

COPPER COMPLEXES FOR TREATMENT OF NEURODEGENERATIVE DISORDERS**CROSS-REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of U.S. Ser. No. 63/070,792, filed August 26,
5 2020, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND

Neurodegenerative diseases are age-dependent disorders that are becoming increasingly prevalent, in part due to the increasing elderly population (Heemels, *Nature*
10 (2016) 539:179).

For example, amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, Lou Gehrig's disease, or Charcot's disease, is estimated to affect 30,000 Americans and over 400,000 people worldwide at any given time. Approximately 5,000 Americans are diagnosed with ALS every year. The disease causes the unrelenting death of
15 motor neurons, resulting in a progressive paralysis that kills its victims within one to five years on average. Most people diagnosed with ALS live 3-5 years after their first signs of disease. About 10% of people with ALS survive at least 10 years. The variable rate of disease progression makes prognosis difficult to predict, and therapies challenging to develop.

20 Only two agents (riluzole and edaravone) have been approved by the FDA for treating ALS, and while both slow disease progression in a subset of patients, and can extend life by up to a few months, neither is able to treat or cure the disease.

Some inherited forms of ALS are caused by genetic mutations. The genetic change alters an enzyme within cells called copper-zinc superoxide dismutase (Cu-Zn superoxide
25 dismutase, now called commonly SOD1). This enzyme serves to keep cells safe from metabolic waste that can cause damage if not rendered harmless.

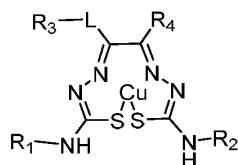
The compound CuATSM has been shown by the rigorous methods established in the art to be protective in transgenic mouse models of ALS where the transgenic mice were engineered to express human SOD1 harboring mutations found in SOD1 familial ALS.

30 However, there is a need in the art for improved therapeutic agents that can treat neurological diseases and/or copper deficiency-related disorders.

SUMMARY

35 Provided herein are compounds useful in methods of treating or preventing a neurodegenerative disease in a subject in need thereof.

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

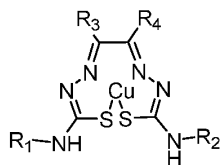


(I),

or a pharmaceutically acceptable salt thereof, wherein L, R₁, R₂, R₃, and R₄ are as defined herein.

- 5 In an embodiment, the compound of Formula (I) is selected from the group consisting of Compounds 1-22, or pharmaceutically acceptable salts thereof.

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

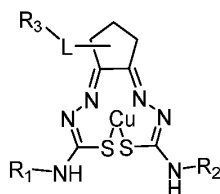


(II),

- 10 or a pharmaceutically acceptable salt thereof, wherein R₁, R₂, R₃, and R₄ are as defined herein.

In an embodiment, the compound of Formula (II) is selected from the group consisting of Compounds 23-46.

In another aspect, the disclosure provides a compound of Formula (III):

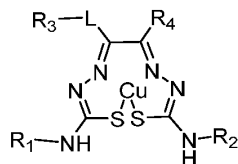


(III),

- 15 or a pharmaceutically acceptable salt thereof, wherein L, R₁, R₂, and R₃ are as defined herein.

- 20 In an embodiment, the compound of Formula (III) is selected from the group consisting of Compounds 47-53.

In another aspect, the disclosure provides a compound of Formula (IV):

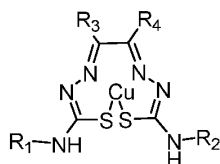


(IV),

or a pharmaceutically acceptable salt thereof, wherein L, R₁, R₂, R₃, and R₄ are as defined herein.

In an embodiment, the compound of Formula (IV) is selected from the group
5 consisting of Compounds 1-22, 57, 59-61, and 66-78.

In another aspect, the disclosure provides a compound of Formula (V):



(V),

or pharmaceutically acceptable salts thereof, wherein R₁, R₂, R₃, and R₄ are as
10 defined herein.

In an embodiment, the compound of Formula (V) is selected from the group consisting of Compounds 23-46 and 79-127.

In another aspect, the disclosure provides a compound selected from the group consisting of Compounds 56-65.

15 In another aspect, the disclosure provides a pharmaceutical composition comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, diluent, or carrier.

In another aspect, the disclosure provides a method of treating or preventing a neurodegenerative disease in a subject in need thereof, the method comprising
20 administering to the subject a therapeutically effective amount of a compound of the disclosure.

In an embodiment, the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontal temporal dementia (FTD), Parkinson's disease, Huntington's disease, and Alzheimer's disease. In another embodiment, the neurodegenerative disease is ALS. In a
25 further embodiment, the ALS is familial or sporadic.

In another aspect, the disclosure provides a method of making a compound of the disclosure.

BRIEF DESCRIPTION OF THE FIGURES

30 FIG. 1A illustrates the compound muscle action potential (CMAP) change from baseline in male SOD1^{G93A} mice after being treated with 10 mg/kg or 30 mg/kg CuATSM or vehicle daily for four weeks. FIG. 1B is the percent of baseline of the same cohort after CuATSM or vehicle dosing.

FIG. 2A illustrates the CMAP change from baseline after administering 10 mg/kg or 30 mg/kg Compound 25 or vehicle (control) to male SOD1^{G93A} mice daily for five weeks. FIG. 2B illustrates the percent of baseline of the same cohort after Compound 25 or vehicle dosing.

5 FIG. 3A compares disease onset of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 25, or 30 mg/kg Compound 25. FIG. 3B compares survival of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 25, or 30 mg/kg Compound 25.

10 FIG. 4 demonstrates the benefits of chronic daily dosing of 30 mg/kg Compound 25 in a litter-matched and gender-balanced survival efficacy study compared to mice treated with vehicle. FIG. 4A illustrates the age of onset of neurological disease, FIG. 4B illustrates extended survival, FIG. 4C demonstrates improved body weight maintenance in Compound 25-treated mice, and FIG. 4D illustrates differences in neurological disease progression.

15 FIG. 5A illustrates CMAP change from baseline after administering 10 mg/kg or 30 mg/kg Compound 9 to male SOD1^{G93A} mice compared to control mice after dosing daily for four weeks. FIG. 5B is the percent of baseline of the same cohort after Compound 9 or vehicle dosing.

20 FIG. 6A compares disease onset of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 9, or 30 mg/kg Compound 25. FIG. 6B compares survival of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 9, or 30 mg/kg Compound 9.

25 FIG. 7A illustrates the CMAP change from baseline after administering 10 mg/kg or 30 mg/kg Compound 24 or vehicle (control) to male SOD1^{G93A} mice daily for three weeks. FIG. 7B illustrates the percent of baseline of the same cohort after Compound 24 or vehicle dosing.

30 FIG. 8A compares disease onset of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 24, or 30 mg/kg Compound 24. FIG. 8B compares survival of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 24, or 30 mg/kg Compound 24.

35 FIG. 9A illustrates the CMAP change from baseline after administering 10 mg/kg or 30 mg/kg Compound 37 or vehicle (control) to male SOD1^{G93A} mice daily for four weeks. FIG. 9B illustrates the percent of baseline of the same cohort after Compound 37 or vehicle dosing.

FIG. 10A compares disease onset of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 37, or 30 mg/kg Compound 37. **FIG. 10B** compares survival of vehicle-treated male SOD1^{G93A} mice, mice treated with 10 mg/kg Compound 37, or 30 mg/kg Compound 37.

FIG. 11A depicts plasma and spinal cord concentrations of Compound 25 in female mice during the hours following administration.

FIG. 11B is a logarithmic depiction of the data in FIG. 11A.

FIG. 12A depicts plasma and spinal cord concentrations of Compound 25 in male mice during the hours following administration.

FIG. 12B is a logarithmic depiction of the data in FIG. 12A.

FIG. 13A depicts plasma and spinal cord concentrations of Compound 34 in female mice during the hours following administration.

FIG. 13B is a logarithmic depiction of the data in FIG. 13A.

FIG. 14A depicts plasma and spinal cord concentrations of Compound 34 in male mice during the hours following administration.

FIG. 14B is a logarithmic depiction of the data in FIG. 14A.

FIG. 15A depicts plasma and spinal cord concentrations of Compound 32 in female mice during the hours following administration.

FIG. 15B is a logarithmic depiction of the data in FIG. 15A.

FIG. 16A depicts plasma and spinal cord concentrations of Compound 32 in male mice during the hours following administration.

FIG. 16B is a logarithmic depiction of the data in FIG. 16A.

FIG. 17A depicts plasma and spinal cord concentrations of Compound 29 in female mice during the hours following administration.

FIG. 17B is a logarithmic depiction of the data in FIG. 17A.

FIG. 18A depicts plasma and spinal cord concentrations of Compound 29 in male mice during the hours following administration.

FIG. 18B is a logarithmic depiction of the data in FIG. 18A.

FIG. 19A illustrates the survival of female SOD1^{G93A} mice treated with Compound 25 as compared to control.

FIG. 19B illustrates the survival of male SOD1^{G93A} mice treated with Compound 25 as compared to control.

FIG. 20A illustrates the survival of female SOD1^{G93A} mice treated with Compound 34 as compared to control.

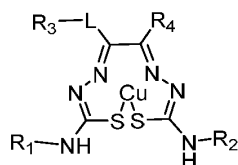
FIG. 20B illustrates the survival of male SOD1^{G93A} mice treated with Compound 34 as compared to control.

FIG. 21A illustrates the survival of female SOD1^{G93A} mice treated with Compound 32 as compared to control.

FIG. 21B illustrates the survival of male SOD1^{G93A} mice treated with Compound 32 as compared to control.

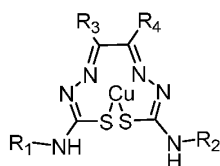
DETAILED DESCRIPTION

Provided herein are compounds of Formula (I):



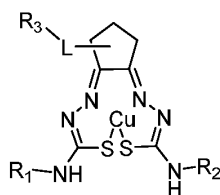
(1)

5 and pharmaceutically acceptable salts thereof, compounds of Formula (II):



(II)

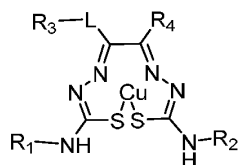
and pharmaceutically acceptable salts thereof, compounds of Formula (III):



(III)

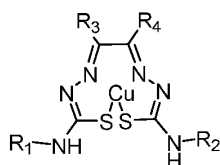
10

and pharmaceutically acceptable salts thereof, compound of Formula (IV):



(IV)

and pharmaceutically acceptable salts thereof, and compound of Formula (V):



(V)

15

and pharmaceutically acceptable salts thereof, all of which are useful in the treatment of neurological diseases and/or copper deficiency-related disorders.

Definitions

Listed below are definitions of various terms used herein. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

5 Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, and peptide chemistry are those well-known and commonly employed in the art.

10 As used herein, the articles "a" and "an" refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element. Furthermore, use of the term "including" as well as other forms, such as "include," "includes," and "included," is not limiting.

15 As used herein, the term "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term "about" is meant to encompass variations of $\pm 20\%$ or $\pm 10\%$, including $\pm 5\%$, $\pm 1\%$, and $\pm 0.1\%$ from the specified value, as such variations are appropriate to perform the disclosed methods.

20 As used in the specification and in the claims, the term "comprising" may include the embodiments "consisting of" and "consisting essentially of." The terms "comprise(s)," "include(s)," "having," "has," "may," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that require the presence of the named ingredients/steps and permit the presence of other ingredients/steps. However,
25 such description should be construed as also describing compositions or processes as "consisting of" and "consisting essentially of" the enumerated compounds, which allows the presence of only the named compounds, along with any pharmaceutically acceptable carriers, and excludes other compounds.

30 As used herein, the term "alkyl," by itself or as part of another substituent means, unless otherwise stated, a straight or branched chain hydrocarbon having the number of carbon atoms designated (i.e., C₁-C₆ alkyl means an alkyl having one to six carbon atoms) and includes straight and branched chains. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, neopentyl, and 1-hexyl.

35 As used herein, the term "haloalkyl" refers to an alkyl group, as defined above, substituted with one or more halo substituents, wherein alkyl and halo are as defined herein. Haloalkyl includes, by way of example, chloromethyl, trifluoromethyl, bromoethyl, chlorofluoroethyl, and the like.

As used herein, the term “alkoxy” refers to the group –O-alkyl, wherein alkyl is as defined herein. Alkoxy includes, by way of example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, t-butoxy and the like.

As used herein, the term “halo” or “halogen” alone or as part of another substituent means, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

As used herein, the term “cycloalkyl” means a non-aromatic carbocyclic system that is partially or fully saturated having the number of carbon atoms designated. The cycloalkyl group may be a monocyclic, a fused polycyclic, a bridged polycyclic, or a spiro polycyclic carbocycle. The term “cycloalkyl” includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[3.1.0]hexyl, spiro[3.3]heptanyl, and bicyclo[1.1.1]pentyl.

As used herein, the term “heterocyclyl” or “heterocycloalkyl” means a non-aromatic saturated or partially saturated monocyclic, fused polycyclic, bridged polycyclic, or spiro polycyclic ring system containing the number of ring atoms designated, and wherein the ring atoms are carbon atoms and 1, 2, 3, or 4 heteroatoms selected independently from N, O, and S. The term “heterocyclyl” includes cyclic esters (i.e., lactones) and cyclic amides (i.e., lactams) and also includes, but is not limited to, epoxidyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl (i.e., oxanyl), pyranal, dioxanyl, aziridinyl, azetidyl, pyrrolidinyl, 2,5-dihydro-1H-pyrrolyl, oxazolidinyl, thiazolidinyl, piperidinyl, morpholinyl, piperazinyl, thiomorpholinyl, 1,3-oxazinanyl, 1,3-thiazinanyl, 2-azabicyclo[2.1.1]hexanyl, 5-azabicyclo[2.1.1]hexanyl, 6-azabicyclo[3.1.1]heptanyl, 2-azabicyclo[2.2.1]heptanyl, 3-azabicyclo[3.1.1]heptanyl, 2-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[3.1.0]hexanyl, 2-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, 3-oxa-7-azabicyclo[3.3.1]nonanyl, 3-oxa-9-azabicyclo[3.3.1]nonanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 6-oxa-3-azabicyclo[3.1.1]heptanyl, 2-azaspiro[3.3]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2-oxaspiro[3.3]heptanyl, 2-oxaspiro[3.5]nonanyl, 3-oxaspiro[5.3]nonanyl, and 8-oxabicyclo[3.2.1]octanyl. Unless otherwise noted, the heterocycle or heterocycloalkyl is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure.

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

As used herein, the term “aryl” means an aromatic carbocyclic system containing the designated number of ring atoms. Aryl groups can be a single rings or multiple rings (up to three rings) which are fused together or linked covalently. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) may be fully saturated, partially unsaturated or fully unsaturated. The term “aryl” includes, but is not limited to, phenyl, naphthyl, indanyl, and 1,2,3,4-tetrahydronaphthalenyl.

As used herein, the term "heteroaryl" means an aromatic carbocyclic system containing 1, 2, 3, or 4 heteroatoms selected independently from N, O, and S. Heteroaryl groups may be single rings or multiple rings (up to three rings) which are fused together or linked covalently. If the rings are fused, one of the rings must be fully unsaturated and the fused ring(s) may be fully saturated, partially unsaturated or fully unsaturated. The term "heteroaryl" includes, but is not limited to, furyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazo[1,2-a]pyridinyl, pyrazolo[1,5-a]pyridinyl, benzo[d][1,3]dioxolyl, 5,6,7,8-tetrahydroisoquinolyl, 5,6,7,8-tetrahydroquinolyl, 6,7-dihydro-5H-cyclopenta[b]pyridinyl, 6,7-dihydro-5H-cyclopenta[c]pyridinyl, 1,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 2,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, 5,6-dihydro-4H-pyrrolo[1,2-b]pyrazolyl, 6,7-dihydro-5H-pyrrolo[1,2-b][1,2,4]triazolyl, 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, 4,5,6,7-tetrahydro-1H-indazolyl and 4,5,6,7-tetrahydro-2H-indazolyl. Unless otherwise noted, the heterocycle or heterocycloalkyl is attached to its pendant group at any heteroatom or carbon atom that results in a stable structure.

As used herein, the term "substituted" means that an atom or group of atoms has replaced hydrogen as the substituent attached to another group.

A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of compounds of the disclosure that are non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. It should possess the desired pharmacological activity of the parent compound. See, generally, G.S. Paulekuhn, et al., "Trends in Active Pharmaceutical Ingredient Salt Selection based on Analysis of the Orange Book Database", J. Med. Chem., 2007, 50:6665-72, S.M. Berge, et al., "Pharmaceutical Salts", J Pharm Sci., 1977, 66:1-19, and Handbook of Pharmaceutical Salts, Properties, Selection, and Use, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002.

The term "treatment" refers to the application of one or more specific procedures used for the amelioration of a disease. In certain embodiments, the specific procedure is the administration of one or more pharmaceutical agents. "Treatment" of an individual (e.g. a mammal, such as a human) or a cell is any type of intervention used in an attempt to alter the natural course of the individual or cell. Treatment includes, but is not limited to, administration of a pharmaceutical composition, and may be performed either prophylactically or subsequent to the initiation of a pathologic event or contact with an etiologic agent. Treatment includes any desirable effect on the symptoms or pathology of a disease or condition, and may include, for example, minimal changes or improvements in one or more measurable markers of the disease or condition being treated.

As used herein, the term “prevent” or “prevention” means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

5 As used herein, the term “use” includes any one or more of the following embodiments of the invention, respectively: the use in the treatment of pain the use for the manufacture of pharmaceutical compositions for use in the treatment of these diseases, e.g., in the manufacture of a medicament; methods of use of compounds of the invention in the treatment of these diseases; pharmaceutical preparations having compounds of the
10 invention for the treatment of these diseases; and compounds of the invention for use in the treatment of these diseases; as appropriate and expedient, if not stated otherwise.

As used herein, the term “patient,” “individual,” or “subject” is intended to include organisms, e.g., prokaryotes and eukaryotes, which are capable of suffering from or afflicted with a disease, disorder or condition associated with the activity of a protein kinase.

15 Examples of subjects include mammals, e.g., humans, dogs, cows, horses, pigs, sheep, goats, cats, mice, rabbits, rats, and transgenic non-human animals. In certain embodiments, the subject is a human, e.g., a human suffering from, at risk of suffering from, or potentially capable of suffering from, ALS. In another embodiment, the subject is a cell. The terms term “patient,” “individual,” or “subject” do not denote a particular age or sex.

20 When used with respect to methods of treatment/prevention and the use of the compounds and pharmaceutical compositions thereof described herein, an individual “in need thereof” may be an individual who has been diagnosed with or previously treated for the condition to be treated. With respect to prevention, the individual in need thereof may also be an individual who is at risk for a condition (e.g., a family history of the condition, life-
25 style factors indicative of risk for the condition, etc.). Typically, when a step of administering a compound of the invention is disclosed herein, the invention further contemplates a step of identifying an individual or subject in need of the particular treatment to be administered or having the particular condition to be treated.

As used herein, the terms “effective amount,” “pharmaceutically effective amount,”
30 and “therapeutically effective amount” refer to a nontoxic but sufficient amount of an agent to provide the desired biological result. That result may be reduction or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. An appropriate therapeutic amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

35 As used herein, the term “composition” or “pharmaceutical composition” refers to a mixture of at least one compound useful within the invention with a pharmaceutically acceptable diluent, excipient, or carrier. The pharmaceutical composition facilitates

administration of the compound to a patient or subject. Multiple techniques of administering a compound exist in the art including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary, and topical administration.

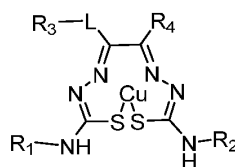
The terms “combination,” “therapeutic combination,” or “pharmaceutical combination” as used herein refer to either a fixed combination in one dosage unit form, or non-fixed combination, or a kit of parts for the combined administration where two or more therapeutic agents may be administered independently, at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g., synergistic, effect.

The term “sporadic” refers to a neurodegenerative disease, ALS for example, that is not inherited. Sporadic ALS accounts for about 90% of cases, where the affected individual is the only member of the family with the disease. The cause of sporadic ALS is not well understood, but may be due to a combination of environmental and genetic risk factors.

The term “familial” refers to a neurodegenerative disease, ALS for example, that is inherited. Familial ALS accounts for about 10% of cases, where more than one person in the family has ALS and sometimes family members have frontotemporal dementia as well. People with familial ALS often start showing symptoms at earlier ages than in sporadic ALS. Familial ALS is most often autosomal dominant.

20 Compounds of the Disclosure

In one aspect, provided herein are compounds of Formula (I):



(I),

or pharmaceutically acceptable salts thereof, wherein:

25 L is C₃-C₇ cycloalkyl, C₁-C₆ alkyl, or absent

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

30 R₃ is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₆-C₁₀ aryl is substituted one, two, or three times with the group R_{3a}, and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C_3 - C_7 cycloalkyl or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl;

R_{3b} independently for each occurrence is C_1 - C_3 alkoxy, C_3 - C_7 cycloalkyl, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl; and

R_4 is hydrogen, C_1 - C_3 alkyl, or C_6 - C_{10} aryl;

provided that when L is absent, R_3 is C_6 - C_{10} aryl substituted one, two, or three times with the group R_{3a} ; or when L is absent, R_3 is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b} .

In an embodiment, L is C_3 - C_7 cycloalkyl or C_1 - C_6 alkyl. In an embodiment, L is C_3 - C_7 cycloalkyl. In an embodiment, L is C_1 - C_6 alkyl. In an embodiment, L is C_3 - C_5 cycloalkyl or C_1 - C_3 alkyl. In an embodiment, L is C_3 - C_5 cycloalkyl. In an embodiment, L is C_1 - C_3 alkyl.

In an embodiment, L is $-CH_2-$. In an embodiment, L is $-CH_2CH_2-$. In an embodiment, L is $-CH_2CH_2CH_2-$. In an embodiment, L is $-CH_2CH_2CH_2CH_2-$. In an embodiment, L is $-CH(CH_3)-$. In an embodiment, L is $-CH(CH_2CH_3)-$. In an embodiment, L is $-C(CH_3)_2-$.

In an embodiment, L is C_3 - C_7 cycloalkyl or C_3 - C_5 cycloalkyl, wherein the cycloalkyl group comprises a quaternary carbon that forms the point of attachment to group R_3 and to the rest of the scaffold. Accordingly, in an embodiment, L is represented by one of the following groups:



In an embodiment, R_1 is C_{1-6} alkyl. In an embodiment, R_1 is C_{1-3} alkyl. In an embodiment, R_1 is methyl or ethyl. In an embodiment, R_1 is methyl. In an embodiment, R_1 is ethyl.

In an embodiment, R_2 is C_{1-6} alkyl. In an embodiment, R_2 is C_{1-3} alkyl. In an embodiment, R_2 is methyl or ethyl. In an embodiment, R_2 is methyl. In an embodiment, R_2 is ethyl.

In an embodiment, R_1 and R_2 are identical.

In an embodiment, R_3 is C_6 - C_{10} aryl, 6- to 10-membered heteroaryl, $C(O)NH-(C_1-C_6 \text{ alkyl})-PPh_3$, hydroxy, C_1 - C_6 alkoxy, or $O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, wherein the C_6 - C_{10} aryl is substituted one, two, or three times with the group R_{3a} , and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b} .

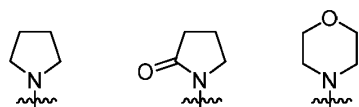
In an embodiment, R_3 is phenyl, pyridinyl, $C(O)NH-(C_1-C_6 \text{ alkyl})-PPh_3$, hydroxy, C_1 - C_6 alkoxy, or $O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, wherein the phenyl is substituted one, two, or

three times with the group R_{3a} , and wherein the pyridinyl is optionally substituted one, two, or three times with the group R_{3b} .

In an embodiment, R_3 is phenyl, pyridinyl, $C(O)NH-(C_1-C_6 \text{ alkyl})-PPh_3$, hydroxy, C_1-C_6 alkoxy, or $O-(C_1-C_6 \text{ alkyl})-O-(C_1-C_6 \text{ alkyl})$, wherein the phenyl is substituted one time with the group R_{3a} , and wherein the pyridinyl is optionally substituted one time with the group R_{3b} .

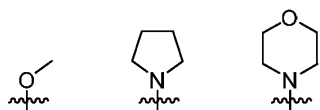
In an embodiment, R_{3a} independently for each occurrence is 4- to 8-membered heterocycle optionally further substituted one, two, or three times with C_1-C_3 alkyl. In an embodiment, R_{3a} independently for each occurrence is 4- to 8-membered heterocycle optionally further substituted one time with methyl.

In an embodiment, R_{3a} independently for each occurrence is pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is optionally further substituted one, two, or three times with C_1-C_3 alkyl. In an embodiment, R_{3a} independently for each occurrence is pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is optionally further substituted one time with methyl. In an embodiment, R_{3a} independently for each occurrence is pyrrolidinyl, pyrrolidinonyl, or morpholinyl. In an embodiment, R_{3a} independently for each occurrence is represented by a group selected from the following:



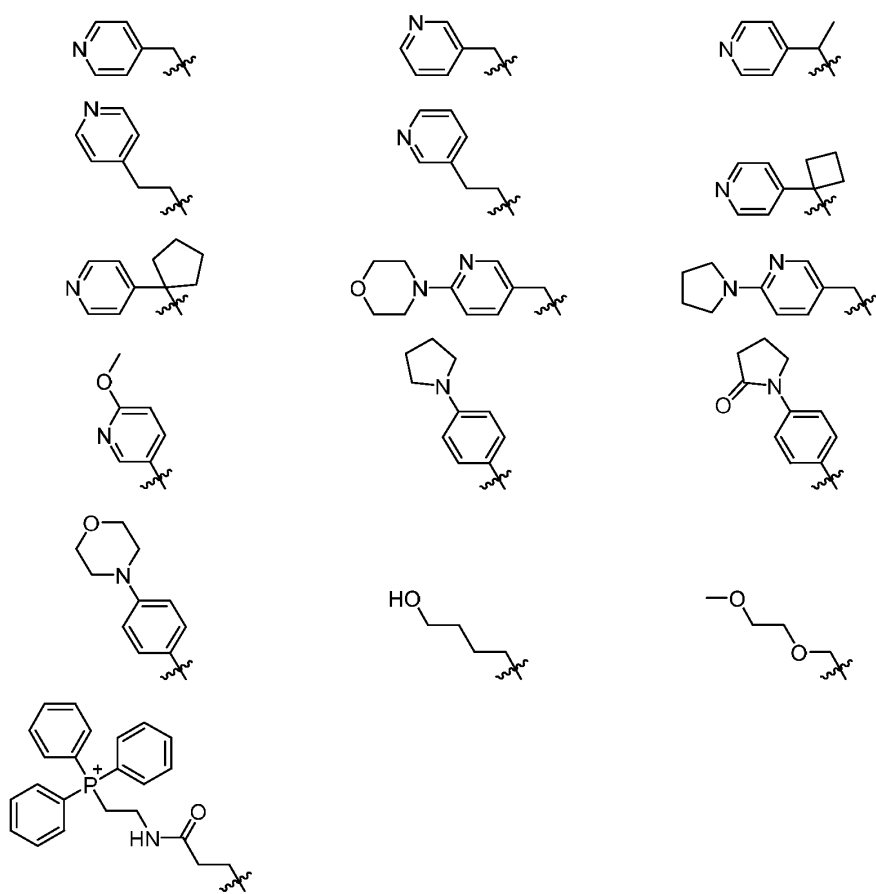
In an embodiment, R_{3b} independently for each occurrence is C_1-C_3 alkoxy or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C_1-C_3 alkyl. In an embodiment, R_{3b} independently for each occurrence is C_1-C_3 alkoxy or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one time with methyl.

In an embodiment, R_{3b} independently for each occurrence is C_1-C_3 alkoxy or a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl, wherein the heterocycle is optionally further substituted one, two, or three times with C_1-C_3 alkyl. In an embodiment, R_{3b} independently for each occurrence is C_1-C_3 alkoxy or a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl, wherein the heterocycle is optionally further substituted one time with methyl. In an embodiment, R_{3b} independently for each occurrence is methoxy or a heterocycle selected from the group consisting of pyrrolidinyl and morpholinyl. In an embodiment, R_{3b} independently for each occurrence is represented by a group selected from the following:



- In an embodiment, R_4 is hydrogen, C_1 - C_3 alkyl, or phenyl. In an embodiment, R_4 is hydrogen, methyl, or phenyl. In an embodiment, R_4 is hydrogen or C_1 - C_3 alkyl. In an embodiment, R_4 is hydrogen or methyl. In an embodiment, R_4 is hydrogen. In an embodiment, R_4 is methyl. In an embodiment, R_4 is phenyl.

In an embodiment, the group represented by R_3 -L has one of the following structures:



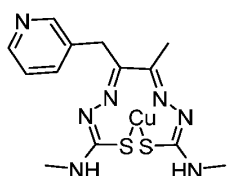
- In an embodiment, R_3 is pyridinyl optionally substituted one, two, or three times with C_1 - C_3 alkoxy or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally substituted one time with C_1 - C_3 alkyl.

In an embodiment, L is absent and R_3 is pyridinyl substituted one, two, or three times with C_1 - C_3 alkoxy.

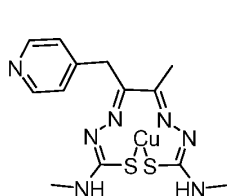
In an embodiment, L is absent and R₃ is phenyl substituted with 4- to 8-membered heterocycle.

In an embodiment, L is C₃-C₅ cycloalkyl or C₁-C₃ alkyl; R₃ is pyridinyl optionally substituted one, two, or three times with 4- to 8-membered heterocycle; and R₄ is methyl.

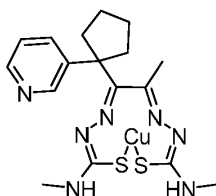
5 In an embodiment, the compound of Formula (I) has the structure of Compound 9:



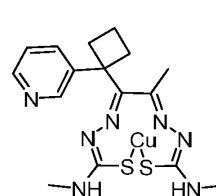
Exemplary compounds of Formula (I) include the compounds described below, or pharmaceutically acceptable salts thereof:



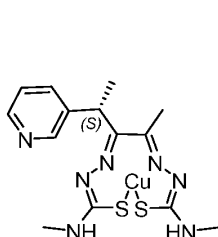
Compound 1



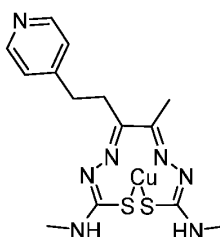
Compound 2



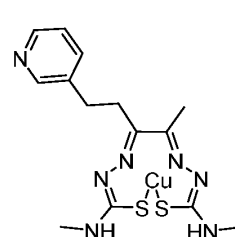
Compound 3



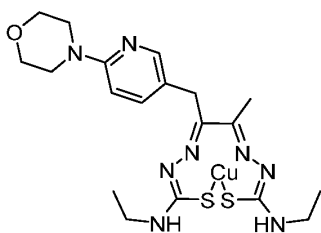
Compound 4



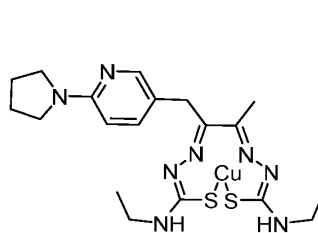
Compound 5



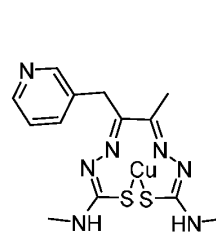
Compound 6



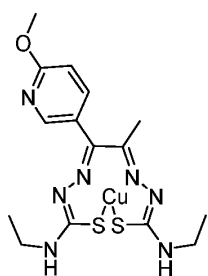
Compound 7



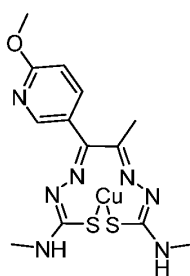
Compound 8



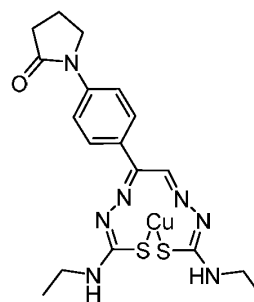
Compound 9



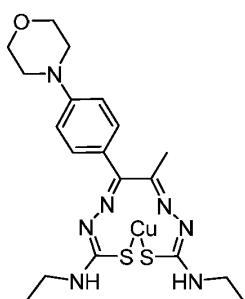
Compound 10



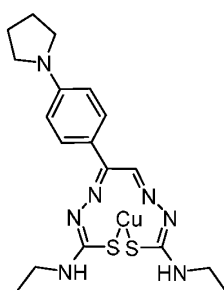
Compound 11



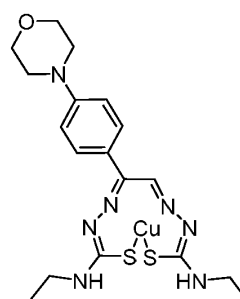
Compound 12



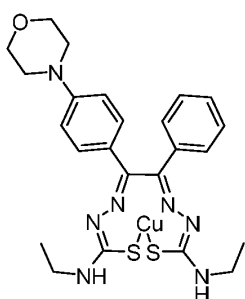
Compound 13



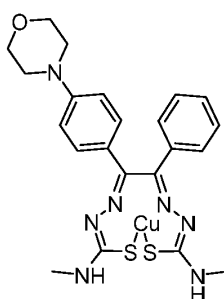
Compound 14



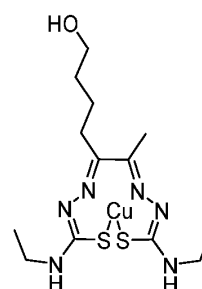
Compound 15



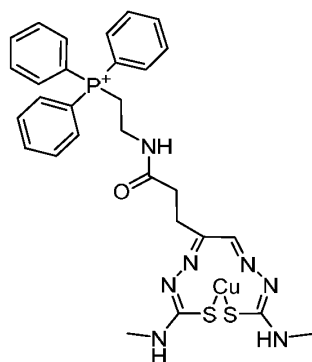
Compound 16



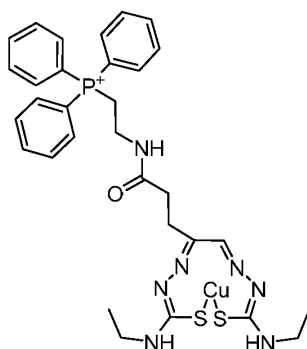
Compound 17



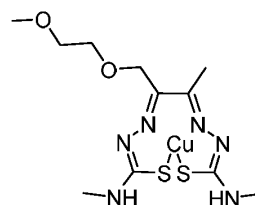
Compound 18



Compound 19

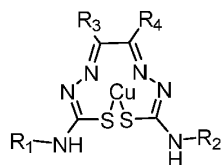


Compound 21



Compound 22.

In another aspect, provided herein are compounds of Formula (II):



(II),

5 or pharmaceutically acceptable salts thereof, wherein:

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

10 R₃ is 4- to 8-membered heterocycle or 5-membered heteroaryl, wherein the 4- to 8-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a}, and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkyl-(C₆-C₁₀ aryl),

15 S(O)₂H, S(O)₂-(C₁-C₆ alkyl), S(O)₂-(C₃-C₇ cycloalkyl), or S(O)₂-(C₆-C₁₀ aryl);

R_{3b} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, halo, nitro, cyano, C(O)-(4- to 8-membered heterocycle), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

20 R₄ is hydrogen or C₁₋₃ alkyl.

In an embodiment, R_1 is C_{1-6} alkyl. In an embodiment, R_1 is C_{1-3} alkyl. In an embodiment, R_1 is methyl or ethyl. In an embodiment, R_1 is methyl. In an embodiment, R_1 is ethyl.

In an embodiment, R_2 is C_{1-6} alkyl. In an embodiment, R_2 is C_{1-3} alkyl. In an embodiment, R_2 is methyl or ethyl. In an embodiment, R_2 is methyl. In an embodiment, R_2 is ethyl.

In an embodiment, R_1 and R_2 are identical.

In an embodiment, R_3 is 6-membered heterocycle or 5-membered heteroaryl, wherein the 6-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a} , and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b} .

In an embodiment, R_3 is morpholinyl, piperidinyl, furyl, thiophenyl, or pyrazolyl, wherein the morpholinyl and piperidinyl are optionally substituted one, two, or three times with the group R_{3a} , and wherein the furyl, thiophenyl, and pyrazolyl are optionally substituted one, two, or three times with the group R_{3b} .

In an embodiment, R_3 is furyl, thiophenyl, or pyrazolyl optionally substituted one, two, or three times with the group R_{3b} . In an embodiment, R_3 is furyl, thiophenyl, or pyrazolyl substituted one, two, or three times with the group R_{3b} .

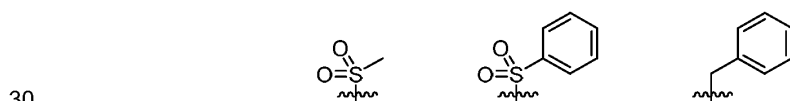
In an embodiment, R_3 is furyl optionally substituted one, two, or three times with the group R_{3b} . In an embodiment, R_3 is furyl substituted one, two, or three times with the group R_{3b} .

In an embodiment, R_3 is morpholinyl or piperidinyl optionally substituted one, two, or three times with the group R_{3a} .

In an embodiment, R_{3a} independently for each occurrence is C_1-C_6 alkyl, C_1-C_6 alkyl- $(C_6-C_{10}$ aryl), $S(O)_2-(C_1-C_6$ alkyl), or $S(O)_2-(C_6-C_{10}$ aryl).

In an embodiment, R_{3a} independently for each occurrence is C_1-C_6 alkyl, C_1-C_6 alkyl-(phenyl), $S(O)_2-(C_1-C_6$ alkyl), or $S(O)_2-(phenyl)$.

In an embodiment, R_{3a} independently for each occurrence is represented by a group selected from the following:

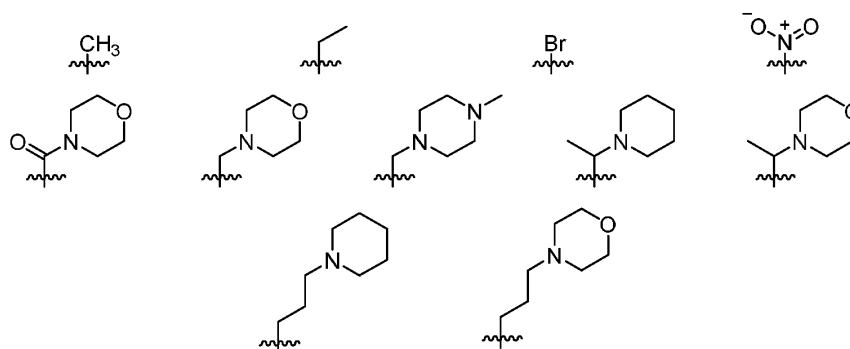


In an embodiment, R_{3b} independently for each occurrence is C_1-C_6 alkyl, halo, nitro, $C(O)-(4- to 8-membered heterocycle)$, or C_1-C_6 alkyl- $(4- to 8-membered heterocycle)$, wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1-C_3 alkyl.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, halo, nitro, $C(O)$ -(4- to 8-membered heterocycle), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is independently selected from the group consisting of pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl, and wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, halo, nitro, $C(O)$ -(4- to 8-membered heterocycle), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is independently selected from the group consisting of morpholinyl, piperidinyl, and piperazinyl, and wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with methyl.

In an embodiment, R_{3b} independently for each occurrence is represented by a group selected from the following:



In an embodiment, R_4 is hydrogen or methyl. In an embodiment, R_4 is hydrogen. In an embodiment, R_4 is methyl.

In an embodiment, R_3 is furyl substituted one, two, or three times with $C(O)$ -(4- to 8-membered heterocycle) or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl.

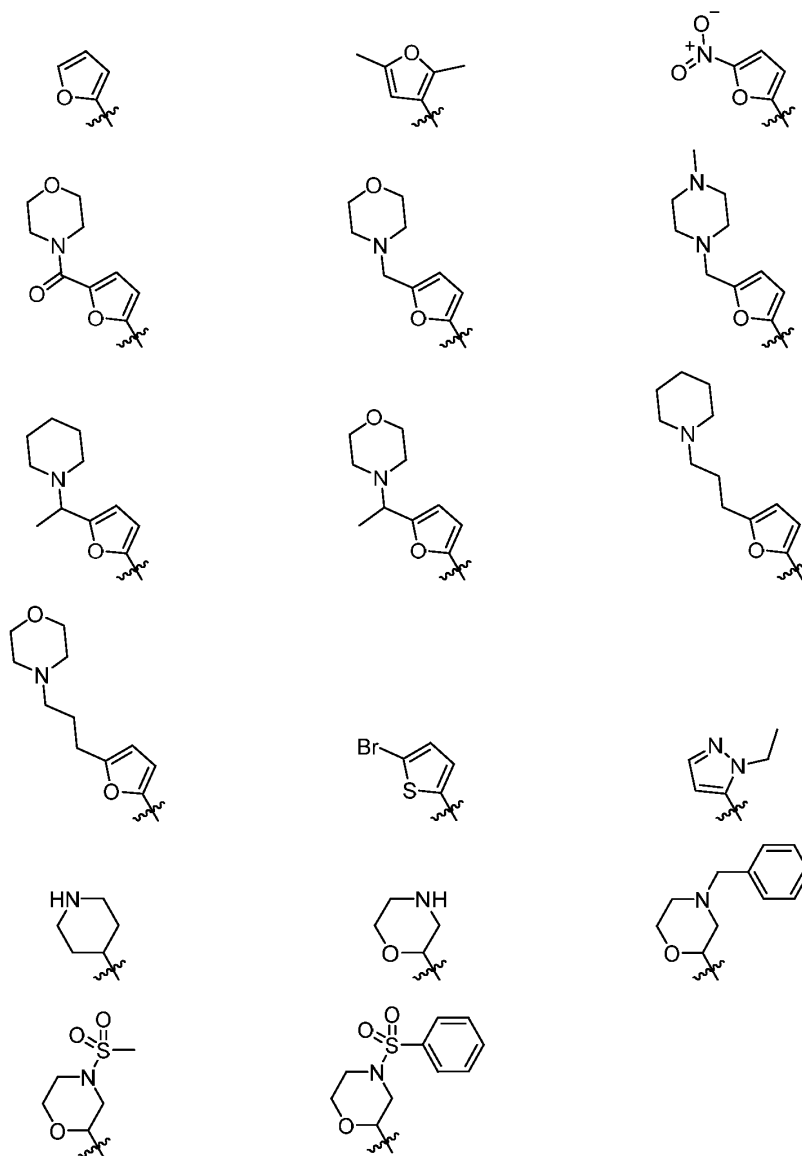
In an embodiment, R_3 is furyl substituted one, two, or three times with $C(O)$ -(4- to 8-membered heterocycle) or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is independently selected from the group consisting of pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl, and wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl.

In an embodiment, R_3 is furyl substituted one, two, or three times with $C(O)$ -(4- to 8-membered heterocycle) or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is independently selected from the group consisting of morpholinyl,

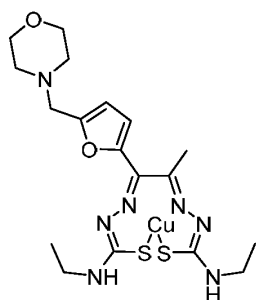
piperidinyl, and piperazinyl, and wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl.

In an embodiment, R₃ is furyl substituted one, two, or three times with C(O)- (morpholinyl) or C₁-C₆ alkyl-(morpholinyl).

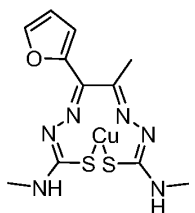
5 In an embodiment, R₃ is represented by a group selected from the following:



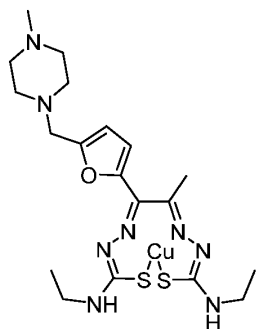
In an embodiment, the compound of Formula (II) has the structure of Compound 24:



In an embodiment, the compound of Formula (II) has the structure of Compound 25:

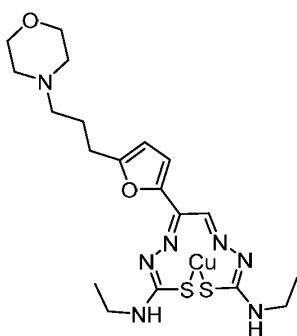


In an embodiment the compound of Formula (II) has the structure of Compound 37:

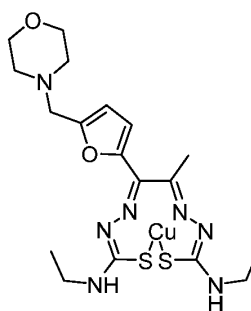


5

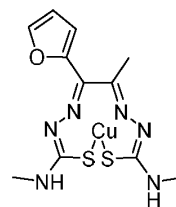
Exemplary compounds of Formula (II) include the compounds described below, or pharmaceutically acceptable salts thereof:



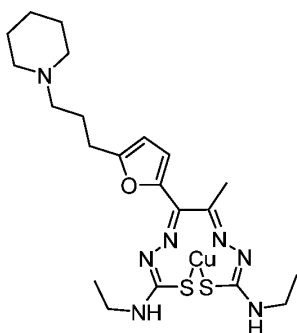
Compound 23



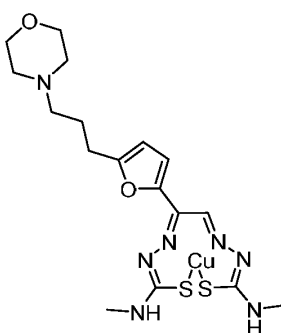
Compound 24



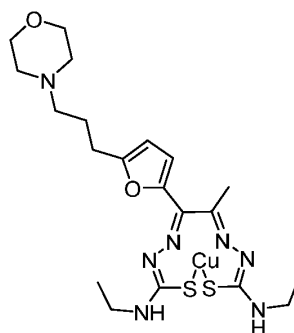
Compound 25



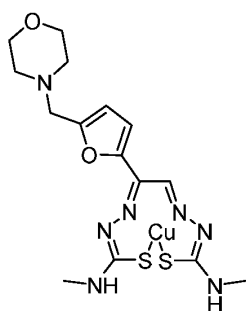
Compound 26



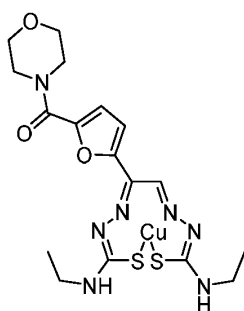
Compound 27



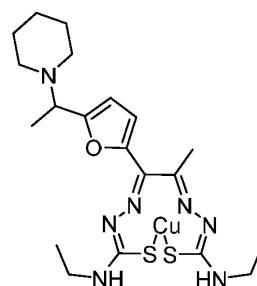
Compound 28



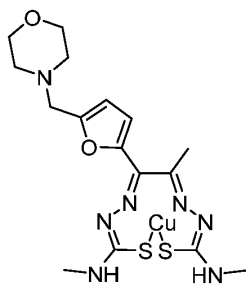
Compound 29



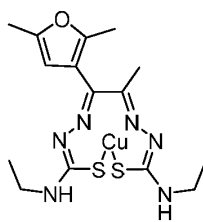
Compound 30



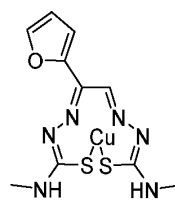
Compound 31



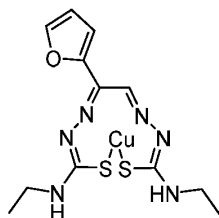
Compound 32



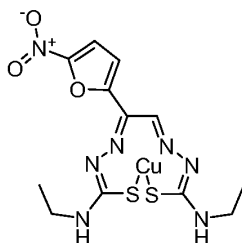
Compound 33



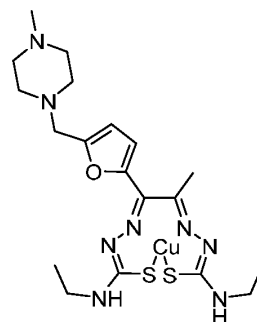
Compound 34



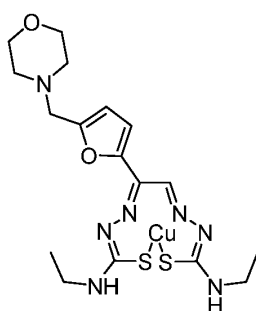
Compound 35



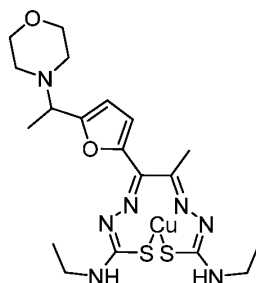
Compound 36



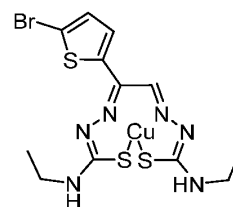
Compound 37



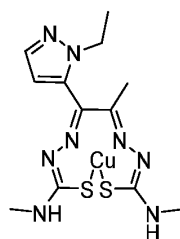
Compound 38



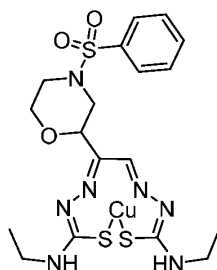
Compound 39



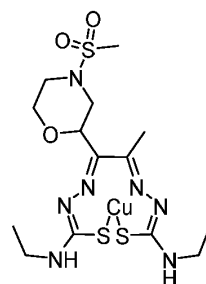
Compound 40



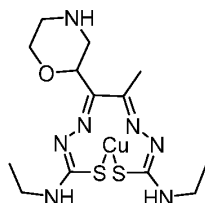
Compound 41



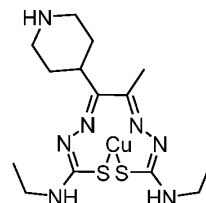
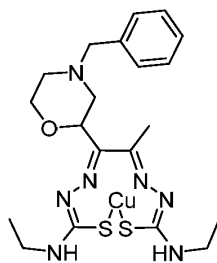
Compound 42



Compound 43



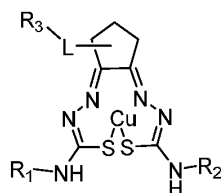
Compound 44



Compound 46.

Compound 45

In yet another aspect, provided herein are compounds of Formula (III):



(III),

5 or pharmaceutically acceptable salts thereof, wherein:

L is C₁-C₆ alkyl or absent

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

10 R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, halo, hydroxy, C(O)NH₂, C(O)NH(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂, or C(O)-(4- to 8-membered heterocycle), wherein the C₁-C₆ alkyl and the C₁-C₆ alkoxy are optionally substituted one, two, or three times with C₆-C₁₀ aryl, and wherein the C(O)-(4- to 8-membered heterocycle) is optionally substituted one, two, or three times with C₁-C₃ alkyl.

15 In an embodiment, L is C₁-C₃ alkyl or absent. In an embodiment, L is C₁-C₃ alkyl. In an embodiment, L is absent.

In an embodiment, R₁ is C₁-C₆ alkyl optionally substituted with NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂. In an embodiment, R₁ is C₁-C₆ alkyl optionally substituted with N(C₁-C₆ alkyl)₂. In an embodiment, R₁ is C₁-C₃ alkyl optionally substituted with N(C₁-C₃ alkyl)₂. In an embodiment, R₁ is methyl or ethyl, wherein the ethyl is optionally substituted with N(CH₂CH₃)₂.

25 In an embodiment, R₂ is C₁-C₆ alkyl optionally substituted with NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂. In an embodiment, R₂ is C₁-C₆ alkyl optionally substituted with N(C₁-C₆ alkyl)₂. In an embodiment, R₂ is C₁-C₃ alkyl optionally substituted with N(C₁-C₃ alkyl)₂. In an embodiment, R₂ is methyl or ethyl, wherein the ethyl is optionally substituted with N(CH₂CH₃)₂.

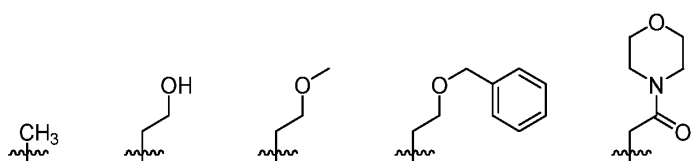
In an embodiment, R₁ and R₂ are identical.

30 In an embodiment, R₃ is C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, or C(O)-(4- to 8-membered heterocycle), wherein the C₁-C₆ alkyl and the C₁-C₆ alkoxy are optionally substituted one time with C₆-C₁₀ aryl and wherein the C(O)-(4- to 8-membered heterocycle) is optionally substituted one time with C₁-C₃ alkyl.

In an embodiment, R_3 is C_1 - C_3 alkyl, C_1 - C_3 alkoxy, hydroxy, or $C(O)$ -(6-membered heterocycle), wherein the C_1 - C_3 alkyl and the C_1 - C_3 alkoxy are optionally substituted one time with phenyl.

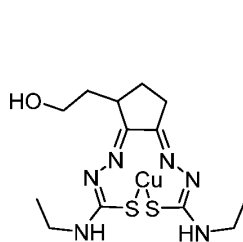
In an embodiment, R_3 is C_1 - C_3 alkyl, C_1 - C_3 alkoxy, hydroxy, or $C(O)$ -(morpholinyl),
 5 wherein the C_1 - C_3 alkyl and the C_1 - C_3 alkoxy are optionally substituted one time with phenyl.

In an embodiment, the group represented by R_3-L has one of the following structures:

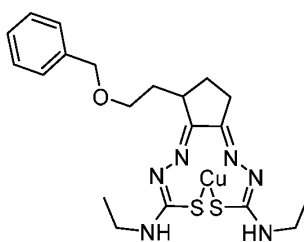


In an embodiment, L is absent and R_3 is C_1 - C_6 alkyl.

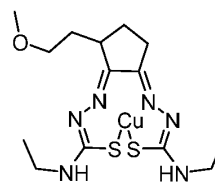
10 Exemplary compounds of Formula (III) include the compounds described below, or pharmaceutically acceptable salts thereof:



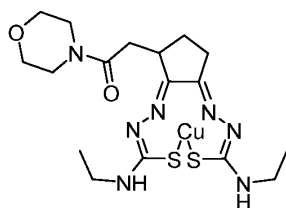
Compound 47



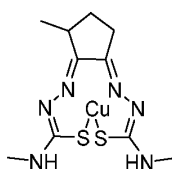
Compound 48



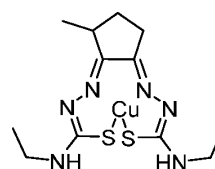
Compound 49



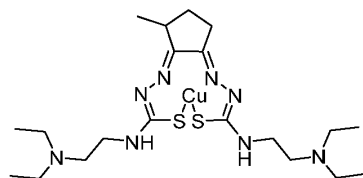
Compound 50



Compound 51

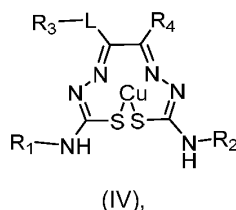


Compound 52



Compound 53.

In another aspect, provided herein are compounds of Formula (IV):



or pharmaceutically acceptable salts thereof, wherein:

5 L is C₃-C₇ cycloalkyl, C₁-C₆ alkyl, or absent;

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

10 R₃ is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C₃-C₁₀ cycloalkyl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₆-C₁₀ aryl is substituted one, two, or three times with the group R_{3a}, and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₃-C₇ cycloalkyl or 4- to 8-membered
15 heterocycle, wherein the 4- to 8-membered heterocycle is optionally further substituted one,
two, or three times with C₁-C₃ alkyl;

R_{3b} independently for each occurrence is C₁-C₃ alkyl, C₁-C₃ alkoxy, C₃-C₇ cycloalkyl, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

20 R₄ is hydrogen, C₁-C₃ alkyl, or C₆-C₁₀ aryl;

provided that when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}; or when L is absent, R₃ is 6- to 10-membered heteroaryl optionally substituted one, two, or three times with the group R_{3b}, and R₄ is H.

25 In an embodiment, L is C₃-C₇ cycloalkyl or C₁-C₆ alkyl. In an embodiment, L is C₃-C₇ cycloalkyl. In an embodiment, L is C₁-C₆ alkyl. In an embodiment, L is C₃-C₅ cycloalkyl or C₁-C₃ alkyl. In an embodiment, L is C₃-C₅ cycloalkyl. In an embodiment, L is C₁-C₃ alkyl.

In an embodiment, L is $-\text{CH}_2-$. In an embodiment, L is $-\text{CH}_2\text{CH}_2-$. In an embodiment, L is $-\text{CH}_2\text{CH}_2\text{CH}_2-$. In an embodiment, L is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$. In an embodiment, L is $-\text{CH}(\text{CH}_3)-$. In an embodiment, L is $-\text{CH}(\text{CH}_2\text{CH}_3)-$. In an embodiment, L is $-\text{C}(\text{CH}_3)_2-$.

In an embodiment, L is C₃-C₇ cycloalkyl or C₃-C₅ cycloalkyl, wherein the cycloalkyl group comprises a quaternary carbon that forms the point of attachment to group R₃ and to

the rest of the scaffold. Accordingly, in an embodiment, L is represented by one of the following groups:



In an embodiment, R_1 is C_{1-6} alkyl. In an embodiment, R_1 is C_{1-3} alkyl. In an embodiment, R_1 is methyl or ethyl. In an embodiment, R_1 is methyl. In an embodiment, R_1 is ethyl.

In an embodiment, R_1 is C_1 - C_6 alkyl optionally substituted with 5-membered heteroaryl. In an embodiment, R_1 is C_1 - C_6 alkyl optionally substituted with furyl. In an embodiment, R_1 is CH_2 -furyl.

In an embodiment, R_2 is C_{1-6} alkyl. In an embodiment, R_2 is C_{1-3} alkyl. In an embodiment, R_2 is methyl or ethyl. In an embodiment, R_2 is methyl. In an embodiment, R_2 is ethyl.

In an embodiment, R_2 is C_1 - C_6 alkyl optionally substituted with 5-membered heteroaryl. In an embodiment, R_2 is C_1 - C_6 alkyl optionally substituted with furyl. In an embodiment, R_2 is CH_2 -furyl.

In an embodiment, R_1 and R_2 are identical.

In an embodiment, R_3 is C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, C_3 - C_{10} cycloalkyl, or C_1 - C_6 alkoxy, wherein the C_6 - C_{10} aryl is substituted one, two, or three times with the group R_{3a} , and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b} .

In an embodiment, R_3 is 5- to 10-membered heteroaryl or C_3 - C_{10} cycloalkyl, wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b} .

In an embodiment, R_3 is phenyl, pyrazolyl, pyridinyl, benzofuranyl, benzothiazolyl, benzodioxolyl, C_3 - C_6 cycloalkyl, adamantyl, $C(O)NH$ -(C_1 - C_6 alkyl)- PPh_3 , hydroxy, C_1 - C_6 alkoxy, or O -(C_1 - C_6 alkyl)- O -(C_1 - C_6 alkyl), wherein the phenyl is substituted one, two, or three times with the group R_{3a} ; and wherein the pyrazolyl, pyridinyl, benzofuranyl, benzothiazolyl, and benzodioxolyl are optionally substituted one, two, or three times with the group R_{3b} .

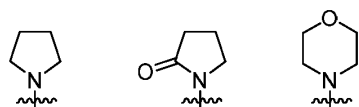
In an embodiment, R_3 is phenyl, pyrazolyl, pyridinyl, benzofuranyl, benzothiazolyl, benzodioxolyl, or C_1 - C_6 alkoxy, wherein the pyrazolyl, pyridinyl, benzofuranyl, benzothiazolyl, and benzodioxolyl are optionally substituted one or two times with the group R_{3b} .

In an embodiment, R_3 is pyridinyl, benzofuranyl, or benzodioxolyl, wherein the pyridinyl, benzofuranyl, and benzodioxolyl are optionally substituted one or two times with the group R_{3b} .

In an embodiment, R_3 is benzofuranyl or benzodioxolyl, wherein the benzofuranyl
5 and benzodioxolyl are optionally substituted one or two times with the group R_{3b} .

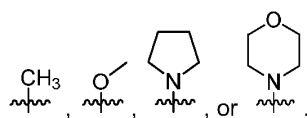
In an embodiment, R_{3a} independently for each occurrence is 4- to 8-membered heterocycle optionally further substituted one, two, or three times with C_1 - C_3 alkyl. In an embodiment, R_{3a} independently for each occurrence is 4- to 8-membered heterocycle optionally further substituted one time with methyl.

10 In an embodiment, R_{3a} independently for each occurrence is pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is optionally further substituted one, two, or three times with C_1 - C_3 alkyl. In an embodiment, R_{3a} independently for each occurrence is pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, or piperazinyl, each of which is
15 optionally further substituted one time with methyl. In an embodiment, R_{3a} independently for each occurrence is pyrrolidinyl, pyrrolidinonyl, or morpholinyl. In an embodiment, R_{3a} independently for each occurrence is represented by a group selected from the following:



In an embodiment, R_{3b} independently for each occurrence is C_1 - C_3 alkyl, C_1 - C_3
20 alkoxy, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl. In an embodiment, R_{3b} independently for each occurrence is C_1 - C_3 alkoxy or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one time with methyl.

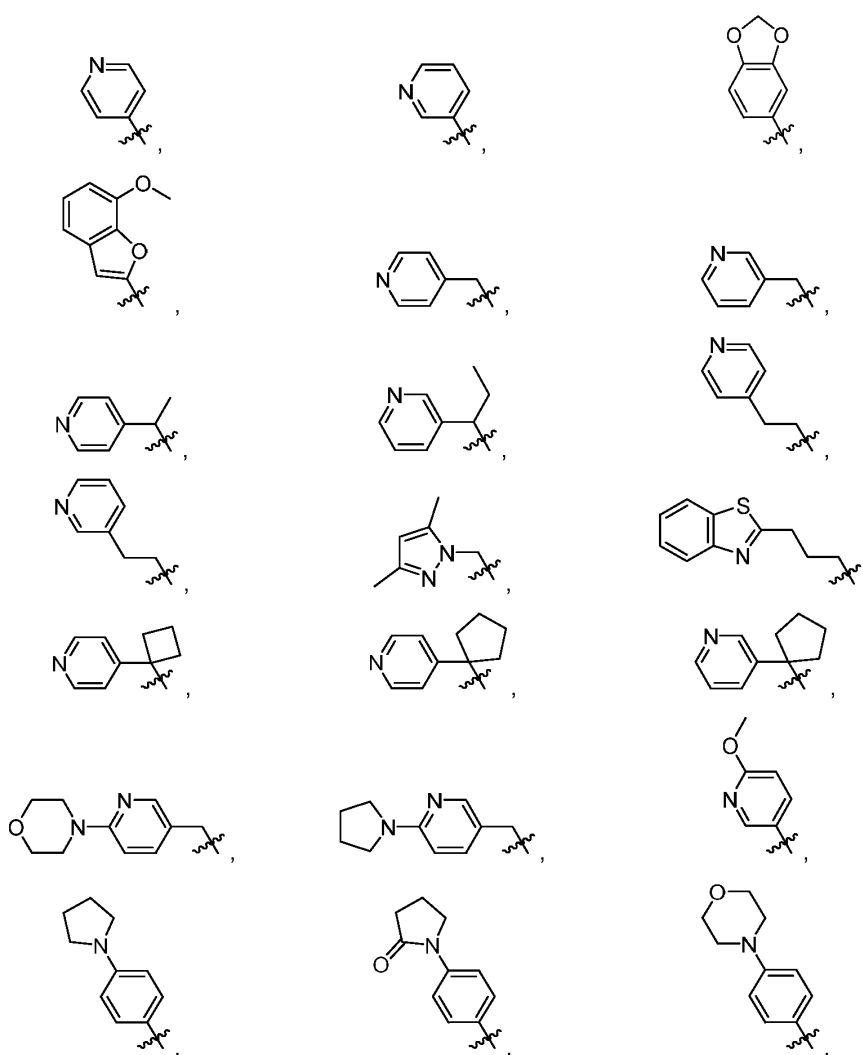
In an embodiment, R_{3b} independently for each occurrence is C_1 - C_3 alkyl, C_1 - C_3
25 alkoxy, or a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl, wherein the heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl. In an embodiment, R_{3b} independently for each occurrence is C_1 - C_3 alkyl, C_1 - C_3 alkoxy or a heterocycle selected from the group consisting of pyrrolidinyl, pyrrolidinonyl,
30 tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl, wherein the heterocycle is optionally further substituted one time with methyl. In an embodiment, R_{3b} independently for each occurrence is methyl, methoxy or a heterocycle selected from the group consisting of pyrrolidinyl and morpholinyl. In an embodiment, R_{3b} independently for each occurrence is represented by a group selected from:

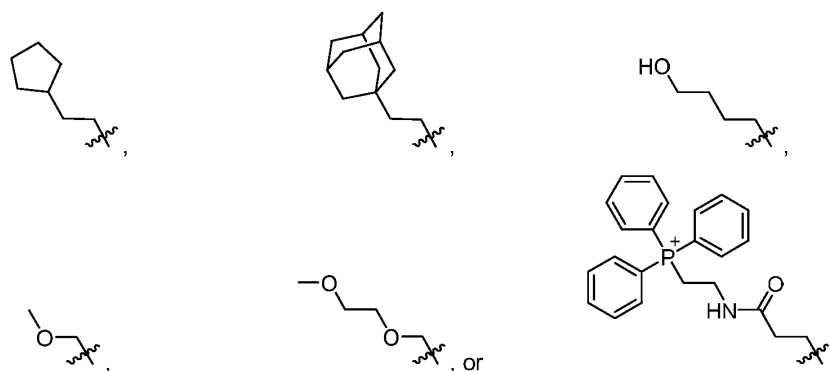


- In an embodiment, R_4 is hydrogen, C_1 - C_3 alkyl, or phenyl. In an embodiment, R_4 is hydrogen, methyl, or phenyl. In an embodiment, R_4 is hydrogen or C_1 - C_3 alkyl. In an embodiment, R_4 is hydrogen or methyl. In an embodiment, R_4 is hydrogen. In an embodiment, R_4 is methyl. In an embodiment, R_4 is phenyl.

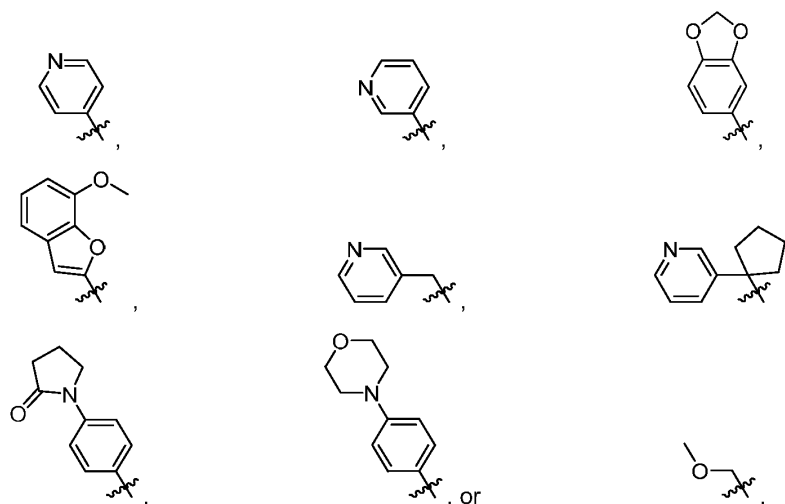
In an embodiment, L is C_1 - C_6 alkyl, and R_3 is C_1 - C_6 alkoxy.

In an embodiment, the group represented by R_3 -L is represented by one of the following:





In an embodiment, the group represented by R_3-L is represented by one of the following:



In an embodiment, R₃ is pyridinyl optionally substituted one, two, or three times with C₁-C₃ alkoxy or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally substituted one time with C₁-C₃ alkyl.

In an embodiment, when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}. In another embodiment, when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl optionally substituted one, two, or three times with the group R_{3b}, and R₄ is H.

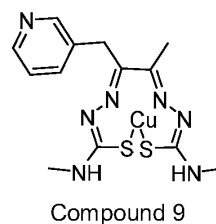
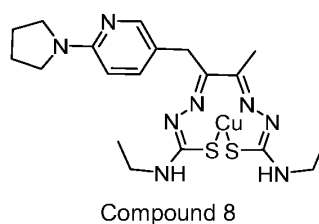
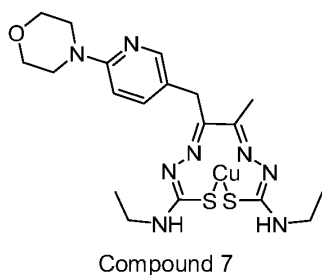
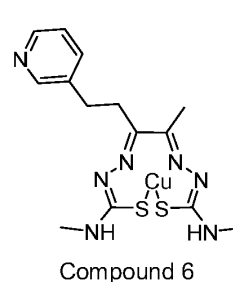
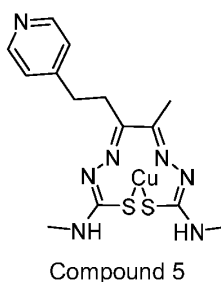
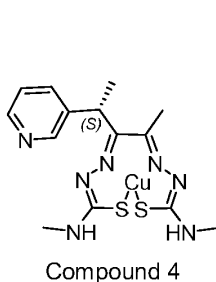
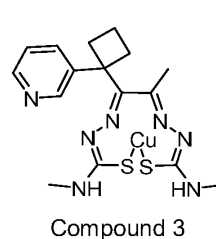
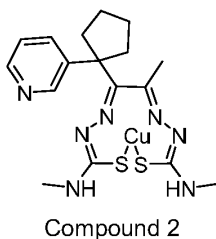
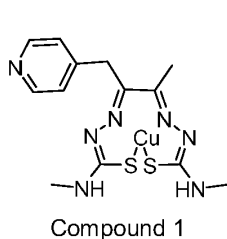
In an embodiment, when L is absent, R₃ is pyridinyl substituted one, two, or three times with C₁-C₃ alkoxy.

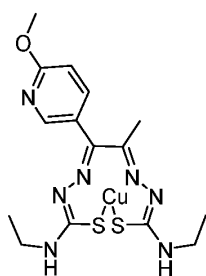
In an embodiment, when L is absent, R₃ is phenyl substituted with 4- to 8-membered heterocycle.

In an embodiment, when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}.

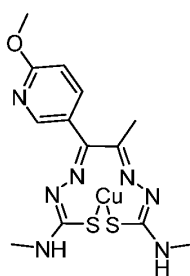
In an embodiment, L is C₃-C₅ cycloalkyl or C₁-C₃ alkyl; R₃ is pyridinyl optionally substituted one, two, or three times with 4- to 8-membered heterocycle; and R₄ is methyl.

Exemplary compounds of Formula (IV) include the following compounds, or pharmaceutically acceptable salts thereof:

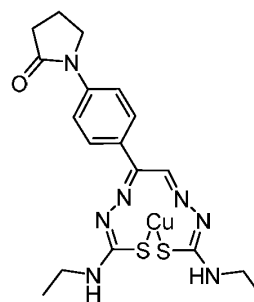




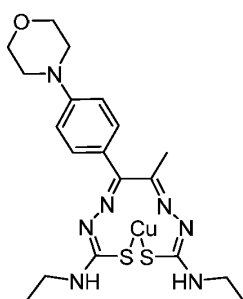
Compound 10



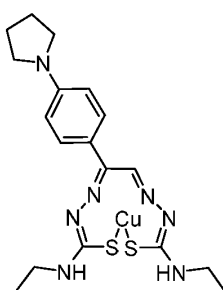
Compound 11



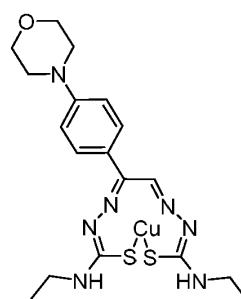
Compound 12



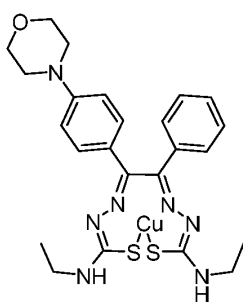
Compound 13



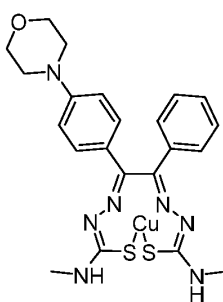
Compound 14



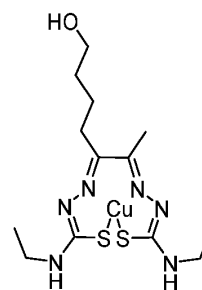
Compound 15



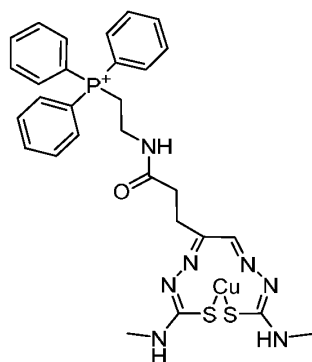
Compound 16



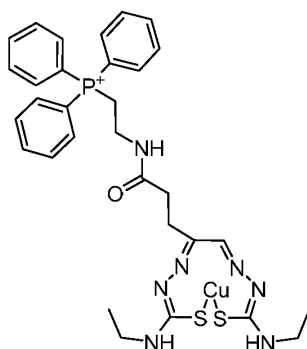
Compound 17



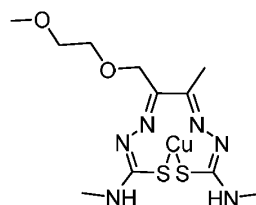
Compound 18



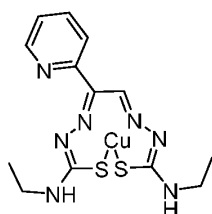
Compound 19



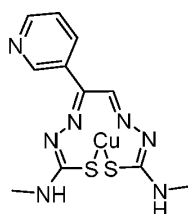
Compound 21



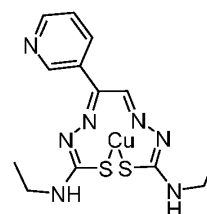
Compound 22



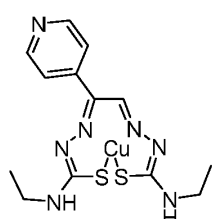
Compound 57



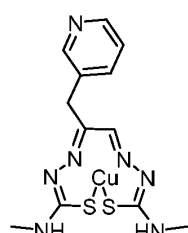
Compound 59



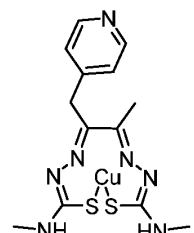
Compound 60



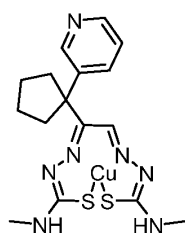
Compound 61



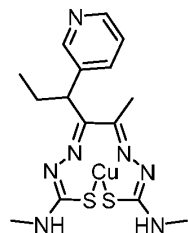
Compound 66



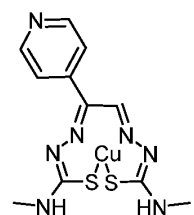
Compound 67



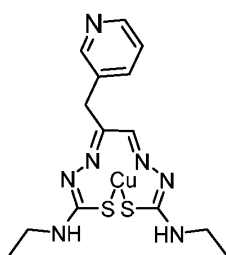
Compound 68



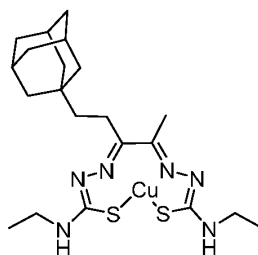
Compound 69



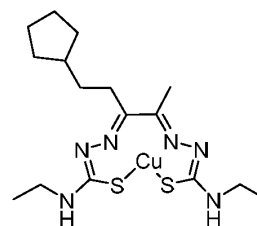
Compound 70



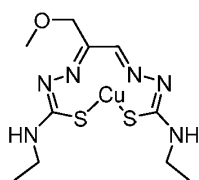
Compound 71



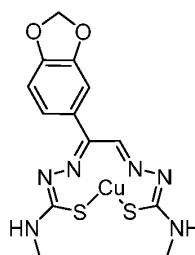
Compound 72



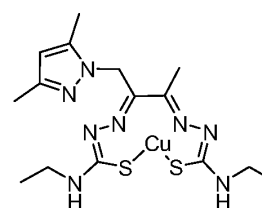
Compound 73



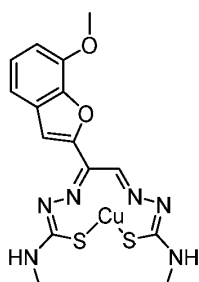
Compound 74



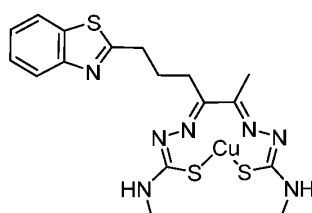
Compound 75



Compound 76

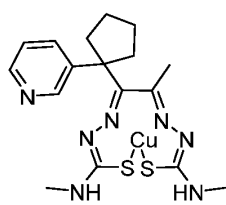


Compound 77

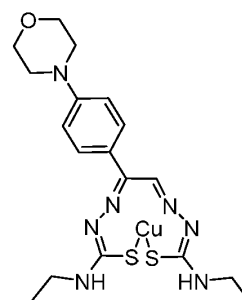
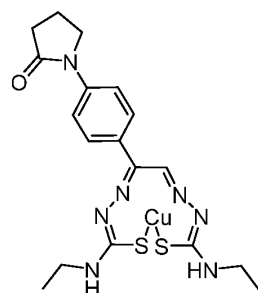


Compound 78

In an embodiment, the compound of Formula (IV) is one of the following compounds, or a pharmaceutically acceptable salt thereof:

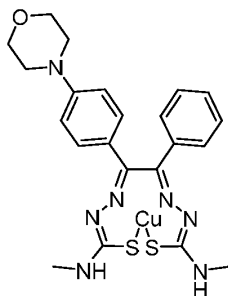


Compound 2

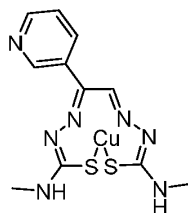


Compound 12

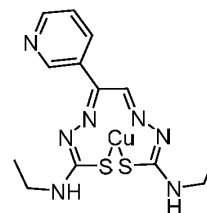
Compound 15



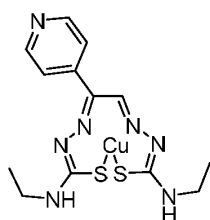
Compound 17



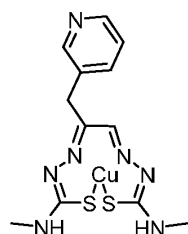
Compound 59



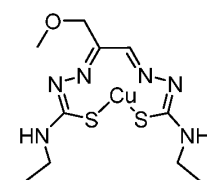
Compound 60



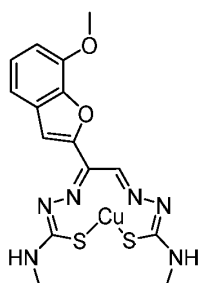
Compound 61



Compound 66

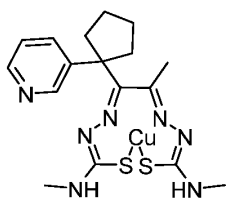


Compound 74

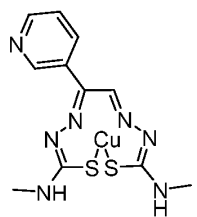


Compound 77

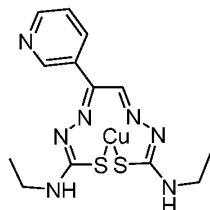
In an embodiment, the compound of Formula (IV) has the structure of Compound 2:



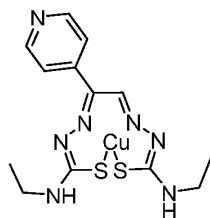
In an embodiment, the compound of Formula (IV) has the structure of Compound 59:



In an embodiment, the compound of Formula (IV) has the structure of Compound 60:

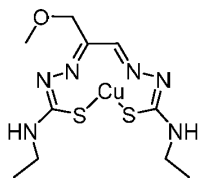


In an embodiment, the compound of Formula (IV) has the structure of Compound 61:

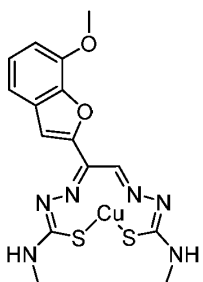


5

In an embodiment, the compound of Formula (IV) has the structure of Compound 74:

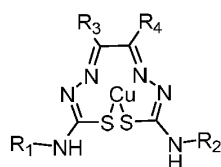


In an embodiment, the compound of Formula (IV) has the structure of Compound 74:



10

In another aspect, provided herein are compounds of Formula (V):



(V),

or pharmaceutically acceptable salts thereof, wherein:

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂,

5 NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂,

NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is 4- to 8-membered heterocycle or 5-membered heteroaryl, wherein the 4- to 8-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a},

10 and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkyl-(C₆-C₁₀ aryl), C₁-C₆ alkyl-(5- to 10-membered heteroaryl), S(O)₂H, S(O)₂-(C₁-C₆ alkyl), S(O)₂-(C₃-C₇ cycloalkyl), or S(O)₂-(C₆-C₁₀ aryl); wherein each heteroaryl is optionally further substituted one to four

15 times with C₁-C₆ alkyl or C₆-C₁₀ aryl; and wherein each C₆-C₁₀ aryl is optionally further substituted one to four times with C₁-C₆ alkyl;

R_{3b} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ alkyl-N(R₅)₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), halo, nitro, cyano, C₆-C₁₀ aryl, C(O)-(4- to 8-membered heterocycle), C₁-C₆ alkyl-(C₆-C₁₀ aryl), C₁-C₆ alkyl-(5- to 10-membered

20 heteroaryl), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo;

R₄ is hydrogen or C₁₋₃ alkyl; and

25 R₅ independently for each occurrence is hydrogen, C₁-C₆ alkyl, or C₁-C₃ alkyl-(C₆-C₁₀ aryl).

In an embodiment, R₁ is C₁₋₆ alkyl. In an embodiment, R₁ is C₁₋₃ alkyl. In an embodiment, R₁ is methyl or ethyl. In an embodiment, R₁ is methyl. In an embodiment, R₁ is ethyl.

In an embodiment, R₁ is C₁-C₆ alkyl optionally substituted with 5-membered heteroaryl. In an embodiment, R₁ is C₁-C₆ alkyl optionally substituted with furyl. In an embodiment, R₁ is CH₂-furyl.

In an embodiment, R₂ is C₁₋₆ alkyl. In an embodiment, R₂ is C₁₋₃ alkyl. In an embodiment, R₂ is methyl or ethyl. In an embodiment, R₂ is methyl. In an embodiment, R₂ is ethyl.

5 In an embodiment, R₂ is C₁₋₆ alkyl optionally substituted with 5-membered heteroaryl. In an embodiment, R₂ is C₁₋₆ alkyl optionally substituted with furyl. In an embodiment, R₂ is CH₂-furyl.

In an embodiment, R₁ and R₂ are identical.

10 In an embodiment, R₃ is 5- to 6-membered heterocycle or 5-membered heteroaryl, wherein the 5- to 6-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a}, and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b}.

15 In an embodiment, R₃ is tetrahydrofuranyl, morpholinyl, piperidinyl, furyl, thiophenyl, pyrrolyl, oxazolyl, pyrazolyl, or imidazolyl, wherein the tetrahydrofuranyl, morpholinyl, and piperidinyl are optionally substituted one, two, or three times with the group R_{3a}, and wherein the furyl, thiophenyl, pyrrolyl, oxazolyl, pyrazolyl, and imidazolyl are optionally substituted one, two, or three times with the group R_{3b}.

20 In an embodiment, R₃ is furyl, thiophenyl, oxazolyl, pyrazolyl, or imidazolyl optionally substituted one, two, or three times with the group R_{3b}. In another embodiment, R₃ is furyl, thiophenyl, oxazolyl, pyrazolyl, or imidazolyl substituted one, two, or three times with the group R_{3b}.

In an embodiment, R₃ is furyl optionally substituted one, two, or three times with the group R_{3b}. In another embodiment, R₃ is furyl substituted one, two, or three times with the group R_{3b}.

25 In an embodiment, R₃ is thiophenyl optionally substituted one, two, or three times with the group R_{3b}. In another embodiment, R₃ is thiophenyl substituted one, two, or three times with the group R_{3b}.

In an embodiment, R₃ is oxazolyl optionally substituted one, two, or three times with the group R_{3b}. In another embodiment, R₃ is oxazolyl substituted one, two, or three times with the group R_{3b}.

30 In an embodiment, R₃ is pyrazolyl optionally substituted one, two, or three times with the group R_{3b}. In another embodiment, R₃ is pyrazolyl substituted one, two, or three times with the group R_{3b}.

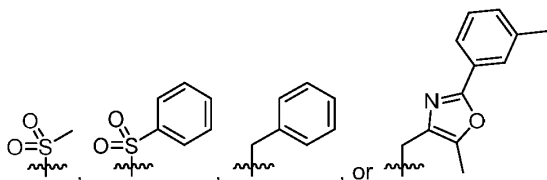
35 In an embodiment, R₃ is imidazolyl optionally substituted one, two, or three times with the group R_{3b}. In another embodiment, R₃ is imidazolyl substituted one, two, or three times with the group R_{3b}.

In an embodiment, R₃ is tetrahydrofuranyl, morpholinyl, or piperidinyl, each of which is optionally substituted one, two, or three times with the group R_{3a}.

In an embodiment, R_{3a} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl-
(C_6 - C_{10} aryl), C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), $S(O)_2$ -(C_1 - C_6 alkyl), or $S(O)_2$ -(C_6 -
 C_{10} aryl), wherein each heteroaryl is optionally further substituted one to four times with C_1 -
 C_6 alkyl or C_6 - C_{10} aryl; and wherein each C_6 - C_{10} aryl is optionally further substituted one to
5 four times with C_1 - C_6 alkyl.

In an embodiment, R_{3a} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl-
(phenyl), C_1 - C_6 alkyl-(5- to 6-membered heteroaryl), $S(O)_2$ -(C_1 - C_6 alkyl), or $S(O)_2$ -(phenyl),
wherein each heteroaryl is optionally further substituted one to four times with C_1 - C_3 alkyl or
phenyl; and wherein each phenyl is optionally further substituted one to four times with C_1 - C_3
10 alkyl.

In an embodiment, R_{3a} independently for each occurrence is:



In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl-
 $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, C_6 - C_{10} aryl, C(O)-(4- to 8-membered
15 heterocycle), C_1 - C_6 alkyl-(C_6 - C_{10} aryl), C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6
alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C_6 - C_{10}
aryl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times
with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl-
20 $N(R_5)_2$, halo, C_6 - C_{10} aryl, C_1 - C_6 alkyl-(4- to 8-membered heterocycle), or C_1 - C_6 alkyl-(C_6 - C_{10}
aryl), wherein each 4- to 8-membered heterocycle and C_6 - C_{10} aryl are optionally further
substituted one to four times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_3 alkyl-
 $N(R_5)_2$, halo, phenyl, C_1 - C_3 alkyl-(5- to 6-membered heterocycle), or C_1 - C_6 alkyl-phenyl,
25 wherein each 5- to 6-membered heterocycle and phenyl are optionally further substituted
one to four times with C_1 - C_3 alkyl or halo.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl-
 $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, C_6 - C_{10} aryl, C(O)-(4- to 8-membered
heterocycle), C_1 - C_6 alkyl-(C_6 - C_{10} aryl), C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6
30 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C_6 - C_{10}
aryl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times
with $-CH_3$, $-CH_2CH_3$, $-OCH_3$, $-CH_2F$, CHF_2 , $-CF_3$, $-F$, or $-Cl$.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl- $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, phenyl, C(O)-(4- to 8-membered heterocycle), C_1 - C_6 alkyl-phenyl, C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle); wherein each 4- to 8-membered heterocycle is

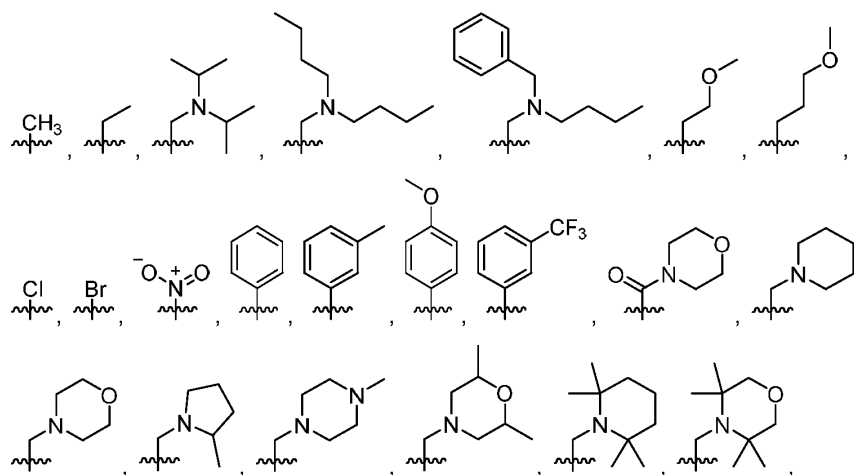
5 independently selected from the group consisting of pyrrolidinyl, pyrrolidinonyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, and piperazinyl; wherein each 5- to 10-membered heteroaryl is selected from the group consisting of furyl and tetrahydroisoquinolinyl; and wherein each 4- to 8-membered heterocycle, phenyl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times with $-CH_3$, -

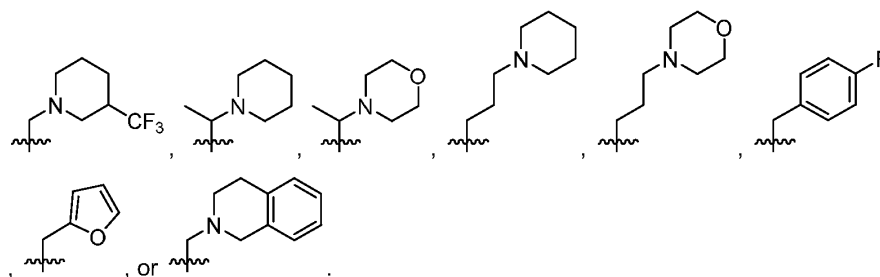
10 CH_2CH_3 , $-OCH_3$, $-CH_2F$, CHF_2 , $-CF_3$, $-F$, or $-Cl$.

In an embodiment, R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl- $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, phenyl, C(O)-(4- to 8-membered heterocycle), C_1 - C_6 alkyl-phenyl, C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle); wherein each 4- to 8-membered heterocycle is

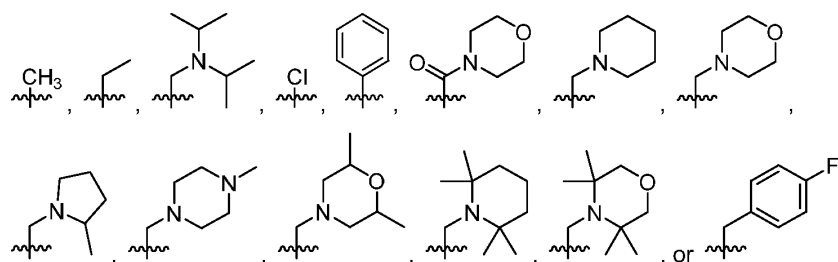
15 independently selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl, and piperazinyl; wherein each 5- to 10-membered heteroaryl is selected from the group consisting of furyl and tetrahydroisoquinolinyl; and wherein each 4- to 8-membered heterocycle, phenyl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times with $-CH_3$, $-OCH_3$, $-CF_3$, or $-F$.

