd, 1H, J = 6.4, 9.2 Hz), 4.05 (dd, 1H, J = 9.2, 9.6 Hz), 5.82 (dd, 1H, J = 6.4, 9.6 Hz), 7.05 (s, 1H), 7.15-7.19 (m, 1H), 7.26-7.34 (m, 2H), 7.41 (s, 1H), 7.50 (d, 1H, J = 8.8 Hz), 7.60 (s, 1H), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 425.1 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound 62)



The 1-(1*H*-benzimidazol-5-yl)-5-{2,3-difluoro-4-[5-(methoxymethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound **62**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203e**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **62**) was obtained as a white solid at a yield of 76%. ¹H NMR (400MHz, CD₃OD) δ 3.34 (s, 3H), 3.45 (dd, 1H, J = 6.8, 9.2 Hz), 4.05 (dd, 1H, J = 9.2, 9.2 Hz), 4.59 (s, 2H), 5.82 (dd, 1H, J = 6.4, 9.2 Hz), 7.17-7.21 (m, 1H), 7.28-7.34 (m, 3H), 7.50 (d, 1H, J = 8.4 Hz), 7.60 (s, 1H), 7.62 (s, 1H), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 441.3 [M + H]⁺.

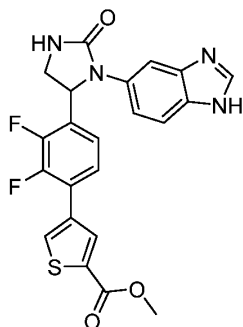
1-(1*H*-benzimidazol-5-yl)-5-{4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorophenyl}imidazolidin-2-one (Compound 63)



The 1-(1*H*-benzimidazol-5-yl)-5-{4-[5-(ethoxymethyl)thiophen-3-yl]-2,3-difluorophenyl}imidazolidin-2-one (Compound **63**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203f**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **63**) was obtained as a white solid at a yield of 72%. ¹H NMR (400MHz, CD₃OD) δ 1.19 (t, 3H, J = 7.2 Hz), 3.45 (dd, 1H, J = 6.4, 9.2 Hz), 3.54 (q, 2H, J = 7.2 Hz), 4.05 (dd, 1H, J = 9.2, 9.6 Hz), 4.63 (s, 2H), 5.83 (dd,

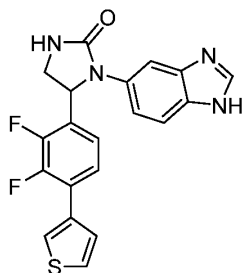
1H, J = 6.4, 9.6 Hz), 7.17-7.20 (m, 1H), 7.26-7.34 (m, 3H), 7.50 (d, 1H, J = 8.4 Hz), 7.61 (m, 2H), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 455.3 [M + H]⁺.

methyl 4-{4-[3-(1*H*-benzimidazol-5-yl)-2-oxoimidazolidin-4-yl]-2,3-difluorophenyl}thiophene-2-carboxylate (Compound 64)



The methyl 4-{4-[3-(1*H*-benzimidazol-5-yl)-2-oxoimidazolidin-4-yl]-2,3-difluorophenyl}thiophene-2-carboxylate (Compound **64**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203g**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **64**) was obtained as a white solid at a yield of 75%. ¹H NMR (300MHz, DMSO-*d*₆) δ 3.16-3.29 (m, 1H), 3.81 (s, 3H), 3.94 (dd, 1H, J = 9.0, 9.3 Hz), 5.84 (dd, 1H, J = 5.4, 9.3 Hz), 7.11 (s, 1H), 7.17 (dd, 1H, J = 6.9, 7.5 Hz), 7.30 (br s, 1H), 7.43-7.54 (m, 2H), 7.61 (s, 1H), 8.06-8.10 (m, 1H), 8.22 (s, 1H), 8.23 (s, 1H), 12.29 (br s, 1H); LC/MS (ESI) *m/z*: 455.1 [M + H]⁺.

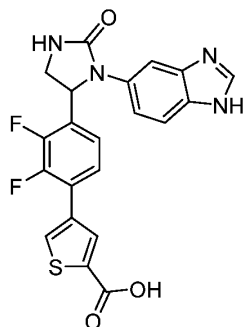
1-(1*H*-benzimidazol-5-yl)-5-[2,3-difluoro-4-(thiophen-3-yl)phenyl]imidazolidin-2-one (Compound 65)



The 1-(1*H*-benzimidazol-5-yl)-5-[2,3-difluoro-4-(thiophen-3-yl)phenyl]imidazolidin-2-one (Compound **65**) was prepared from the cycloaddition of 1,1'-carbonyl diimidazole and compound **203h**. The experimental procedures were the same as the synthesis of Compound **1**. The product (Compound **65**) was obtained as a white solid at a yield of 79%. ¹H NMR (400MHz, CD₃OD) δ 3.45 (dd, 1H, J = 6.8, 9.2 Hz), 4.06 (dd, 1H, J = 9.2, 9.6 Hz), 5.83 (dd,

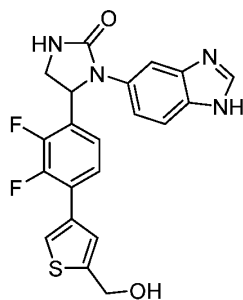
1H, J = 6.8, 9.6 Hz), 7.20 (m, 1H), 7.31-7.36 (m, 3H), 7.44-7.52 (m, 2H), 7.61 (s, 1H), 7.66 (s, 1H), 8.08 (s, 1H); LC/MS (ESI) *m/z*: 397.1 [M + H]⁺.

4-{4-[3-(1*H*-benzimidazol-5-yl)-2-oxoimidazolidin-4-yl]-2,3-difluorophenyl}thiophene-2-carboxylic acid (Compound 66)



To the solution of the compound **64** (0.45 g, 1.0 mmol) in methanol (10 mL), potassium hydroxide (0.07 g, 1.2 mmol) was added. The reaction mixture was stirred at 60 °C for 1.5 hours and then cooled to room temperature. The reaction mixture was neutralized by 1N HCl_(aq) to pH 7. After removing the solvent, the crude residue was purified by reverse phase column chromatography on C-18 silica gel using methanol/H₂O (1/1) as eluent to give the product **66** as a white solid at a yield of 81%. ¹H NMR (400MHz, DMSO-*d*₆) δ 3.26 (dd, 1H, J = 5.6, 9.2 Hz), 3.92 (dd, 1H, J = 9.2, 9.2 Hz), 4.18 (br s, 1H), 5.80 (dd, 1H, J = 5.6, 9.2 Hz), 7.12-7.15 (m, 2H), 7.29 (br s, 1H), 7.40-7.46 (m, 2H), 7.52 (s, 1H), 7.61 (s, 1H), 7.67 (s, 1H), 8.09 (s, 1H); LC/MS (ESI) *m/z*: 441.0 [M + H]⁺.