20 In an embodiment, R_{3b} independently for each occurrence is:

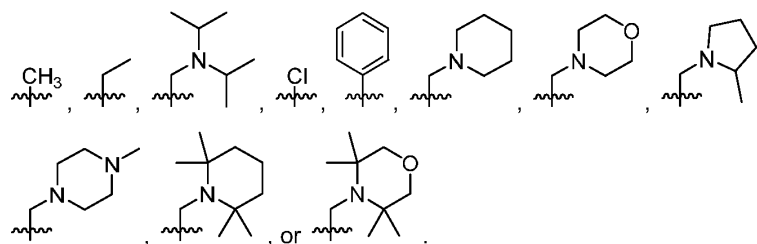




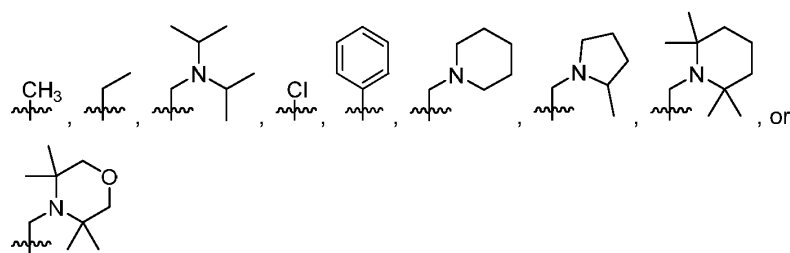
In an embodiment, R_{3b} independently for each occurrence is:



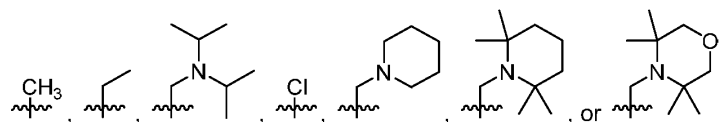
In an embodiment, R_{3b} independently for each occurrence is:



In an embodiment, R_{3b} independently for each occurrence is:



In an embodiment, R_{3b} independently for each occurrence is:



In an embodiment, R₃ is furyl optionally substituted one, two, or three times with C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ alkyl-N(R₅)₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), halo, nitro, cyano, C₆-C₁₀ aryl, C(O)-(4- to 8-membered heterocycle), C₁-C₆ alkyl-(C₆-C₁₀ aryl), C₁-

C₆ alkyl-(5- to 10-membered heteroaryl), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo.

5 In an embodiment, R₃ is furyl optionally substituted one, two, or three times with C₁-C₆ alkyl, C₁-C₆ alkyl-N(R₅)₂, halo, C(O)-(4- to 8-membered heterocycle), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo.

In an embodiment, R₃ is furyl optionally substituted one, two, or three times with C₁-C₆ alkyl-N(R₅)₂ or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo.

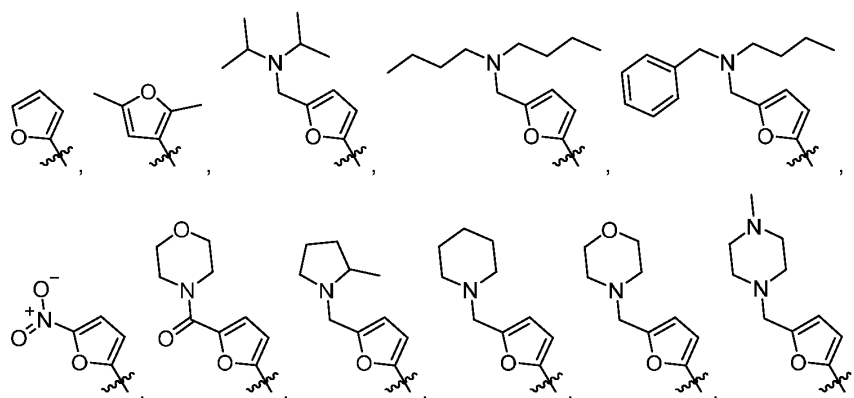
In an embodiment, R₃ is furyl optionally substituted one time with C₁-C₃ alkyl-N(C₁-C₄ alkyl)₂ or C₁-C₃ alkyl-(5- to 6-membered heterocycle), wherein the 5- to 6-membered
15 heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl.

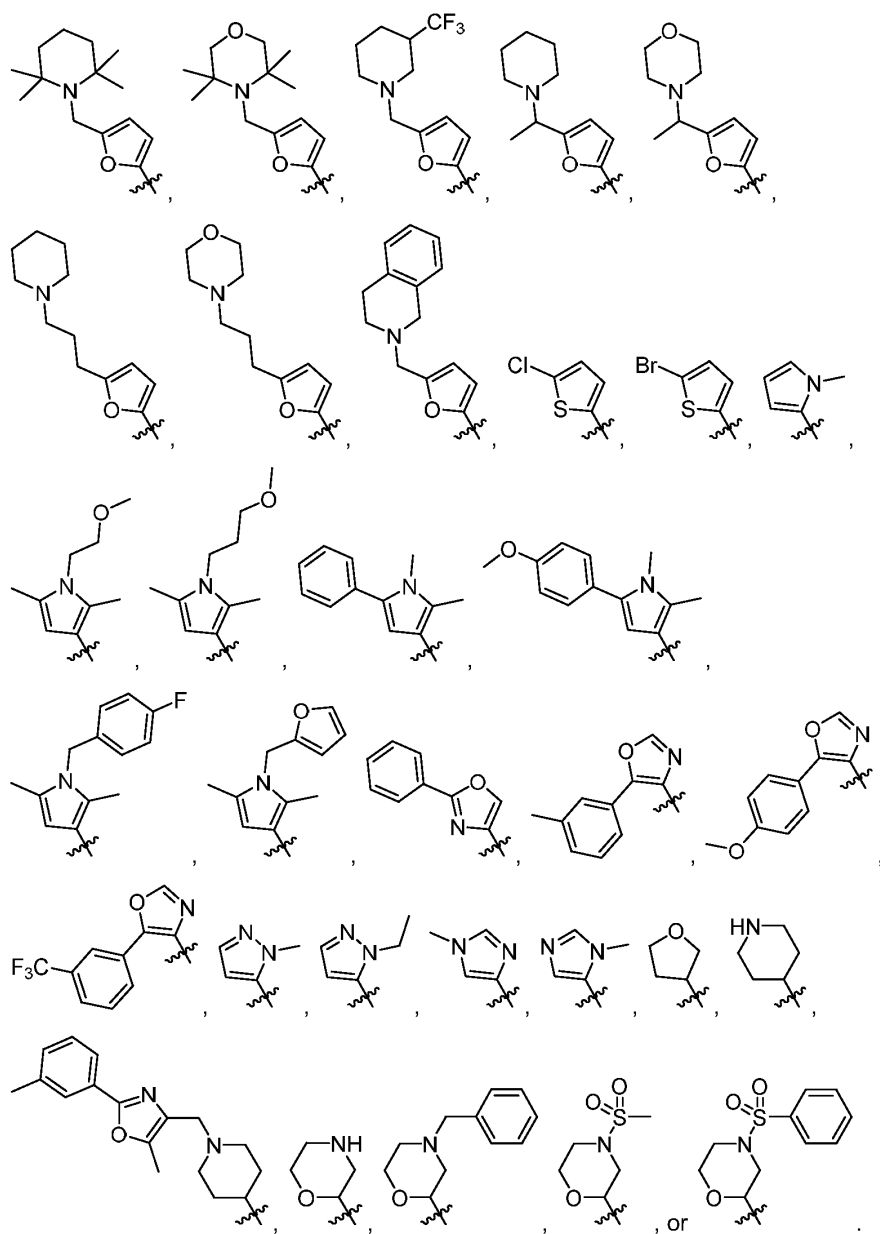
In an embodiment, R₃ is furyl substituted one time with C₁-C₃ alkyl-N(C₁-C₄ alkyl)₂ or C₁-C₃ alkyl-(5- to 6-membered heterocycle), wherein the 5- to 6-membered heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl.

In an embodiment, R₃ is thiophenyl, oxazolyl, pyrazolyl, or imidazolyl, optionally
20 substituted one, two, or three times with C₁-C₆ alkyl, halo, C₆-C₁₀ aryl, or C₁-C₆ alkyl-(C₆-C₁₀ aryl), wherein each C₆-C₁₀ aryl is optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo.

In an embodiment, R₃ is thiophenyl, oxazolyl, pyrazolyl, or imidazolyl, optionally substituted one, two, or three times with methyl, ethyl, halo, phenyl, or C₁-C₃ alkyl-phenyl,
25 wherein each phenyl is optionally further substituted one to four times with C₁-C₃ alkyl or halo.

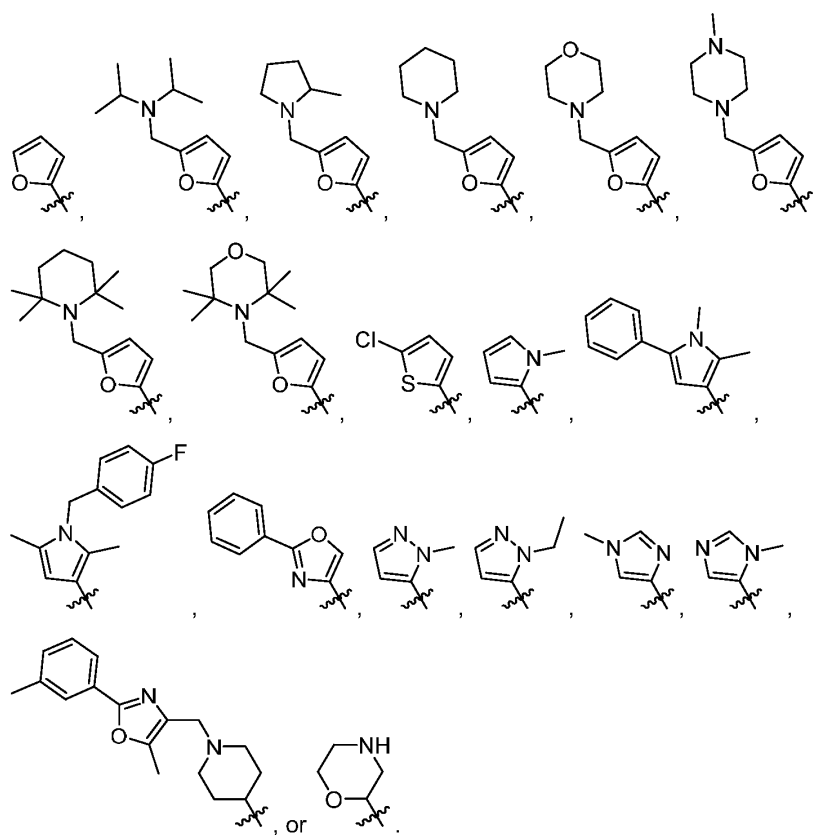
In an embodiment, R₃ is:



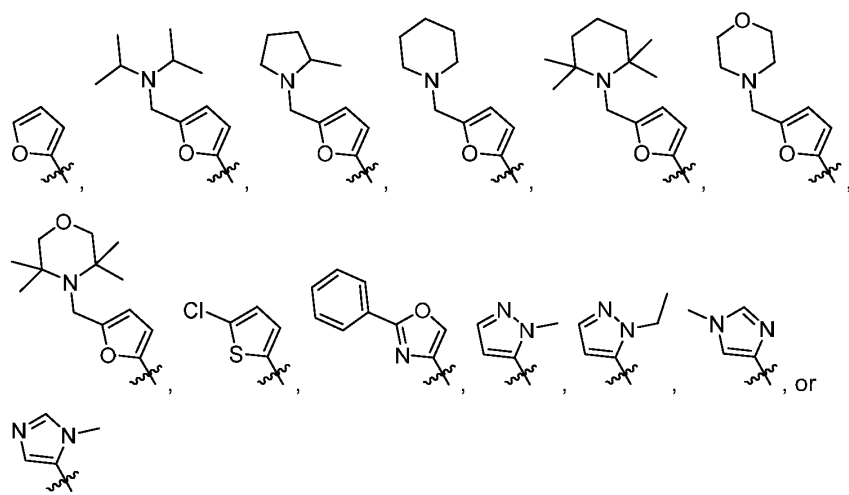


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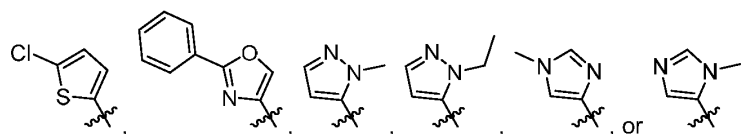
In an embodiment, R₃ is:



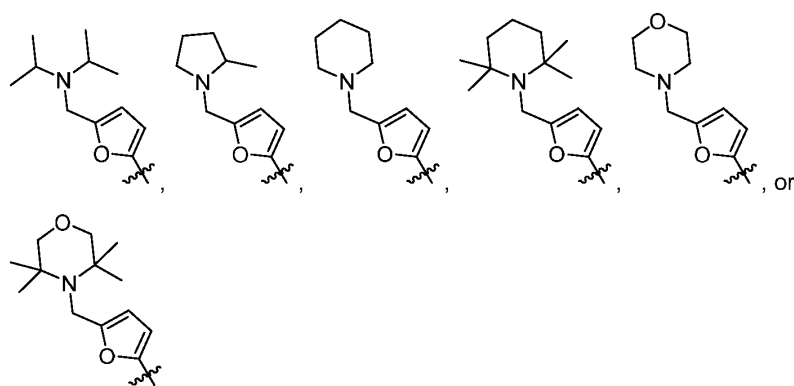
5 In an embodiment, R_3 is:



In an embodiment, R_3 is:



In an embodiment, R_3 is:



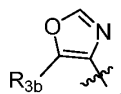
- 5 In an embodiment, R_4 is hydrogen or methyl. In an embodiment, R_4 is hydrogen. In an embodiment, R_4 is methyl.

In an embodiment, R_5 is C_1 - C_6 alkyl or C_1 - C_3 alkyl-(C_6 - C_{10} aryl). In another embodiment, R_5 is C_1 - C_4 alkyl or C_1 - C_3 alkyl-phenyl. In another embodiment, R_5 is C_1 - C_4 alkyl or benzyl.

- 10 In an embodiment, when R_1 is not methyl, R_2 is not methyl, and R_4 is not hydrogen, then R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl- $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, cyano, C_6 - C_{10} aryl, C(O)-(4- to 8-membered heterocycle), C_1 - C_6 alkyl-(C_6 - C_{10} aryl), C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C_6 - C_{10} aryl, and 5- to 10-membered heteroaryl are optionally further substituted
- 15 one or two times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.

- In an embodiment, when R_4 is not hydrogen, then R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl- $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, cyano, C_6 - C_{10} aryl, C(O)-(4- to 8-membered heterocycle), C_1 - C_6 alkyl-(C_6 - C_{10} aryl), C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C_6 - C_{10} aryl, and 5- to 10-membered heteroaryl are optionally further substituted one or two times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.
- 20

In an embodiment, when R_3 is oxazolyl, R_3 does not have the following structure:



In a particular embodiment of the compound of Formula (V), or a pharmaceutically acceptable salt thereof:

R₁ is C₁-C₃ alkyl;

5 R₂ is C₁-C₃ alkyl;

R₃ is a 5-membered heteroaryl that is optionally substituted one, two, or three times with the group R_{3b};

R_{3b} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkyl-N(R₅)₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), halo, C₆-C₁₀ aryl, C(O)-(4- to 8-membered heterocycle), C₁-C₆ alkyl-(C₆-C₁₀ aryl), C₁-C₆ alkyl-(5- to 10-membered heteroaryl), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo;

R₄ is hydrogen or methyl; and

15 R₅ independently for each occurrence is C₁-C₄ alkyl or benzyl.

In another embodiment of the compound of Formula (V), or a pharmaceutically acceptable salt thereof:

R₁ is C₁-C₃ alkyl;

R₂ is C₁-C₃ alkyl;

20 R₃ is a furyl that is optionally substituted one, two, or three times with the group R_{3b};

R_{3b} independently for each occurrence is C₁-C₆ alkyl-N(R₅)₂ or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo;

R₄ is hydrogen or methyl; and

25 R₅ independently for each occurrence is C₁-C₄ alkyl or benzyl.

In another embodiment of the compound of Formula (V), or a pharmaceutically acceptable salt thereof:

R₁ is C₁-C₃ alkyl;

R₂ is C₁-C₃ alkyl;

30 R₃ is a furyl that is optionally substituted one, two, or three times with the group R_{3b};

R_{3b} independently for each occurrence is C₁-C₆ alkyl-N(R₅)₂ or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo;

R₄ is hydrogen or methyl; and

35 R₅ independently for each occurrence is C₁-C₄ alkyl or benzyl;

provided that when R_1 is C_2 - C_3 alkyl, R_2 is C_2 - C_3 alkyl, and R_4 is methyl, then R_{3b} independently for each occurrence is C_1 - C_6 alkyl- $N(R_5)_2$ or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one or two times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.

5 In another embodiment of the compound of Formula (V), or a pharmaceutically acceptable salt thereof:

R_1 is C_1 - C_3 alkyl;

R_2 is C_1 - C_3 alkyl;

R_3 is a furyl that is optionally substituted one, two, or three times with the group R_{3b} ;

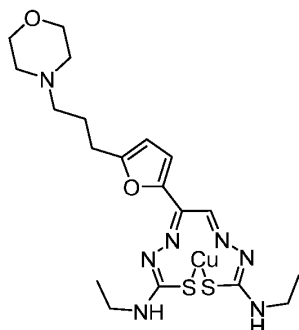
10 R_{3b} independently for each occurrence is C_1 - C_6 alkyl- $N(R_5)_2$ or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one to four times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo;

R_4 is hydrogen or methyl; and

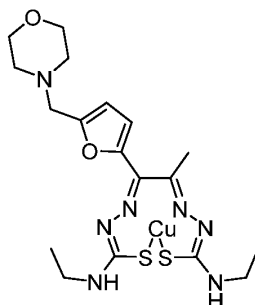
R_5 independently for each occurrence is C_1 - C_4 alkyl or benzyl;

15 provided that when R_4 is methyl, then R_{3b} independently for each occurrence is C_1 - C_6 alkyl- $N(R_5)_2$ or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one or two times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.

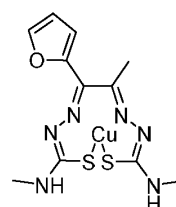
20 Exemplary compounds of Formula (V) include the following compounds, or pharmaceutically acceptable salts thereof:



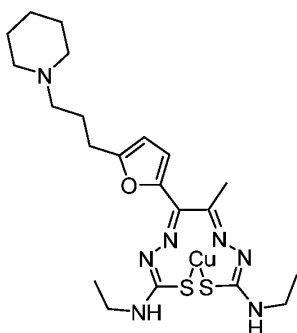
Compound 23



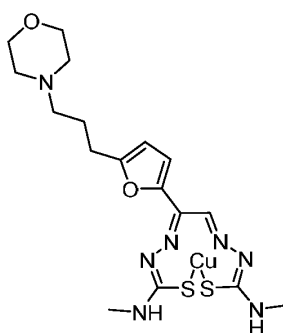
Compound 24



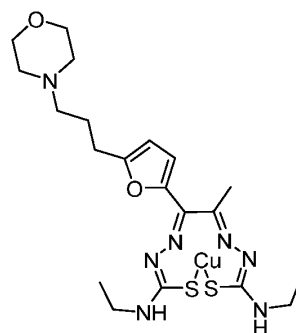
Compound 25



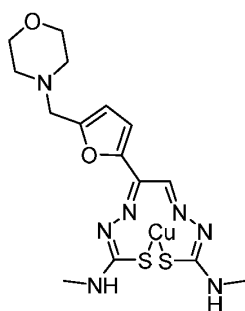
Compound 26



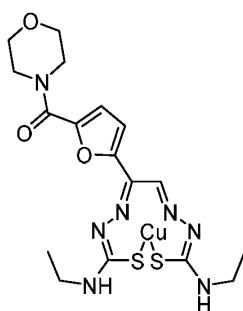
Compound 27



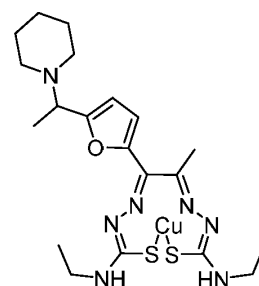
Compound 28



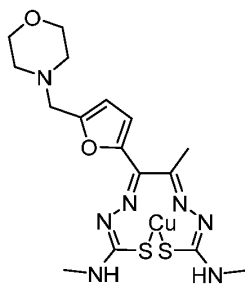
Compound 29



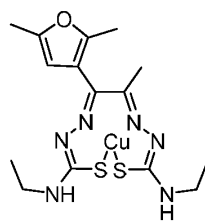
Compound 30



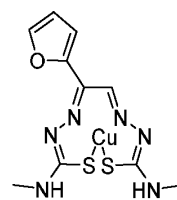
Compound 31



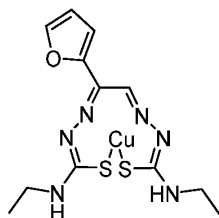
Compound 32



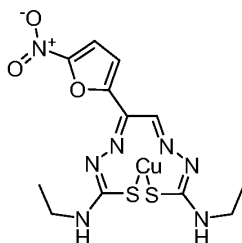
Compound 33



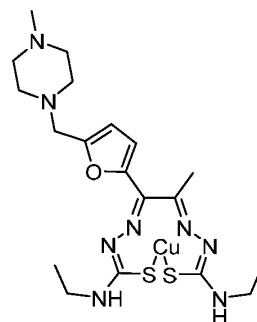
Compound 34



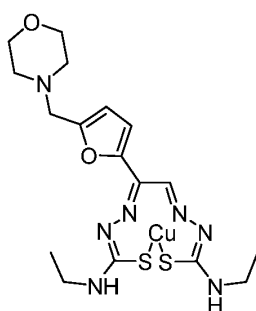
Compound 35



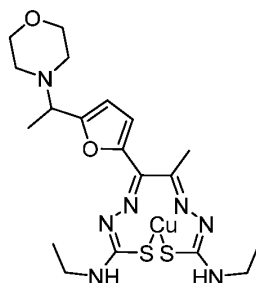
Compound 36



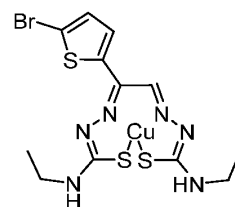
Compound 37



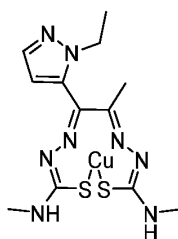
Compound 38



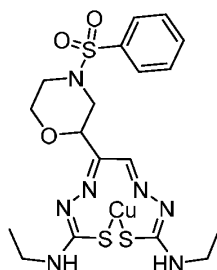
Compound 39



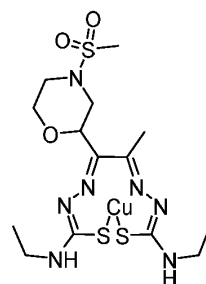
Compound 40



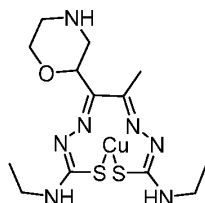
Compound 41



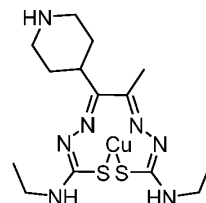
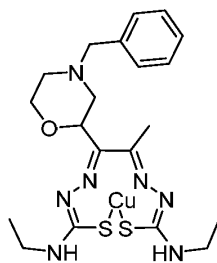
Compound 42



Compound 43

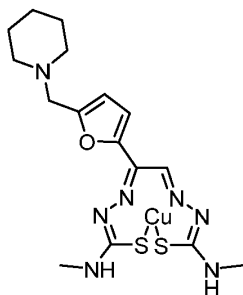


Compound 44

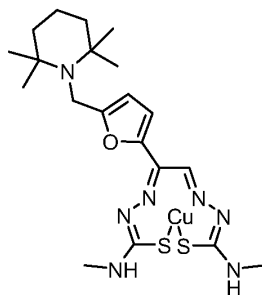


Compound 46.

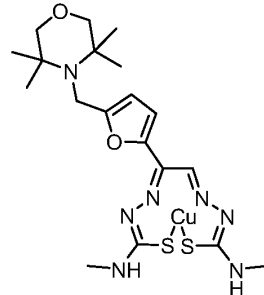
Compound 45



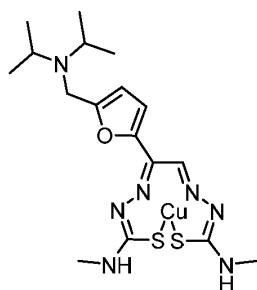
Compound 79



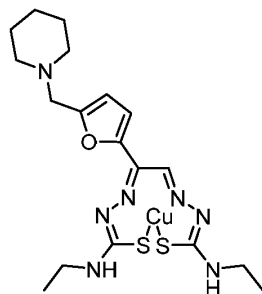
Compound 80



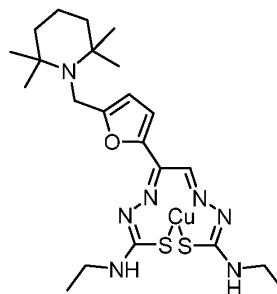
Compound 81



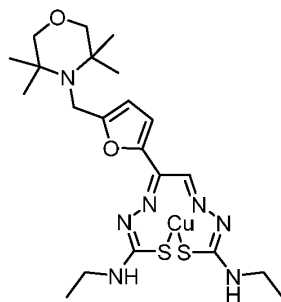
Compound 82



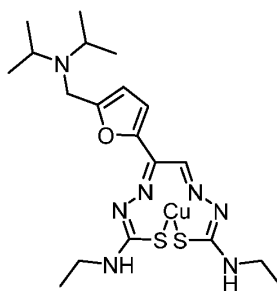
Compound 83



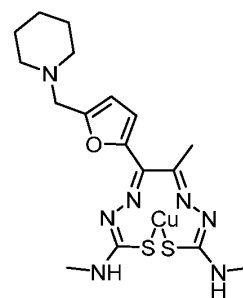
Compound 84



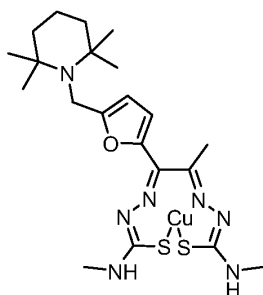
Compound 85



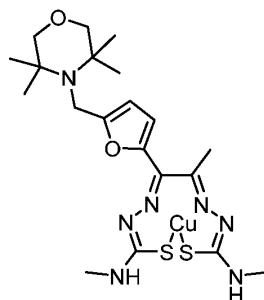
Compound 86



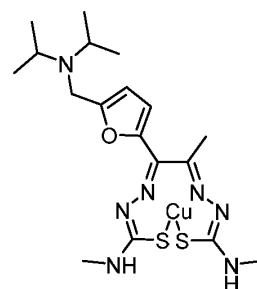
Compound 87



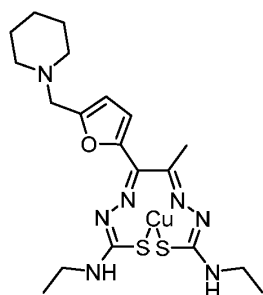
Compound 88



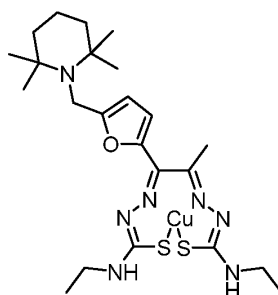
Compound 89



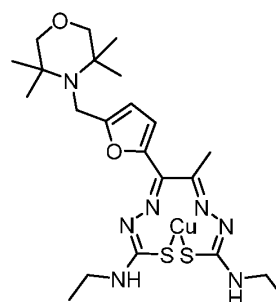
Compound 90



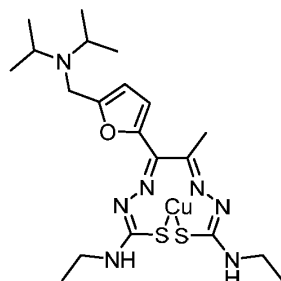
Compound 91



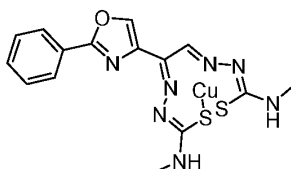
Compound 92



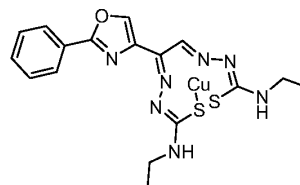
Compound 93



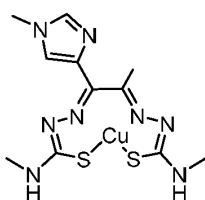
Compound 94



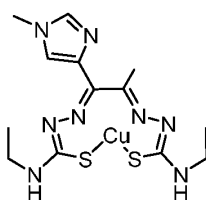
Compound 95



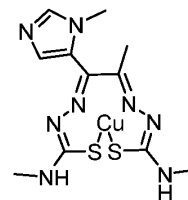
Compound 96



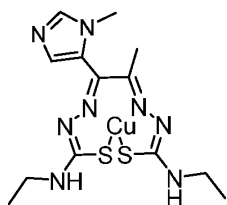
Compound 97



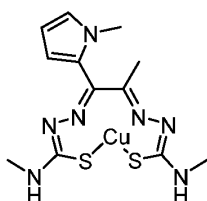
Compound 98



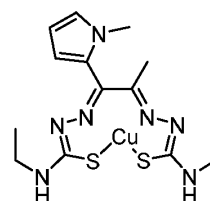
Compound 99



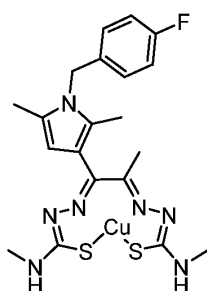
Compound 100



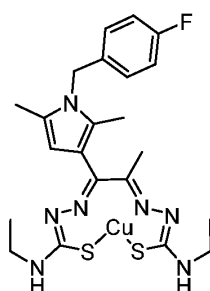
Compound 101



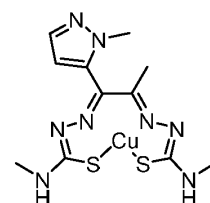
Compound 102



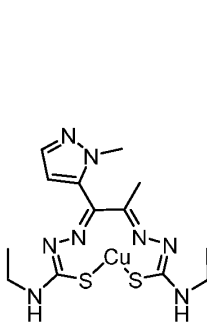
Compound 103



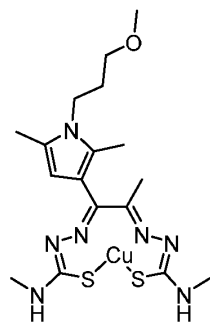
Compound 104



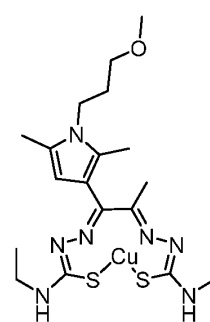
Compound 105



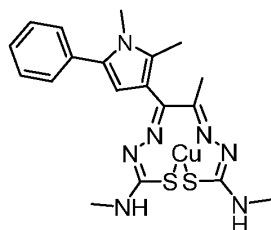
Compound 106



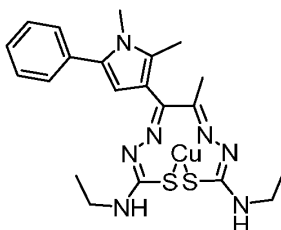
Compound 107



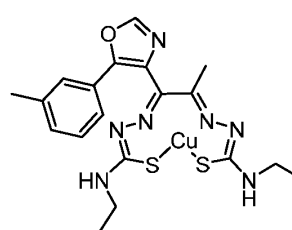
Compound 108



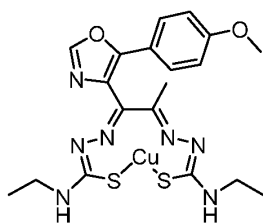
Compound 109



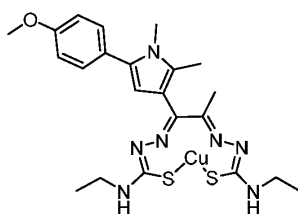
Compound 110



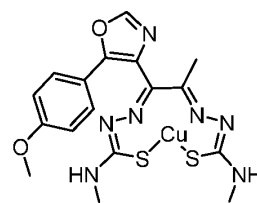
Compound 111



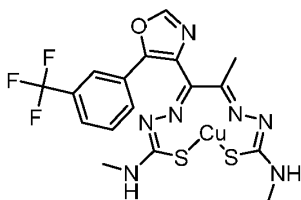
Compound 112



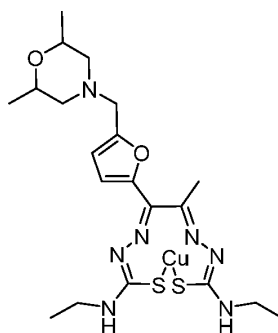
Compound 113



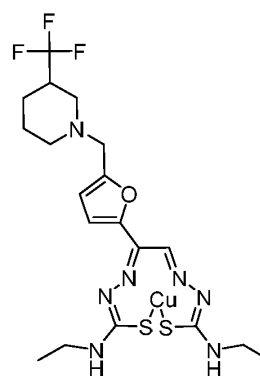
Compound 114



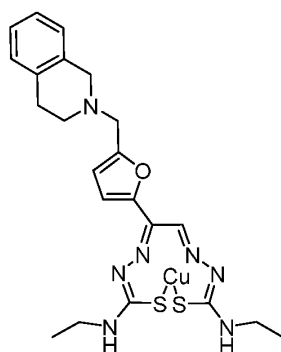
Compound 115



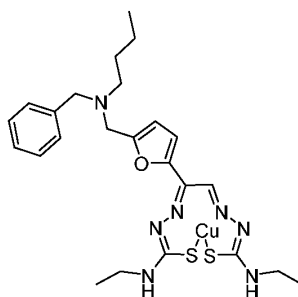
Compound 116



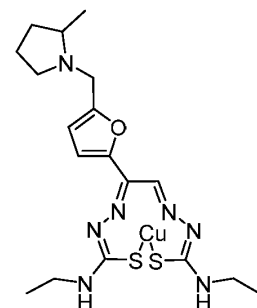
Compound 117



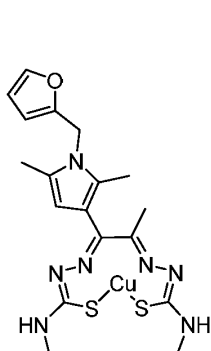
Compound 118



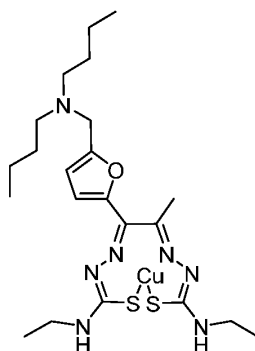
Compound 119



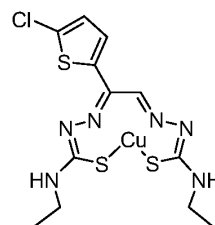
Compound 120



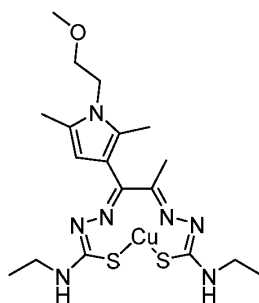
Compound 121



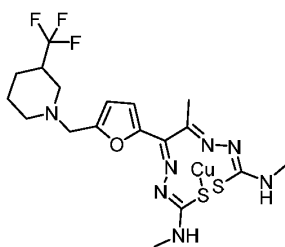
Compound 122



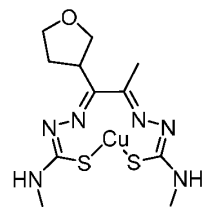
Compound 123



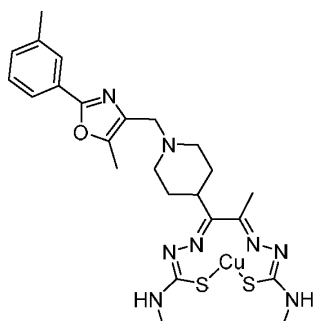
Compound 124



Compound 125

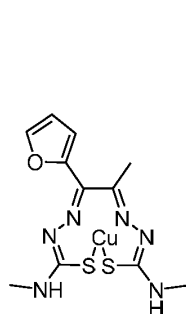


Compound 126

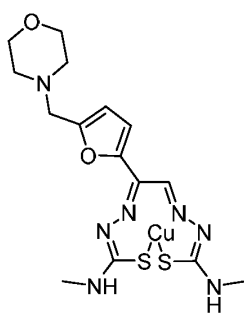


Compound 127

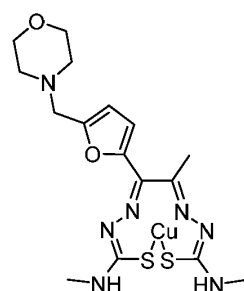
In an embodiment, the compound of Formula (V) is one of the following compounds, or a pharmaceutically acceptable salt thereof:



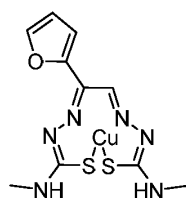
Compound 25



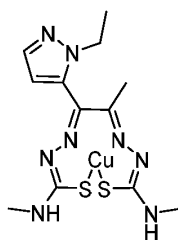
Compound 29



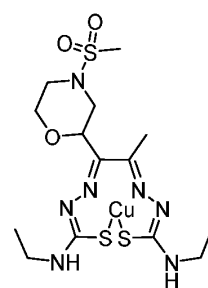
Compound 32



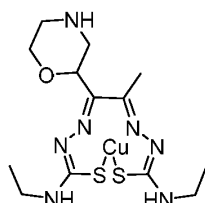
Compound 34



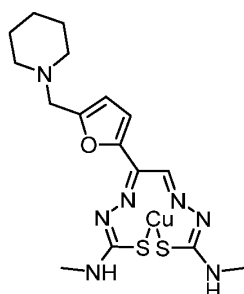
Compound 41



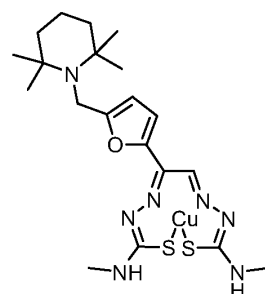
Compound 43



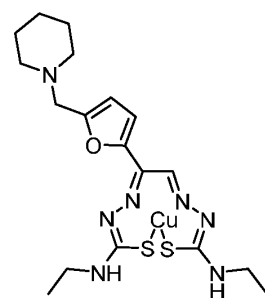
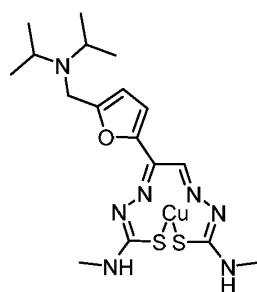
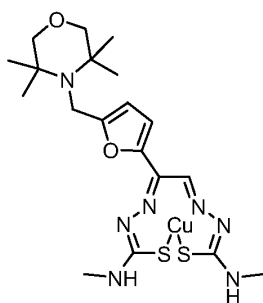
Compound 44



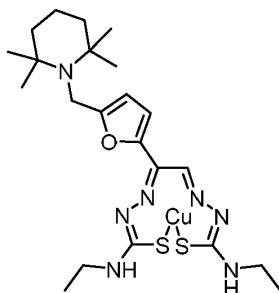
Compound 79



Compound 80

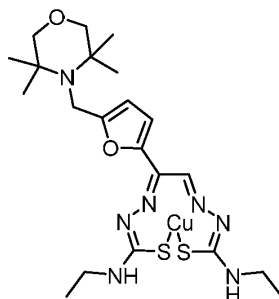


Compound 81



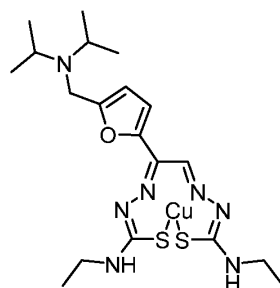
Compound 84

Compound 82

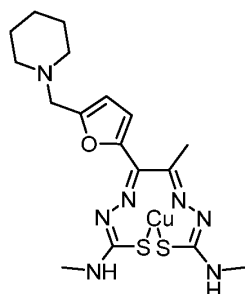


Compound 85

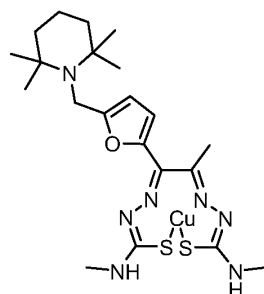
Compound 83



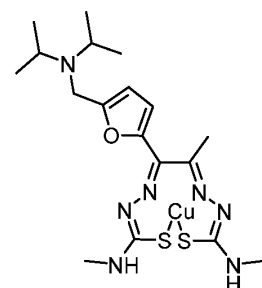
Compound 86



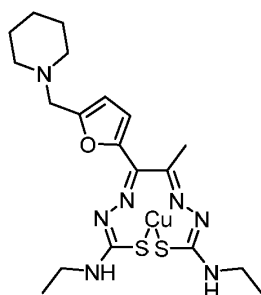
Compound 87



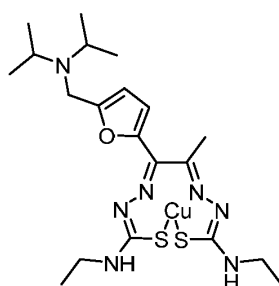
Compound 88



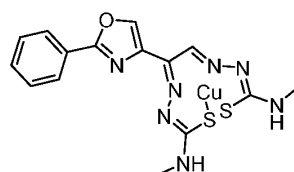
Compound 90



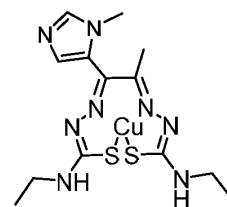
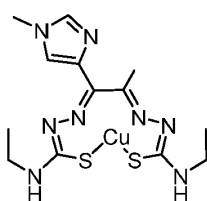
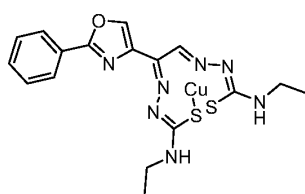
Compound 91



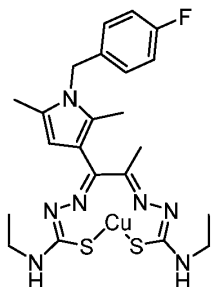
Compound 94



Compound 95

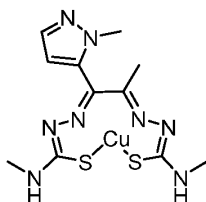


Compound 96



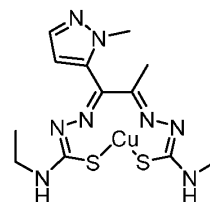
Compound 104

Compound 98

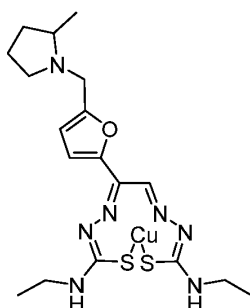


Compound 105

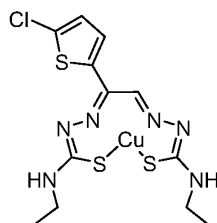
Compound 100



Compound 106

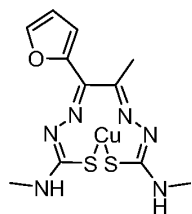


Compound 120

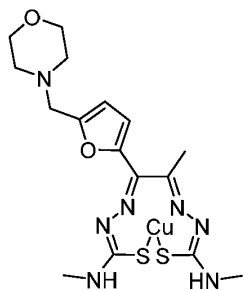


Compound 123

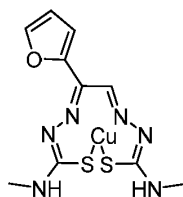
In an embodiment, the compound of Formula (V) has the structure of Compound 25:



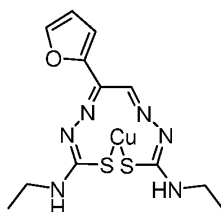
In an embodiment, the compound of Formula (V) has the structure of Compound 32:



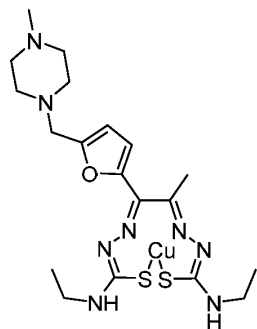
In an embodiment the compound of Formula (V) has the structure of Compound 34:



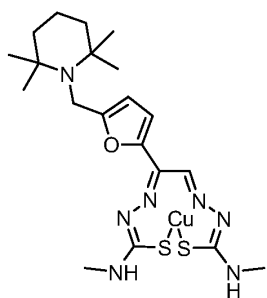
In an embodiment the compound of Formula (V) has the structure of Compound 35:



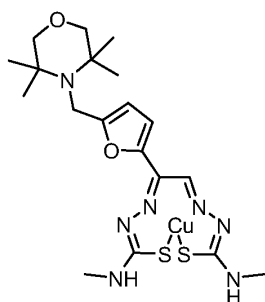
5 In an embodiment the compound of Formula (V) has the structure of Compound 37:



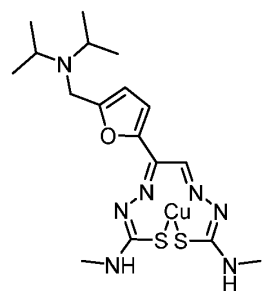
In an embodiment the compound of Formula (V) has the structure of Compound 80:



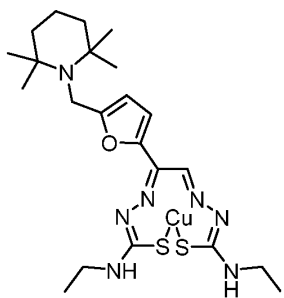
In an embodiment the compound of Formula (V) has the structure of Compound 81:



In an embodiment the compound of Formula (V) has the structure of Compound 82:

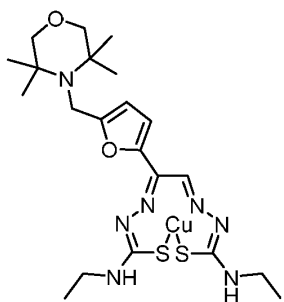


In an embodiment the compound of Formula (V) has the structure of Compound 84:

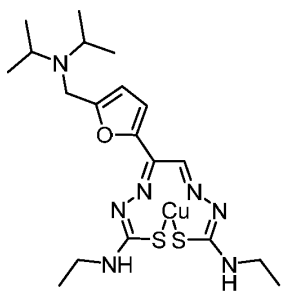


5

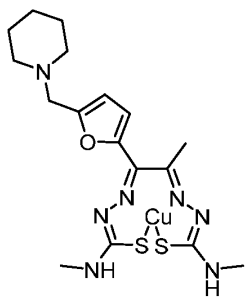
In an embodiment the compound of Formula (V) has the structure of Compound 85:



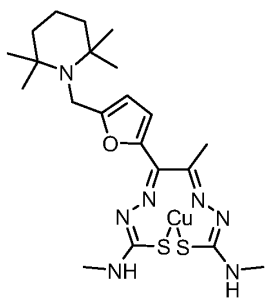
In an embodiment the compound of Formula (V) has the structure of Compound 86:



In an embodiment the compound of Formula (V) has the structure of Compound 87:

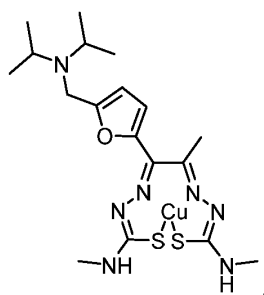


In an embodiment the compound of Formula (V) has the structure of Compound 88:

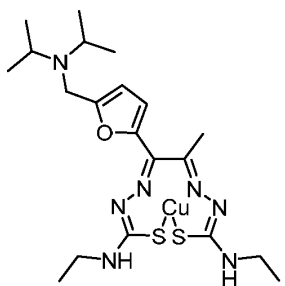


5

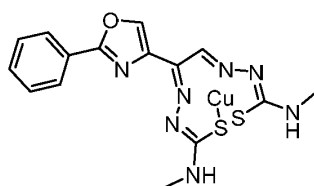
In an embodiment the compound of Formula (V) has the structure of Compound 90:



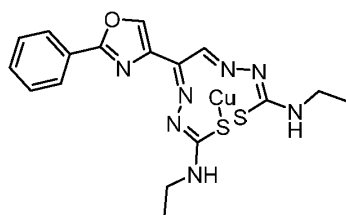
In an embodiment the compound of Formula (V) has the structure of Compound 94:



In an embodiment the compound of Formula (V) has the structure of Compound 95:

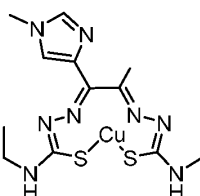


In an embodiment the compound of Formula (V) has the structure of Compound 96:

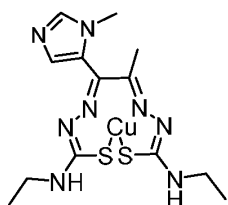


5

In an embodiment the compound of Formula (V) has the structure of Compound 98:

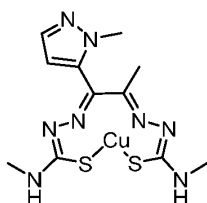


In an embodiment the compound of Formula (V) has the structure of Compound 100:

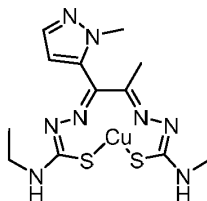


10

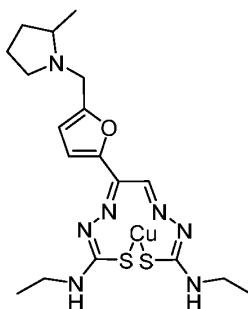
In an embodiment the compound of Formula (V) has the structure of Compound 105:



In an embodiment the compound of Formula (V) has the structure of Compound 106:

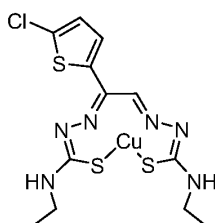


In an embodiment the compound of Formula (V) has the structure of Compound 120:

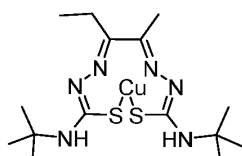
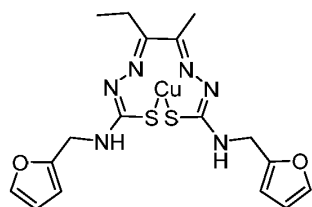


5

In an embodiment the compound of Formula (V) has the structure of Compound 123:



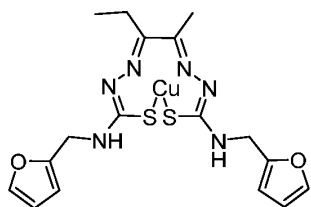
Another aspect of the present disclosure is a compound selected from the group
 10 consisting of the compounds described below, or a pharmaceutically acceptable salt thereof:



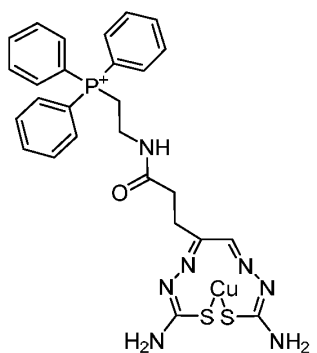
Compound 55.

Compound 54

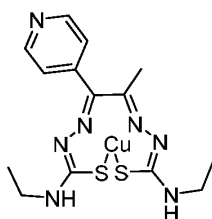
In an embodiment the disclosure provides a compound having the structure of Compound 54:



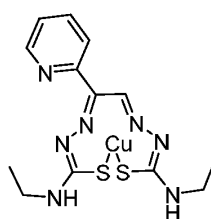
In another aspect, the present disclosure provides a compound having the structure of Compound 20:



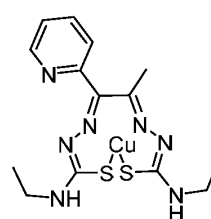
A further aspect of the present disclosure is a compound selected from the group consisting of the compounds described below, or a pharmaceutically acceptable salt thereof:



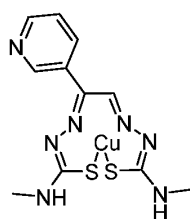
Compound 56



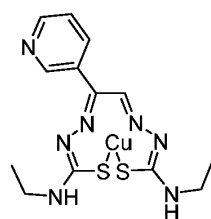
Compound 57



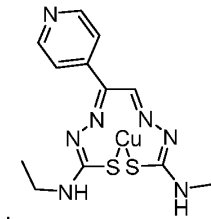
Compound 58



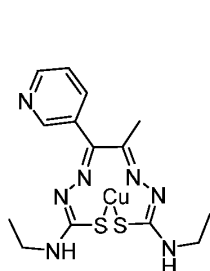
Compound 59



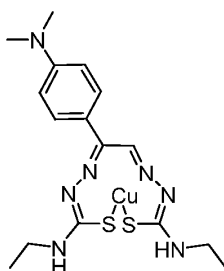
Compound 60



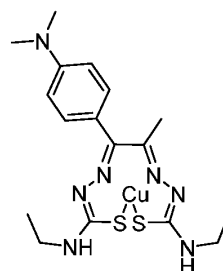
Compound 61



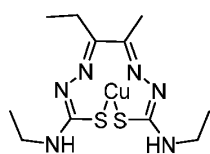
Compound 62



Compound 63

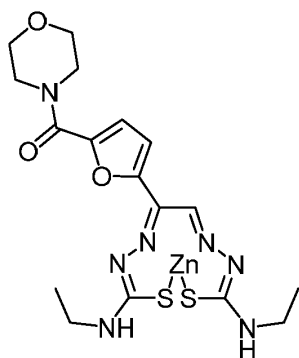


Compound 64

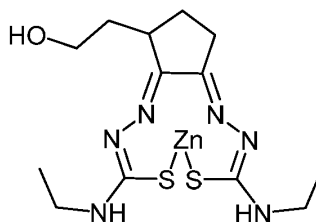


Compound 65.

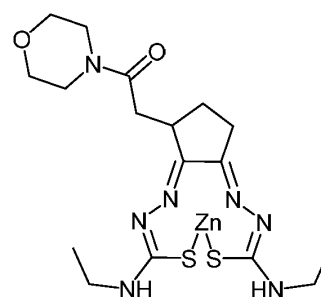
A further aspect of the present disclosure is a compound selected from the group consisting of the compounds described below, or a pharmaceutically acceptable salt thereof:



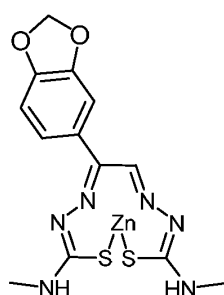
ZN-30



ZN-47



ZN-50

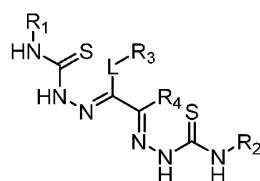


ZN-75

Synthetic Intermediates

In another aspect, the present disclosure also relates to synthetic intermediates of the copper complexes described herein. In some embodiments, the synthetic intermediate

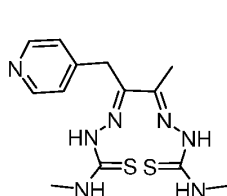
5 has a structure represented by Formula (I-A):



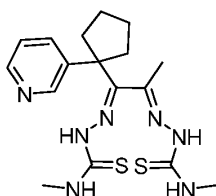
(I-A),

wherein variables L, R₁, R₂, R₃, and R₄ correspond to the variables of the same name as defined in Formula (I).

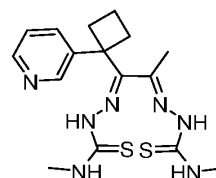
10 Exemplary synthetic intermediates represented by Formula (I-A) include the following:



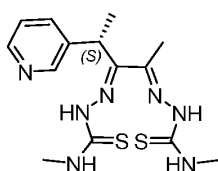
INT-1



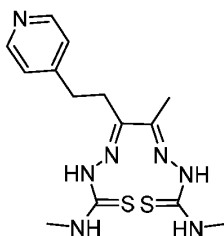
INT-2



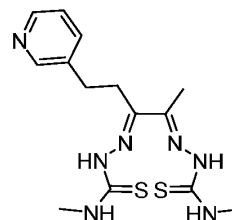
INT-3



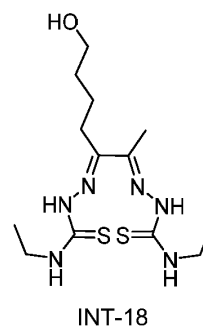
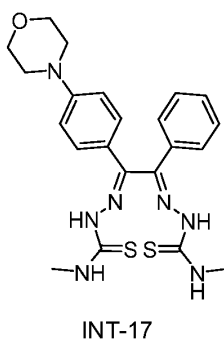
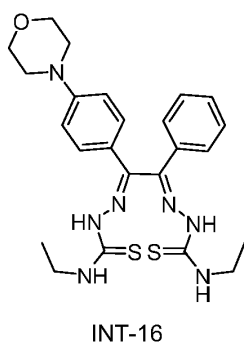
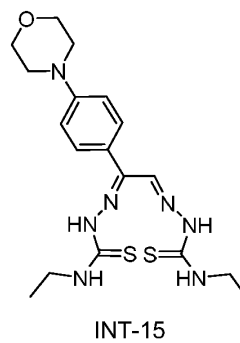
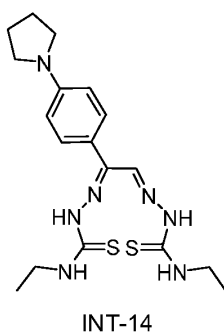
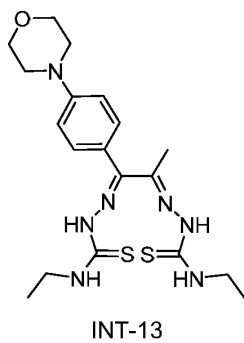
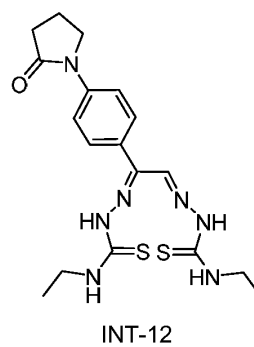
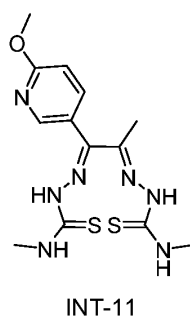
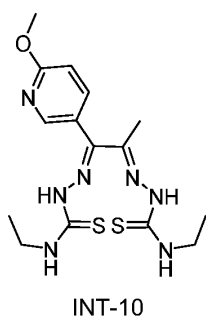
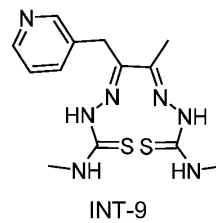
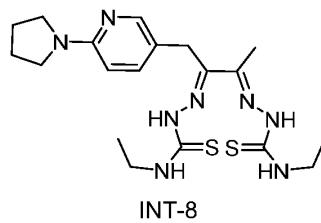
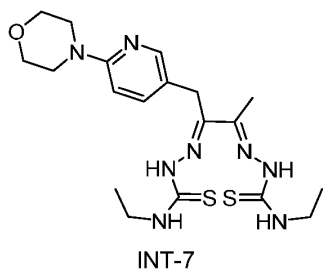
INT-4

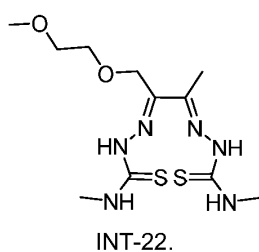
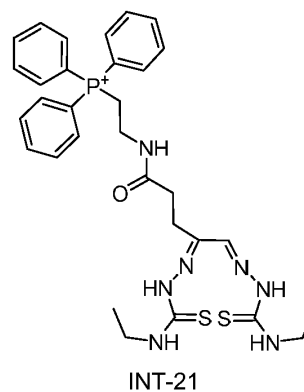
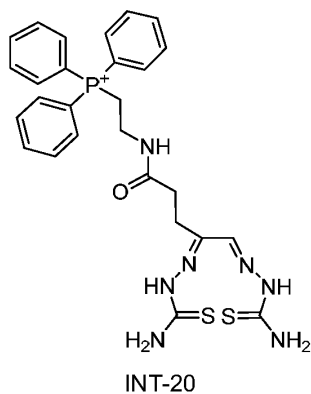
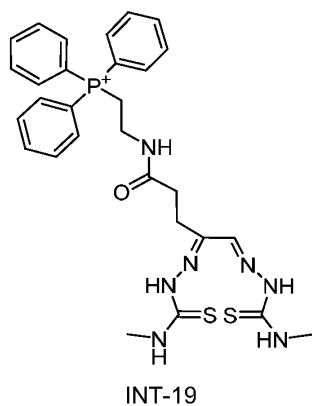


INT-5

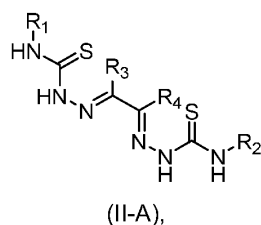


INT-6





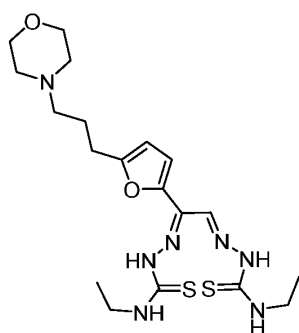
In some embodiments, the synthetic intermediate has a structure represented by Formula (II-A):



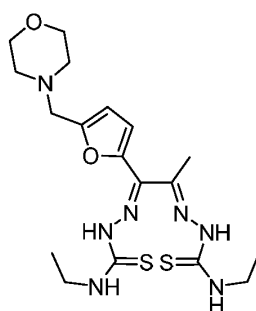
5

wherein variables R_1 , R_2 , R_3 , and R_4 correspond to the variables of the same name as defined in Formula (II).

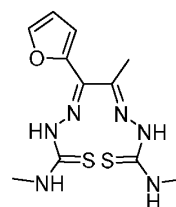
Exemplary synthetic intermediates represented by Formula (II-A) include the following:



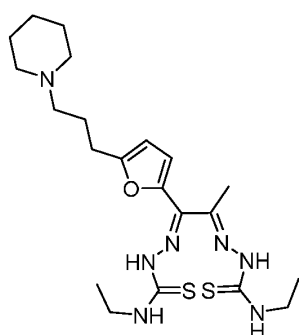
INT-23



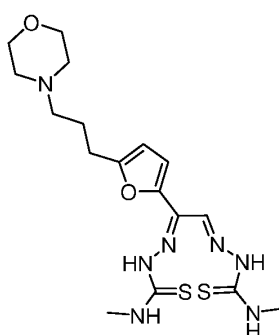
INT-24



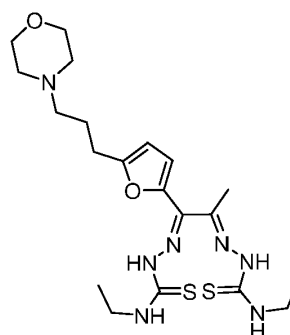
INT-25



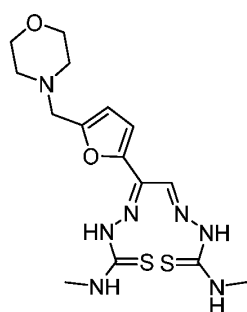
INT-26



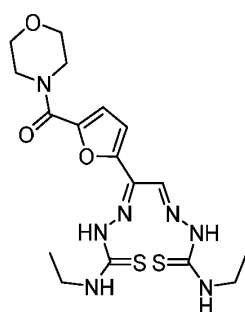
INT-27



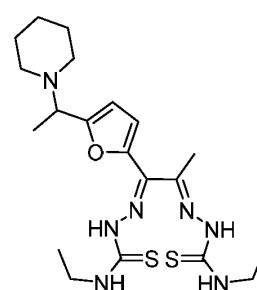
INT-28



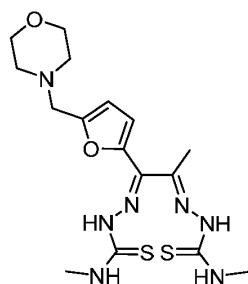
INT-29



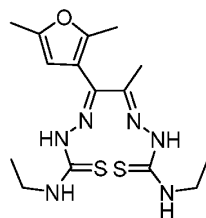
INT-30



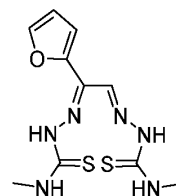
INT-31



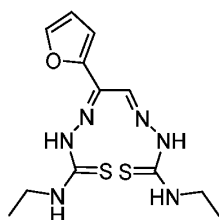
INT-32



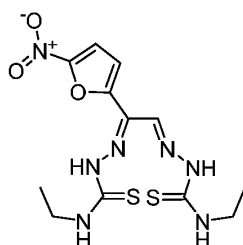
INT-33



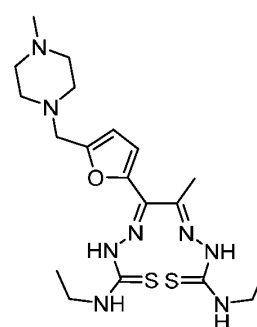
INT-34



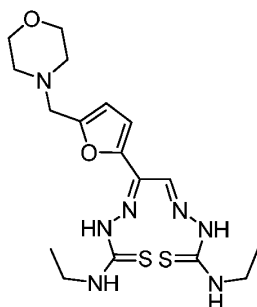
INT-35



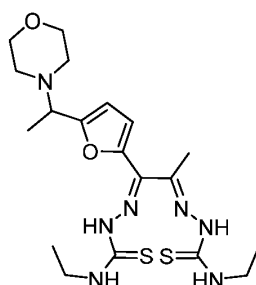
INT-36



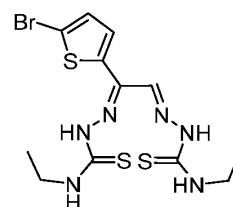
INT-37



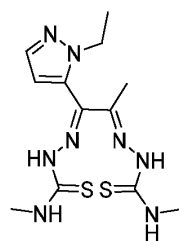
INT-38



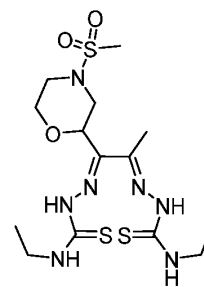
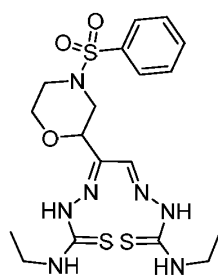
INT-39



INT-40

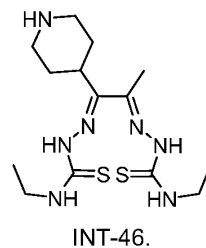
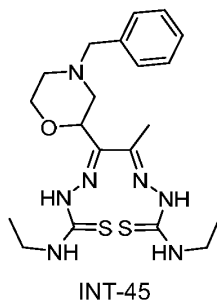
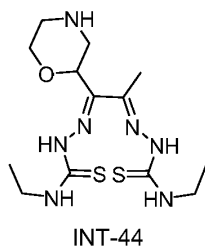


INT-41

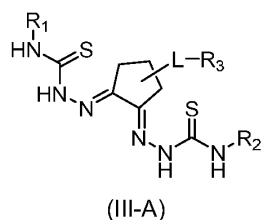


INT-42

INT-43



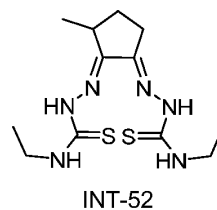
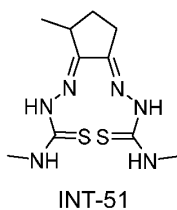
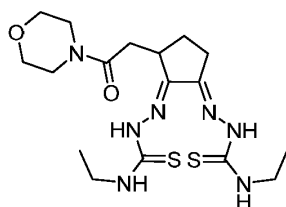
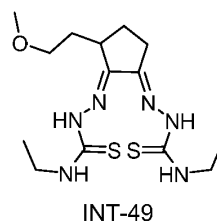
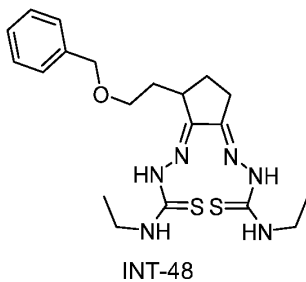
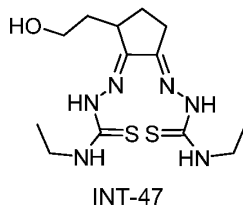
In some embodiments, the synthetic intermediate has a structure represented by Formula (III-A):



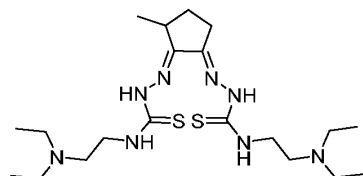
5

wherein variables L, R₁, R₂, and R₃ correspond to the variables of the same name as defined in Formula (III).

Exemplary synthetic intermediates represented by Formula (III-A) include the following:

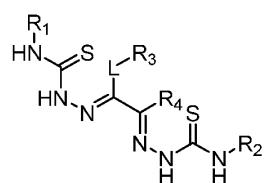


INT-50



INT-53.

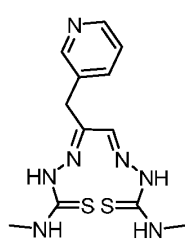
In another aspect, the present disclosure also relates to synthetic intermediates of the copper complexes described herein. In some embodiments, the synthetic intermediate has a structure represented by Formula (IV-A):



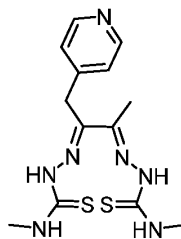
(IV-A),

wherein variables L, R₁, R₂, R₃, and R₄ correspond to the variables of the same name as defined in Formula (IV).

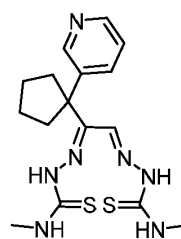
Exemplary synthetic intermediates represented by Formula (IV-A) include the following:



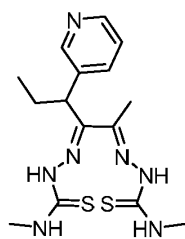
INT-66



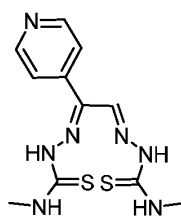
INT-67



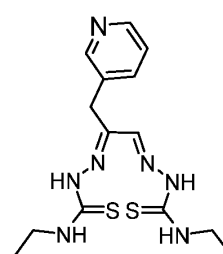
INT-68



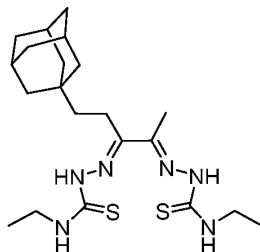
INT-69



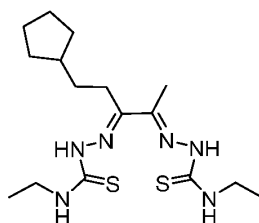
INT-70



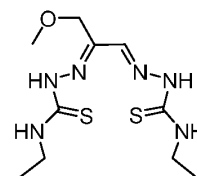
INT-71



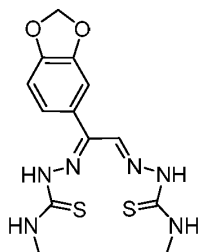
INT-72



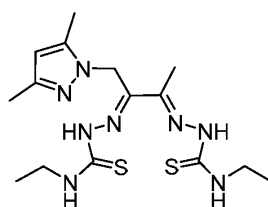
INT-73



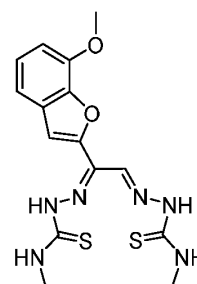
INT-74



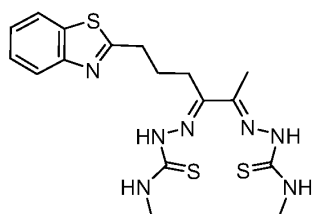
INT-75



INT-76

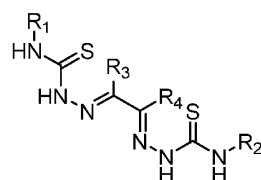


INT-77



INT-78

In some embodiments, the synthetic intermediate has a structure represented by Formula (V-A):

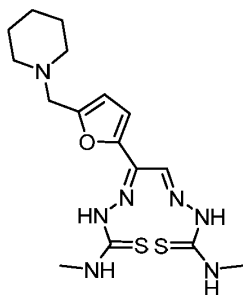


(V-A),

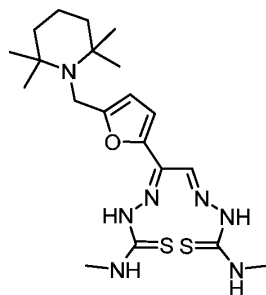
5

wherein variables R₁, R₂, R₃, and R₄ correspond to the variables of the same name as defined in Formula (V).

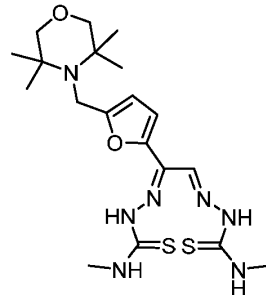
Exemplary synthetic intermediates represented by Formula (V-A) include the following:



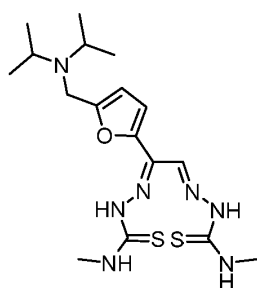
INT-79



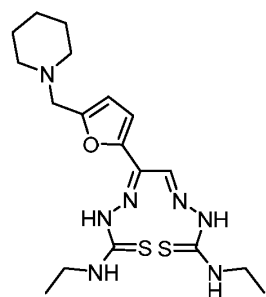
INT-80



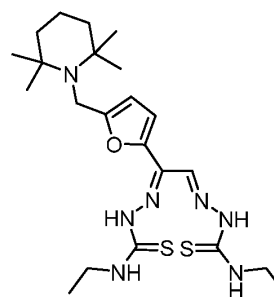
INT-81



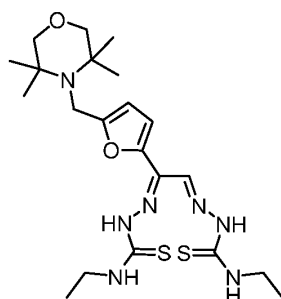
INT-82



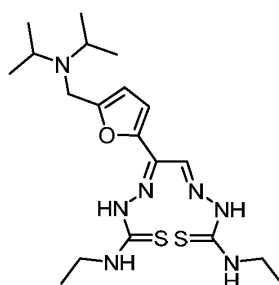
INT-83



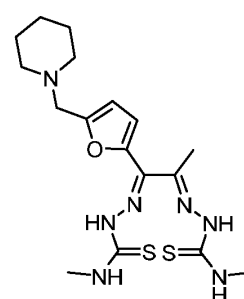
INT-84



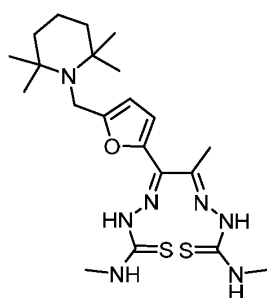
INT-85



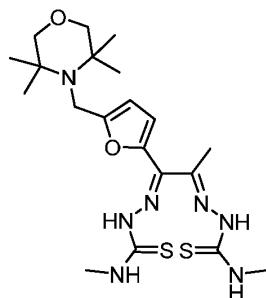
INT-86



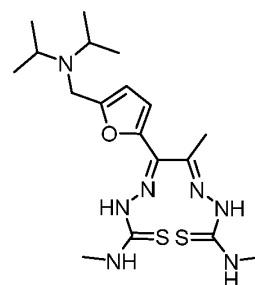
INT-87



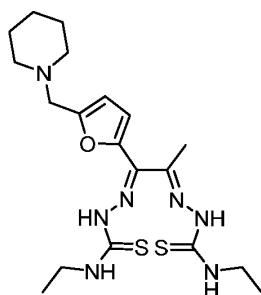
INT-88



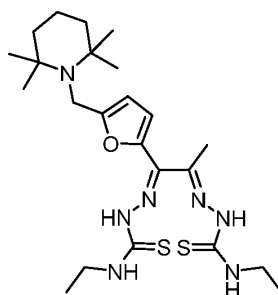
INT-89



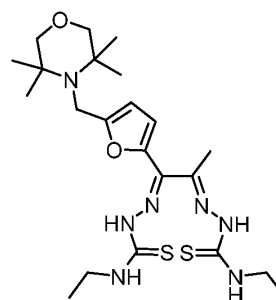
INT-90



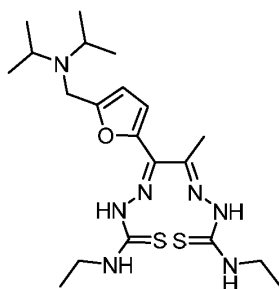
INT-91



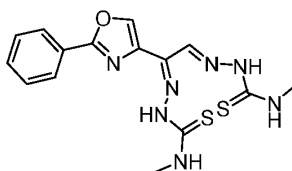
INT-92



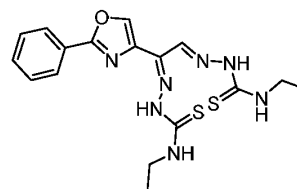
INT-93



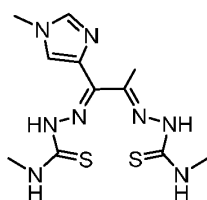
INT-94



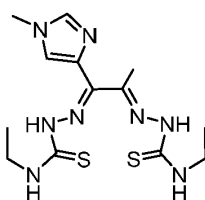
INT-95



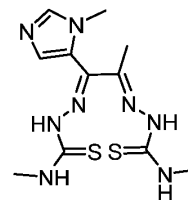
INT-96



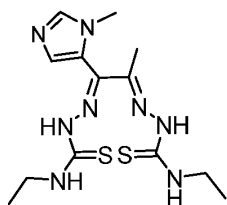
INT-97



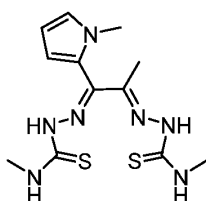
INT-98



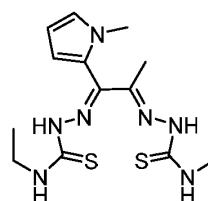
INT-99



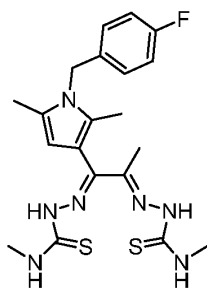
INT-100



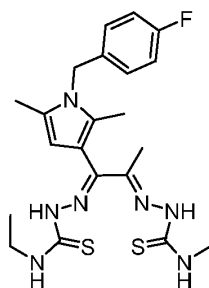
INT-101



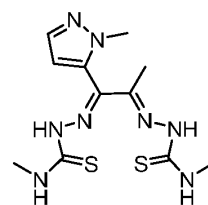
INT-102



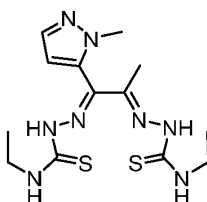
INT-103



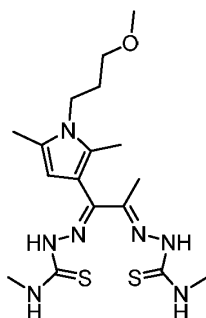
INT-104



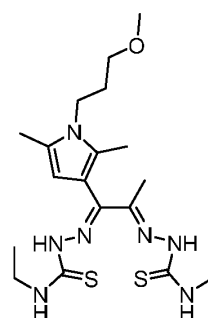
INT-105



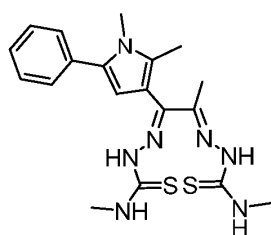
INT-106



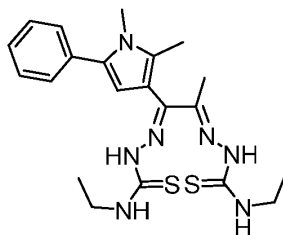
INT-107



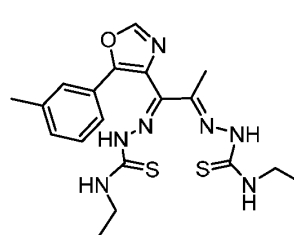
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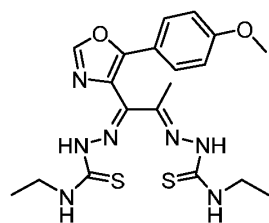
INT-109



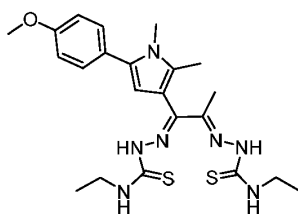
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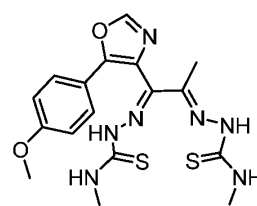
INT-111



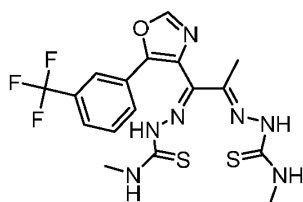
INT-112



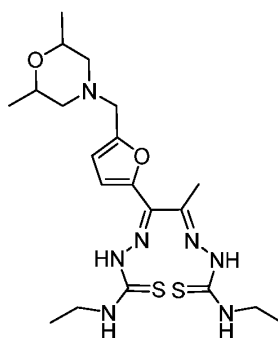
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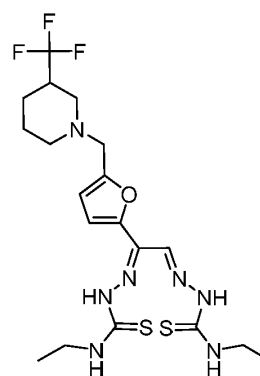
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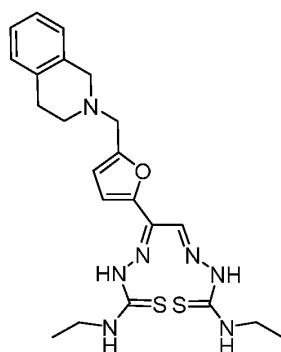
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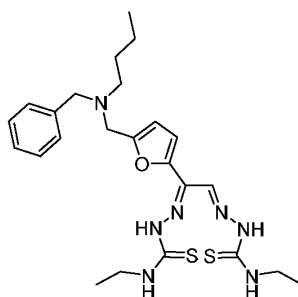
INT-116



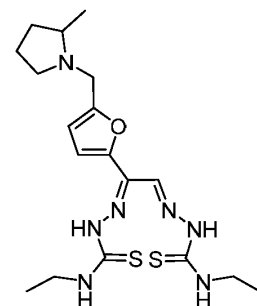
INT-117



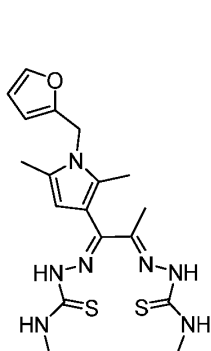
INT-118



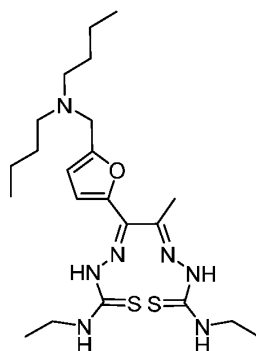
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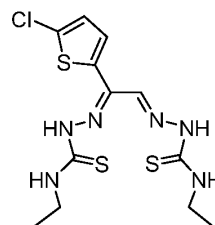
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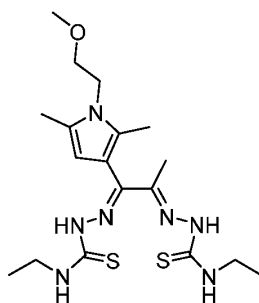
INT-121



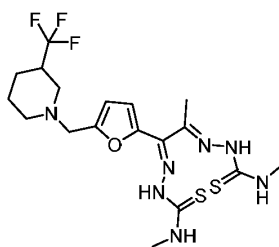
INT-122



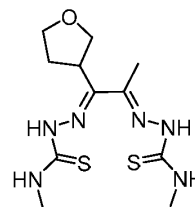
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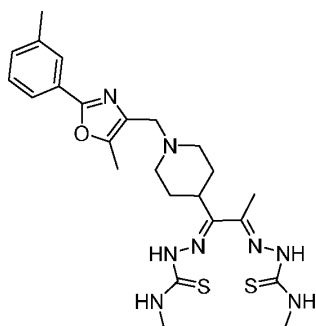
INT-124



INT-125

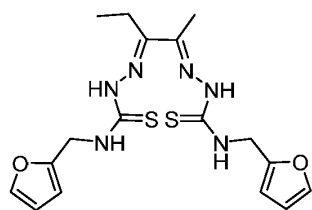


INT-126

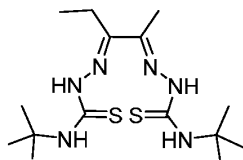


INT-127

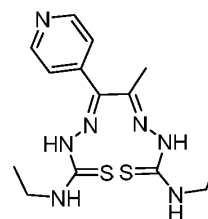
Further exemplary synthetic intermediates of the disclosure include the following compounds:



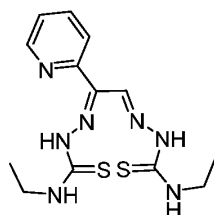
INT-54



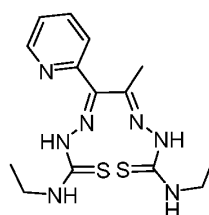
INT-55



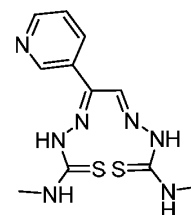
INT-56



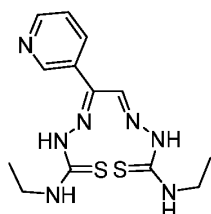
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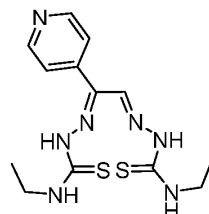
INT-58



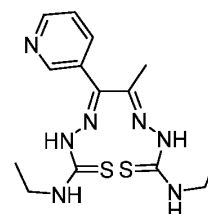
INT-59



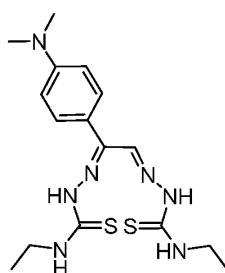
INT-60



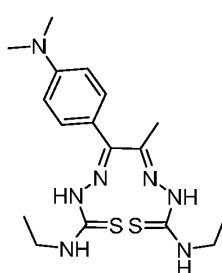
INT-61



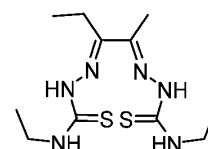
INT-62



INT-63



INT-64



INT-65.

Pharmaceutical Compositions

In another aspect, provided herein are pharmaceutical compositions comprising a compound of the disclosure, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, diluent, or carrier.

The formulation of therapeutic compositions and their subsequent administration (dosing) is within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a sufficient diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient.

Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potencies of the compounds of the disclosure, and can generally be estimated based on EC₅₀ values found to be effective in in vitro and in vivo animal models. In general, dosage is from 0.01 µg to 100 g/kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the drug in bodily fluids or tissues. Following successful treatment, it may be desirable to have the patient undergo maintenance therapy to prevent the recurrence of the disease state, wherein a compound of the disclosure is administered in maintenance doses, ranging from 0.01 µg to 100 g/kg of body weight, once or more daily, to once every 20 years.

Different dosage regimens may be used to treat neurodegenerative diseases (e.g., ALS). In some embodiments, a daily dosage, such as any of the exemplary dosages described above, is administered once, twice, three times, or four times a day for three, four, five, six, seven, eight, nine, or ten days. Depending on the stage and severity of the disease being treated, a shorter treatment time (e.g., up to five days) may be employed along with a high dosage, or a longer treatment time (e.g., ten or more days, or weeks, or a month, or longer) may be employed along with a low dosage. In some embodiments, a once- or twice-daily dosage is administered every other day.

In an aspect, the compound of the disclosure may be administered alone or in combination with at least one pharmaceutically acceptable excipient. The expression "pharmaceutically acceptable" means acceptable for use in the pharmaceutical and veterinary arts, i.e., not being unacceptably toxic or otherwise unsuitable. Examples of pharmaceutically acceptable adjuvants, diluents, excipients and the like can be found in "Remington's: The Science and Practice of Pharmacy," 21st Ed., Lippincott Williams and Wilkins, 2005, the contents of which are incorporated herein by reference.

The compounds of the disclosure, in pure form or in appropriate pharmaceutical compositions, can be administered via any of the accepted modes of administration or agents known in the art. The compounds of the disclosure can be administered, for example, orally, nasally, parenterally (intravenous, intramuscular, or subcutaneous), topically,

transdermally, intravaginally, intravesically, intracisternally, or rectally. The dosage form can be, for example, a solid, semi-solid, lyophilized powder, or liquid dosage forms, such as for example, tablets, pills, soft elastic or hard gelatin capsules, powders, solutions, suspensions, suppositories, aerosols, or the like, for example, in unit dosage forms suitable for simple administration of precise dosages. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methylcellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil; sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. A particular route of administration is oral, particularly one in which a convenient daily dosage regimen can be adjusted according to the degree of severity of the disease to be treated.

Auxiliary and adjuvant agents may include, for example, preserving, wetting, suspending, sweetening, flavoring, perfuming, emulsifying, and dispensing agents. Emulsifiers can include polysorbates, such as TWEEN, for example TWEEN-20 and TWEEN-80. Prevention of the action of microorganisms is generally provided by various antibacterial and antifungal agents, such as, parabens, chlorobutanol, phenol, sorbic acid, and the like. Isotonic agents, such as sugars, sodium chloride, and the like, may also be included. Prolonged absorption of an injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin. The auxiliary agents also can include wetting agents, emulsifying agents, pH buffering agents, and antioxidants, such as, for example, citric acid, sorbitan monolaurate, triethanolamine oleate, butylated hydroxytoluene, and the like.

Solid dosage forms can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They can contain pacifying agents and can be of such composition that they release a compound of the disclosure in a certain part of the intestinal tract in a delayed manner. Examples of embedded compositions that can be used are polymeric substances and waxes. The compound of the disclosure also can be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. Such dosage forms are prepared, for example, by dissolving, dispersing, etc., a compound of the disclosure, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like; solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl

benzoate, propyleneglycol, 1,3- butyleneglycol, dimethyl formamide; oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan; or mixtures of these substances, and the like, to thereby form a solution or suspension.

5 Generally, depending on the intended mode of administration, the pharmaceutically acceptable compositions will contain about 1% to 99% by weight of a compound disclosed herein, and 99% to 1% by weight of a pharmaceutically acceptable excipient. In one example, the composition will be between about 5% and about 75% by weight of a compound of the disclosure, with the rest being suitable pharmaceutical excipients.

10 Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art. Reference is made, for example, to Remington's Pharmaceutical Sciences, 18th Ed. (Mack Publishing Company, Easton, Pa., 1990).

Methods of Treatment

15 The methods described herein comprise administering a therapeutically effective amount of a compound disclosed herein to a subject in need thereof. A "therapeutically effective amount" is an amount of a compound of the disclosure that, when administered to a patient by itself, effectively treats a neurodegenerative disease. An amount that proves to be a "therapeutically effective amount" in a given instance, for a particular subject, may not be
20 effective for 100% of subjects similarly treated for the disease or condition under consideration, even though such dosage is deemed a "therapeutically effective amount" by skilled practitioners. The amount of a compound of the disclosure that corresponds to a therapeutically effective amount is strongly dependent on the type of disease, stage of the disease, the age of the patient being treated, and other facts.

25 Accordingly, in an aspect, the disclosure provides a method of treating or preventing a neurodegenerative disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure. In particular, the method comprises administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), (III), (IV), or (V). Non-limiting examples
30 of neurodegenerative diseases that can be treated or prevented with the compounds disclosed herein include amyotrophic lateral sclerosis (ALS), frontal temporal dementia (FTD), Parkinson's disease, Huntington's disease, and Alzheimer's disease. In a preferred embodiment, the neurodegenerative disease to be treated or prevented by a compound of the disclosure is ALS. In an embodiment, the ALS is familial ALS. In an embodiment, the
35 ALS is sporadic ALS.

 While the amounts of the compounds disclosed herein should result in the effective treatment or prevention of neurodegenerative disease, the amounts are preferably not

excessively toxic to the patient (i.e., the amounts are preferably within toxicity limits as established by medical guidelines). In some embodiments, either to prevent excessive toxicity or provide a more efficacious treatment, or both, of the neurodegenerative disease, a limitation on the total administered dosage is provided. Typically, the amounts considered
5 herein are per day; however, half-day and two-day or three-day cycles are also considered herein.

In certain embodiments, the subject in need thereof is treatment naïve. In certain embodiments, the subject in need thereof has received previous treatment for ALS, wherein the previous treatment is other than administration of a compound of the disclosure, and
10 wherein said previous treatment has been inadequate (e.g., assessed by the subject and/or a physician), ineffective, and/or has not resulted in a detectable improvement in one or more parameters or symptoms associated with ALS and/or has not caused a biological effect that is correlated with the underlying pathology giving rise to the symptoms of ALS.

In certain embodiments, the subject in need thereof is human, and the human has a
15 genetic mutation associated with ALS. In further embodiments, the genetic mutation associated with ALS comprises a mutation in the *SOD1* gene.