1-(1*H*-benzimidazol-5-yl)-5-{2,3-difluoro-4-[5-(hydroxymethyl)thiophen-3-yl]phenyl}imidazolidin-2-one (Compound 67)



A solution of compound **64** (0.45 g, 1.0 mmol) in dry THF (5 mL) was added dropwise to a refluxing, magnetically stirring slurry of LAH (1.5 mmol) in dry THF (7.5 mL). The reaction mixture was held at reflux for 3 hours, terminated by dropwise addition of 1 mL saturated MgSO₄ solution and filtered by Celite. The filtrate was partitioned between

ethyl acetate and water. The organic phases were dried over MgSO₄ and evaporated on a rotary evaporator. The residue was purified by column chromatography on silica gel using methanol/DCM (1/10) as eluent to give the product **67** as a white solid at a yield of 92%.

Separation of Enantiomers of Compound 8

The chiral separation of Compound **8** was completed by HPLC using CHIRALPAK IC. The isomer fractions were respectively collected and the optical pure isomers (Compounds **9** and **10**) were thus obtained by removing the solvent under reduced pressure. Results of this separation are shown below:

Column: CHIRALPAK IC (IC00CE-OL002),
Column size: 0.46 cm I.D. x 25 cm L,
Injection: 0.5 ul,
Mobile phase: 100% methanol,
Flow rate: 1.0 ml/min,
Detection: UV 214 nm,
Temperature: 35 °C,
HPLC equipment: Shimadzu LC-20AD (CP-HPLC-06),
Retention E1 (Compound **9**): 5.494 min,
Retention E2 (Compound **10**): 6.379 min.

Separation of Enantiomers of Compound 13

The chiral separation of Compound **13** was completed by HPLC using CHIRALPAK AD-H. The isomer fractions were respectively collected and the optical pure isomers (Compounds **33** and **34**) were thus obtained by removing the solvent under reduced pressure. Results of this separation are shown below:

Column: CHIRALPAK AD-H (ADH0CD-UE022),
Column size: 0.46 cm I.D. x 15 cm L,
Injection: 1.0 ul,
Mobile phase: Hexane/EtOH=60/40 (v/v),
Flow rate: 1.0 ml/min,
Detection: UV 214 nm,
Temperature: 35 °C,
HPLC equipment: Shimadzu LC-20AT (CP-HPLC-09),
Retention E1 (Compound **33**): 4.270 min,
Retention E2 (Compound **34**): 5.679 min.

Separation of Enantiomers of Compound 16

The chiral separation of Compound **16** was completed by HPLC using CHIRALPAK AD-H. The isomer fractions were respectively collected and the optical pure isomers (Compounds **35** and **36**) were thus obtained by removing the solvent under reduced pressure.

Results of this separation are shown below:

Column: CHIRALPAK AD-H (ADH0CD-UE022),
Column size: 0.46 cm I.D. x 15 cm L,
Injection: 2.0 ul,
Mobile phase: Hexane/EtOH=70/30 (v/v),
Flow rate: 1.0 ml/min,
Detection: UV 214 nm,
Temperature: 35 °C,
HPLC equipment: Shimadzu LC-20AD (CP-HPLC-08),
Retention E1 (Compound **35**): 7.273 min,
Retention E2 (Compound **36**): 9.232 min.

Separation of Enantiomers of Compound 25

The chiral separation of Compound **25** was completed by HPLC using CHIRALPAK AD-H. The isomer fractions were respectively collected and the optical pure isomers (Compounds **53** and **54**) were thus obtained by removing the solvent under reduced pressure.

Results of this separation are shown below:

Column: CHIRALPAK AD-H (ADH0CD-UE022),
Column size: 0.46 cm I.D. x 15 cm L,
Injection: 2.0 ul,
Mobile phase: Hexane/EtOH=70/30 (v/v),
Flow rate: 1.0 ml/min,
Detection: UV 214 nm,
Temperature: 35 °C,
HPLC equipment: Shimadzu LC-20AD (CP-HPLC-08),
Retention E1 (Compound **53**): 2.166 min,
Retention E2 (Compound **54**): 2.767 min.

Separation of Enantiomers of Compound 28

The chiral separation of Compound **28** was completed by HPLC using CHIRALPAK AD-H. The isomer fractions were respectively collected and the optical pure isomers

(Compounds **55** and **56**) were thus obtained by removing the solvent under reduced pressure.

Results of this separation are shown below:

Column: CHIRALPAK AD-H (ADH0CD-UE022),

Column size: 0.46 cm I.D. x 15 cm L,

Injection: 2.0 μ l,

Mobile phase: Hexane/EtOH=70/30 (v/v),

Flow rate: 1.0 ml/min,

Detection: UV 214 nm,

Temperature: 35 °C,

HPLC equipment: Shimadzu LC-20AD (CP-HPLC-08),

Retention E1 (Compound **55**): 3.827 min,

Retention E2 (Compound **56**): 7.914 min.

EXAMPLE 2: *In vitro* Activity Screening of Compounds

QC Activity Assay

An enzymatic activity assay of QC was conducted at 25°C using a fluorescent substrate, i.e., L-glutaminy 2-naphthylamide (Gln- β NA). See Huang et al., *Biochem. J.* 2008, 411,181-190. A 100 μ l reaction mixture was prepared. It contained 300 μ M of fluorogenic substrate, ~0.2 units of auxiliary enzyme human pyroglutamyl aminopeptidase I (PAP I) (in which one unit is defined as the amount of human PAP I needed to hydrolyzes 1 μ mol of pGlu- β NA per minute under the same assay condition), and an appropriately diluted aliquot of recombinant QC in 50 mM of Tris-HCl at pH 8.0. Excitation and emission wavelengths were set at 320 and 410 nm, respectively. The reaction was initiated by the addition of QC. The enzymatic activity of QC was determined from the amount of released β NA and was calculated using a standard curve for β NA under the same assay conditions. Measurements were made using a Synergy H4 microplate reader (BioTek, Winooski, Vermont, USA).