In certain embodiments, the compound of the disclosure is administered to the subject in combination with an additional ALS treatment therapy. Current treatment for ALS includes administration of riluzole and edaravone, which have been shown to be modestly
20 effective. Other therapies for ALS include medications to treat specific symptoms associated with the disease, for example muscle relaxants such as baclofen or diazepam may be prescribed to treat muscle cramps, spasms, and spasticity. Gabapentin may be prescribed to help control pain. Such medicines like amitriptyline, trihexyphenidyl, scopaderm, and glycopyrrolate can be administered to treat excess saliva in the mouth due to difficulty
25 swallowing. Medication may also be required for the treatment of constipation, fatigue, depression, difficulty sleeping, and pseudobulbar affect associated with ALS.

In certain embodiments, the compound of the disclosure is administered at a dose that achieves a plasma C_{max} of about 50-650 ng/mL in the subject. The term " C_{max} " is defined as the maximum concentration of active compound achieved in the plasma or spinal cord
30 following administration of the drug.

In another aspect, the disclosure provides a method of treating, preventing, or diagnosing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure. In particular, isotopes (e.g., ^{64}Cu) of the compounds disclosed herein may be used in PET imaging to
35 detect the presence of cancer cells in a subject in need thereof. Accordingly, in another aspect, the disclosure provides a method of performing positron emission tomography (PET) imaging of a subject in need thereof, the method comprising administering to the subject an

effective amount of a compound of the disclosure and subsequently performing a PET scan on the subject.

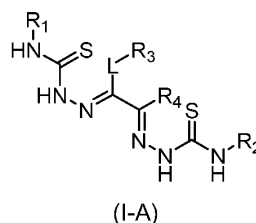
In yet another aspect, the disclosure provides a method of treating or preventing an infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure.

In a further aspect, the disclosure provides a method of treating a disease or disorder associated with aberrant copper metabolism (e.g., Menkes disease or Wilson's disease) in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of the disclosure. In some embodiments, the subject has a congenital SOD1 deficiency or mutation. In some embodiments, the subject does not have a congenital SOD1 deficiency or mutation.

Preparation Methods

An aspect of the disclosure relates to a process for the preparation of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described herein.

In an embodiment, the process comprises at least the step of mixing a compound of Formula (I-A):



with a copper (II) salt to form the compound of Formula (I), or a pharmaceutically acceptable salt thereof;

wherein:

L is C₃-C₇ cycloalkyl, C₁-C₆ alkyl, or absent

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₆-C₁₀ aryl is substituted one, two, or three times with the group R_{3a}, and wherein the 5- 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₃-C₇ cycloalkyl or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl;

R_{3b} independently for each occurrence is C₁-C₃ alkoxy, C₃-C₇ cycloalkyl, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

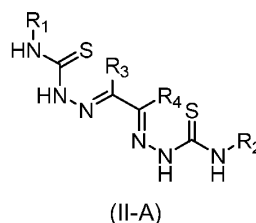
R₄ is hydrogen, C₁-C₃ alkyl, or C₆-C₁₀ aryl;

provided that when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}.

In an embodiment, the copper (II) salt is CuCl₂ or Cu(OAc)₂, or a hydrate thereof.

Another aspect of the disclosure relates to a process for the preparation of a compound of Formula (II), or a pharmaceutically acceptable salt thereof, as described herein.

In an embodiment, the process comprises at least the step of mixing a compound of Formula (II-A):



with a copper (II) salt to form the compound of Formula (II);
wherein:

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is 4- to 8-membered heterocycle or 5-membered heteroaryl, wherein the 4- to 8-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a}, and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkyl-(C₆-C₁₀ aryl), S(O)₂H, S(O)₂-(C₁-C₆ alkyl), S(O)₂-(C₃-C₇ cycloalkyl), or S(O)₂-(C₆-C₁₀ aryl);

R_{3b} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, halo, nitro, cyano, C(O)-(4- to 8-membered heterocycle), or C₁-C₆ alkyl-(4- to 8-membered

heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

R₄ is hydrogen or C₁₋₃ alkyl.

In an embodiment, the copper (II) salt is CuCl₂ or Cu(OAc)₂, or a hydrate thereof.

- 5 In another embodiment, the process comprises at least the steps of mixing a compound of Formula (II-A) with a zinc salt to form a compound of Formula (II-B):



(II-B),

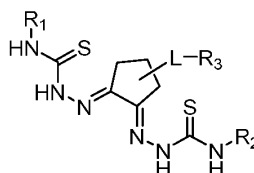
- 10 and mixing the compound of Formula (II-B) with a copper (II) salt to form the compound of Formula (II).

In an embodiment, the zinc salt is Zn(OAc)₂ or a hydrate thereof.

In an embodiment, the copper (II) salt is CuCl₂ or Cu(OAc)₂, or a hydrate thereof.

- 15 Yet another aspect of the disclosure relates to a process for the preparation of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, as described herein.

In an embodiment, the process comprises at least the step of mixing a compound of Formula (III-A):



(III-A)

- 20 with a copper (II) salt to form the compound of Formula (III);
wherein:

L is C₁-C₆ alkyl or absent

- 25 R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

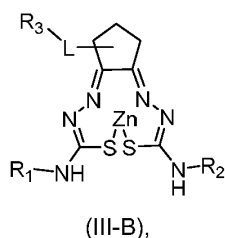
R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

- 30 R₃ is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, halo, hydroxy, C(O)NH₂, C(O)NH(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂, or C(O)-(4- to 8-membered heterocycle), wherein the C₁-C₆ alkyl and the C₁-C₆ alkoxy are optionally substituted one, two, or three times with C₆-C₁₀ aryl,

and wherein the C(O)-(4- to 8-membered heterocycle) is optionally substituted one, two, or three times with C₁-C₃ alkyl.

In an embodiment, the copper (II) salt is CuCl₂ or Cu(OAc)₂, or a hydrate thereof.

In another embodiment, the process comprises at least the steps of mixing a
5 compound of Formula (III-A) with a zinc salt to form a compound of Formula (III-B):



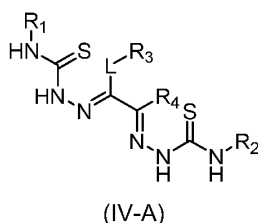
and mixing the compound of Formula (III-B) with a copper (II) salt to form the compound of Formula (III).

10 In an embodiment, the zinc salt is Zn(OAc)₂ or a hydrate thereof.

In an embodiment, the copper (II) salt is CuCl₂ or Cu(OAc)₂, or a hydrate thereof.

Another aspect of the disclosure relates to a process for the preparation of a
15 compound of Formula (IV), or a pharmaceutically acceptable salt thereof, as described herein.

In an embodiment, the process comprises at least the step of mixing a compound of Formula (IV-A):



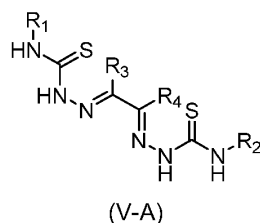
20 with a copper (II) salt to form the compound of Formula (IV), or a pharmaceutically acceptable salt thereof;

wherein variables L, R₁, R₂, R₃, and R₄ correspond to the variables of the same name as defined in Formula (IV).

In an embodiment, the copper (II) salt is CuCl₂ or Cu(OAc)₂, or a hydrate thereof
25

In yet another aspect of the disclosure relates to a process for the preparation of a compound of Formula (V), or a pharmaceutically acceptable salt thereof, as described herein.

In an embodiment, the process comprises at least the step of mixing a compound of Formula (V-A):

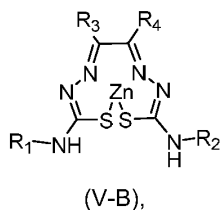


- 5 with a copper (II) salt to form the compound of Formula (V), or a pharmaceutically acceptable salt thereof;

wherein variables R_1 , R_2 , R_3 , and R_4 correspond to the variables of the same name as defined in Formula (V).

In an embodiment, the copper (II) salt is CuCl_2 or $\text{Cu}(\text{OAc})_2$, or a hydrate thereof.

- 10 In another embodiment, the process comprises at least the steps of mixing a compound of Formula (V-A) with a zinc salt to form a compound of Formula (V-B):



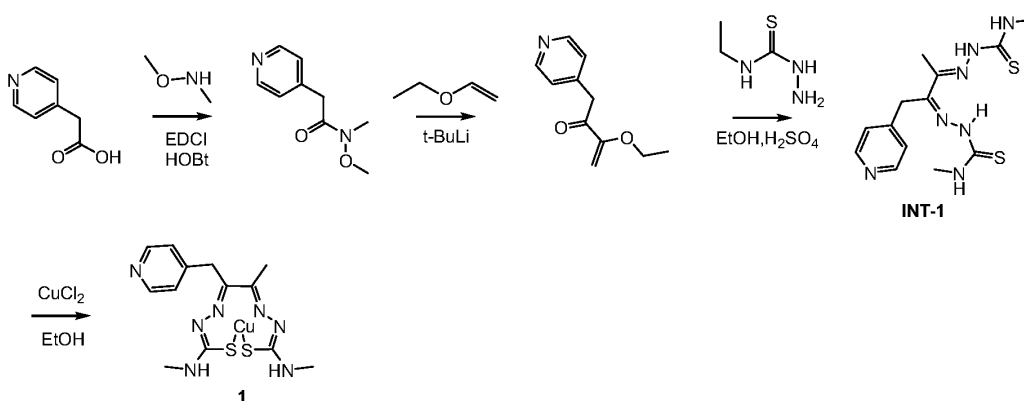
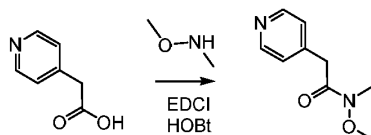
- 15 and mixing the compound of Formula (V-B) with a copper (II) salt to form the compound of Formula (V).

In an embodiment, the zinc salt is $\text{Zn}(\text{OAc})_2$ or a hydrate thereof.

In an embodiment, the copper (II) salt is CuCl_2 or $\text{Cu}(\text{OAc})_2$, or a hydrate thereof.

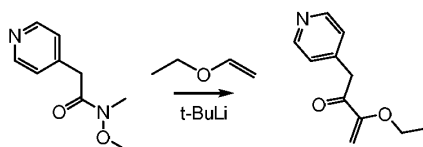
EXAMPLES

The disclosure further relates to the following experimental examples. These examples are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure, and are not intended to limit the disclosure. Thus, the disclosure should in no way be construed as being limited to the following examples, but rather, should be construed to encompass any and all variation which become evident as a result of the teaching provided herein.

Example 1: Preparation of Compounds 1-22**10 Scheme 1: Synthesis of Compound 1****Synthesis of N-methoxy-N-methyl-2-(pyridin-4-yl)acetamide:**

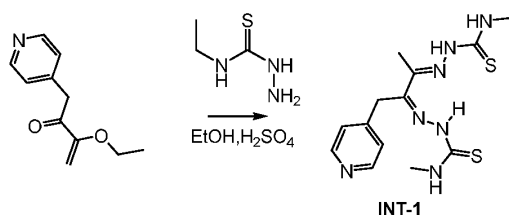
To a stirred mixture of 4-pyridineacetic acid (4.2g, 24.2 mmol), N,O-dimethylhydroxylamine (2.8g, 29.1mmol), HOBt (3.9g, 29.1mmol) and TEA (12ml, 84.7mmol) in DCM (100ml) at 4°C EDCI (5.6g, 29.1mmol) was added. The reaction was stirred overnight at ambient temperature. The mixture was washed with water (100ml), and brine (100ml). The organic layer was dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH). Yield 2.9g (66%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.14 min). MS (ESI) m/z 232.3 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 3.21 (s, 3H), 3.66 (s, 3H), 3.78 (s, 2H), 7.24 (d, 2H), 8.55 (d, 2H).

Synthesis of 3-ethoxy-1-(pyridin-4-yl)but-3-en-2-one:



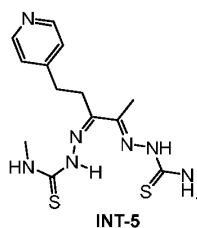
A solution of ethyl vinyl ether (3.1g, 42.9mmol) in tetrahydrofuran (100ml) was cooled to -78°C, and *tert*-butyllithium (1.7M, 23.0ml, 38.8mmol) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-2-(pyridin-4-yl)acetamide (0.7g, 3.8 mmol) in tetrahydrofuran (20 mL) was added, and reaction was stirred at 0°C for 2h. The progress of the reaction was monitored by TLC. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3 × 50ml). The combined extracts were dried over Na₂SO₄, solution was decanted, and solvents were removed under reduced pressure. The titular compound was used for the next step without further purification. Yield 0.2g (27%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.72 min). MS (ESI) m/z 192.4 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.40 (t, 3H), 3.83 (q, 2H), 3.99 (s, 2H), 4.41 (d, 1H), 5.25 (d, 1H), 7.18 (dd, 1H), 8.55 (dd, 1H), 8.54 (dd, 2H).

Synthesis of INT-1 ((2Z,2'E)-2,2'-(1-(pyridin-4-yl)butane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



3-Ethoxy-1-(pyridin-4-yl)but-3-en-2-one (0.2g, 1.04mmol) was dissolved in EtOH (5ml), methyl thiosemicarbazide (0.22g, 2.08mmol) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h reflux and overnight at ambient temperature. The progress of the reaction was monitored by TLC. The precipitate was filtered, washed with EtOH, Et₂O, and dried. Yield 0.21g (60%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.98 min). MS (ESI) m/z 338.9 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.28 (s, 3H), 2.98 (d, 3H), 3.02 (d, 3H), 4.76 (s, 2H), 7.72 (d, 2H), 8.36 (dd, 1H), 8.50 (dd, 1H), 8.78 (d, 2H), 10.35 (s, 1H), 10.85 (s, 1H).

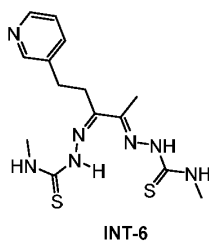
Synthesis of INT-5 ((2Z,2'E)-2,2'-(5-(pyridin-4-yl)pentane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



INT-5 was made using a procedure analogous to the procedure to prepare **INT-1**.

Yield 1.54g (85%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.94 min). MS (ESI) m/z 352.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.15 (s, 3H), 2.66 (t, 2H), 3.01 (d, 6H), 3.28 (t, 2H), 7.32 (d, 2H), 8.21 (dd, 1H), 8.33 (dd, 1H), 8.45 (d, 2H), 10.21 (s, 1H), 10.67 (s, 1H).

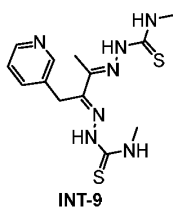
Synthesis of INT-6 ((2Z,2'E)-2,2'-(5-(pyridin-3-yl)pentane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



INT-6 was made using a procedure analogous to the procedure to prepare **INT-1**.

Yield 0.42g (49%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.94 min). MS (ESI) m/z 352.4 [MH]⁺.

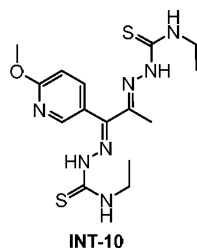
Synthesis of INT-9 ((2E,2'E)-2,2'-(1-(pyridin-3-yl)butane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



INT-9 was made using a procedure analogous to the procedure to prepare **INT-1**.

Yield 8.6g (76%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.91 min). MS (ESI) m/z 338.4 [MH]⁺.

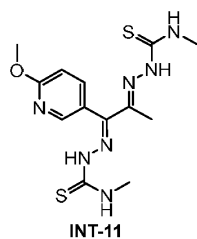
Synthesis of INT-10 ((2E,2'E)-2,2'-(1-(6-methoxypyridin-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-10 was made using a procedure analogous to the procedure to prepare **INT-1**.

- 5 Yield 1.2 g (46.2%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.52 min, MS (ESI) m/z 382.0 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 0.94 (t, 3H), 1.15 (t, 3H), 2.35 (s, 3H), 3.34 (q, 2H), 3.60 (q, 2H), 3.91 (s, 3H), 6.44 (d, 1H), 7.62 (d, 1H), 8.05 (s, 1H), 8.68 (br.s, 1H), 9.54 (s, 1H), 10.71 (s, 1H).

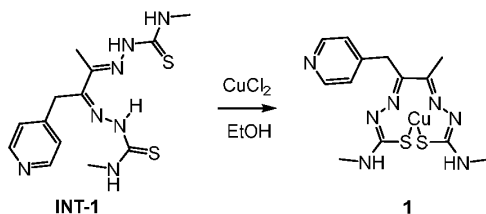
- 10 **Synthesis of INT-11 ((2E,2'E)-2,2'-(1-(6-methoxypyridin-3-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):**



INT-11 was made using a procedure analogous to the procedure to prepare **INT-1**.

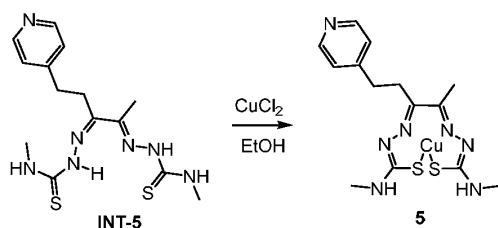
- 15 Yield 0.7 g (56.6%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.41 min, MS (ESI) m/z 354.5 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 2.36 (s, 3H), 2.87 (s, 3H), 3.03 (s, 3H), 3.92 (s, 3H), 6.95 (d, 1H), 7.15 (br.s, 1H), 7.61 (d, 1H), 8.04 (s, 1H), 8.62 (br.s, 1H), 9.54 (s, 1H), 10.56 (s, 1H).

Synthesis of Compound 1:



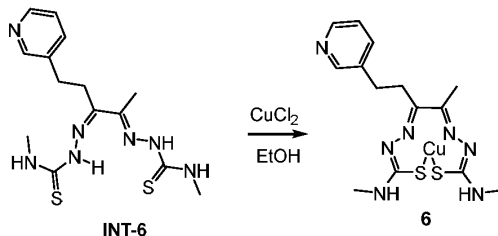
CuCl₂·2H₂O (0.08g, 0.48mmol) was added to **INT-1** (0.15g, 0.44mmol) in ethanol (6 ml). The mixture was stirred overnight at ambient temperature. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.075g (42%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.29). MS (ESI) m/z 399.1 [MH]⁺.

Synthesis of Compound 5:



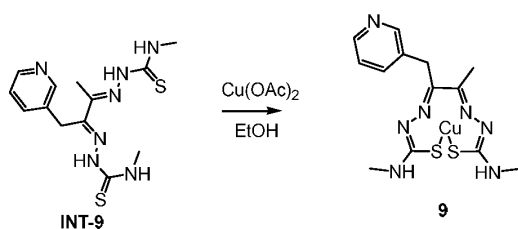
The titular compound was prepared from **INT-5** according to the method to prepare compound 1. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.5g (78%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.26). MS (ESI) m/z 413.4 [MH]⁺.

Synthesis of Compound 6:



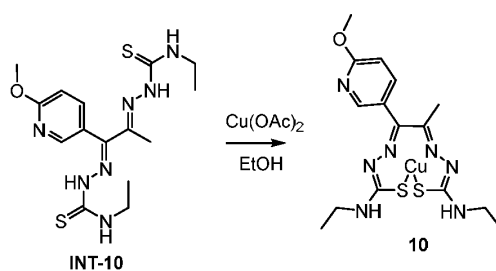
The titular compound was prepared from **INT-6** according to the method to prepare compound 1. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.18g (95%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.25). MS (ESI) m/z 412.9 [MH]⁺.

Synthesis of Compound 9:



The titular compound was prepared from **INT-9** according to the method to prepare compound 1. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 2.3g (97%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.30). MS (ESI) m/z 399.1 [MH]⁺.

Synthesis of Compound 10:

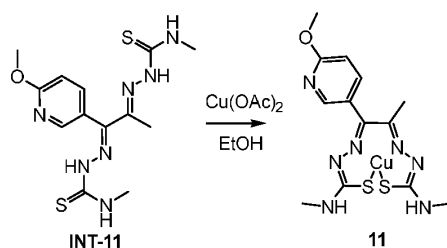


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The titular compound was prepared from **INT-10** according to the method to prepare compound 1. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.13 g (37.3%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.31). MS (ESI) m/z 443.5 [MH]⁺.

15

Synthesis of Compound 11:

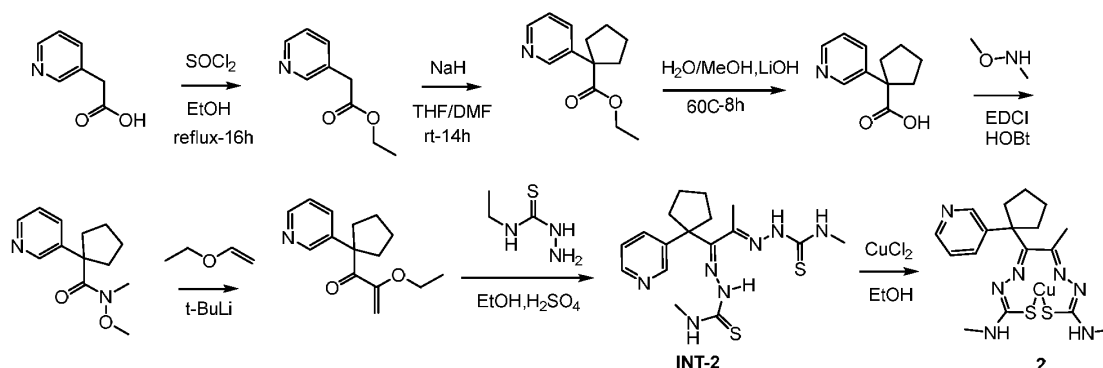


The titular compound was prepared from **INT-11** according to the method to prepare compound 1. The formed complex was precipitated from the mixture as a red-brown powder.

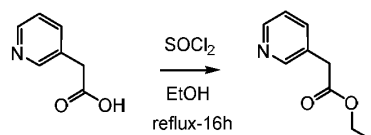
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The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.12g (34.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.97). MS (ESI) m/z 415.3 [MH]⁺.

5 Scheme 2: Synthesis of Compound 2

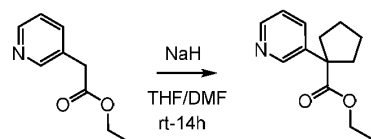


Synthesis of ethyl 2-(pyridin-3-yl)acetate:



To a stirred solution of 3-pyridineacetic acid (25.0 g, 145 mmol) in EtOH (250ml) at 0-5°C was added SOCl₂ (11.6ml, 160mmol) over period of 15 min. Then the reaction was heated to reflux for additional 16 h. EtOH was evaporated under reduced pressure. To the residue was added aq. 2M Na₂CO₃ (30 ml), and the resulting mixture was extracted with EtOAc (3 × 400 ml). Combined organic layers were washed with brine (100mL), dried over anhydrous Na₂SO₄, filtered, and concentrated giving the titular compound as a colorless liquid. Yield 22.3g (93%). ¹H-NMR (400MHz, CDCl₃): δ (ppm): 1.26 (t, 3 H), 3.62 (s, 2 H), 4.17 (q, 2 H), 7.27-7.28 (m, 1 H), 7.64-7.65 (m, 1 H), 8.53 (m, 2 H).

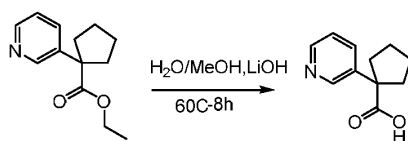
Synthesis of ethyl 1-(pyridin-3-yl)cyclopentane-1-carboxylate:



To a stirred suspension of sodium hydride (7.3g, 181mmol, 60% in oil) in dry THF (160 ml) at 0 °C was added dropwise a solution of ethyl 2-(pyridin-3-yl)acetate (10.0g, 60.5mmol) in dry THF (35 ml). The reaction mixture was stirred at 0°C for 30 min (until ending gas formation). Then dibromo butane (19.6 g, 90.5mmol) was added at 0 °C and the reaction mixture was stirred at ambient temperature for 14 h. Subsequently, the reaction

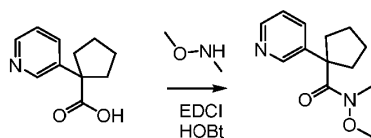
mixture was quenched with aqueous saturated ammonium chloride (60 ml). The reaction mixture was extracted with EtOAc (3 × 40 ml). The organic phase was washed with brine (100ml), dried over anhydrous Na₂SO₄, filtered, and concentrated. The obtained dark solid was purified by flash chromatography (silica gel, eluting with hexane-ethyl acetate, 4:1 to 1:1). Yield 9.8g (74%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.01 min). MS (ESI) m/z 220.6 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.16 (t, 3H), 1.74-1.78 (m, 4H), 1.88-1.98 (m, 2H), 2.67-2.73 (m, 2H), 4.09 (q, 2H), 7.23-7.27 (m, 1H), 7.67-7.71 (m, 1H), 8.49 (dd, 1H), 8.65 (dd, 1H).

Synthesis of 1-(pyridin-3-yl)cyclopentane-1-carboxylic acid:



A solution of ethyl 1-(pyridin-3-yl)cyclopentane-1-carboxylate (8.4g, 38.5mmol) in MeOH (60ml) was added to 20% aqueous solution of LiOH (2.5g, 96.2mmol). The reaction mixture was stirred for 8 h at 60°C. Then the solvent was removed by freeze-drying, and the corresponding crude product was used for the next step without further purification. Yield 7g (80%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.82 min). MS (ESI) m/z 192.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.66-1.70 (m, 4H), 1.85-1.92 (m, 2H), 2.52-2.58 (m, 2H), 7.56 (dd, 1H), 7.98-8.02 (m, 1H), 8.58 (dd, 1H), 8.66 (d, 1H), 12.66 (br.s, 1H).

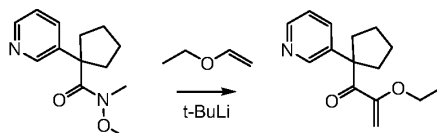
Synthesis of N-methoxy-N-methyl-1-(pyridin-3-yl)cyclopentane-1-carboxamide:



To a stirred mixture of 1-(pyridin-3-yl)cyclopentane-1-carboxylic acid (5.0g, 22.0 mmol), N,O-dimethylhydroxylamine (2.6g, 26.4mmol), HOBt (3.6g, 26.4mmol) and TEA (10.8ml, 77mmol) in DCM (150ml) at 4°C EDCI (5.1g, 26.4mmol) was added. The reaction was stirred overnight at ambient temperature. The mixture was washed with water (100ml), and brine (100ml). The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH) to afford the titular compound. Yield 2.5g (49%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.84 min). MS (ESI) m/z

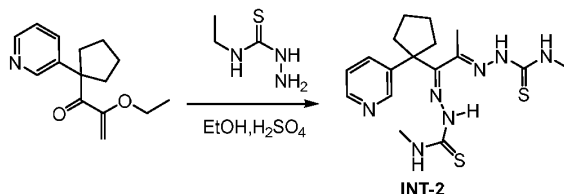
235.3 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.66-1.81 (m, 4H), 2.05-2.11 (m, 2H), 2.42-2.48 (m, 2H), 2.89 (s, 3H), 3.13 (s, 3H), 7.34 (q, 1H), 7.65 (d, 1H), 8.49 (d, 1H), 8.59 (d, 1H).

Synthesis of 2-ethoxy-1-(1-(pyridin-3-yl)cyclopentyl)prop-2-en-1-one:



5 A solution of ethyl vinyl ether (1.69g, 23.6mmol) in tetrahydrofuran (40ml) was cooled to -78°C, and *tert*-butyllithium (1.7M, 13.0ml, 21.5mmol) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-1-(pyridin-3-yl)cyclopentane-1-carboxamide (1.0g, 4.3mmol) in THF
10 (15ml) was added, and the reaction was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl (100ml) and extracted with Et₂O (3 × 50ml). The combined extracts were dried over Na₂SO₄. The solution was decanted, and solvents were removed under reduced pressure. The titular compound was used without further purification. Yield 0.85g (81%). LCMS (C18 column 20 × 2 mm, particle
15 size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.11 min). MS (ESI) m/z 246.4 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.05 (t, 3H), 1.69-1.73 (m, 4H), 2.06-2.08 (m, 2H), 2.46-2.52 (m, 2H), 3.50 (q, 2H), 4.30 (d, 1H), 5.18 (d, 1H), 7.21-7.25 (m, 1H), 7.51-7.54 (m, 1H), 8.45 (dd, 1H), 8.52 (d, 1H).

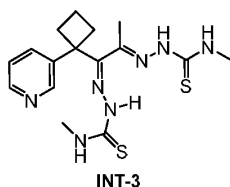
Synthesis of INT-2 ((2Z,2'E)-2,2'-(1-(1-(pyridin-3-yl)cyclopentyl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



2-Ethoxy-1-(1-(pyridin-3-yl)cyclopentyl)prop-2-en-1-one (0.85g, 3.5mmol) was dissolved in EtOH (5ml), methyl thiosemicarbazide (0.80g, 7.7mmol) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and overnight at ambient
25 temperature. The progress of the reaction was monitored by TLC. The precipitate was filtered, washed with EtOH, Et₂O, and dried. Yield 0.21g (15%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.00 min). MS (ESI) m/z 392.3 [MH]⁺.

Synthesis of INT-3 ((2Z,2'E)-2,2'-(1-(1-(pyridin-3-yl)cyclobutyl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

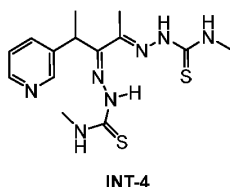
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INT-3 was made using a procedure analogous to the procedure to prepare **INT-2**.

Yield 0.08g (10%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.01 min). MS (ESI) m/z 378.5 [MH]⁺.

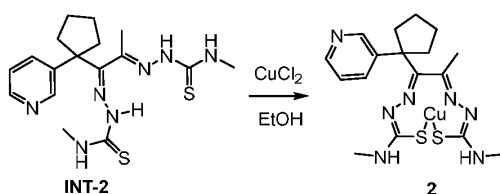
Synthesis of INT-4 ((2Z,2'E)-2,2'-(4-(pyridin-3-yl)pentane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



INT-4 was made using a procedure analogous to the procedure to prepare **INT-2**.

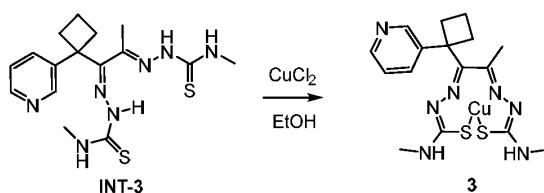
Yield 0.58g (42%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.96 min). MS (ESI) m/z 352.3 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.52 (d, 3H), 2.24 (s, 3H), 2.90 (d, 3H), 3.00 (d, 3H), 5.23 (q, 1H), 7.32-7.34 (m, 1H), 7.39-7.42 (m, 1H), 7.62 (d, 1H), 8.40 (s, 1H), 8.46 (d, 2H), 9.84 (s, 1H), 10.30 (s, 1H).

Synthesis of Compound 2:



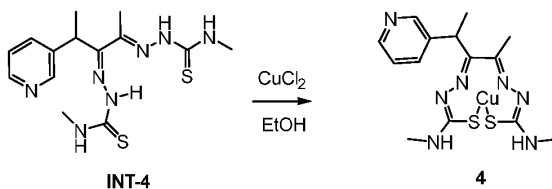
CuCl₂·2H₂O (0.08g, 0.5mmol) was added to **INT-2** (0.18g, 0.46mmol) in ethanol (6 mL). The mixture was stirred overnight at ambient temperature. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.08g (39%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.01). MS (ESI) m/z 453.4 [MH]⁺.

Synthesis of Compound 3:



The titular compound was prepared from **INT-3** according to the method to prepare compound 2. The formed complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.05g (61%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.49). MS (ESI) m/z 439.0 [MH]⁺.

Synthesis of Compound 4:

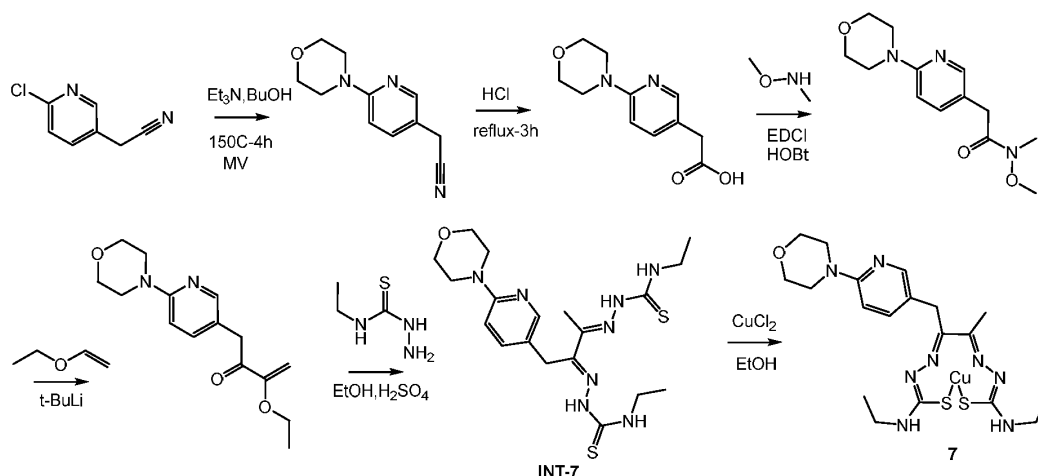


10

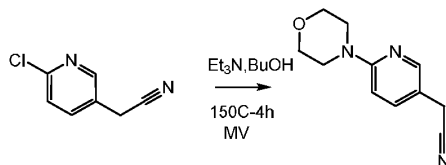
The titular compound was prepared from **INT-4** according to the method to prepare compound 2. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.61g (89%).

15 LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.30). MS (ESI) m/z 413.5 [MH]⁺.

Scheme 3: Synthesis of Compound 7

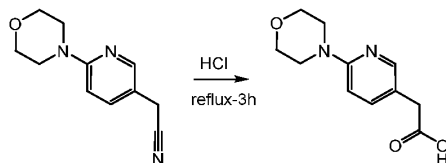


Synthesis of 2-(6-morpholinopyridin-3-yl)acetonitrile:

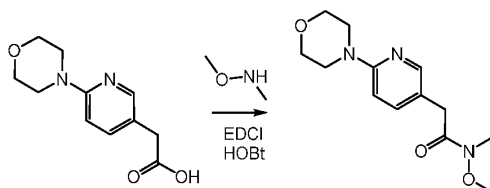


A solution of (6-chloropyridin-3-yl)acetonitrile (1.8g, 11.8 mmol), triethylamine (3.3ml, 23.5mmol) and morpholine (1.13g, 13.1mmol) in *n*-butanol (15 ml) was heated for 2h at 150°C, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, CCl₄-ethyl acetate 8:2). Yield 0.7g (29%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.91 min). MS (ESI) *m/z* 204.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 2.42 (d, 4H), 3.69 (d, 4H), 3.86-3.88 (m, 2H), 6.83-6.87 (m, 1H), 7.52-7.55 (m, 1H), 8.08 (s, 1H).

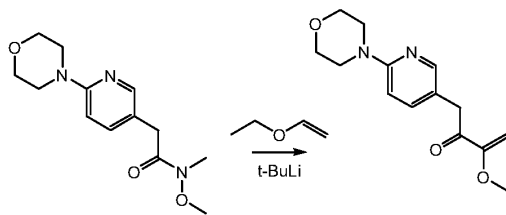
Synthesis of 2-(6-morpholinopyridin-3-yl)acetic acid:



A mixture of 2-(6-morpholinopyridin-3-yl)acetonitrile (1.0g, 5.2 mmol) in conc. hydrochloric acid (15 mL) was refluxed for 3 h. The liquids were stripped off in vacuo to yield the crude product as a white solid (1.40 g, 86.8%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.51 min). MS (ESI) *m/z* 223.6 [MH]⁺. ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 3.66 (s, 2H), 3.73 (s, 8H), 7.36 (d, 1H), 7.94 (dd, 1H), 7.97 (d, 1H), 13.94 (br.s, 1H).

Synthesis of N-methoxy-N-methyl-2-(6-morpholinopyridin-3-yl)acetamide:

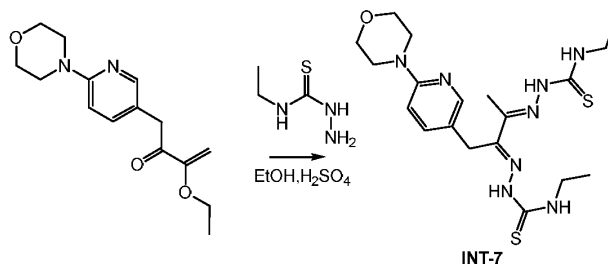
To a mixture of 2-(6-morpholinopyridin-3-yl)acetic acid (1.4g, 4.5 mmol), N,O-dimethylhydroxylamine (0.53g, 5.4mmol), HOBt (0.73g, 5.4mmol) and TEA (2.2ml, 15.7mmol) in DCM (25ml) at 4°C EDCI (1.03g, 5.4mmol) was added. The reaction was stirred overnight at ambient temperature. The mixture was washed with water (100ml), brine (100ml). The organic layer was dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH) to afford the crude titular product. Yield 1.0g (84%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.91 min). MS (ESI) m/z 266.5 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 3.20 (s, 3H), 3.48 (t, 4H), 3.65 (s, 2H), 3.68 (s, 3H), 3.82 (t, 4H), 6.63 (d, 1H), 7.52 (dd, 1H), 8.09 (d, 1H).

Synthesis of 3-ethoxy-1-(6-morpholinopyridin-3-yl)but-3-en-2-one:

A solution of ethyl vinyl ether (3.0g, 41.8mmol) in tetrahydrofuran (50ml) was cooled to -78°C, and *tert*-butyllithium (1.7M, 20.2 ml, 34.6mmol) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45min, cooled down to -30°C, and magnesium bromide etherate (8.9 g, 34.6 mmol) was added. The mixture was warmed to 0°C over a period of 15 min and a solution of N-methoxy-N-methyl-2-(6-morpholinopyridin-3-yl)acetamide (1.0g, 3.8 mmol) in tetrahydrofuran (20 mL) was added. The mixture was allowed to reach r.t. on its own accord and stirred overnight. The progress of the reaction was monitored by TLC. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3 × 50ml). The combined extracts were dried over Na₂SO₄. The solution was decanted, and solvents were removed under reduced pressure. The titular compound was used for the next step without further purification. Yield 0.26g (25%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.96 min). MS (ESI) m/z 277.5 [MH]⁺. ¹H-NMR (400MHz,

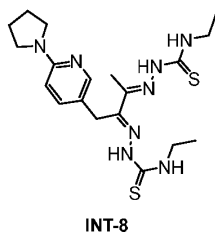
CDCl₃): δ (ppm) 1.43 (t, 3H), 2.01-2.04 (m, 4H), 3.46-3.51 (m, 4H), 3.82 (q, 2H), 3.84 (s, 2H), 4.41 (d, 1H), 5.22 (d, 1H), 6.39 (dd, 1H), 7.38 (dd, 1H), 8.01 (dd, 1H).

Synthesis of INT-7 ((2E,2'E)-2,2'-(1-(6-morpholinopyridin-3-yl)butane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



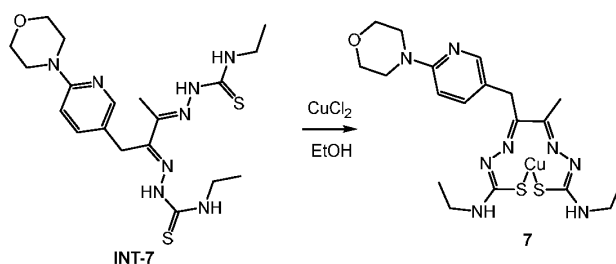
5 3-Ethoxy-1-(6-morpholinopyridin-3-yl)but-3-en-2-one (0.26g, 0.94mmol) was dissolved in EtOH (5ml), ethyl thiosemicarbazide (0.22g, 1.88mmol) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and overnight at ambient temperature. The progress of the reaction was monitored by TLC. The precipitate was
10 filtered, washed with EtOH, Et₂O, and dried. Yield 0.41g (97%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μ m, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.14 min). MS (ESI) m/z 451.5 [MH]⁺.

Synthesis of INT-8 ((2E,2'E)-2,2'-(1-(6-(pyrrolidin-1-yl)pyridin-3-yl)butane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



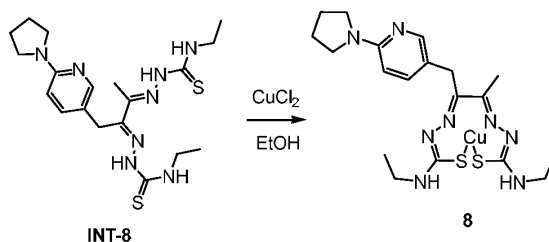
15 INT-8 was made using a procedure analogous to the procedure to prepare INT-7. Yield 0.25g (99%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μ m, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.17 min). MS (ESI) m/z 435.5 [MH]⁺.

20 **Synthesis of Compound 7:**



$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.07g, 0.4mmol) was added to **INT-7** (0.18g, 0.4mmol) in ethanol (6 mL). The mixture was stirred overnight at ambient temperature. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water ($2 \times 50\text{ml}$), ethanol ($2 \times 50\text{ml}$), and copious amounts of diethyl ether ($5 \times 50\text{ml}$), and then dried *in vacuo*. Yield 0.03g (14%). LCMS (C18 column $20 \times 2\text{ mm}$, particle size $2.5\text{ }\mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.55). MS (ESI) m/z 512.7 $[\text{MH}]^+$.

Synthesis of Compound 8:

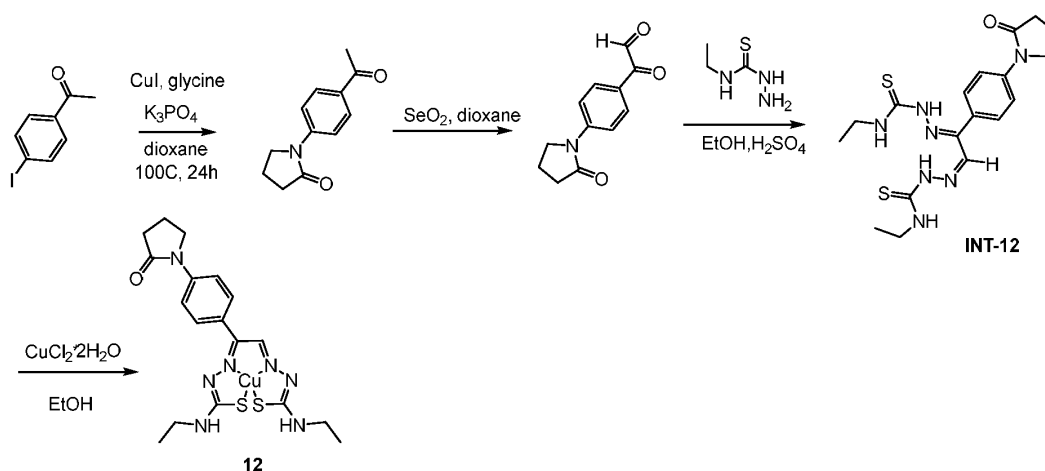


10

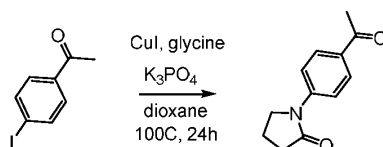
The titular compound was prepared from **INT-8** according to the method to prepare compound 7. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water ($2 \times 50\text{ml}$), ethanol ($2 \times 50\text{ml}$), and copious amounts of diethyl ether ($5 \times 50\text{ml}$), and then dried *in vacuo*. Yield 0.05g (16%). LCMS (C18 column $20 \times 2\text{ mm}$, particle size $2.5\text{ }\mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.57). MS (ESI) m/z 496.5 $[\text{MH}]^+$.

15

Scheme 4: Synthesis of Compound 12

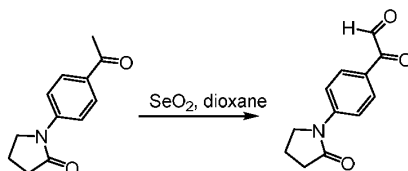


Synthesis of 1-(4-acetylphenyl)pyrrolidin-2-one:



To a mixture of pyrrolidin-2-one (1.7g, 20.0 mmol), 1-(4-iodophenyl)ethanone (4.1g, 16.7 mmol), CuI (0.32g, 1.67 mmol), glycine (0.25g, 3.34 mmol) was added potassium phosphate (2.1g, 40.0 mmol). A glass tube was evacuated, filled with argon at room temperature, and sealed. DMF (0.5 mL) was added under argon via syringe. The mixture was then stirred for 24h at 100°C. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, eluting with gradient 1:8 to 1:2 ethyl acetate-hexanes) to give the titular compound. Yield 3.2 g (94%). ¹H-NMR (400MHz, CDCl₃): δ (ppm) 2.22 (m, 2H), 2.60 (s, 3H), 2.66 (t, 2H), 3.92 (t, 2H), 7.77 (dd, 2H), 7.99 (dd, 2H).

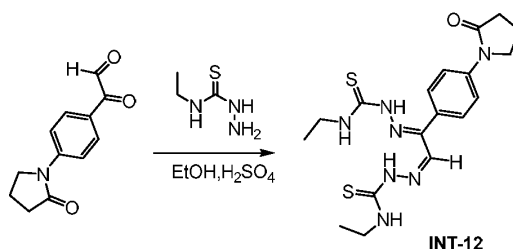
Synthesis of 2-oxo-2-(4-(2-oxopyrrolidin-1-yl)phenyl)acetaldehyde:



A flask was charged with SeO₂ (0.16g, 1.5mmol), 1,4-dioxane (3ml), and water (0.5ml). The mixture was heated to 50°C and stirred until most of SeO₂ was dissolved. 1-(4-acetylphenyl)pyrrolidin-2-one (0.3g, 1.47 mmol) was added, and the reaction was heated at

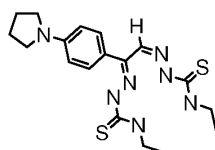
gentle reflux overnight. The progress of the reaction was monitored by TLC (CCl₄-EtOAc 7:3). Selenium solids precipitated over the course of the reaction. The mixture was cooled over an ice bath and filtered through diatomaceous earth to remove the selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was concentrated in vacuo until most of 1,4-dioxane was removed. The crude product was used for the next step without purification. Yield 0.25 g (83%).

Synthesis of INT-12 ((2Z,2'E)-2,2'-(1-(4-(2-oxopyrrolidin-1-yl)phenyl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



2-Oxo-2-(4-(2-oxopyrrolidin-1-yl)phenyl)acetaldehyde (0.25g, 1.2 mmol) was dissolved in EtOH (5 mL), ethyl thiosemicarbazide (0.35g, 2.4 mmol) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The progress of the reaction was monitored by TLC (CCl₄-EtOAc 7:3). The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.45g (73%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.49 min). MS (ESI) m/z 420.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.15 (t, 3H), 1.19 (t, 3H), 2.94-2.11 (m, 2H), 2.28 (s, 1H), 3.36-3.47 (m, 1H), 3.57-3.65 (m, 4H), 3.82 (t, 2H), 7.69-7.82 (m, 4H), 7.94 (d, 1H), 8.23 (s, 1H), 8.91 (t, 1H), 11.77 (s, 1H), 12.31 (s, 1H).

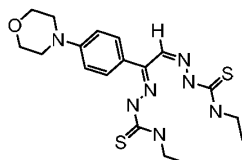
Synthesis of INT-14 ((2Z,2'E)-2,2'-(1-(4-(pyrrolidin-1-yl)phenyl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-14 was made using a procedure analogous to the procedure to prepare **INT-12**. Yield 0.3g (15.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.92 min, MS (ESI) m/z 406.3 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.12-1.24 (m, 6H), 1.91-2.06 (m,

4H), 3.19-3.29 (m, 4H), 3.53-3.66 (m, 4H), 6.58 (d, 2H), 7.65 (d, 2H), 7.93 (br.s, 1H), 8.22 (s, 1H), 8.74 (br.s, 1H), 11.73 (s, 1H), 12.16 (s, 1H).

Synthesis of INT-15 ((2Z,2'E)-2,2'-(1-(4-morpholinophenyl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

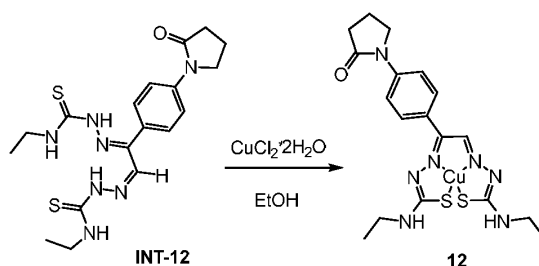


INT-15

INT-15 was made using a procedure analogous to the procedure to prepare **INT-12**.

Yield 1.1 g (53.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.66 min, MS (ESI) m/z 422.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.16 (t, 3H), 1.20 (t, 3H), 3.16-3.24 (m, 4H), 3.54-3.66 (m, 4H), 3.71-3.79 (m, 4H), 7.00 (d, 2H), 7.23 (br.s, 1H), 7.70 (d, 2H), 7.95 (br.s, 1H), 8.83 (br.s, 1H), 11.74 (s, 1H), 12.23 (s, 1H).

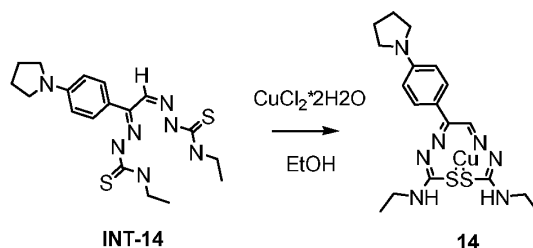
Synthesis of Compound 12:



12

CuCl₂·2H₂O (0.16 g, 0.9mmol) was added to **INT-12** (0.4 g, 0.9mmol) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.016g (4%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.84). MS (ESI) m/z 481.3 [MH]⁺.

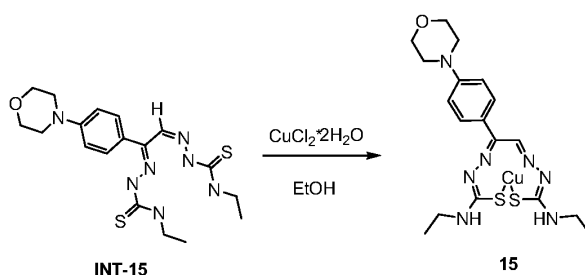
Synthesis of Compound 14:



14

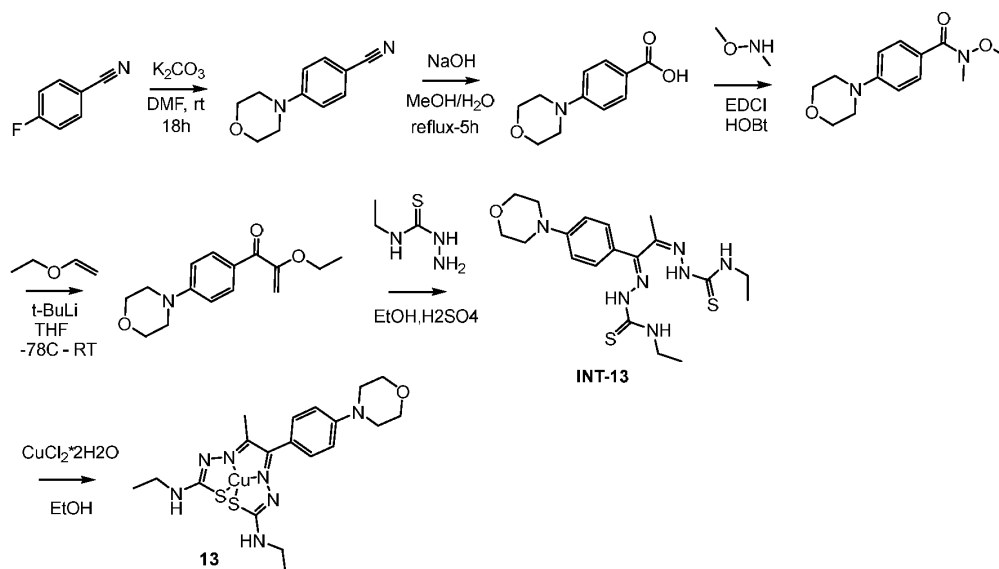
The titular compound was prepared from **INT-14** according to the method to prepare compound 12. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.057 g (49.6%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.34). MS (ESI) m/z 467.0 [MH]⁺.

Synthesis of Compound 15:

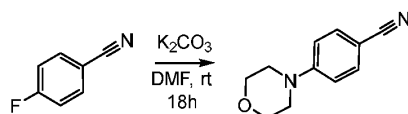


The titular compound was prepared from **INT-15** according to the method to prepare compound 12. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo* to afford the titular product. Yield 0.17g (85%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.97). MS (ESI) m/z 483.5 [MH]⁺.

Scheme 5: Synthesis of Compound 13

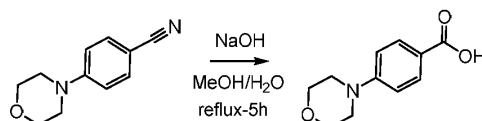


Synthesis of 4-morpholinobenzonitrile:



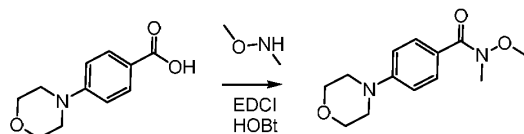
A stirred solution of 4-fluorobenzonitrile (2.0g, 16.5mmol) in anhydrous dimethylformamide (5 ml), morpholine (1.44g, 16.5mmol) and K₂CO₃ (2.85g, 20.6mmol) were added was heated for 18h at 110°C. Water was added and formed precipitate was
 5 filtered, washed with water and hexane. Yield 2.6g (83%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.24 min). MS (ESI) m/z 189.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 3.27 (t, 4H), 3.72 (t, 4H), 7.02 (d, 2H), 7.60 (d, 2H).

Synthesis of 4-morpholinobenzoic acid:



A stirred solution of 4-morpholin-4-yl-benzonitrile (2.6g, 14.7mmol) and sodium hydroxide (2.2g, 58.8mmol) in a mixture of water (90ml) and MeOH (5ml) was heated to reflux over a water bath for 5 hours. Then the solution was cooled to room temperature and acidified with aq HCl (10%). The precipitate was filtered, washed with water, dried *in vacuo*
 15 at 60°C and crystallized from EtOH to give compound **2**. Yield 2.0 g (70%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 3.12 (t, 2H), 3.24 (t, 2H), 3.73 (t, 4H), 6.96 (t, 2H), 7.77 (t, 2H), 12.31 (br.s, 1H).

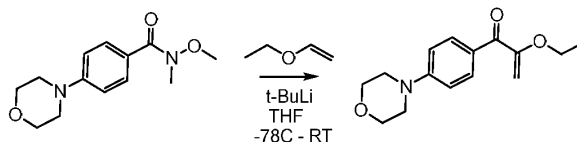
Synthesis of N-methoxy-N-methyl-4-morpholinobenzamide:



To a mixture of 4-morpholinobenzoic acid (1.4g, 6.7mmol), N,O-dimethylhydroxylamine (1.3g, 8.7mmol), HOBT (1.0g, 7.7mmol) and TEA (0.9ml, 9mmol) in DCM (25ml) at 4°C EDCI (1.4g, 9 mmol) was added. The reaction was stirred overnight at ambient temperature. The mixture was washed with water (15ml), aq. 1N HCl (20ml), water (50ml), brine (100ml). The organic layer was dried over anhydrous Na₂SO₄, filtered, and then
 25 concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH) to afford the crude titular product. Yield 0.97g (58%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.12 min). MS (ESI) m/z

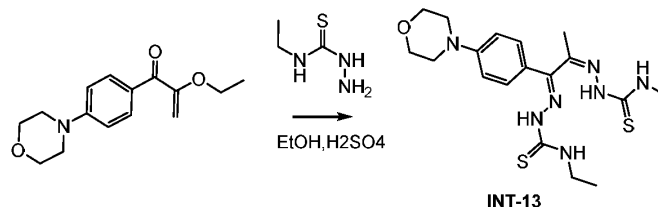
251.6 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 3.26 (t, 4H), 3.36 (s, 3H), 3.59 (s, 3H), 3.89 (t, 4H), 6.89 (d, 2H), 7.74 (d, 2H).

Synthesis of 2-ethoxy-1-(4-morpholinophenyl)prop-2-en-1-one:



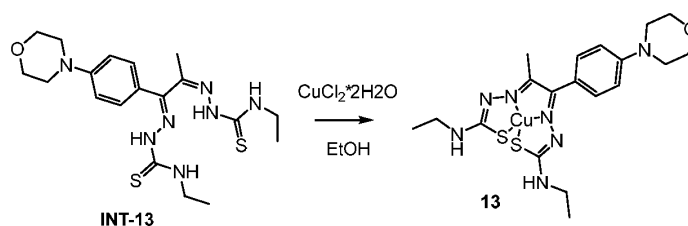
- 5 A solution of ethyl vinyl ether (0.9g, 12.2mmol) in dry tetrahydrofuran (25 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M, 6.6ml, 11.1mmol) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. Then a solution of N-methoxy-N-methyl-4-morpholinobenzamide (0.93g, 3.7mmol) in THF (10ml) was added, and the mixture was stirred at 0°C for 4 h. The progress of the reaction
- 10 was monitored by TLC. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over Na₂SO₄, filtered, and evaporated. The product was used for the next step without additional purification. Yield 0.6 g (62%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.40 min). MS (ESI) m/z
- 15 262.0 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.42 (t, 3H), 3.33 (t, 4H), 3.87 (t, 4H), 3.94 (q, 2H), 4.65 (d, 1H), 4.91 (d, 1H), 6.87 (d, 2H), 7.92 (d, 2H).

Synthesis of INT-13 ((2Z,2'E)-2,2'-(1-(4-morpholinophenyl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



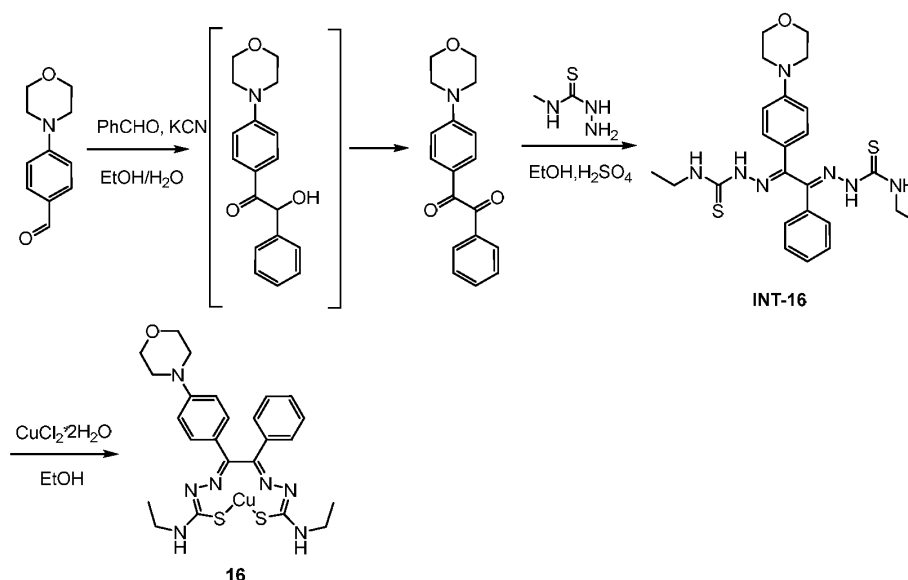
- 20 2-Ethoxy-1-(4-morpholinophenyl)prop-2-en-1-one (0.6g, 2.3 mmol) was dissolved in EtOH (5 ml), ethyl thiosemicarbazide (0.6 g, 5.1 mmol) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.3g (30%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-
- 25 acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.49 min). MS (ESI) m/z 436.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 0.93 (t, 3H), 1.15 (t, 3H), 2.33 (s, 3H), 3.19 (t, 4H), 3.34-3.38 (m, 2H), 3.56-3.63 (m, 2H), 3.75 (t, 4H), 6.97 (t, 1H), 7.12 (q, 4H), 8.70 (s, 1H), 8.74 (t, 1H), 10.75 (s, 1H).

Synthesis of Compound 13:

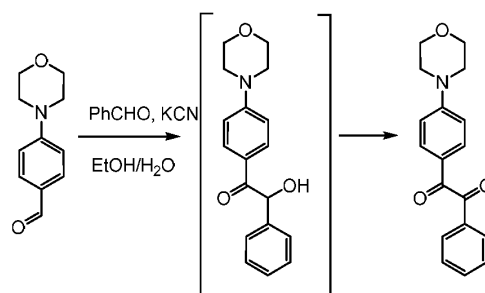


$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.07g, 0.4mmol) was added to **INT-13** (0.17 g, 0.4mmol) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.2 g (99%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.87). MS (ESI) m/z 497.4 $[\text{MH}]^+$.

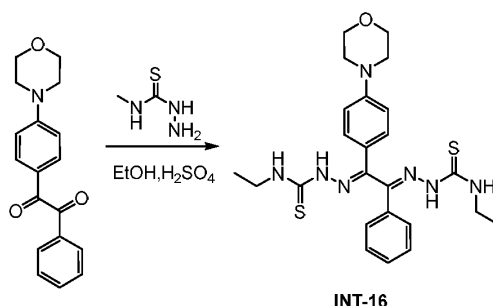
Scheme 6: Synthesis of Compound 16



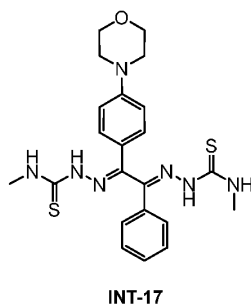
10 Synthesis of 1-(4-morpholinophenyl)-2-phenylethane-1,2-dione:



- To a stirred solution of 4-morpholinobenzaldehyde (24.0g, 125 mmol) and benzaldehyde (13.3g, 125 mmol) in EtOH (50 mL) was added a solution of potassium cyanide (0.43g, 66 mmol) in water (35 ml). The mixture was stirred at reflux for 5h, cooled down to ambient temperature. The solution was placed in a refrigerator for a fractional crystallization at ~8°C. The formed precipitate primarily composed of the alpha-hydroxy ketone was removed by filtration and discarded, the filtrate was evaporated to dryness in vacuo. The residue was purified by column chromatography (silica gel, eluent EtOAc-hexane). Yield 2.2g (6%). ¹H-NMR (400MHz, CDCl₃): δ (ppm) 3.36-3.40 (m, 4H), 3.84-3.89 (m, 4H), 6.87 (d, 2H), 7.50 (dd, 2H), 7.64 (dd, 1H), 7.88 (d, 2H), 7.99 (d, 2H).
- 10 **Synthesis of INT-16 ((2E,2'E)-2,2'-(1-(4-morpholinophenyl)-2-phenylethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**



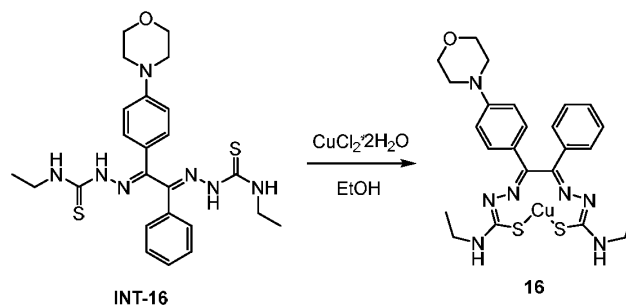
- 1-(4-morpholinophenyl)-2-phenylethane-1,2-dione (0.61g, 2.06 mmol, 1 eq) was dissolved in EtOH (15 ml), methyl thiosemicarbazide (0.45g, 2 eq) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.45 g (44%). ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 1.13-1.19 (m, 6H), 3.17-3.20 (m, 4H), 3.55 (q, 4H), 3.70-3.75 (m, 4H), 6.94 (d, 2H), 7.42-7.47 (m, 3H), 7.55 (d, 2H), 7.70-7.74 (m, 2H), 8.88 (ddd, 2H), 9.49 (d, 2H).
- 20 **Synthesis of INT-17 ((2E,2'E)-2,2'-(1-(4-morpholinophenyl)-2-phenylethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):**



INT-17 was made using a procedure analogous to the procedure to prepare **INT-16**.

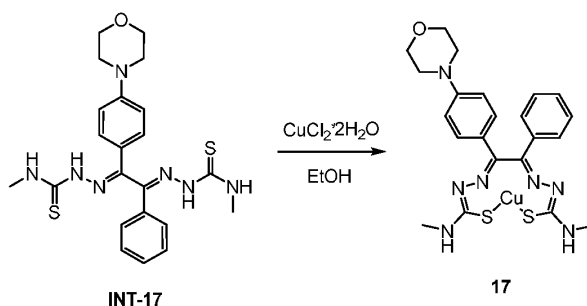
Yield 0.31 g (36%). ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 2.99-3.06 (m, 6H), 3.17-3.20 (m, 4H), 3.70-3.74 (m, 4H), 6.94 (d, 2H), 7.42-7.47 (m, 3H), 7.55 (d, 2H), 7.70-7.74 (m, 2H), 8.84 (ddd, 2H), 9.49 (d, 2H).

5 **Synthesis of Compound 16:**



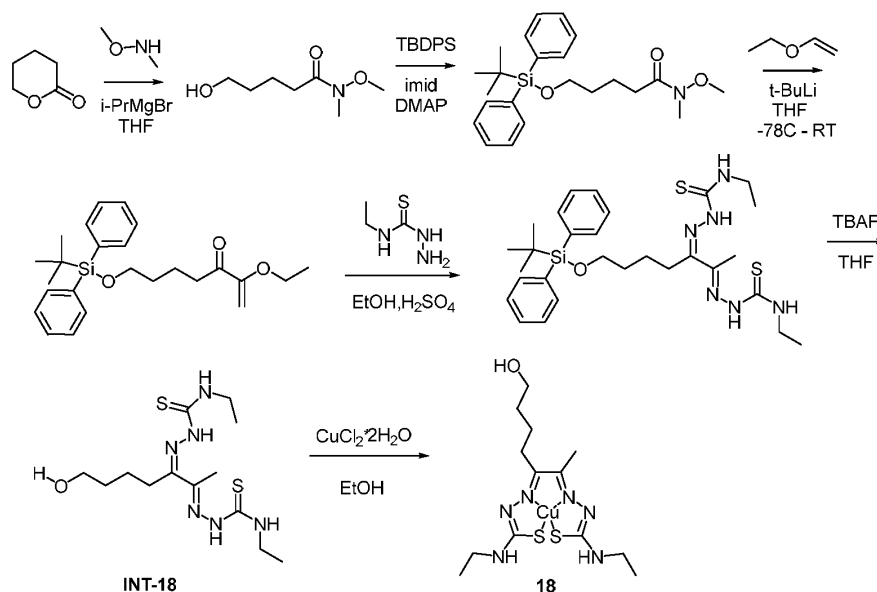
$\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (0.06g, 1.1 eq) was added to **INT-16** (0.12g, 0.26 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.03g (22%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.21 min). MS (ESI) *m/z* 559.0 [MH]⁺.

Synthesis of Compound 17:

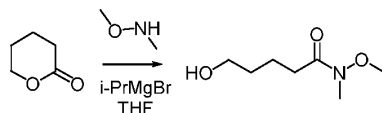


The titular compound was prepared from **INT-17** according to the method to prepare compound 16. The formed complex was precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.03g (22%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.24 min). MS (ESI) *m/z* 531.2 [MH]⁺.

Scheme 7: Synthesis of Compound 18

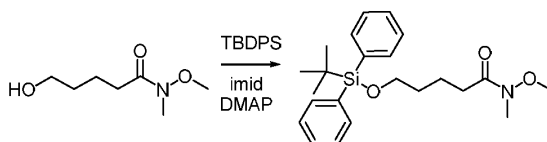


Synthesis of 5-hydroxy-N-methoxy-N-methylpentanamide:



- To a suspension of lactone (4 g, 40 mmol, 1 eq) and N,O-dimethylhydroxylamine hydrochloride (6.04 g, 1.55 eq) in THF (150 ml) at -20°C, 2.9 M solution of *i*-PrMgBr in 2-methyltetrahydrofuran (50 ml, 3.6 eq) was added dropwise over a period of 30 minutes. The mixture was stirred at -20°C for 3 hours and quenched with 50mL of saturated NH₄Cl solution. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated *in vacuo*. The residue was purified by column chromatography (eluent 80/20 EtOAc/hexanes to 100% EtOAc). Yield 2.0g (31%). NMR (400MHz, CDCl₃): 1.57-1.63 (m, 2H), 1.70-1.76 (m, 2H), 2.44-2.50 (m, 2H), 3.18 (s, 3H), 3.62 (t, 2H), 3.68 (s, 2H). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.90 min), MS (ESI) *m/z* 162.4 [MH]⁺.

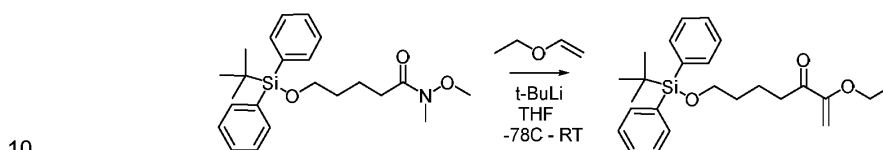
- Synthesis of 5-((tert-butyldiphenylsilyl)oxy)-N-methoxy-N-methylpentanamide:**



A mixture of 5-hydroxy-N-methoxy-N-methylpentanamide (2.1 g, 13 mmol, 1 eq), *tert*-butyldiphenylsilyl chloride (5.4g, 5 ml, 1.5 eq), imidazole (1.6g, 1.8 eq) and DMAP (0.16g,

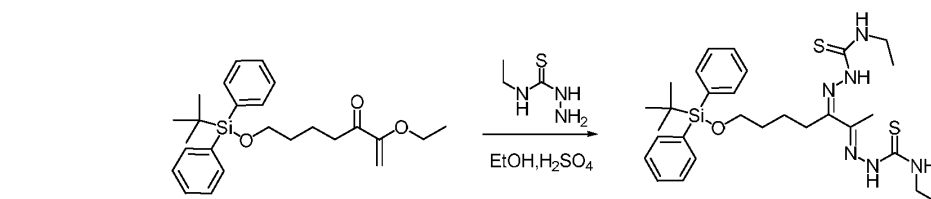
0.1 eq) in DMF (25 ml) was stirred for 15h at ambient temperature. The reaction mixture was diluted with water (200 ml) and extracted with EtOAc (3 × 60 ml). Combined organic layers were dried over Na₂SO₄, filtered and solvents were evaporated. The residue was purified by column chromatography SiO₂/hexane, hexane:EtOAc 5:1. Yield 3g (58.6%). NMR (400MHz, CDCl₃): 1.20 (s, 9H), 1.60-1.66 (m, 2H), 1.70-1.78 (m, 2H), 2.41-2.47 (m, 2H), 3.19 (s, 3H), 3.65 (s, 3H), 3.70 (t, 2H), 7.38-7.44 (m, 6H), 7.66-7.71 (m, 4H). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 2.20 min), MS (ESI) m/z 400.5 [MH]⁺.

Synthesis of 7-((tert-butylidiphenylsilyl)oxy)-2-ethoxyhept-1-en-3-one:



A solution of ethyl vinyl ether (1.8g, 2.4 ml, 3.3 eq) in dry tetrahydrofuran (50 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M, 13 ml, 3 eq) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. 5-((tert-butylidiphenylsilyl)oxy)-N-methoxy-N-methylpentanamide was added (3.0g, 7.5 mmol, 1 eq) in THF, and the mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered and solvents were evaporated. The product was used for the next step without additional purification. Yield 2.5g (81%). NMR (400MHz, CDCl₃): 1.02 (s, 9H), 1.35 (t, 3H), 1.58-1.62 (m, 2H), 1.70-1.76 (m, 2H), 2.69 (t, 2H), 3.68 (t, 2H), 3.81 (q, 2H), 4.40 (d, 1H), 5.18 (d, 1H), 7.38-7.43 (m, 6H), 7.64-7.68 (m, 4H).

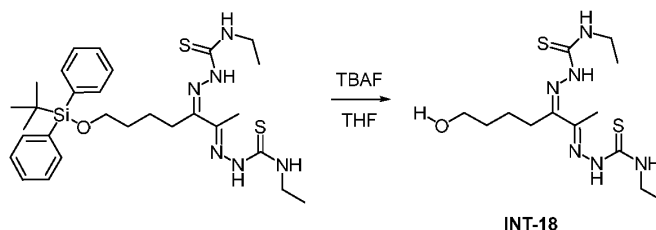
Synthesis of (2Z,2'E)-2,2'-(7-((tert-butylidiphenylsilyl)oxy)heptane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide):



7-((tert-butylidiphenylsilyl)oxy)-2-ethoxyhept-1-en-3-one (2.0g, 4.9mmol, 1 eq) was dissolved in EtOH (50 ml), ethyl thiosemicarbazide (1.16g, 2 eq) and 3 drops of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 1.71 g (60%). NMR (400MHz, DMSO-*d*₆): 0.88 (s, 9H), 6.72 (t, 6H), 1.40-

1.60 (m, 4H), 2.18 (s, 3H), 3.38-3.43 (m, 4H), 3.56-3.62 (m, 4H), 7.38-7.44 (m, 6H), 7.56-7.61 (m, 4H), 10.21-10.23 (m, 2H), 10.38-10.42 (m, 2H).

Synthesis of INT-18 ((2Z,2'E)-2,2'-(7-(tert-butyldiphenylsilyl)oxy)heptane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

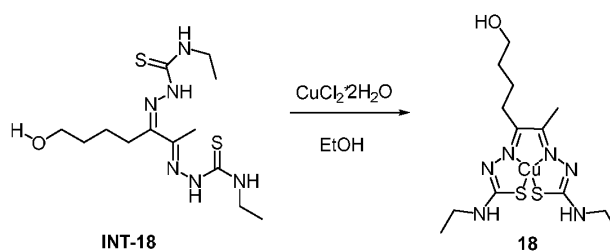


5

A mixture of (2Z,2'E)-2,2'-(7-((tert-butyldiphenylsilyl)oxy)heptane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide) (1.3g, 2.3 mmol) and *n*-tetrabutylammonium fluoride trihydrate (0.88 g, 1.2 eq) in THF (25 ml) was stirred at ambient temperature for 15h. The reaction mixture was diluted with water (150 ml) and extracted with EtOAc (3 × 60 ml). The organic layer was separated, dried over Na₂SO₄, filtered and solvents were evaporated. Yield 0.53 g (65%). NMR (400MHz, DMSO-*d*₆): 1.10-1.16 (m, 6H), 1.38-1.48 (m, 4H), 2.19 (s, 3H), 2.84-2.87 (m, 2H), 3.41-3.47 (m, 2H), 3.58-3.62 (m, 4H), 4.50 (t, 1H), 8.26-8.38 (m, 2H), 10.20 (s, 1H), 10.41 (s, 1H).

10

Synthesis of Compound 18:

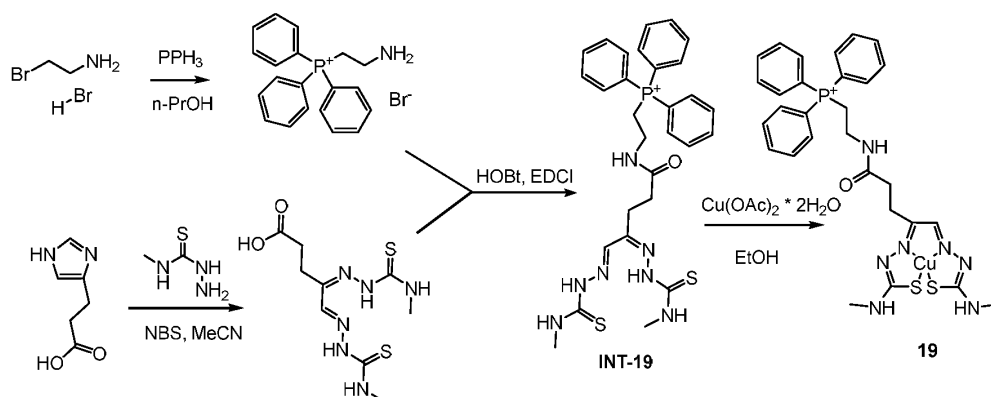


15

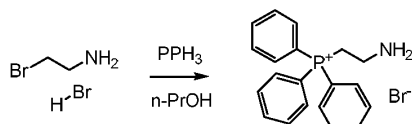
Cu(OAc)₂·2H₂O (0.12 g, 1.1 eq) was added to INT-18 (0.18 g, 0.5 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.06 g (25%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.74 min). MS (ESI) *m/z* 408.5 [MH]⁺.

20

Scheme 8: Synthesis of Compound 19

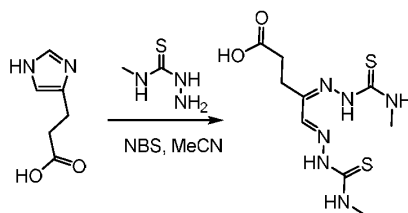


Synthesis of (2-aminoethyl)triphenylphosphonium bromide:



A stirred solution of triphenylphosphine (4.3 g, 16.6 mmol) and 2-bromoethylamine hydrobromide (3.4g, 16.6 mmol) in *n*-propanol (100 ml) was heated to reflux for 72 hr under nitrogen atmosphere. Then the mixture was cooled to r.t., solids were filtered, washed with portions of dry ether, and dried *in vacuo*. The product was dissolved in 50 ml of water, insoluble solids were filtered, and filtrate was concentrated *in vacuo* to dryness resulting in the titular compound (6.40g, 100%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.25 min, MS (ESI) *m/z* 306.5 [MH]⁺.

Synthesis of (4Z,5E)-4,5-bis(2-(methylcarbamothioyl)hydrazineylidene)pentanoic acid:

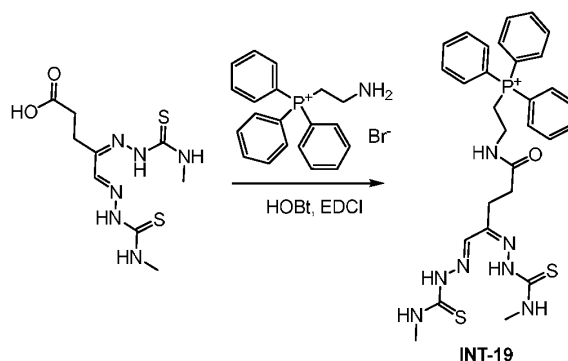


To a stirred solution of imidazole propionic acid (0.5 g, 3.6 mmol) in water (18mL) a solution of NBS (0.63 g, 1 eq) in acetonitrile (5.5 mL) was added in a single portion. After stirring for 20 min. acetonitrile was removed *in vacuo*. To the reaction mixture a solution of sodium acetate trihydrate (0.7 g) and methyl thiosemicarbazide (1.12 g, 3 eq) in water (7.5 mL) was added. Crystals started forming within 5 min. The crystallization continued for 14h at ambient temperature, the precipitate was filtered, and recrystallized from water. Yield 0.34g (31.3%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-

acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.10 min, MS (ESI) m/z 305.0 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.41 (br.s, 2H), 2.91 (br.s, 2H), 2.99 (br.s, 6H), 7.60 (s, 1H), 8.29 (br.s, 1H), 8.54 (br.s, 1H), 10.80 (s, 1H), 11.73 (s, 1H).

Synthesis of INT-19 ((2-((4Z,5E)-4,5-bis(2-

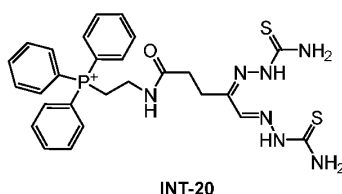
5 (methylcarbamothioyl)hydrazineylidene)pentanamido)ethyl)triphenylphosphonium):



A mixture of (4Z,5E)-4,5-bis(2-(methylcarbamothioyl)hydrazineylidene)pentanoic acid (0.44 g, 1.4 mmol), (2-aminoethyl)triphenylphosphonium bromide (0.55 g, 1 eq.), EDCI (0.3 g, 1.1 eq), and HOBt (0.21 g, 1.1 eq) in DMF (15 ml) was stirred overnight at r.t. The reaction mixture was diluted with water (50 ml), extracted with dichloromethane (3x20 ml), extracts were dried over Na₂SO₄, filtered, and evaporated. Yield 0.2 g (23.3%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.17 min, MS (ESI) m/z 592.8 [MH]⁺.

Synthesis of INT-20 ((2-((4Z,5E)-4,5-bis(2-

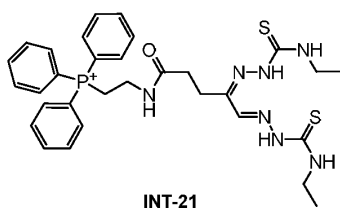
15 carbamothioyl)hydrazineylidene)pentanamido)ethyl)triphenylphosphonium):



INT-20 was made using a procedure analogous to the procedure to prepare **INT-19**. Yield 0.76 g (74.4%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.30-2.43 (m, 2H), 2.77-2.92 (m, 2H), 7.59 (s, 1H), 7.80 (br.s, 1H), 7.92 (br.s, 1H), 8.33 (br.s, 1H), 8.39 (br.s, 1H), 10.76 (s, 1H), 11.65 (s, 1H).

Synthesis of INT-21 ((2-((4Z,5E)-4,5-bis(2-

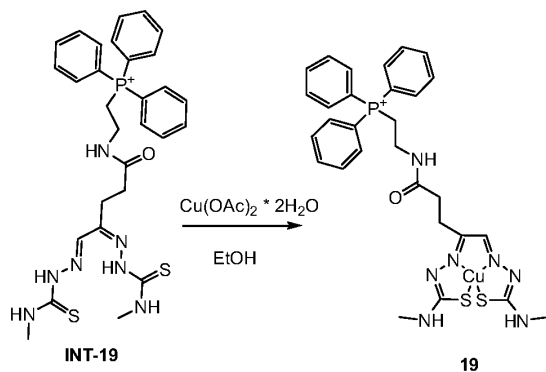
(ethylcarbamothioyl)hydrazineylidene)pentanamido)ethyl)triphenylphosphonium):



INT-21 was made using a procedure analogous to the procedure to prepare **INT-19**.

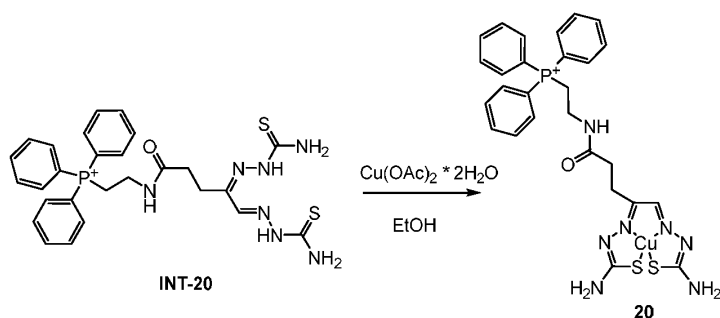
Yield 0.76 g (74.4%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.33 min, MS (ESI) m/z 620.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.00-1.21 (m, 6H), 2.29 (br.s, 2H), 2.87 (br.s, 2H), 3.34 (br.s, 2H), 3.49-3.55 (m, 4H), 3.65-3.77 (m, 2H), 7.58 (s, 1H), 7.77-7.96 (m, 15H), 8.41 (br.s, 1H), 8.53 (br.s, 1H), 8.60 (br.s, 1H), 10.74 (s, 1H), 11.74 (s, 1H).

Synthesis of Compound 19:



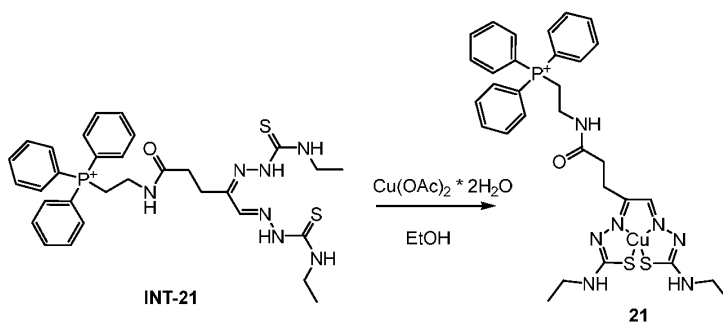
INT-19 (0.087g, 0.1 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.018g (19%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.56 min). MS (ESI) m/z 653.3 [MH]⁺.

Synthesis of Compound 20:



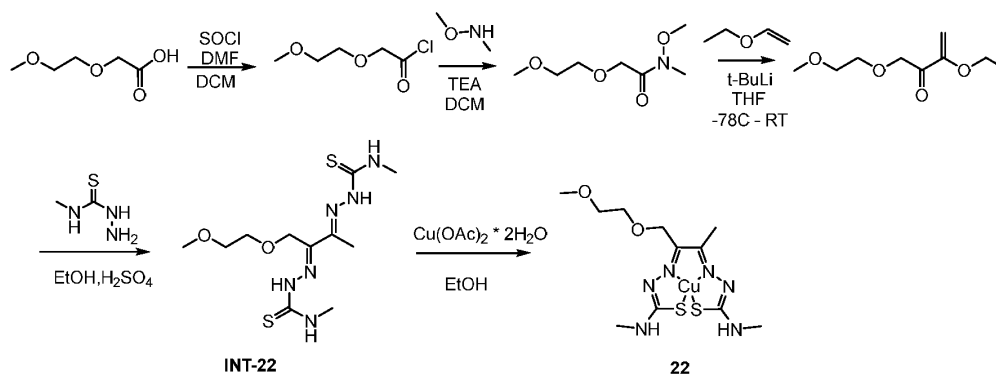
The titular compound was prepared from **INT-20** according to the method to prepare compound 19. The product was precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.09g (45%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.49 min). MS (ESI) m/z 625.3 $[\text{MH}]^+$.

Synthesis of Compound 21:

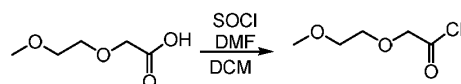


The titular compound was prepared from **INT-21** according to the method to prepare compound 19. The product was precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.09g (45%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.79 min). MS (ESI) m/z 681.2 $[\text{MH}]^+$.

Scheme 9: Synthesis of Compound 22

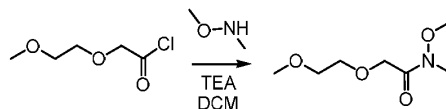


Synthesis of 2-(2-methoxyethoxy)acetyl chloride:



To a solution of acid (1) (5.0g, 37 mmol) in CH_2Cl_2 (100 mL) few drops of DMF were added followed by SOCl_2 (13.3g, 3 eq) and the mixture was stirred at ambient temperature for 15h. The solvents were evaporated giving compound (2) (4.4g, 78%) that was used for the next step without additional purification. NMR (400MHz, CDCl_3): 3.37 (s, 3H), 3.57-3.60 (m, 2H), 3.74-3.78 (m, 2H), 4.50 (s, 2H).

Synthesis of N-methoxy-2-(2-methoxyethoxy)-N-methylacetamide:

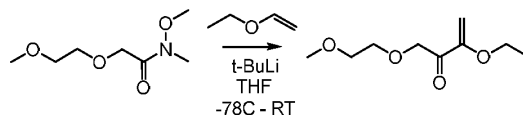


10

To a solution of 2-(2-methoxyethoxy)acetyl chloride (4.4g, 29 mmol) in CH_2Cl_2 (100 mL) N,O-dimethylhydroxylamine hydrochloride was added (3.4g, 1.2 eq) followed by Et_3N (11.7g, 4 eq). The mixture was stirred at ambient temperature for 15h, quenched with 10% aq HCl, extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 , filtered and solvents were evaporated. The residue was purified on silica gel eluting with a gradient from 10% to 75% EtOAc in hexane giving compound (3) (2.7g, 53%). NMR (400MHz, CDCl_3): 3.18 (s, 3H), 3.39 (s, 3H), 3.57-3.64 (m, 2H), 3.68 (s, 3H), 3.73-3.77 (m, 2H), 4.34 (s, 2H).

15

Synthesis of 3-ethoxy-1-(2-methoxyethoxy)but-3-en-2-one:

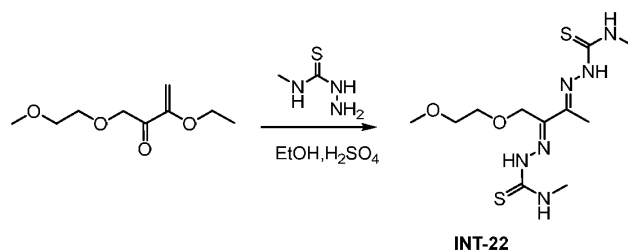


20

A solution of ethyl vinyl ether (2.0g, 2.7 ml, 3.3 eq) in dry tetrahydrofuran (75 mL) was cooled to -78°C , and *tert*-butyllithium (1.7M, 15 ml, 3 eq) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -

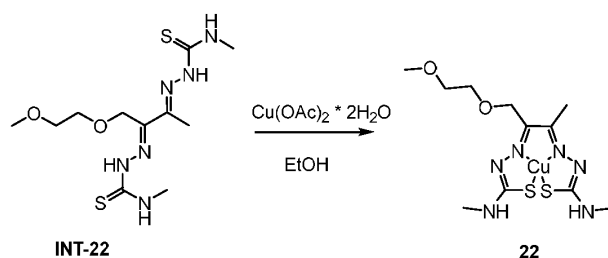
30°C. N-methoxy-2-(2-methoxyethoxy)-N-methylacetamide was added (1.53g, 8.6 mmol, 1 eq) in THF, and the mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered and solvents were evaporated. The product was used for the next step without additional purification. Yield 0.73g (45%) NMR (400MHz, DMSO-*d*₆): 1.28 (t, 3H), 3.22 (s, 3H), 3.32 (s, 2H), 3.42-3.46 (m, 2H), 3.53-3.58 (m, 2H), 4.52 (s, 2H), 4.62 (d, 1H), 5.10 (d, 1H).

Synthesis of INT-22 ((2Z,2'E)-2,2'-(1-(2-methoxyethoxy)butane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



3-ethoxy-1-(2-methoxyethoxy)but-3-en-2-one (0.73 g, 3.9 mmol, 1 eq) was dissolved in EtOH (100 ml), methyl thiosemicarbazide (0.82 g, 2 eq) and 3 drops of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.2 g (15%). NMR (400MHz, DMSO-*d*₆): 2.20 (s, 3H), 3.02, 3.04 (m, 6H), 3.28 (s, 3H), 3.48-3.60 (m, 4H), 4.84 (s, 2H), 8.38-8.50 (m, 2H), 10.23 (s, 1H), 10.58 (s, 1H). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.34 min), MS (ESI) *m/z* 335.6 [MH]⁺.

Synthesis of Compound 22:

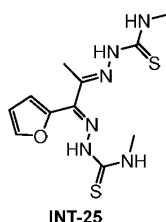


Cu(OAc)₂·2H₂O (0.16 g, 1.1 eq) was added to thiosemicarbazone 5 (0.2 g, 0.66 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in*

vacuo. Yield 0.06 g (25%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.77 min). MS (ESI) m/z 396.3 [MH]⁺.

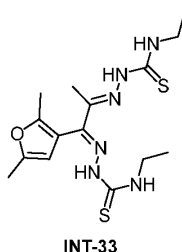
5 Example 2: Preparation of Compounds 23-46

Synthesis of INT-25 ((2Z,2'E)-2,2'-(1-(furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



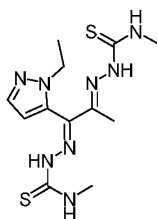
10 **INT-25** was made using a procedure analogous to the procedure to prepare **INT-1** of Example 1. Yield 6.78g (78%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.34 min). MS (ESI) m/z 313.4 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 2.25 (s, 3H), 3.20 (s, 3H), 3.28 (s, 3H), 6.62 (d, 1H), 6.84 (d, 1H), 7.31 (s, 1H), 7.33 (s, 1H), 7.53 (s, 1H), 7.71 (s, 1H), 8.79 (s, 1H), 10.52 (s, 1H).

15 **Synthesis of INT-33 ((2E,2'E)-2,2'-(1-(2,5-dimethylfuran-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**



20 **INT-33** was made using a procedure analogous to the procedure to prepare **INT-1** of Example 1. Yield 1.8g (48%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.60 min). MS (ESI) m/z 369.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.07 (t, 3H), 1.15 (t, 3H), 2.06 (s, 3H), 2.28 (s, 3H), 2.30 (s, 3H), 3.41-3.48 (m, 2H), 3.55-3.63 (m, 2H), 6.09 (s, 1H), 6.84 (d, 1H), 7.37 (t, 1H), 8.69 (t, 1H), 9.52-10.52 (m, 1H).

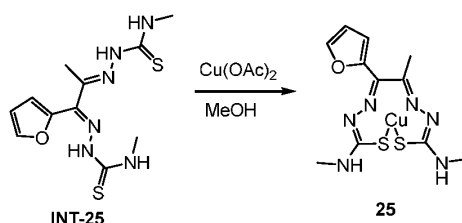
25 **Synthesis of INT-41 ((2E,2'E)-2,2'-(1-(1-ethyl-1H-pyrazol-5-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):**



INT-41

INT-41 was made using a procedure analogous to the procedure to prepare INT-1 of Example 1. Yield 0.55 g (52.9%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.83 min, MS (ESI) m/z 341.3 [MH]⁺.

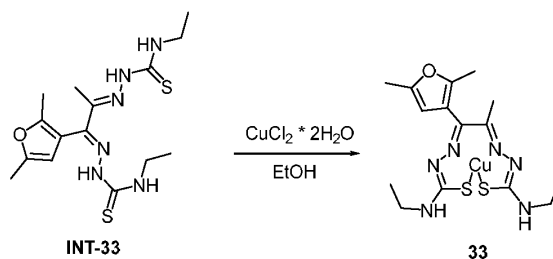
Synthesis of Compound 25:



The titular compound was prepared from INT-25 according to the method to prepare compound 1 of Example 1. Yield 6.2g (76%). ICP/MS Sulfur:17.36%, Copper: 16.518%.

- 10 LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.11 min). MS (ESI) m/z 374.1 [MH]⁺.

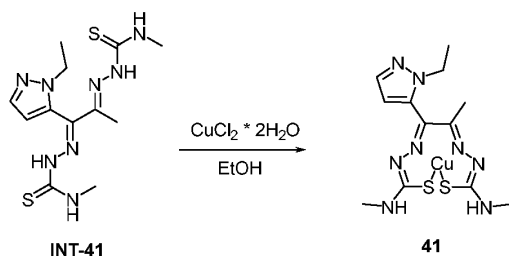
Synthesis of Compound 33:



- 15 The titular compound was prepared from INT-33 according to the method to prepare compound 1 of Example 1. The product was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.7g (75%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-

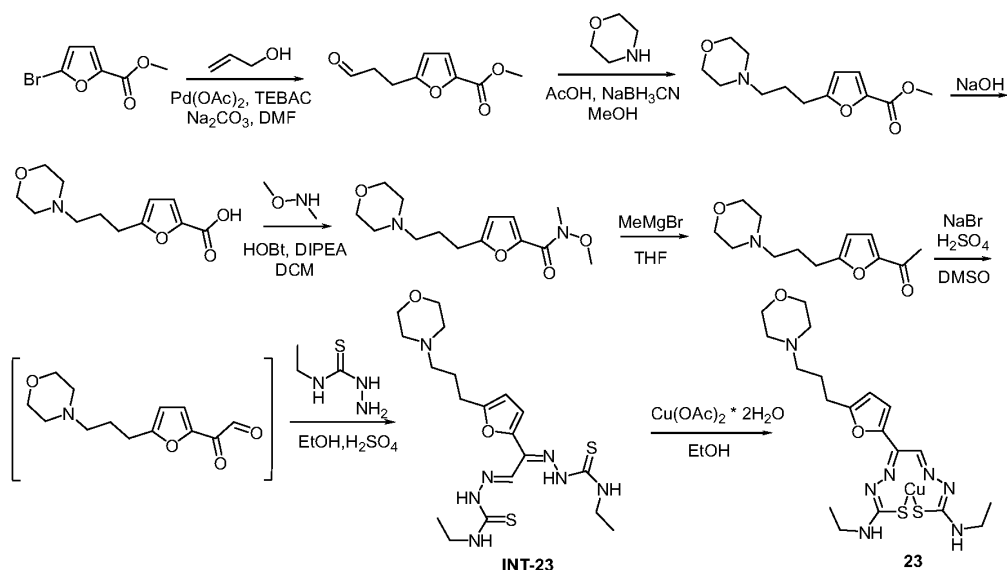
acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.34 min). MS (ESI) m/z 430.5 [MH]⁺.

Synthesis of Compound 41:

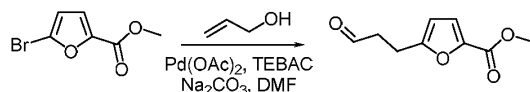


- 5 The titular compound was prepared from **INT-41** according to the method to prepare compound 1 of Example 1. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.18g (55.7%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for
- 10 4min, retention time 1.80 min). MS (ESI) m/z 401.8 [MH]⁺.

Scheme 10: Synthesis of Compound 23



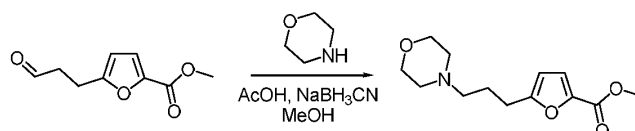
Synthesis of methyl 5-(3-oxopropyl)furan-2-carboxylate:



- 15 Under inert atmosphere, to a stirred solution of methyl 5-bromofuroate (5.7g, 28mmol, 1 eq) in DMF (550 ml) were added allyl alcohol (2.28g, 1.4 eq), Pd(OAc)₂

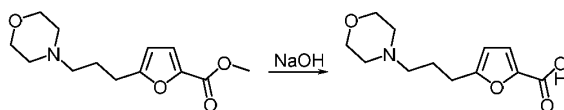
(0.189g, 0.03 eq), TEBAAC (6.39 g, 1 eq) and Na_2CO_3 (6.85g, 2 eq). Then the mixture was stirred at 80°C for 2 h. Once the reaction has reached completion, the resulting mixture was filtered through Celite, concentrated at $\leq 40^\circ\text{C}$ in vacuo, diluted with ethyl acetate, washed with brine, concentrated in vacuo to dryness, and the residue was purified by column chromatography (ethyl acetate : hexane 1 : 3). Yield 2.7g (53%). $^1\text{H-NMR}$ (400MHz, CDCl_3): δ (ppm) 2.89(dd, 2H), 3.05(dd, 2H), 3.89(s, 3H), 6.19(s, 1H), 7.09(s, 1H), 9.83(s, 1H).

Synthesis of methyl 5-(3-morpholinopropyl)furan-2-carboxylate:



Methyl 5-(3-oxopropyl)furan-2-carboxylate (1.6g, 9mmol, 1 eq) was dissolved in MeOH (90 ml) and molecular sieves 3A (2.64g) were added to the solution. After stirring for 15 min, the mixture was cooled to 0°C. To the stirred solution of aldehyde was added a solution of morpholine (1.15g, 1.5 eq) and acetic acid (1.05g, 2 eq) in methanol (42 ml). After stirring for 2 min, NaBH_3CN (1.66g, 3 eq) was added. The resulting mixture was stirred for 14 h at 0°C allowing to reach ambient temperature on its own accord. The reaction mixture was diluted with DCM, filtered through Celite, and filtrate was washed with aq. NaHCO_3 . The aqueous phase was extracted with DCM twice. The organic phase was dried over Na_2SO_4 , filtered, and solvents were evaporated. The residue was purified by column chromatography (SiO_2 , eluting with EtOAc-hexane 1:5 to 1:3 to 1:1 to 100% EtOAc, and then with CH_2Cl_2 -MeOH, 10:1). Yield 1.5g (68%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.28 min. MS (ESI) m/z 254.4 $[\text{MH}]^+$, retention time 0.8 min. MS (ESI) m/z 254.6 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400MHz, CDCl_3): δ (ppm) 1.86-1.94 (m, 2H), 2.39-2.44 (m, 2H), 2.44-2.53 (m, 4H), 2.66-2.86 (m, 2H), 3.68-3.77 (m, 4H), 3.88(s, 3H), 6.16(d, 1H), 7.11(d, 1H).

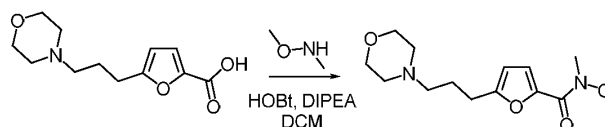
Synthesis of 5-(3-morpholinopropyl)furan-2-carboxylic acid:



To a solution of methyl 5-(3-morpholinopropyl)furan-2-carboxylate (1.5g, 6.0mmol) in methanol (20 ml) was added a solution of NaOH (0.6g, 2 eq) in water (5 ml) and the reaction mixture was stirred at room temperature overnight. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated in vacuo to dryness and treated with isopropanol. Solid salts were filtered, and filtrate was evaporated in vacuo to dryness. Yield 1.4g (73.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min,

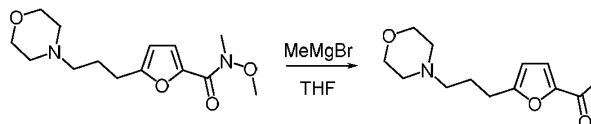
retention time 0.28 min. MS (ESI) m/z 240.4 [MH]⁺, retention time 0.67 min. MS (ESI) m/z 240.1 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.98-2.15 (m, 2H), 2.68-2.80 (m, 2H), 2.91-3.17 (m, 4H), 3.37-3.49 (m, 2H), 3.75-3.99 (m, 4H), 6.41 (s, 1H), 7.14 (s, 1H), 11.26 (br.s, 1H), 12.91 (br.s, 1H).

5 **Synthesis of N-methoxy-N-methyl-5-(3-morpholinopropyl)furan-2-carboxamide:**



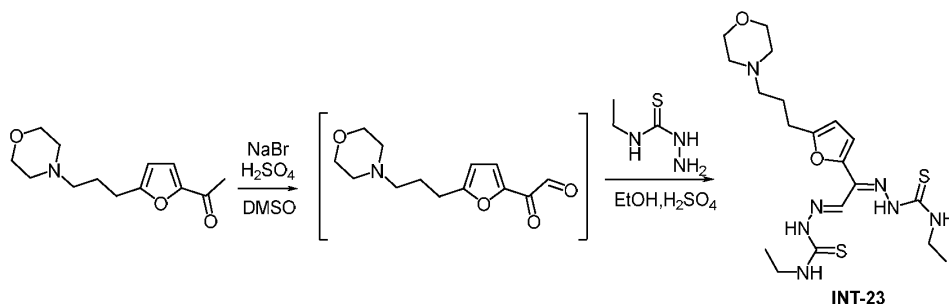
To a stirred mixture of 5-(3-morpholinopropyl)furan-2-carboxylic acid (1.2g, 4.0mmol, 1 eq), N,O-dimethylhydroxylamine (0.55g, 1.3 eq), HOBT (0.65g, 1.1 eq) and DIPEA (3 ml, 4eq) in CH₂Cl₂ (25 ml) at 5°C EDCI (0.83g, 1 eq) was added. The reaction was stirred for 15h at ambient temperature. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and solvents were concentrated under reduced pressure. The product was used without further purification. Yield 0.9g (73%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.34 min. MS (ESI) m/z 283.6 [MH]⁺, retention time 0.85 min. MS (ESI) m/z 283.5 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.86-1.94 (m, 2H), 2.40-2.53 (m, 6H), 2.71-2.81 (m, 2H), 3.34 (s, 3H), 3.68-3.74 (m, 4H), 3.76 (s, 3H), 6.15 (d, 1H), 7.07 (d, 1H).

Synthesis of 1-(5-(3-morpholinopropyl)furan-2-yl)ethan-1-one:

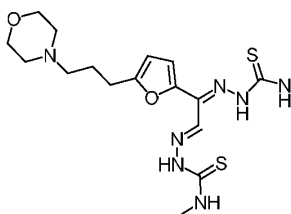


A solution of N-methoxy-N-methyl-5-(3-morpholinopropyl)furan-2-carboxamide (0.9g, 3.0 M, 1 eq) in THF (50 ml) was cooled to 5°C and methylmagnesium bromide solution in THF (3.4 M, 2.8 ml, 3 eq), was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, and evaporated. The titular product was used in the next step without purification. Yield 0.6g (79%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.3 min, MS (ESI) m/z 238.4 [MH]⁺, retention time 0.8 min, MS (ESI) m/z 238.4 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.88-1.96 (m, 2H), 2.35-2.64 (m, 9H), 2.73-2.79 (m, 2H), 3.66-3.90 (m, 4H), 6.20 (s, 1H), 7.11 (s, 1H).

30 **Synthesis of INT-23 ((2E,2'E)-2,2'-(1-(5-(3-morpholinopropyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**

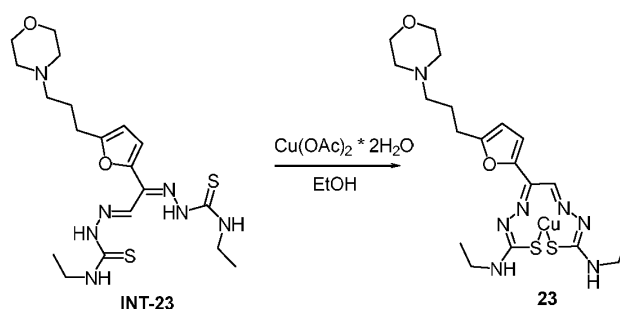


- A mixture of 1-(5-(3-morpholinopropyl)furan-2-yl)ethan-1-one (0.5g, 2.0mmol, 1 eq), NaBr (0.11g, 0.5 eq), and DMSO (1.1 ml) was heated to 85°C, then H₂SO₄ (6 drops) was added (foaming), and the reaction temperature began to rise. The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH and to the solution added ethyl thiosemicarbazide (0.5g, 2 eq). The reaction mixture was refluxed for 2 hours, then cooled to room temperature, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. Na₂CO₃ and extracted with EtOAc (3 × 50 ml). The organic layer was separated, dried over Na₂SO₄, filtered, and solvents were evaporated. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give the pure titular compound. Yield 0.2g (21%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.18 min, MS (ESI) m/z 454.4 [MH]⁺.
- Synthesis of INT-27 ((2E,2'E)-2,2'-(1-(5-(3-morpholinopropyl)furan-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):**

**INT-27**

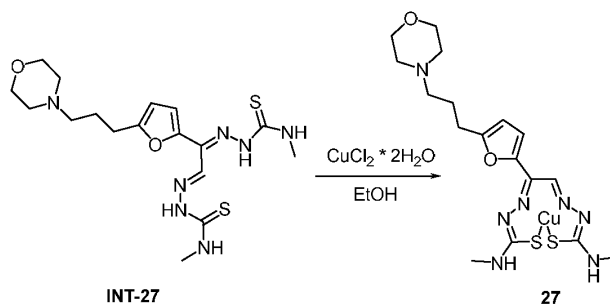
- INT-21** was made using a procedure analogous to the procedure to prepare **INT-19**. Yield 0.16g (15%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.02 min, MS (ESI) m/z 426.3 [MH]⁺.

Synthesis of Compound 23:



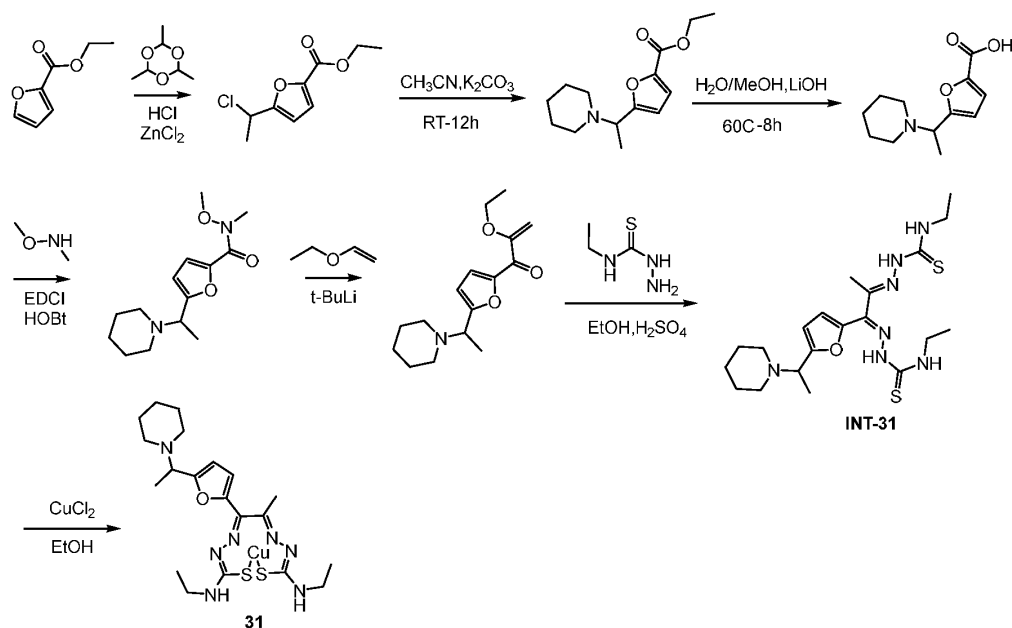
CuCl₂·2H₂O (0.034g, 1 eq) was added to the thiosemicarbazone **6** (0.09g, 0.2mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated out of the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.05g (48%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.56 min). MS (ESI) m/z 515.4 [MH]⁺.

Synthesis of Compound 27:

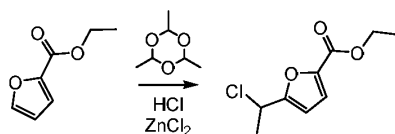


The titular compound was prepared from **INT-27** according to the method to prepare compound 23. The product was precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.095g (87%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.46 min). MS (ESI) m/z 487.5 [MH]⁺.

Scheme 11: Synthesis of Compound 31

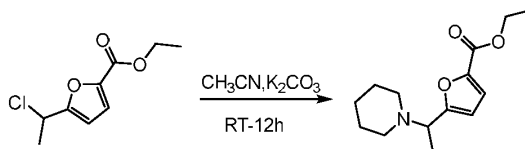


Synthesis of ethyl 5-(1-chloroethyl)furan-2-carboxylate:



- Zinc chloride (3.9g, 28.6mmol) was added to a solution of paraldehyde (17.3g, 131.1mmol) and ethyl 2-furoate (16.9g, 120.7mmol) in chloroform (36 mL). Hydrogen chloride was passed through the mixture during 5 h at 25-30°C under vigorous stirring. Then, 250 mL of chloroform was added; the reaction mixture was washed with water (2 × 30 mL), and then dried over calcium chloride. Solvent was removed under reduced pressure, to give the target product **1** that was used for the next step without additional purification. Yield 35g (31%). ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.18 (d, 3H), 1.33 (t, 3H), 4.32 (q, 2H), 5.09 (q, 1H), 6.41 (d, 1H), 7.07 (d, 1H).

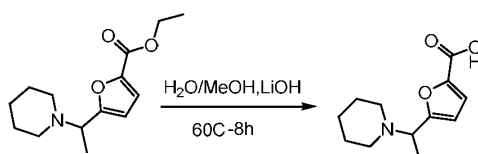
Synthesis of ethyl 5-(1-(piperidin-1-yl)ethyl)furan-2-carboxylate:



- A suspension of ethyl 5-(1-chloroethyl)furan-2-carboxylate (5.0g, 24.6mmol), piperidine (4.2g, 49.2mmol), and potassium carbonate (6.8g, 49.2mmol) in CH₃CN (100ml) was stirred at 50°C for 12 h. The mixture was cooled to room temperature. CH₃CN was

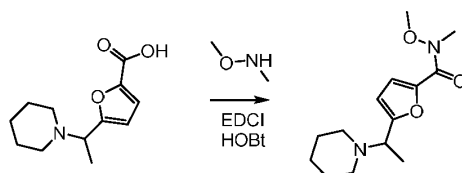
removed by evaporation, and the residue was diluted with 20 ml of aq. 2N sodium carbonate and extracted with dichloromethane. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and evaporated to dryness. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH) to afford the titular product that was used for the next step without additional purification. Yield 5.1g (82%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.90 min). MS (ESI) m/z 252.1 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.36 (d, 2H), 1.38 (d, 3H), 1.44 (d, 3H), 1.58 (q, 4H), 2.35-2.41 (m, 2H), 2.48-2.53 (m, 2H), 3.81 (q, 1H), 4.35 (q, 2H), 6.29 (d, 1H), 7.17 (d, 1H).

Synthesis of 5-(1-(piperidin-1-yl)ethyl)furan-2-carboxylic acid:



A solution of ethyl 5-(1-(piperidin-1-yl)ethyl)furan-2-carboxylate (5.1g, 20.3mmol) in MeOH (50ml) was added to a 20% aqueous solution of LiOH (1.6g, 60.9mmol). The reaction mixture was stirred for 8 h at 60°C. Then the solvent was removed by freeze-drying, and the corresponding crude product was used for the next step without further purification. Yield 4.4g (83%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.65 min). MS (ESI) m/z 224.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.33-1.38 (m, 2H), 1.43 (d, 3H), 1.57-1.61 (m, 4H), 2.07 (s, 1H), 2.60-2.63 (m, 2H), 4.07 (q, 2H), 4.32 (s, 1H), 6.52 (d, 1H), 7.04 (d, 1H).

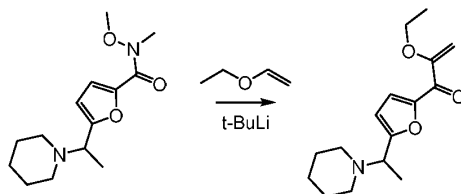
Synthesis of N-methoxy-N-methyl-5-(1-(piperidin-1-yl)ethyl)furan-2-carboxamide:



To a stirred mixture of 5-(1-(piperidin-1-yl)ethyl)furan-2-carboxylic acid (5.2g, 20mmol), N,O-dimethylhydroxylamine (2.3g, 24mmol), HOBT (3.2g, 24mmol) and TEA (12ml, 90mmol) in DCM (80ml) at 4°C was added EDCI (4.6g, 24mmol) and the mixture was then stirred overnight at r.t. The mixture was washed with water (15ml), brine (100ml). The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH) to afford crude product. Yield 2.2g (42%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for

3min, retention time 0.77 min). MS (ESI) m/z 267.5 $[MH]^+$. ^1H -NMR (400MHz, $CDCl_3$): δ (ppm) 1.38 (t, 2H), 1.46 (d, 3H), 1.54-1.60 (m, 4H), 2.36-2.41 (m, 2H), 2.50-2.55 (m, 2H), 3.33 (s, 3H), 3.78 (s, 3H), 3.81-3.87 (m, 1H), 6.26 (dd, 1H), 7.23 (dd, 1H).

Synthesis of 2-ethoxy-1-(5-(1-(piperidin-1-yl)ethyl)furan-2-yl)prop-2-en-1-one:



5

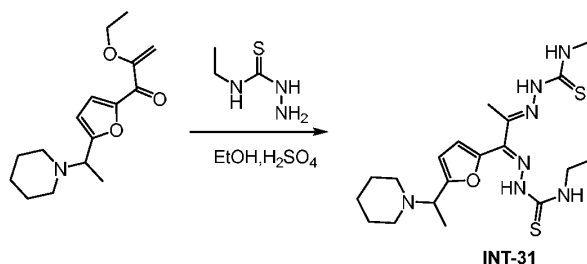
A solution of ethyl vinyl ether (1.8g, 24.4mmol) in tetrahydrofuran (50ml) was cooled to $-78^\circ C$, and *tert*-butyllithium (1.7M, 14.0ml, 22.2mmol) in pentane was added. The mixture was warmed to $0^\circ C$ over 1h period, stirred for 45min, and cooled down to $-30^\circ C$. To the mixture a solution of N-methoxy-N-methyl-5-(1-(piperidin-1-yl)ethyl)furan-2-carboxamide (1.0g, 3.7mmol) in THF (15ml) was added, and the mixture was stirred at $0^\circ C$ for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq. NH_4Cl (100ml) and extracted with Et_2O (3 $\times$ 50ml). The combined extracts were dried over Na_2SO_4 . The product solution was then decanted, and the solvent was removed under reduced pressure giving the titular compound that was used for the next step without further

10

purification. Yield 1.1g (87%). LCMS (C18 column 20×2 mm, particle size $2.5 \mu m$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.97 min). MS (ESI) m/z 278.6 $[MH]^+$. ^1H -NMR (400MHz, $CDCl_3$): δ (ppm) 1.38 (t, 2H), 1.46 (d, 3H), 1.47 (d, 3H), 1.55-1.63 (m, 4H), 2.38-2.44 (m, 2H), 2.51-2.56 (m, 2H), 3.81-3.87 (m, 1H), 3.93 (q, 2H), 4.58 (d, 1H), 5.33 (d, 1H), 6.31 (d, 1H), 7.47 (d, 1H).

20

Synthesis of INT-31 ((2Z,2'E)-2,2'-(1-(5-(1-(piperidin-1-yl)ethyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



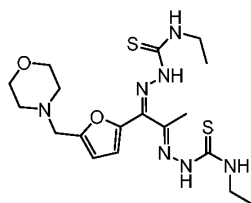
INT-31

2-Ethoxy-1-(5-(1-(piperidin-1-yl)ethyl)furan-2-yl)prop-2-en-1-one (1.1g, 3.7mmol) was dissolved in EtOH (30ml), ethyl thiosemicarbazide (0.9g, 7.4mmol) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h and then maintained overnight at ambient temperature. The progress of the reaction was monitored by TLC ($CCl_4/EtOAc$ 7:3). The precipitate was filtered, washed with EtOH, water, Et_2O , and dried.

25

Yield 0.5g (33%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.17 min). MS (ESI) m/z 452.0 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.07 (t, 3H), 1.15 (t, 3H), 1.38-1.55 (m, 3H), 1.60-1.66 (m, 4H), 1.70-1.79 (m, 4H), 2.33 (s, 3H), 3.41-3.48 (m, 2H), 3.55-3.63 (m, 2H), 4.72 (s, 1H), 6.91 (dd, 1H), 7.14 (dd, 1H), 7.73 (t, 1H), 8.73 (t, 1H), 9.08-9.78 (m, 2H), 10.48 (s, 1H), 10.55 (s, 1H).

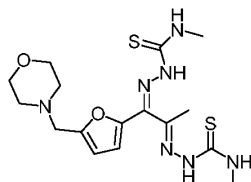
Synthesis of INT-24 ((2E,2'E)-2,2'-(1-(5-(morpholinomethyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-24

INT-24 was made using a procedure analogous to the procedure to prepare **INT-31**. Yield 4.6g (63%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.01 min). MS (ESI) m/z 440.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.10 (t, 3H), 1.16 (t, 3H), 1.39, 2.32 (s, 3H), 2.35-2.47 (m, 4H), 3.42-3.58 (m, 2H), 3.58-3.76 (m, 8H), 6.61 (s, 1H), 7.01 (s, 1H), 7.78 (br.s, 1H), 8.70 (br.s, 1H), 10.40 (s, 1H), 10.51 (s, 1H).

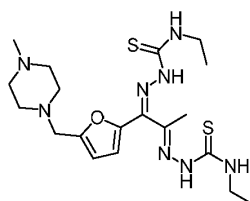
Synthesis of INT-32 ((2E,2'E)-2,2'-(1-(5-(morpholinomethyl)furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



INT-32

INT-32 was made using a procedure analogous to the procedure to prepare **INT-31**. Yield 0.25g (54%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.06 min). MS (ESI) m/z 412.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.33 (s, 3H), 2.92-3.00 (m, 4H), 3.03-3.10 (m, 4H), 3.12-3.45 (m, 4H), 3.70-3.82 (m, 4H), 4.5 (s, 3H), 6.9 (s, 1H), 7.07 (s, 1H), 7.71 (s, 1H), 8.67 (s, 1H), 10.39 (s, 1H), 10.54 (s, 1H).

Synthesis of INT-37 ((2E,2'E)-2,2'-(1-(5-((4-methylpiperazin-1-yl)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

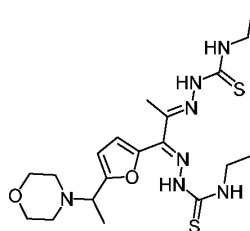


INT-37

INT-37 was made using a procedure analogous to the procedure to prepare **INT-31**.

Yield 0.9g (61.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.06 min). MS (ESI) m/z 453.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.10 (t, 3H), 1.16 (t, 3H), 1.39 (s, 3H), 2.32 (s, 3H), 2.55-2.74 (m, 2H), 2.79-2.89 (m, 4H), 3.42-3.59 (m, 6H), 3.62 (q, 2H), 3.97 (s, 3H), 6.71 (s, 1H), 7.08 (s, 1H), 7.76 (s, 1H), 8.74 (s, 1H), 10.44 (s, 1H), 10.54 (s, 1H).

Synthesis of INT-39 ((2Z,2'E)-2,2'-(1-(5-(1-morpholinoethyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

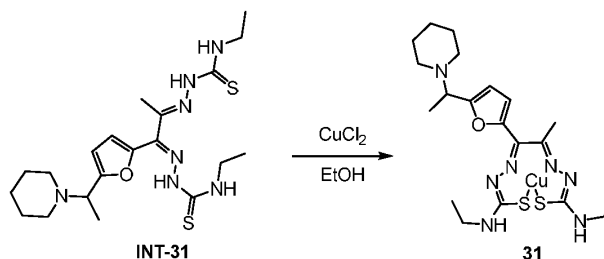


INT-39

INT-39 was made using a procedure analogous to the procedure to prepare **INT-31**.

Yield 0.2g (20%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.11 min). MS (ESI) m/z 454.3 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.10 (t, 3H), 1.16 (t, 3H), 1.39 (dd, 3H), 2.32 (s, 3H), 2.34-2.38 (m, 2H), 2.47-2.49 (m, 2H), 3.48-3.53 (m, 2H), 3.56-3.65 (m, 4H), 3.60-3.65 (m, 2H), 3.84-3.90 (m, 1H), 6.56 (dd, 1H), 7.06 (dd, 1H), 7.87 (t, 1H), 8.70 (t, 1H), 10.47 (d, 1H), 10.59 (d, 1H).

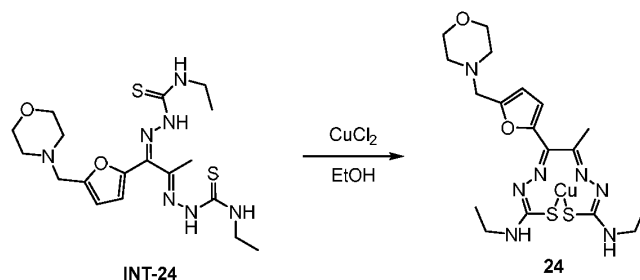
Synthesis of Compound 31:



$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.2g, 2.4mmol) was added to compound **6** (0.5g, 1.2mmol) in 30 ml of ethanol. The mixture was stirred for 15h at ambient temperature. The formed precipitate was collected by filtration after cooling, washed with water ($2 \times 50\text{ml}$), ethanol ($2 \times 50\text{ml}$), and copious amounts of diethyl ether ($5 \times 50\text{ml}$), and then dried *in vacuo*. Yield 0.4g (75%).

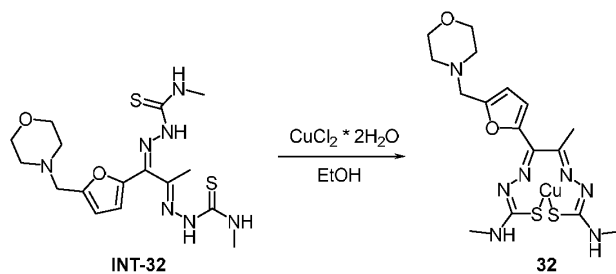
- 5 LCMS (C18 column $20 \times 2\text{ mm}$, particle size $2.5\text{ }\mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.66 min). MS (ESI) m/z 513.3 $[\text{MH}]^+$.

Synthesis of Compound 24:



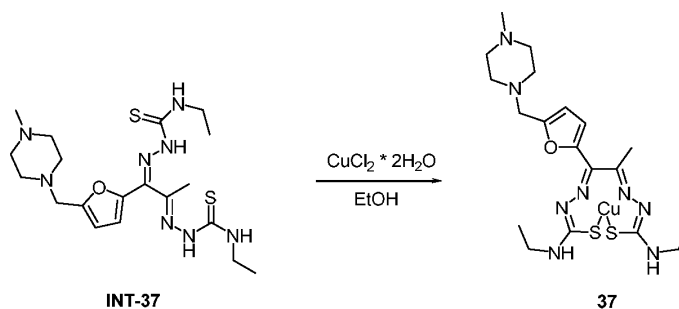
- 10 The titular compound was prepared from **INT-24** according to the method to prepare compound 31. The product precipitated out of the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 4.7g (92%). LCMS (C18 column $20 \times 2\text{ mm}$, particle size $2.5\text{ }\mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time
- 15 1.48 min). MS (ESI) m/z 501.3 $[\text{MH}]^+$.

Synthesis of Compound 32:



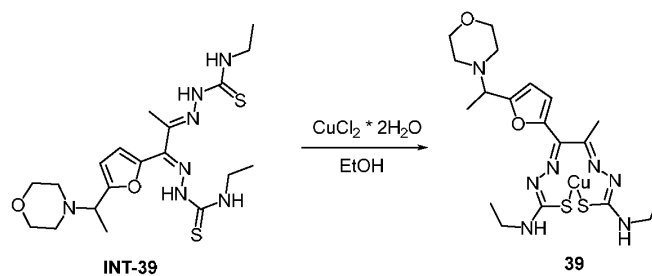
- The titular compound was prepared from **INT-32** according to the method to prepare compound 31. The product precipitated from the reaction mixture as a red-brown powder.
- 20 The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.14 g (97%). LCMS (C18 column $20 \times 2\text{ mm}$, particle size $2.5\text{ }\mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.38 min). MS (ESI) m/z 473.0 $[\text{MH}]^+$.

Synthesis of Compound 37:



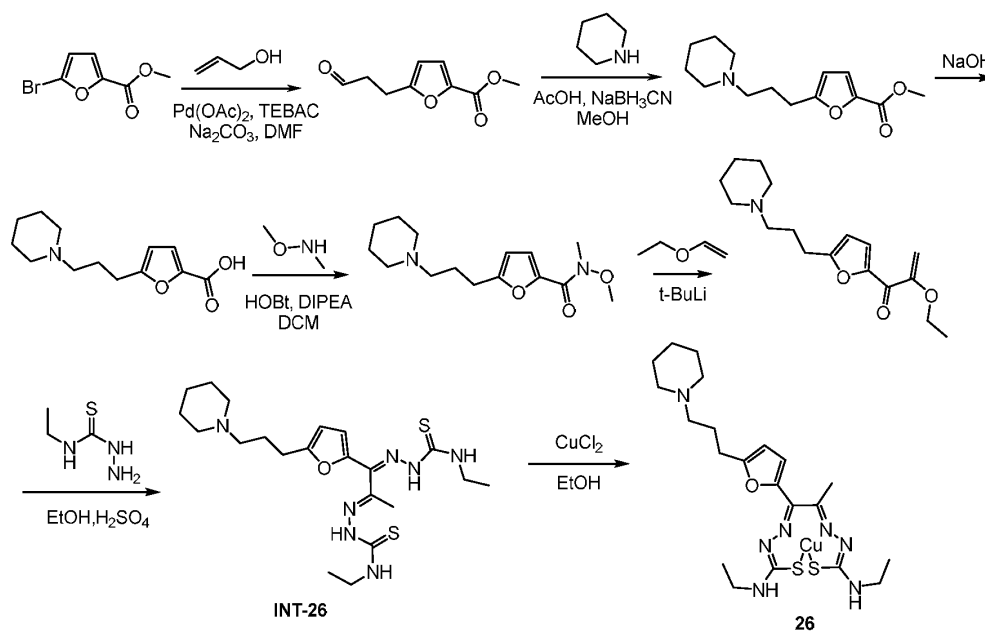
The titular compound was prepared from **INT-37** according to the method to prepare compound 31. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.8g (96%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.52 min). MS (ESI) m/z 514.3 [MH]⁺.

Synthesis of Compound 39:

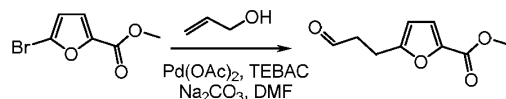


The titular compound was prepared from **INT-39** according to the method to prepare compound 31. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.15g (86%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.57 min). MS (ESI) m/z 515.2 [MH]⁺.

Scheme 12: Synthesis of Compound 26

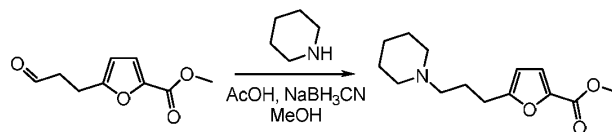


Synthesis of methyl 5-(3-oxopropyl)furan-2-carboxylate:



Under inert atmosphere, 5-bromo-methyl furan-2-carboxylate (5.7g, 28mmol, 1 eq) was dissolved in 550 ml DMF. Allyl alcohol (2.28g, 1.4 eq), Pd(OAc)₂ (0.189g, 0.03 eq), TEBAC (6.39 g, 1 eq) and Na₂CO₃ (6.85g, 2 eq) were added. Then the mixture was stirred at 80°C for 2 h. Upon completion, the resulting mixture was filtered through Celite, filtrate was concentrated in vacuo at ≤40°C, diluted with ethyl acetate, washed with brine, concentrated to dryness, and the residue was purified by column chromatography (silica gel, ethyl acetate - hexane 1:3). Yield 2.7g (53%). ¹H-NMR (400MHz, CDCl₃): δ (ppm) 2.89(dd, 2H), 3.05(dd, 2H), 3.89(s, 3H), 6.19(s, 1H), 7.09(s, 1H), 9.83(s, 1H).

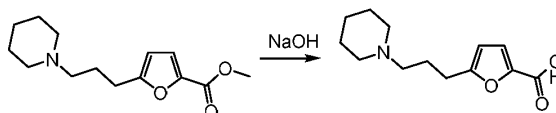
Synthesis of methyl 5-(3-(piperidin-1-yl)propyl)furan-2-carboxylate:



methyl 5-(3-oxopropyl)furan-2-carboxylate (2.7g, 15mmol, 1 eq) was dissolved in MeOH (150 ml), and molecular sieves (4.4g) were added to the solution. After stirring for 15 min, the mixture was cooled down to 0°C. To the stirred solution of aldehyde **1** a solution of piperidine (1.9g, 1.5 eq) and acetic acid (1.8g, 2 eq) in methanol (70 ml) was added at 0°C. After stirring for 2 min, NaBH₃CN (2.8g, 3 eq) was added. The resulting mixture was stirred

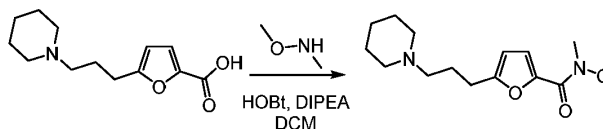
for 14 h allowing to warm up from 0°C to room temperature on its own accord. Then the reaction mixture was diluted with DCM, filtered through Celite, and filtrate was washed with aq. NaHCO₃. The aqueous phase was extracted with DCM twice. The organic phase was dried over Na₂SO₄, filtered, and concentrated in vacuo to dryness. The residue was purified by column chromatography (SiO₂, eluting first with EtOAc/hexane, gradient 1:5 to 1:3 to 1:1 to 100% EtOAc, and afterwards with CH₂Cl₂/MeOH, 10:1). Yield 1.8g (49%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.94 min. MS (ESI) m/z 252.4 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.45-1.66 (m, 2H), 1.78-1.88 (m, 2H), 1.96-2.17 (m, 4H), 2.57-2.88 (m, 6H), 3.41-3.56 (m, 2H), 3.88 (s, 3H), 6.23 (s, 1H), 7.09 (s, 1H).

Synthesis of 5-(3-(piperidin-1-yl)propyl)furan-2-carboxylic acid:



To a stirred solution of methyl 5-(3-(piperidin-1-yl)propyl)furan-2-carboxylate (1.8g, 7.0mmol) in methanol (20 ml) a solution of NaOH (0.73g, 2.6 eq) in water (25 ml) was added. The reaction mixture was stirred for 15h at ambient temperature. Methanol was removed *in vacuo*, the residue diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and residue was treated with isopropanol. Solid salts were filtered, and filtrate was evaporated to dryness. Yield 1.35g (68%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.35 min. MS (ESI) m/z 238.3 [MH]⁺, retention time 0.86 min. MS (ESI) m/z 238.3 [MH]⁺.

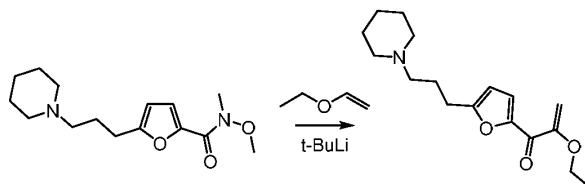
Synthesis of N-methoxy-N-methyl-5-(3-(piperidin-1-yl)propyl)furan-2-carboxamide:



To a mixture of methyl 5-(3-(piperidin-1-yl)propyl)furan-2-carboxylate (1.35g, 5.0M, 1 eq), N,O-dimethylhydroxylamine (0.72g, 1.3 eq), HOBt (0.83g, 1.1 eq), and DIPEA (3.3 ml, 4eq) in CH₂Cl₂ (25 ml) at 5°C EDCI (1.04g, 1.1 eq) was added. The reaction then was stirred for 15h at ambient temperature. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. Product was used further without purification. Yield 0.4g (29%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.35 min. MS (ESI) m/z 281.5 [MH]⁺, retention time 0.93 min. MS (ESI) m/z 281.3 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.38-1.48

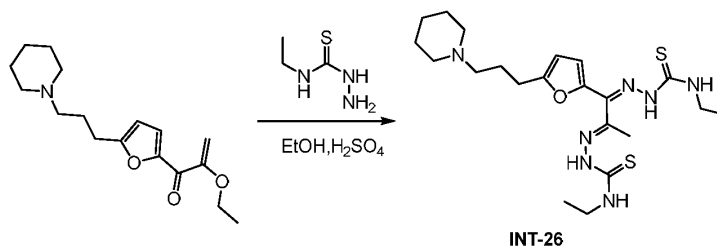
(m,2H), 1.55-1.64(m, 4H), 1.86-1.97(m, 2H), 2.31-2.48(m, 6H), 2.69-2.81(m, 2H), 3.34(s, 3H), 3.76(s, 3H), 6.14(d, 1H), 7.07(d, 1H).

Synthesis of 2-ethoxy-1-(5-(3-(piperidin-1-yl)propyl)furan-2-yl)prop-2-en-1-one:



- 5 A solution of ethyl vinyl ether (0.72g, 0.96 ml, 7 eq) in dry tetrahydrofuran (20 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M, 5 ml, 6q) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-5-(3-(piperidin-1-yl)propyl)furan-2-carboxamide (0.4g, 1.4mmol, 1 eq) in THF was added, and the mixture was stirred at 0°C for 4 h. The progress
- 10 of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 0.39g (93%).
- LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.04 min. MS (ESI) m/z
- 15 292.3 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.18-1.48(m, 5H), 1.50-1.64 (m,4H), 1.82-2.03(m,2H), 2.27-2.48 (m, 6H), 2.62-2.78(m, 2H), 3.84-3.98(m, 2H), 3.92(q, 2H), 4.56(s, 1H), 5.31(s, 1H), 6.21(d, 1H), 7.44(d, 1H).

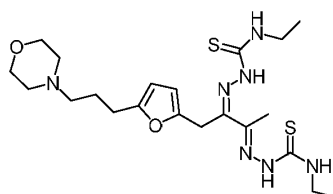
Synthesis of INT-26 ((2*E*,2'*E*)-2,2'-(1-(5-(3-(piperidin-1-yl)propyl)furan-2-yl)propane-1,2-diylidene)bis(*N*-ethylhydrazine-1-carbothioamide)):



- 20 2-ethoxy-1-(5-(3-(piperidin-1-yl)propyl)furan-2-yl)prop-2-en-1-one (0.41g, 1.45mmol, 1 eq) was dissolved in EtOH (10 ml), ethyl thiosemicarbazide (0.33g, 2 eq) and 1 drop of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with
- 25 EtOH, water, Et₂O and crystallized from EtOH. Yield 0.08g (12%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.21 min. MS (ESI) m/z 466.5 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ

(ppm) 1.11(t, 3H), 1.16(t, 1H), 1.53-1.91(m, 6H), 2.05-2.15(m, 2H), 2.32(s, 3H), 2.77-2.89(m, 2H), 3.05-3.19(m, 2H), 3.35-3.45(m, 4H), 3.53(q, 2H), 3.62(q, 2H), 6.49(s, 1H), 7.05(s, 1H), 7.78(s, 1H), 8.72(s, 1H), 10.48(s, 1H), 10.52(s, 1H).

Synthesis of INT-28 ((2Z,2'E)-2,2'-(1-(5-(3-morpholinopropyl)furan-2-yl)butane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

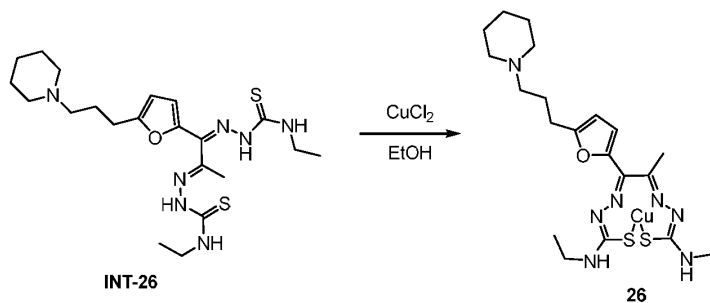


INT-28

INT-28 was made using a procedure analogous to the procedure to prepare INT-26.

Yield 0.18g (50%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.15 min. MS (ESI) m/z 468.5 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.11(t, 3H), 1.16(t, 1H), 2.04-2.14(m, 2H), 2.32(s, 3H), 2.77-2.86(m, 2H), 3.17-3.26(m, 2H), 3.39-3.73(m, 10H), 3.91-4.04(m, 2H), 6.5(s, 1H), 7.06(s, 1H), 7.8(s, 1H), 8.72(s, 1H), 10.47(s, 1H), 10.52(s, 1H).

Synthesis of Compound 26:

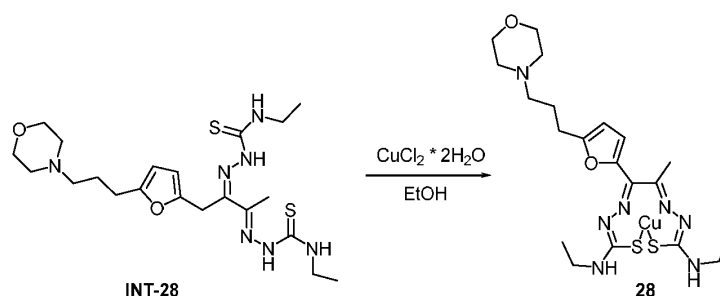


INT-26

26

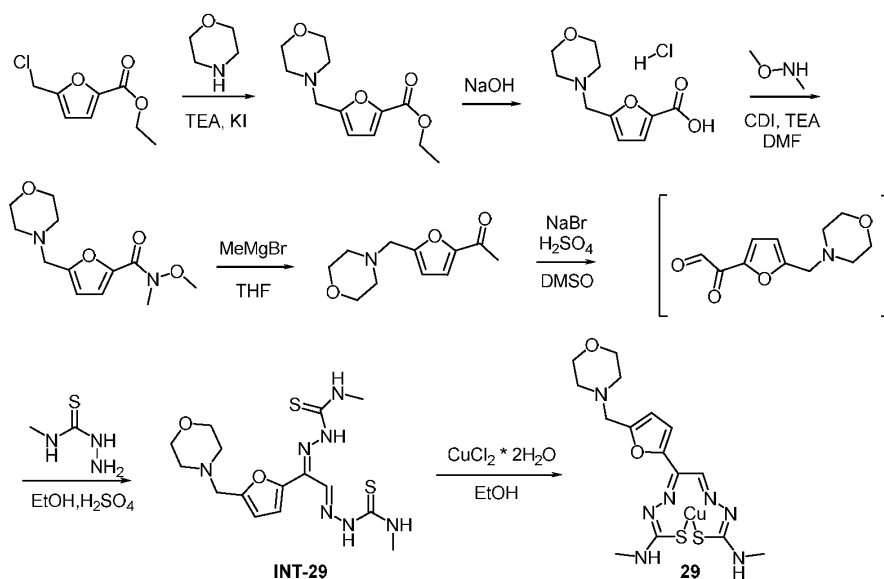
CuCl₂·2H₂O (0.026g, 1 eq) was added to thiosemicarbazone **6** (0.07g, 0.15mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.054g (68%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.76 min). MS (ESI) m/z 527.5 [MH]⁺.

Synthesis of Compound 28:

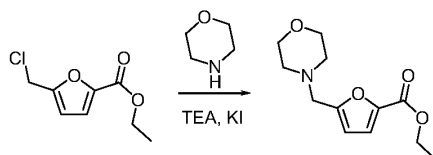


The titular compound was prepared from **INT-28** according to the method to prepare compound 26. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.14g (85%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.65 min). MS (ESI) *m/z* 529.0 [MH]⁺.

Scheme 13: Synthesis of Compound 29



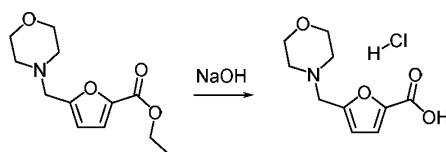
10 Synthesis of ethyl 5-(morpholinomethyl)furan-2-carboxylate:



To a stirred solution of ethyl 2-chloromethyl-5-furoate (9.6g, 50mmol) in CH₂Cl₂ (200 ml) were added morpholine (4.43g, 4.4 ml, 1 eq), triethylamine (10.3g, 14 ml, 2 eq) and KI

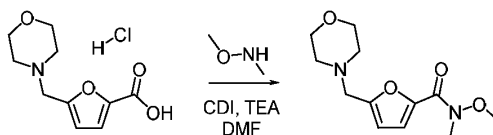
(0.1 g). The reaction mixture was stirred for 15h at room temperature, then washed with water (3 × 50 ml). The organic layer was separated, dried over Na₂SO₄, filtered, and solvents were evaporated. Yield 8g (66%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.82 min). MS (ESI) m/z 240.1 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.38 (t, 3H), 2.50-2.55 (m, 4H), 3.62 (s, 3H), 3.70-3.75 (m, 4H), 4.37 (q, 2H), 6.36 (d, 1H), 7.13 (d, 1H).

Synthesis of 5-(morpholinomethyl)furan-2-carboxylate hydrochloride:



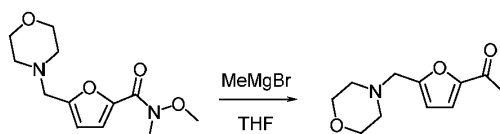
To a solution of ethyl 5-(morpholinomethyl)furan-2-carboxylate (4.6g, 20mmol) in methanol (100 ml) a solution of NaOH (2g, 2 eq) in water (10 ml) was added, and the reaction mixture was stirred for 15h at ambient temperature. Methanol was stripped off in vacuo, the residue diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and the residue was treated with isopropanol. Solid salts were filtered, and filtrate was evaporated to dryness. Yield 4.4g (86%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.29 min). MS (ESI) m/z 212.3 [MH]⁺.

Synthesis of N-methoxy-N-methyl-5-(morpholinomethyl)furan-2-carboxamide:



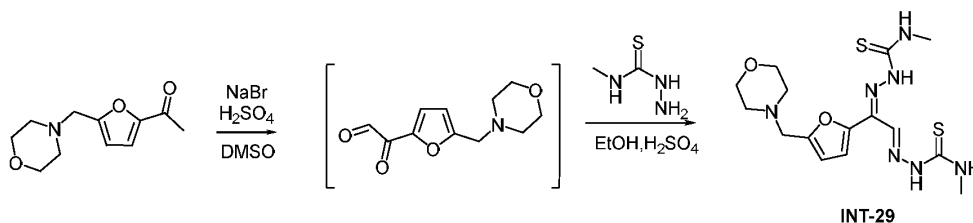
A mixture of 5-(morpholinomethyl)furan-2-carboxylate hydrochloride (7.1g, 29mmol) and 1,1'-carbonyldiimidazole (5.57g, 1.2 eq) in DMF (47mL) was stirred at 60°C for 30 min. Then N,O-dimethylhydroxylamine (3.35g, 1.2 eq) and triethylamine (3.2g, 4.4 ml, 1.1 eq) were added. The mixture was stirred at 80°C for 16 h, then the volatiles were evaporated in vacuo, and the residue was partitioned between EtOAc and H₂O. The organic layer was separated, dried over Na₂SO₄, filtered, and solvents were evaporated. Yield 7g (96%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.28 min. MS (ESI) m/z 255.6 [MH]⁺, retention time 0.78 min. MS (ESI) m/z 255.6 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 2.52-2.55 (m, 4H), 3.35 (s, 3H), 3.64 (s, 2H), 3.71-3.74 (m, 4H), 6.36 (d, 1H), 6.71 (d, 1H).

Synthesis of 1-(5-(morpholinomethyl)furan-2-yl)ethan-1-one:



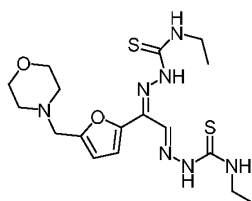
A solution of N-methoxy-N-methyl-5-(morpholinomethyl)furan-2-carboxamide (3.4g, 13mmol, 1 eq) in THF (150 ml) was cooled to 5°C and methylmagnesium bromide solution in THF (1.4 M, 26 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered, and solvents were evaporated. Compound **3** was used for the next step without purification. Yield 2.6g (93%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.31 min, MS (ESI) m/z 210.1 [MH]⁺, retention time 0.67 min, MS (ESI) m/z 210.3 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.34-2.45 (m, 7H), 3.49-3.63 (m, 6H), 6.54 (s, 1H), 7.46 (s, 1H).

Synthesis of INT-29 ((2E,2'E)-2,2'-(1-(5-(morpholinomethyl)furan-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



A mixture of 1-(5-(morpholinomethyl)furan-2-yl)ethan-1-one (1.4g, 7.0mmol, 1 eq), NaBr (0.33g, 0.5 eq), and DMSO (3.45 ml) was heated to 85°C, then H₂SO₄ (6 drops) was added (foaming), and the reaction temperature began to rise. The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH and to the solution added methylthiosemicarbazide (1.41g, 2 eq). The reaction mixture was refluxed for 2 hours, then cooled to room temperature, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. Na₂CO₃ and extracted with EtOAc (3 × 50 ml). The organic layer was separated, dried over Na₂SO₄, filtered, and solvents were evaporated. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give the pure titular compound. Yield 0.7g (26%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.08 min, MS (ESI) m/z 398.3 [MH]⁺.

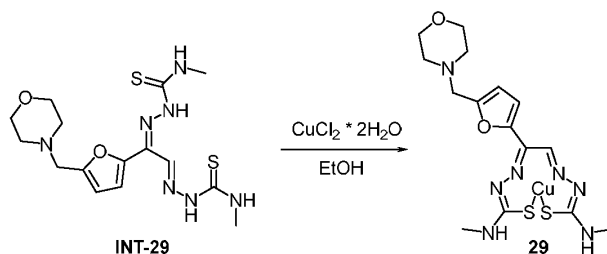
Synthesis of INT-38 ((2E,2'E)-2,2'-(1-(5-(morpholinomethyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

**INT-38**

INT-38 was made using a procedure analogous to the procedure to prepare **INT-29**.

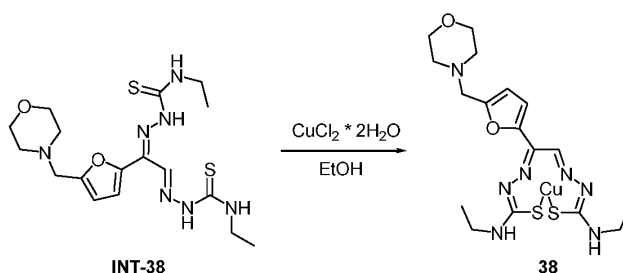
Yield 0.5g (37%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.12 min, MS (ESI) m/z 426.0 [MH]⁺.

Synthesis of Compound 29:



$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.062g, 1 eq) was added to thiosemicarbazone **6** (0.14g, 0.4mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated out of the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.055g (32%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.29 min). MS (ESI) m/z 459.5 [MH]⁺.

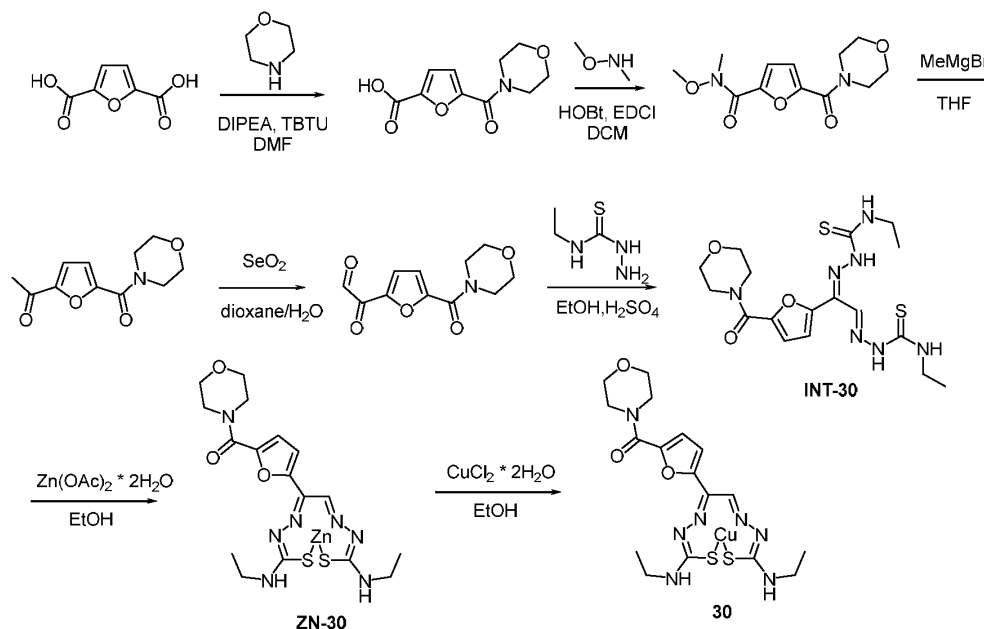
Synthesis of Compound 38:



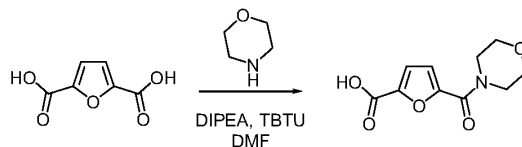
The titular compound was prepared from **INT-36** according to the method to prepare compound 29. The product precipitated out of the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.07g (77%). LCMS (C18 column 20 × 2 mm, particle size 2.5

μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.47 min). MS (ESI) m/z 487.4 $[\text{MH}]^+$.

Scheme 14: Synthesis of Compound 30

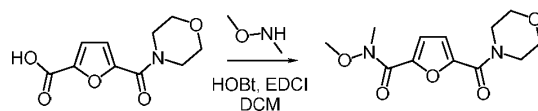


5 Synthesis of 5-(morpholine-4-carbonyl)furan-2-carboxylic acid:



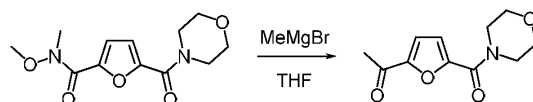
- To a stirred solution of furan 2,5-dicarboxylic acid (5g, 32mmol, 1 eq) in DMF (100 ml) DIPEA was added (14.5g, 19.5 ml, 3.5 eq), the reaction flask was flushed with argon, and the solution of TBUTU (12.3g, 1.2 eq) in DMF (75 ml) was added dropwise at ambient temperature over 1 h. The reaction mixture was stirred for an additional hour. Then morpholine was added in one portion and the mixture was stirred at ambient temperature for 2h. The mixture was cooled in an ice-bath, HCl (2N, 170 ml) was added and the product was extracted with EtOAc, EtOAc was evaporated, the residue was washed with EtOH and ether. Yield 6.19g (85%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.33 min). MS (ESI) m/z 226.3 $[\text{MH}]^+$, retention time 0.84 min). MS (ESI) m/z 226.3 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ (ppm) 3.52-3.88(m, 8H), 7.09 (d, 1H), 7.29(d, 1H).

Synthesis of N-methoxy-N-methyl-5-(morpholine-4-carbonyl)furan-2-carboxamide:



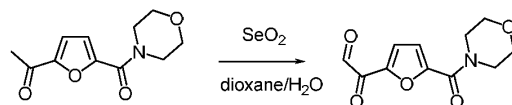
To a mixture of 5-(morpholine-4-carbonyl)furan-2-carboxylic acid (2.6g, 11mmol, 1 eq), N,O-dimethylhydroxylamine (1.46g, 1.3 eq), HOBT (1.71, 1eq) and DIPEA (2 ml) in DCM (150 ml) was added EDCI (2.21g, 1 eq) at 4°C and the mixture was stirred overnight at room temperature. The reaction mixture was treated with water. The solid substance insoluble in water and DCM was removed by filtration. Organic layer was separated, dried over Na₂SO₄, filtered, and solvents were evaporated. The residue was purified by column chromatography (SiO₂, CH₂Cl₂ 100%). Yield 2.1g (68%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.95 min). MS (ESI) m/z 269.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 3.26 (s, 3H), 3.54-3.73 (m, 8H), 3.76 (s, 3H), 7.10 (d, 1H), 7.22 (d, 1H).

Synthesis of 1-(5-(morpholine-4-carbonyl)furan-2-yl)ethan-1-one:



A solution of N-methoxy-N-methyl-5-(morpholine-4-carbonyl)furan-2-carboxamide (1.45g, 5.4mmol, 1 eq) in THF (50 ml) was cooled down to 5°C and methylmagnesium bromide solution in THF (1.4M, 11 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered, and solvents were evaporated. The titular product was used for the next step without purification. Yield 0.45g (37%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.92 min). MS (ESI) m/z 224.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 2.46 (s, 3H), 3.57-3.79 (m, 8H), 3.76 (s, 3H), 7.14 (d, 1H), 7.50 (d, 1H).

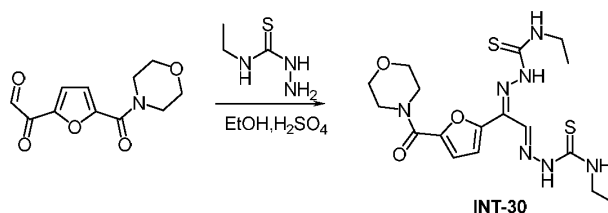
Synthesis of 2-(5-(morpholine-4-carbonyl)furan-2-yl)-2-oxoacetaldehyde:



A three-necked flask was charged with SeO₂ (0.42g, 1.4 eq), 1,4-dioxane (6 mL), and water (0.36 mL). The mixture was heated to 50°C and stirred until most of SeO₂ was dissolved. 1-(5-(Morpholine-4-carbonyl)furan-2-yl)ethan-1-one (0.6g, 0.003M, 1 eq) was added, and the reaction was heated to gentle reflux overnight. Selenium solids precipitated during the course of the reaction. The mixture was cooled in an ice bath and filtered through diatomaceous earth to remove the selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was concentrated to yield 0.5g of crude titular product, it was used

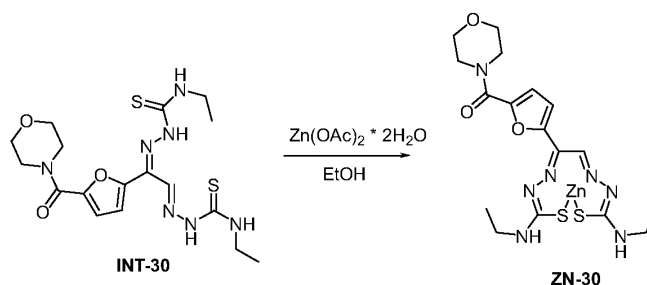
for the next step without purification. Yield 0.5g (78%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.92 min, MS (ESI) m/z 238.1 [MH]⁺.

Synthesis of INT-30 ((2E,2'E)-2,2'-(1-(5-(morpholine-4-carbonyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



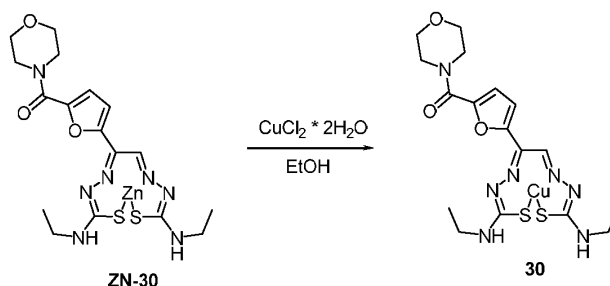
Crude 2-(5-(morpholine-4-carbonyl)furan-2-yl)-2-oxoacetaldehyde (0.5g, 2.0mmol, 1 eq) was dissolved in EtOH (25 ml), ethyl thiosemicarbazide (0.5g, 2 eq) and 2 drops of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. Formed precipitate was filtered, washed with EtOH, MeCN, water, Et₂O, and dried. Yield 0.25g (27%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.37 min, MS (ESI) m/z 440.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.00-1.26 (m, 6H), 3.43-4.09 (m, 13H), 7.19 (s, 1H), 7.24 (s, 1H), 6.06 (br.s, 1H), 8.92 (br.s, 1H), 11.98 (s, 1H), 12.29 (s, 1H).

Synthesis of Intermediate ZN-30:



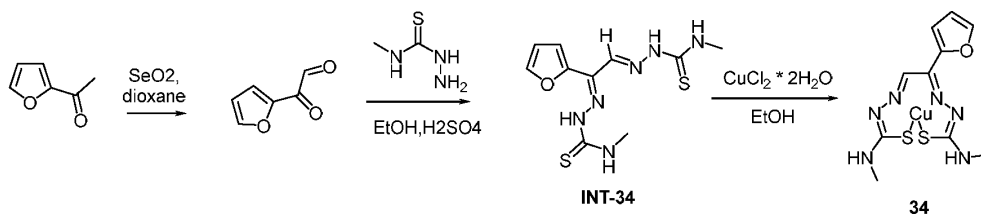
Zn(OAc)₂ · 2H₂O (0.19g, 1.5 eq) was added to **INT-30** (0.73g, 2.0mmol, 1 eq) in ethanol. The mixture was refluxed for 4 h. The formed complex was precipitated from the mixture as a yellow powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.175g (61%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.11(t, 3H), 1.19 (t, 3H), 3.36-3.85 (m, 13H), 7.11 (s, 1H), 7.15 (s, 1H), 8.20 (s, 1H), 8.43 (s, 1H).

Synthesis of Compound 30:

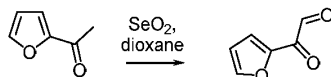


ZN-30 (0.175g, 0.3mmol, 1 eq) was dissolved in DMSO (4 ml) and a solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.076g, 1.1 eq) in water (4 ml) was added. The mixture was stirred for 5 min, filtered and washed with water and Et_2O . Yield 0.08g (46%). LCMS (C18 column 20×2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.86 min). MS (ESI) m/z 501.3 $[\text{MH}]^+$.

Scheme 15: Synthesis of Compound 34



Synthesis of 2-(furan-2-yl)-2-oxoacetaldehyde:



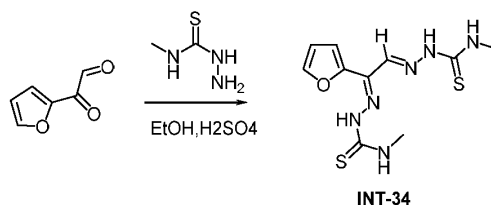
10

A three-necked flask was charged with SeO_2 (3.2g, 28.6mmol), 1,4-dioxane (37ml), and water (2.5ml). The mixture was heated to 50°C and stirred until most of SeO_2 was dissolved. 1-(2-Furyl)ethanone (3g, 27.2mmol) was added, and the reaction was heated to gentle reflux overnight. The progress of the reaction was monitored by TLC ($\text{CCl}_4/\text{EtOAc}$ 7:3). Selenium solids precipitated during the course of the reaction. The mixture was cooled over an ice bath and filtered through diatomaceous earth to remove the selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was concentrated to give 3.0 g of crude compound **1**, it was used for the next step without purification. Yield 3.0 g (88%).

15

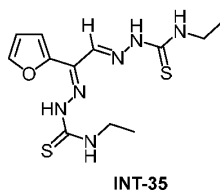
Synthesis of INT-34 ((2Z,2'E)-2,2'-(1-(furan-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

20



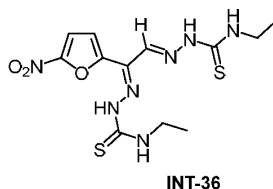
2-(Furan-2-yl)-2-oxoacetaldehyde (0.7g, 6 mmol) was dissolved in EtOH (20 mL), methyl thiosemicarbazide (1.3g, 12 mmol) and 3 drops of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The progress of the reaction was monitored by TLC (CCl₄/EtOAc 7:3). The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.57g (32%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.35 min). MS (ESI) m/z 299.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 3.02 (d, 3H), 3.01 (d, 3H), 6.78 (q, 1H), 7.52 (d, 1H), 7.84 (s, 1H), 7.99-8.04 (m, 1H), 8.13 (dd, 1H), 8.88-8.92 (m, 1H), 10.81 (s, 1H), 11.79 (s, 1H).

Synthesis of INT-35 ((2Z,2'E)-2,2'-(1-(furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-35 was made using a procedure analogous to the procedure to prepare **INT-34**. Yield 0.47g (24%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 2.23 min). MS (ESI) m/z 327.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.07 (t, 3H), 1.15 (t, 3H), 3.41-3.48 (m, 2H), 3.55-3.63 (m, 2H), 6.78 (q, 1H), 7.52 (d, 1H), 7.84 (s, 1H), 7.99-8.04 (m, 1H), 8.13 (dd, 1H), 8.88-8.92 (m, 1H), 10.81 (s, 1H), 11.79 (s, 1H).

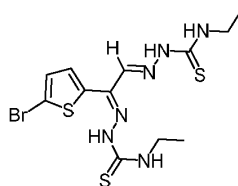
Synthesis of INT-36 ((2Z,2'E)-2,2'-(1-(5-nitrofuran-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-36 was made using a procedure analogous to the procedure to prepare **INT-34**.

Yield 0.02g (24%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 10min, retention time 8.11 min). MS (ESI) m/z 372.5 [MH]⁺.

- 5 **Synthesis of INT-40 ((2Z,2'E)-2,2'-(1-(5-bromothiophen-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**

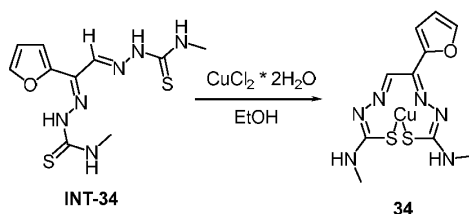


INT-40

INT-40 was made using a procedure analogous to the procedure to prepare **INT-34**.

- 10 Yield 0.24g (39%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.85 min). MS (ESI) m/z 422.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.15 (t, 3H), 1.18 (t, 3H), 3.41-3.49 (m, 4H), 7.25 (d, 1H), 7.33 (d, 1H), 8.09 (t, 1H), 8.16 (s, 1H), 8.60 (t, 1H), 11.75 (s, 1H), 11.90 (s, 1H).

Synthesis of Compound 34:

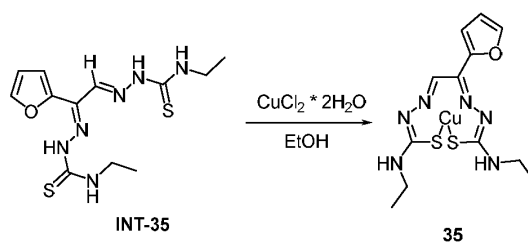


- 15

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.33g, 1.9mmol) was added to **INT-34** (0.57g, 1.9mmol) in 10 ml of ethanol. The mixture was stirred overnight. Complex was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*.

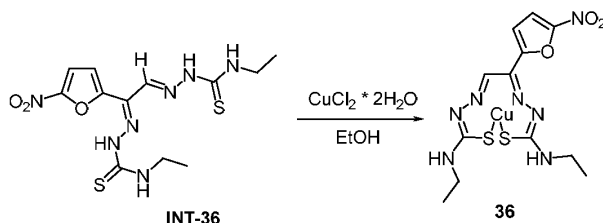
- 20 Yield 0.3g (47%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.40 min). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.83 min). MS (ESI) m/z 360.3 [MH]⁺.

Synthesis of Compound 35:



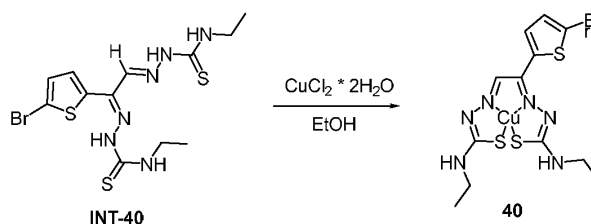
The titular compound was prepared from **INT-35** according to the method to prepare compound 34. The product was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5x50ml), and then dried *in vacuo*. Yield 0.3g (57%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.18 min). MS (ESI) m/z 388.5 [MH]⁺.

Synthesis of Compound 36:



The titular compound was prepared from **INT-36** according to the method to prepare compound 34. The product was isolated as a red-brown powder. Yield 0.026g (40%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.70 min). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.69 min). MS (ESI) m/z 433.2 [MH]⁺.

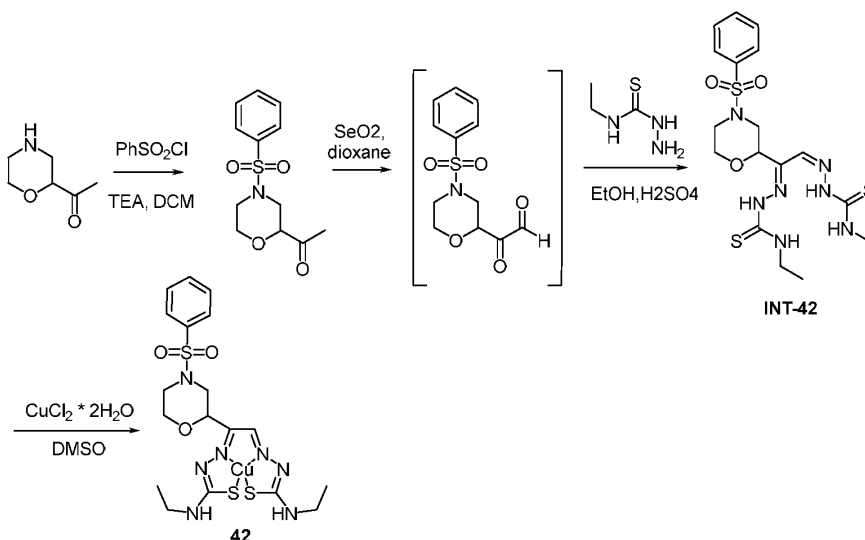
Synthesis of Compound 40:



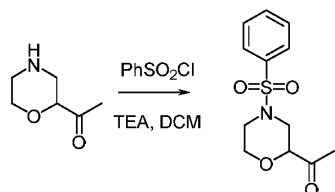
The titular compound was prepared from **INT-40** according to the method to prepare compound 34. The product was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.01g (6%).

LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.72 min). MS (ESI) m/z 484.1 [MH]⁺.

Scheme 16: Synthesis of Compound 42



Synthesis of 1-(4-(phenylsulfonyl)morpholin-2-yl)ethan-1-one:

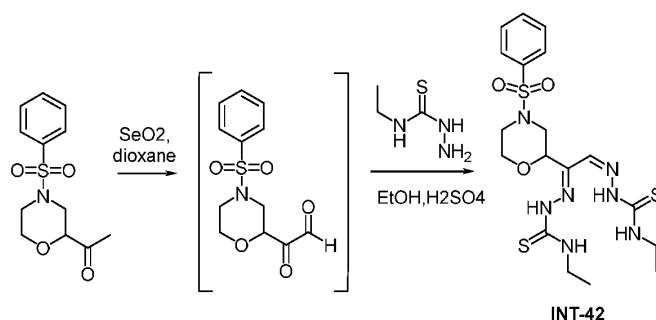


To a solution of 1-morpholin-2-yl-ethanone (0.3g, 2.3mmol) in DCM (50 ml) triethylamine (0.59g, 2.5 eq) was added at 5°C followed by benzenesulfonyl chloride (0.51g, 1.25 eq). The mixture was stirred at ambient temperature for 15h, acidified with aq. 10% HCl, extracted with DCM. The combined organic extracts were dried over Na₂SO₄, filtered, and evaporated. The residue was purified by column chromatography (silica gel, eluent 10% EtOAc in hexane). Yield 0.30g (48%). NMR (400MHz, CDCl₃): 2.20 (s, 3H), 2.22-2.28 (m, 1H), 2.46 (ddd, 1H), 3.58-3.61 (m, 1H), 3.76 (ddd, 1H), 3.90-3.95 (m, 1H), 4.00-4.09 (m, 2H), 7.54-7.60 (m, 2H), 7.63-7.67 (m, 1H), 7.77-7.80 (m, 2H).

10

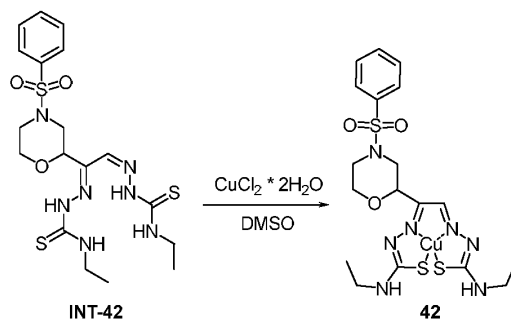
15

Synthesis of INT-42 ((2Z,2'Z)-2,2'-(1-(4-(phenylsulfonyl)morpholin-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide))



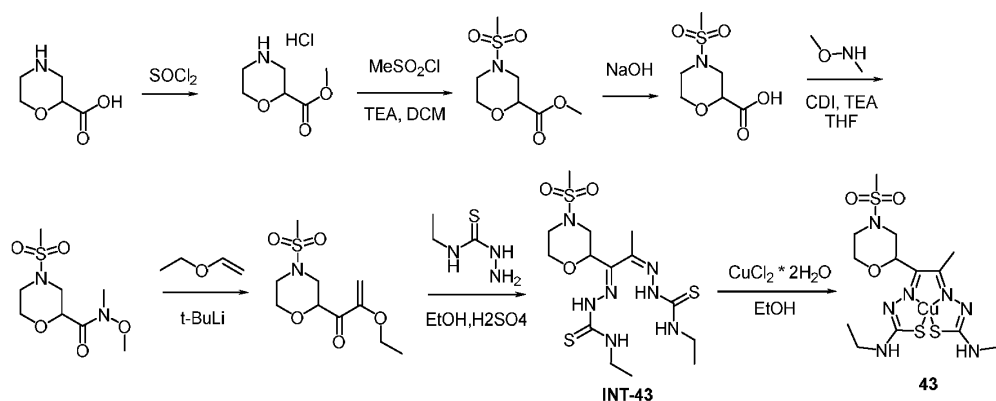
A flask was charged with SeO_2 (0.14g, 1.1 eq), 1,4-dioxane (3.5 mL), and water (0.1 mL). The mixture was warmed up to 50°C and was stirred until most of SeO_2 was dissolved. 1-(4-(phenylsulfonyl)morpholin-2-yl)ethan-1-one was added, and the reaction was heated at gentle reflux for 4 h. Selenium solids were precipitated over the course of the reaction. The mixture was cooled over an ice bath and filtered through diatomaceous earth to remove the selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was concentrated in vacuo until most of 1,4-dioxane was removed. The residue was dissolved in EtOH and filtered. To the filtrate thiosemicarbazide and 1 drop of H_2SO_4 were added and the reaction mixture was refluxed for 2 h. The precipitate was filtered. Yield 0.08g (15%). LCMS (C18 column 20×2 mm, particle size $2.5 \mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.62 min), MS (ESI) m/z 486.5 $[\text{MH}]^+$.

Synthesis of Compound 42:

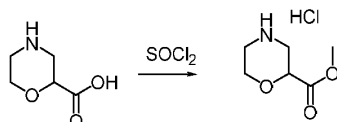


INT-42 (0.08g, 0.17 mmol) was dissolved in DMSO (0.4 ml) and a solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (28mg, 1.0 eq) in water (0.4 ml) was added. The mixture was stirred for 5 min, filtered, and precipitate was washed with saturated solution of potassium carbonate, water and Et_2O . Yield 0.015g (17%). LCMS (C18 column 20×2 mm, particle size $2.5 \mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.27 min). MS (ESI) m/z 547.5 $[\text{MH}]^+$.

Scheme 17: Synthesis of Compound 43

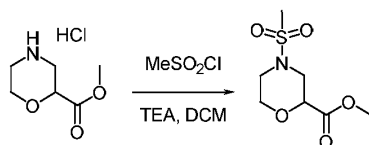


Synthesis of methyl morpholine-2-carboxylate hydrochloride:



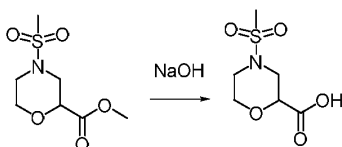
- To a suspension of morpholine-2 carboxylic acid (1.94g, 15 mmol, 1 eq) in methanol (75 ml) thionyl chloride (8.8g, 5.4 ml, 5 eq) was added dropwise at 0-10°C. The reaction mixture was stirred at room temperature for 1 h and then heated for 4 h to reflux. The reaction mixture was evaporated. Yield 2.3 g (85.6%). NMR (400MHz, DMSO-*d*₆): 2.78-3.15 (m, 3H), 3.25-3.35 (m, 1H), 3.69 (s, 3H), 3.69-3.81 (m, 1H), 3.95-4.05 (m, 1H), 4.60 (dd, 1H), 9.80-10.40 (m, 2H).

10 Synthesis of methyl 4-(methanesulfonyl)morpholine-2-carboxylate:



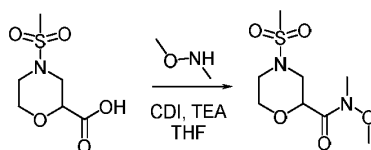
- A mixture of methyl morpholine-2-carboxylate hydrochloride (2.3g, 12.7 mmol, 1 eq), methanesulfonyl chloride (1.74g, 1.1 ml, 1.2 eq) and triethylamine (3.2g, 4.4 ml, 2.5 eq) in methylene chloride (100 ml) was stirred for 15h at ambient temperature. The reaction mixture was washed with water, dried over Na₂SO₄, filtered, and solvents were evaporated. Yield 1.3g (46%). NMR (400MHz, CDCl₃): 2.83 (s, 3H), 2.95-3.04 (m, 2H), 3.50-3.58 (m, 1H), 3.74-3.80 (m, 1H), 3.82 (s, 3H), 3.83-3.88 (m, 1H), 4.09 (ddd, 1H), 4.27 (dd, 1H).

Synthesis of 4-(methanesulfonyl)morpholine-2-carboxylic acid:



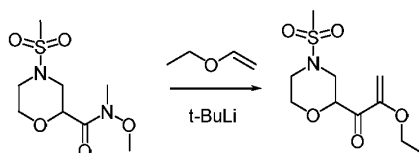
Methyl 4-(methylsulfonyl)morpholine-2-carboxylate (1.3g, 5.8 mmol, 1 eq) was dissolved in methanol (50 ml) and a solution of NaOH (0.58g, 2.5 eq) in water (10 ml) was added. The reaction mixture was stirred overnight at room temperature. Methanol was removed *in vacuo*, the residue diluted with water, acidified with conc. HCl to pH 1 and
 5 extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Yield 0.95g (78%). NMR (400MHz, DMSO-*d*₆): 2.32 (s, 3H), 2.87-2.95 (m, 1H), 3.20-3.25 (m, 2H), 3.51-3.59 (m, 2H), 3.83-3.99 (m, 2H).

Synthesis of N-methoxy-N-methyl-4-(methylsulfonyl)morpholine-2-carboxamide:



To a stirred solution of the 4-(methylsulfonyl)morpholine-2-carboxylic acid (0.97g, 5 mmol, 1 eq) in THF (25 ml) at 0°C carbonyldiimidazole (0.69 g, 0.5 eq) was added. Then N,O-dimethylhydroxylamine hydrochloride (0.45g, 1 eq) and triethylamine (2.34g, 3.2 ml, 5 eq) were added to the solution, and ice bath was removed. The reaction mixture was stirred at room temperature until disappearance of the acid, as determined using TLC. After
 15 completion, triethylamine hydrochloride was removed by filtration. Filtrate was concentrated to dryness via rotary evaporation. The residue was purified by a short-path silica gel column chromatography eluting with 20% ethyl acetate in hexane. Yield 0.26g (22%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.99 min), MS (ESI) *m/z* 253.1 [MH]⁺.

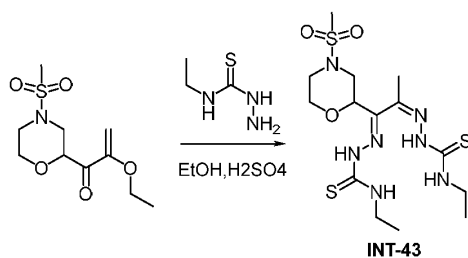
Synthesis of 2-ethoxy-1-(4-(methylsulfonyl)morpholin-2-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (0.82g, 11 eq) in dry tetrahydrofuran (20 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M, 6 ml, 9.9 eq) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C.
 25 Magnesium bromide etherate (2.5g, 9.9 eq) was added. Then the mixture was warmed to 0°C over a 15 min period and N-methoxy-N-methyl-4-(methylsulfonyl)morpholine-2-carboxamide was added (0.26g, 1 mmol, 1 eq) in THF. The mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered and
 30 solvents evaporated. The product was used for the next step without additional purification.

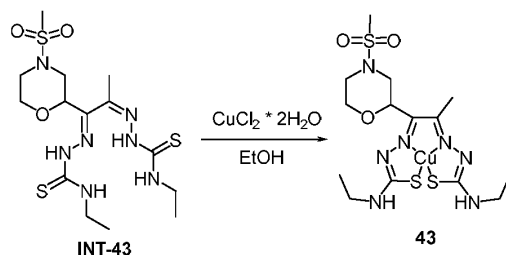
Yield 0.17g (62%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.36 min), MS (ESI) m/z 527.3 [2MH]⁺

Synthesis of INT-43 ((2Z,2'Z)-2,2'-(1-(4-(methylsulfonyl)morpholin-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

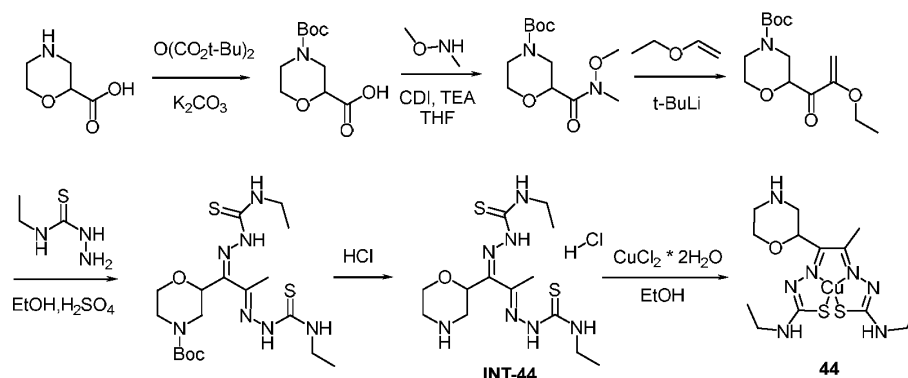
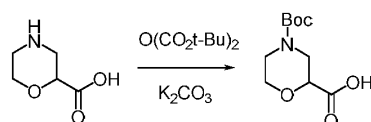


2-Ethoxy-1-(4-(methylsulfonyl)morpholin-2-yl)prop-2-en-1-one (0.16g, 0.6 mmol, 1 eq) was dissolved in EtOH (20 ml), ethyl thiosemicarbazide (0.14g, 2 eq) and 1 drop of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.15g (55%). NMR (400MHz, DMSO-*d*₆): 1.10-1.21 (m, 6H), 1.47-1.53 (m, 1H), 2.16-2.21 (m, 1H), 2.47-2.55 (m, 4H), 2.78-2.84 (m, 1H), 2.95 (br.d, 1H), 3.08-3.16 (m, 1H), 3.30 (s, 3H), 3.42-3.50 (m, 4H), 7.78 (br.s, 1H), 8.69 (br.s, 1H), 10.75 (s, 1H), 12.18 (s, 1H). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.47 min), MS (ESI) m/z 438.4 [MH]⁺.

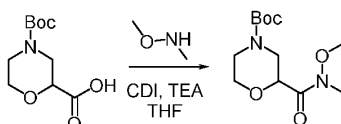
Synthesis of Compound 43:



CuCl₂·2H₂O (0.058g, 1 eq) was added to thiosemicarbazone 6 (0.15g, 0.3 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.07g (41%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.06 min). MS (ESI) m/z 499.5 [MH]⁺.

Scheme 18: Synthesis of Compound 44**Synthesis of 4-(tert-butoxycarbonyl)morpholine-2-carboxylic acid:**

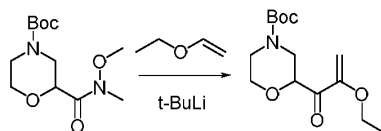
- 5 Morpholine-2-carboxylic acid (2g, 15.6 mmol) was dissolved in dioxane-water (8ml /4ml) mixture, then potassium carbonate (4.3g, 2 eq) was added and the mixture was stirred for 30 min. Di-*tert*-butyl dicarbonate (3.7g, 1.1 eq) was added and the reaction mixture was stirred overnight, solvents evaporated, the residue was dissolved in water and solution was acidified with 10% H₂SO₄, product was extracted with EtOAc. The organic layer was
- 10 separated, dried over Na₂SO₄, filtered and solvents were evaporated.. Yield 1.7g (47%). NMR (400MHz, DMSO-*d*₆): 1.40 (s, 9H), 3.04-3.10 (m, 2H), 3.42-3.56 (m, 2H), 3.78-3.84 (m, 2H), 4.01-4.07 (m, 1H), 12.95 (br.s, 1H).

Synthesis of tert-butyl 2-(methoxy(methyl)carbamoyl)morpholine-4-carboxylate:

- 15 A solution of CDI in THF (7 ml) was added to a solution of 4-(tert-butoxycarbonyl)morpholine-2-carboxylic acid in THF (7ml) at 0°C. The mixture was stirred at RT for 1 h. Then the mixture was cooled to 0°C and a suspension of triethylamine (0.7 ml) and N,O-dimethylhydroxylamine in MeCN (10ml) was added at 0°C, and the reaction was stirred at r.t. for 16 h. Then solvents were evaporated, the residue was dissolved in DCM,
- 20 solution was washed with water, acetic acid (20% solution), and sat.NaHCO₃. The organic layer was separated, dried The organic layer was washed with water, separated, dried over Na₂SO₄, filtered and solvents were evaporated. The residue was purified by column chromatography SiO₂/hexane:EtOAc 2:1. Yield 0.78 g (73%). NMR (400MHz, CDCl₃): 1.49

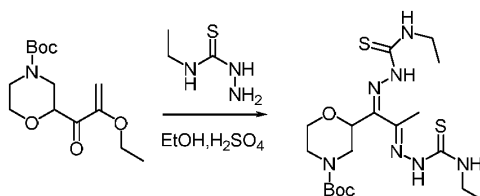
(s, 9H), 3.02 (br.s, 1H), 3.24 (s, 3H), 3.60 (dd, 1H), 3.75 (s, 3H), 3.90 (br.s, 1H), 4.00-4.30 (m, 2H), 4.85 (br.s, 1H).

Synthesis of tert-butyl 2-(2-ethoxyacryloyl)morpholine-4-carboxylate:



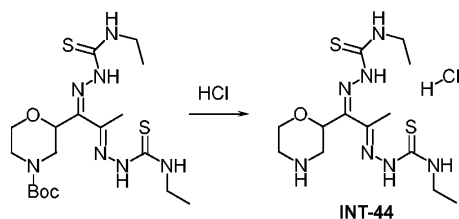
- 5 A solution of ethyl vinyl ether (2g, 2.6 ml, 11 eq) in dry tetrahydrofuran (75 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M, 13 ml, 8.9 eq) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. Magnesium bromide etherate (5.2 g, 8.9 eq) was added. Then the mixture was warmed to 0°C over a 15 min period and *tert*-butyl 2-
- 10 (methoxy(methyl)carbamoyl)morpholine-4-carboxylate was added (0.7g, 2.6 mmol, 1 eq) in THF. The mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, and evaporated. The product was used for the next step without additional purification. Yield 0.6g (82 %). LCMS (C18 column 20 × 2 mm, particle size 2.5
- 15 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.33 min), MS (ESI) m/z 286.1 [MH]⁺.