Enzyme Kinetic Assay

Kinetic constants were determined at pH 8.0 and 25°C using Gln- β NA as the substrate. Also see Huang et al., *Biochem. J.* 2008, 411, 181-190. The reaction was initiated by adding QC to the 100 μ l reaction mixture described above. The initial rate was measured with less than 10% substrate depletion for the first 2-12 minutes. Since a weak substrate inhibition was observed, kinetic parameters K_m , V , and K_i were evaluated by fitting an equation, i.e., $v_0 = V_{\max}[S]/(K_m + [S] + [S]^2/K_i)$, to initial velocity data by nonlinear regression using a *KaleidaGraph* software (Synergy Software, Reading, Pennsylvania, USA),

where v_0 is an initial velocity, $V_{\max}$ is an limiting rate, $[S]$ is a substrate concentration, K_m is a Michaelis constant, and K_i is an inhibition constant.

QC Inhibition Assay

An inhibition activity assay of QC inhibitors was conducted. See Huang et al., *J. Biol. Chem.* 2011, 286, 12439-12449. A reaction mixture containing 300 μM of Gln- β NA and ~ 0.2 units of human PAP I was prepared. QC was first incubated with an inhibitor at 25°C for 30 minutes and the enzyme–inhibitor mixture was then added to the reaction mixture to initiate the cyclization reaction. An IC_{50} value was obtained by fitting an initial reaction rate versus an inhibitor concentration using *KaleidaGraph*. A K_i value of the inhibitor was calculated according to an equation $\text{IC}_{50} = K_i(1 + [S]/K_m)$. See Segel, *Enzyme Kinetics: Behavior and Analysis of Rapid Equilibrium and Steady-State Enzyme Systems*, pp. 100-118. New York: John Wiley & Sons, 1993. In this equation, $[S]$ is a substrate (i.e., Gln- β NA) concentration and K_m is a Michaelis–Menten constant. The lower the K_i value, the higher the inhibitor's QC inhibition rate.

The K_i values of Compounds **1-29**, **33-57**, and **59-65**, obtained from the inhibition assay set forth above, are shown in Table 2 below.

Table 2

Compound	K_i (μM)	Compound	K_i (μM)	Compound	K_i (μM)
1	0.053	25	0.071	49	0.010
2	0.100	26	0.114	50	0.013
3	0.348	27	0.066	51	0.024
7	0.021	28	0.039	52	0.397
8	0.049	29	0.072	53	3.417
9	0.016	33	0.736	54	0.023
10	0.964	34	0.069	55	1.592
11	0.100	35	2.053	56	0.007
12	0.132	36	0.032	57	0.087
13	0.124	37	0.018	59	0.019
14	0.106	38	0.004	60	0.007
15	0.076	39	0.004	61	0.016
16	0.112	40	0.009	62	0.006
17	0.151	41	0.012	63	0.011
18	0.134	42	0.005	64	0.013
19	0.058	43	0.008	65	0.020
20	0.057	44	0.010		
21	0.036	45	0.004		
22	0.156	46	0.008		
23	0.124	47	0.006		
24	0.101	48	0.010		

As shown in this table, Compounds **1-29**, **33-57**, and **59-65** all have K_i values within the nano molar range. Note that a low K_i value indicates a high QC inhibition rate. Clearly, these compounds possess superior inhibition potency against QC.

Inhibition of QC has been reported to diminish aggregation of A β and HTT in cultured macrophage cells and in *Drosophila* and mouse models. Thus, Compounds **1-29**, **33-57**, and **59-65**, as potent QC inhibitors, are drug candidates for treating AD or HD.

EXAMPLE 3: *In vivo* Activity of Compounds

Compound **37** showed strong potency ($K_i = 0.018 \mu\text{M}$) in inhibiting QC and a desired pharmacokinetic property ($F\% = 11$) in mice ($F\%$ being the fraction of an oral administered drug that reaches systemic circulation). The compound was therefore selected for further animal studies in a transgenic mouse model using APP/PS1 mice (Jackson Lab, ME). See Schilling et al., *Nat. Med.* 2008, 14, 1106-1111 and Li et al., *J. Med. Chem.* 2017, 60, 6664-6677. APP/PS1 mice are double transgenic mice expressing a chimeric mouse/human amyloid precursor protein (Mo/HuAPP695swe) and a mutant human presenilin 1 (PS1-dE9), both directed to CNS neurons. These two mutations are associated with early-onset Alzheimer's disease. In the animal studies, 4-month-old APP/PS1 mice were housed at a 12 hour day/12 hour night cycle with free access to water and food. Compound **37** was orally administered to the APP/PS1 mice for 3.5 months to determine its *in vivo* activity. The cognitive function and brain pathology of each mouse were analyzed after the administration. The resultant analytical data exhibited depletion of A β deposits in brain tissues of the APP/PS1 mice.

The same *in vivo* assay was performed on Compound **28**, which showed that this compound had high inhibitory activity ($K_i = 0.039 \mu\text{M}$) and a superior pharmacokinetic property with desired oral bioavailability ($F\% = 25$) in APP/PS1 mice.

The above two assays demonstrate both the potency and the efficacy of Compounds **28** and **37** as QC inhibitors for treating AD.

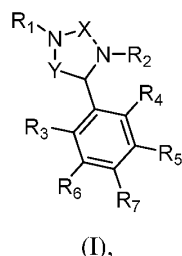
OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated otherwise, each feature disclosed herein is only an example of a series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. Thus, other embodiments are also within the scope of the following claims.

What is claimed is:

1. A compound of formula (I):



wherein

R₁ is H or C₁₋₆ alkyl;

R₂ is a moiety containing a phenyl ring fused to a 5-membered heteroaryl ring, R₂ being linked to N through the phenyl ring;

R₃, R₄, R₅, R₆, and R₇, independently, are H, halo, nitro, cyano, amino, OH, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl that is optionally substituted by one or more substituents selected from halo, nitro, cyano, amino, OH, CF₃, -COOH, -COOC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl,

in which

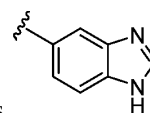
at least one of R₃, R₄, R₅, R₆, and R₇ is heteroaryl; and

each of C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, second or third occurrence, is optionally substituted with halo, nitro, cyano, amino, OH, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