Synthesis of tert-butyl 2-((6E,8E)-8-methyl-4,11-dithioxo-3,5,6,9,10,12-hexaazatetradeca-6,8-dien-7-yl)morpholine-4-carboxylate:



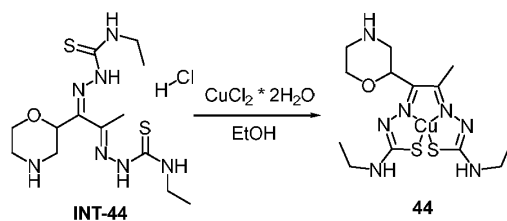
- 20 Tert-butyl 2-(2-ethoxyacryloyl)morpholine-4-carboxylate (0.39g, 1.4 mmol, 1 eq) was dissolved in EtOH (150 ml), ethyl thiosemicarbazide (0.33g, 2 eq) and 3 drops of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.23g (37.2%). NMR (400MHz, DMSO-d₆): 1.10-1.18 (m, 6H),
- 25 1.40 (br.d, 9H), 2.20 (s, 3H), 2.90-2.06 (m, 1H), 3.18 (br.s, 1H), 3.52-3.80 (m, 6H), 3.82-3.87 (m, 1H), 4.02-4.07 (m, 2H), 5.12 (br.s, 1H), 8.28 (br.s, 1H), 8.51 (t, 1H), 10.24 (s, 1H), 11.20 (br.s, 1H).

Synthesis of INT-44 (2E,2'E)-2,2'-(1-(morpholin-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide) hydrochloride:



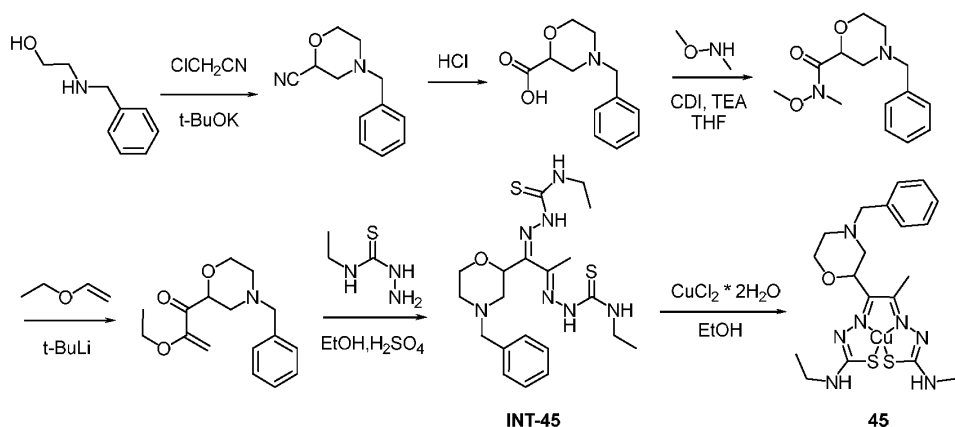
To a solution of tert-butyl 2-((6E,8E)-8-methyl-4,11-dithioxo-3,5,6,9,10,12-hexaazatetradeca-6,8-dien-7-yl)morpholine-4-carboxylate (0.23g, 0.5 mmol) in dioxane HCl/dioxane (3M, 6 ml) was added. The reaction mixture was stirred at room temperature overnight. Formed precipitate was filtered. Yield 0.15g (76%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.13 min), MS (ESI) m/z 360.4 [MH]⁺.

Synthesis of Compound 44:

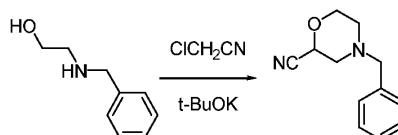


$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.036g, 1 eq) was added to **INT-44** (0.1 g, 0.2 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.03g (33%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.47 min). MS (ESI) m/z 421.0 [MH]⁺.

Scheme 19: Synthesis of Compound 45

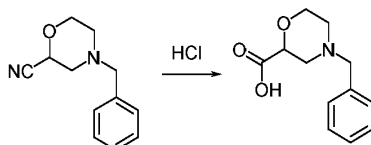


Synthesis of 4-benzylmorpholine-2-carbonitrile:



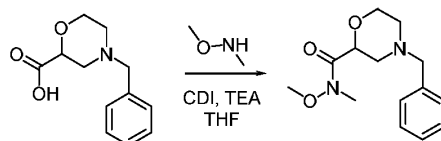
2-Chloroacetonitrile (6 g, 1.03 eq) was dissolved in toluene (16 ml). A solution of N-benzyloethanolamine (10 g, 66 mmol) in toluene (5 ml) was added and the reaction mixture was stirred for 15 h at ambient temperature. Then toluene (30 ml) was added and the solution was cooled down to -5°C. Suspension of *t*-BuOK (7.6g, 1.03 eq) in THF (128ml) was slowly added and the mixture was stirred at -5°C for 50 min. The mixture was washed with brine, dried and evaporated. The residue was purified by column chromatography (silica gel, hexane:EtOAc gradient 3:1 to 1:1. Yield 8.4 g (62.8%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.22 min), MS (ESI) *m/z* 203.4 [MH]⁺.

Synthesis of 4-benzylmorpholine-2-carboxylic acid:



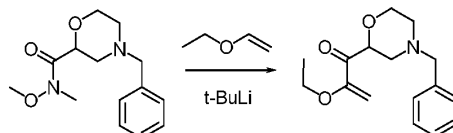
4-Benzylmorpholine-2-carbonitrile (1.6g, 7.9 mmol, 1 eq) was dissolved in HCl (6M, 65 ml) and the reaction mixture was refluxed for 2.5 h. Then toluene (15 ml) was added and refluxing was continued for additional 3 h. The reaction mixture was evaporated to dryness. Yield 1.6g (78.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.65 min), MS (ESI) *m/z* 222.4 [MH]⁺.

Synthesis of 4-benzyl-N-methoxy-N-methylmorpholine-2-carboxamide:



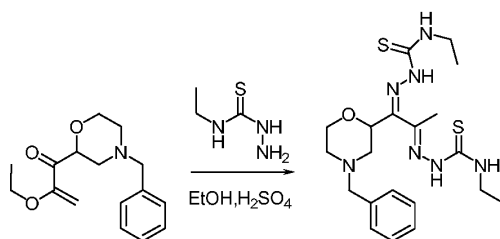
A solution of CDI (1.2g, 1.2 eq) in THF (12 ml) was added to a solution of 4-benzylmorpholine-2-carboxylic acid (1.6g, 6.2 mmol, 1 eq) and triethylamine (0.8 ml) in THF (12 ml) at 0°C. The mixture was stirred at room temperature for 1 h. Then the mixture was cooled to 0°C and a suspension of triethylamine (1.2 ml) and N,O-dimethylhydroxylamine (0.73g, 1.2 eq) in MeCN (17ml) at 0°C was added, and the reaction was stirred at room temperature for 16 h. Then the solvents were evaporated. The residue was dissolved in DCM, solution was washed with water, then with acetic acid (20% aq solution) and aq. sat. NaHCO₃. The organic layer was separated, dried over Na₂SO₄, filtered and solvents were evaporated. Yield 0.9g (54.8%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.00 min), MS (ESI) m/z 265.1 [MH]⁺.

Synthesis of 1-(4-benzylmorpholin-2-yl)-2-ethoxyprop-2-en-1-one:

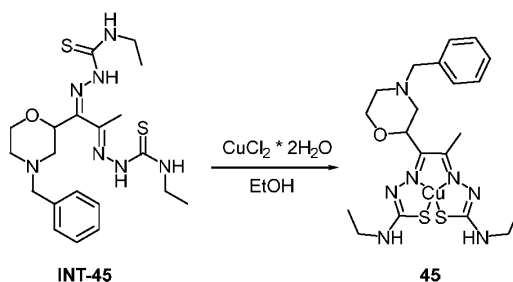


A solution of ethyl vinyl ether (0.34g, 0.5 ml, 3.3 eq) in dry tetrahydrofuran (20 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M, 2.4 ml, 3 eq) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. 4-Benzyl-N-methoxy-N-methylmorpholine-2-carboxamide was added (3.0g, 7.5mmol, 1 eq) in THF, and the mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over Na₂SO₄, filtered and solvents were evaporated. The product was used for the next step without additional purification. Yield 0.3 g (82 %). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.03 min), MS (ESI) m/z 276.1 [MH]⁺.

Synthesis of INT-45 ((2E,2'E)-2,2'-(1-(4-benzylmorpholin-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide):

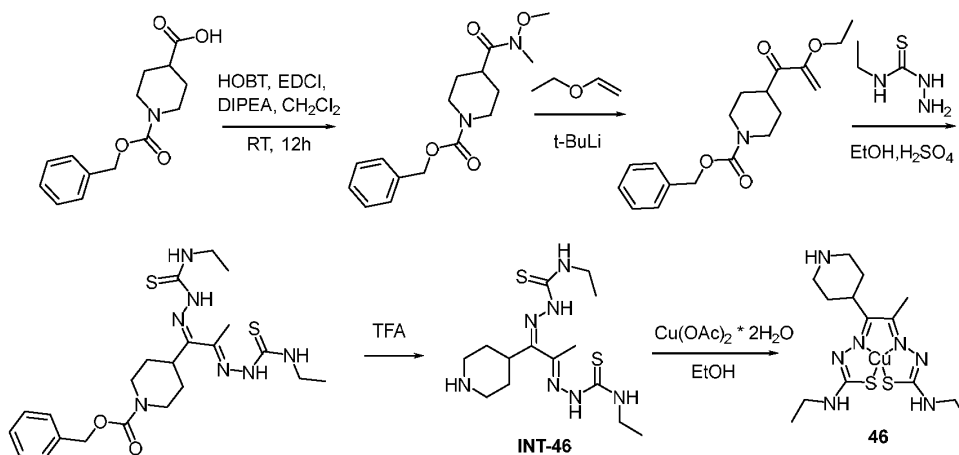
**INT-45**

1-(4-Benzylmorpholin-2-yl)-2-ethoxyprop-2-en-1-one (0.3g, 1 mmol, 1 eq) was dissolved in EtOH (10 ml), ethyl thiosemicarbazide (0.26 g, 2 eq) and 1 drop of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.08g (16%). NMR (400MHz, DMSO-*d*₆): 1.05 (t, 6H), 2.37 (s, 3H), 3.50-3.56 (m, 4H), 3.80 (br.s, 1H), 4.25 (br.s, 2H), 5.65 (br.s, 1H), 7.30-7.48 (m, 4H), 8.09 (br.s, 1H), 8.59 (br.s, 1H), 10.22 (s, 1H), 10.80 (br.s, 1H). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.20 min), MS (ESI) *m/z* 450.4 [MH]⁺.

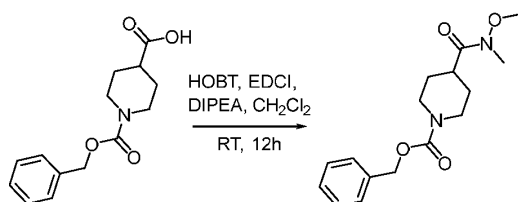
Synthesis of Compound 45:**INT-45****45**

CuCl₂·2H₂O (0.017g, 1 eq) was added to **INT-45** (0.045g, 0.1 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.035 g (68.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.70 min). MS (ESI) *m/z* 511.3 [MH]⁺.

Scheme 20: Synthesis of Compound 46

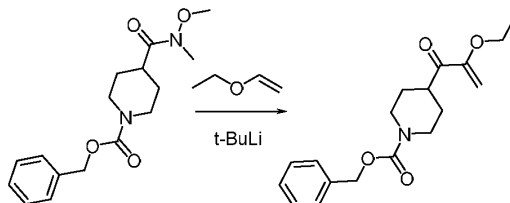


Synthesis of benzyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate:



- To a mixture of 1-((benzyloxy)carbonyl)piperidine-4-carboxylic acid (21.2g, 80.6mmol), N,O-dimethylhydroxylamine (10.2g, 96.7mmol), HOBT (12.1g, 96.7mmol) and TEA (18.5ml, 241.8mmol) in DCM (300ml) was added EDCI (17.1g, 96.7mmol) at 4°C and the mixture was stirred for 15h at ambient temperature. The mixture was washed with water (50ml), 1N HCl (aq) (50ml), water (100ml), brine (150ml). The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent 100% DCM to 5% MeOH) to afford crude **1**. Yield 22.7g (92%). NMR (400MHz, DMSO-*d*₆): 1.36-1.43 (m, 2H), 1.64-1.70 (m, 2H), 2.84-2.98 (m, 2H), 3.09 (s, 3H), 3.68 (s, 3H), 4.00-4.06 (m, 2H), 5.07-s, 2H), 7.30-7.41 (m, 5H).

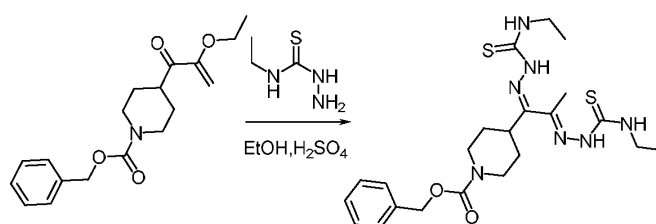
Synthesis of benzyl 4-(2-ethoxyacryloyl)piperidine-1-carboxylate:



- A solution of ethyl vinyl ether (2.0g, 28.1mmol) in dry tetrahydrofuran (45 ml) was cooled down to -78°C, and *tert*-butyllithium (1.7M, 15.6ml, 25.5mmol) in pentane was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -

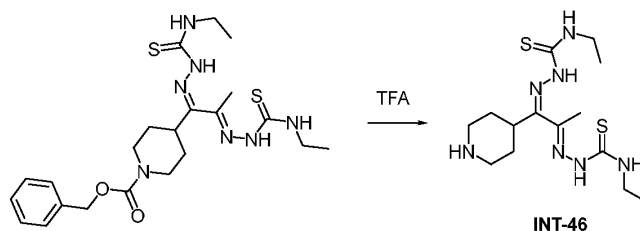
30°C. Benzyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (2.6g, 8.5mmol) was added in THF (15ml), stirring at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into diluted NH₄Cl (100ml) and extracted with Et₂O (3 × 100ml). The combined extracts were dried over Na₂SO₄, filtered and solvents were evaporated. The product was used for the next step without additional purification. Yield 0.77g (29%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.58 min), MS (ESI) m/z 318.2 [MH]⁺.

Synthesis of benzyl 4-((6Z,8E)-8-methyl-4,11-dithioxo-3,5,6,9,10,12-hexaazatetradeca-6,8-dien-7-yl)piperidine-1-carboxylate:



Benzyl 4-(2-ethoxyacryloyl)piperidine-1-carboxylate (1.5g, 4.6mmol) was dissolved in EtOH (80ml), ethyl thiosemicarbazide (1.2g, 10.1mmol) and 3 drops of H₂SO₄ were added. Reaction mixture was stirred and heated to reflux for 4h and then maintained for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.3g (14%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.47 min), MS (ESI) m/z 492.2 [MH]⁺.

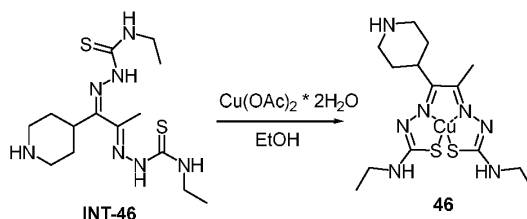
Synthesis of INT-46 ((2Z,2'E)-2,2'-(1-(piperidin-4-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



Benzyl 4-((6Z,8E)-8-methyl-4,11-dithioxo-3,5,6,9,10,12-hexaazatetradeca-6,8-dien-7-yl)piperidine-1-carboxylate (0.35 g, 0.7 mmol) was dissolved in CF₃COOH (5 ml) and solution was heated to reflux for 2.5 h. After cooling down to ambient temperature, the reaction mixture was diluted with aq. sat. NaHCO₃ solution, and extracted with CH₂Cl₂ (3 × 15ml). The organic layer was washed with water, separated, dried over Na₂SO₄, filtered and solvents were evaporated. The residue was purified by column chromatography (silica gel,

eluent 100% DCM to 5% MeOH) to afford the crude titular product. Yield 0.25g (98%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.11 min), MS (ESI) m/z 358.5 [MH]⁺.

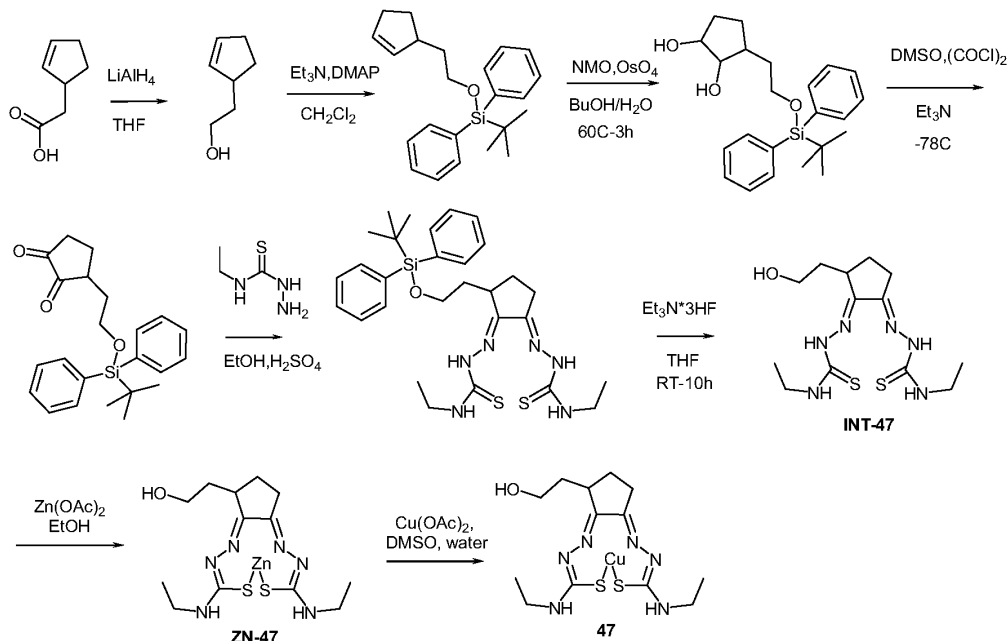
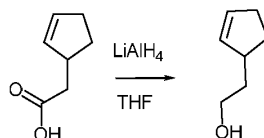
Synthesis of Compound 46:



5

Cu(OAc)₂·2H₂O (0.02 g, 0.09mmol) was added to **INT-46** (0.03 g, 0.08 mmol) in methanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.04 g (90%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.85 min). MS (ESI) m/z 419.5 [MH]⁺.

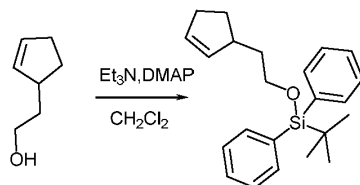
10

Example 3: Preparation of Compounds 47-53**Scheme 21: Synthesis of Compound 47****Synthesis of 2-(cyclopent-2-en-1-yl)ethan-1-ol:**

5

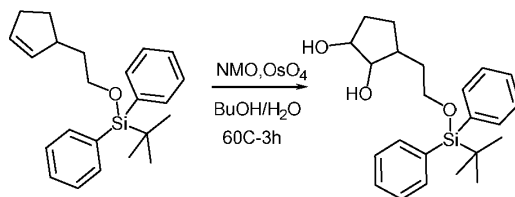
To a stirred suspension of LiAlH_4 (3.76 g, 99.0 mmol, 2.5 equiv) in THF (250 ml) a solution of cyclopent-2-eneacetic acid (5.0 g, 39.6 mmol, 1.0 equiv) in THF (50 ml) was slowly added at 0°C . The mixture was heated to reflux for 3 h, and then cooled to 0°C . The reaction was quenched with Na_2SO_4 (10%) and extracted with Et_2O ($3 \times 100\text{ml}$). The combined extracts were dried over Na_2SO_4 , filtered and evaporated. The product was used for the next step without additional purification. Yield 4.06 g (91%). $^1\text{H-NMR}$ (400MHz, CDCl_3): δ (ppm) 1.40-1.48 (m, 1H), 1.50-1.51 (m, 1H), 1.56-1.64 (m, 1H), 1.67-1.76 (m, 1H), 2.04-2.13 (m, 1H), 2.27-2.37 (m, 2H), 2.78 (br.s, 1H), 3.66-3.75 (m, 2H), 5.68-5.71 (m, 1H), 5.74-5.76 (m, 1H).

15 **Synthesis of tert-butyl(2-(cyclopent-2-en-1-yl)ethoxy)diphenylsilane:**



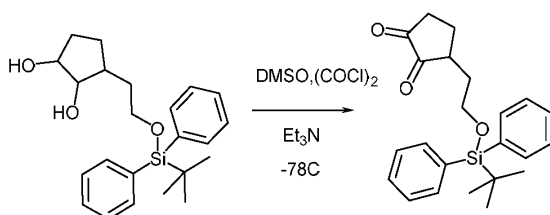
To a solution of 2-(cyclopent-2-en-1-yl)ethan-1-ol (4.05g, 36.1mmol) in dichloromethane (200 ml) was added *tert*-butyldiphenylsilyl chloride (11.9g, 43.3mmol), triethylamine (4.7g, 46.9mmol), and 4-(dimethylamino)pyridine (0.22g, 1.8mmol), the mixture was stirred at room temperature for 3 hours. After quenching the reaction by the addition of 1N hydrochloric acid, the mixture was extracted with dichloromethane. The organic extracts were washed with water, aq. sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, filtered and then concentrated *in vacuo*. Flash chromatography (silica gel, hexane-ethyl acetate 50:1) of the residue gave compound **2**. Yield 11.3 g (89%). ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 0.99 (s, 9H), 1.26-1.35 (m, 1H), 1.43-1.51 (m, 1H), 1.61-1.69 (m, 1H), 1.88-1.97 (m, 1H), 2.13-2.30 (m, 2H), 2.70-2.76 (m, 1H), 3.68 (t, 2H), 5.62-5.65 (m, 1H), 5.66-5.70 (m, 1H), 7.41-7.46 (m, 6H), 7.60-7.62 (m, 4H).

Synthesis of 3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentane-1,2-diol:



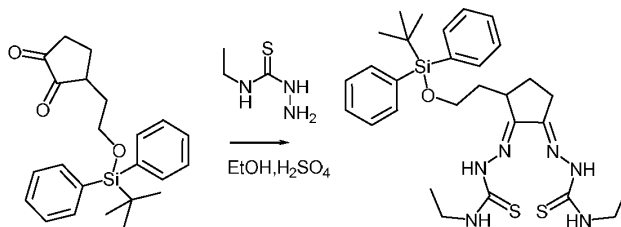
Tert-butyl(2-(cyclopent-2-en-1-yl)ethoxy)diphenylsilane (9.0g, 25.6mmol) was dissolved in an H₂O-*t*BuOH (1:3) mixture then *N*-methylmorpholine *N*-oxide (3.9g, 33.3mmol) and OsO₄ (0.004g of 4% solution in water, 0.001 eq) were added. The reaction mixture was stirred at 60°C until completion, monitoring by TLC (CHCl₃-CH₃OH 20:1), solid catalyst was filtered, rinsed with EtOAc, and the filtrate quenched with an aqueous solution of Na₂S₂O₃ (10%). The aqueous layer was extracted with EtOAc, the organic extracts combined, dried over Na₂SO₄, filtered and solvents were evaporated. The crude product was purified by flash chromatography (gradient CHCl₃-MeOH from 1:0 to 95:5), to afford diol **3**. Yield 6.3 g (64%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.99 min). MS (ESI) *m/z* 385.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 0.98 (s, 9H), 1.26-1.55 (m, 2H), 1.66-1.68 (m, 1H), 1.69-1.78 (m, 2H), 1.79-1.88 (m, 2H), 3.59-3.60 (m, 1H), 3.67 (q, 2H), 3.74-3.88 (m, 1H), 4.09 (dd, 1H), 4.32 (dd, 1H), 7.41-7.48 (m, 6H), 7.60-7.62 (m, 4H).

Synthesis of 3-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)cyclopentane-1,2-dione:



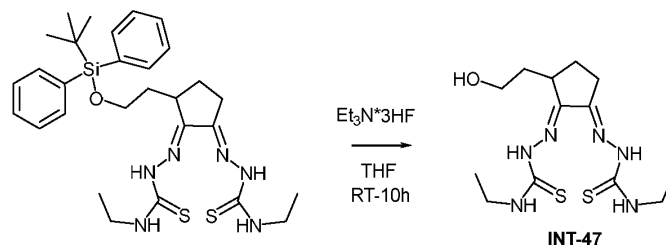
Dimethyl sulfoxide (3.6g, 46.8 mmol) was added to a stirred solution of oxalyl chloride (2.97g, 23.4 mmol) in dichloromethane (100 ml) at -78°C . After 15 min a solution of 3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)cyclopentane-1,2-diol (3.0g, 7.9mmol) in dichloromethane (20 ml) was slowly added (over period of 15 min) and the resulting solution was stirred at -78°C for 1 h. Then triethylamine (7.3g, 70 mmol) was added, the mixture was stirred for 15 min at -78°C and then warmed to ambient temperature. The reaction mixture was washed with water, organic layer was dried over Na_2SO_4 , filtered, and evaporated. Yield 1.6 g (54%). LCMS (C18 column 20×2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 2.01 min). MS (ESI) m/z 381.1 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ (ppm) 0.97 (s, 9H), 1.90 (t, 1H), 2.27-2.35 (m, 2H), 2.46-2.51 (m, 2H), 3.52-3.46 (m, 2H), 3.63-3.86 (m, 2H), 7.41-7.48 (m, 6H), 7.60-7.62 (m, 4H).

Synthesis of (2E,2'E)-2,2'-(3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)cyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide):



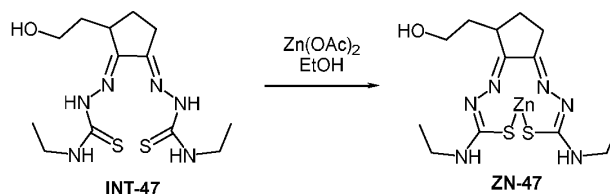
3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)cyclopentane-1,2-dione (1.6 g, 4.2 mmol) was dissolved in EtOH (25 ml), ethyl thiosemicarbazide (1.02g, 4.4 mmol) and 3 drops of H_2SO_4 were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et_2O , and dried to afford the product **5**. Yield 1.75 g (74%). LCMS (C18 column 20×2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 2.58 min). MS (ESI) m/z 583.3 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ (ppm) 0.99 (s, 9H), 1.11 (t, 3H), 1.20 (t, 3H), 1.41-1.59 (m, 2H), 1.96-2.03 (m, 2H), 2.21-2.29 (m, 1H), 2.71-2.85 (m, 2H), 3.53-3.62 (m, 4H), 3.71-3.83 (m, 2H), 7.41-7.48 (m, 6H), 7.61-7.63 (m, 4H), 7.75 (t, 1H), 8.57 (t, 1H), 10.73 (s, 1H), 12.26 (s, 1H).

Synthesis of INT-47 ((2E,2'E)-2,2'-(3-(2-hydroxyethyl)cyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



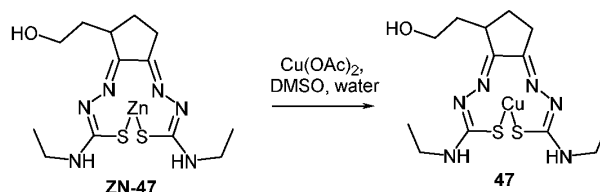
To a solution of (2E,2'E)-2,2'-(3-(2-((tert-butyl) diphenylsilyl)oxy)ethyl)cyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide) (0.85 g, 1.46 mmol) in THF (25 ml) was added triethylamine trihydrofluoride at ambient temperature. The resulting mixture was stirred at ambient temperature for 10 h, treated with sat. aq. ammonium chloride. The solution was extracted with ether, washed with aqueous sat. aq. ammonium chloride and brine. The organic layer was dried over Na₂SO₄, filtered, and solvents were concentrated under reduced pressure providing the crude titular product. Yield 0.18 g (36%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.30 min). MS (ESI) m/z 345.0 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.28 (t, 3H), 1.35 (t, 3H), 1.58-1.81 (m, 2H), 1.86-1.95 (m, 1H), 2.03-2.13 (m, 1H), 2.24-2.33 (m, 1H), 2.44-2.57 (m, 1H), 2.65-2.77 (m, 1H), 2.85-2.93 (m, 1H), 3.31-3.53 (m, 1H), 3.68-2.82 (m, 5H), 7.25-7.32 (m, 1H), 7.41-7.48 (m, 1H), 8.75 (s, 1H), 12.27 (s, 1H).

Synthesis of ZN-47:



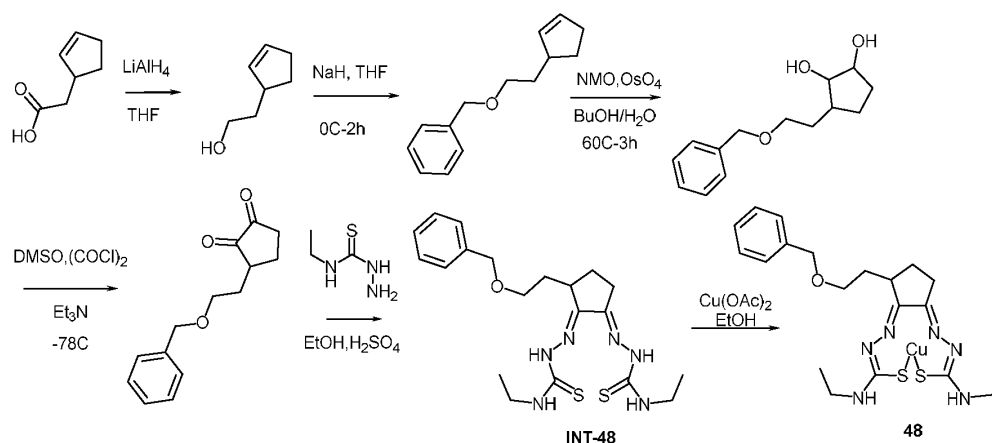
Zn(OAc)₂ 2H₂O (0.58g, 2.7 mmol) was added to **INT-47** (0.61g, 1.8 mmol) in ethanol. The mixture was refluxed for 4 h. The formed complex was precipitated from the mixture as a yellow powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.72g (99%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.09 (t, 3H), 1.14 (t, 3H), 1.35-1.48 (m, 2H), 2.01-2.11 (m, 2H), 2.51-2.55 (m, 2H), 2.67-2.73 (m, 1H), 2.76-2.84 (m, 1H), 3.47-3.56 (m, 4H), 4.34 (t, 1H), 4.42 (t, 1H), 7.37 (br.s, 1H), 7.85 (t, 1H).

Synthesis of Compound 47:



- ZN-47** (0.72g, 1.7 mmol) was dissolved in DMSO (3.6 ml) and a solution of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.39 g, 1.9mmol) in water (3.6 ml) was added. The mixture was stirred for 5 min, precipitate was filtered and washed with saturated solution of potassium carbonate, water and Et_2O . Yield 0.09g (13%). LCMS (C18 column 20×2 mm, particle size $2.5 \mu\text{m}$, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.81 min). MS (ESI) m/z 406.5 $[\text{MH}]^+$.

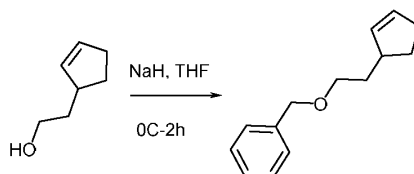
Scheme 22: Synthesis of Compound 48



10 Synthesis of 2-(cyclopent-2-en-1-yl)ethan-1-ol:

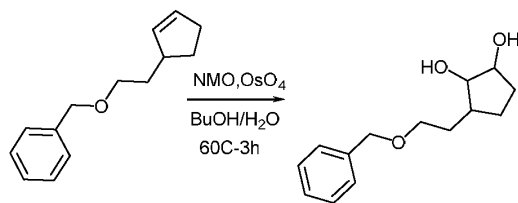
- To a stirred suspension of LiAlH_4 (4.14g, 109.0 mmol) in THF (250 ml) cooled to 0°C , a solution of cyclopent-2-eneacetic acid (5.5g, 43.6 mmol, 1.0 equiv) in THF (50 ml) was slowly added. The mixture was heated to reflux for 3 h, and then cooled to 0°C . The reaction was quenched with Na_2SO_4 (10%) and extracted with Et_2O ($3 \times 100\text{ml}$). The combined extracts were dried over Na_2SO_4 , filtered and evaporated. The product was used for the next step without additional purification. Yield 4.4g (90%). $^1\text{H-NMR}$ (400MHz, CDCl_3): δ (ppm) 1.40-1.49 (m, 1H), 1.50-1.51 (m, 1H), 1.58-1.64 (m, 1H), 1.67-1.76 (m, 1H), 2.04-2.13 (m, 1H), 2.42-2.37 (m, 2H), 2.78 (br.s, 1H), 3.69-3.77 (m, 2H), 5.68-5.71 (m, 1H), 5.74-5.77 (m, 1H).

20 Synthesis of ((2-(cyclopent-2-en-1-yl)ethoxy)methyl)benzene:



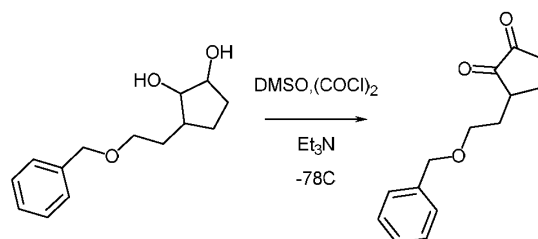
To a stirred solution of 2-(cyclopent-2-en-1-yl)ethan-1-ol (1.0g, 8.9 mmol) in DMF (12 ml) at 0°C in one portion NaH (0.5g, 13.5 mmol, 60-65% in mineral oil) was added. After stirring for 30 min to the solution was added benzyl chloride (2.03g, 16.1mmol). The reaction
 5 was stirred overnight, then quenched with water (15ml) and extracted three times with Et₂O. The combined extracts were washed with water, brine, dried over Na₂SO₄, filtered and solvents were evaporated. The crude product was used without purification. Yield 1.8g (99%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.33-1.41 (m, 1H), 1.46-1.55 (m, 1H), 1.61-1.69 (m, 1H), 1.93-2.02 (m, 1H), 2.14-2.33 (m, 2H), 2.70 (t, 1H), 3.47 (t, 2H), 4.45 (s, 2H),
 10 5.70 (t, 2H), 7.25-7.32 (m, 3H), 7.34-7.45 (m, 2H).

Synthesis of 3-(2-(benzyloxy)ethyl)cyclopentane-1,2-diol:



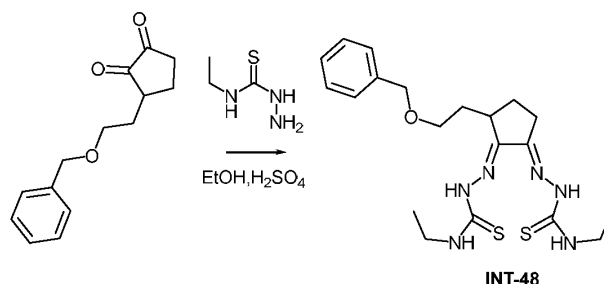
((2-(cyclopent-2-en-1-yl)ethoxy)methyl)benzene (2.2g, 11.1 mmol) was dissolved in an H₂O - tBuOH mixture (1:3) then N-methylmorpholine N-oxide (1.7g, 14.4mmol) and OsO₄
 15 (0.008 g of 4% solution in water, 0.001 eq) were added. The reaction mixture was stirred at 60°C until completion, monitored by TLC (CHCl₃-CH₃OH 20:1), solid catalyst was filtered, rinsed with EtOAc, and the filtrate was quenched with an aqueous solution of Na₂S₂O₃ (10%). The aqueous layer was extracted with EtOAc, the organic extracts were combined, dried over Na₂SO₄, filtered and solvents were evaporated. The crude product purified by
 20 flash chromatography (CHCl₃-MeOH gradient 1:0 to 95:5), to afford the titular product. Yield 1.64 g (62%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.20 min). MS (ESI) m/z 237.0 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 0.95-1.03 (m, 1H), 1.29-1.59 (m, 2H), 1.66-1.68 (m, 1H), 1.69-1.78 (m, 2H), 1.79-1.88 (m, 1H), 3.41-3.48 (m, 2H), 3.45 (qq, 1H),
 25 3.75-3.91 (m, 1H), 4.09 (dd, 1H), 4.32 (dd, 1H), 4.41-4.48 (m, 2H), 7.25-7.36 (m, 5H).

Synthesis of 3-(2-(benzyloxy)ethyl)cyclopentane-1,2-dione:



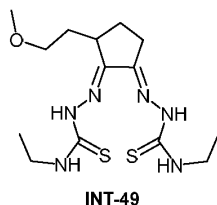
Dimethyl sulfoxide (6.1g, 78.0 mmol) was added to a stirred solution of oxalyl chloride (4.9g, 39.0 mmol) in dichloromethane (150 ml) at -78°C. After 15 min a solution of 3-(2-(benzyloxy)ethyl)cyclopentane-1,2-diol (3.1g, 13.0 mmol) in dichloromethane (20 ml) was slowly added (over period of 15 min) and the resulting solution was stirred at -78°C for 1 h. Then triethylamine (11.8g, 117.0 mmol) was added, the mixture was stirred for 15 min at -78°C and then warmed to ambient temperature. The reaction mixture was washed with water, organic layer was dried over Na₂SO₄, filtered and solvents were evaporated. Yield 2.6 g (87%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.26 min). MS (ESI) m/z 233.1 [MH]⁺.

Synthesis of INT-48 ((2E,2'E)-2,2'-(3-(2-(benzyloxy)ethyl)cyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



3-(2-(benzyloxy)ethyl)cyclopentane-1,2-dione (2.6g, 11.4 mmol) was dissolved in EtOH (35 ml), ethyl thiosemicarbazide (2.86g, 23.9 mmol) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried to afford the product. Yield 0.40 g (9%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.86 min). MS (ESI) m/z 435.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.12 (t, 3H), 1.19 (t, 3H), 1.46-1.58 (m, 2H), 2.05-2.15 (m, 1H), 2.22-2.32 (m, 1H), 2.53-2.58 (m, 1H), 2.74-2.82 (m, 2H), 3.41-3.63 (m, 6H), 4.47 (d, 2H), 7.26-7.37 (m, 5H), 7.77 (t, 1H), 8.66 (t, 1H), 10.74 (s, 1H), 12.25 (s, 1H).

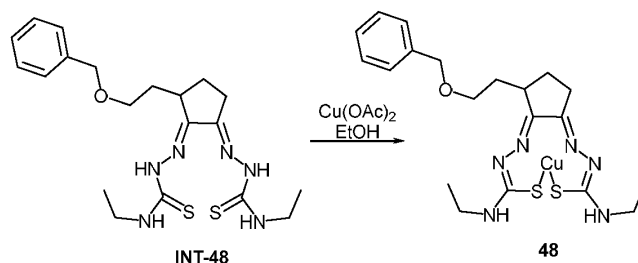
Synthesis of INT-49 ((2E,2'E)-2,2'-(3-(2-methoxyethyl)cyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-49 was made using a procedure analogous to the procedure to prepare INT-48.

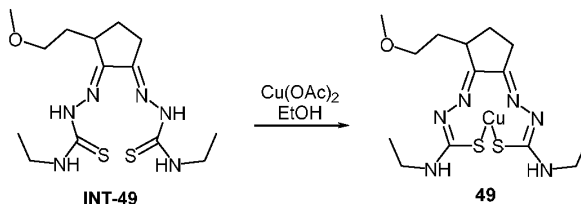
- 5 Yield 1.1 g (72%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.73 (t, 2H), 1.97-2.01 (m, 2H), 2.24-2.27 (m, 1H), 2.36-2.39 (m, 1H), 2.53-2.57 (m, 1H), 2.62-2.67 (m, 1H), 3.12 (d, 3H), 3.38-3.45 (m, 1H).

Synthesis of Compound 48:



- 10 Cu(OAc)₂ 2H₂O (0.26g, 1.12mmol) was added to INT-48 5 (0.4g, 0.92mmol) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.1g (22%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.98 min). MS (ESI) m/z
- 15 496.5 [MH]⁺.

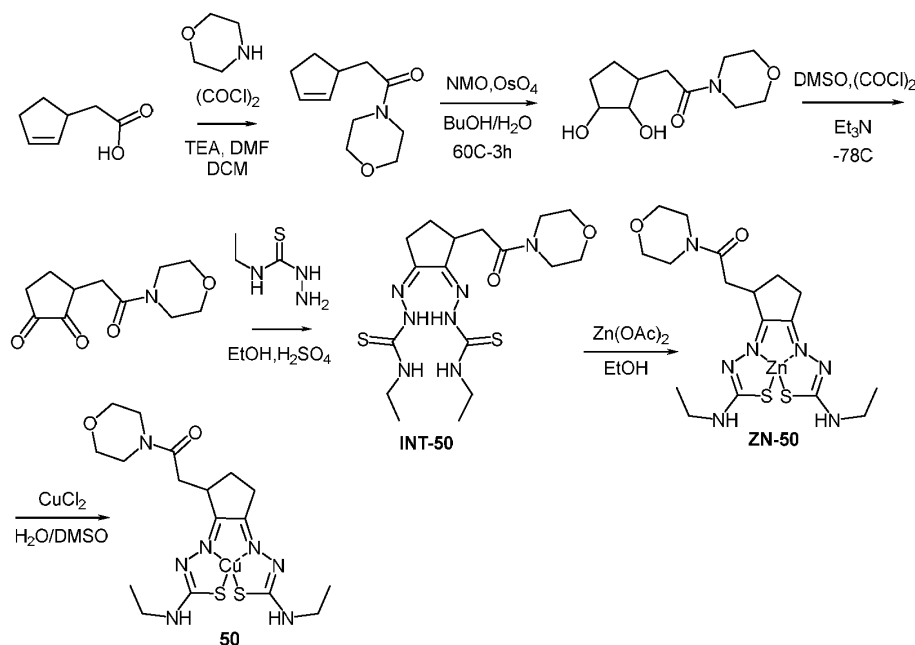
Synthesis of Compound 49:



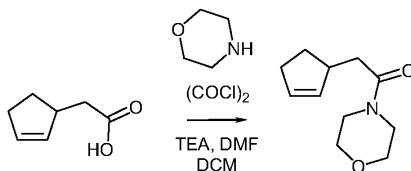
- 20 The titular compound was prepared from INT-49 according to the method to prepare compound 48. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.03g (35%). LCMS (C18 column 20 × 2 mm, particle size 2.5

μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.33 min). MS (ESI) m/z 420.5 $[\text{MH}]^+$.

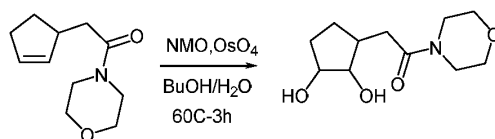
Scheme 23: Synthesis of Compound 50



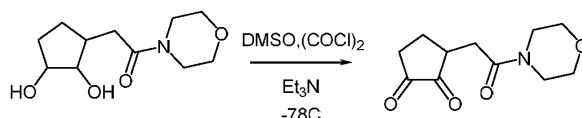
5 Synthesis of 2-(cyclopent-2-en-1-yl)-1-morpholinoethan-1-one:



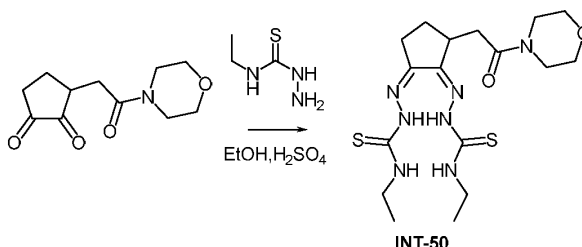
- Oxalyl chloride (2.41g, 1.2 eq) was added to a solution of 2-cyclopentene-1-acetic acid (2.0g, 16 mmol) in dichloromethane (100 ml), 1 drop of DMF was added and the mixture was stirred at ambient temperature for 2 h. Solvents were evaporated under reduced pressure, the residue was dissolved in EtOAc, to the solution were added Et₃N (1.92g, 1.2 eq) and morpholine (1.38g, 1 eq). The reaction was stirred overnight at ambient temperature. The reaction mixture was washed with water, organic layer was dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO₂, CH₂Cl₂ - MeOH, 10:1). Yield 2.1g (67.8%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.16 min, MS (ESI) m/z 196.4 $[\text{MH}]^+$. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.41-1.53 (m, 1H), 2.12-2.25 (m, 1H), 2.29-2.46 (m, 4H), 3.09-3.21 (m, 1H), 3.42-3.54 (m, 2H), 3.58-3.76 (m, 6H), 5.70-5.74 (m, 1H), 5.75-5.83 (m, 1H).

Synthesis of 2-(2,3-dihydroxycyclopentyl)-1-morpholinoethan-1-one:

2-(Cyclopent-2-en-1-yl)-1-morpholinoethan-1-one (2.1g, 10.7 mmol) was dissolved in an H₂O-*t*BuOH mixture (1:3) and to the stirred solution N-methylmorpholine-N-oxide (1.64 eq) and OsO₄ (0.035g of 4% solution in water, 0.001 eq) were added. The reaction mixture was stirred at 60°C for 4 h and then at ambient temperature for 15h. The reaction was quenched with Na₂S₂O₃ (10%) and extracted with EtOAc, organic layer was dried over Na₂SO₄, filtered and evaporated. Yield 1.7 g (68.9%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 0.83 min, MS (ESI) m/z 230.3 [MH]⁺.

Synthesis of 3-(2-morpholino-2-oxoethyl)cyclopentane-1,2-dione:

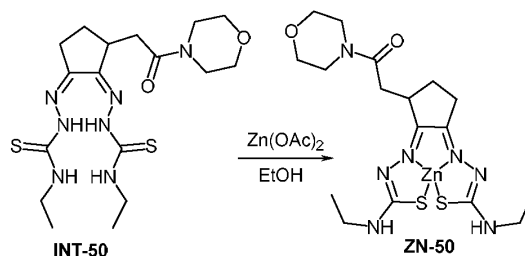
Dimethyl sulfoxide (1.5g, 1.4 ml, 4 eq) was added to a stirred solution of oxalyl chloride (1.83g, 1.2 ml, 3 eq) in dichloromethane (40 ml) at -78°C. After 5 min, a solution of 2-(2,3-dihydroxycyclopentyl)-1-morpholinoethan-1-one (1.1g, 4.8 mmol, 1 eq) in dichloromethane (80 ml) was slowly added (over period of 15 min) and the resulting solution was stirred at -78°C for 1 h. Then triethylamine (2.9g, 4 ml, 6 eq) was added, the mixture was stirred for 15 min at -78°C and then warmed to ambient temperature. The reaction mixture was washed with water, organic layer was dried over Na₂SO₄, filtered and evaporated. Yield 0.89 g (82.3%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 0.88 min, MS (ESI) m/z 225.9 [MH]⁺.

Synthesis of INT-50 ((2Z,2'Z)-2,2'-(3-(2-morpholino-2-oxoethyl)cyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

25

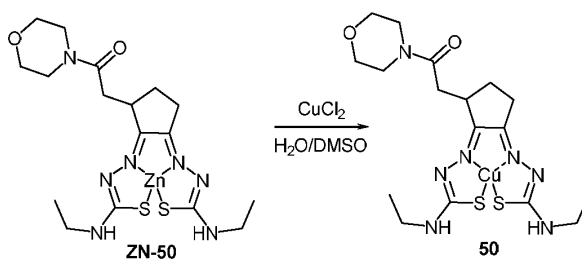
3-(2-Morpholino-2-oxoethyl)cyclopentane-1,2-dione (0.89 g, 4 mmol, 1 eq) was dissolved in EtOH (25 ml), ethyl thiosemicarbazide (0.94g, 2 eq) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water and crystallized from isopropyl alcohol. Yield 0.6g (35.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.33 min, MS (ESI) m/z 428.5 [MH]⁺. ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.14 (t, 3H), 1.20 (t, 3H), 1.46-1.56 (m, 1H), 2.14-2.21 (m, 1H), 2.45-2.55 (m, 2H), 2.74-2.87 (m, 1H), 2.89-2.96 (m, 1H), 3.06-3.13 (m, 1H), 3.46 (br.s, 4H), 3.53-3.65 (m, 8H), 7.78 (br.s, 1H), 8.69 (br.s, 1H), 10.75 (br.s, 1H), 12.18 (s, 1H).

Synthesis of ZN-50:



Zn(OAc)₂ 2H₂O (0.15 g, 1.5 eq) was added to **INT-50** (0.2g, 0.5 mmol, 1 eq) in ethanol. The mixture was refluxed for 4 h. The formed complex was precipitated out of the mixture as yellow powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.1 g (43.5 %). ¹H-NMR (400MHz, CDCl₃): δ (ppm) 1.1 (t, 3H), 1.15 (t, 3H), 1.37-1.49 (m, 1H), 2.06-2.17 (m, 1H), 2.33-2.47 (m, 2H), 2.77-2.87 (m, 1H), 2.88-2.96 (m, 1H), 3.00-3.09 (m, 1H), 3.40-3.65 (m, 12H), 7.40 (br.s, 1H), 7.95 (br.s, 1H).

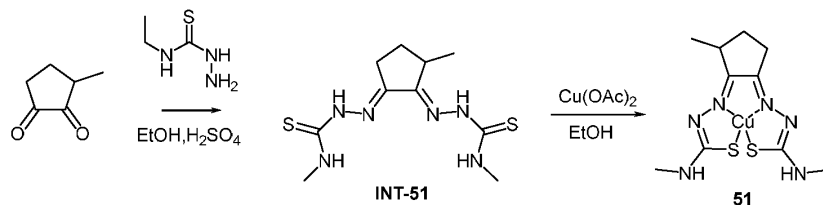
Synthesis of Compound 50:



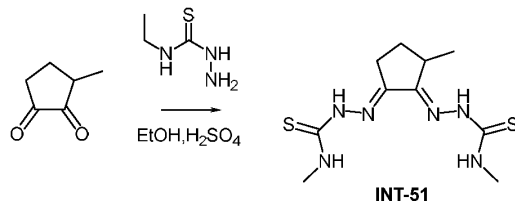
ZN-50 (0.075g, 0.15 mmol, 1 eq) was dissolved in DMSO (1.8 ml) and a solution of CuCl₂ 2H₂O (0.034 g, 1.1 eq) in water (1.8 ml) was added. The mixture was stirred for 5 min, filtered, and precipitate was washed with saturated solution of potassium carbonate, water and Et₂O. Yield 0.044g (58.8%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore

size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.85 min). MS (ESI) m/z 489.4 [MH]⁺.

Scheme 24: Synthesis of Compound 51:

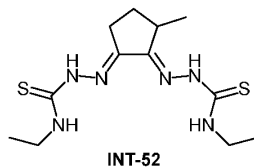


5 Synthesis of INT-51 ((2E,2'E)-2,2'-(3-methylcyclopentane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



3-Methyl-1,2-cyclopentanedione (2g, 17.8 mmol, 1 eq) was dissolved in EtOH (100 ml), methylthiosemicarbazide (3.75g, 2 eq) and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and for 15h at ambient temperature. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 3.87g (80%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.34 min, MS (ESI) m/z 287.0 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.05-1.27 (m, 9H), 1.35-1.48 (m, 1H), 2.01-2.15 (m, 1H), 2.47-2.56 (m, 1H), 2.71-2.82 (m, 2H), 3.49-3.63 (m, 4H), 7.74 (br.s, 1 H), 8.65 (br.s, 1H), 10.74 (s, 1H), 12.23 (s, 1H).

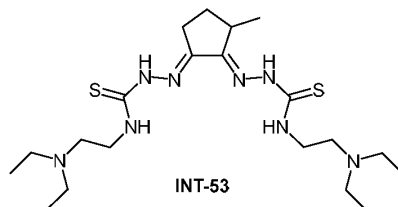
Synthesis of INT-52 ((2E,2'E)-2,2'-(3-methylcyclopentane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



20 INT-52 was made using a procedure analogous to the procedure to prepare **INT-51**. Yield 5 g (90.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3 min, retention time 1.59 min, MS (ESI) m/z 315.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.16 (d, 3H), 1.36-1.47 (m, 1H),

2.09-2.16 (m, 1H), 2.45-2.65 (m, 1H), 2.69-2.82 (m, 2H), 3.02 (br.s, 6H), 7.88 (br.s, 1 H), 8.60 (br.s, 1H), 10.82 (s, 1H), 12.33 (s, 1H).

Synthesis of INT-53 ((2E,2'E)-2,2'-(3-methylcyclopentane-1,2-diylidene)bis(N-(2-(diethylamino)ethyl)hydrazine-1-carbothioamide)):

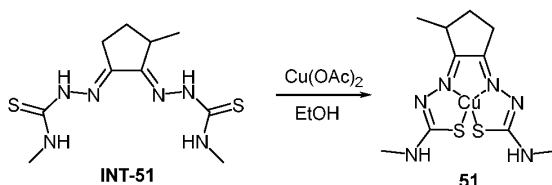


5

INT-53 was made using a procedure analogous to the procedure to prepare **INT-51**.

Yield 0.5 g (25%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 0.92-0.99 (m, 12H), 1.17 (d, 3H), 1.38-1.47 (m, 1H), 2.10-2.18 (m, 1H), 2.58-2.67 (m, 4H), 2.74-2.82 (m, 2H), 3.54-3.63 (m, 4H), 7.79 (br.s, 1 H), 8.50 (br.s, 1H), 10.80 (s, 1H), 12.21 (s, 1H).

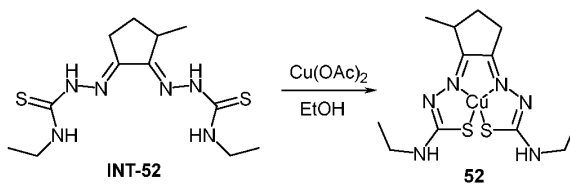
10 **Synthesis of Compound 51:**



Cu(OAc)₂ 2H₂O (0.61 g, 1.1 eq) was added to thiosemicarbazone **1** (0.73g, 2.5 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.46g (51.9%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.51 min). MS (ESI) m/z 348.0 [MH]⁺.

15

Synthesis of Compound 52:

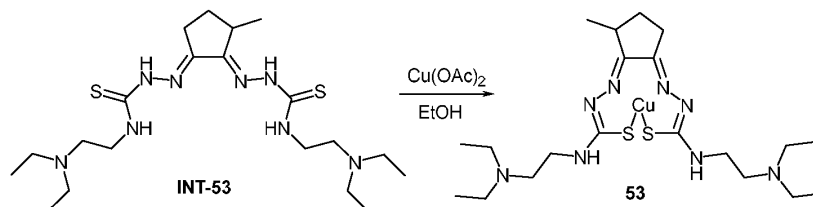


20

The titular compound was prepared from **INT-52** according to the method to prepare compound 51. The complex precipitated out of the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.7g (79%). LCMS (C18 column 20 × 2 mm, particle size 2.5

μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.62 min). MS (ESI) m/z 376.3 $[\text{MH}]^+$.

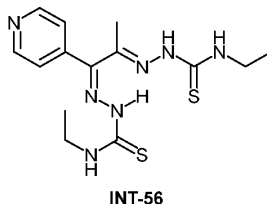
Synthesis of Compound 53:



5 The titular compound was prepared from **INT-53** according to the method to prepare compound 51. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.07g (15%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm , pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.25 min). MS (ESI) m/z 518.3 $[\text{MH}]^+$.

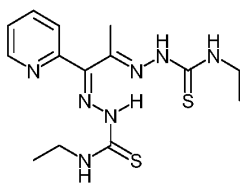
Example 4: Preparation of Compounds 54-65

Synthesis of INT-56 ((2Z,2'E)-2,2'-(1-(pyridin-4-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



15 **INT-55** was made using a procedure analogous to the procedure to prepare **INT-1** of Example 1. Yield 0.030g (5%). LCMS (C18 column 100 × 4.6 mm, 5.0 μm , pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 10min, retention time 5.01 min). MS (ESI) m/z 352.6 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400MHz, DMSO-d_6): δ (ppm) 0.89 (t, 3H), 1.16 (t, 3H), 2.36 (s, 3H), 3.60 (m, 4H), 6.82 (t, 1H), 7.32 (d, 2H), 7.73 (d, 1H), 8.73 (d, 2H), 9.37 (s, 1H), 10.77 (s, 1H).

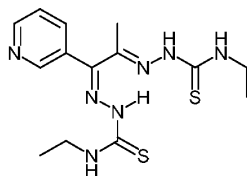
Synthesis of INT-58 ((2Z,2'E)-2,2'-(1-(pyridin-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-58

INT-58 was made using a procedure analogous to the procedure to prepare INT-1 of Example 1. Yield 0.75 g (76.4%). ¹H-NMR (400MHz, DMSO D₆): δ (ppm) 0.99 (t, 3H), 1.16 (t, 3H), 2.38 (s, 3H), 3.36-3.46 (m, 2H), 3.56-3.66 (m, 2H), 7.36 (t, 1H), 7.55 (dd, 1H), 7.66 (d, 1H), 8.01 (t, 1H), 8.73-8.75 (m, 2H), 10.58 (s, 1H), 11.82 (s, 1H).

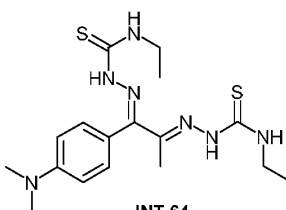
Synthesis of INT-62 ((2Z,2'E)-2,2'-(1-(pyridin-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



INT-62

INT-62 was made using a procedure analogous to the procedure to prepare INT-1 of Example 1. Yield 0.69g (65%). LCMS (C18 column 100 × 4.6 mm, 5.0 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 10min, retention time 4.71 min). MS (ESI) m/z 352.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 0.90 (t, 3H), 1.15 (t, 3H), 2.37 (s, 3H), 3.60 (m, 4H), 6.81 (t, 1H), 7.53 (m, 1H), 7.71 (d, 1H), 8.43 (s, 1H), 8.65-8.70 (m, 2H), 9.73 (br.s, 1H), 10.65 (br.s, 1H).

Synthesis of INT-64 ((2E,2'E)-2,2'-(1-(4-(dimethylamino)phenyl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

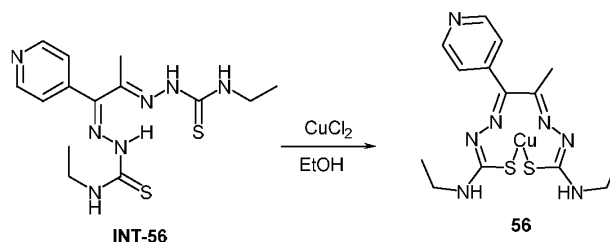


INT-64

INT-64 was made using a procedure analogous to the procedure to prepare INT-1 of Example 1. Yield 0.67 g (68.4%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.54 min, MS (ESI) m/z 394.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 0/94 (t, 3H), 1.15 (t, 3H),

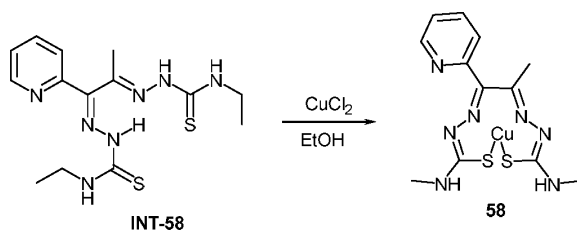
2.33 (s, 3H), 2.87 (s, 6H), 6.85 (d, 2H), 7.02 (br.s), 7.11 (d, 2H), 8.71 (br.s, 1H), 10.72 (s, 1H).

Synthesis of Compound 56:



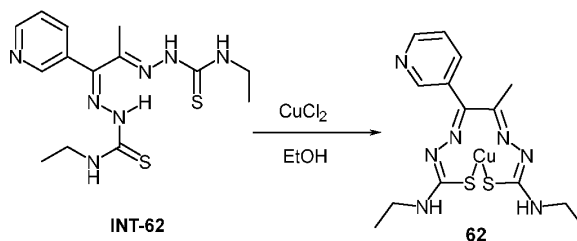
- 5 The titular compound was prepared from **INT-56** according to the method to prepare compound 1 of Example 1. Complex was isolated as a red-brown powder. The product was collected by filtration after cooling, washed with water (2 × 15ml), ethanol (2 × 15ml), and then dried *in vacuo* to afford the titular product. Yield 0.010g (28%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 3.41 min). MS (ESI) m/z 413.5 [MH]⁺.
- 10

Synthesis of Compound 58:



- The titular compound was prepared from **INT-58** according to the method to prepare compound 1 of Example 1. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and then dried *in vacuo*. Yield 0.044 g (18.6%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.36 min). MS (ESI) m/z 413.4 [MH]⁺.
- 15

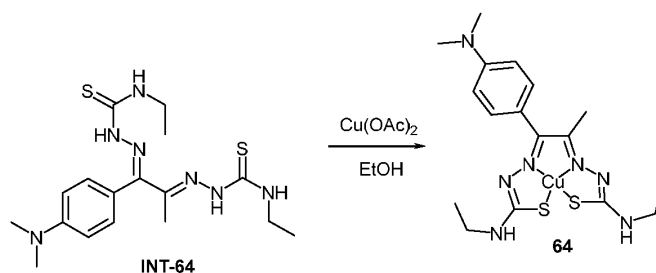
Synthesis of Compound 62:



20

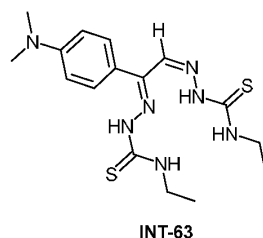
- The titular compound was prepared from **INT-62** according to the method to prepare compound 1 of Example 1. The product was isolated as a red-brown powder. The formed precipitate was collected by filtration after cooling, washed with water (2 × 15ml), ethanol (2 × 15ml), and then dried *in vacuo*. Yield 0.094g (27%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.72 min). MS (ESI) m/z 413.5 [MH]⁺.

Synthesis of Compound 64



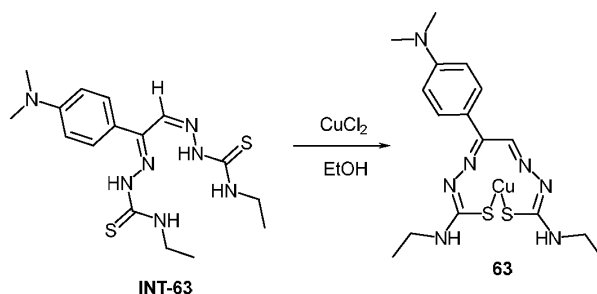
- The titular compound was prepared from **INT-64** according to the method to prepare compound 1 of Example 1. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.037g (18%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.31 min). MS (ESI) m/z 455.1 [MH]⁺.

- Synthesis of INT-63 ((2Z,2'E)-2,2'-(1-(4-(dimethylamino)phenyl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**



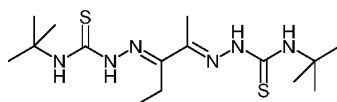
- INT-63** was made using a procedure analogous to the procedure to prepare **INT-34** of Example 2. Yield 0.57g (35%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.63 min, MS (ESI) m/z 380.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.12-1.24 (m, 6H), 2.96 (s, 6H), 3.53-3.67 (m, 4H), 6.75 (d, 2H), 7.64 (d, 2H), 7.88 (br.s, 1H), 8.22 (s, 1H), 8.76 (br.s, 1H), 11.73 (s, 1H), 12.18 (s, 1H).

Synthesis of Compound 63:



The titular compound was prepared from **INT-63** according to the method to prepare compound 43 of Example 2. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.075g (47%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.07 min). MS (ESI) *m/z* 441.1 [MH]⁺.

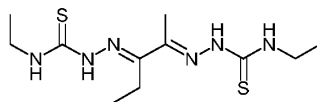
Synthesis of INT-55 ((2*E*,2'*E*)-2,2'-(pentane-2,3-diylidene)bis(*N*-(*tert*-butyl)hydrazine-1-carbothioamide)):



INT-55

INT-55 was made using a procedure analogous to the procedure to prepare **INT-51** of Example 3. Yield 1.97 g (34%). NMR (400MHz, DMSO-*d*₆): 0.96 (s, 3H), 1.50 (s, 9H), 1.52 (s, 9H), 2.10 (s, 3H), 2.74 (q, 2H), 7.75 (s, 1H), 7.79 (s, 1H), 10.30-10.48 (m, 2H).

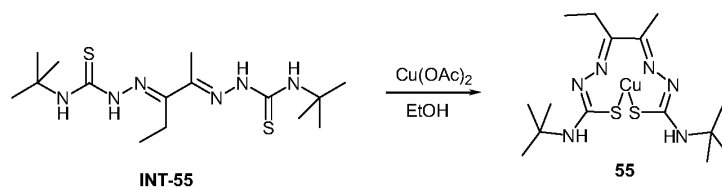
Synthesis of INT-65 ((2*E*,2'*E*)-2,2'-(pentane-2,3-diylidene)bis(*N*-ethylhydrazine-1-carbothioamide)):



INT-65

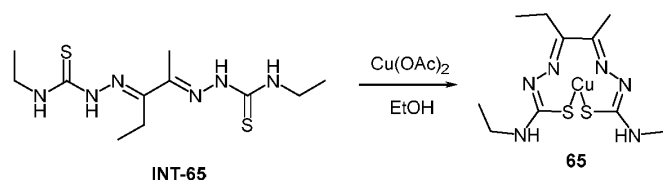
INT-65 was made using a procedure analogous to the procedure to prepare **INT-51** of Example 3. Yield 2.37 g (49%). ¹H-NMR (400MHz, DMSO-*d*₆): δ (ppm) 0.91 (t, 3H), 1.14 (t, 6H), 2.19 (s, 3H), 2.80 (q, 2H), 3.54 (q, 4H), 8.25-8.40 (m, 2H), 10.15 (s, 1H), 10.27 (s, 1H).

Synthesis of Compound 55:



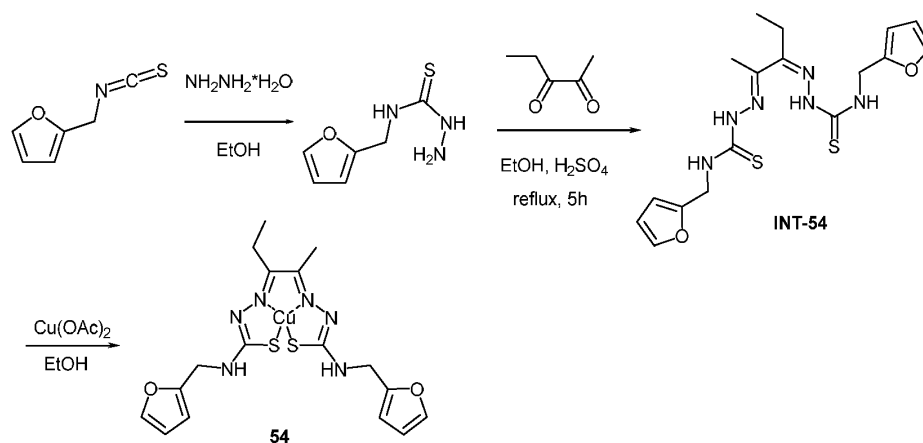
The titular compound was prepared from **INT-55** according to the method to prepare compound 51 of Example 3. The product precipitated from the reaction mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.4g (82%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 3.41 min). MS (ESI) *m/z* 420.6 [MH]⁺.

Synthesis of Compound 65:

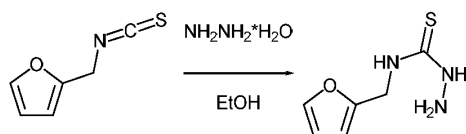


The titular compound was prepared from **INT-65** according to the method to prepare compound 51 of Example 3. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.4g (82 %). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.68 min). MS (ESI) *m/z* 364.3 [MH]⁺.

Scheme 25: Synthesis of Compound 54

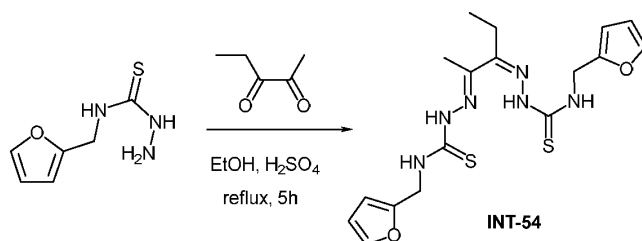


Synthesis of *N*-(furan-2-ylmethyl)hydrazinecarbothioamide:



To a solution of 2-(isothiocyanatomethyl)tetrahydrofuran (10g, 71.8 mmol) in EtOH (100ml) was added at 0°C hydrazine hydrate (4.5g, 89.75mmol) and the reaction mixture was stirred for 3h. The formed precipitate was collected by filtration, washed with ethanol (2 × 150ml), and dried to afford **1**. Yield 9.3g (76%). ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.52-1.60 (m, 1H), 1.76-1.90 (m, 3H), 3.39-3.45 (m, 1H), 3.59-3.66 (m, 2H), 3.76 (q, 1H), 3.93-3.99 (m, 1H), 4.47 (s, 2H), 7.74 (s, 1H), 8.67 (s, 1H).

Synthesis of INT-54 ((2Z,2'E)-2,2'-(pentane-2,3-diylidene)bis(N-(furan-2-ylmethyl)hydrazine-1-carbothioamide)):

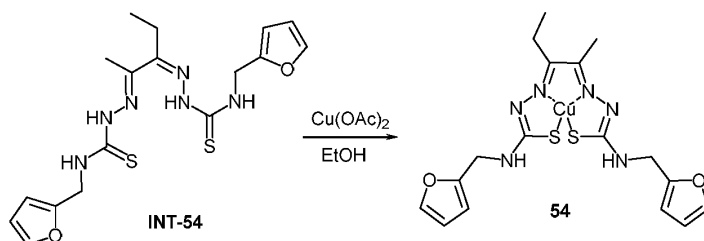


10

The 2,3-pentanedione (0.4g, 4mmol) was dissolved in EtOH (60ml), N-(furan-2-ylmethyl)hydrazinecarbothioamide (1.37g, 8mmol), and 3 drops of H₂SO₄ were added and the reaction mixture was stirred for 4h at reflux and additionally overnight at r.t. The progress of the reaction was monitored by TLC (CHCl₃-MeOH 10:1). The precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.9g (55%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.70 min). MS (ESI) m/z 407.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 0.90 (t, 3H), 2.19 (s, 3H), 2.90 (q, 2H), 4.82 (d, 4H), 6.27-6.29 (m, 2H), 6.40 (s, 2H), 7.58 (s, 2H), 8.65 (t, 1H), 8.73 (t, 1H), 10.42 (s, 1H), 10.53 (s, 1H).

20

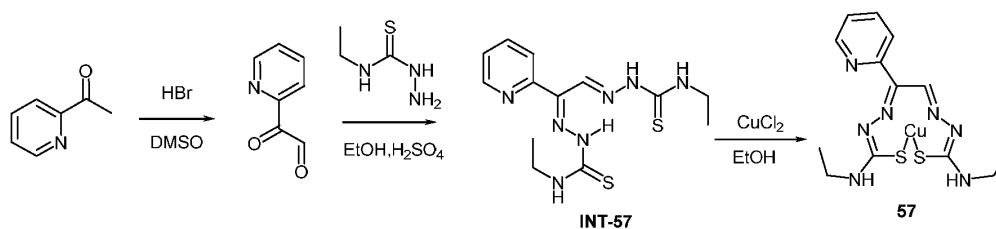
Synthesis of Compound 54:



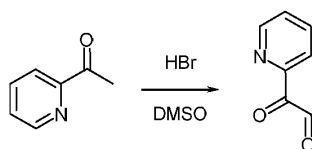
Cu(OAc)₂·2H₂O (0.12g, 1.1 eq) was added to **INT-54** (0.2g, 0.5 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex was precipitated from the mixture as a red-brown powder. The precipitate was collected by

filtration, washed with water, methanol, and diethyl ether, and then dried *in vacuo*. Yield 0.022g (9.5%). LCMS (C18 column 20 × 2 mm, particle size 2.5 μm, pore size 100A, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 2.62 min). MS (ESI) m/z 468.4 [MH]⁺.

5 Scheme 26: Synthesis of Compound 57

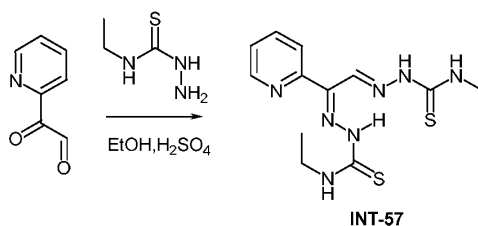


Synthesis of 2-oxo-2-(pyridin-2-yl)acetaldehyde:



- To a solution of 1-(pyridin-2-yl)ethan-1-one (10.0 g, 82.5 mmol) in DMSO (150 ml) 47% HBr (28ml, 247.5 mmol) was added and the mixture was stirred at 60°C overnight. The reaction was quenched with NaHCO₃ and diluted with water to a total volume of 1000 ml. The product was extracted with EtOAc (3x150 ml), the combined organic layers were dried over anhydrous Na₂SO₄, filtered, and solvents were removed under reduced pressure yielding crude product as a yellow oil. Yield 2.8 g (23%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 0.32 min). MS (ESI) m/z 136.1 [MH]⁺.

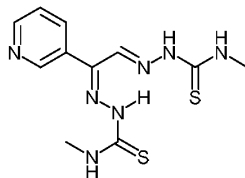
Synthesis of INT-57 ((2Z,2'E)-2,2'-(1-(pyridin-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



- Ethyl thiosemicarbazide (1.76 g, 14.0 mmol) and 1 drop of H₂SO₄ were added to a solution of 2-oxo-2-(pyridin-2-yl)acetaldehyde (1.0 g, 7.0 mmol) in EtOH (50ml), the reaction was heated to reflux for 4 h. The precipitate was filtered, washed with EtOH, Et₂O and dried. Yield 0.123 g (5.9%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 3min, retention time 1.41 min). MS (ESI) m/z

338.3 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.21 (dt, 6H), 3.56-3.70 (m, 4H), 7.42 (dd, 1H), 7.86-7.93 (m, 2H), 8.41 (d, 1H), 8.58 (d, 1H), 8.89(s, 1H), 8.79 (s, 1H), 9.20 (t, 1H), 12.01 (s, 1H), 12.80 (s, 1H).

Synthesis of INT-59 ((2Z,2'E)-2,2'-(1-(pyridin-3-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



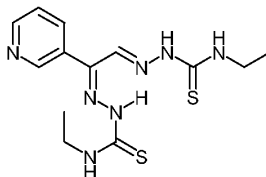
INT-59

INT-59 was made using a procedure analogous to the procedure to prepare INT-57.

Yield 0.53g (19%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 10min, retention time 4.49 min). MS (ESI) m/z

310.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 3.0 (s, 3H), 3.06 (s, 3H), 7.80 (dd, 1H), 8.2(s, 1H), 8.58(d, 1H), 8.78(d, 1H), 8.89(s, 1H), 8.92-8.98(m, 1H), 9.16(s, 1H), 11.78(s, 1H), 12.09(s, 1H).

Synthesis of INT-60 ((2Z,2'E)-2,2'-(1-(pyridin-3-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



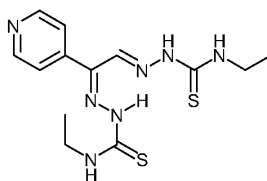
INT-60

INT-60 was made using a procedure analogous to the procedure to prepare INT-57.

Yield 0.90g (30%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 10min, retention time 5.26 min). MS (ESI) m/z

338.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.17 (t, 6H), 3.61 (q, 4H), 7.47 (dd, 1H), 8.0(t, 1H), 8.18(d, 1H), 8.22(s, 1H), 8.62(d, 1H), 8.98-9.07(m, 1H), 11.77(s, 1H), 12.31(s, 1H).

Synthesis of INT-61 ((2Z,2'E)-2,2'-(1-(pyridin-4-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

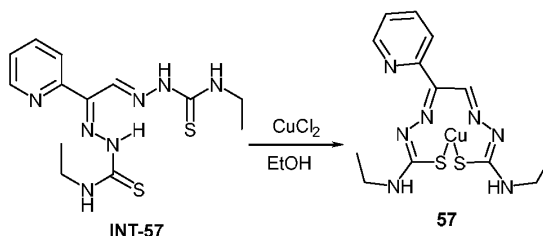


INT-61

INT-61 was made using a procedure analogous to the procedure to prepare **INT-57**.

Yield 180mg (7%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 10min, retention time 4.97 min). MS (ESI) m/z 338.5 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆): δ (ppm) 1.18 (t, 3H), 1.20 (t, 3H), 3.58 (q, 2H), 3.64 (q, 2H), 7.80 (d, 1H), 8.04(t, 1H), 8.24(s, 1H), 8.65(d, 1H), 9.12(t, 1H), 11.79(s, 1H), 12.47(s, 1H).

Synthesis of Compound 57:

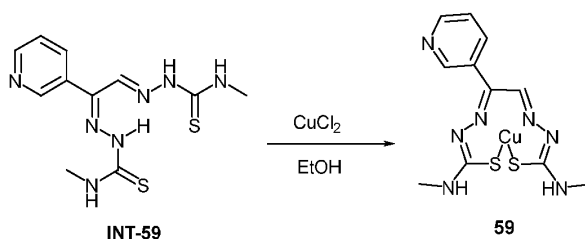


INT-57

57

To a solution of **INT-57** (0.123 g, 0.365 mmol) in EtOH (10ml) a solution of CuCl₂·2H₂O (0.062 g, 0.365 mmol) in EtOH (2 ml) was added. The mixture was stirred overnight at r.t. The formed precipitate was collected by filtration, washed with water (2×10 ml), ethanol (2×10 ml), diethyl ether (5×5 ml), and dried in vacuo. Yield 0.06 g (41.4%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.39). MS (ESI) m/z 399.0 [MH]⁺.

Synthesis of Compound 59:



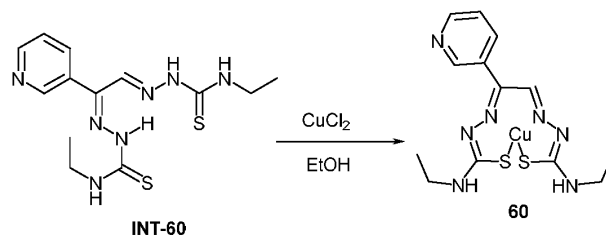
INT-59

59

The titular compound was prepared from **INT-59** according to the method to prepare compound 57. The titular product was collected by filtration, washed with water (2 × 50ml), ethanol (2 × 50ml), and diethyl ether (5 × 50ml), and then dried in vacuo. Yield 230mg

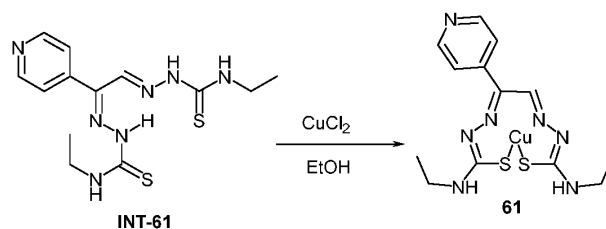
(95%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.34, 1.47 min. MS (ESI) m/z 371.0 [MH]⁺.

Synthesis of Compound 60:



- 5 The titular compound was prepared from **INT-60** according to the method to prepare compound 57. The titular product was collected by filtration, washed with water (2 × 50ml), ethanol (2 × 50ml), and diethyl ether (5 × 50ml), and then dried in vacuo. Yield 218mg (92%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.58, 1.73 min. MS (ESI) m/z 399.0 [MH]⁺.

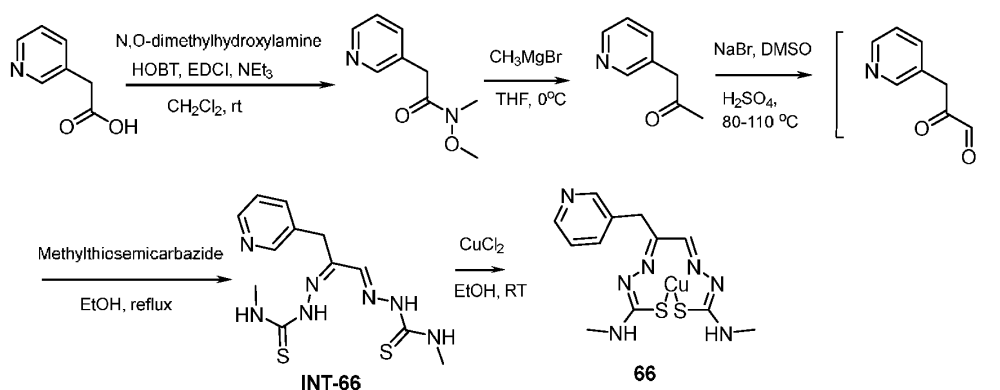
10 **Synthesis of Compound 61:**



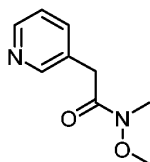
- The titular compound was prepared from **INT-61** according to the method to prepare compound 57. The product was collected by filtration, washed with water (2 × 50ml), ethanol (2 × 50ml), and diethyl ether (5 × 50ml), and then dried in vacuo. Yield 140mg (66%). LCMS (C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% for 4min, retention time 1.48, 1.66 min. MS (ESI) m/z 399.0 [MH]⁺.
- 15

Example 5: Preparation of Compounds 66-78

Scheme 27: Synthesis of Compound 66

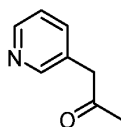


Synthesis of N-methoxy-N-methyl-2-(pyridin-3-yl)acetamide:



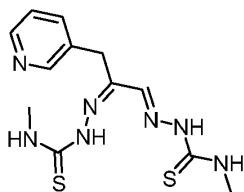
To a mixture of 3-pyridineacetic acid (25.0g, 0.144 mol), Weinreb amine (16.8g, 0.172 mol), HOBt (23.3g, 0.172 mol), and triethylamine (71ml, 0.5 mol) in DCM (400ml) at 5°C was added EDCI (33.2g, 172 mol) and reaction was stirred for 15h at ambient temperature. The mixture was washed with water (150ml) and brine (250ml). The organic layer was dried over anhydrous Na_2SO_4 , filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent EtOAc-hexane, 2:1) to afford compound 1. Yield 20.0g (77%). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 8.63 – 8.27 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.28 – 7.03 (m, 1H), 3.76 (s, 2H), 3.67 (s, 3H), 3.19 (s, 3H).

Synthesis of 1-(pyridin-3-yl)propan-2-one:



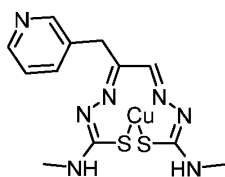
A solution of N-methoxy-N-methyl-2-(pyridin-3-yl)acetamide (9.5 g, 52.7mmol, 1 eq) in THF (200 ml) was cooled to 5°C and methylmagnesium bromide (1.4M in THF, 46.5 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH_4Cl and extracted with Et_2O . The combined extracts were dried over anhydrous Na_2SO_4 and evaporated in vacuo. Compound 2 was used for the next step without purification. Yield 6.1 g (86%). LC-MS 0.27 min, m/z 136.6 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 8.48 (d, J = 4.7 Hz, 1H), 8.41 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.31 – 7.12 (m, 1H), 3.67 (d, J = 19.5 Hz, 2H), 2.18 (s, 3H).

Synthesis of INT-66 ((2Z,2'E)-2,2'-(3-(pyridin-3-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



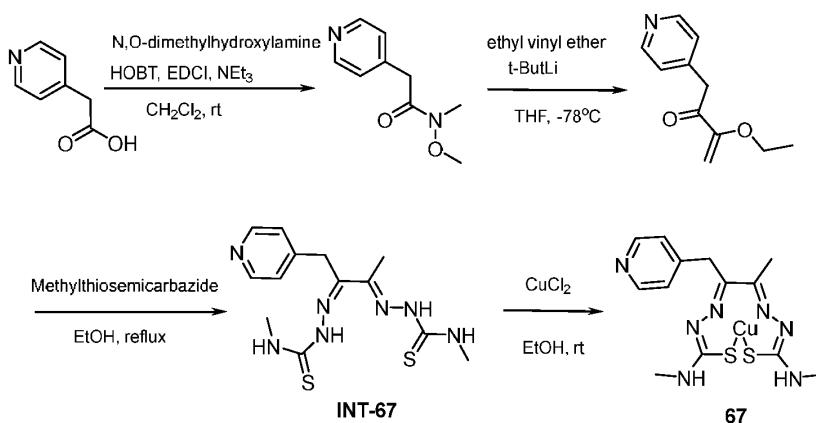
A mixture of 1-(pyridin-3-yl)propan-2-one (1.3g, 6.9mmol, 1 eq), NaBr (0.7g, 1 eq) and DMSO (2 ml) was heated to 85°C and H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated at 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous oil was dissolved in EtOH and methylthiosemicarbazide (2.023g, 2 eq) was added. The reaction mixture was heated to reflux for 4h, then stirred overnight at rt. The precipitate was collected by filtration, washed with EtOH, MeCN, water, Et₂O, and dried to afford the titular product. Yield 0.95 g (30%). LC-MS 0.97 min, m/z 324.6 [MH]⁺.

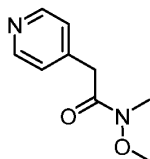
Synthesis of Compound 66:



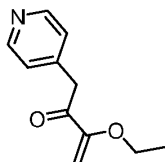
Copper(II) acetate dihydrate (0.72g, 1.1 eq) was added to a stirred solution of INT-66 (0.12g, 0.38 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.14g (99%).

Scheme 28: Synthesis of Compound 67



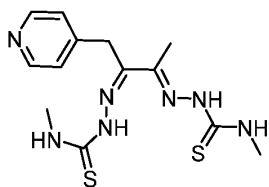
Synthesis of *N*-methoxy-*N*-methyl-2-(pyridin-4-yl)acetamide:

- To a mixture of 4-pyridineacetic acid (4.2g, 24.2 mmol), Weinreb amine (2.8g, 29.0 mmol), HOBt (3.9g, 29.0 mmol), and triethylamine (11.9 ml, 84.7 mmol) in DCM (100ml) at 5°C was added EDCI (5.6g, 29.0 mmol) and reaction was stirred for 15h at rt. The mixture was washed with water (150ml) and brine (250ml). The organic layer was dried over anhydrous Na₂SO₄, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent EtOAc-hexane 2:1) to afford the titular compound. Yield 2.9g (66%). LC-MS 0.97 min, m/z 324.6 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 8.55 (d, *J* = 5.3 Hz, 2H), 7.36 – 7.08 (m, 2H), 3.78 (s, 2H), 3.66 (s, 3H), 3.21 (s, 3H).

Synthesis of 3-ethoxy-1-(pyridin-4-yl)but-3-en-2-one:

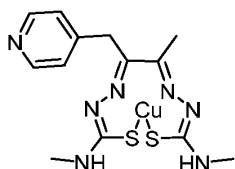
- A solution of ethyl vinyl ether (4.1 ml, 41.8 mmol) in dry THF (30 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 23 ml, 38.8 mmol) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of *N*-methoxy-*N*-methyl-2-(pyridin-4-yl)acetamide (0.7g, 3.8 mmol) in THF (15ml) was added, and the reaction was stirred at 0°C for 4h. The progress of the reaction was monitored by TLC. The mixture was poured into aq. NH₄Cl (30ml) and extracted with Et₂O (3 × 50ml). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 0.2g (27%). LC-MS 0.66 min, m/z 192.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 8.54 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.23 – 7.06 (m, 2H), 5.23 (t, *J* = 11.8 Hz, 1H), 4.42 (t, *J* = 14.5 Hz, 1H), 3.99 (s, 2H), 3.83 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H).

- Synthesis of INT-67 ((2*Z*,2'*E*)-2,2'-(1-(pyridin-4-yl)butane-2,3-diylidene)bis(*N*-methylhydrazine-1-carbothioamide)):**



3-Ethoxy-1-(pyridin-4-yl)but-3-en-2-one (0.2 g, 1.05 mmol, 1 eq) was dissolved in EtOH (20 ml), methylthiosemicarbazide (0.22 g, 2.1 mmol, 2 eq) and 3 drops of H₂SO₄ were added and the reaction mixture was heated to reflux for 4h and then stirred for 15h at rt. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.21 g (60.2%). LC-MS 0.91 min, m/z 338.9 [MH]⁺. ¹H-NMR (400 MHz, DMSO), δ (ppm) : 10.85 (s, 1H), 10.35 (s, 1H), 8.78 (d, *J* = 6.6 Hz, 2H), 8.51 (d, *J* = 4.6 Hz, 1H), 8.34 (d, *J* = 4.5 Hz, 1H), 7.72 (d, *J* = 6.5 Hz, 2H), 4.76 (s, 2H), 3.00 (dd, *J* = 14.4, 4.6 Hz, 6H), 2.28 (s, 3H).

Synthesis of Compound 67:

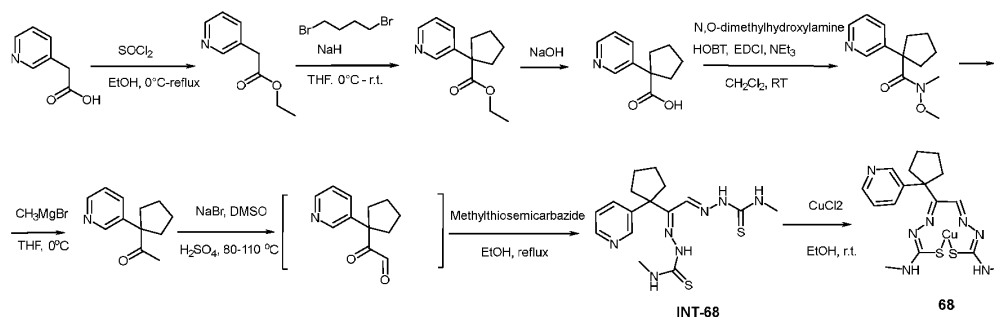


10

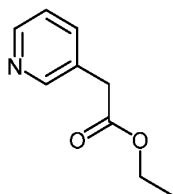
Copper(II) acetate dihydrate (0.09g, 0.46 mmol) was added to a stirred solution of thiosemicarbazone **3** (0.15 g, 0.44 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.075 g (42.3%).

15

Scheme 29: Synthesis of Compound 68

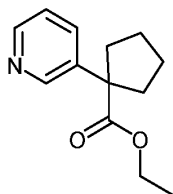


Synthesis of ethyl 2-(pyridin-3-yl)acetate:



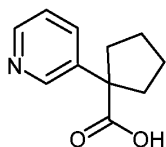
To a stirred solution of 3-pyridineacetic acid (25.0 g, 145 mmol) in EtOH (250ml) at 0-5°C was added SOCl₂ (11.6ml, 160mmol) in small portions over 15 min interval. After completing addition, the reaction was heated to reflux for additional 16h, and EtOH was evaporated under reduced pressure. To the residue was added 2M aqueous Na₂CO₃ (30 ml), and the resulting mixture was extracted with EtOAc (3 × 400 ml). The combined organic layers were washed with brine (100mL), dried over anh. Na₂SO₄, filtered, and concentrated in vacuo to afford compound **1** as a colorless liquid. Yield 22.3g (93%). ¹H-NMR (400MHz, CDCl₃), δ (ppm) : 1.26 (t, 3 H), 3.62 (s, 2 H), 4.17 (q, 2 H), 7.27-7.28 (m, 1 H), 7.64-7.65 (m, 1 H), 8.53 (m, 2 H).

Synthesis of ethyl 1-(pyridin-3-yl)cyclopentane-1-carboxylate:



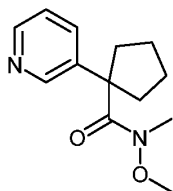
To a stirred suspension of sodium hydride (7.3g, 181mmol, 60% in mineral oil) in dry THF (160 ml) at 0°C was added dropwise a solution of ethyl 2-(pyridin-3-yl)acetate (10.0g, 60.5mmol) in dry THF (35 ml). The reaction mixture was stirred at 0°C until no more effervescence. Then 1,4-dibromobutane (19.6 g, 90.5mmol) was added at 0°C and the reaction mixture was stirred for 14h at rt. Subsequently, the reaction mixture was quenched with aqueous saturated ammonium chloride (60 ml). The reaction mixture was extracted with EtOAc (3 × 40 ml). The organic phase was washed with brine (100ml), dried over anh. Na₂SO₄, filtered, and concentrated in vacuo to dryness. Crude material (19g) was obtained as a dark solid, and then was purified by flash chromatography (silica gel, eluent hexane/ethyl acetate from 4:1 to 1:1). Yield 9.8g (74%). LC-MS 1.01 min, m/z 220.6 [MH]⁺. ¹H-NMR (400MHz, CDCl₃), δ (ppm) : 1.16 (t, 3H), 1.74-1.78 (m, 4H), 1.88-1.98 (m, 2H), 2.67-2.73 (m, 2H), 4.09 (q, 2H), 7.23-7.27 (m, 1H), 7.67-7.71 (m, 1H), 8.49 (dd, 1H), 8.65 (dd, 1H).

Synthesis of 1-(pyridin-3-yl)cyclopentane-1-carboxylic acid:



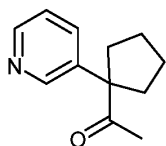
A solution of ethyl 1-(pyridin-3-yl)cyclopentane-1-carboxylate (8.4g, 38.5mmol) in MeOH (60ml) was added to a solution of LiOH (2.5g, 96.2mmol) in water (10 ml). The reaction mixture was stirred at 60°C for 8h. Then the solvent was removed by freeze-drying, and the corresponding crude product was used for the next step without further purification. Yield 7g (80%). LC-MS 0.82 min, m/z 192.1 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆), δ (ppm) : 1.66-1.70 (m, 4H), 1.85-1.92 (m, 2H), 2.52-2.58 (m, 2H), 7.56 (dd, 1H), 7.98-8.02 (m, 1H), 8.58 (dd, 1H), 8.66 (d, 1H), 12.66 (br.s, 1H).

Synthesis of N-methoxy-N-methyl-1-(pyridin-3-yl)cyclopentane-1-carboxamide:



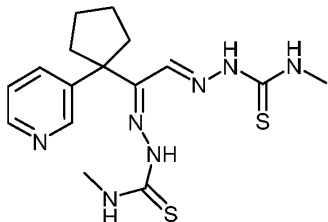
To a mixture of 1-(pyridin-3-yl)cyclopentane-1-carboxylic acid (5.0g, 22.0 mmol), Weinreb amine (2.6g, 26.4mmol), HOBt (3.6g, 26.4mmol), and triethylamine (10.8ml, 77mmol) in DCM (150ml) at 4°C was added EDCI (5.1g, 26.4mmol) and reaction was stirred overnight at rt. Then the mixture was washed with water (100ml) and brine (100ml). The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent DCM 100% to DCM/MeOH 95:5 v/v) to afford crude product. Yield 2.5g (49%). LC-MS 0.84 min, m/z 235.3 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 1.66-1.81 (m, 4H), 2.05-2.11 (m, 2H), 2.42-2.48 (m, 2H), 2.89 (s, 3H), 3.13 (s, 3H), 7.34 (q, 1H), 7.65 (d, 1H), 8.49 (d, 1H), 8.59 (d, 1H).

Synthesis of 1-(1-(pyridin-3-yl)cyclopentyl)ethan-1-one:

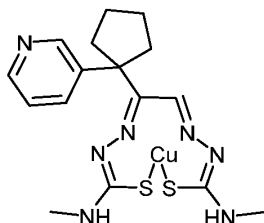


A solution of N-methoxy-N-methyl-1-(pyridin-3-yl)cyclopentane-1-carboxamide (1.27 g, 5.42mmol, 1 eq) in THF (100 ml) was cooled to 5°C and methylmagnesium bromide (1.4M in THF, 39.1 ml, 10 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anh. Na₂SO₄, and evaporated in vacuo. The titular product was used for the next step without purification. Yield 1 g (97%). LC-MS 1.14 min, m/z 190.6 [MH]⁺.

Synthesis of INT-68 ((2Z,2'E)-2,2'-(1-(1-(pyridin-3-yl)cyclopentyl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide))

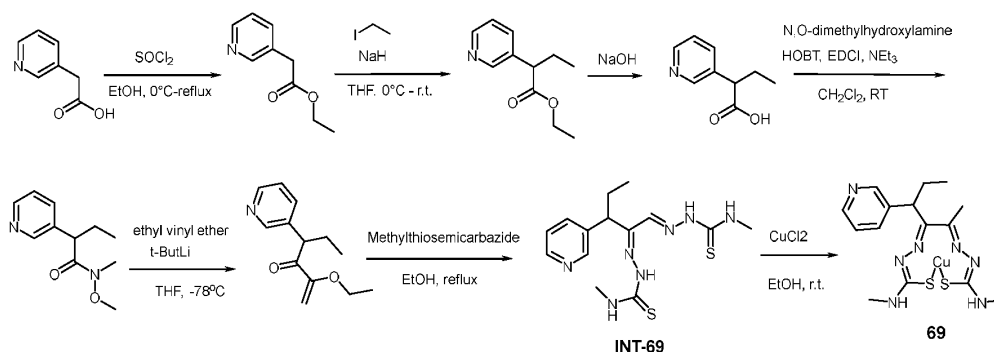


- Compound 6.** A mixture of 1-(1-(pyridin-3-yl)cyclopentyl)ethan-1-one (1.3g, 6.9mmol, 1 eq), NaBr (0.7g, 1 eq) and DMSO (2 ml) was heated to 85°C and H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated at 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous oil was dissolved in EtOH and methylthiosemicarbazide (1.44g, 2 eq) was added. The reaction mixture was heated to reflux for 4h, then stirred overnight at rt. The precipitate was collected by filtration, washed with EtOH, MeCN, water, Et₂O, and dried to afford the titular product. Yield 0.5 g (19%). LC-MS 1.10 min, m/z 378.8 [MH]⁺. ¹H-NMR (400 MHz, DMSO), δ (ppm) : 12.05 (s, 1H), 11.51 (s, 1H), 8.57 (s, 2H), 8.44 (d, *J* = 3.9 Hz, 1H), 7.76 (dd, *J* = 24.5, 5.8 Hz, 2H), 7.59 (s, 1H), 7.36 (dd, *J* = 7.7, 4.8 Hz, 1H), 3.02 (dd, *J* = 46.9, 4.3 Hz, 6H), 2.50 (s, 1H), 2.46 (s, 2H), 2.00 (d, *J* = 12.5 Hz, 2H), 1.64 (s, 4H).
- Synthesis of Compound 68**

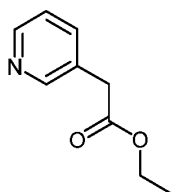


- Copper(II) chloride dihydrate (0.078g, 0.46mmol) was added to a stirred solution of **INT-68** (0.16g, 0.42mmol) in ethanol (30 ml). The mixture was stirred for 15h at rt. Complex was isolated as a red-brown powder. The formed precipitate was filtered, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.04g (22%).

Scheme 30: Synthesis of Compound 69

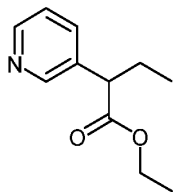


Synthesis of ethyl 2-(pyridin-3-yl)acetate:



To a stirred solution of 3-pyridineacetic acid (25.0 g, 145 mmol) in EtOH (250ml) at 0-5°C was added SOCl₂ (11.6ml, 160mmol) over 15 min interval. After completing addition, the reaction was heated to reflux for additional 16h, then EtOH was evaporated under reduced pressure. To the residue was added 2M aqueous Na₂CO₃ (30 ml), and the resulting mixture was extracted with EtOAc (3 × 400 ml). The combined organic layers were washed with brine (100mL), dried over anh. Na₂SO₄, filtered, and concentrated in vacuo to afford the titular product as a colorless liquid. Yield 22.3g (93%). ¹H-NMR (400MHz, CDCl₃), δ (ppm) : 1.26 (t, 3 H), 3.62 (s, 2 H), 4.17 (q, 2 H), 7.27-7.28 (m, 1 H), 7.64-7.65 (m, 1 H), 8.53 (m, 2 H).

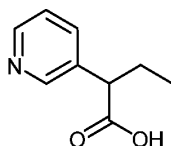
Synthesis of ethyl 2-(pyridin-3-yl)butanoate:



To a solution of ethyl 2-(pyridin-3-yl)acetate (10.08 g, 61 mmol) in THF (100 mL) was added sodium hydride (2.54g, 66 mmol, 60% dispersion in mineral oil) in small portions. After stirring at rt for 10 min, iodoethane (5.1 ml, 66 mmol) was added, and the resulting mixture was stirred overnight at rt. Then the reaction mixture was quenched with aq. solution NH₄Cl, extracted with EtOAc, dried over anh. Na₂SO₄, filtered, and concentrated in vacuo resulting in compound **2** as a colorless liquid. Yield 10.6g (86%). LC-MS 0.77 min, m/z 194.1 [MH]⁺. ¹H-NMR (400MHz, CDCl₃), δ (ppm) : 0.91 (t, J=8Hz, 3H), 1.22 (t, J=8Hz, 3H), 1.74-

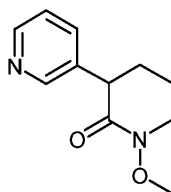
1.85 (m, 1H), 2.07-2.18 (m, 1H), 3.46 (t, J=7.6Hz, 1H), 4.07-4.21 (m, 2H), 7.25-7.28 (m, 1H), 7.67-7.70 (m, 1H), 8.51-8.54 (m, 2H).

Synthesis of 2-(pyridin-3-yl)butanoic acid:



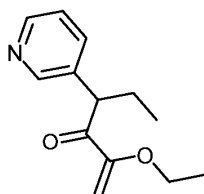
- 5 A solution of ethyl 2-(pyridin-3-yl)butanoate (10.6g, 54.8mmol) in MeOH (60ml) was added to a solution of NaOH (5.5g, 137.2mmol) in water (22 ml). The reaction mixture was stirred for 8h at rt. Then the solvent was removed by freeze-drying, and the corresponding crude product was used for the next step without further purification. Yield 10.3g (93%). LC-MS 0.51 min, m/z 166.1 [MH]⁺. ¹H-NMR (400MHz, CDCl₃), δ (ppm) : 0.81 (t, J=6.8Hz, 3H),
- 10 1.67-1.78 (m, 1H), 1.96-2.05 (m, 1H), 2.08 (s, 1H), 3.60 (t, J=7.6Hz, 1H), 7.53-7.56 (m, 1H), 7.92-7.95 (m, 1H), 8.56-8.61 (m, 2H).

Synthesis of N-methoxy-N-methyl-2-(pyridin-3-yl)butanamide:



- To a mixture of 2-(pyridin-3-yl)butanoic acid (10.3g, 51.0 mmol), Weinreb amine
- 15 (5.9g, 61.2mmol), HOBt (8.3g, 61.2mmol), and triethylamine (25ml, 176mmol) in DCM (150ml) at 4°C was added EDCl (11.7g, 61.2mmol) and reaction was stirred overnight at rt. The mixture was washed with water (100ml) and brine (100ml). The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent DCM 100% to DCM/MeOH 95:5 v/v) to afford
- 20 crude product. Yield 7.3g (68%). LC-MS 0.76 min, m/z 208.9 [MH]⁺. ¹H-NMR (400MHz, CDCl₃), δ (ppm) : 0.90 (t, J=7.6Hz, 3H), 1.73-1.80 (m, 1H), 2.08-2.15 (m, 1H), 3.17 (s, 3H), 3.57 (s, 3H), 3.91-3.96 (m, 1H), 7.26-7.28 (m, 1H), 7.74-7.77 (m, 1H), 8.48-8.50 (m, 1H), 8.53 (d, J=2Hz, 1H).

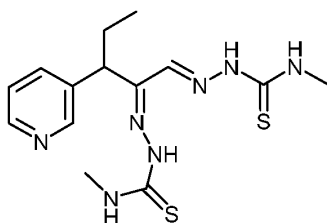
Synthesis of 2-ethoxy-4-(pyridin-3-yl)hex-1-en-3-one:



25

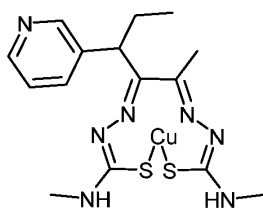
A solution of ethyl vinyl ether (4.3 ml, 45.1 mmol) in dry tetrahydrofuran (30 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 24 ml, 41 mmol) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-2-(pyridin-3-yl)butanamide (1.7g, 8.2 mmol) in THF (35ml) was added, and the reaction was stirred at 0°C for 4h. The progress of the reaction was monitored by TLC. The mixture was poured into aq. NH₄Cl (30ml) and extracted with Et₂O (3 × 50ml). The combined extracts were dried over anhyd. Na₂SO₄, filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.15g (64%). LC-MS 1.15 min, m/z 219.9 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 0.86 (t, J=7.2Hz, 3H), 1.34 (t, J=6.8Hz, 3H), 1.68-1.79 (m, 1H), 2.04-2.15 (m, 1H), 3.62-3.70 (m, 1H), 3.74-3.82 (m, 1H), 4.27 (t, J=8Hz, 1H), 4.35 (d, J=2Hz, 1H), 5.20(d, J=2.8Hz, 1H), 7.23-7.27 (m, 1H), 7.55-7.58 (m, 1H), 8.47-8.49 (m, 1H), 8.52 (d, J=2Hz, 1H).

Synthesis of INT-69 ((2Z,2'E)-2,2'-(3-(pyridin-3-yl)pentane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

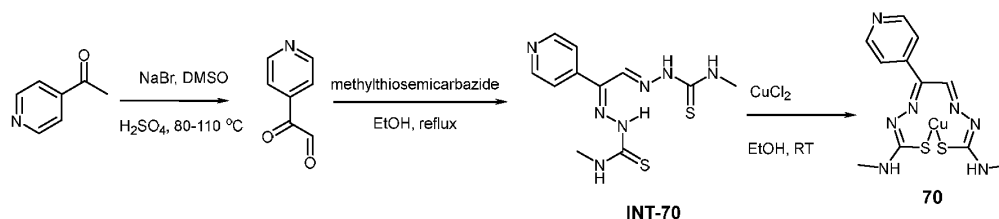
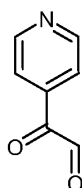


Compound 6. To a stirred solution of 2-ethoxy-4-(pyridin-3-yl)hex-1-en-3-one (0.89 g, 4.05 mmol, 1 eq) in EtOH (20 ml) methyl thiosemicarbazide (0.85 g, 8.1 mmol, 2 eq) and 3 drops of H₂SO₄ were added and the reaction mixture was heated to reflux for 4h, and then stirred for 15h at rt. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 0.67 g (45%). LC-MS 1.01 min, m/z 366.3 [MH]⁺.

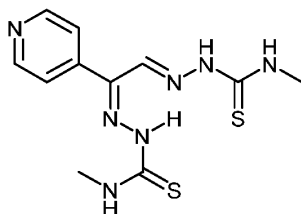
Synthesis of Compound 69



Copper(II) chloride dihydrate (0.12g, 0.73mmol) was added to a stirred solution of **INT-69** (0.24g, 0.67mmol) in ethanol (30 ml). The mixture was stirred overnight at rt. Complex was isolated as a red-brown powder. The formed precipitate was filtered, washed with water (2 × 50ml), ethanol (2 × 50ml), and copious amounts of diethyl ether (5 × 50ml), and then dried *in vacuo*. Yield 0.13g (45%).

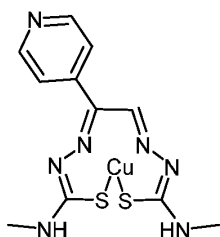
Scheme 31: Synthesis of Compound 70**Synthesis of 2-oxo-2-(pyridin-4-yl)acetaldehyde:**

- 5 To a solution of 1-pyridin-4-ylethanone (10.0g, 82.5mmol) in DMSO (100ml) was added conc. HBr (28ml, 247.5mmol) and the mixture was stirred at 50°C overnight. The reaction mixture was quenched with NaHCO₃ then diluted with water to a total volume of 1000ml. The obtained solution was extracted with EtOAc (3x150 ml), the combined organic layers were dried over anh. Na₂SO₄ and evaporated in vacuo to give the product **1** as a
- 10 yellow oil. Yield 2.0g (18%). LC-MS 0.35 min, m/z 136.1 [MH]⁺.

Synthesis of INT-70 ((2Z,2'E)-2,2'-(1-(pyridin-4-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

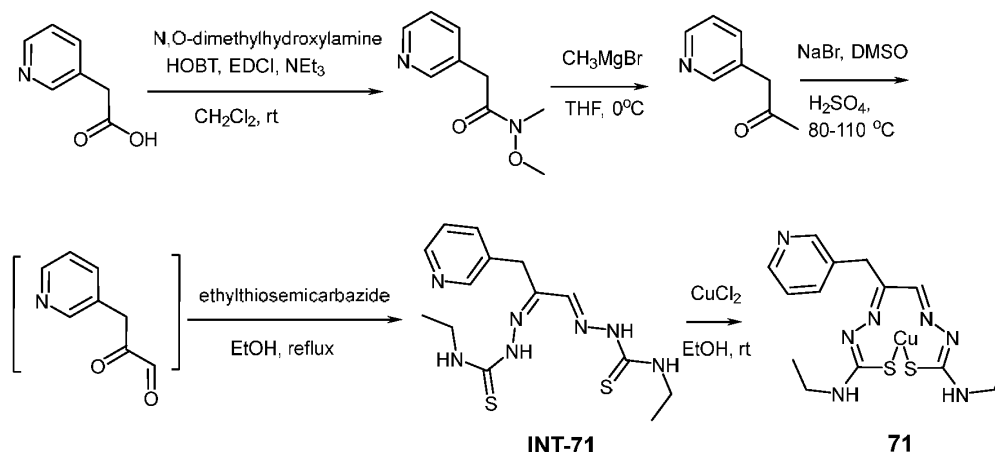
- 15 To a solution of 2-oxo-2-(pyridin-4-yl)acetaldehyde (1.2g, 8.9mmol) in EtOH (100ml) was added methyl thiosemicarbazide (1.87g, 19.8mmol) followed by 2 drops of H₂SO₄ then the reaction mixture was heated to reflux for 4h and stirred overnight at rt. The precipitate was filtered, washed with EtOH, Et₂O, and dried to afford compound **2**. Yield 70mg (4%). LC-MS (reverse phase C18 column 20 × 2 mm, 2.5 μm, pore size 100 Å, water-acetonitrile+0.1% TFA, gradient 5 to 87% over 10min) 4.27 min, (ESI) m/z 310.1 [MH]⁺.

Synthesis of Compound 70

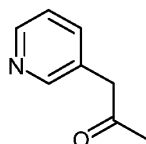


To a solution of **INT-70** (70mg, 0.2mmol) in EtOH (10ml) was added a solution of copper(II) chloride dihydrate (42mg, 0.22mmol) in EtOH (2ml). The mixture was stirred overnight at rt. The formed precipitate was collected by filtration, washed with water (2 × 5ml), ethanol (2 × 5ml), diethyl ether (5 × 5ml), and then dried in vacuo to give the product as a dry powder. Yield 42mg (50%).

Scheme 32: Synthesis of Compound 71



Synthesis of 1-(pyridin-3-yl)propan-2-one:

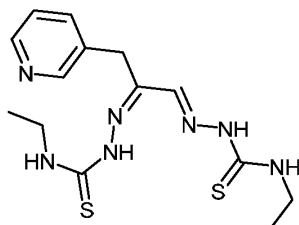


10

A solution of N-methoxy-N-methyl-2-(pyridin-3-yl)acetamide (9.5 g, 52.7mmol, 1 eq) in THF (200 ml) was cooled to 5°C and methylmagnesium bromide (1.4M in THF, 46.5 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhyd. Na₂SO₄, and evaporated in vacuo. The titular product was used for the next step without purification. Yield 6.1 g (86%). LC-MS 0.27 min, m/z 136.6 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 8.48 (d, J = 4.7 Hz, 1H), 8.41 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.31 – 7.12 (m, 1H), 3.67 (d, J = 19.5 Hz, 2H), 2.18 (s, 3H).

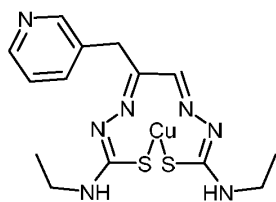
15

Synthesis of INT-71 ((2Z,2'E)-2,2'-(3-(pyridin-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



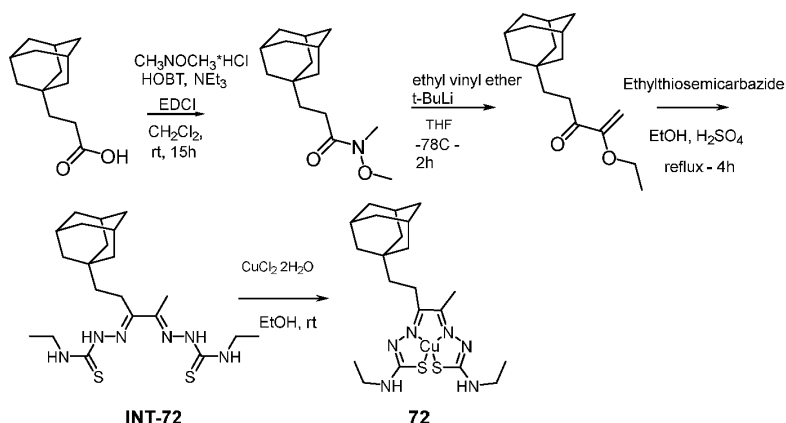
A mixture of 1-(pyridin-3-yl)propan-2-one (1.5g, 11.1mmol, 1 eq), NaBr (1.14g, 1 eq) and DMSO (2 ml) was heated to 85°C and H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated at 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous oil was dissolved in EtOH and ethylthiosemicarbazide (2.64 g, 2 eq) was added. The reaction mixture was heated to reflux for 4h, then stirred overnight at rt. The precipitate was collected by filtration, washed with EtOH, MeCN, water, Et₂O, and dried to afford the titular product. Yield 0.175 g (4.5%). LC-MS 1.19 min, m/z 352.8 [MH]⁺.

Synthesis of Compound 71:

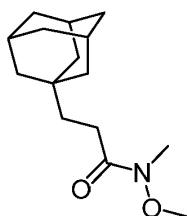


Copper(II) acetate dihydrate (0.055g, 1 eq) was added to a stirred solution of **INT-71** (0.175g, 0.5 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.14g (69%).

Scheme 33: Synthesis of Compound 72

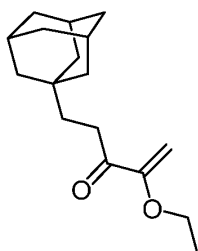


Synthesis of 3-((3r,5r,7r)-adamantan-1-yl)-N-methoxy-N-methylpropanamide:



- To a stirred mixture of 3-((3r,5r,7r)-adamantan-1-yl)propanoic acid (5 g, 24 mmol),
- 5 N,O-dimethylhydroxylamine (2.81 g, 1.2 eq), HOBt (3.89 g, 1.2 eq), and triethylamine (8.5 ml, 6.11 g, 2.5 eq) in DCM (50 ml) at 5°C was added EDCI (5.52 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was purified by column chromatography (silica gel, eluent CCl₄ 100% then CCl₄/EtOAc 8:2). Yield
- 10 3.5 g (58%). LC-MS 1.88 min, m/z 252.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 3.71 (d, J = 1.6 Hz, 3H), 3.19 (s, 3H), 2.42 – 2.31 (m, 2H), 1.97 (s, 3H), 1.72 (d, J = 11.9 Hz, 3H), 1.68 – 1.58 (m, 4H), 1.50 (s, 6H), 1.43 (dd, J = 9.8, 7.1 Hz, 2H).

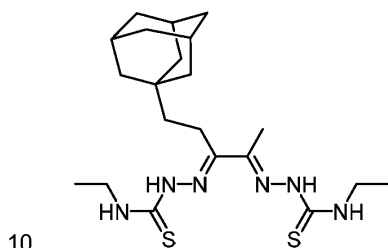
Synthesis of 5-((3r,5r,7r)-adamantan-1-yl)-2-ethoxypent-1-en-3-one:



- 15 A solution of ethyl vinyl ether (2.01 g, 2.7 ml, 3.3 eq) in dry THF (150 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 16 ml, 3 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution

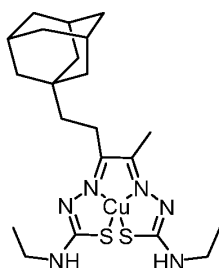
of 3-((3*r*,5*r*,7*r*)-adamantan-1-yl)-N-methoxy-N-methylpropanamide (2.12 g, 8.4 mmol) in THF (15ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 2.2 g (99.9%). ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 5.18 (s, 1H), 4.36 (d, *J* = 33.6 Hz, 1H), 3.82 (q, *J* = 6.9 Hz, 2H), 2.64 (dd, *J* = 20.9, 13.1 Hz, 2H), 1.97 (s, 4H), 1.79 – 1.53 (m, 8H), 1.56 – 1.15 (m, 13H).

Synthesis of INT-72 ((2*E*,2'*E*)-2,2'-(5-((3*r*,5*r*,7*r*)-adamantan-1-yl)pentane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide):



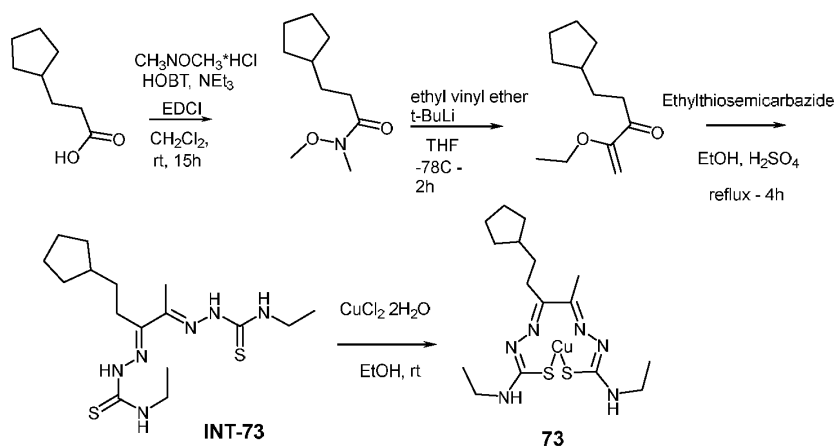
5-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2-ethoxypent-1-en-3-one (2.21 g, 8.4 mmol) was dissolved in EtOH (60 ml), ethylthiosemicarbazide (2.01 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq. sat. Na₂CO₃, water, Et₂O, and dried. Yield 2.2 g (59.6%). LC-MS 2.17 min, *m/z* 437.5 [MH]⁺.

Synthesis of Compound 72

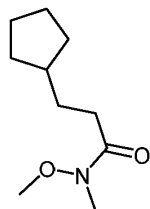


Copper(II) chloride dihydrate (0.23 g, 1 eq) was added to a stirred solution of **INT-72** (0.59 g) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.61g (90.8%).

Scheme 34: Synthesis of Compound 73

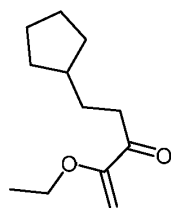


Synthesis of 3-cyclopentyl-N-methoxy-N-methylpropanamide:



- To a stirred mixture of 3-cyclopentylpropanoic acid (3.12 g, 21.9 mmol), N,O-dimethylhydroxylamine (2.57 g, 1.2 eq), HOBT (4.03 g, 1.2 eq), and triethylamine (6.1 ml, 4.43 g, 2eq) in DCM (100 ml) at 5°C was added EDCI (5.05 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was purified by column chromatography (silica gel, eluent DCM 100% to DCM/MeOH 99:1). Yield 3.11 g (76.5%). LC-MS 1.63 min, m/z 186.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 3.69 (s, 3H), 3.19 (s, 3H), 2.42 (dd, J = 18.1, 10.2 Hz, 2H), 2.53 – 2.33 (m, 2H), 1.87 – 1.73 (m, 4H), 1.70 – 1.57 (m, 5H), 1.58 – 1.44 (m, 2H), 1.19 – 1.01 (m, 2H).

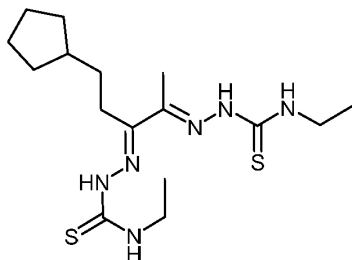
Synthesis of 5-cyclopentyl-2-ethoxypent-1-en-3-one:



- A solution of ethyl vinyl ether (3.85 g, 5.1 ml, 6.6 eq) in dry THF (100 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 28 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of 3-cyclopentyl-N-methoxy-N-methylpropanamide (1.5 g, 8 mmol) in THF (15ml) was added

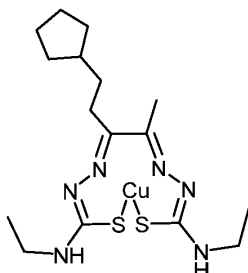
and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH_4Cl (100ml) and extracted with Et_2O (3x100ml). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.05 g (99.0%). LC-MS 0.91 min, m/z 180.9 $[\text{MH}]^+$.

5 **Synthesis of INT-73 ((2E,2'E)-2,2'-(5-cyclopentylpentane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**



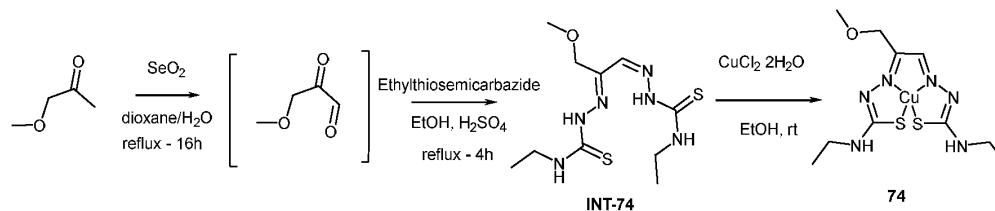
5-cyclopentyl-2-ethoxypent-1-en-3-one (1.05 g, 8 mmol) was dissolved in EtOH (25 ml), ethylthiosemicarbazide (1.93 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred
 10 reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq. sat. Na_2CO_3 , water, Et_2O , and dried. Yield 2 g (68%). LC-MS 1.83 min, m/z 371.5 $[\text{MH}]^+$.

Synthesis of Compound 73:



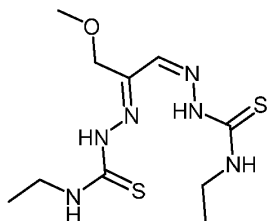
15 Copper(II) chloride dihydrate (0.23g, 1 eq) was added to a stirred solution of **INT-73** (0.5 g, 1.3 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.5g (88.7%).

Scheme 35: Synthesis of Compound 74



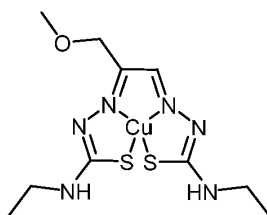
20

Synthesis of INT-74 ((2Z,2'Z)-2,2'-(3-methoxypropane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



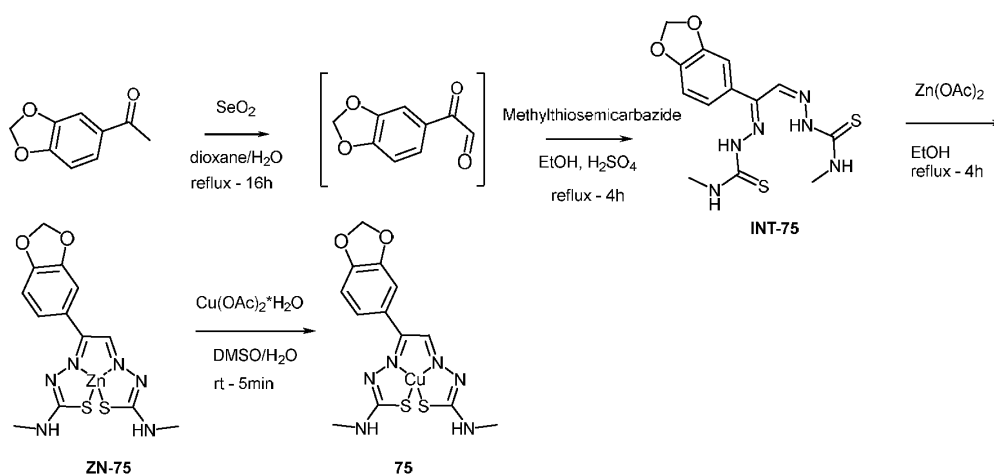
A three-necked flask was charged with SeO_2 (3.6 g, 1.05 eq), 1,4-dioxane (70 mL),
 5 and water (14 mL). The mixture was heated to 50°C and stirred until most of SeO_2 dissolves.
 1-methoxypropan-2-one (2.72 g, 30.9 mmol) was added, and the reaction was heated to
 gentle reflux overnight. Selenium solids precipitated during the course of the reaction. The
 mixture was cooled in an ice bath and filtered through diatomaceous earth to remove
 selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was
 10 evaporated to dryness and dissolved in EtOH (100 ml). Ethylthiosemicarbazide (7.35 g, 2
 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for
 4h. Formed precipitate was filtered, washed with EtOH, aq.sat. Na_2CO_3 , water, Et_2O , and
 dried. Yield 2.4 g (25.5%). LC-MS 1.37 min, m/z 305.5 $[\text{MH}]^+$.

Synthesis of Compound 74:

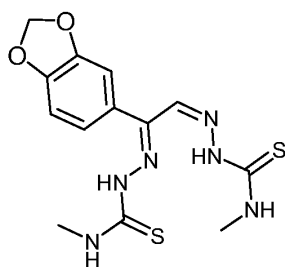


15 Copper(II) chloride dihydrate (0.1 g, 1 eq) was added to a stirred solution of **INT-74**
 (0.184 g, 0.6 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex
 precipitated as a red-brown powder. The precipitate was collected by filtration, washed with
 water, diethyl ether, and dried. Yield 0.1g (45.2%).

20 **Scheme 36: Synthesis of Compound 75**

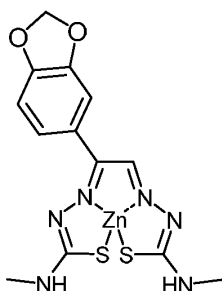


Synthesis of INT-75 ((2Z,2'E)-2,2'-(1-(benzo[d][1,3]dioxol-5-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



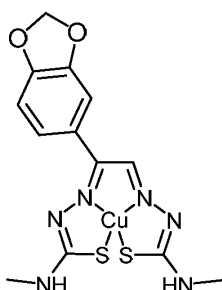
- 5 A three-necked flask was charged with SeO_2 (2.12 g, 1.05 eq), 1,4-dioxane (41 mL), and water (9 mL). The mixture was heated to 50°C and stirred until most of SeO_2 dissolves. 1-(benzo[d][1,3]dioxol-5-yl)ethan-1-one (2.72 g, 30.9 mmol) was added, and the reaction was heated to gentle reflux overnight. Selenium solids precipitated during the course of the reaction. The mixture was cooled in an ice bath and filtered through diatomaceous earth to
- 10 remove selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was evaporated to dryness and dissolved in EtOH (100 mL). Methylthiosemicarbazide (3.84 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h. Formed precipitate was filtered, washed with EtOH, aq. sat. Na_2CO_3 , water, Et_2O , and dried. Yield 2.16 g (33.5%). LC-MS 1.53 min, m/z 353.3 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO-
- 15 d_6), δ (ppm) : 12.13 (s, 1H), 11.71 (s, 1H), 8.82 (d, $J = 4.3$ Hz, 1H), 8.21 – 8.04 (m, 2H), 7.60 (d, $J = 1.5$ Hz, 1H), 7.18 (d, $J = 8.2$ Hz, 1H), 6.98 (d, $J = 8.2$ Hz, 1H), 6.08 (s, 2H), 3.04 (dd, $J = 15.0, 4.5$ Hz, 6H).

Synthesis of ZN-75:



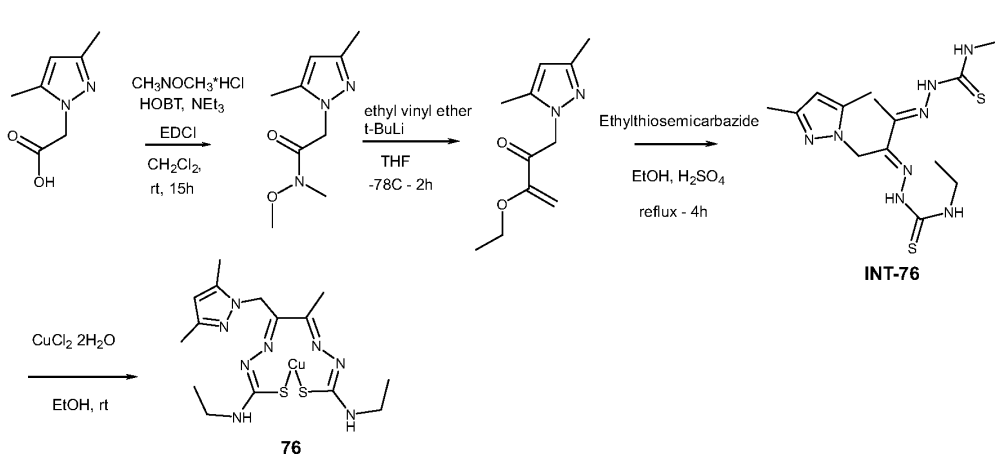
Zinc acetate (0.28 g, 1.5 eq) was added to **INT-75** (0.36g, 1 mmol) in ethanol. The mixture was heated to reflux for 4 h. The formed complex precipitated as a yellow powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.33 g (76.8 %).

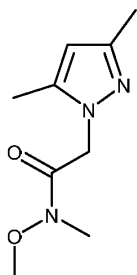
Synthesis of Compound 75:



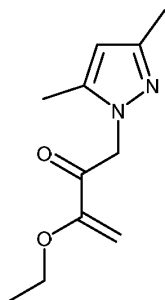
ZN-75 (0.32 g, 0.8 mmol) was dissolved in DMSO (9 ml) and a solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.17 g, 1.1 eq) in water (9 ml) was added. The mixture was stirred for 5 min, filtered, and precipitate was washed with saturated solution of potassium carbonate, water, and Et_2O . Yield 0.15 g (48.5%).

Scheme 37: Synthesis of Compound 76:



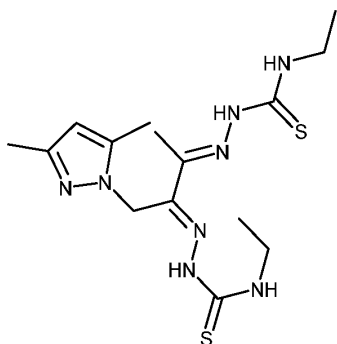
Synthesis of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-methoxy-N-methylacetamide:

To a stirred mixture of 2-(3,5-dimethyl-1H-pyrazol-1-yl)acetic acid (1.95 g, 12.6 mmol), N,O-dimethylhydroxylamine (1.48 g, 1.2 eq), HOBT (2.32 g, 1.2 eq), and triethylamine (3.5 ml, 2.54 g, 2eq) in DCM (80 ml) at 5°C was added EDCI (2.9 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was used further without additional purification. Yield 1.7 g (68.1%). LC-MS 0.88 min, m/z 198.3 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 5.88 (s, 1H), 4.98 (s, 2H), 3.79 (s, 3H), 3.22 (s, 3H), 2.23 (d, J = 6.6 Hz, 6H).

Synthesis of 1-(3,5-dimethyl-1H-pyrazol-1-yl)-3-ethoxybut-3-en-2-one:

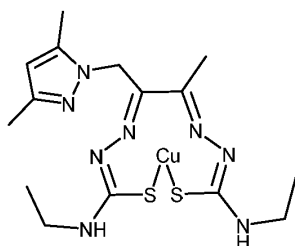
A solution of ethyl vinyl ether (6.83 g, 9 ml, 11 eq) in dry THF (150 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 50 ml, 10 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-N-methoxy-N-methylacetamide (1.7 g, 8.6 mmol) in THF (20 ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 0.4 g (22.2%). LC-MS 1.15 min, m/z 209.1 [MH]⁺.

Synthesis of INT-76 ((2E,2'E)-2,2'-(1-(3,5-dimethyl-1H-pyrazol-1-yl)butane-2,3-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



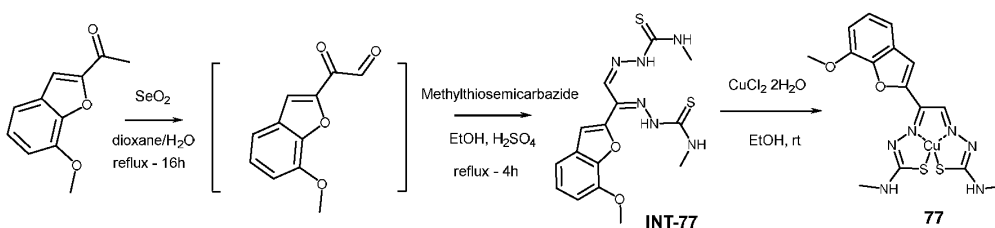
1-(3,5-dimethyl-1H-pyrazol-1-yl)-3-ethoxybut-3-en-2-one (0.4 g, 1.9 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (0.46 g, 2 eq) and 1 drop of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.05 g (6.8%). LC-MS 1.62 min, m/z 383.5 [MH]⁺.

Synthesis of Compound 76:

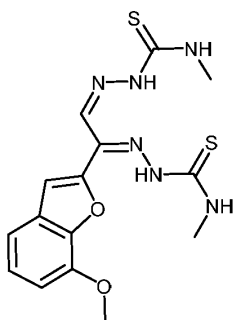


Copper(II) chloride dihydrate (0.23g, 1 eq) was added to a stirred solution of **INT-76** (0.5 g, 1.3 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.5g (88.7%).

Scheme 38: Synthesis of Compound 77:

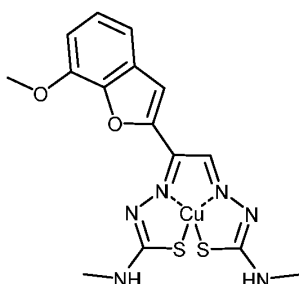


Synthesis of INT 77 ((2Z,2'Z)-2,2'-(1-(7-methoxybenzofuran-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



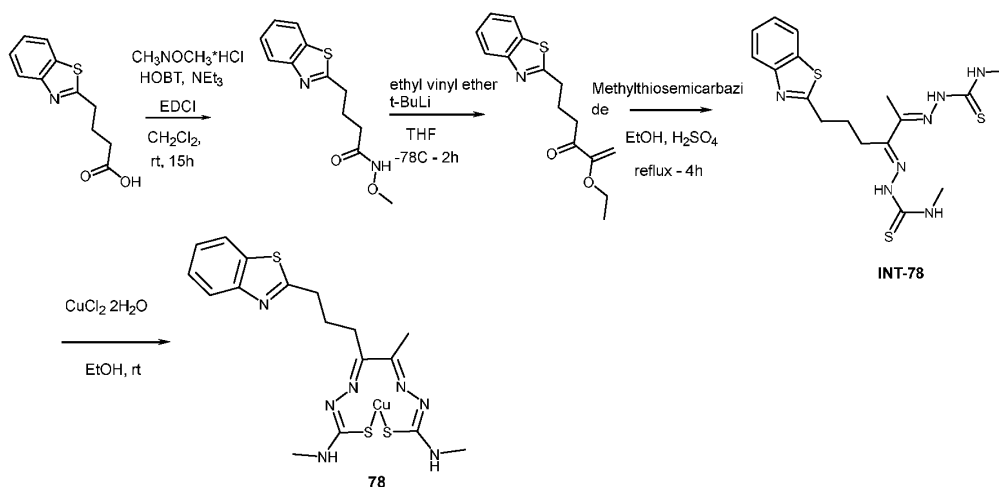
A three-necked flask was charged with SeO_2 (1.84 g, 1.05 eq), 1,4-dioxane (36 mL), and water (8 mL). The mixture was heated to 50°C and stirred until most of SeO_2 dissolves. 1-(7-methoxybenzofuran-2-yl)ethan-1-one (3 g, 15.8 mmol) was added, and the reaction was
 5 heated to gentle reflux overnight. Selenium solids precipitated during the course of the reaction. The mixture was cooled in an ice bath and filtered through diatomaceous earth to remove selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was evaporated to dryness and dissolved in EtOH (100 ml). Methylthiosemicarbazide (3.32 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for
 10 4h. Formed precipitate was filtered, washed with EtOH, aq.sat. Na_2CO_3 , water, Et_2O , and dried. Yield 2.15 g (36%). LC-MS 1.63 min, m/z 379.3 $[\text{MH}]^+$.

Synthesis of Compound 77:

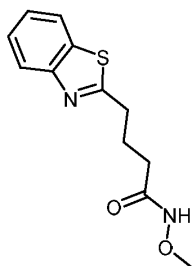


Copper(II) chloride dihydrate (0.15g, 1 eq) was added to a stirred solution of **INT-77**
 15 (0.34 g, 0.89 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.34 g (86.8%).

Scheme 39: Synthesis of Compound 78

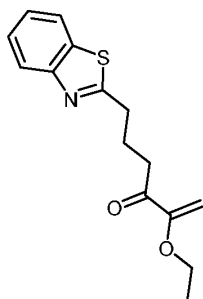


Synthesis of 4-(benzo[d]thiazol-2-yl)-N-methoxybutanamide:



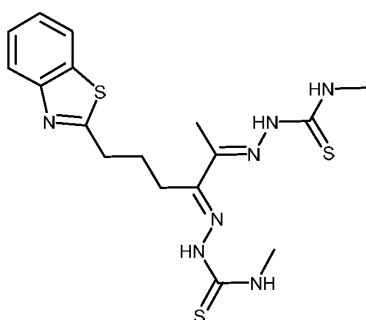
To a stirred mixture of 4-(benzo[d]thiazol-2-yl)butanoic acid (1.22 g, 5.5 mmol), N,O-dimethylhydroxylamine (0.65 g, 1.2 eq), HOBT (0.89 g, 1.2 eq), and triethylamine (2 ml, 1.44 g, 2.5 eq) in DCM (50 ml) at 5°C was added EDCI (1.27 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure. The product was used further without additional purification. Yield 1.46 g (99.9 %). LC-MS 1.3 min, m/z 265.1 $[\text{MH}]^+$. ^1H -NMR (400 MHz, CDCl_3), δ (ppm) : 7.92 (dd, J = 46.1, 8.1 Hz, 2H), 7.41 (dt, J = 15.2, 7.3 Hz, 2H), 3.66 (s, 3H), 3.33 – 3.11 (m, 5H), 2.60 (t, J = 7.1 Hz, 2H), 2.25 (p, J = 7.3 Hz, 2H).

Synthesis of 6-(benzo[d]thiazol-2-yl)-2-ethoxyhex-1-en-3-one:



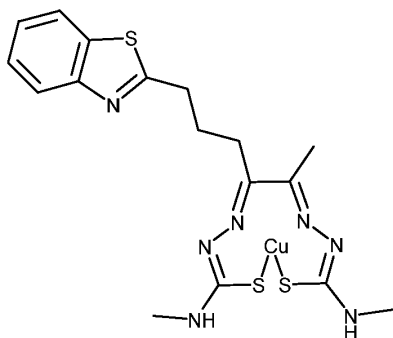
A solution of ethyl vinyl ether (1.2 g, 1.6 ml, 5.5 eq) in dry THF (40 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 9.4 ml, 5 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of 4-(benzo[d]thiazol-2-yl)-N-methoxybutanamide (0.8 g, 3 mmol) in THF (5 ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (15 ml) and extracted with Et₂O (3x25 ml). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 0.83 g (99.6%). LC-MS 1.62 min, m/z 276.3 [MH]⁺.

Synthesis of INT-78 ((2E,2'E)-2,2'-(6-(benzo[d]thiazol-2-yl)hexane-2,3-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



6-(benzo[d]thiazol-2-yl)-2-ethoxyhex-1-en-3-one (0.86 g, 3.1 mmol) was dissolved in EtOH (30 ml), methylthiosemicarbazide (0.66 g, 2 eq) and 1 drop of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq. sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.79 g (60.1%). LC-MS 1.57 min, m/z 422.3 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 10.61 (s, 1H), 10.24 (s, 1H), 8.40 (d, J = 4.4 Hz, 1H), 8.23 (d, J = 4.5 Hz, 1H), 8.07 (dd, J = 25.5, 8.0 Hz, 2H), 7.44 (dt, J = 33.7, 7.7 Hz, 2H), 3.21 (t, J = 7.2 Hz, 2H), 3.14 – 2.92 (m, 8H), 2.21 (s, 3H), 1.89 (d, J = 7.3 Hz, 2H).

Synthesis of Compound 78:

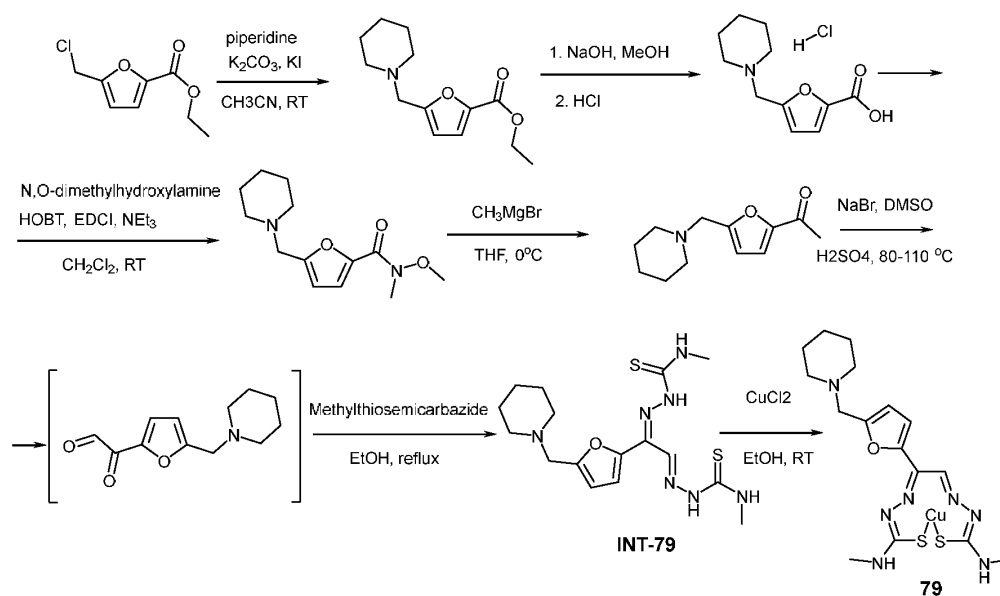


Copper(II) chloride dihydrate (0.32g, 1 eq) was added to a stirred solution of **INT-78** (0.79 g, 1.3 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.66 g (73.2%).

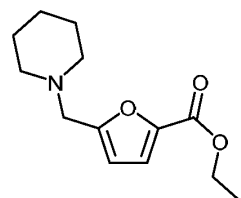
5

Example 6: Preparation of Compounds 79-127

Scheme 40: Synthesis of Compound 79



Synthesis of ethyl 5-(piperidin-1-ylmethyl)furan-2-carboxylate:



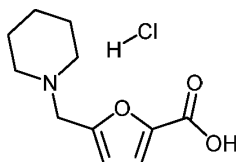
10

To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (5 g, 27 mmol) in CH_3CN (150 ml) were added piperidine (2.56 g, 1 eq), potassium carbonate (7.33 g, 2 eq), and potassium iodide (1.3 g, 0.3 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3×50 ml). Organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. Yield 3.6g (57%). LC-MS 0.87 min, m/z 238.3 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6), δ (ppm) : 7.22 (d, $J = 3.4$ Hz, 1H), 6.48 (d, $J =$

15

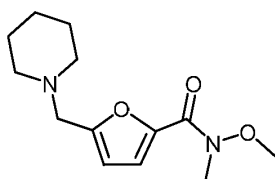
3.4 Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 3.50 (s, 2H), 2.34 (s, 4H), 1.56 – 1.42 (m, 4H), 1.40 – 1.22 (m, 5H).

Synthesis of 5-(piperidin-1-ylmethyl)furan-2-carboxylic acid:



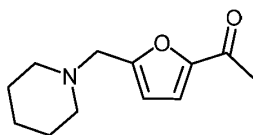
- 5 To a solution of ethyl 5-(piperidin-1-ylmethyl)furan-2-carboxylate (3.6g, 15 mmol) in methanol (80 ml), a solution of NaOH (1.52 g, 2.5 eq) in water (10 ml) was added, and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered, and filtrate was evaporated in vacuo to
- 10 dryness. Yield 2.94g (79%). LC-MS 0.61 min, m/z 210.4 [MH]⁺. ¹H NMR (400 MHz, DMSO-d₆), δ (ppm) : 13.31 (br.s, 1H), δ 10.96 (br.s, 1H), 7.26 (s, 1H), δ 6.92 (s, 1H), 4.40 (s, 1H), 3.14-3.41 (br.s, 2H), 2.76-3.10 (br.s, 2H), 1.34 – 1.91 (m, 6H).

Synthesis of N-methoxy-N-methyl-5-(piperidin-1-ylmethyl)furan-2-carboxamide:



- 15 To a stirred mixture of 5-(piperidin-1-ylmethyl)furan-2-carboxylic acid (2.94 g, 12 mmol), N,O-dimethylhydroxylamine (1.4 g, 1.2 eq), HOBt (2.2 g, 1.2 eq), and triethylamine (6.7 ml, 4.84 g, 4eq) in DCM (100 ml) at 5°C was added EDCI (2.75 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. Product was
- 20 used without further purification. Yield 2.2 g (73%). LC-MS 0.76 min, m/z 253.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.09 (d, $J = 3.4$ Hz, 1H), 6.36 (d, $J = 3.4$ Hz, 1H), 3.77 (s, 3H), 3.66 (s, 2H), 3.34 (s, 3H), 2.42 (d, $J = 68.1$ Hz, 4H), 1.61 (dt, $J = 11.1, 5.6$ Hz, 4H), 1.42 (d, $J = 5.4$ Hz, 2H).

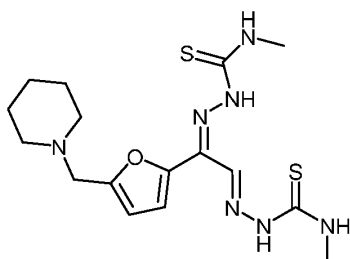
Synthesis of 1-(5-(piperidin-1-ylmethyl)furan-2-yl)ethan-1-one:



- 25 A solution of N-methoxy-N-methyl-5-(piperidin-1-ylmethyl)furan-2-carboxamide (2.2 g, 8.7 mmol) in THF (100 ml) was cooled to 5°C and methylmagnesium bromide (1.4M in

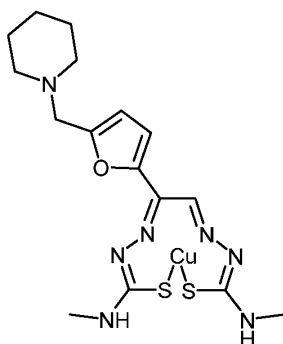
THF, 19 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 1.7 g (94.6%). LC-MS 0.74 min, m/z 208.1 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.14 (d, *J* = 3.5 Hz, 1H), δ 6.37 (d, *J* = 3.4 Hz, 1H), δ 3.61 (s, 2H), δ 2.47 (s, 7H), δ 1.60 (dt, *J* = 11.0, 5.6 Hz, 4H), δ 1.48 – 1.39 (m, 2H).

Synthesis of INT-79 ((2*E*,2'*E*)-2,2'-(1-(5-(piperidin-1-ylmethyl)furan-2-yl)ethane-1,2-diylidene)bis(*N*-methylhydrazine-1-carbothioamide)):



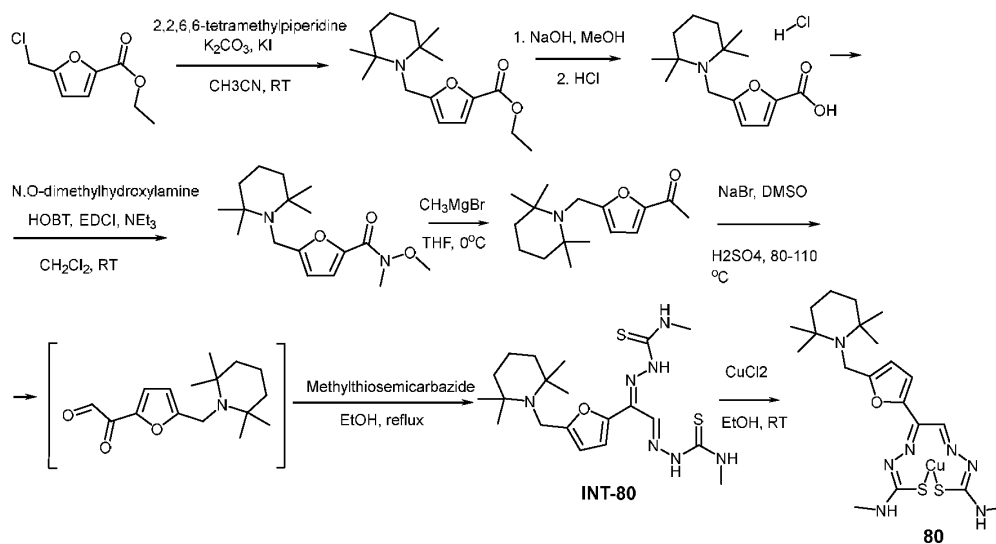
A mixture of 1-(5-(piperidin-1-ylmethyl)furan-2-yl)ethan-1-one (1.15 g, 5.5 mmol), NaBr (0.57 g, 1 eq), and DMSO (3 ml) was heated to 85°C, then H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and methylthiosemicarbazide (1.16 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. K₂CO₃ and extracted with EtOAc (3 × 50 ml). The organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular product. Yield 1.16 g (52.8%). LC-MS 1.08 min, m/z 396.1 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 11.67 (s, 1H), 8.75 (s, 1H), 7.19 (s, 1H), 6.93 (d, *J* = 3.1 Hz, 1H), 6.44 (d, *J* = 2.9 Hz, 1H), 6.13 (s, 1H), 5.37 (s, 1H), 3.45 (d, *J* = 22.7 Hz, 2H), 3.33 (m, 3H), 2.76 (d, *J* = 4.2 Hz, 3H), 2.35 (s, 4H), 1.41-1.55 (m, 6H).

Synthesis of Compound 79:

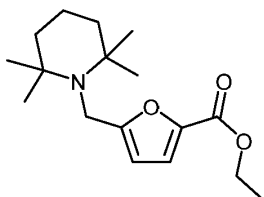


Copper(II) chloride dihydrate (0.08g, 1 eq) was added to a stirred solution of **INT-79** (0.186 g, 0.47 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.1g (46.5%).

Scheme 41: Synthesis of Compound 80



Synthesis of ethyl 5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxylate:

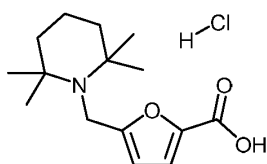


To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (6.75 g, 35.8 mmol) in CH₃CN (150 ml) were added 2,2,6,6-tetramethylpiperidine (5.06g, 1 eq), potassium carbonate (9.89 g, 2 eq), and sodium iodide (1.07, 0.2 eq). The reaction mixture was stirred

overnight at rt. Solids were filtered, and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. Yield 10.5 g (99.9%).

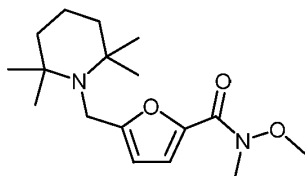
LC-MS 1.01 min, m/z 294.6. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6), δ (ppm) : 7.19 (t, $J = 10.1$ Hz, 1H), 6.43 (t, $J = 16.6$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.72 (s, 2H), 1.53 (d, $J = 3.3$ Hz, 2H), 1.45 – 1.39 (m, 4H), 1.26 (t, $J = 7.1$ Hz, 3H), 0.99 (s, 12H).

Synthesis of 5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxylic acid:



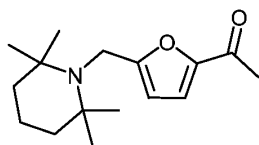
To a solution of ethyl 5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxylate (10.5 g, 354.8 mmol) in methanol (200 ml) was added a solution of NaOH (3.58 g, 2.5 eq) in water (20 ml) and the reaction mixture was stirred overnight at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified with conc. HCl to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered and filtrate was evaporated in vacuo to dryness. Yield 10.8 g (99.8 %). LC-MS 0.88 min, m/z 266.5 $[\text{MH}]^+$.

Synthesis of N-methoxy-N-methyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxamide:



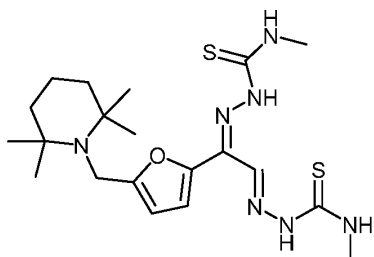
To a stirred mixture of 5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxylic acid (10.8 g, 35.8 mmol), N,O-dimethylhydroxylamine (4.18 g, 1.2 eq), HOBt (5.8 g, 1.2 eq), and triethylamine (18 ml, 12.94 g, 3.5eq) in DCM (200 ml) at 5°C was added EDCI (8.38 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Product was purified by column chromatography (SiO_2 , eluent $\text{CCl}_4/\text{EtOAc}$ from 8:2 to 7:3, then $\text{CHCl}_3/\text{MeOH}$ from 99:1 to 98:2). Yield 7.42 g (75.9%). LC-MS 0.74 min, m/z 269.5 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 7.08 (d, $J = 3.4$ Hz, 1H), 6.33 (s, 1H), 3.76 (s, 3H), 3.71 (m, 6H), 3.33 (s, 3H), 3.16 – 2.98 (m, 2H), 1.02 (d, $J = 6.5$ Hz, 12H).

Synthesis of 1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)ethan-1-one:



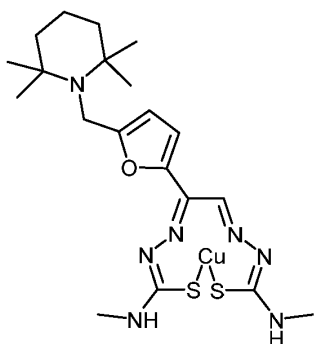
A solution of N-methoxy-N-methyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxamide (6 g, 19.4 mmol) in THF (120 ml) was cooled to 5°C and methylmagnesium bromide (3.4M in THF/toluene, 17 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq. NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 4.2 g (82%). LCMS 0.67 min, m/z 264.6 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm): 7.12 (d, J = 3.3 Hz, 1H), 6.52 – 6.35 (m, 1H), 3.77 (s, 2H), 2.43 (d, J = 0.9 Hz, 3H), 1.63 – 1.55 (m, 2H), 1.48 (dd, J = 15.2, 10.0 Hz, 4H), 1.03 (t, J = 2.1 Hz, 12H).

Synthesis of INT-80 ((2E,2'E)-2,2'-(1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



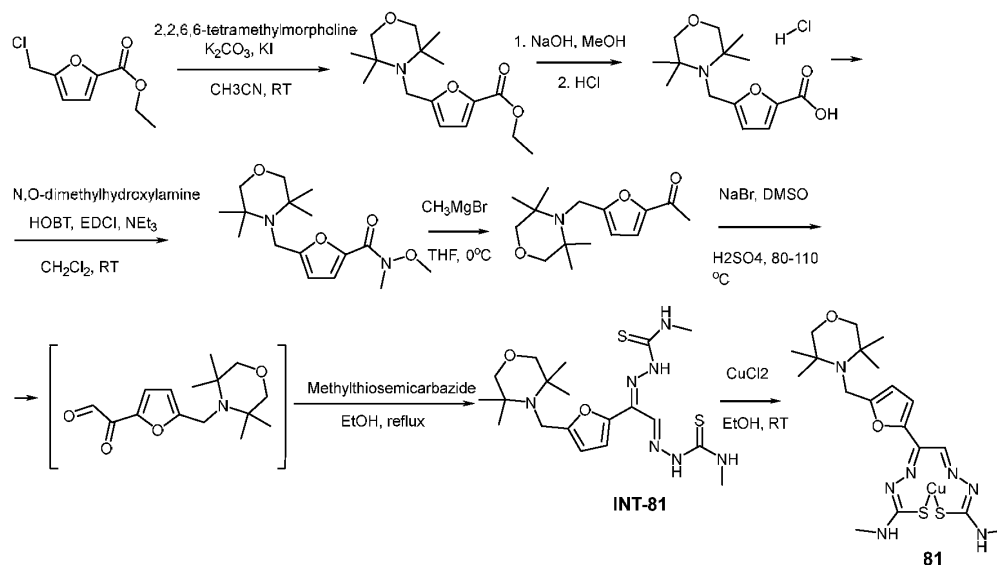
A mixture of 1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)ethan-1-one (0.93 g, 3.5 mmol), NaBr (0.36 g, 1 eq), and DMSO (1.8 ml) was heated to 85°C, then H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and methylthiosemicarbazide (1.16 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq. sat. K₂CO₃ and extracted with EtOAc (3 × 60 ml). The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular product. Yield 1.05 g (65.8%). LC-MS 1.17 min, m/z 452.3 [MH]⁺.

Synthesis of Compound 80:

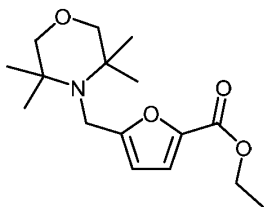


Copper(II) chloride dihydrate (0.036g, 1 eq) was added to a stirred solution of **INT-80** (0.099 g, 4.7 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.08g (71.2%).

Scheme 42: Synthesis of Compound 81



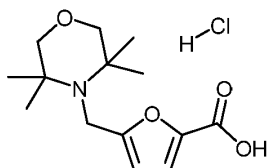
Synthesis of ethyl 5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxylate:



To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (4 g, 21.2 mmol) in CH₃CN (100 ml) were added 2,2,6,6-tetramethylmorpholine hydrochloride (3.81 g, 1 eq), potassium

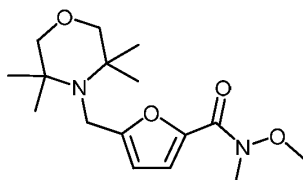
carbonate (8.79 g, 3 eq), and potassium iodide (1.06 g, 0.3 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. Yield 4.9 g (78.2%). LC-MS 0.98 min, m/z 296.5 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.10 (d, J = 3.4 Hz, 1H), 6.38 (d, J = 3.4 Hz, 1H), 4.42 – 4.29 (m, 2H), 3.77 (s, 2H), 3.43 (s, 4H), 1.44 – 1.35 (m, 3H), 1.03 (s, 12H).

Synthesis of 5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxylic acid:



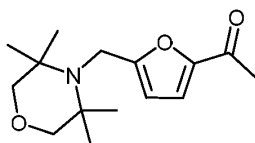
- 10 To a solution of ethyl 5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxylate (4.9 g, 16.6 mmol) in methanol (100 ml) was added a solution of NaOH (1.66 g, 2.5 eq) in water (10 ml) and the reaction mixture was stirred overnight at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified with conc. HCl to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered and
- 15 filtrate was evaporated in vacuo to dryness. Yield 3.91 g (77.6 %). LC-MS 0.74 min, m/z 268.6 [MH]⁺.

Synthesis of N-methoxy-N-methyl-5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxamide:



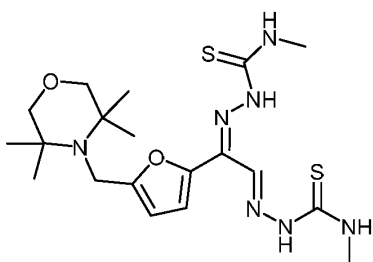
- 20 To a stirred mixture of 5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxylic acid (3.91 g, 12.9 mmol), N,O-dimethylhydroxylamine (1.51 g, 1.2 eq), HOBt (2.36 g, 1.2 eq), and triethylamine (7.2 ml, 5.2 g, 4 eq) in DCM (100 ml) at 5°C was added EDCI (2.96 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure.
- 25 Product was purified by column chromatography (SiO₂, eluent CCl₄/EtOAc from 8:2 to 2:1). Yield 2.3 g (57.6%). LC-MS 0.78 min, m/z 311.5 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 7.08 (d, J = 3.1 Hz, 1H), 6.41 (s, 1H), 3.73 (s, 5H), 3.31 (d, J = 2.6 Hz, 6H), 3.21 (s, 3H), 0.98 (s, 12H).

Synthesis of 1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)ethan-1-one:



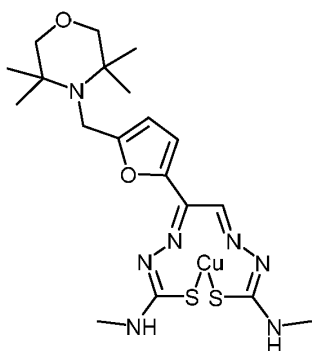
A solution of N-methoxy-N-methyl-5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxamide (1.3 g, 4.2 mmol) in THF (50 ml) was cooled to 5°C and methylmagnesium bromide (1.4M in THF, 9 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq. NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 1.0 g (90%). LC-MS 0.80 min, m/z 266.3 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 7.35 (d, J = 3.2 Hz, 1H), 6.48 (s, 1H), 3.74 (s, 2H), 3.31 (s, 6H), 2.35 (s, 3H), 0.97 (s, 12H).

Synthesis of INT-81 ((2E,2'E)-2,2'-(1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



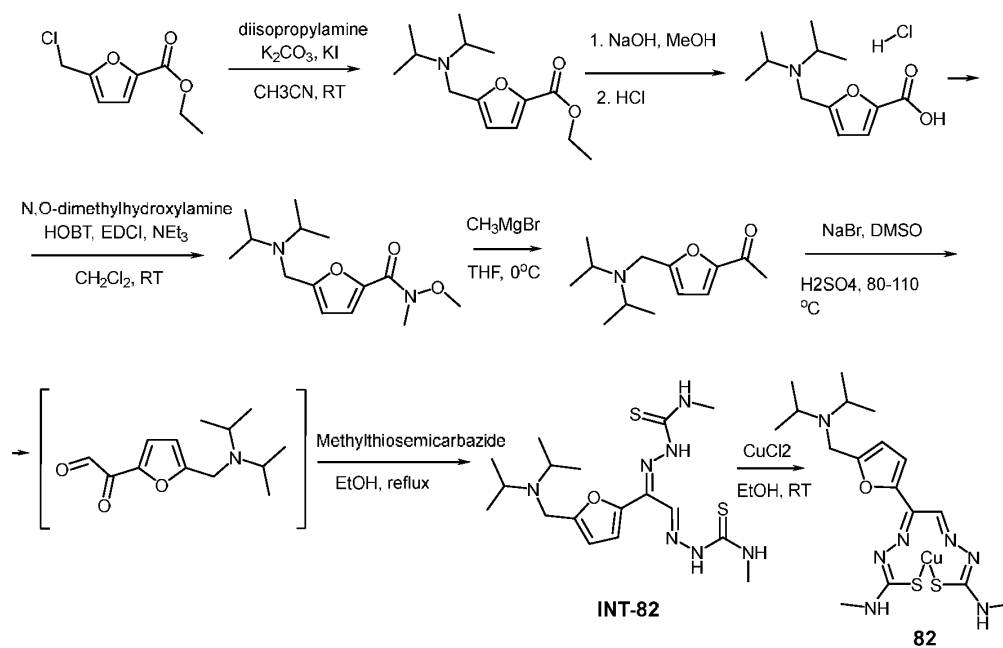
A mixture of 1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)ethan-1-one (0.48 g, 1.8 mmol), NaBr (0.19 g, 1 eq), and DMSO (1 ml) was heated to 85°C, then H₂SO₄ (3 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and methylthiosemicarbazide (1.16 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq. sat. K₂CO₃ and extracted with EtOAc (3 × 60 ml). The organic layer was separated, dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular product. Yield 0.28 g (34%). LC-MS 1.05 min, m/z 454.4 [MH]⁺.

Synthesis of Compound 81:

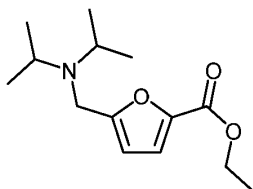


Copper(II) chloride dihydrate (0.053, 1 eq) was added to a stirred solution of **INT-81** (0.14 g, 0.3 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.15 g (94.2%).

Scheme 43: Synthesis of Compound 82

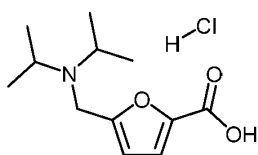


Synthesis of ethyl 5-((diisopropylamino)methyl)furan-2-carboxylate:



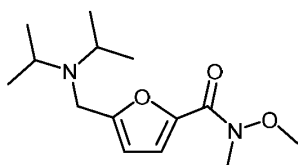
To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (7.78 g, 41.2 mmol) in CH₃CN (150 ml) were added diisopropylamine (4.17 g, 5.8 ml, 1 eq), potassium carbonate (11.4 g, 2 eq), and sodium iodide (1.27 g, 0.2 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. Yield 10 g (95.7%). LC-MS 0.93 min, m/z 254.3 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆), δ (ppm) : 7.19 (d, J = 3.4 Hz, 1H), 6.40 (d, J = 3.4 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.66 (s, 2H), 3.00 (hept, J = 6.5 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.6 Hz, 12H).

Synthesis of 5-((diisopropylamino)methyl)furan-2-carboxylic acid:



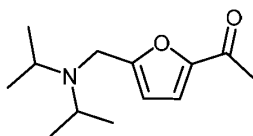
To a solution of ethyl 5-((diisopropylamino)methyl)furan-2-carboxylate (10 g, 39.5 mmol) in methanol (65 ml) was added a solution of NaOH (1.66 g, 2.5 eq) in water (20 ml) and the reaction mixture was stirred overnight at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified with conc. HCl to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered, and filtrate was evaporated in vacuo to dryness. Yield 9.53 g (92.2 %). LC-MS 0.6 min, m/z 226.5 [MH]⁺.

Synthesis of 5-((diisopropylamino)methyl)-N-methoxy-N-methylfuran-2-carboxamide:



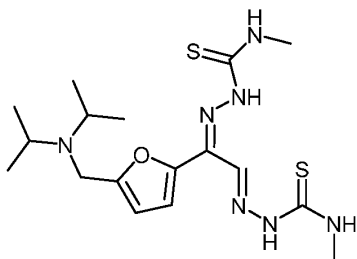
To a stirred mixture of 5-((diisopropylamino)methyl)furan-2-carboxylic acid (9.53 g, 36.4 mmol), N,O-dimethylhydroxylamine (4.26 g, 1.2 eq), HOBt (5.9 g, 1.2 eq) and triethylamine (18 ml, 12.94 g, 3.5 eq) in DCM (100 ml) at 5°C was added EDCI (2.96 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. Product was purified by column chromatography (SiO₂, eluent CCl₄/EtOAc from 8:2 to 2:1). Yield 2.3 g (57.6%). LC-MS 0.78 min, m/z 311.5 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.08 (d, J = 3.4 Hz, 1H), 6.33 (s, 1H), 3.76 (s, 3H), 3.71 (s, 2H), 3.33 (s, 3H), 3.18 – 2.94 (m, 2H), 1.02 (d, J = 6.5 Hz, 12H).

Synthesis of 1-(5-((diisopropylamino)methyl)furan-2-yl)ethan-1-one:



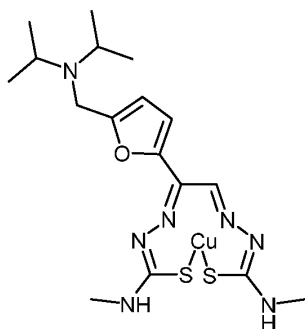
A solution of 5-((diisopropylamino)methyl)-N-methoxy-N-methylfuran-2-carboxamide (2.68 g, 10 mmol) in THF (75 ml) was cooled to 5°C and methylmagnesium bromide (1.4 M in THF, 22 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 2.0 g (89.7%). LC-MS 0.87 min, m/z 224.4 [MH]⁺. ¹H-NMR (400MHz, DMSO-d₆), δ (ppm) : 7.13 (d, *J* = 3.5 Hz, 1H), 6.38 (s, 1H), 3.70 (s, 2H), 3.08 (dt, *J* = 12.7, 6.2 Hz, 2H), 2.44 (s, 3H), 1.04 (d, *J* = 6.5 Hz, 12H).

Synthesis of INT 82 ((2*E*,2'*E*)-2,2'-(1-(5-((diisopropylamino)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



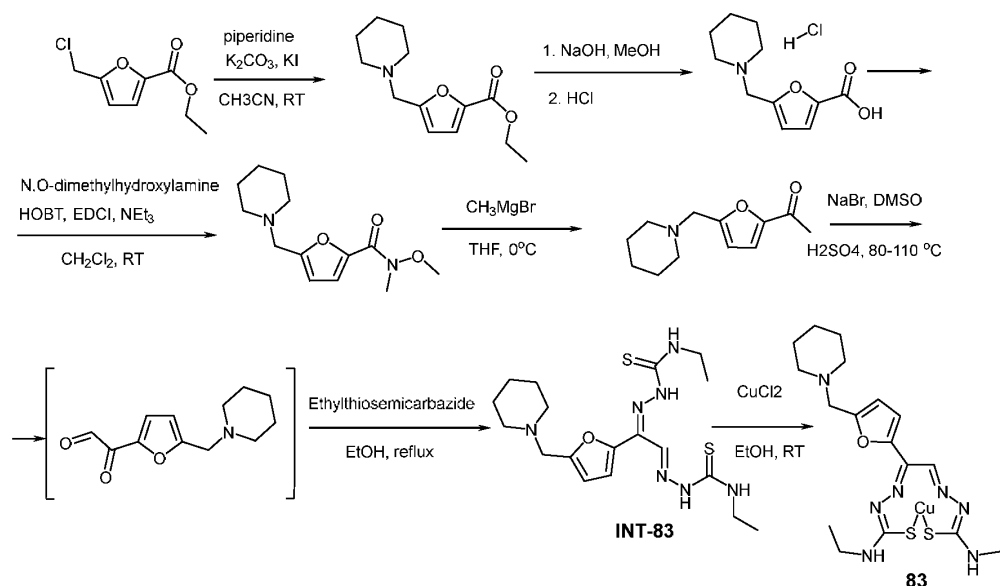
A mixture of 1-(5-((diisopropylamino)methyl)furan-2-yl)ethan-1-one (1.0 g, 4.5 mmol), NaBr (0.46 g, 1 eq), and DMSO (2.5 ml) was heated to 85°C, then H₂SO₄ (3 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and methylthiosemicarbazide (0.94 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2 h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. K₂CO₃ and extracted with EtOAc (3 × 60 ml). The organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular compound. Yield 0.4 g (21.7%). LC-MS 1.12 min, m/z 412.3 [MH]⁺.

Synthesis of Compound 82:

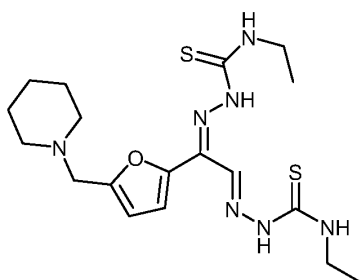


Copper(II) chloride dihydrate (0.041, 1 eq) was added to a stirred solution of **INT-82** (0.1 g, 0.24 mmol) in ethanol. The mixture was stirred for 15h at ambient temperature. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.066 g (57.3%).

Scheme 44: Synthesis of Compound 83

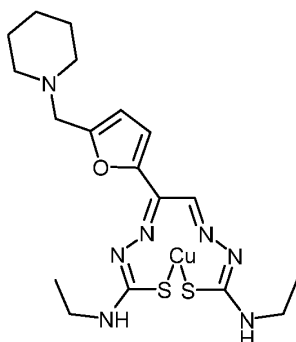


Synthesis of INT-83 ((2E,2'E)-2,2'-(1-(5-(piperidin-1-ylmethyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



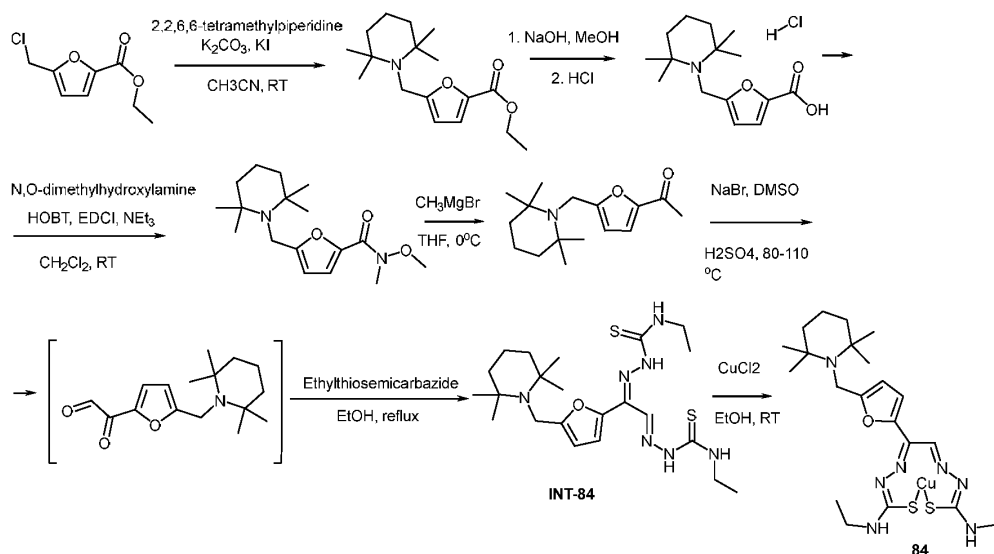
- A mixture of 1-(5-(piperidin-1-ylmethyl)furan-2-yl)ethan-1-one (1.2 g, 5.8 mmol), NaBr (0.6 g, 1 eq), and DMSO (3 ml) was heated to 85°C, then H₂SO₄ (3 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (1.16 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. K₂CO₃ and extracted with EtOAc (3 × 50 ml). The organic layer was separated, dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular product. Yield 0.85 g (34.7%). LC-MS 1.2 min, m/z 424.5 [MH]⁺.

Synthesis of Compound 83:

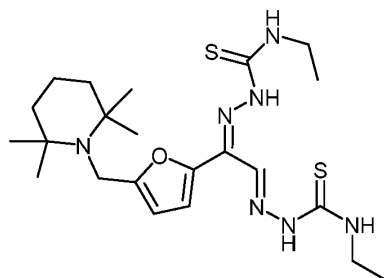


- Copper(II) chloride dihydrate (0.043g, 1 eq) was added to a stirred solution of **INT-83** (0.107 g, 0.25 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.082g (66.8%).

Scheme 45: Synthesis of Compound 84

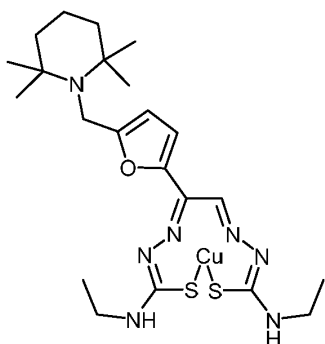


Synthesis of INT-84 ((2E,2'E)-2,2'-(1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



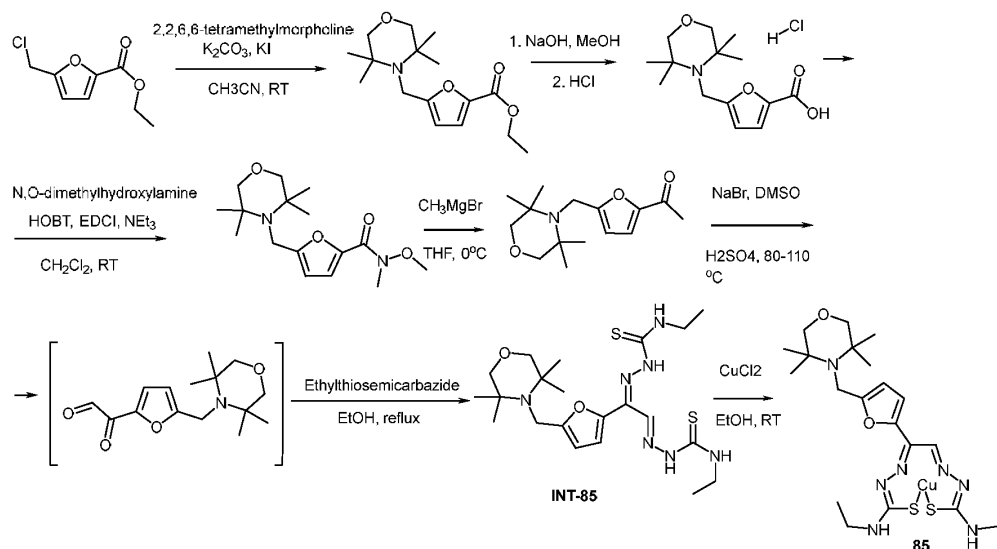
- 5 A mixture of 1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)ethan-1-one (0.9 g, 3.4 mmol), NaBr (0.35 g, 1 eq), and DMSO (1.8 ml) was heated to 85°C, then H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and
- 10 ethylthiosemicarbazide (1.16 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. K₂CO₃ and extracted with EtOAc (3 × 60 ml). The organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular product. Yield 0.6 g (36.6%). LC-MS 1.19 min, m/z 480.6 [MH]⁺.
- 15

Synthesis of Compound 84:

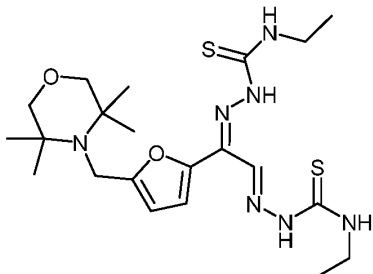


Copper(II) chloride dihydrate (0.068g, 1 eq) was added to a stirred solution of **INT-84** (0.192 g, 4.7 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.08g (37%).

Scheme 46: Synthesis of Compound 85

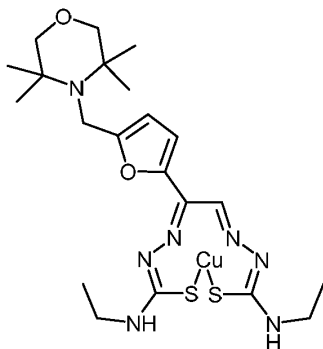


Synthesis of INT-85 ((2E,2'E)-2,2'-(1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



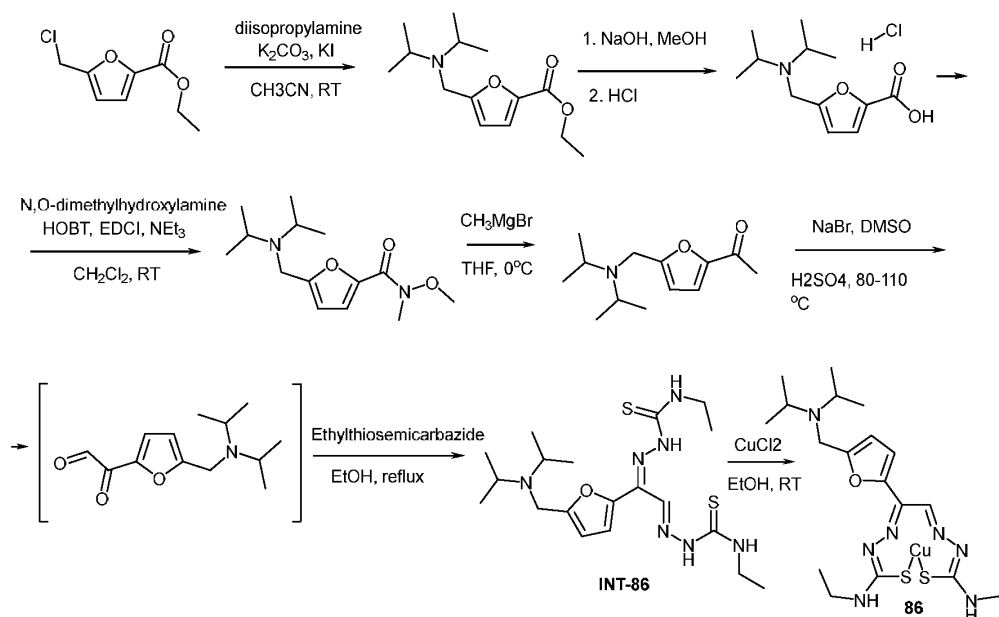
A mixture of 1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)ethan-1-one (0.4 g, 1.5 mmol), NaBr (0.16 g, 1 eq), and DMSO (1 ml) was heated to 85°C, then H₂SO₄ (3 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (0.36 g, 2 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to rt, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq.sat. K₂CO₃ and extracted with EtOAc (3 × 60 ml). The organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated. The residue was treated with water. The formed precipitate was filtered and washed with EtOH to give pure titular product. Yield 0.24 g (32.4%). LC-MS 1.25 min, m/z 482.5 [MH]⁺.

Synthesis of Compound 85:

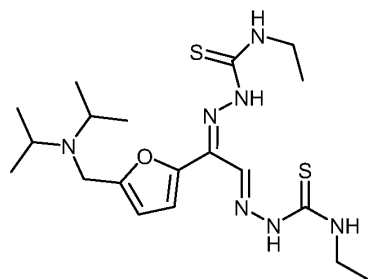


Copper(II) chloride dihydrate (0.053, 1 eq) was added to a stirred solution of **INT-85** (0.15 g, 0.3 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.11 g (65.1%).

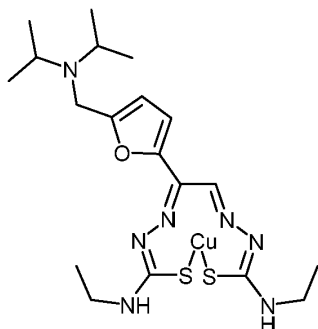
Scheme 47: Synthesis of Compound 86



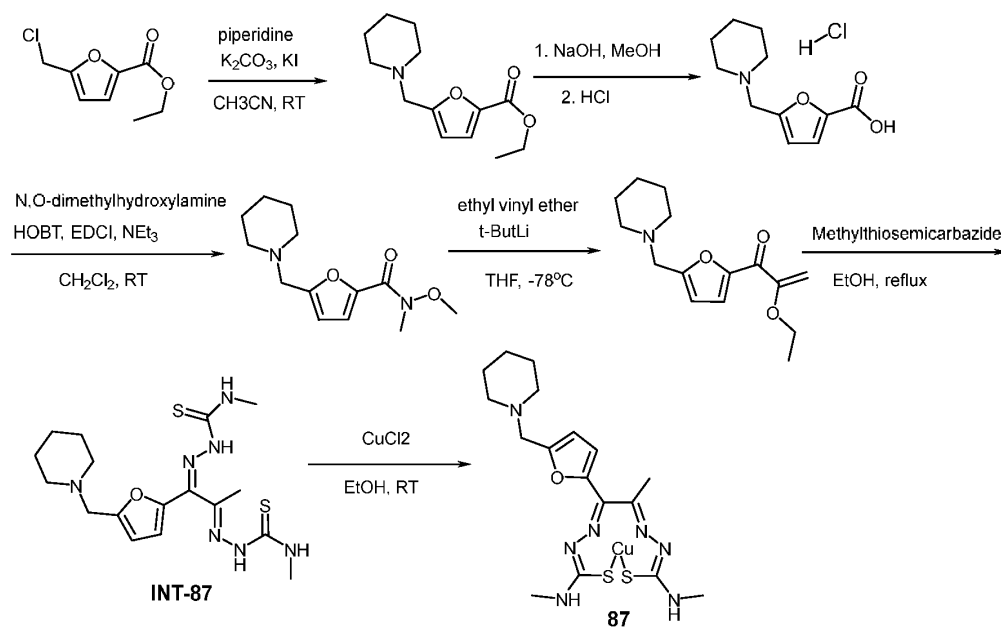
Synthesis of INT-86 ((2E,2'E)-2,2'-(1-(5-((diisopropylamino)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide))):

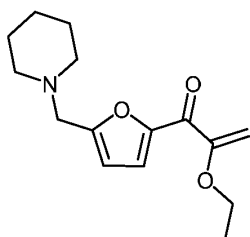


- 5 A mixture of 1-(5-((diisopropylamino)methyl)furan-2-yl)ethan-1-one (1.0 g, 4.5 mmol), NaBr (0.46 g, 1 eq), and DMSO (2.5 ml) was heated to $85^\circ C$, then H_2SO_4 (3 drops) was added (foaming, exothermic). The reaction was heated to $110-115^\circ C$ until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (1.07 g, 2
- 10 eq) was added to the filtrate. The reaction mixture was heated to reflux for 2h, then cooled to room temperature, solvents were evaporated in vacuo, the residue was dissolved in water (25 ml), neutralized with aq. sat. K_2CO_3 and extracted with EtOAc (3×60 ml). The organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. The residue was treated with water. The formed precipitate was filtered and washed
- 15 with EtOH to give pure titular product. Yield 0.5 g (25.4%). LC-MS 1.18 min, m/z 440.7 $[MH]^+$.