X is CH₂ or C=O; and

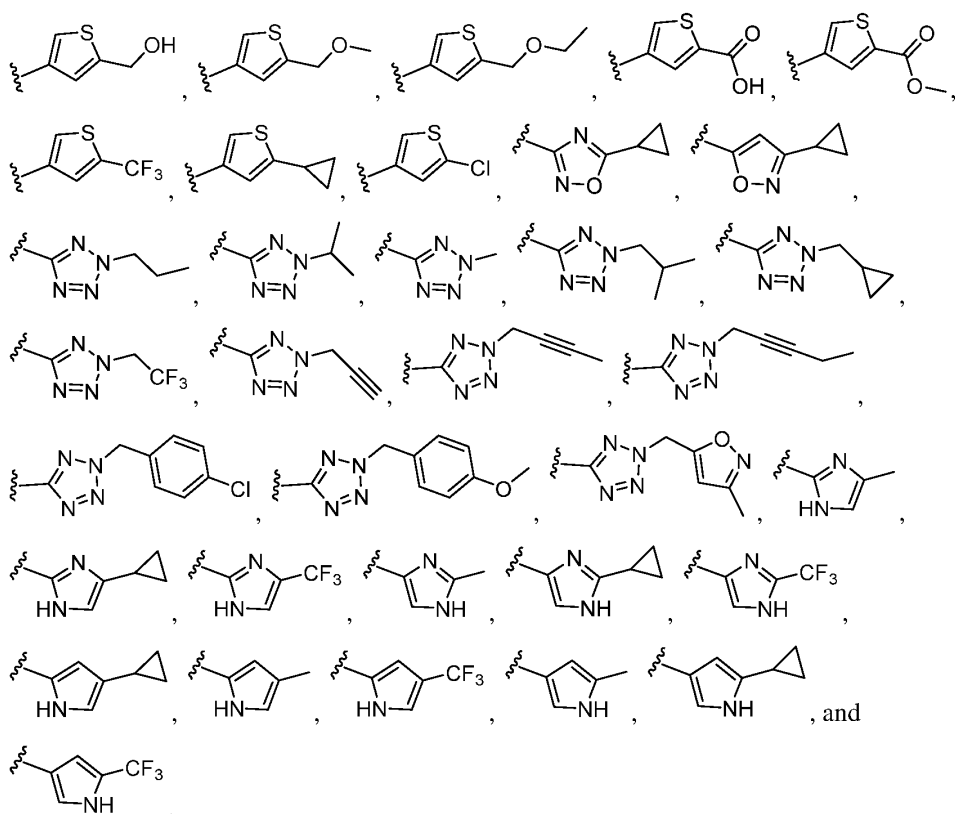
Y is CH₂ or C=O.

2. The compound of claim 1, wherein Y is CH₂.



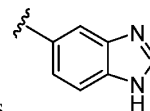
3. The compound of claim 2, wherein R₁ is H, X is C=O, and R₂ is

4. The compound of claim 3, wherein R₃, R₄, R₅, and R₆, independently, are H, CH₃, Cl, or F.



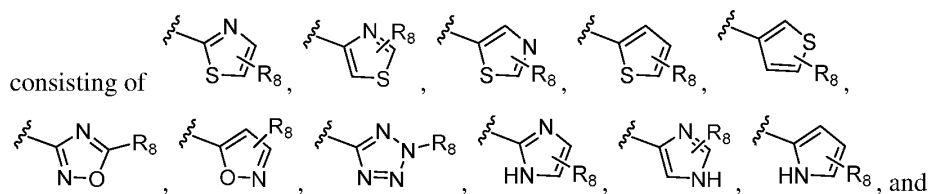
8. The compound of claim 1, wherein Y is C=O.

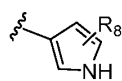
9. The compound of claim 8, wherein R₁ is H, X is C=O, and R₂ is



10. The compound of claim 9, wherein R₃, R₄, R₅, and R₆, independently, are H, CH₃, Cl, or F.

11. The compound of claim 10, wherein R₇ is heteroaryl selected from the group

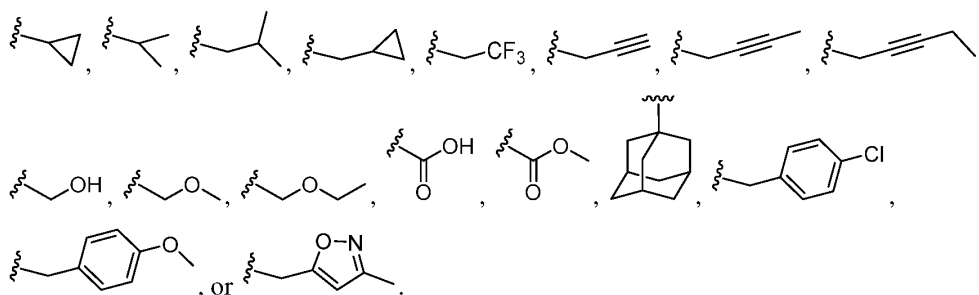




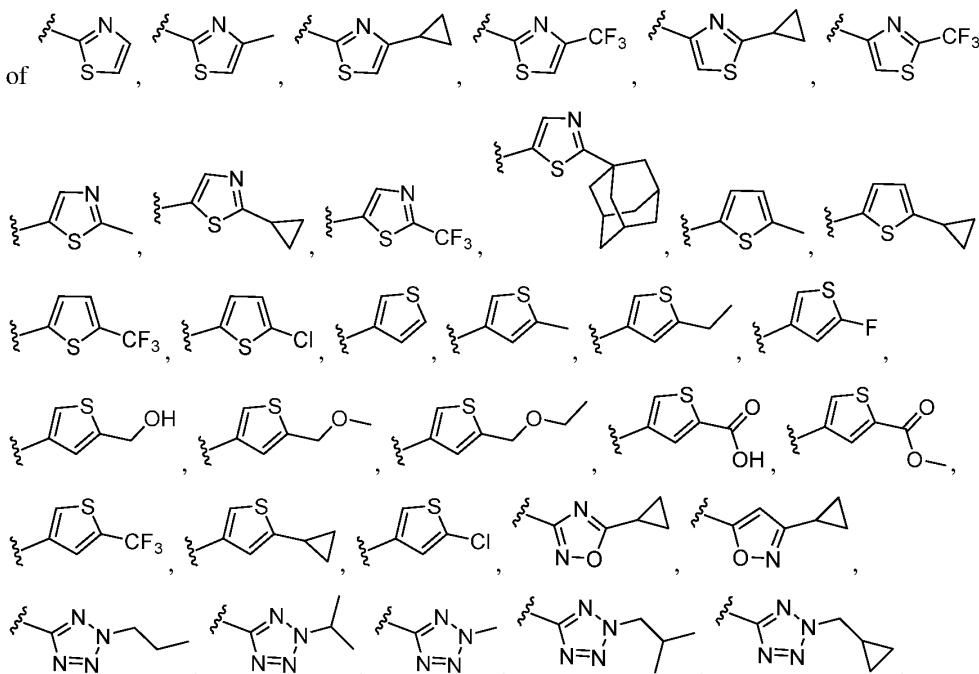
, in which R₈ is H, halo, nitro, cyano, amino, OH, CF₃, -COOH, -COOC₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

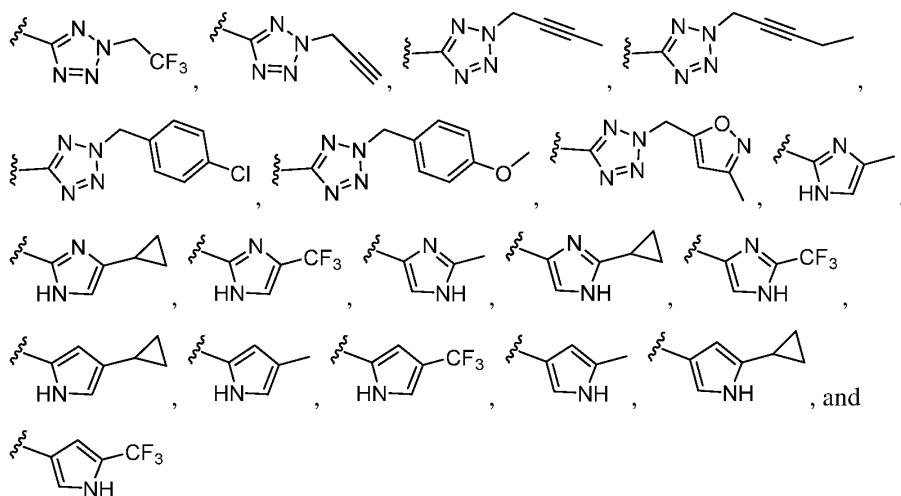
each of C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano, amino, OH, CF₃, C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

12. The compound of claim 11, wherein R₈ is H, F, Cl, CH₃, CF₃, ethyl, n-propyl,

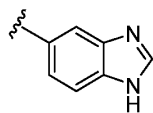


13. The compound of claim 12, wherein R₇ is selected from the group consisting





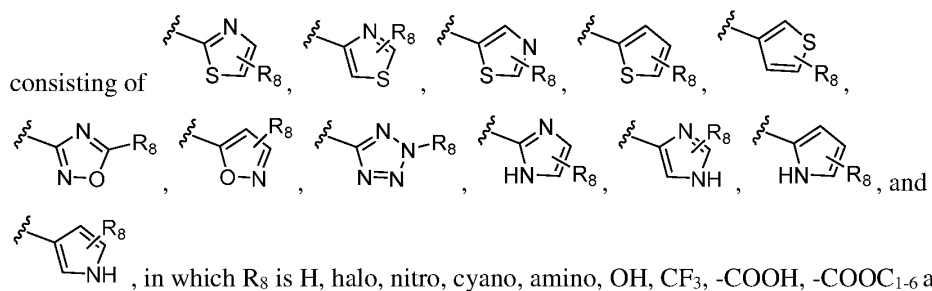
14. The compound of claim 1, wherein R₁ is H and X is C=O.



15. The compound of claim 1, wherein R₂ is

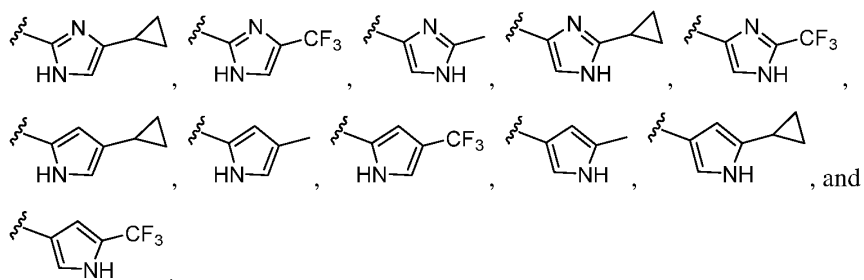
16. The compound of claim 1, wherein R₃, R₄, R₅, and R₆, independently, are H, CH₃, Cl, or F.