Synthesis of Compound 86:

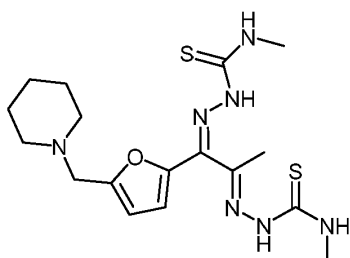
Copper(II) chloride dihydrate (0.049, 1 eq) was added to a stirred solution of **INT-86** (0.126 g, 0.29 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex
 5 precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.063 g (43.8%).

Scheme 48: Synthesis of Compound 87**Synthesis of 2-ethoxy-1-(5-(piperidin-1-ylmethyl)furan-2-yl)prop-2-en-1-one:**



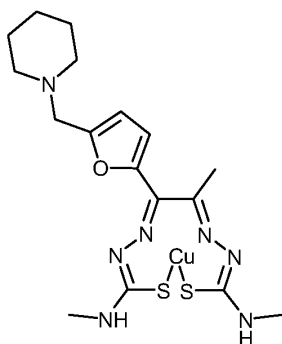
- A solution of ethyl vinyl ether (3.93 g, 5.2 ml, 5.5 eq) in dry THF (100 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 31 ml, 5 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-5-(piperidin-1-ylmethyl)furan-2-carboxamide (2.5g, 9.9 mmol, 1 eq) in THF was added, and then the reaction was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification.
- Yield 2.3 g (88%). LC-MS 1.00 min, m/z 264.1 [MH]⁺.

Synthesis of INT-87 ((2E,2'E)-2,2'-(1-(5-(piperidin-1-ylmethyl)furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



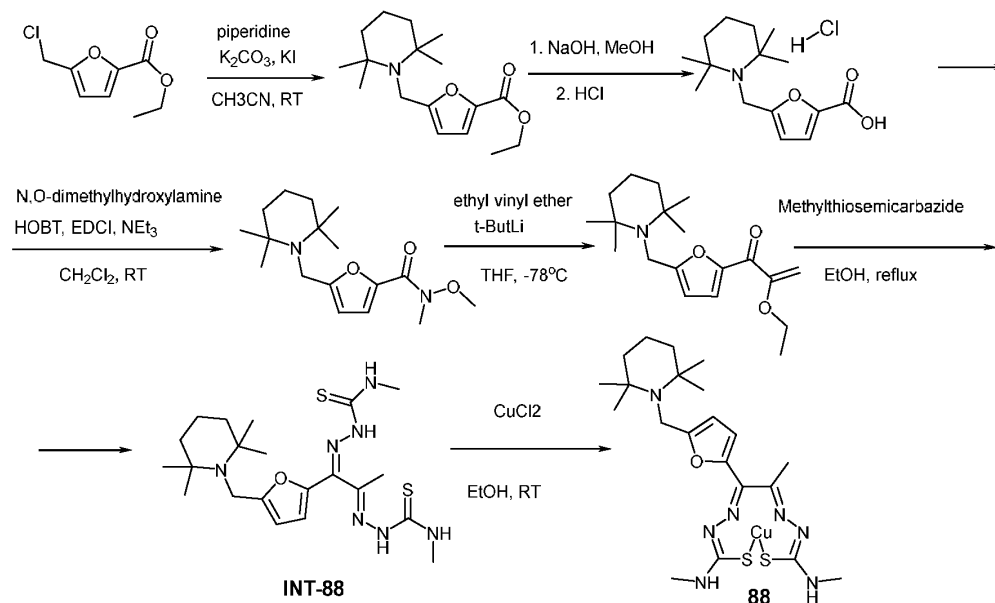
- 2-ethoxy-1-(5-(piperidin-1-ylmethyl)furan-2-yl)prop-2-en-1-one (1.15 g, 4.4 mmol, 1 eq) was dissolved in EtOH (10 ml), methylthiosemicarbazide (0.918 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated for 4h to reflux and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. Yield 1.1g (61.5%). LC-MS 1.04 min, m/z 410.4 [MH]⁺.

Synthesis of Compound 87:

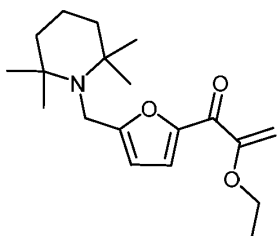


Copper(II) chloride dihydrate (0.183 g, 1.1 eq) was added to **INT-87** (0.4 g, 9.8 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.16 g (34.8 %).

Scheme 49: Synthesis of Compound 88

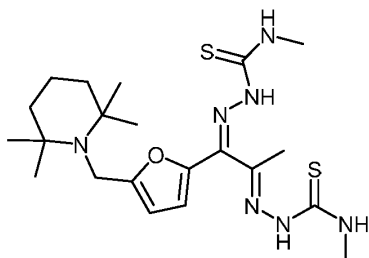


Synthesis of 2-ethoxy-1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)prop-2-en-1-one:



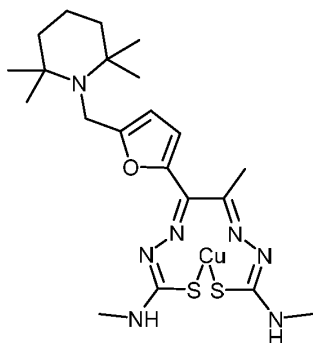
A solution of ethyl vinyl ether (3.65 g, 4.85 ml, 6.6 eq) in dry THF (80 mL) was cooled to -78°C, and *tert*-butyllithium (1.6 M in pentane, 28 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-carboxamide (2.06 g, 7.7 mmol) in THF was added, and the mixture was stirred for 4 h at 0°C. The progress of the reaction was monitored by TLC (hexane/EtOAc 10:1). The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and evaporated. The product was used for the next step without additional purification. Yield 2.09 g (97.5%). LC-MS 0.87 min, m/z 280.7 [MH]⁺.

Synthesis of INT-88 ((2E,2'E)-2,2'-(1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



2-ethoxy-1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)prop-2-en-1-one (1 g, 3.6 mmol) was dissolved in EtOH (50 ml), methylthiosemicarbazide (0.75 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et₂O, and dried. Yield 0.56 g (36.7%). LC-MS 1.08 min, m/z 426.3 [MH]⁺.

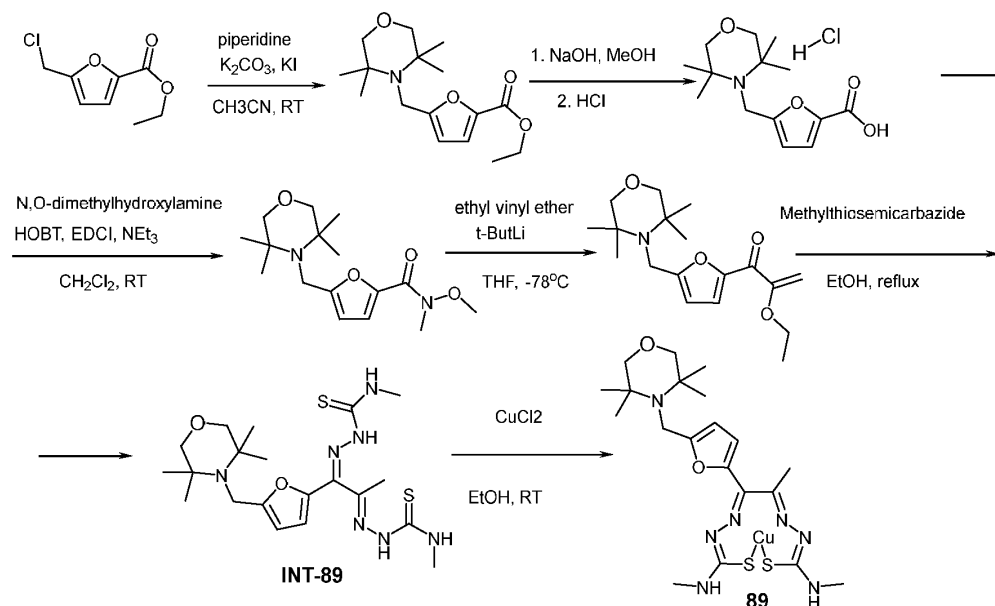
Synthesis of Compound 88:



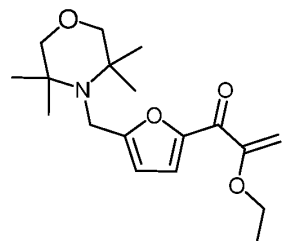
Copper(II) chloride dihydrate (0.049g, 1 eq) was added to **INT-88** (0.126 g, 0.3 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a

red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.063 g (43.8%).

Scheme 50: Synthesis of Compound 89

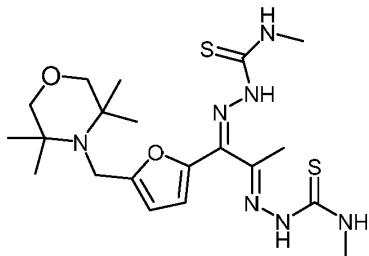


5 Synthesis of 2-ethoxy-1-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)prop-2-en-1-one:



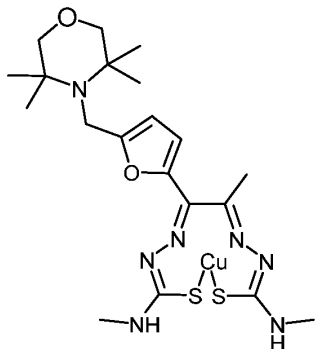
A solution of ethyl vinyl ether (1.53 g, 2.03 ml, 6.6 eq) in dry THF (25 mL) was cooled to -78°C, and *tert*-butyllithium (1.6M in pentane, 12 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of N-methoxy-N-methyl-5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-carboxamide (2 g, 6.4 mmol,) in THF was added, and the mixture was stirred for 4h at 0°C. The progress of the reaction was monitored by TLC (hexane/EtOAc 10:1). The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 1 g (96.5%). LC-MS 1.05 min, m/z 322.8 [MH]⁺.

Synthesis of INT-89 ((2E,2'E)-2,2'-(1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



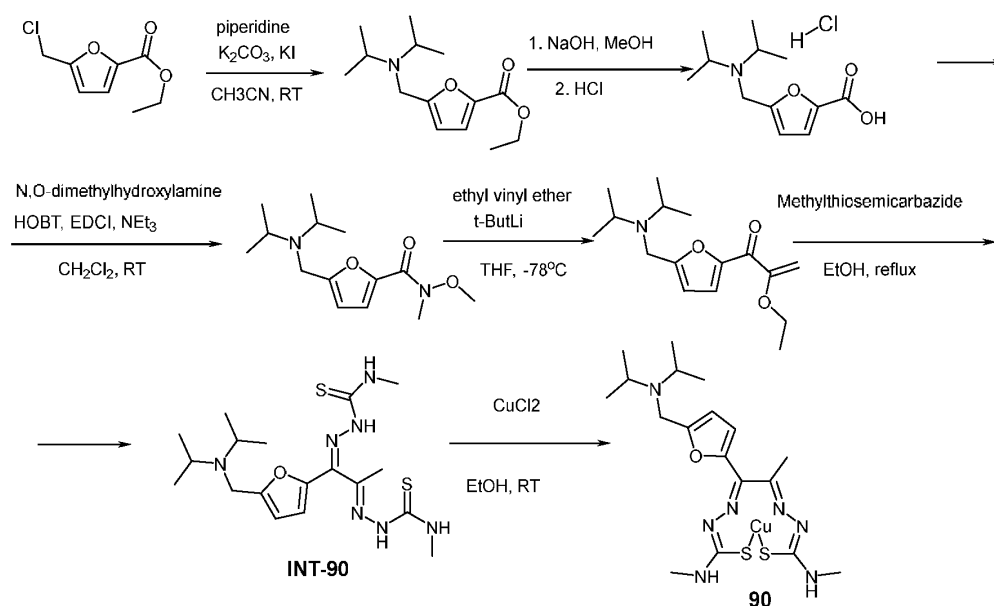
2-ethoxy-1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)prop-2-en-1-one (0.5 g, 1.6 mmol) was dissolved in EtOH (15 ml), methylthiosemicarbazide (0.33 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et₂O, and dried. Yield 0.28 g (38.5%). LC-MS 1.09 min, m/z 468.8 [MH]⁺.

Synthesis of Compound 89:

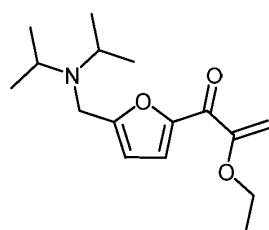


Copper(II) chloride dihydrate (0.05 g, 1 eq) was added to **INT-89** (0.137 g, 0.3 mmol 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.135 g (89.7%).

Scheme 51: Synthesis of Compound 90

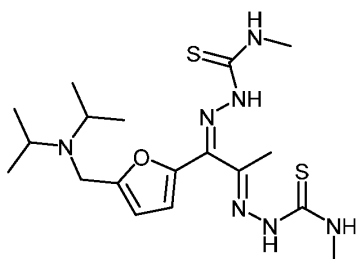


Synthesis of 1-(5-((diisopropylamino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one:



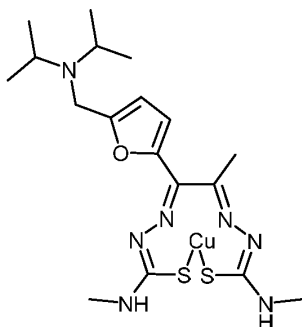
A solution of ethyl vinyl ether (1.53 g, 2.03 ml, 6.6 eq) in dry THF (25 mL) was cooled to -78°C, and *tert*-butyllithium (1.6M in pentane, 12 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of 5-((diisopropylamino)methyl)-N-methoxy-N-methylfuran-2-carboxamide (2 g, 6.4 mmol) in THF was added and mixture was stirred for 4 h at 0°C. The progress of the reaction was monitored by TLC (hexane/EtOAc 10:1). The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhyd. Na₂SO₄, filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 1 g (96.5%). LC-MS 1.05 min, m/z 322.8 [MH]⁺.

Synthesis of INT-90 ((2E,2'E)-2,2'-(1-(5-((diisopropylamino)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



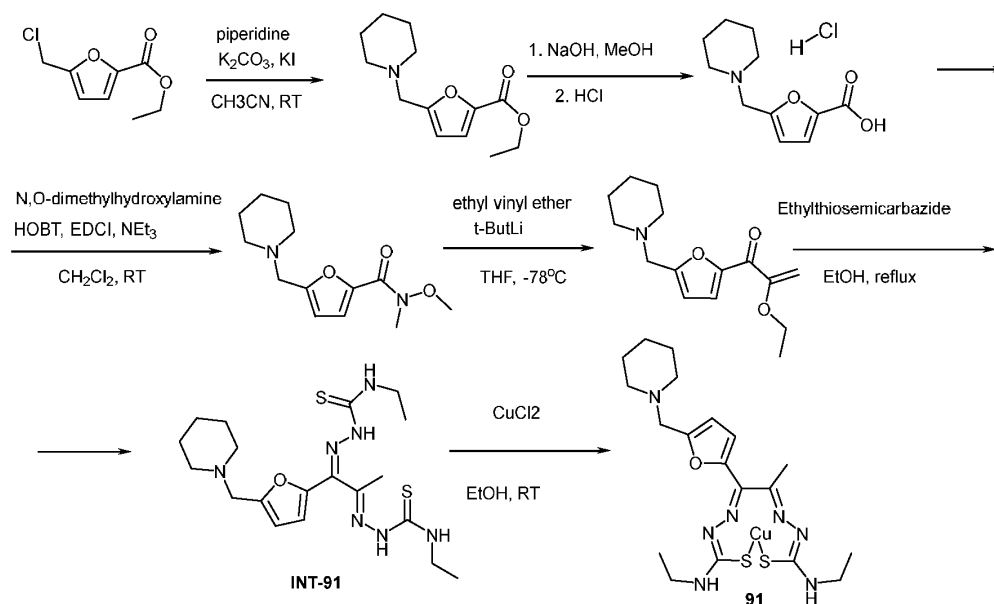
- 1-(5-((diisopropylamino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one (1 g, 3.6 mmol) was dissolved in EtOH (25 ml), methylthiosemicarbazide (0.37 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et₂O, and dried. Yield 0.56 g (36.7%). LC-MS 1.1 min, m/z 426.4 [MH]⁺.

Synthesis of Compound 90:

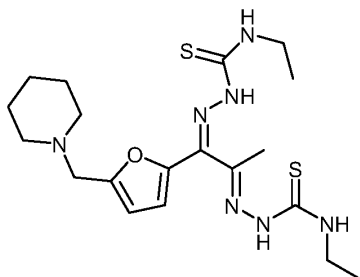


- Copper(II) chloride dihydrate (0.04 g, 1 eq) was added to **INT-90** (0.1 g, 2.4 mmol 1 eq) in ethanol. The mixture was stirred for 15 h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, and diethyl ether, and dried. Yield 0.025 g (21.7%)

Scheme 52: Synthesis of Compound 91

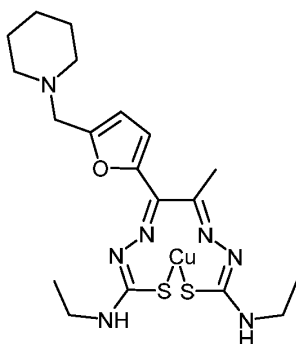


Synthesis of INT-91 ((2E,2'E)-2,2'-(1-(5-(piperidin-1-ylmethyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



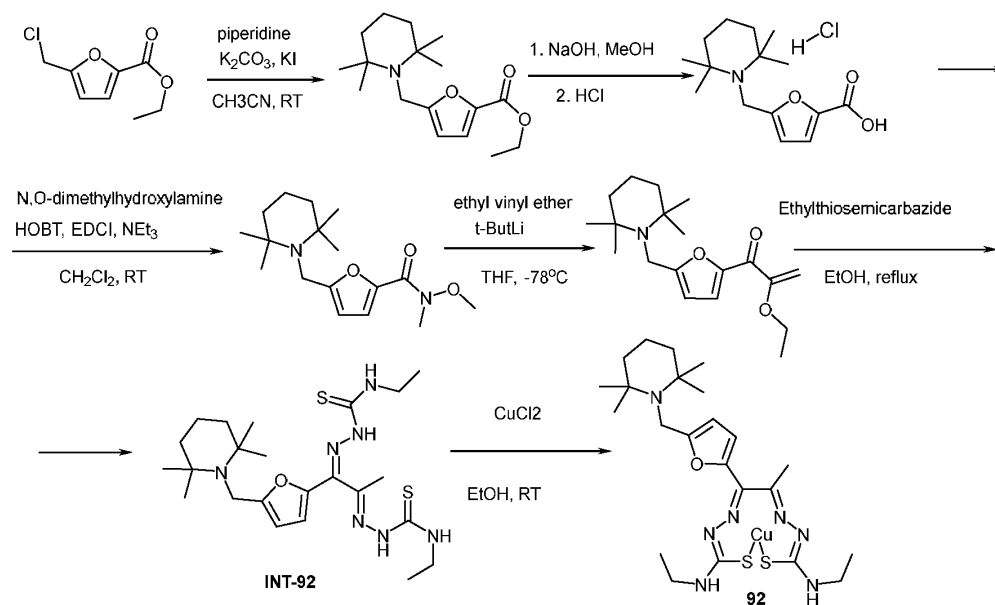
- 5 2-ethoxy-1-(5-(piperidin-1-ylmethyl)furan-2-yl)prop-2-en-1-one (1.15 g, 4.4 mmol, 1 eq) was dissolved in EtOH (10 ml), ethyl thiosemicarbazide (1.04 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, water, Et_2O , and dried. Yield 0.5 g (26.1%). LC-MS 1.27 min, m/z 438.5 $[MH]^+$.

10 **Synthesis of Compound 91:**

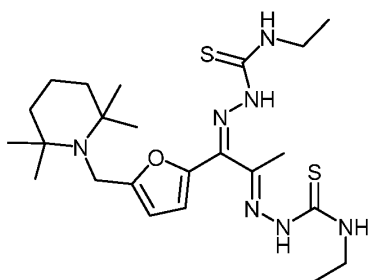


Copper(II) chloride dihydrate (0.214 g, 1.1 eq) was added to **INT-91** (0.5 g, 11.4 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.51 g (89.9 %).

Scheme 53: Synthesis of Compound 92

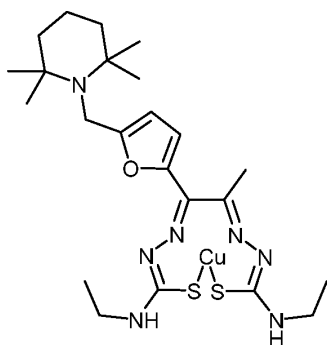


Synthesis of INT-92 ((2*E*,2'*E*)-2,2'-(1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)propane-1,2-diylidene)bis(*N*-ethylhydrazine-1-carbothioamide)):



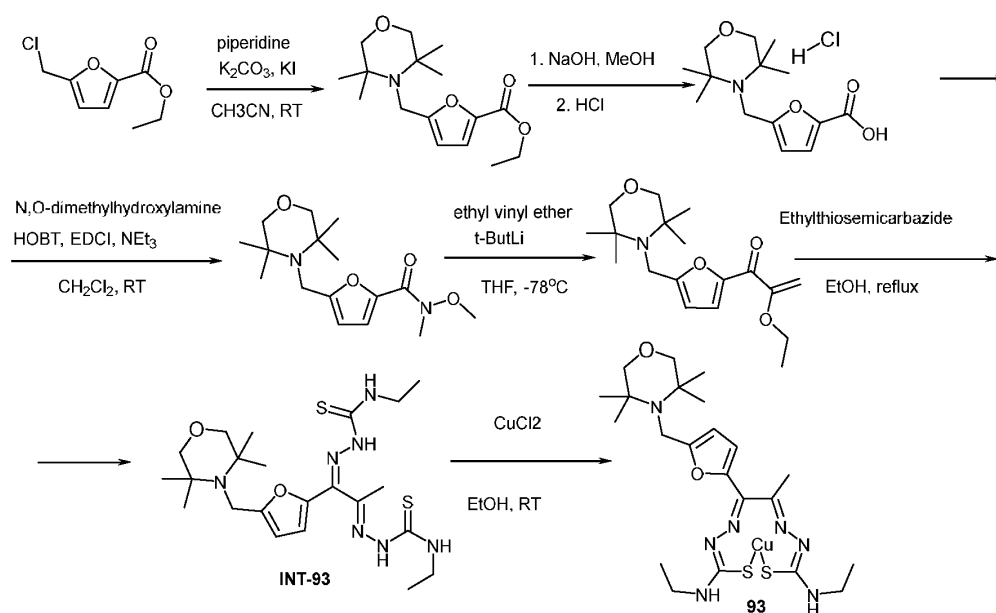
2-ethoxy-1-(5-((2,2,6,6-tetramethylpiperidin-1-yl)methyl)furan-2-yl)prop-2-en-1-one (1 g, 3.1 mmol) was dissolved in EtOH (50 ml), ethyl thiosemicarbazide (0.75 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et₂O, and dried. Yield 0.80 g (51.9%). LC-MS 1.19 min, m/z 494.7 [MH]⁺.

Synthesis of Compound 92:

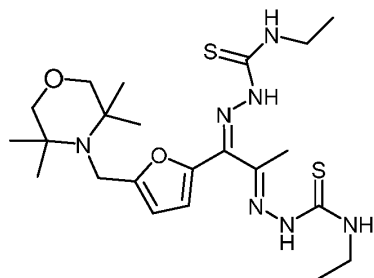


Copper(II) chloride dihydrate (0.24 g, 1 eq) was added to **INT-92** (0.083 g, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.23 g (85.2%)

Scheme 54: Synthesis of Compound 93

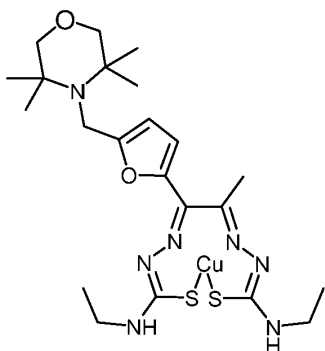


Synthesis of INT-92 ((2E,2'E)-2,2'-(1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



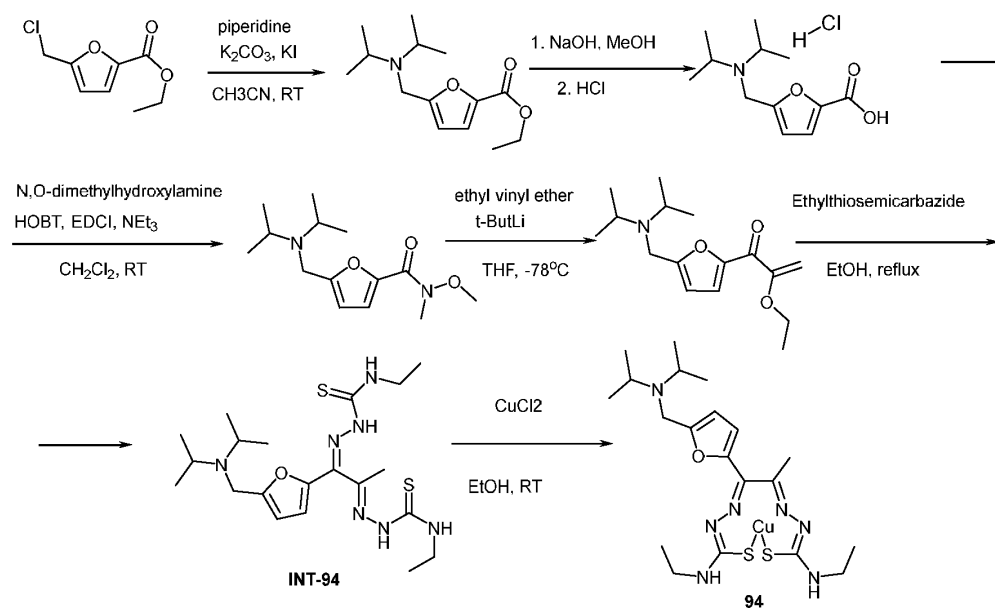
- 5 2-ethoxy-1-(5-((3,3,5,5-tetramethylmorpholino)methyl)furan-2-yl)prop-2-en-1-one (0.5 g, 1.6 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (0.37 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et_2O , and dried. Yield 0.24 g (31.1%). LC-MS 1.26
- 10 min, m/z 496.6 $[MH]^+$.

Synthesis of Compound 93

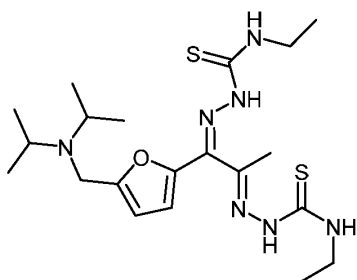


Copper(II) chloride dihydrate (0.04 g, 1 eq) was added to **INT-93** (0.130 g, 0.3 mmol, 1 eq) in ethanol. The mixture was stirred for 15 h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.14 g (98.7%).

Scheme 55: Synthesis of Compound 94

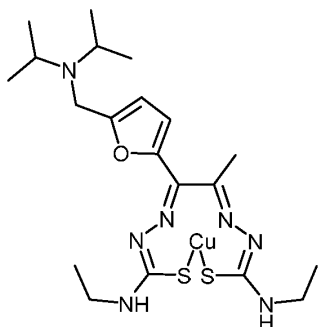


Synthesis of INT-94 ((2*E*,2'*E*)-2,2'-(1-(5-((diisopropylamino)methyl)furan-2-yl)propane-1,2-diylidene)bis(*N*-ethylhydrazine-1-carbothioamide)):



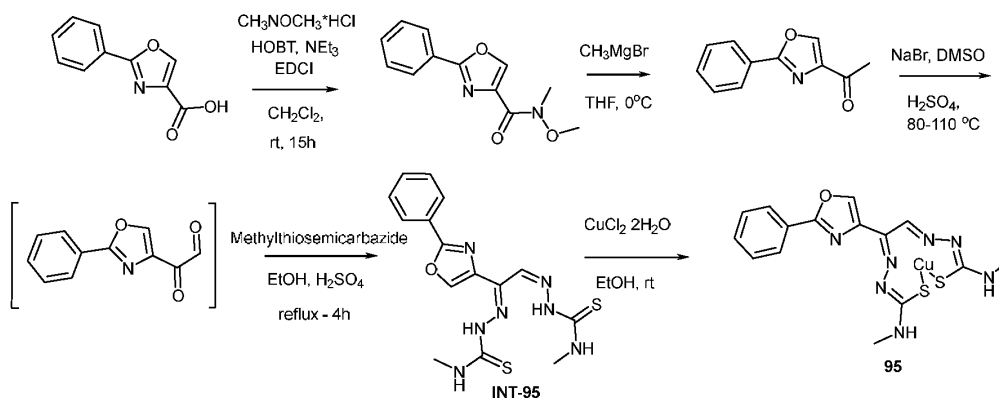
1-(5-((diisopropylamino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one (1 g, 3.6 mmol) was dissolved in EtOH (25 ml), ethyl thiosemicarbazide (0.85 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et₂O, and dried. Yield 0.8 g (49.3%). LC-MS 1.23 min, m/z 454.5 [MH]⁺.

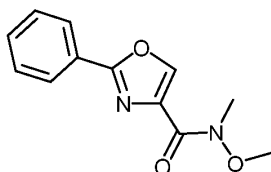
Synthesis of Compound 94:



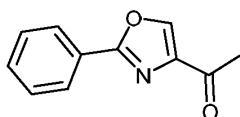
Copper(II) chloride dihydrate (0.05 g, 1 eq) was added to **INT-94** (0.126 g, 0.3 mmol) in ethanol. The mixture was stirred for 15 h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.063 g (43.8%).

Scheme 56: Synthesis of Compound 95

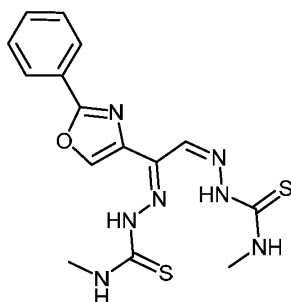


Synthesis of N-methoxy-N-methyl-2-phenyloxazole-4-carboxamide:

To a stirred mixture of 2-phenyloxazole-4-carboxylic acid (3.8 g, 20 mmol), N,O-dimethylhydroxylamine (2.35 g, 1.2 eq), HOBt (3.69 g, 1.2 eq), and triethylamine (6.02 g, 8.9 ml, 3 eq) in DCM (150 ml) at 5°C was added EDCI (4.62 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. Product was used without further purification. Yield 2.46 g (52.7%). LC-MS 1.2 min, m/z 233.1 [MH]⁺.

Synthesis of 1-(2-phenyloxazol-4-yl)ethan-1-one:

A solution of N-methoxy-N-methyl-2-phenyloxazole-4-carboxamide (1.49 g, 6.4 mmol) in THF (40 ml) was cooled to 5°C and methylmagnesium bromide (1.4M in THF, 14 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 0.8 g (66.6%). LC-MS 1.44 min, m/z 188.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 8.31 – 8.10 (m, 2H), 7.89 (s, 1H), 7.57 – 7.42 (m, 3H), 2.68 (s, 3H).

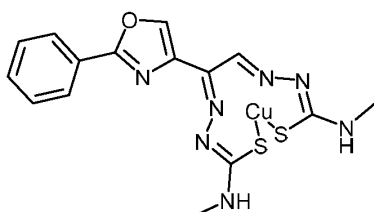
Synthesis of INT-95 ((2Z,2'E)-2,2'-(1-(2-phenyloxazol-4-yl)ethane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

A three-necked flask was charged with SeO₂ (0.26g, 1.1 eq), 1,4-dioxane (7 mL), and water (0.2 mL). The mixture was heated to 50°C and stirred until most of SeO₂ was dissolved. 1-(2-phenyloxazol-4-yl)ethan-1-one (0.4g, 2.1mmol) was added, and the reaction was heated to gentle reflux overnight. Selenium solids precipitated during the course of the

reaction. The mixture was cooled in an ice bath and filtered through diatomaceous earth to remove selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was evaporated to dryness and dissolved in EtOH (20 ml). Methylthiosemicarbazide (0.45 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction was heated to reflux for 4h.

- 5 Formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.13g (16.2%). LC-MS 1.37 min, m/z 376.5 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 11.67 (s, 1H), 10.85 (s, 1H), 8.89 (d, *J* = 4.5 Hz, 1H), 8.76 (s, 1H), 7.80 (s, 1H), 7.56 – 7.32 (m, 5H), 6.88 (d, *J* = 4.7 Hz, 1H), 3.00 (t, *J* = 16.0 Hz, 3H), 2.70 (d, *J* = 4.6 Hz, 3H).

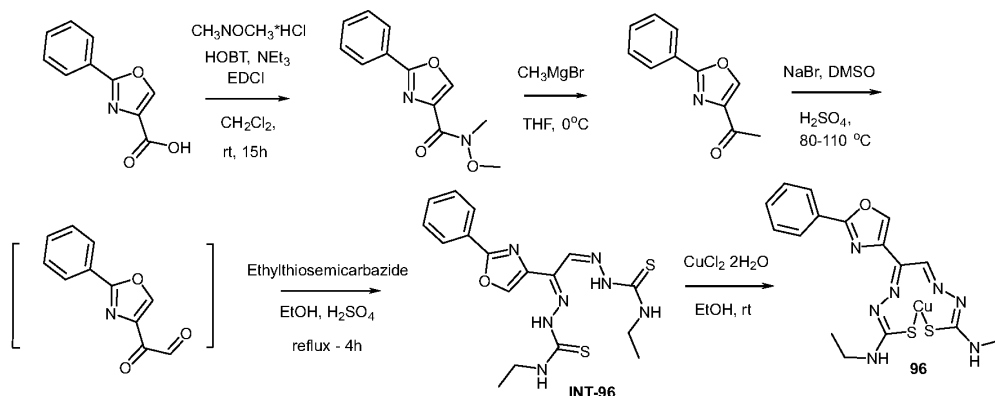
Synthesis of Compound 95:



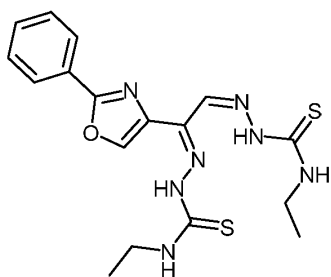
10

Copper(II) chloride dihydrate (0.06g, 1 eq) was added to a stirred solution of **INT-95** (0.13 g, 0.34 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.065g (43%).

15 **Scheme 57: Synthesis of Compound 96**

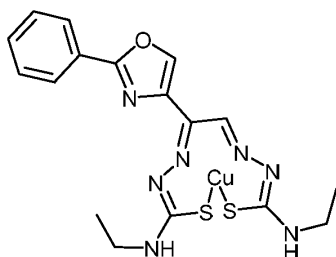


Synthesis of INT-96 ((2Z,2'E)-2,2'-(1-(2-phenyloxazol-4-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide))



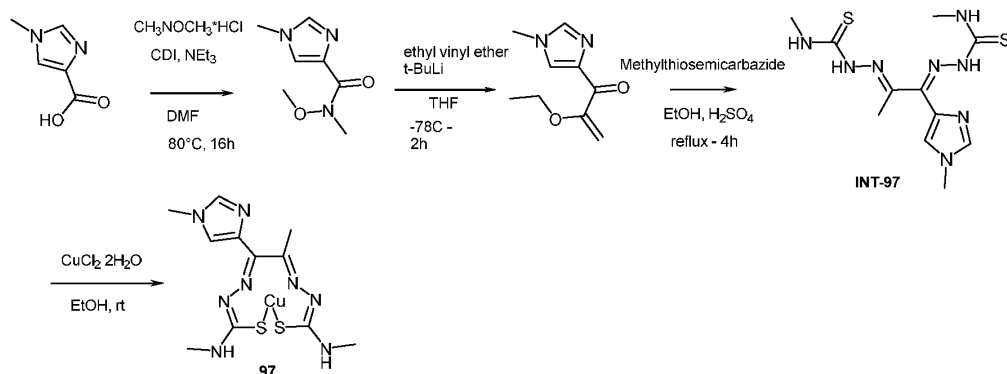
- A three-necked flask was charged with SeO_2 (0.55 g, 1.2 eq), 1,4-dioxane (14 mL), and water (0.4 mL). The mixture was heated to 50°C and stirred until most of SeO_2 dissolves. 1-(2-phenyloxazol-4-yl)ethan-1-one (0.78g, 4.2mmol) was added, and the reaction was heated to gentle reflux overnight. Selenium solids precipitated during the course of the reaction. The mixture was cooled in an ice bath and filtered through diatomaceous earth to remove selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was evaporated to dryness and dissolved in EtOH (40 ml). Ethylthiosemicarbazide (0.99 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h.
- The formed precipitate was filtered, washed with EtOH, aq.sat. Na_2CO_3 , water, Et_2O , and dried. Yield 0.19g (11.3%). LC-MS 1.51 min, m/z 404.6 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6), δ (ppm) : 11.65 (s, 1H), 10.76 (s, 1H), 8.93 (t, $J = 5.7$ Hz, 1H), 8.77 (s, 1H), 7.82 (s, 1H), 7.60 – 7.30 (m, 5H), 6.87 (t, $J = 5.9$ Hz, 1H), 3.67 – 3.53 (m, 2H), 3.29 – 3.19 (m, 2H), 1.16 (t, $J = 7.1$ Hz, 3H), 0.88 (t, $J = 7.1$ Hz, 3H).

Synthesis of Compound 96:

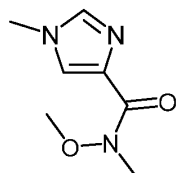


- Copper(II) chloride dihydrate (0.077g, 1 eq) was added to a stirred solution of **INT-96** (0.18 g, 0.45 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried Yield 0.11g (52.2%).

Scheme 58: Synthesis of Compound 97

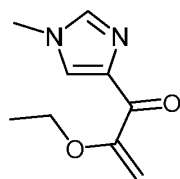


Synthesis of N-methoxy-N,1-dimethyl-1H-imidazole-4-carboxamide:



A mixture of 1-methyl-1H-imidazole-4-carboxylic acid (2.7g, 22 mmol) and 1,1'-carbonyldiimidazole (4.21 g, 1.2 eq) in DMF (100 mL) was stirred at 60°C for 30 min. Then N,O-dimethylhydroxylamine (2.11 g, 1 eq) and triethylamine (2.41 g, 3.3 ml, 1.1 eq) were added. The mixture was stirred at 80°C for 16h, then the volatiles were evaporated in vacuo, and the residue was partitioned between EtOAc and H₂O. The organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluent DCM 100% to DCM/MeOH 98:2 v/v). Yield 1.24g (33.9%). LC-MS 0.64 min, m/z 170.3 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.51 (d, *J* = 20.8 Hz, 1H), 7.45 (s, 1H), 3.73 (t, *J* = 12.7 Hz, 6H), 3.46 (d, *J* = 11.0 Hz, 3H).

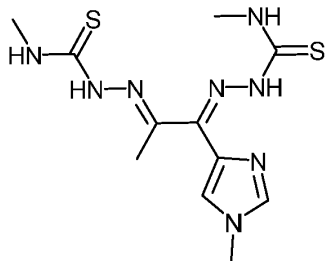
Synthesis of 2-ethoxy-1-(1-methyl-1H-imidazol-4-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (3.4g, 4.5 ml, 6.6 eq) in dry THF (100 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 24 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-N,1-dimethyl-1H-imidazole-4-carboxamide (1.2 g, 7mmol) in THF (15ml) was added, and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄,

filtered, and solvents were evaporated in vacuo. The product was used in the next step without additional purification. Yield 1 g (78.2%). LC-MS 0.76 min, m/z 181.1 [MH]⁺.

Synthesis of INT-97 ((2E,2'E)-2,2'-(1-(1-methyl-1H-imidazol-4-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

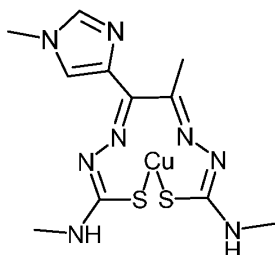


5

2-ethoxy-1-(1-methyl-1H-imidazol-4-yl)prop-2-en-1-one (0.5 g, 2.7 mmol) was dissolved in EtOH (15 ml), methylthiosemicarbazide (0.58 g, 2 eq) and 2 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq. sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.17 g (18.8%). LC-MS 1.11 min, m/z 327.4 [MH]⁺.

10

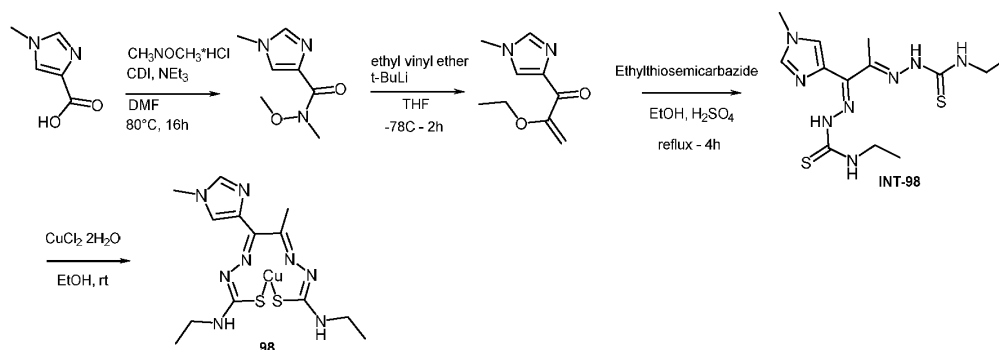
Synthesis of Compound 97:

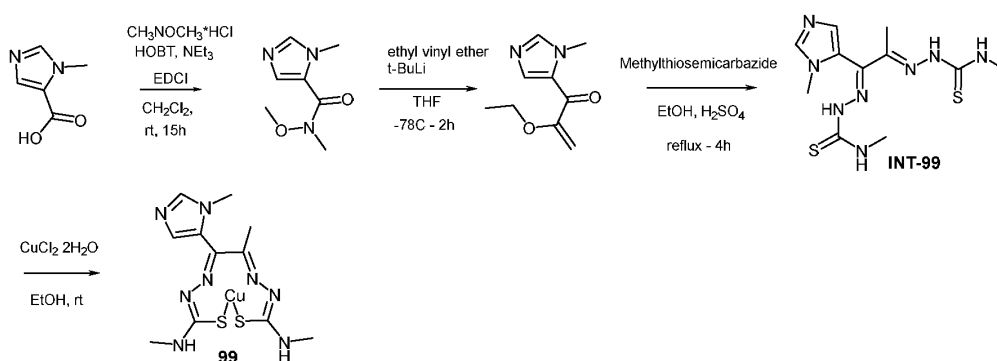


Copper(II) chloride dihydrate (0.1g, 1 eq) was added to a stirred solution of **INT-97** (0.17 g, 0.52 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.043g (21.3%).

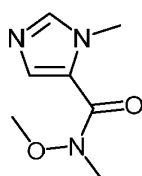
15

Scheme 59: Synthesis of Compound 98



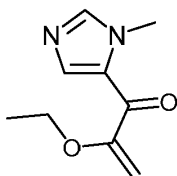


Synthesis of N-methoxy-N,1-dimethyl-1H-imidazole-5-carboxamide:



To a stirred mixture of 1-methyl-1H-imidazole-5-carboxylic acid (1.07 g, 8.4 mmol),
 5 N,O-dimethylhydroxylamine (0.99 g, 1.2 eq), HOBt (1.56 g, 1.2 eq), and triethylamine (2.2 ml, 1.6 g, 2eq) in DCM (50 ml) at 5°C was added EDCI (1.85 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was purified by column chromatography (silica gel, eluent 100% DCM to DCM/MeOH 99:1). Yield
 10 0.6 g (41.8%). LC-MS 0.38 min, m/z 169.9 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.75 (s, 1H), 7.55 (d, J = 19.3 Hz, 1H), 3.96 – 3.89 (m, 3H), 3.78 – 3.64 (m, 3H), 3.38 – 3.28 (m, 3H).

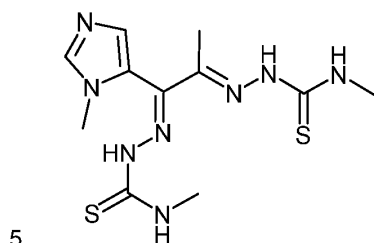
Synthesis of 2-ethoxy-1-(1-methyl-1H-imidazol-5-yl)prop-2-en-1-one:



15 A solution of ethyl vinyl ether (1.57 g, 2.1 ml, 6.6 eq) in dry THF (20 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 12 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-N,1-dimethyl-1H-imidazole-5-carboxamide (0.56 g, 7mmol) in THF (15ml) was added, and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml)
 20 and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄,

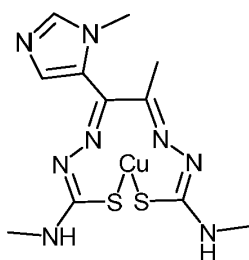
filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 0.5 g (83.8%). LC-MS 0.91 min, m/z 180.9 [MH]⁺.

Synthesis of INT-99 ((2E,2'E)-2,2'-(1-(1-methyl-1H-imidazol-5-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



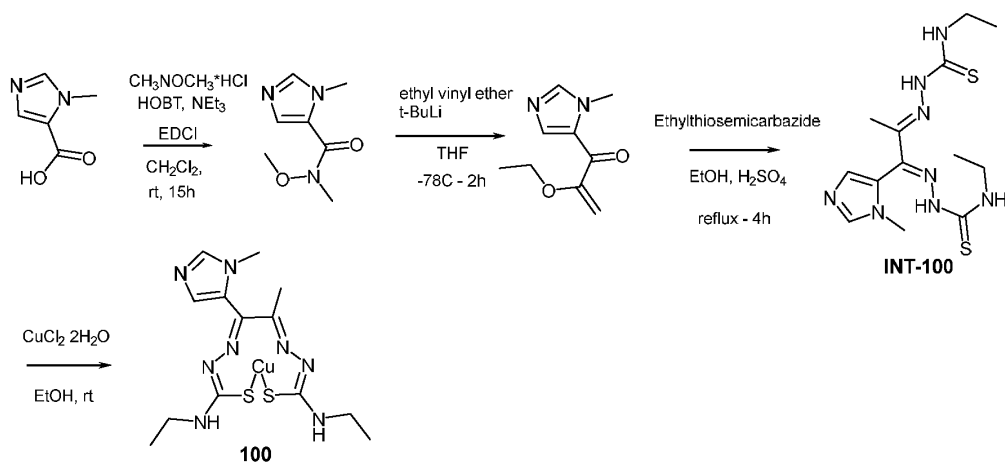
2-ethoxy-1-(1-methyl-1H-imidazol-5-yl)prop-2-en-1-one (0.25 g, 1.4 mmol) was dissolved in EtOH (15 ml), methylthiosemicarbazide (0.29 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.073 g (16.1%). LC-MS 0.91 min, m/z 327.1 [MH]⁺.

Synthesis of Compound 99:

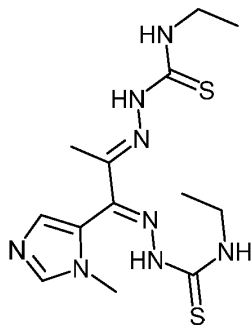


Copper(II) chloride dihydrate (0.038g, 1 eq) was added to a stirred solution of **INT-99** (0.073 g, 0.22 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.07g (80.5%).

Scheme 61: Synthesis of Compound 100

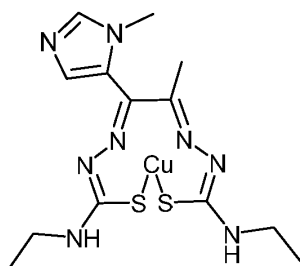


Synthesis of INT-100 ((2E,2'E)-2,2'-(1-(1-methyl-1H-imidazol-5-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



- 5 2-ethoxy-1-(1-methyl-1H-imidazol-5-yl)prop-2-en-1-one (0.25 g, 1.4 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (0.33 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.13 g (26.4%). LC-MS 1.04 min, m/z 355.5 [MH]⁺.

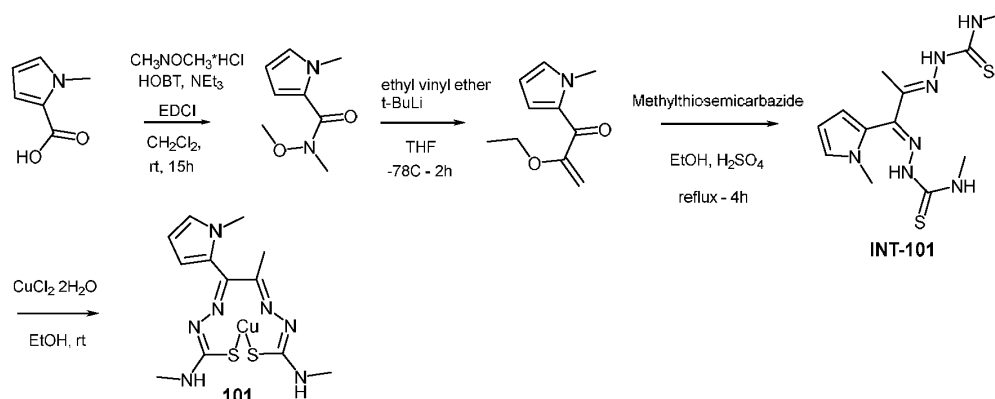
10 **Synthesis of Compound 100:**



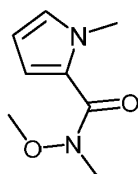
Copper(II) chloride dihydrate (0.062g, 1 eq) was added to a stirred solution of **INT-100** (0.13 g, 0.36 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed

complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.073g (47.8%).

Scheme 62: Synthesis of Compound 101

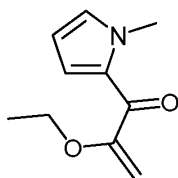


5 Synthesis of N-methoxy-N,1-dimethyl-1H-pyrrole-2-carboxamide:



To a stirred mixture of 1-methyl-1H-pyrrole-2-carboxylic acid (5.4 g, 43.1 mmol), N,O-dimethylhydroxylamine (5.05 g, 1.2 eq), HOBT (7.93 g, 1.2 eq) and Triethylamine (12 ml, 8.7 g, 2eq) in DCM (200 ml) at 5°C was added EDCI (9.93 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Product was used without further purification. Yield 6.5 g (80.5%). LC-MS 0.38 min, m/z 169.9 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 6.93 (dd, $J = 4.0, 1.7$ Hz, 1H), 6.86 – 6.60 (m, 1H), 6.13 (dd, $J = 4.0, 2.6$ Hz, 1H), 3.92 (s, 3H), 3.71 (s, 3H), 3.34 (s, 3H).

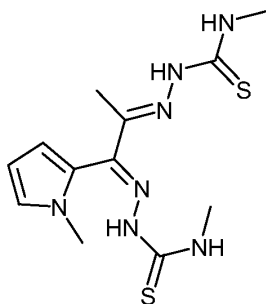
15 Synthesis of 2-ethoxy-1-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (4.53 g, 6 ml, 6.6 eq) in dry THF (80 ml) was cooled to -78°C , and *tert*-butyllithium (1.7M in pentane, 33 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C . A solution of N-methoxy-N,1-dimethyl-1H-pyrrole-2-carboxamide (1.6 g, 9.5 mmol) in THF (25ml) was

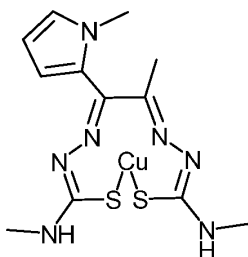
added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.64 g (96.2%).

5 **Synthesis of INT-101 ((2E,2'E)-2,2'-(1-(1-methyl-1H-pyrrol-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):**



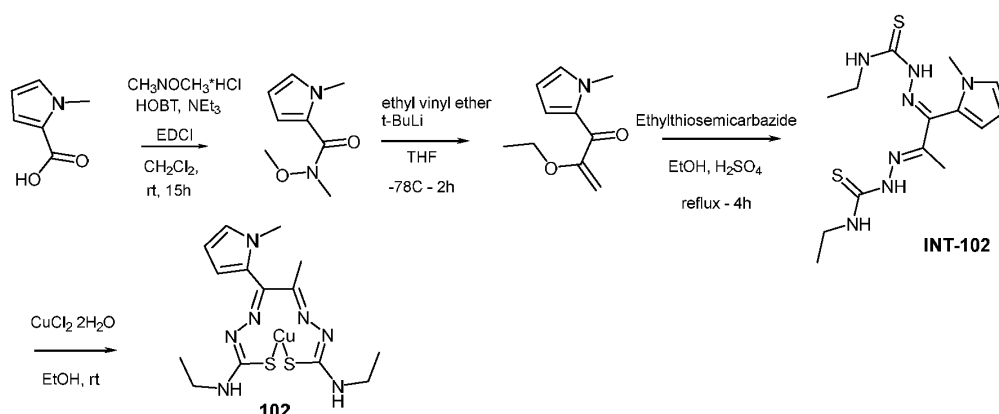
2-ethoxy-1-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (0.82 g, 4.6 mmol) was dissolved in EtOH (15 ml), methylthiosemicarbazide (0.96 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The solvent was evaporated in vacuo. The residue was dissolved in EtOAc and washed with aq.sat. NaHCO₃, water, dried with anh. Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CCl₄/EtOAc 7:3). Yield 0.22 g (14.5%). LC-MS 1.34 min, m/z 326.5 [MH]⁺.

15 **Synthesis of Compound 101:**

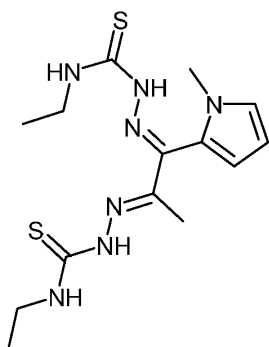


Copper(II) chloride dihydrate (0.12g, 1 eq) was added to a stirred solution of **INT-101** (0.22 g, 0.66 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.22 g (84.1%).

Scheme 63: Synthesis of Compound 102

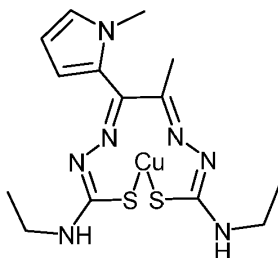


Synthesis of INT-102 ((2E,2'E)-2,2'-(1-(1-methyl-1H-pyrrol-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



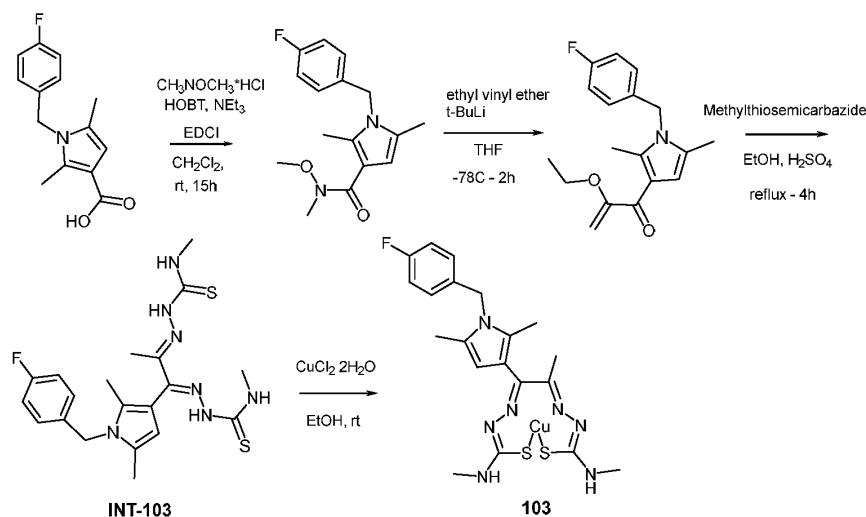
- 5 2-ethoxy-1-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (0.82 g, 4.6 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (1.1 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The solvent was evaporated in vacuo. The residue was dissolved in EtOAc and washed with aq. sat. NaHCO₃, water, dried with anh. Na₂SO₄ and concentrated under reduced
- 10 pressure. The residue was purified by column chromatography (silica gel, eluent CCl₄/EtOAc 7:3). Yield 0.13 g (8.03%). LC-MS 1.56 min, m/z 354.3 [MH]⁺.

Synthesis of Compound 102:

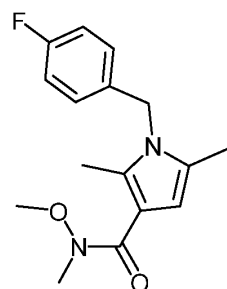


Copper(II) chloride dihydrate (0.06 g, 1 eq) was added to a stirred solution of **INT-102** (0.13 g, 0.37 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder; precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.13 g (91%).

5 **Scheme 64: Synthesis of Compound 103**

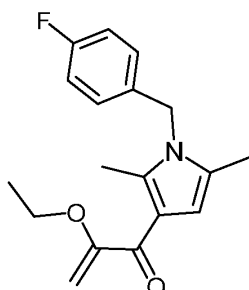


Synthesis of 1-(4-fluorobenzyl)-N-methoxy-N,2,5-trimethyl-1H-pyrrole-3-carboxamide:



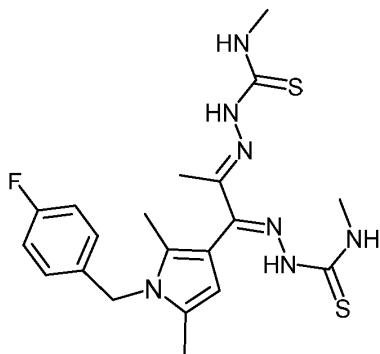
- To a stirred mixture of 1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid (5.1 g, 20.6 mmol), N,O-dimethylhydroxylamine (2.41 g, 1.2 eq), HOBt (3.8 g, 1.2 eq), and triethylamine (5.7 ml, 6.3 g, 2eq) in DCM (200 ml) at 5°C was added EDCI (4.74 g, 1.2 eq) and reaction was then stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent hexane/EtOAc 2:1). Yield 2.8 g (46.8%). LC-MS 1.51 min, m/z 291.3 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 6.99 (d, J = 6.3 Hz, 2H), 6.87 (s, 2H), 6.32 (s, 1H), 5.01 (s, 2H), 3.80 – 3.61 (m, 3H), 3.46 – 3.13 (m, 3H), 2.41 (s, 3H), 2.13 (s, 3H).

Synthesis of 2-ethoxy-1-(1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (1.97 g, 2.61 ml, 6.6 eq) in dry THF (50 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 14 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of 1-(4-fluorobenzyl)-N-methoxy-N,2,5-trimethyl-1H-pyrrole-3-carboxamide (1.2 g, 4.1 mmol) in THF (25ml) was added and stirring continued for 4 h at 0°C. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.2 g (96.3%). LC-MS 1.70 min, m/z 302.3 [MH]⁺.

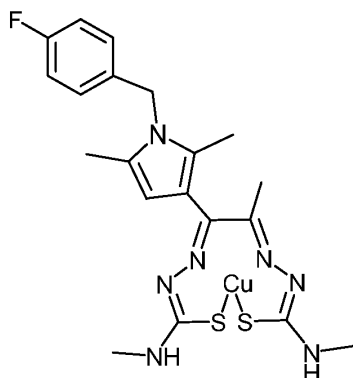
Synthesis of INT-103 ((2*E*,2'*E*)-2,2'-(1-(1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(*N*-methylhydrazine-1-carbothioamide)):



2-ethoxy-1-(1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (0.6 g, 2 mmol) was dissolved in EtOH (15 ml), methylthiosemicarbazide (0.42 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.32 g (35.9%). LC-MS 1.68 min, m/z 448.1 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 10.58 (s, 1H), 8.99 (s, 1H), 8.62 (d, *J* = 4.4 Hz, 1H), 7.37 (d, *J* = 4.5 Hz, 1H), 7.17 (t, *J* = 8.8 Hz, 2H), 7.07 – 6.83 (m, 2H), 5.86 (s, 1H), 5.16

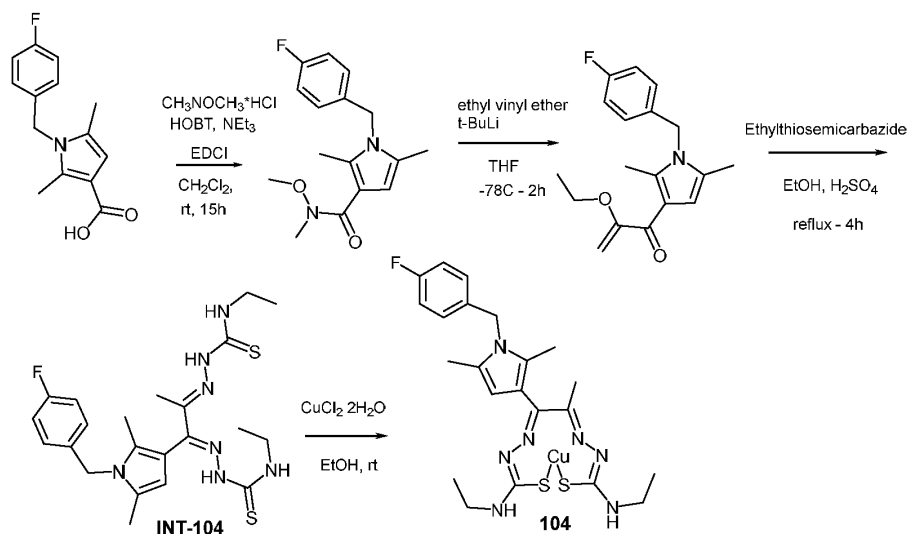
(s, 2H), 3.03 (d, $J = 4.5$ Hz, 3H), 2.86 (d, $J = 4.7$ Hz, 3H), 2.32 (s, 3H), 2.16 (s, 3H), 1.87 (s, 3H).

Synthesis of Compound 103:



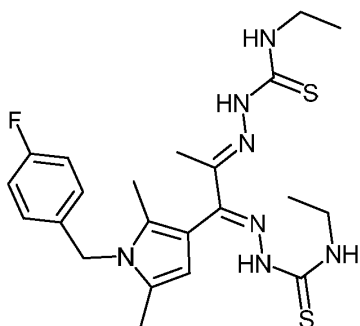
- 5 Copper(II) chloride dihydrate (0.12g, 1 eq) was added to a stirred solution of **INT-103** (0.32 g, 0.7 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.31 g (86.5%).

Scheme 65: Synthesis of Compound 104



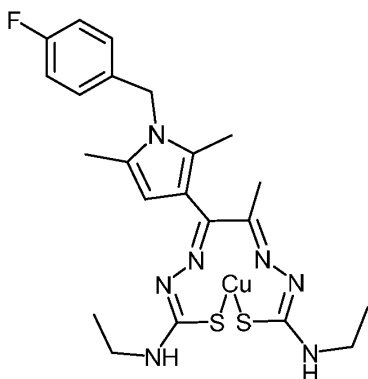
10

Synthesis of INT-104 ((2E,2'E)-2,2'-(1-(1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



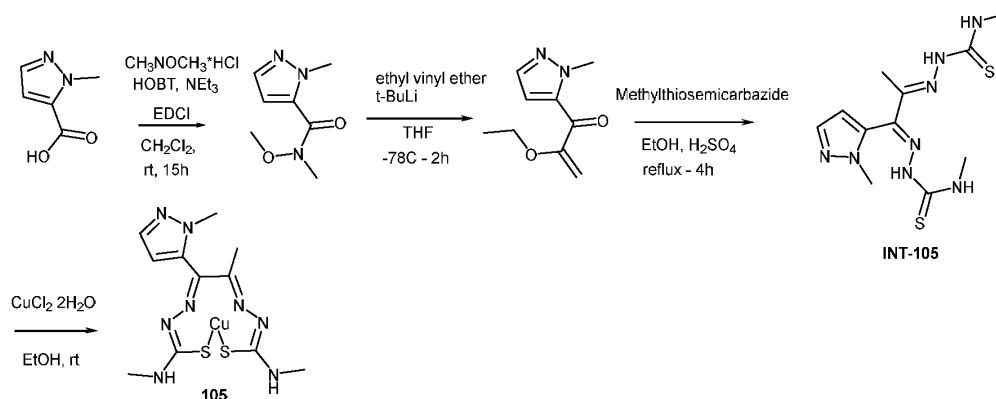
- 2-ethoxy-1-(1-(4-fluorobenzyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (0.6 g, 2 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (0.47 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.24 g (25.3%). LC-MS 1.83 min, m/z 476.5 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 10.58 – 10.25 (m, 1H), 8.90 (s, 1H), 8.67 (t, J = 5.9 Hz, 1H), 7.37 (s, 1H), 7.17 (t, J = 8.8 Hz, 2H), 7.07 – 6.87 (m, 2H), 5.87 (s, 1H), 5.16 (s, 2H), 3.67 – 3.54 (m, 2H), 3.40 (dd, J = 13.5, 7.0 Hz, 2H), 2.32 (s, 3H), 2.12 (d, J = 20.2 Hz, 3H), 1.89 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H).

Synthesis of Compound 104:

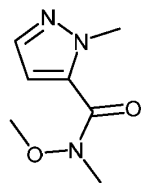


- Copper(II) chloride dihydrate (0.085g, 1 eq) was added to a stirred solution of **INT-104** (0.24 g, 0.5 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.12 g (43%).

Scheme 66: Synthesis of Compound 105

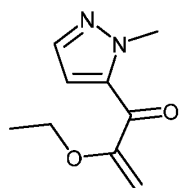


Synthesis of *N*-methoxy-*N*,1-dimethyl-1*H*-pyrazole-5-carboxamide



To a stirred mixture of 1-methyl-1*H*-pyrazole-5-carboxylic acid (4.87 g, 38.6 mmol), *N*,*O*-dimethylhydroxylamine (4.52 g, 1.2 eq), HOBT (6.26 g, 1.2 eq), and triethylamine (13.6 ml, 9.88 g, 2.5eq) in DCM (200 ml) at 5°C was added EDCI (8.88 g, 1.2 eq) and reaction was then stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The product was used without further purification. Yield 6.45 g (98.7%). LC-MS 0.86 min, m/z 170.4 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 7.47 (d, $J = 2.0$ Hz, 1H), 6.76 (d, $J = 2.0$ Hz, 1H), 4.12 (s, 3H), 3.67 (d, $J = 11.4$ Hz, 3H), 3.35 (s, 3H).

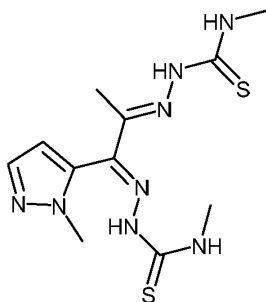
Synthesis of 2-ethoxy-1-(1-methyl-1*H*-pyrazol-5-yl)prop-2-en-1-one



A solution of ethyl vinyl ether (2.25 g, 3 ml, 3.3 eq) in dry THF (100 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 17.5 ml, 3 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of *N*-methoxy-*N*,1-dimethyl-1*H*-pyrazole-5-carboxamide (1.6 g, 9.5 mmol) in THF (25ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH_4Cl (100ml) and extracted with Et_2O (3x100ml). The combined extracts were dried over anhydrous Na_2SO_4 ,

filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.7 g (99%). LC-MS 1.29 min, m/z 181.1 [MH]⁺.

Synthesis of INT-105 ((2E,2'E)-2,2'-(1-(1-methyl-1H-pyrazol-5-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):

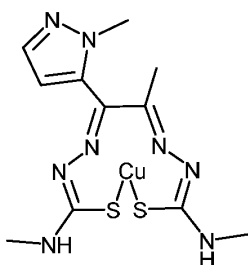


5

2-ethoxy-1-(1-methyl-1H-pyrazol-5-yl)prop-2-en-1-one (1.7 g, 9.5 mmol) was dissolved in EtOH (50 ml), methylthiosemicarbazide (2 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq. sat. Na₂CO₃, water, Et₂O, and dried. Yield 1.81 g (58.6%). LC-MS 1.17 min, m/z 327.5 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 10.70 (s, 1H), 9.43 (s, 1H), 8.75 (d, J = 4.5 Hz, 1H), 7.61 (d, J = 1.9 Hz, 1H), 7.09 (d, J = 4.6 Hz, 1H), 6.41 (d, J = 1.9 Hz, 1H), 3.57 (s, 3H), 3.02 (t, J = 11.5 Hz, 3H), 2.89 (t, J = 4.7 Hz, 3H), 2.37 (s, 3H).

10

Synthesis of Compound 105:

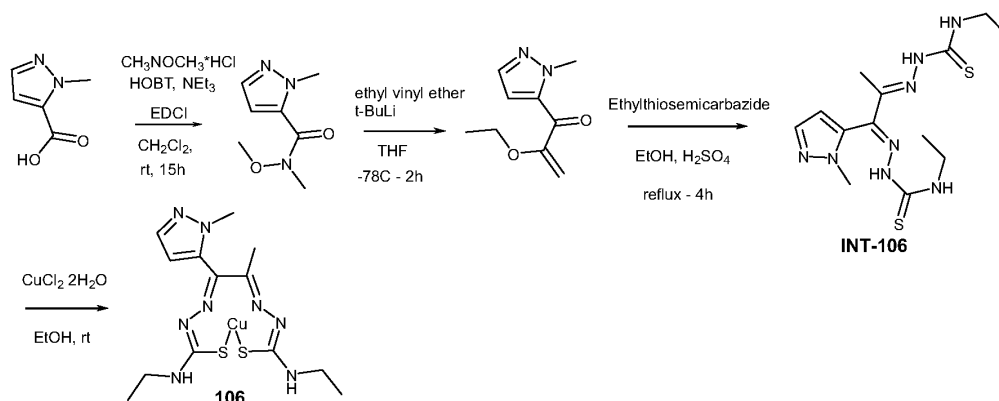


15

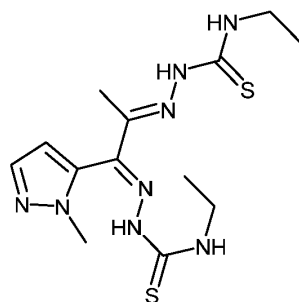
Copper(II) chloride dihydrate (0.19g, 1 eq) was added to a stirred solution of **INT-105** (0.36 g, 1.1 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.38 g (87%).

20

Scheme 67: Synthesis of Compound 106

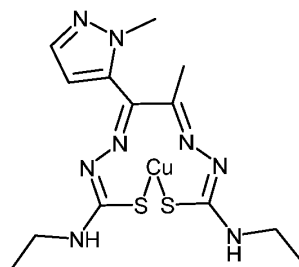


Synthesis of INT-106 ((2E,2'E)-2,2'-(1-(1-methyl-1H-pyrazol-5-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



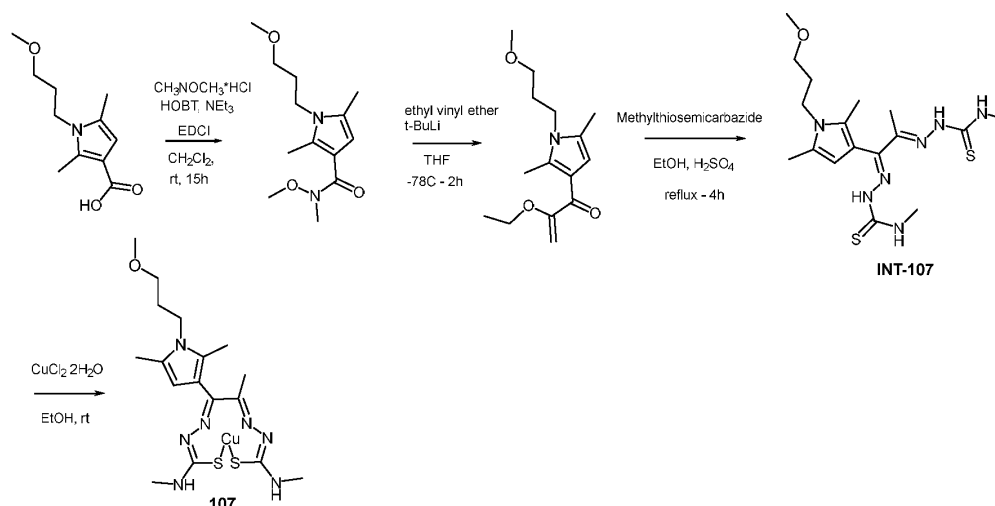
- 5 2-ethoxy-1-(1-methyl-1H-pyrazol-5-yl)prop-2-en-1-one (2.3 g, 12.9 mmol) was dissolved in EtOH (75 ml), methylthiosemicarbazide (2 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 1.81 g (58.6%). LC-MS 1.34 min, m/z 355.4 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 10.82 (s, 1H), 9.50 (s, 1H), 8.78 (s, 1H), 7.82 – 7.43 (m, 1H), 6.94 (s, 1H), 6.58 – 6.13 (m, 1H), 3.74 – 3.53 (m, 5H), 3.45 – 3.27 (m, 2H), 2.44 – 2.03 (m, 3H), 1.34 – 1.05 (m, 3H), 1.07 – 0.78 (m, 3H).
- 10

Synthesis of Compound 106:

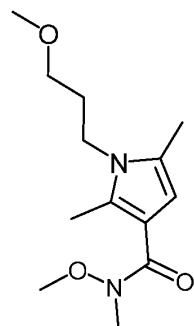


Copper(II) chloride dihydrate (0.11g, 1 eq) was added to a stirred solution of **INT-106** (0.22 g, 0.6 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.12g (44.9%).

5 **Scheme 68: Synthesis of Compound 107**

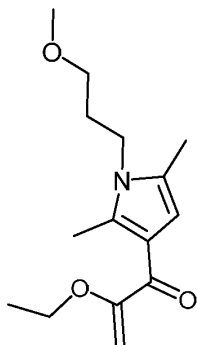


Synthesis of *N*-methoxy-1-(3-methoxypropyl)-*N*,2,5-trimethyl-1*H*-pyrrole-3-carboxamide:



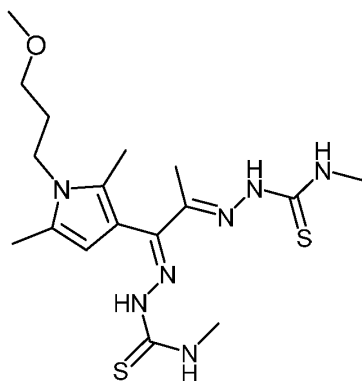
- 10 To a stirred mixture of 1-(3-methoxypropyl)-2,5-dimethyl-1*H*-pyrrole-3-carboxylic acid (5 g, 23.7 mmol), *N*,*O*-dimethylhydroxylamine (2.77 g, 1.2 eq), HOBt (3.84 g, 1.2 eq), and triethylamine (8.5 ml, 6.11 g, 2.5eq) in DCM (200 ml) at 5°C was added EDCI (5.44 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure.
- 15 The residue was purified by column chromatography (silica gel, $\text{CCl}_4/\text{EtOAc}$ from 8:2 to 1:3). Yield 3.7 g (61.5%). LC-MS 1.26 min, m/z 255.6 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 6.32 (d, $J = 0.9$ Hz, 1H), 4.02 – 3.80 (m, 2H), 3.44 – 3.26 (m, 5H), 2.55 (s, 3H), 2.22 (s, 3H), 1.98 – 1.74 (m, 2H).

Synthesis of 2-ethoxy-1-(1-(3-methoxypropyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one:

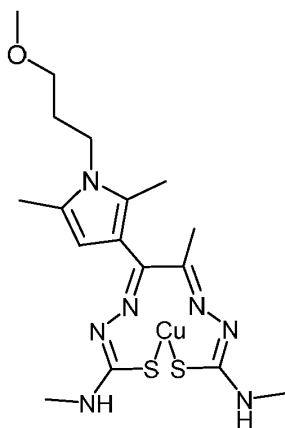


5 A solution of ethyl vinyl ether (1.68 g, 2.2 ml, 3.3 eq) in dry THF (100 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 13.2 ml, 3 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-1-(3-methoxypropyl)-N,2,5-trimethyl-1H-pyrrole-3-carboxamide (1.8 g, 7 mmol) in THF (25ml) was added and stirring continued for 4 h at 0°C. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried
10 over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.74 g (92%). LC-MS 1.51 min, m/z 266.4 [MH]⁺.

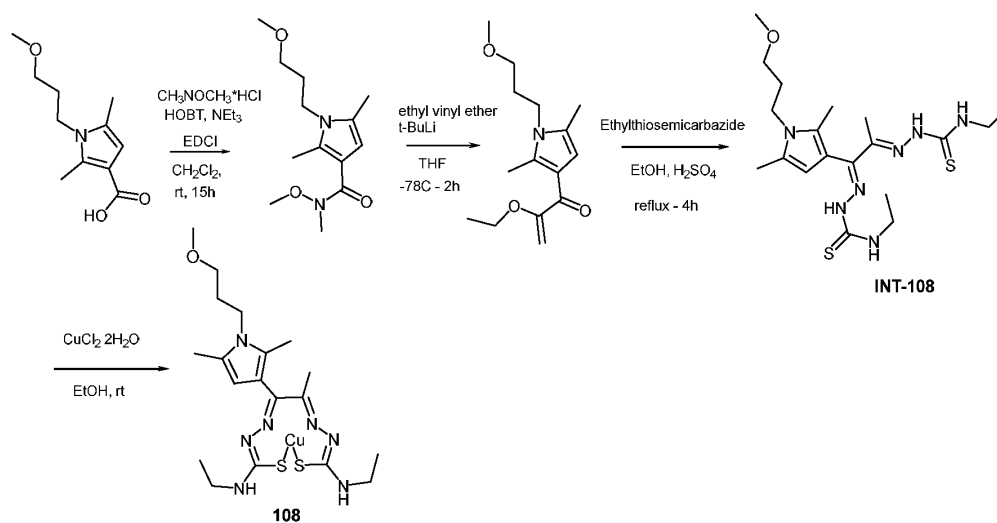
Synthesis of INT-107 ((2*E*,2'*E*)-2,2'-(1-(1-(3-methoxypropyl)-2,5-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



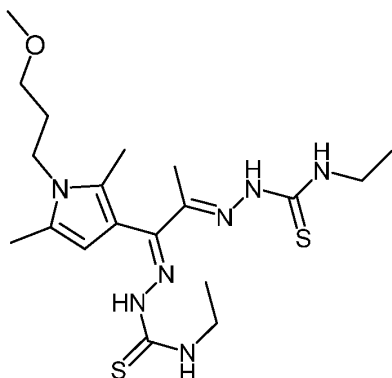
15 2-ethoxy-1-(1-(3-methoxypropyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (0.85 g, 3.2 mmol) was dissolved in EtOH (50 ml), methylthiosemicarbazide (0.67 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat.
20 Na₂CO₃, water, Et₂O, and dried. Yield 0.5 g (37.5%). LC-MS 1.78 min, m/z 412.5 [MH]⁺.

Synthesis of Compound 107:

Copper(II) chloride dihydrate (0.06g, 1 eq) was added to a stirred solution of **INT-107** (0.155 g, 0.4 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.037 g (20.7%).

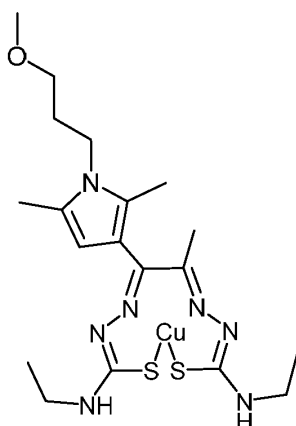
Scheme 69: Synthesis of Compound 108

Synthesis of INT-108 ((2E,2'E)-2,2'-(1-(1-(3-methoxypropyl)-2,5-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



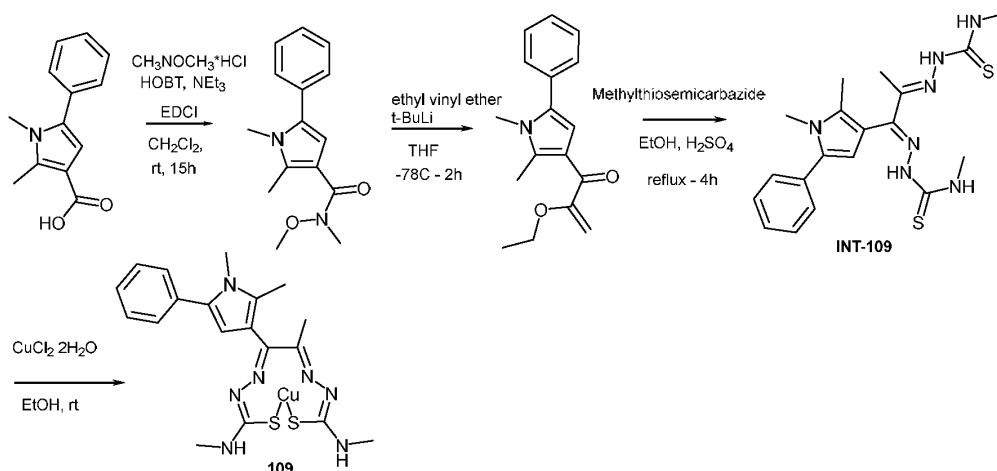
2-ethoxy-1-(1-(3-methoxypropyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (0.9 g, 3.4 mmol) was dissolved in EtOH (50 ml), ethylthiosemicarbazide (0.81 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.37 g (24.8%). LC-MS 1.71 min, m/z 440.5 [MH]⁺.

Synthesis of Compound 108:

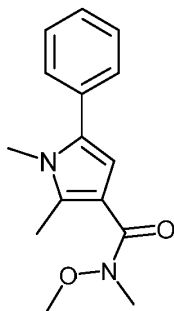


Copper(II) chloride dihydrate (0.144g, 1 eq) was added to a stirred solution of **INT-108** (0.37 g, 0.84 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.26 g (60.9%).

Scheme 70: Synthesis of Compound 109

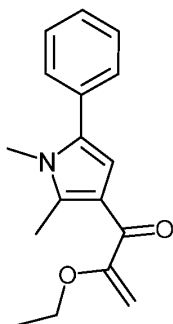


Synthesis of N-methoxy-N,1,2-trimethyl-5-phenyl-1H-pyrrole-3-carboxamide:



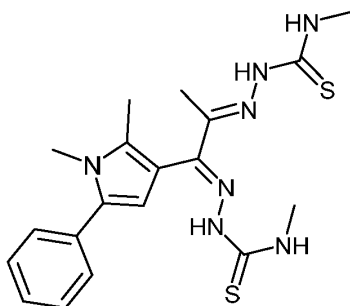
- To a stirred mixture of 1,2-dimethyl-5-phenyl-1H-pyrrole-3-carboxylic acid (3.28 g, 15.2 mmol), N,O-dimethylhydroxylamine (1.78 g, 1.2 eq), HOBt (2.47 g, 1.2 eq), and triethylamine (5.5 ml, 3.95 g, 2.5eq) in DCM (200 ml) at 5°C was added EDCI (3.5 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $\text{CCl}_4/\text{EtOAc}$ from 9:1 to 1:3). Yield 3.5 g (88.9%). LC-MS 1.44 min, m/z 259.4 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : δ 7.51 – 7.23 (m, 5H), 6.64 – 6.46 (m, 1H), 3.70 (ddd, J = 6.1, 3.1, 1.4 Hz, 3H), 3.58 – 3.45 (m, 3H), 3.34 (ddd, J = 6.0, 3.1, 1.4 Hz, 3H), 2.64 – 2.48 (m, 3H).

Synthesis of 1-(1,2-dimethyl-5-phenyl-1H-pyrrol-3-yl)-2-ethoxyprop-2-en-1-one:



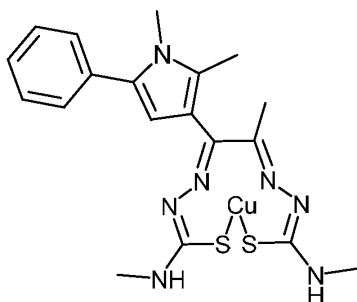
A solution of ethyl vinyl ether (3.22 g, 4.3 ml, 3.3 eq) in dry THF (130 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 25 ml, 3 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-N,1,2-trimethyl-5-phenyl-1H-pyrrole-3-carboxamide (3.5 g, 13.5 mmol) in THF (25ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 3.45 g (94.5%). LC-MS 1.71 min, m/z 270.6 [MH]⁺.

Synthesis of INT-109 ((2*E*,2'*E*)-2,2'-(1-(1,2-dimethyl-5-phenyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



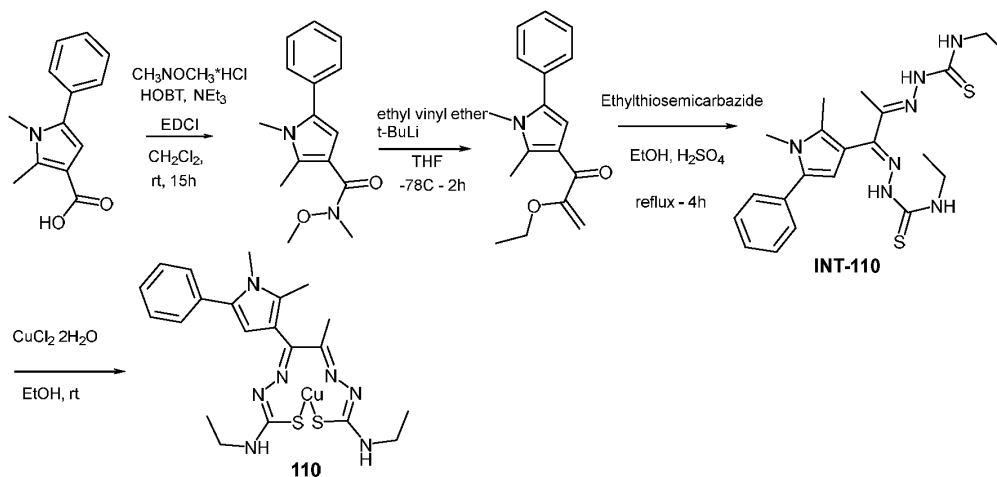
1-(1,2-dimethyl-5-phenyl-1H-pyrrol-3-yl)-2-ethoxyprop-2-en-1-one (1.75 g, 6.5 mmol) was dissolved in EtOH (50 ml), methylthiosemicarbazide (1.37 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.91 g (33.6%). LC-MS 1.65 min, m/z 416.6 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 10.58 (s, 1H), 9.07 (s, 1H), 8.64 (d, *J* = 4.6 Hz, 1H), 7.67 – 7.11 (m, 6H), 6.17 (s, 1H), 3.57 (s, 3H), 3.04 (d, *J* = 4.5 Hz, 3H), 2.94 (d, *J* = 4.7 Hz, 3H), 2.34 (s, 3H), 2.08 (d, *J* = 20.8 Hz, 3H).

Synthesis of Compound 109:

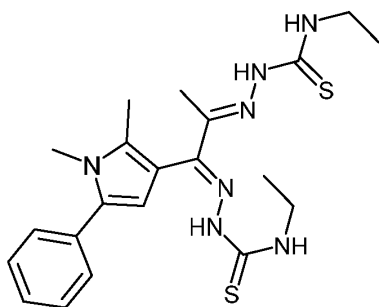


Copper(II) chloride dihydrate (0.082 g, 1 eq) was added to a stirred solution of **INT-109** (0.2 g, 0.48 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.2 g (87.7%).

Scheme 71: Synthesis of Compound 110



Synthesis of INT-110 ((2E,2'E)-2,2'-(1-(1,2-dimethyl-5-phenyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

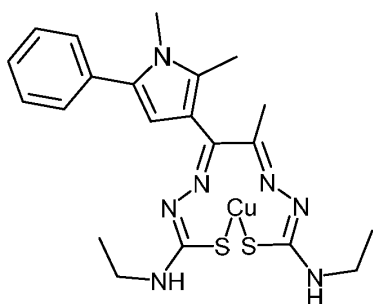


10

1-(1,2-dimethyl-5-phenyl-1H-pyrrol-3-yl)-2-ethoxyprop-2-en-1-one (1.7 g, 6.3 mmol) was dissolved in EtOH (50 ml), ethylthiosemicarbazide (1.5 g, 2 eq) and 3 drops of H₂SO₄

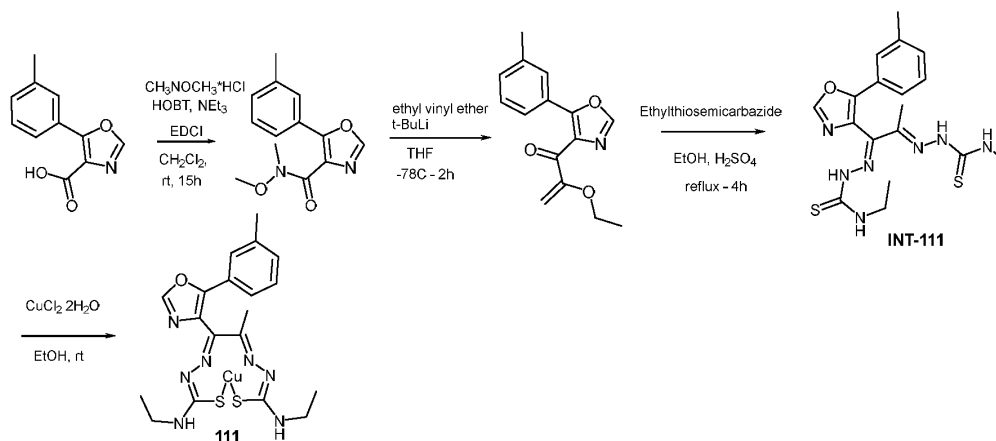
were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na_2CO_3 , water, Et_2O , and dried. Yield 1.03 g (36.8%). LC-MS 1.85 min, m/z 444.9 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6), δ (ppm) : 10.64 (s, 1H), 9.01 (s, 1H), 8.69 (t, $J = 5.7$ Hz, 1H), 7.59 – 7.13 (m, 6H), 6.16 (s, 1H), 3.73 – 3.52 (m, 5H), 3.49 – 3.33 (m, 2H), 2.34 (s, 3H), 2.05 (s, 3H), 1.24 – 1.09 (m, 3H), 0.88 (t, $J = 7.2$ Hz, 3H).

Synthesis of Compound 110:

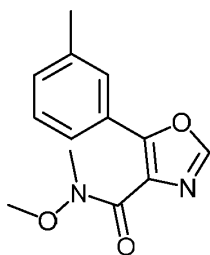


Copper(II) chloride dihydrate (0.077 g, 1 eq) was added to a stirred solution of **INT-110** (0.2 g, 0.45 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.15 g (66.3%).

Scheme 72: Synthesis of Compound 111

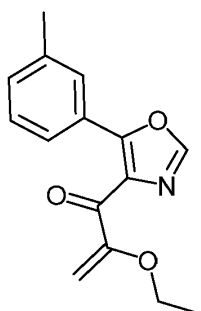


Synthesis of N-methoxy-N-methyl-5-(m-tolyl)oxazole-4-carboxamide:



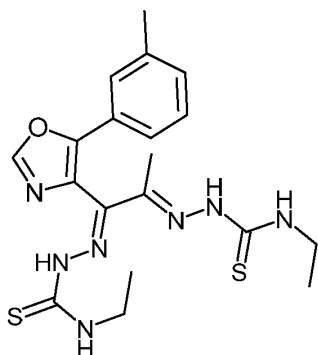
To a stirred mixture of 5-(*m*-tolyl)oxazole-4-carboxylic acid (2.02 g, 9.9 mmol), *N*,*O*-dimethylhydroxylamine (1.16 g, 1.2 eq), HOBT (1.83 g, 1.2 eq), and triethylamine (2.7 ml, 1.96 g, 2 eq) in DCM (50 ml) at 5°C was added EDCI (2.28 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent hexane/EtOAc 3:1). Yield 1.92 g (78.4%). LC-MS 1.24 min, m/z 247.4 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 7.89 (s, 1H), 7.65 (d, J = 6.4 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.39 (s, 3H), 2.41 (s, 3H).

Synthesis of 2-ethoxy-1-(5-(*m*-tolyl)oxazol-4-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (3.7g, 4.9 ml, 6.6 eq) in dry THF (100 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 27 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of compound **2** (1.92 g, 7.8 mmol) in THF (15ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH_4Cl (100ml) and extracted with Et_2O (3x100ml). The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.98 g (99%). LC-MS 0.64 min, m/z 431.5 $[\text{MH}]^+$.

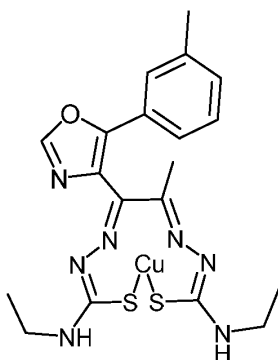
Synthesis of INT-111 ((2*E*,2'*E*)-2,2'-(1-(5-(*m*-tolyl)oxazol-4-yl)propane-1,2-diylidene)bis(*N*-ethylhydrazine-1-carbothioamide)):



2-ethoxy-1-(5-(m-tolyl)oxazol-4-yl)prop-2-en-1-one (0.98 g, 7.7 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (1.86 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt.