17. The compound of claim 1, wherein R₇ is heteroaryl selected from the group

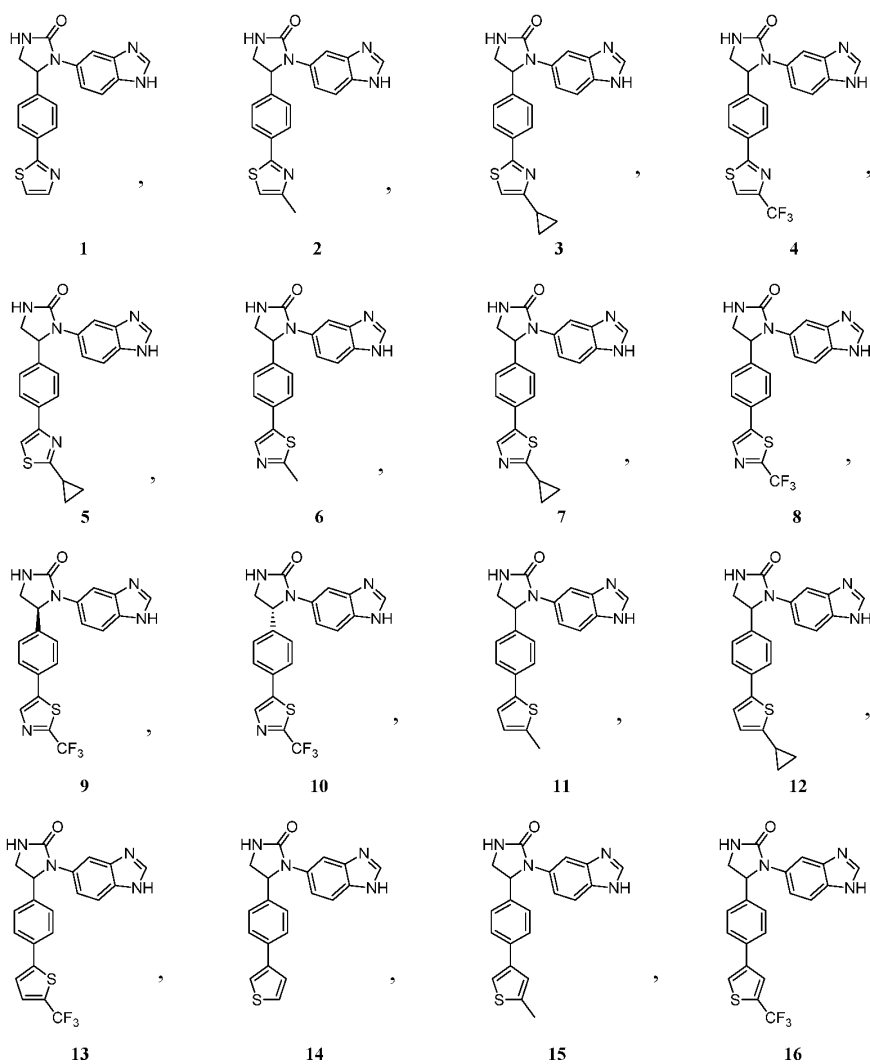


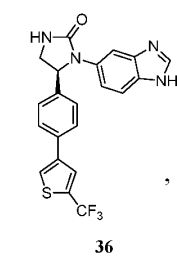
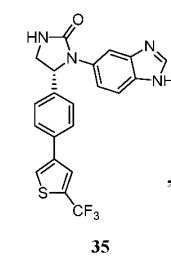
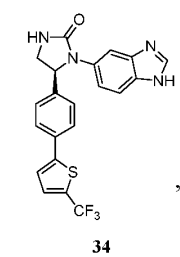
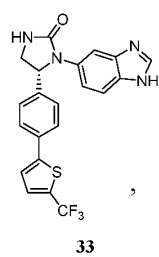
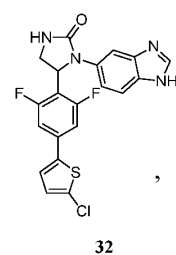
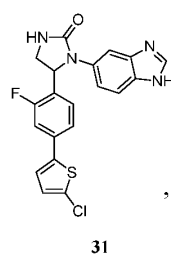
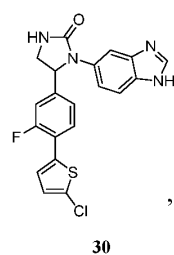
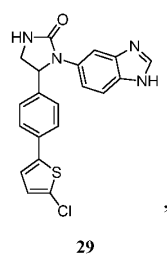
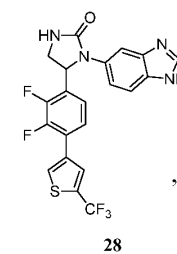
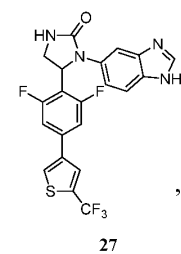
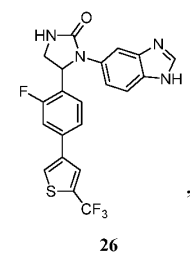
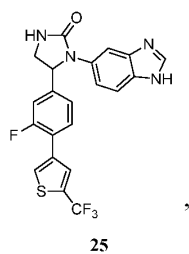
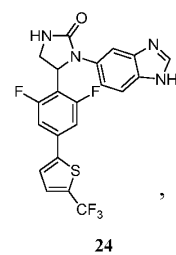
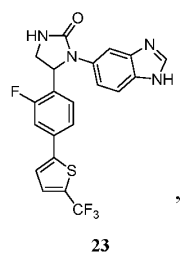
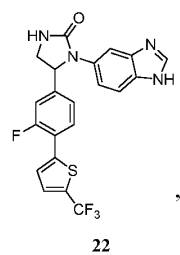
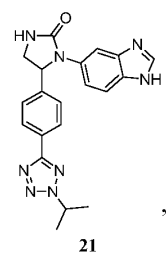
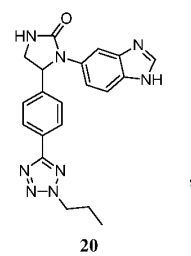
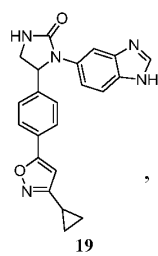
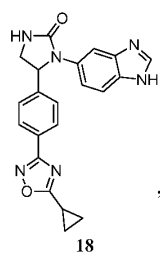
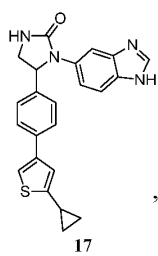
C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, or heteroaryl,

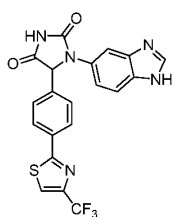
each of C₁₋₆ alkoxy, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ cycloalkyl, heterocycloalkyl, aryl, and heteroaryl being optionally substituted with halo, nitro, cyano,



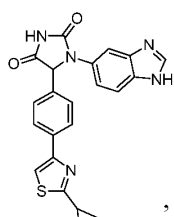
20. The compound of claim 1, wherein the compound is one of the following compounds:



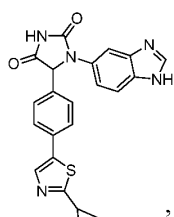




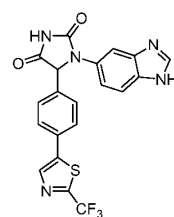
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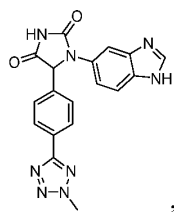
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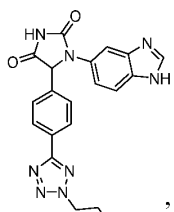
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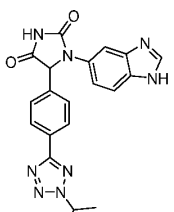
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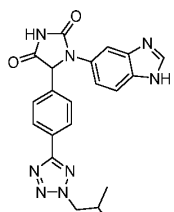
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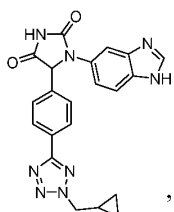
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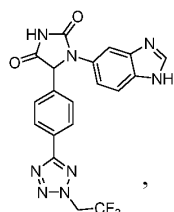
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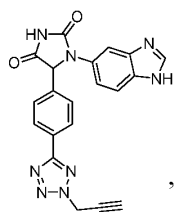
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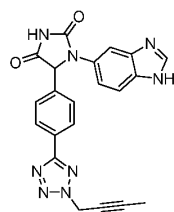
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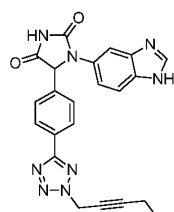
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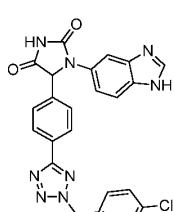
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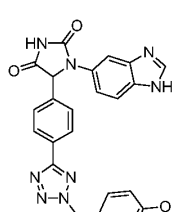
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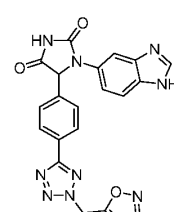
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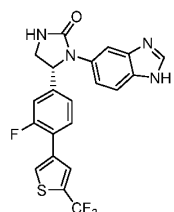
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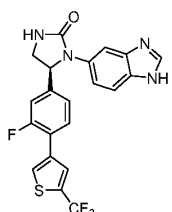
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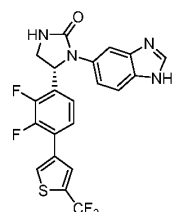
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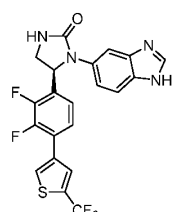
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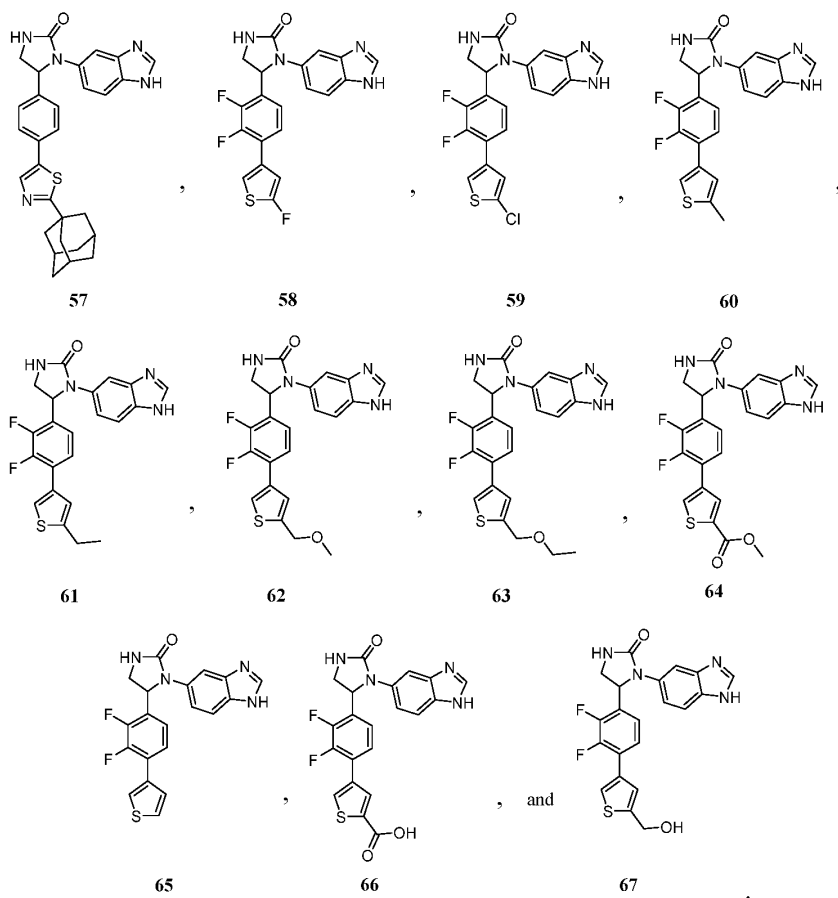
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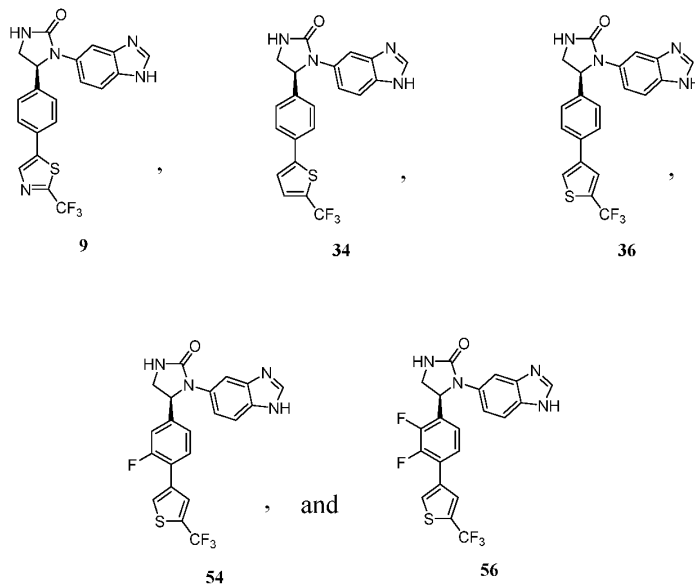
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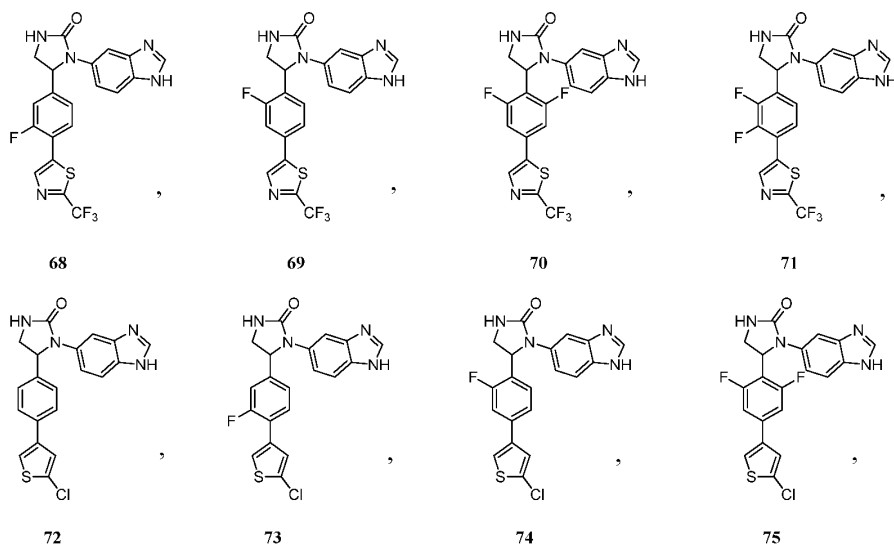
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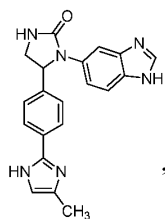


21. The compound of claim 20, wherein the compound is one of the following compounds:

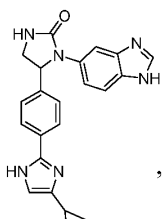


22. The compound of claim 1, wherein the compound is one of the following compounds:

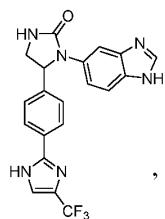




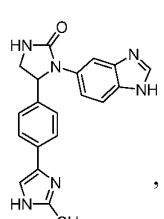
76



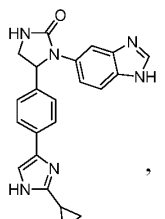
77



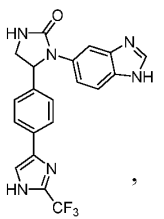
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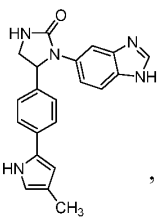
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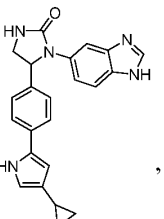
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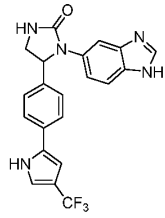
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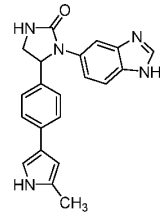
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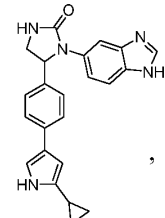
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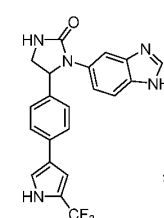
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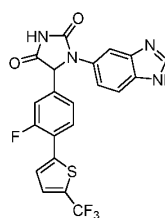
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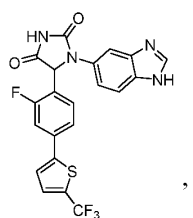
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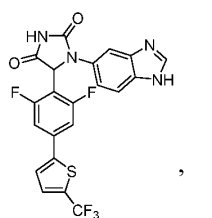
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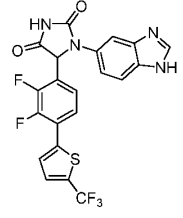
88



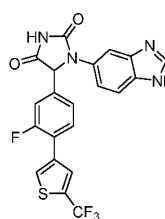
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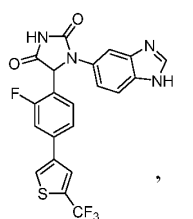
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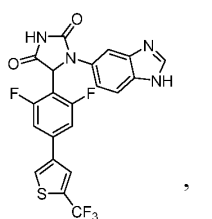
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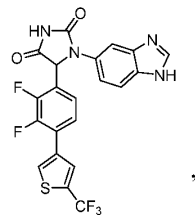
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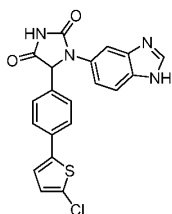
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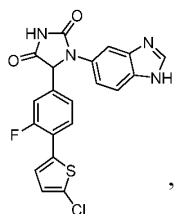
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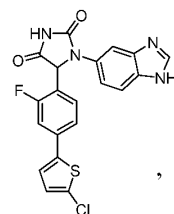
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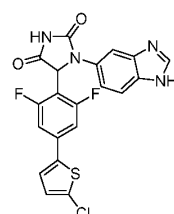
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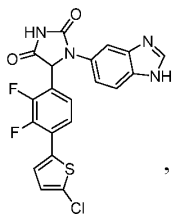
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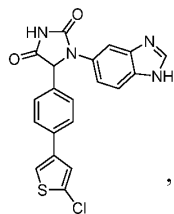
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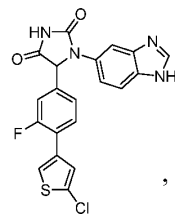
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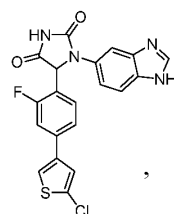
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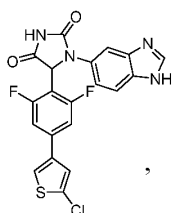
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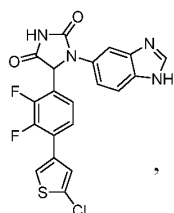
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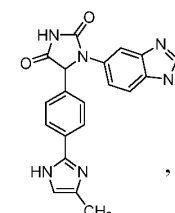
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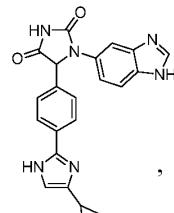
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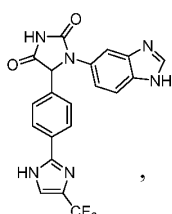
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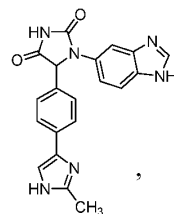
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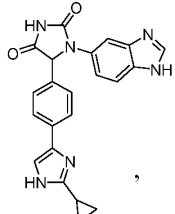
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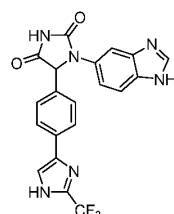
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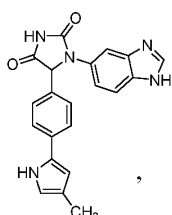
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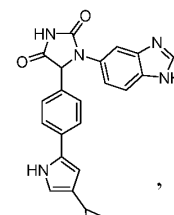
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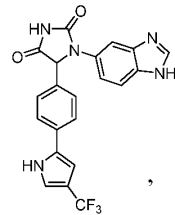
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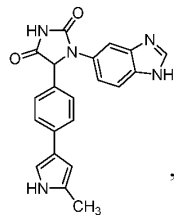
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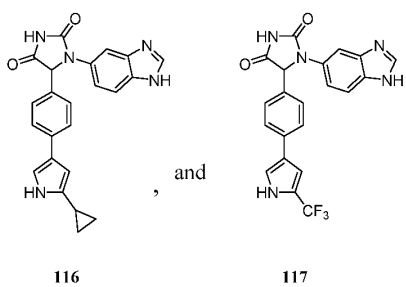
113



114



115



23. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

24. A method of treating Alzheimer's disease or Huntington's disease by administering to a subject in need thereof an effective amount of a compound of claim 1.