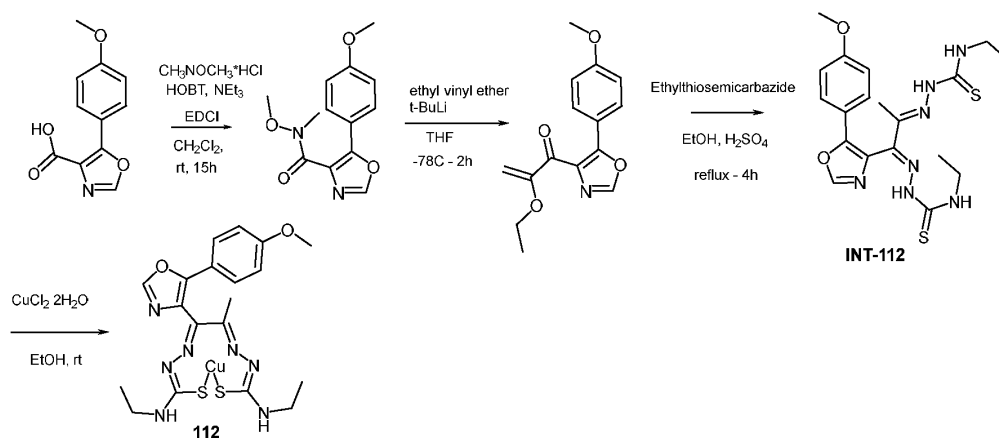
- 5 The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.8 g (23%). LC-MS 1.68 min), m/z 432.5 [MH]⁺.

Synthesis of Compound 111:

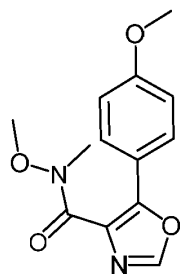


- 10 Copper(II) chloride dihydrate (0.071g, 1 eq) was added to a stirred solution of **INT-111** (0.18 g, 0.42 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.153 g (78.9%).

Scheme 73: Synthesis of Compound 112

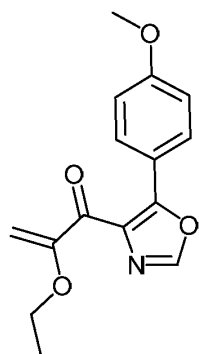


Synthesis of *N*-methoxy-5-(4-methoxyphenyl)-*N*-methyloxazole-4-carboxamide:



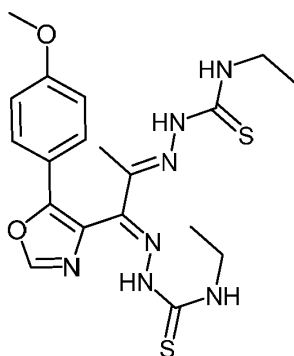
To a stirred mixture of 5-(4-methoxyphenyl)oxazole-4-carboxylic acid (4 g, 18.2 mmol), *N*,*O*-dimethylhydroxylamine (2.14 g, 1.2 eq), HOBt (3.35 g, 1.2 eq), and triethylamine (5 ml, 3.6 g, 2 eq) in DCM (100 ml) at 5°C was added EDCI (2.28 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent hexane/EtOAc 2:1). Yield 4 g (83.6%). LC-MS 1.23 min, *m/z* 263.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 8.00 – 7.68 (m, 3H), 7.05 – 6.86 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.39 (s, 3H).

Synthesis of 2-ethoxy-1-(5-(4-methoxyphenyl)oxazol-4-yl)prop-2-en-1-one:



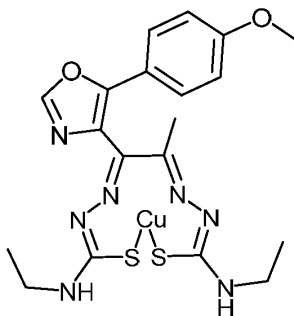
A solution of ethyl vinyl ether (3.7 g, 4.9 ml, 6.6 eq) in dry THF (100 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 27 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-5-(4-methoxyphenyl)-N-methyloxazole-4-carboxamide (1.92 g, 7.8 mmol) in THF (15ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.98 g (99%).

Synthesis of INT-112 ((2*E*,2'*E*)-2,2'-(1-(5-(4-methoxyphenyl)oxazol-4-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



2-ethoxy-1-(5-(4-methoxyphenyl)oxazol-4-yl)prop-2-en-1-one (0.98 g, 7.7 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (1.86 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.8 g (23%). LC-MS 1.68 min), m/z 432.5 [MH]⁺.

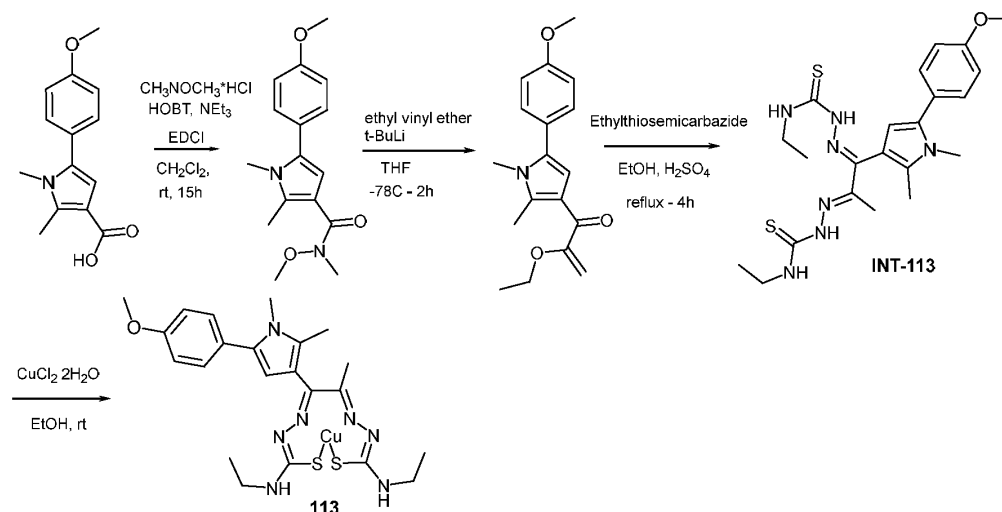
Synthesis of Compound 112:



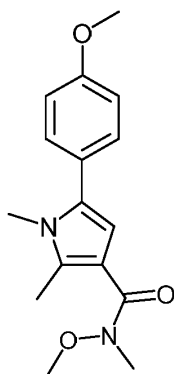
Copper(II) chloride dihydrate (0.071g, 1 eq) was added to a stirred solution of **INT-112** (0.18 g, 0.42 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed

complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.153 g (78.9%).

Scheme 74: Synthesis of Compound 113

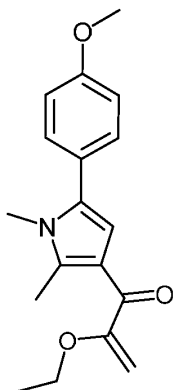


5 Synthesis of *N*-methoxy-5-(4-methoxyphenyl)-*N*,1,2-trimethyl-1*H*-pyrrole-3-carboxamide:



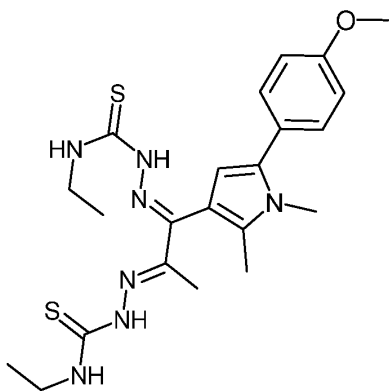
To a stirred mixture of 5-(4-methoxyphenyl)-1,2-dimethyl-1*H*-pyrrole-3-carboxylic acid (3 g, 12.2 mmol), *N*,*O*-dimethylhydroxylamine (1.43 g, 1.2 eq), HOBT (1.98 g, 1.2 eq), and triethylamine (4.3 ml, 3.09 g, 2.5 eq) in DCM (100 ml) at 5°C was added EDCI (2.81 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CCl₄/EtOAc from 8:2 to 1:3). Yield 2.1 g (59.5%). LC-MS 1.4 min, *m/z* 289.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.41 – 7.17 (m, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.49 (s, 1H), 3.86 (s, 2H), 3.70 (s, 2H), 3.48 (s, 2H), 3.34 (s, 2H), 2.56 (s, 2H).

Synthesis of 2-ethoxy-1-(5-(4-methoxyphenyl)-1,2-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (1.73 g, 2.3 ml, 3.3 eq) in dry THF (130 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 14 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-5-(4-methoxyphenyl)-N,1,2-trimethyl-1H-pyrrole-3-carboxamide (2.1 g, 7.3 mmol) in THF (15ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 2.12 g (97.2%). LC-MS 1.68 min, m/z 300.4 [MH]⁺.

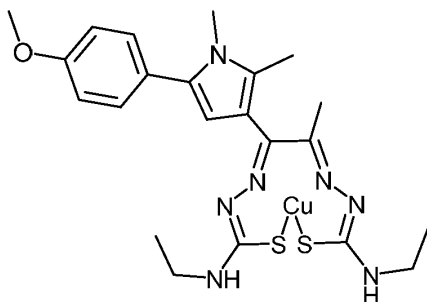
Synthesis of INT-113 ((2E,2'E)-2,2'-(1-(5-(4-methoxyphenyl)-1,2-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



2-ethoxy-1-(5-(4-methoxyphenyl)-1,2-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (1.9 g, 6.3 mmol) was dissolved in EtOH (50 ml), ethylthiosemicarbazide (1.851g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then

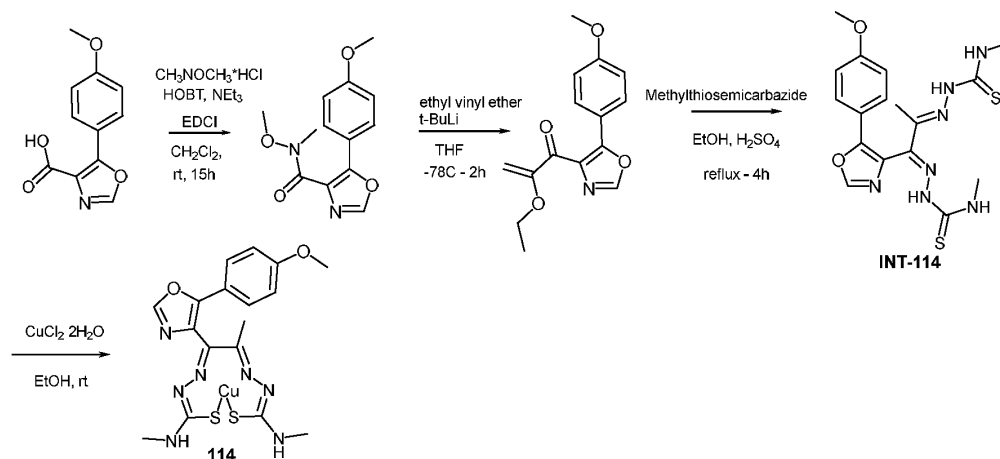
maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.8 g (23%). LC-MS 1.82 min, m/z 474.5 [MH]⁺.

Synthesis of Compound 113:



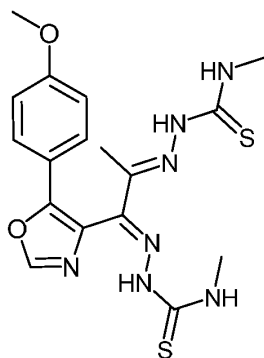
- 5 Copper(II) chloride dihydrate (0.091g, 1 eq) was added to a stirred solution of **INT-113** (0.25 g, 0.5 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.12 g (42.5%).

Scheme 75: Synthesis of Compound 114



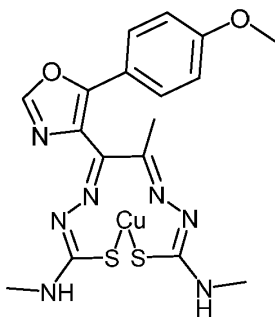
10

Synthesis of INT-114 ((2E,2'E)-2,2'-(1-(5-(4-methoxyphenyl)oxazol-4-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



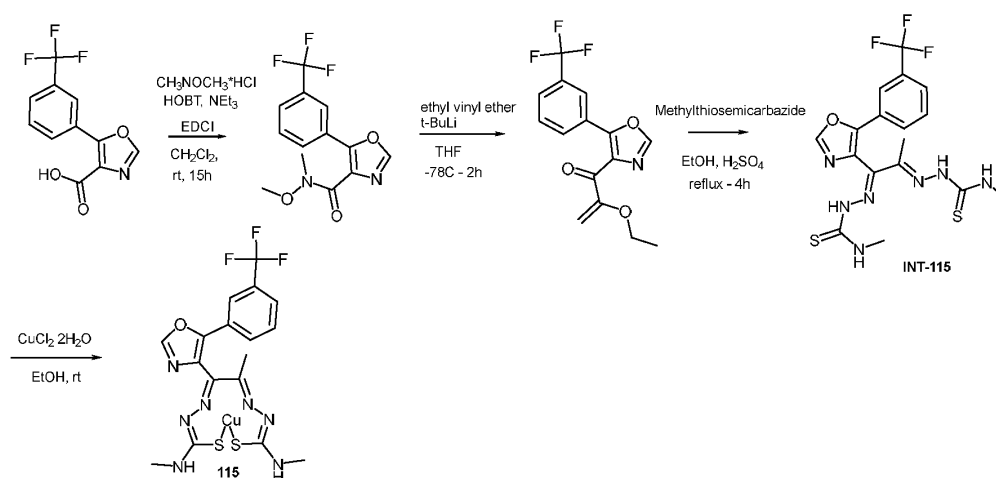
2-ethoxy-1-(5-(4-methoxyphenyl)oxazol-4-yl)prop-2-en-1-one (0.78 g, 2.85 mmol) was dissolved in EtOH (15 ml), methylthiosemicarbazide (0.6 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.2 g (216.7%). LC-MS 1.42 min, m/z 420.3 [MH]⁺.

Synthesis of Compound 114:

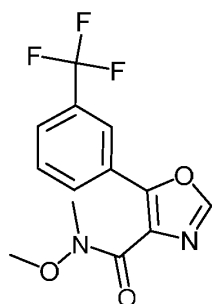


Copper(II) chloride dihydrate (0.081g, 1 eq) was added to a stirred solution of **INT-114** (0.2 g, 0.48 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.188 g (81.9%).

Scheme 76: Synthesis of Compound 115

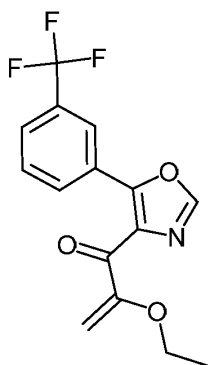


Synthesis of N-methoxy-N-methyl-5-(3-(trifluoromethyl)phenyl)oxazole-4-carboxamide:



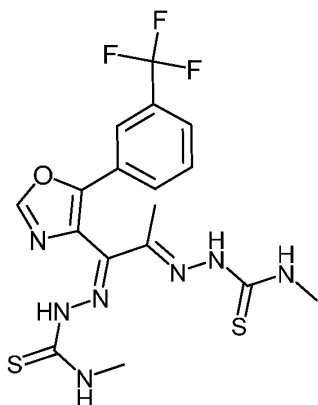
- 5 To a stirred mixture of 5-(3-(trifluoromethyl)phenyl)oxazole-4-carboxylic acid (2.0 g, 7.7 mmol), N,O-dimethylhydroxylamine (0.91 g, 1.2 eq), HOBT (1.43 g, 1.2 eq), and triethylamine (1.14 ml, 0.83 g, 2 eq) in DCM (50 ml) at 5°C was added EDCI (1.79 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure.
- 10 Product was used without further purification. Yield 2.0 g (85.6%). LC-MS 1.51 min, m/z 301.5 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 8.12 (s, 2H), 7.95 (s, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 3.79 (s, 3H), 3.41 (s, 3H).

Synthesis of 2-ethoxy-1-(5-(3-(trifluoromethyl)phenyl)oxazol-4-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (1.08 g, 1.4 ml, 6.6 eq) in dry THF (20 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 8 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-N-methyl-5-(3-(trifluoromethyl)phenyl)oxazole-4-carboxamide (0.68 g, 2.3 mmol) in THF (15ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 0.7 g (100%). LC-MS 0.64 min, m/z 431.5 [MH]⁺.

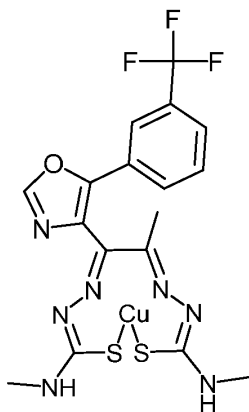
Synthesis of INT-115 ((2*E*,2'*E*)-2,2'-(1-(5-(3-(trifluoromethyl)phenyl)oxazol-4-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



2-ethoxy-1-(5-(3-(trifluoromethyl)phenyl)oxazol-4-yl)prop-2-en-1-one (0.7 g, 2.2 mmol) was dissolved in EtOH (25 ml), methylthiosemicarbazide (0.48 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The solvent was evaporated in vacuo. The residue was dissolved in EtOAc and washed with aq.sat. NaHCO₃, water, dried with anh. Na₂SO₄ and concentrated

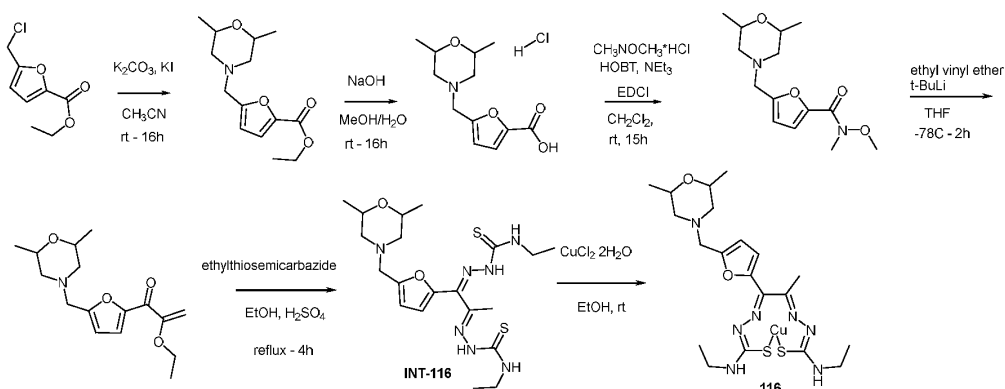
under reduced pressure. The residue was purified by column chromatography (silica gel, eluent $\text{CCl}_4/\text{EtOAc}$ 7:3). Yield 0.12 g (11.6%). LC-MS 1.56 min, m/z 458.5 $[\text{MH}]^+$.

Synthesis of Compound 115:



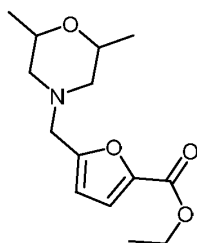
- 5 Copper(II) chloride dihydrate (0.039 g, 1 eq) was added to a stirred solution of **INT-115** (0.1 g, 0.23 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.1 g (89.6%).

Scheme 77: Synthesis of Compound 116



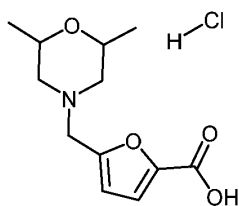
10

Synthesis of ethyl 5-((2,6-dimethylmorpholino)methyl)furan-2-carboxylate:



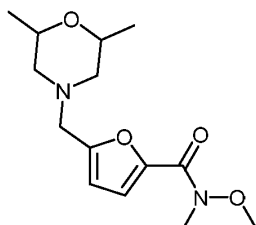
To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (3 g, 15.9 mmol) in CH₃CN (100 ml) were added 2,6-dimethylmorpholine (1.92 g, 1.05 eq), potassium carbonate (4.4 g, 2 eq), and sodium iodide (0.48 g, 0.2 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used without further purification. Yield 4.2 g (98.8%). LC-MS 0.88 min, m/z 268.3 [MH]⁺.

Synthesis of 5-((2,6-dimethylmorpholino)methyl)furan-2-carboxylic acid:



To a solution of ethyl 5-((2,6-dimethylmorpholino)methyl)furan-2-carboxylate (4.25 g, 15.9 mmol) in methanol (100 ml) was added a solution of NaOH (3.58 g, 2.5 eq) in water (10 ml) and the reaction mixture was stirred overnight at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified with conc. HCl to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered, and filtrate was evaporated in vacuo to dryness. Yield 4.38 g (99.9 %). LC-MS 0.6 min, m/z 240.3 [MH]⁺.

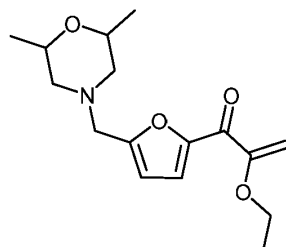
Synthesis of 5-((2,6-dimethylmorpholino)methyl)-N-methoxy-N-methylfuran-2-carboxamide:



To a stirred mixture of 5-((2,6-dimethylmorpholino)methyl)furan-2-carboxylic acid (4.38 g, 15.9 mmol), N,O-dimethylhydroxylamine (1.86 g, 1.2 eq), HOBt (2.57 g, 1.2 eq), and triethylamine (8 ml, 5.75 g, 3.5 eq) in DCM (100 ml) at 5°C was added EDCI (3.65 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhyd. Na₂SO₄ and then concentrated under reduced pressure. Product was purified by column chromatography (SiO₂, eluent CCl₄/EtOAc from 8:2 to 7:3, then CHCl₃/MeOH from 99:1 to 98:2). Yield 2.1 g (46.8%). LC-MS 0.69 min, m/z 283.5 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.11 (d, J = 3.4 Hz, 1H), 6.36 (d, J = 3.4 Hz,

1H), 3.78 (s, 3H), 3.69 (ddd, $J = 12.5, 8.3, 4.1$ Hz, 2H), 3.64 (d, $J = 15.3$ Hz, 2H), 3.35 (s, 3H), 2.75 (d, $J = 10.4$ Hz, 2H), 1.86 (t, $J = 10.7$ Hz, 2H), 1.15 (d, $J = 6.3$ Hz, 6H).

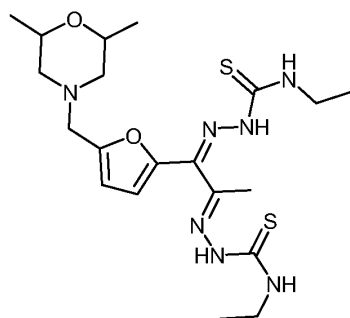
Synthesis of 1-(5-((2,6-dimethylmorpholino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one



5

A solution of ethyl vinyl ether (1.77 g, 2.35 ml, 3.3 eq) in dry THF (130 mL) was cooled to -78°C , and *tert*-butyllithium (1.6M in pentane, 14 ml, 3 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C . A solution of 5-((2,6-dimethylmorpholino)methyl)-N-methoxy-N-methylfuran-2-carboxamide (2.1 g, 7.4 mmol) in THF was added, and the mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC (hexane/EtOAc 10:1). The mixture was poured into aq NH_4Cl and extracted with Et_2O . The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 2.1 g (96.2%). LC-MS 1.00 min, m/z 294.4 $[\text{MH}]^+$.

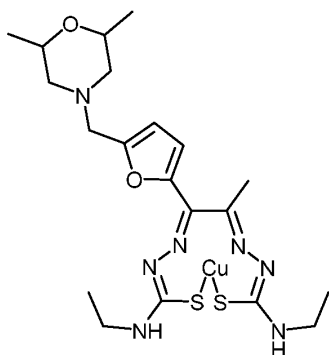
Synthesis of INT-116 ((2E,2'E)-2,2'-(1-(5-((2,6-dimethylmorpholino)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



1-(5-((2,6-dimethylmorpholino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one (2.12 g, 7.2 mmol) was dissolved in EtOH (150 ml), ethylthiosemicarbazide (1.72 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et_2O and dried. Yield 1.17 g (34.6%). LC-MS 1.20 min, m/z 468.3 $[\text{MH}]^+$.

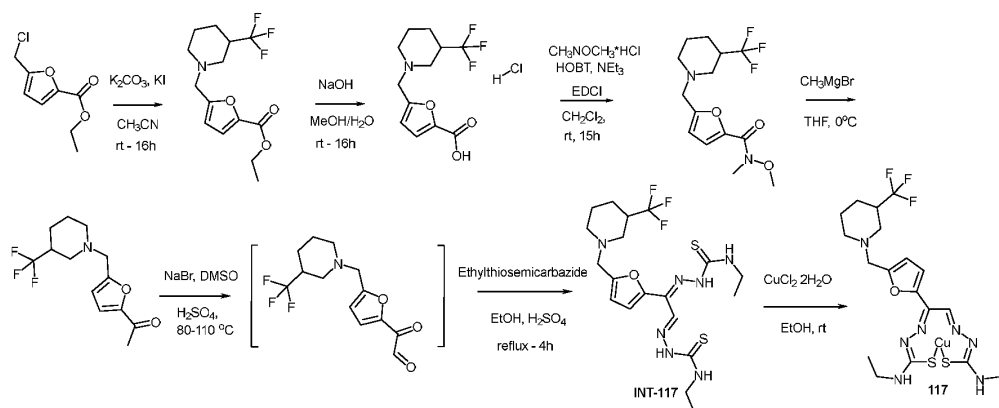
20

Synthesis of Compound 116:

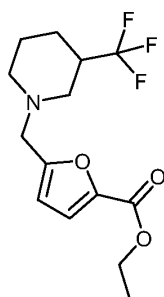


Copper(II) chloride dihydrate (0.15 g, 1 eq) was added to **INT-116** (0.41 g, 8.7 mmol, 1 eq) in ethanol. The mixture was stirred for 15 h at rt. The formed complex precipitated from the mixture as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.46 g (98.9%)

Scheme 78: Synthesis of Compound 117



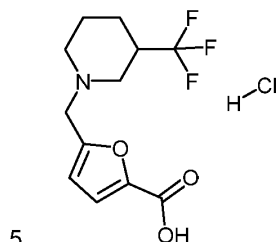
Synthesis of ethyl 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylate:



To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (2.5 g, 13.2 mmol) in CH_3CN (100 ml) were added 3-(trifluoroethyl)piperidine (2.03 g, 1 eq), potassium carbonate (5.5 g, 3 eq), and potassium iodide (0.66 g, 0.3 eq). The reaction mixture was stirred overnight rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was

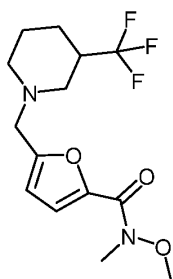
dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. The product was used without purification. Yield 3.9g (96.3%). LC-MS 1.00 min, m/z 306.3 $[\text{MH}]^+$.

Synthesis of 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylic acid



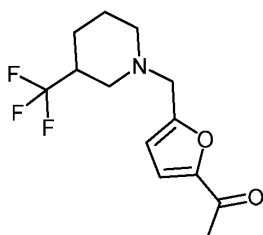
To a solution of ethyl 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylate (3.9 g, 12.7 mmol) in methanol (80 ml), a solution of NaOH (1.27 g, 2.5 eq) in water (10 ml) was added, and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solid salts were filtered, and filtrate was evaporated in vacuo to dryness. Yield 3.88 g (96.8%). LC-MS 0.7 min, m/z 278.5 $[\text{MH}]^+$.

Synthesis of N-methoxy-N-methyl-5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxamide:



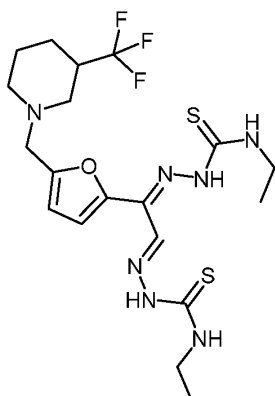
To a stirred mixture of 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylic acid (3.88 g, 12.4 mmol), N,O-dimethylhydroxylamine (1.45 g, 1.2 eq), HOBt (2.23 g, 1.2 eq), and triethylamine (6.9 ml, 5 g, 4eq) in DCM (100 ml) at 5°C was added EDCI (2.85 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent $\text{CCl}_4/\text{EtOAc}$ 1:1). Yield 2.91 g (73.5%). LC-MS 0.93 min, m/z 321.4 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 7.11 (d, J = 3.4 Hz, 1H), 6.34 (d, J = 3.3 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 2H), 3.35 (s, 3H), 3.07 (d, J = 10.7 Hz, 1H), 2.92 (d, J = 11.3 Hz, 1H), 2.50 – 2.23 (m, 1H), 2.15 – 1.99 (m, 2H), 1.94 (d, J = 12.2 Hz, 1H), 1.75 (d, J = 19.3 Hz, 1H), 1.59 (q, J = 13.1 Hz, 1H).

Synthesis of 1-(5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-yl)ethan-1-one:

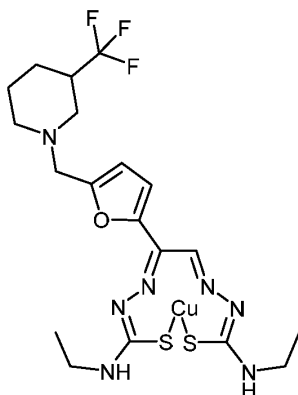


A solution of N-methoxy-N-methyl-5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxamide (1.75 g, 5.4 mmol) in THF (50 ml) was cooled to 5°C and methylmagnesium bromide (3.4M in THF, 4.8 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2h, poured into aq. NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhyd. Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 1.25 g (83.1%). LC-MS 0.84 min, m/z 376/3 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.14 (d, J = 3.5 Hz, 1H), 6.37 (d, J = 3.5 Hz, 1H), 3.67 (d, J = 14.9 Hz, 2H), 3.12 – 3.02 (m, 1H), 2.90 (d, J = 11.1 Hz, 1H), 2.47 (s, 3H), 2.40 – 2.26 (m, 1H), 2.13 – 2.01 (m, 2H), 1.77 (d, J = 13.3 Hz, 1H), 1.69 – 1.53 (m, 1H), 1.35 – 1.16 (m, 1H).

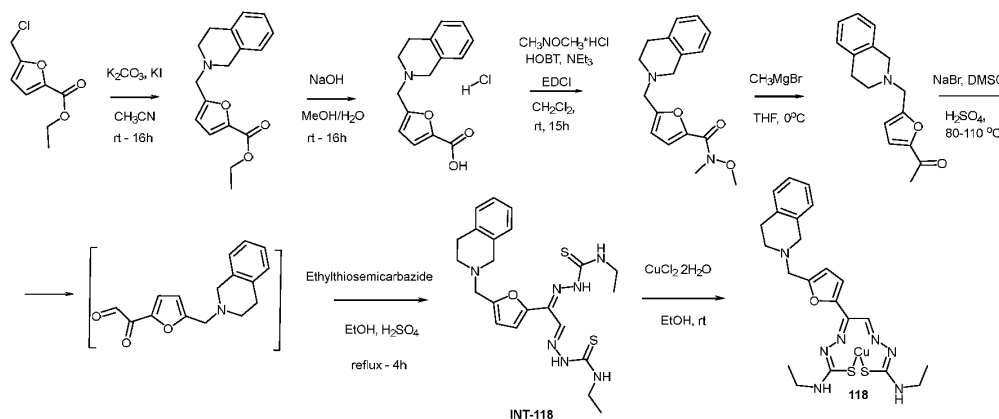
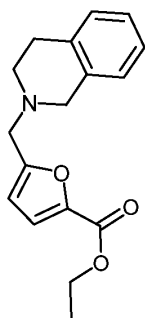
Synthesis of INT-117 ((2E,2'E)-2,2'-(1-(5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



A mixture of 1-(5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-yl)ethan-1-one (1.25 g, 4.5 mmol), NaBr (0.47 g, 1 eq), and DMSO (2.5 ml) was heated to 85°C, then H₂SO₄ (6 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (1.08 g, 2 eq) was added to the filtrate. The reaction mixture was refluxed for 2 hours, then cooled to room temperature. Formed precipitate was filtered, washed with EtOH, aq. sat. K₂CO₃, water, Et₂O, and dried. Yield 0.54g (24.2%). LC-MS 1.30 min, m/z 492.3 [MH]⁺.

Synthesis of Compound 117:

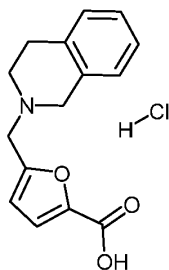
Copper(II) chloride dihydrate (0.19g, 1 eq) was added to a stirred solution of **INT-117** (0.54 g, 1.1 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex
 5 precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.4g (67.2%).

Scheme 79: Synthesis of Compound 118**Synthesis of ethyl 5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-carboxylate:**

10

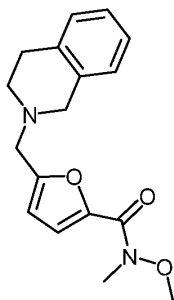
To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (2.96 g, 15.7 mmol) in CH₃CN (100 ml) were added 1,2,3,4-tetrahydroisoquinoline (2.09 g, 1 eq), potassium carbonate (6.51 g, 3 eq), and potassium iodide (0.78 g, 0.3 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was purified by column chromatography (silica gel, eluent hexane/EtOAc 10:1). Yield 3.81 g (85.08%). LC-MS 1.07 min, m/z 286.4 [MH]⁺. ¹H-NMR (400 MHz, DMSO-d₆), δ (ppm) : 7.25 (d, *J* = 2.4 Hz, 1H), 7.09 (s, 3H), 7.02 (s, 1H), 6.58 (s, 1H), 4.26 (dt, *J* = 9.3, 4.7 Hz, 2H), 3.74 (s, 2H), 3.57 (s, 2H), 2.81 (s, 2H), 2.72 (s, 2H), 1.35 – 1.19 (m, 3H).

Synthesis of 5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-carboxylic acid:



To a solution of ethyl 5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-carboxylate (3.81 g, 13.3 mmol) in methanol (100 ml) a solution of NaOH (1.33 g, 2.5 eq) in water (10 ml) was added and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered, and filtrate was evaporated in vacuo to dryness. Yield 3.9 g (99.4%). LC-MS 0.76 min and 0.86 min, m/z 258.0 [MH]⁺.

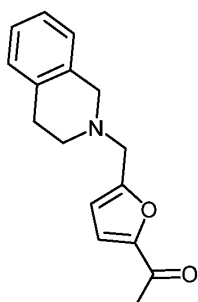
Synthesis of 5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-N-methoxy-N-methylfuran-2-carboxamide:



To a stirred mixture of 5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-carboxylic acid (3.9 g, 13.3 mmol), N,O-dimethylhydroxylamine (1.55 g, 1.2 eq), HOBt (2.44 g, 1.2 eq),

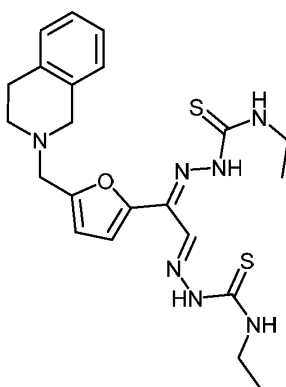
and triethylamine (7.4 ml, 537 g, 4eq) in DCM (100 ml) at 5°C was added EDCI (3.05 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. Yield 2.42 g (60.7%). LC-MS 0.90 min, m/z 301.4 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.28 (s, 1H), 7.12 (m, 3H), 7.02 (s, 1H), 6.43 (s, 1H), 3.85 (s, 2H), 3.78 (s, 3H), 3.74 (s, 2H), 3.36 (s, 3H), 2.93 (s, 2H), 2.85 (s, 2H).

Synthesis of 1-(5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-yl)ethan-1-one:



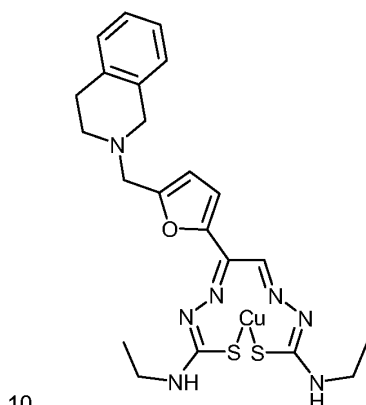
A solution of 5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)-N-methoxy-N-methylfuran-2-carboxamide (2.42 g, 8 mmol) in THF (75 ml) was cooled to 5°C and methylmagnesium bromide (3.4M in 2-methylTHF, 7 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 1.72 g (83.6%). LC-MS 0.46 min, m/z 256.5 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.17 (t, J = 5.2 Hz, 1H), 7.15 – 7.08 (m, 3H), 7.02 (d, J = 5.5 Hz, 1H), 6.46 (d, J = 3.5 Hz, 1H), 3.83 (s, 2H), 3.73 (s, 2H), 2.94 (t, J = 5.8 Hz, 2H), 2.84 (t, J = 5.8 Hz, 2H), 2.48 (s, 3H).

Synthesis of (2E,2'E)-2,2'-(1-(5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide):



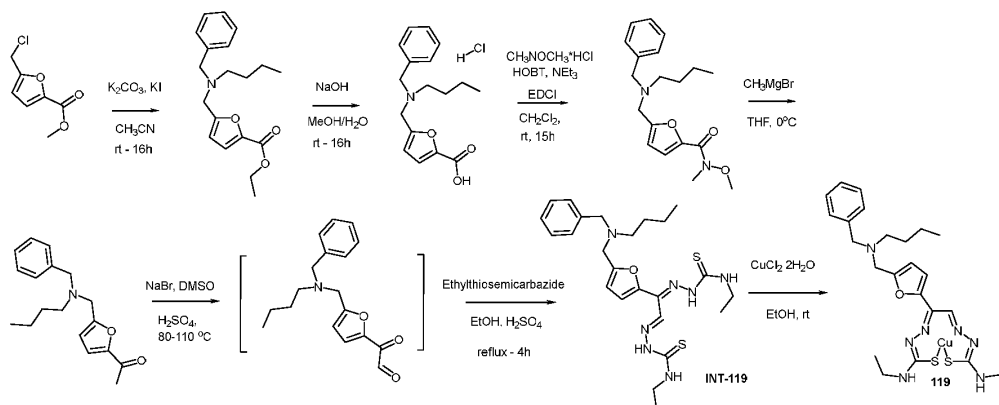
A mixture of 1-(5-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)furan-2-yl)ethan-1-one (0.89 g, 3.5 mmol), NaBr (0.36 g, 1 eq), and DMSO (2 ml) was heated to 85°C, then H₂SO₄ (3 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The
 5 formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (0.83 g, 2 eq) was added to the filtrate. The reaction mixture was refluxed for 2 h, then cooled to rt. Formed precipitate was filtered, washed with EtOH, aq. sat. K₂CO₃, water, Et₂O, and dried. Yield 0.52 g (31.6%). LC-MS 1.34 min, m/z 472.4 [MH]⁺.

Synthesis of Compound 118:

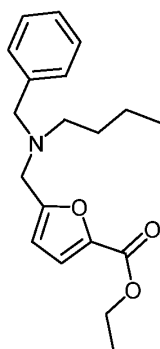


Copper(II) chloride dihydrate (0.19g, 1 eq) was added to a stirred solution of **INT-118** (0.18 g, 0.4 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.053g (26%).

15 **Scheme 80: Synthesis of Compound 119**

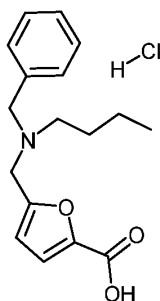


Synthesis of ethyl 5-((benzyl(butyl)amino)methyl)furan-2-carboxylate:



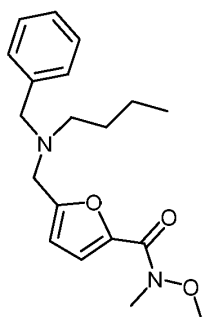
To a solution of methyl 5-(chloromethyl)furan-2-carboxylate (3.0 g, 15.9 mmol) in CH₃CN (200 ml) were added N-benzylbutylamine (2.73 g, 1.05 eq), potassium carbonate (4.4 g, 2 eq), and potassium iodide (0.48 g, 0.2 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 75 ml). Organic layer was separated, dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used without further purification. Yield 5 g (99.7%). LC-MS 1.16 min, m/z 316.3 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : δ 7.48 – 7.24 (m, 5H), 7.13 (d, *J* = 3.4 Hz, 1H), 6.33 (d, *J* = 3.2 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 2H), 3.62 (s, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.54 (dd, *J* = 19.9, 12.2 Hz, 2H), 1.42 – 1.26 (m, 5H), 0.89 (t, *J* = 7.3 Hz, 3H).

Synthesis of 5-((benzyl(butyl)amino)methyl)furan-2-carboxylic acid:



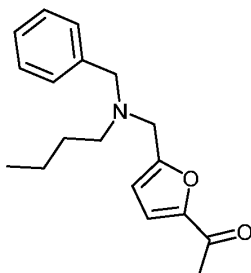
To a solution of ethyl 5-((benzyl(butyl)amino)methyl)furan-2-carboxylate (5 g, 15.9 mmol) in methanol (30 ml) a solution of NaOH (1.33 g, 2.5 eq) in water (10 ml) was added and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered, and filtrate was evaporated in vacuo to dryness. Yield 5.14 g (99.9%). LC-MS 0.9 min, m/z 288.4 [MH]⁺.

Synthesis of 5-((benzyl(butyl)amino)methyl)-N-methoxy-N-methylfuran-2-carboxamide:



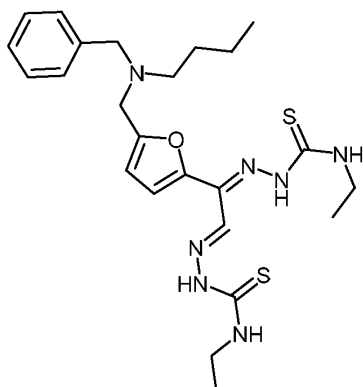
- To a stirred mixture of 5-((benzyl(butyl)amino)methyl)furan-2-carboxylic acid (5 g, 15.4 mmol), N,O-dimethylhydroxylamine (1.8 g, 1.2 eq), HOBt (2.5 g, 1.2 eq), and triethylamine (7.8 ml, 5.6 g, 3.5eq) in DCM (100 ml) at 5°C was added EDCI (3.55 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. Yield 4 g (78.4%). LC-MS 1.06 min, m/z 331.4 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6), δ (ppm) : 7.37 – 7.28 (m, 4H), 7.23 (t, J = 6.6 Hz, 1H), 7.12 (d, J = 3.4 Hz, 1H), 6.48 (d, J = 3.4 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 2H), 3.32 (s, 2H), 3.20 (d, J = 18.8 Hz, 3H), 2.38 (t, J = 7.1 Hz, 2H), 1.53 – 1.37 (m, 2H), 1.32 – 1.18 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H).

Synthesis of 1-(5-((benzyl(butyl)amino)methyl)furan-2-yl)ethan-1-one:



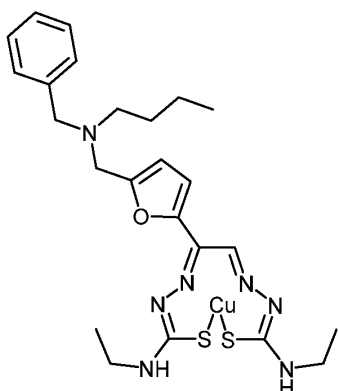
- A solution of 5-((benzyl(butyl)amino)methyl)-N-methoxy-N-methylfuran-2-carboxamide (3 g, 9.1 mmol) in THF (200 ml) was cooled to 5°C and methylmagnesium bromide (3.4M in 2-methylTHF, 8 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH_4Cl and extracted with Et_2O . The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 2.45 g (94.6%). LC-MS 1.04 min, m/z 286.5 $[\text{MH}]^+$. $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 7.45 – 7.19 (m, 5H), 7.14 (d, J = 3.4 Hz, 1H), 6.36 (d, J = 3.3 Hz, 1H), 3.68 (d, J = 16.3 Hz, 2H), 3.63 (s, 2H), 2.64 – 2.45 (m, 5H), 1.59 – 1.48 (m, 2H), 1.32 (dt, J = 25.1, 8.9 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H).

Synthesis of INT-119 ((2E,2'E)-2,2'-(1-(5-((benzyl(butyl)amino)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



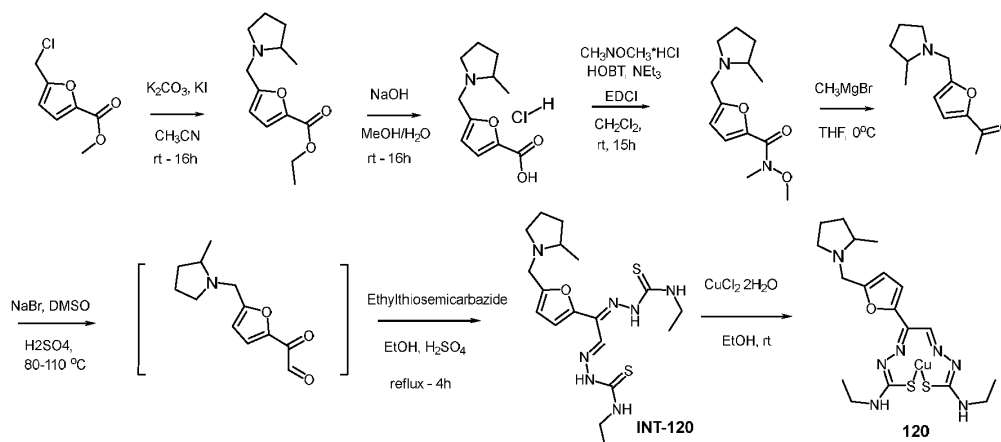
A mixture of 1-(5-((benzyl(butyl)amino)methyl)furan-2-yl)ethan-1-one (1 g, 3.5 mmol), NaBr (0.36 g, 1 eq), and DMSO (2 ml) was heated to 85°C, then H₂SO₄ (3 drops) was added (foaming, exothermic). The reaction was heated to 110-115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (0.83 g, 2 eq) was added to the filtrate. The reaction mixture was refluxed for 2 h then cooled to room temperature. Formed precipitate was filtered, washed with EtOH, aq. sat. K₂CO₃, water, Et₂O, and dried. Yield 0.51 g (29%). LC-MS 1.41 min, m/z 502.5 [MH]⁺.

Synthesis of Compound 119:

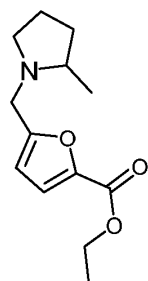


Copper(II) chloride dihydrate (0.088g, 1 eq) was added to a stirred solution of **INT-119** (0.26 g, 0.5 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.25g (84.7%).

Scheme 81: Synthesis of Compound 120

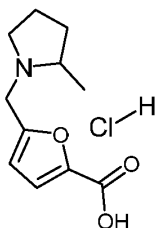


Synthesis of ethyl 5-((2-methylpyrrolidin-1-yl)methyl)furan-2-carboxylate:



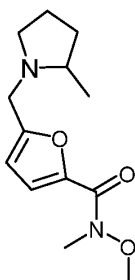
- To a solution of methyl 5-(chloromethyl)furan-2-carboxylate (3.11 g, 16.5 mmol) in
- 5 CH₃CN (100 ml) were added 2-methylpyrrolidine (1.4 g, 1 eq), potassium carbonate (6.84 g, 3 eq), and potassium iodide (0.82 g, 0.3 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 50 ml). Organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. The residue was purified by
- 10 column chromatography (silica gel, eluent hexane/EtOAc 10:1). Yield 3.84 g (98.1%). LC-MS 0.95 min, m/z 238.1 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.11 (d, *J* = 3.4 Hz, 1H), 6.31 (d, *J* = 3.4 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.96 (d, *J* = 14.6 Hz, 1H), 3.47 (d, *J* = 14.6 Hz, 1H), 3.06 (td, *J* = 8.8, 2.7 Hz, 1H), 2.50 – 2.36 (m, 1H), 2.30 (q, *J* = 8.9 Hz, 1H), 1.99 – 1.86 (m, 1H), 1.79 (dd, *J* = 5.1, 3.0 Hz, 1H), 1.85 – 1.57 (m, 2H), 1.45 (m, 1H), 1.31 – 1.20
- 15 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 3H).

Synthesis of 5-((2-methylpyrrolidin-1-yl)methyl)furan-2-carboxylic acid:



To a solution of ethyl 5-((2-methylpyrrolidin-1-yl)methyl)furan-2-carboxylate (3.84 g, 16.2 mmol) in methanol (100 ml) a solution of NaOH (1.62 g, 2.5 eq) in water (10 ml) was added and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered, and filtrate was evaporated in vacuo to dryness. Yield 3.09 g (77.7%). LC-MS 0.63 min, m/z 210.4 [MH]⁺.

Synthesis of *N*-methoxy-*N*-methyl-5-((2-methylpyrrolidin-1-yl)methyl)furan-2-carboxamide:



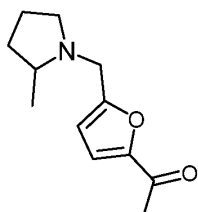
10

To a stirred mixture of 5-((2-methylpyrrolidin-1-yl)methyl)furan-2-carboxylic acid (3.09 g, 12.6 mmol), *N*,*O*-dimethylhydroxylamine (1.47 g, 1.2 eq), HOBt (2.31 g, 1.2 eq), and triethylamine (5.3 ml, 3.85 g, 3 eq) in DCM (100 ml) at 5°C was added EDCI (2.89 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent hexane/EtOAc 1:1). Yield 2.41 g (76%). LC-MS 0.73 min, m/z 253.4 [MH]⁺. Yield 2.42 g (60.7%). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (d, J = 3.4 Hz, 1H), 8.27 (d, J = 3.4 Hz, 1H), 5.90 (t, J = 13.1 Hz, 1H), 5.69 (s, 3H), 5.48 (t, J = 13.0 Hz, 1H), 5.27 (s, 3H), 5.02 (td, J = 9.0, 2.7 Hz, 1H), 4.45 – 4.34 (m, 1H), 4.28 (q, J = 8.9 Hz, 1H), 3.90 – 3.78 (m, 1H), 3.78 – 3.64 (m, 1H), 3.63 – 3.51 (m, 1H), 3.44 – 3.30 (m, 1H), 3.08 (d, J = 6.0 Hz, 3H).

15

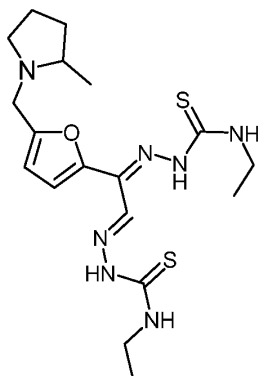
20

Synthesis of 1-(5-((2-methylpyrrolidin-1-yl)methyl)furan-2-yl)ethan-1-one:



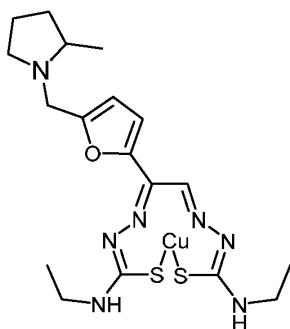
A solution of N-methoxy-N-methyl-5-((2-methylpyrrolidin-1-yl)methyl)furan-2-carboxamide (2.41 g, 9.5 mmol) in THF (75 ml) was cooled to 5°C and methylmagnesium bromide (3.4M in 2-methylTHF, 8.5 ml, 3 eq) was added. The reaction mixture was stirred at 5°C for 2 h, poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. Compound **5** was used for the next step without purification. Yield 1.35 g (68.1%). LC-MS 0.68 min, m/z 207.9 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm): 7.14 (d, J = 3.5 Hz, 1H), 6.38 (d, J = 3.2 Hz, 1H), 3.98 (d, J = 14.7 Hz, 1H), 3.51 (d, J = 14.8 Hz, 1H), 3.10 (t, J = 7.3 Hz, 1H), 2.47 (s, 4H), 2.34 (dd, J = 17.8, 9.1 Hz, 1H), 1.94 (dt, J = 12.3, 9.8 Hz, 1H), 1.78 (d, J = 8.5 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.46 (dd, J = 23.5, 14.0 Hz, 1H), 1.16 (d, J = 6.0 Hz, 3H).

Synthesis of INT-120 ((2E,2'E)-2,2'-(1-(5-((2-methylpyrrolidin-1-yl)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



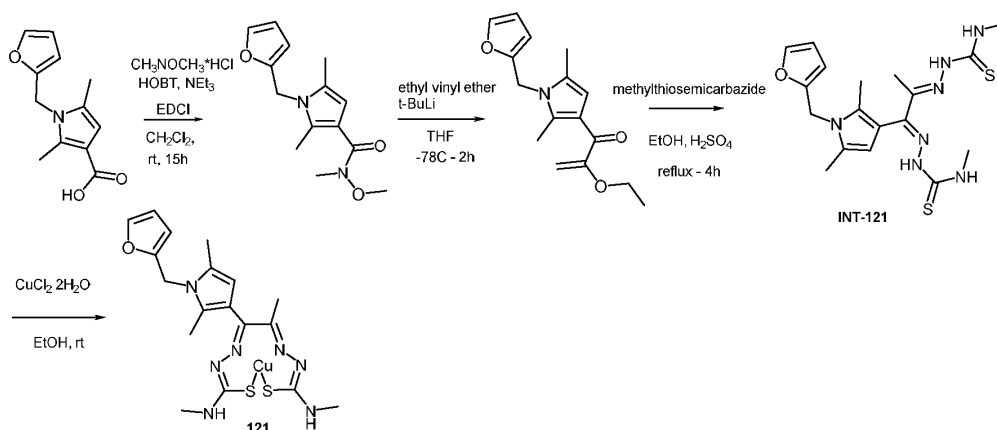
A mixture of 1-(5-((2-methylpyrrolidin-1-yl)methyl)furan-2-yl)ethan-1-one (0.75 g, 3.6 mmol), NaBr (0.37 g, 1 eq), and DMSO (2 ml) was heated to 85°C, then H₂SO₄ (2 drops) was added (foaming, exothermic). The reaction was heated to 110–115°C until the formation of dimethyl sulfide has stopped, and the reaction mixture became viscous. The formed viscous substance was dissolved in EtOH, solids were filtered and ethylthiosemicarbazide (0.86 g, 2 eq) was added to the filtrate. The reaction mixture was refluxed for 2 h, then cooled to rt. Formed precipitate was filtered, washed with EtOH, aq. sat. K₂CO₃, water, Et₂O, and dried. Yield 0.5 g (32.6%). LC-MS 1.21 min, m/z 424.4 [MH]⁺.

Synthesis of Compound 120:

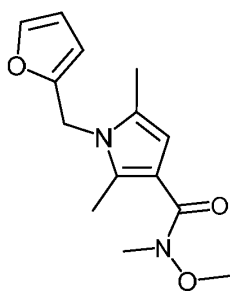


Copper(II) chloride dihydrate (0.12g, 1 eq) was added to a stirred solution of **INT-120** (0.3 g, 0.7 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried *in vacuo*. Yield 0.3g (92.7%).

Scheme 82: Synthesis of Compound 121



Synthesis of 1-(furan-2-ylmethyl)-N-methoxy-N,2,5-trimethyl-1H-pyrrole-3-carboxamide:



10

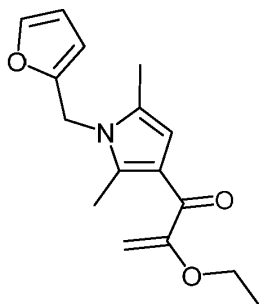
To a stirred mixture of 1-(furan-2-ylmethyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid (3.27 g, 14.9 mmol), N,O-dimethylhydroxylamine (1.74 g, 1.2 eq), HOBT (2.42 g, 1.2 eq), and triethylamine (5.3 ml, 3.81 g, 2.5 eq) in DCM (50 ml) at 5°C was added EDCI (3.43 g, 1.2 eq)

and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na_2SO_4 and then concentrated under reduced pressure.

The product was purified by column chromatography (silica gel, eluent DCM 100% then DCM/EtOAc 8:2). Yield 2.8 g (71.6%). $^1\text{H-NMR}$ (400 MHz, CDCl_3), δ (ppm) : 7.35 (s, 1H),

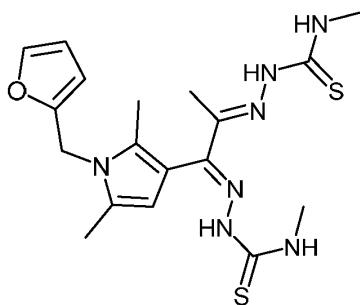
6.35 – 6.28 (m, 1H), 6.24 (s, 1H), 6.05 (d, $J = 3.2$ Hz, 1H), 4.94 (s, 2H), 3.67 (s, 3H), 3.30 (s, 3H), 2.53 (s, 3H), 2.27 (s, 3H).

Synthesis of 2-ethoxy-1-(1-(furan-2-ylmethyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one:



A solution of ethyl vinyl ether (4.23 g, 5.6 ml, 5.5 eq) in dry THF (130 ml) was cooled to -78°C , and *tert*-butyllithium (1.7M in pentane, 33 ml, 5 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C . A solution of 1-(furan-2-ylmethyl)-N-methoxy-N,2,5-trimethyl-1H-pyrrole-3-carboxamide (0.56 g, 7mmol) in THF (15ml) was added, and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH_4Cl (100ml) and extracted with Et_2O (3x100ml). The combined extracts were dried over anh. Na_2SO_4 , filtered, and solvents were evaporated. The product was used for the next step without additional purification. Yield 1.6 g (99.8%). LC-MS 1.56 min, m/z 274.5 $[\text{MH}]^+$.

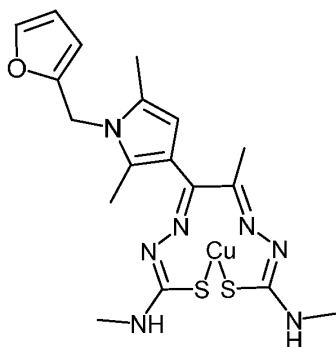
Synthesis of INT-121 ((2E,2'E)-2,2'-(1-(1-(furan-2-ylmethyl)-2,5-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



2-ethoxy-1-(1-(furan-2-ylmethyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (2.91 g, 10.6 mmol) was dissolved in EtOH (150 ml), methylthiosemicarbazide (2.24 g, 2 eq) and 3

drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na_2CO_3 , water, Et_2O , and dried. Yield 1.6 g (35.8%). LC-MS 1.63 min, m/z 420.5 $[\text{MH}]^+$.

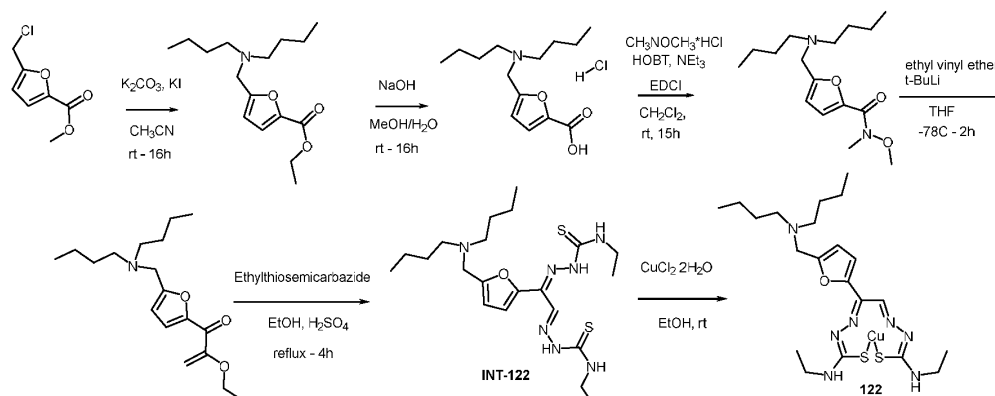
Synthesis of Compound 121:



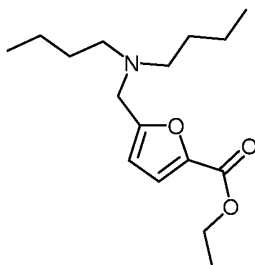
5

Copper(II) chloride dihydrate (0.31 g, 1 eq) was added to a stirred solution of **INT-121** (0.75 g, 1 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.6g (68.9%).

10 **Scheme 83: Synthesis of Compound 122**

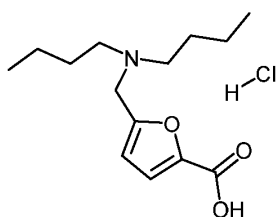


Synthesis of ethyl 5-((dibutylamino)methyl)furan-2-carboxylate:



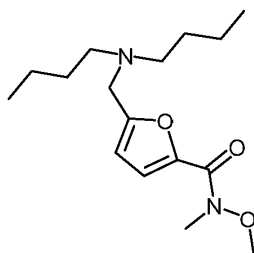
To a solution of methyl 5-(chloromethyl)furan-2-carboxylate (4 g, 21.2 mmol) in CH₃CN (200 ml) were added di-butylamine (2.88 g, 1.05 eq), potassium carbonate (5.86 g, 2 eq), and potassium iodide (0.63 g, 0.2 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3 × 100 ml). Organic layer was separated, dried over Na₂SO₄, filtered, and solvents were evaporated. The product was used without purification. Yield 5.9 g (98.9%). LC-MS 1.08 min, m/z 282.5 [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 7.12 (d, J = 3.3 Hz, 1H), 6.30 (d, J = 3.4 Hz, 1H), 4.47 – 4.25 (m, 2H), 3.71 (d, J = 12.0 Hz, 2H), 2.54 – 2.31 (m, 4H), 1.53 – 1.20 (m, 12H), 0.90 (t, J = 7.3 Hz, 6H).

Synthesis of 5-((dibutylamino)methyl)furan-2-carboxylic acid:



To a solution of ethyl 5-((dibutylamino)methyl)furan-2-carboxylate (5.9 g, 21 mmol) in methanol (50 ml) a solution of NaOH (2.1 g, 2.5 eq) in water (10 ml) was added and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered and filtrate was evaporated in vacuo to dryness. Yield 6.07 g (99.9%). LC-MS 1.09 min, m/z 254.9 [MH]⁺.

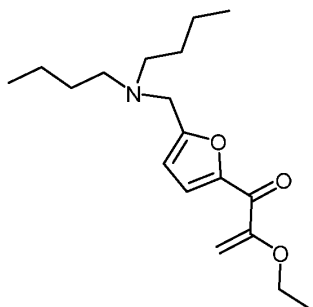
Synthesis of 5-((dibutylamino)methyl)-N-methoxy-N-methylfuran-2-carboxamide:



To a stirred mixture of 5-((dibutylamino)methyl)furan-2-carboxylic acid (6.07 g, 21 mmol), N,O-dimethylhydroxylamine (2.45 g, 1.2 eq), HOBt (3.4 g, 1.2 eq), and triethylamine (10.3 ml, 7.4 g, 3.5 eq) in DCM (100 ml) at 5°C was added EDCI (4.81 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was purified by column chromatography (silica gel, eluent DCM 100% then DCM/MeOH 96:4). Yield 4.28 g (69%). LC-MS 0.93 min, m/z 297.6 [MH]⁺. ¹H-NMR (400

MHz, CDCl_3 , δ (ppm) : 7.10 (d, J = 3.4 Hz, 1H), 6.31 (d, J = 3.3 Hz, 1H), 3.77 (s, 3H), 3.72 (s, 2H), 3.34 (s, 3H), 2.53 – 2.40 (m, 4H), 1.46 (dt, J = 14.9, 7.4 Hz, 4H), 1.30 (dt, J = 14.7, 7.3 Hz, 4H), 0.90 (t, J = 7.3 Hz, 6H).

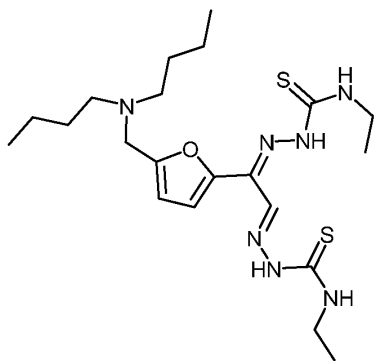
Synthesis of 1-(5-((dibutylamino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one:



5

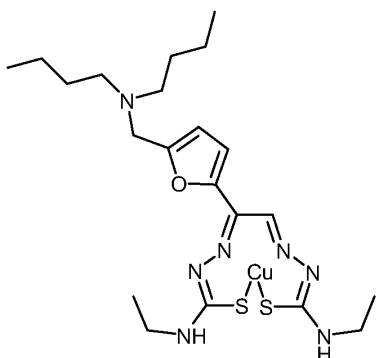
A solution of ethyl vinyl ether (2.68 g, 3.55 ml, 5.5 eq) in dry THF (130 mL) was cooled to -78°C , and *tert*-butyllithium (1.6M in pentane, 21 ml, 5 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C . A solution of 5-((dibutylamino)methyl)-N-methoxy-N-methylfuran-2-carboxamide (2.1 g, 7.4 mmol) in THF was added and the mixture was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC (hexane/EtOAc 10:1). The mixture was poured into aq NH_4Cl and extracted with Et_2O . The combined extracts were dried over anhyd. Na_2SO_4 , filtered, and evaporated in vacuo. The product was used for the next step without additional purification. Yield 2.07 g (99.8%). LC-MS 1.19 min, m/z 308.6 $[\text{MH}]^+$.

Synthesis of INT-122 ((2E,2'E)-2,2'-(1-(5-((dibutylamino)methyl)furan-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):

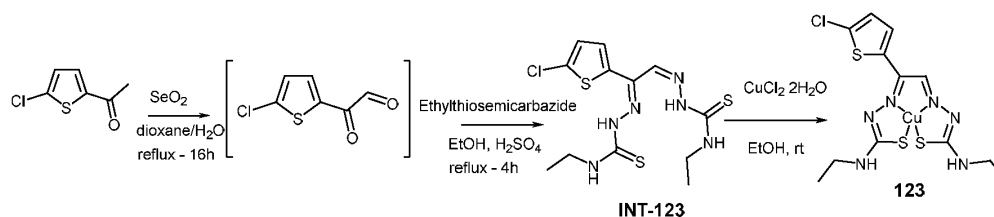


1-(5-((dibutylamino)methyl)furan-2-yl)-2-ethoxyprop-2-en-1-one (2.07 g, 6.7 mmol) was dissolved in EtOH (150 ml), ethylthiosemicarbazide (1.6 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, potassium carbonate solution, water, Et_2O , and dried. Yield 0.79 g (24.3%). LC-MS 1.32 min, m/z 482.4 $[\text{MH}]^+$.

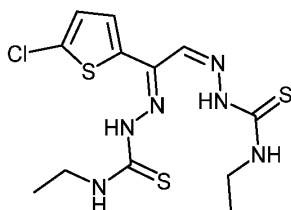
20

Synthesis of Compound 122:

- Copper(II) chloride dihydrate (0.18 g, 1 eq) was added to **INT-122** (0.51 g, 1 mmol) in ethanol. The mixture was stirred for 15 h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.41 g (71.3%).

Scheme 84: Synthesis of Compound 123

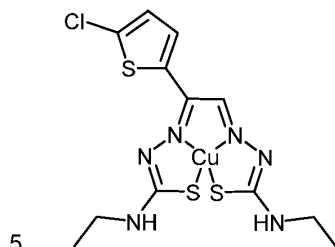
- Synthesis of INT-123 ((2Z,2'Z)-2,2'-(1-(5-chlorothiophen-2-yl)ethane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):**



- A three-necked flask was charged with SeO_2 (0.76 g, 1.05 eq), 1,4-dioxane (14 mL), and water (2.5 mL). The mixture was heated to 50°C and stirred until most of SeO_2 dissolves. 1-(5-chlorothiophen-2-yl)ethan-1-one (1 g, 6.2 mmol) was added, and the reaction was heated to gentle reflux overnight. Selenium solids precipitated during the course of the reaction. The mixture was cooled in an ice bath and filtered through diatomaceous earth to remove selenium. The filter cake was washed with portions of 1,4-dioxane. The filtrate was evaporated to dryness and dissolved in EtOH (50 ml). Ethylthiosemicarbazide (1.48 g, 2 eq) and 3 drops of H_2SO_4 were added. The stirred reaction mixture was heated to reflux for 4h.

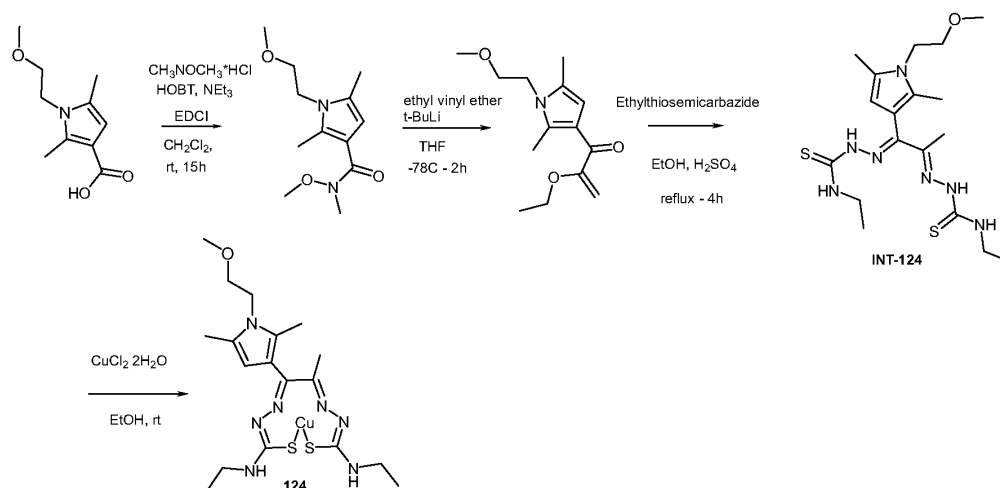
Formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried.
The product was crystallized from acetonitrile. Yield 1.3 g (55.8%). LC-MS 1.78 min, m/z 377.4 [MH]⁺.

Synthesis of Compound 123:

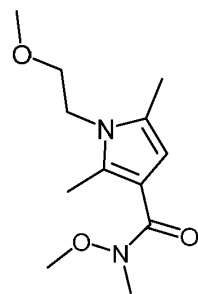


Copper(II) chloride dihydrate (0.095 g, 1 eq) was added to a stirred solution of **INT-123** (0.21 g, 0.6 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.24g (98.7%).

10 Scheme 85: Synthesis of Compound 124

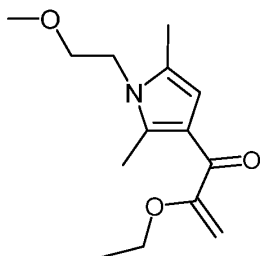


Synthesis of N-methoxy-1-(2-methoxyethyl)-N,2,5-trimethyl-1H-pyrrole-3-carboxamide:



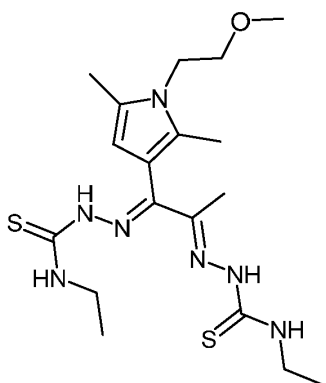
To a stirred mixture of 1-(2-methoxyethyl)-2,5-dimethyl-1H-pyrrole-3-carboxylic acid (2.69 g, 13.6 mmol), N,O-dimethylhydroxylamine (1.6 g, 1.2 eq), HOBt (2.5 g, 1.2 eq), and triethylamine (3.8 ml, 2.76 g, 2eq) in DCM (100 ml) at 5°C was added EDCI (3.14 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was used further without additional purification. Yield 2.33 g (71.1%). LC-MS 1.15 min, m/z 241.4. [MH]⁺. ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 6.19 (s, 1H), 3.96 (q, J = 6.4 Hz, 2H), 3.66 (t, J = 3.3 Hz, 3H), 3.58 – 3.44 (m, 2H), 3.36 – 3.21 (m, 6H), 2.47 (s, 3H), 2.22 (s, 3H).

Synthesis of 2-ethoxy-1-(1-(2-methoxyethyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one:



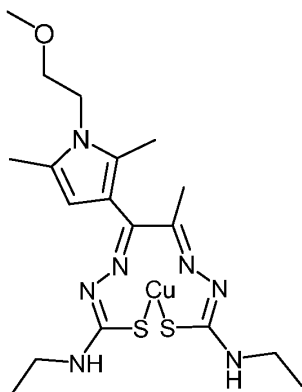
A solution of ethyl vinyl ether (2.01 g, 2.7 ml, 6.7 eq) in dry THF (50 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 15 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution of N-methoxy-1-(2-methoxyethyl)-N,2,5-trimethyl-1H-pyrrole-3-carboxamide (1 g, 4.1 mmol) in THF (15 ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (50ml) and extracted with Et₂O (3x50ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.02 g (98%). LC-MS 1.41 min, m/z 252.4 [MH]⁺.

Synthesis of INT-124 ((2E,2'E)-2,2'-(1-(1-(2-methoxyethyl)-2,5-dimethyl-1H-pyrrol-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



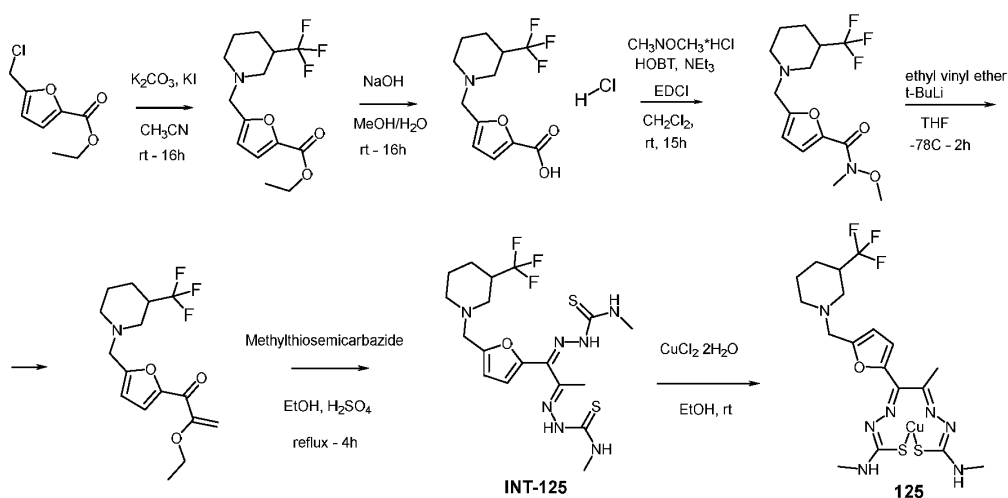
- 2-ethoxy-1-(1-(2-methoxyethyl)-2,5-dimethyl-1H-pyrrol-3-yl)prop-2-en-1-one (1.02 g, 4 mmol) was dissolved in EtOH (25 ml), ethylthiosemicarbazide (0.99 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. Yield 0.48 g (27%). LC-MS 1.63 min, m/z 426.0 [MH]⁺.

Synthesis of Compound 124:

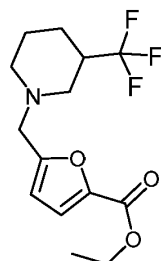


- Copper(II) chloride dihydrate (0.23g, 1 eq) was added to a stirred solution of **INT-124** (0.5 g, 1.3 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.5g (88.7%).

Scheme 86: Synthesis of Compound 125

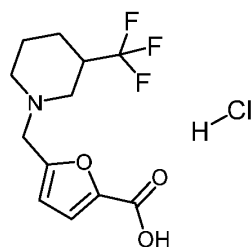


Synthesis of ethyl 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylate:



- To a solution of ethyl 5-(chloromethyl)furan-2-carboxylate (2.5 g, 13.2 mmol) in
- 5 CH_3CN (100 ml) were added 3-(trifluoroethyl)piperidine (2.03 g, 1 eq), potassium carbonate (5.5 g, 3 eq), and potassium iodide (0.66 g, 0.3 eq). The reaction mixture was stirred overnight at rt. Solids were filtered and filtrate was concentrated in vacuo. The residue was dissolved in DCM and washed with water (3×50 ml). Organic layer was separated, dried over anh. Na_2SO_4 , filtered, and solvents were evaporated in vacuo. Yield 3.9g (96.3%). LC-MS 1.00 min, m/z 306.3 $[\text{MH}]^+$.
 - 10

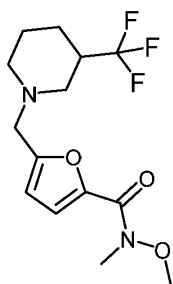
Synthesis of 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylic acid:



To a solution of ethyl 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylate (3.9 g, 12.7 mmol) in methanol (80 ml) a solution of NaOH (1.27 g, 2.5 eq) in water (10 ml)

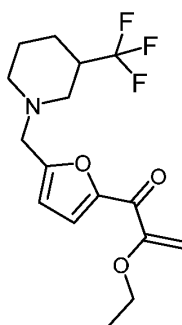
was added and the reaction mixture was stirred for 15h at rt. Methanol was removed in vacuo, the residue was diluted with water and acidified to pH 1. The acidified solution was evaporated to dryness and treated with acetonitrile. Solids were filtered and filtrate was evaporated in vacuo to dryness. Yield 3.88 g (96.8%). LC-MS 0.7 min, m/z 278.5 [MH]⁺.

5 **Synthesis of N-methoxy-N-methyl-5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxamide:**



To a stirred mixture of 5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxylic acid (3.88 g, 12.4 mmol), N,O-dimethylhydroxylamine (1.45 g, 1.2 eq), HOBt (2.23 g, 1.2 eq),
 10 and triethylamine (6.9 ml, 5 g, 4eq) in DCM (100 ml) at 5°C was added EDCI (2.85 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent CCl₄/EtOAc 1:1). Yield 2.91 g (73.5%). LC-MS 0.93 min, m/z 321.4 [MH]⁺. ¹H NMR (400 MHz, CDCl₃), δ
 15 (ppm) : 7.11 (d, J = 3.4 Hz, 1H), 6.34 (d, J = 3.3 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 2H), 3.35 (s, 3H), 3.07 (d, J = 10.7 Hz, 1H), 2.92 (d, J = 11.3 Hz, 1H), 2.50 – 2.23 (m, 1H), 2.15 – 1.99 (m, 2H), 1.94 (d, J = 12.2 Hz, 1H), 1.75 (d, J = 19.3 Hz, 1H), 1.59 (q, J = 13.1 Hz, 1H).

Synthesis of 2-ethoxy-1-(5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-yl)prop-2-en-1-one:



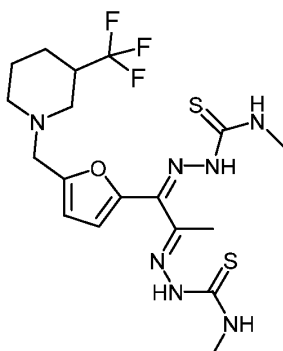
20

A solution of ethyl vinyl ether (1.66 g, 2.2 ml, 6.7 eq) in dry THF (80 mL) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 12 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and cooled down to -30°C. A solution of N-

methoxy-N-methyl-5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-carboxamide (1.1 g, 3.4 mmol) in THF was added, and then the reaction was stirred at 0°C for 4 h. The progress of the reaction was monitored by TLC. The mixture was poured into aq NH₄Cl and extracted with Et₂O. The combined extracts were dried over anhydrous Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification.

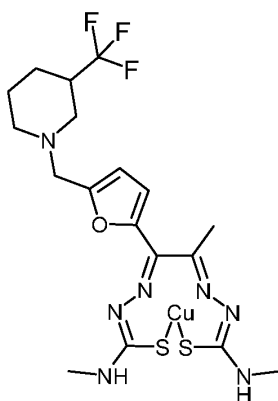
Yield 1.13 g (99%). LC-MS 1.1 min, m/z 332.6 [MH]⁺.

Synthesis of INT-125 ((2E,2'E)-2,2'-(1-(5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-yl)propane-1,2-diylidene)bis(N-methylhydrazine-1-carbothioamide)):



2-ethoxy-1-(5-((3-(trifluoromethyl)piperidin-1-yl)methyl)furan-2-yl)prop-2-en-1-one (1.13 g, 3.3 mmol, 1 eq) was dissolved in EtOH (50 ml), methylthiosemicarbazide (0.72 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, water, Et₂O, and dried. The product was purified by column chromatography (silica gel, eluent CCl₄/EtOAc 1:1) Yield 0.22g (13.2%). LC-MS 1.15 min, m/z 478.5 [MH]⁺.

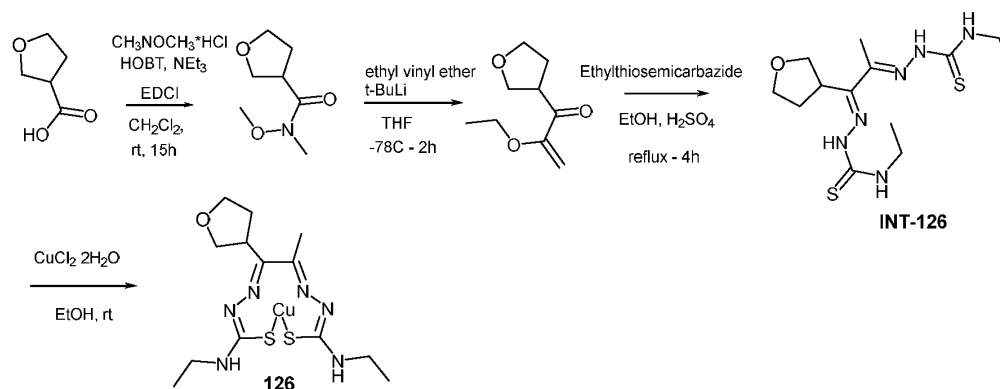
Synthesis of Compound 125:



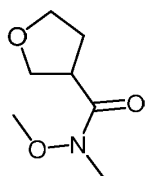
Copper(II) chloride dihydrate (0.183 g, 1.1 eq) was added to INT-125 (0.4 g, 9.8 mmol, 1 eq) in ethanol. The mixture was stirred for 15h at rt. The formed complex

precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, methanol, diethyl ether, and dried. Yield 0.16 g (34.8 %).

Scheme 87: Synthesis of Compound 126

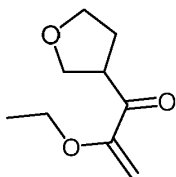


5 Synthesis of N-methoxy-N-methyltetrahydrofuran-3-carboxamide:



- To a stirred mixture of tetrahydrofuran-3-carboxylic acid (3.71 g, 31.9 mmol), N,O-dimethylhydroxylamine (3.74 g, 1.2 eq), HOBT (5.87 g, 1.2 eq), and triethylamine (8.9 ml, 6.46 g, 2eq) in DCM (100 ml) at 5°C was added EDCI (7.35 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na₂SO₄ and then concentrated under reduced pressure. The product was purified by column chromatography (silica gel, eluent DCM 100% then DCM/EtOAc 8:2). Yield 3.06 g (60.1%). ¹H-NMR (400 MHz, CDCl₃), δ (ppm) : 4.01 (t, *J* = 8.3 Hz, 1H), 3.89 – 3.73 (m, 3H), 3.68 (d, *J* = 1.0 Hz, 3H), 3.38 (dd, *J* = 17.7, 10.3 Hz, 1H), 3.18 (d, *J* = 11.2 Hz, 3H), 2.25 – 2.14 (m, 1H), 2.10 – 1.97 (m, 1H).

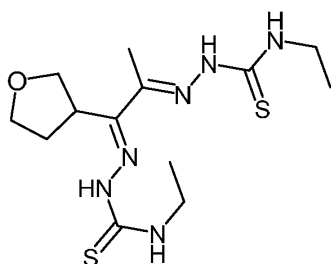
Synthesis of 2-ethoxy-1-(tetrahydrofuran-3-yl)prop-2-en-1-one:



- A solution of ethyl vinyl ether (4.48 g, 6 ml, 6.6 eq) in dry THF (1000 ml) was cooled to -78°C, and *tert*-butyllithium (1.7M in pentane, 33 ml, 6 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C. A solution

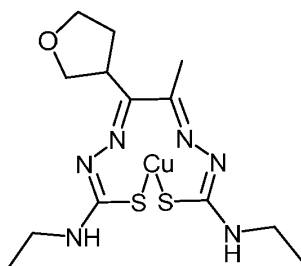
- of N-methoxy-N-methyltetrahydrofuran-3-carboxamide (0.56 g, 7mmol) in THF (15ml) was added, and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH₄Cl (100ml) and extracted with Et₂O (3x100ml). The combined extracts were dried over anh. Na₂SO₄, filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 1.6 g (99.8%). LC-MS 0.91 min, m/z 180.9 [MH]⁺.

Synthesis of INT-126 ((2E,2'E)-2,2'-(1-(tetrahydrofuran-3-yl)propane-1,2-diylidene)bis(N-ethylhydrazine-1-carbothioamide)):



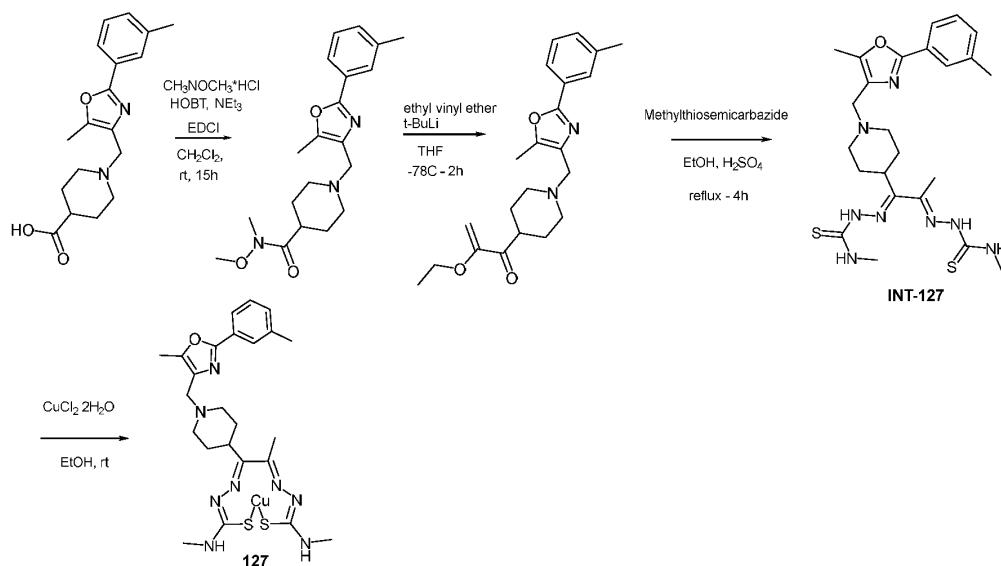
- 2-ethoxy-1-(tetrahydrofuran-3-yl)prop-2-en-1-one (1.6 g, 9.4 mmol) was dissolved in EtOH (15 ml), ethylthiosemicarbazide (0.33 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The formed precipitate was filtered, washed with EtOH, aq.sat. Na₂CO₃, water, Et₂O, and dried. The product was purified by crystallization from CH₃CN. Yield 0.13 g (26.4%). LC-MS 1.25 min, m/z 317.3 [MH]⁺.

Synthesis of Compound 126:

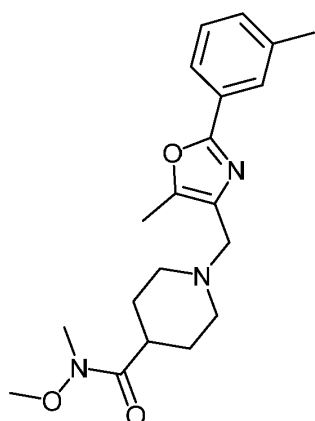


- Copper(II) chloride dihydrate (0.17g, 1 eq) was added to a stirred solution of **INT-126** (0.32 g, 1 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.34g (88.7%).

Scheme 88: Synthesis of Compound 127



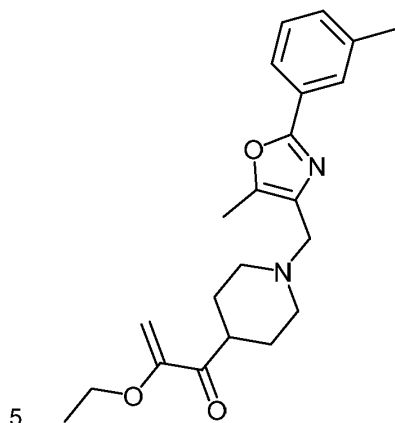
Synthesis of N-methoxy-N-methyl-1-((5-methyl-2-(m-tolyl)oxazol-4-yl)methyl)piperidine-4-carboxamide:



- 5 To a stirred mixture of 1-((5-methyl-2-(m-tolyl)oxazol-4-yl)methyl)piperidine-4-carboxylic acid (5.1 g, 16.2 mmol), N,O-dimethylhydroxylamine (1.9 g, 1.2 eq), HOBt (2.63 g, 1.2 eq), and triethylamine (5.6 ml, 4.03 g, 2.5 eq) in DCM (50 ml) at 5°C was added EDCI (3.73 g, 1.2 eq) and reaction was stirred for 15h at rt. The mixture was washed with water and brine. The organic layer was dried over anh. Na_2SO_4 and then concentrated under reduced pressure. Product was purified by column chromatography (SiO_2 , eluent DCM 100% then DCM/MeOH 96:4). Yield 2.3 g (39.7%). LC-MS 1.16 min, m/z 358.5 $[\text{MH}]^+$. ^1H -NMR (400 MHz, CDCl_3), δ (ppm) : 7.87 (s, 1H), 7.81 (d, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.22 (d, $J = 7.6$ Hz, 1H), 3.70 (s, 3H), 3.51 (s, 2H), 3.18 (s, 3H), 3.06 (d, $J = 11.1$ Hz,
- 10

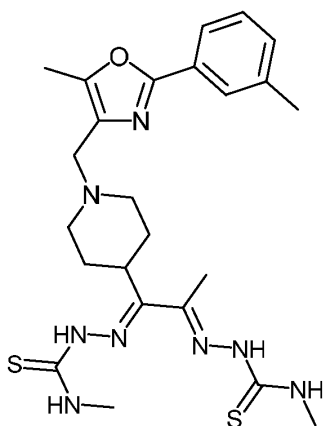
2H), 2.67 (s, 1H), 2.40 (d, $J = 1.1$ Hz, 6H), 2.15 (s, 2H), 1.89 (dd, $J = 22.2, 10.5$ Hz, 2H), 1.78 (s, 2H).

Synthesis of 2-ethoxy-1-(1-((5-methyl-2-(*m*-tolyl)oxazol-4-yl)methyl)piperidin-4-yl)prop-2-en-1-one:



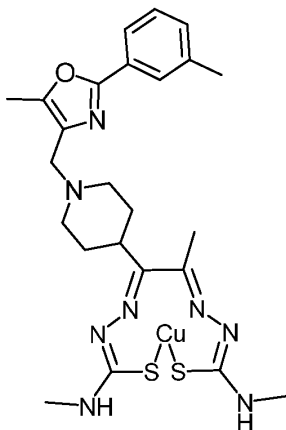
A solution of ethyl vinyl ether (2.55 g, 3.4 ml, 5.5 eq) in dry THF (130 ml) was cooled to -78°C , and *tert*-butyllithium (1.7M in pentane, 20 ml, 5 eq) was added. The mixture was warmed to 0°C over 1h period, stirred for 45 min, and then cooled down to -30°C . A solution of N-methoxy-N-methyl-1-((5-methyl-2-(*m*-tolyl)oxazol-4-yl)methyl)piperidine-4-carboxamide (2.3 g, 6.4 mmol) in THF (15ml) was added and stirring continued at 0°C for 4 h. The mixture was poured into aq. NH_4Cl (100ml) and extracted with Et_2O (3x100ml). The combined extracts were dried over anhyd. Na_2SO_4 , filtered, and solvents were evaporated in vacuo. The product was used for the next step without additional purification. Yield 2.37 g (100%). LC-MS 1.25 min, m/z 369.4 $[\text{MH}]^+$.

15 **Synthesis of INT-127 ((2*E*,2'*E*)-2,2'-(1-(1-((5-methyl-2-(*m*-tolyl)oxazol-4-yl)methyl)piperidin-4-yl)propane-1,2-diylidene)bis(*N*-methylhydrazine-1-carbothioamide)):**



2-ethoxy-1-(1-((5-methyl-2-(m-tolyl)oxazol-4-yl)methyl)piperidin-4-yl)prop-2-en-1-one (2.37 g, 2.2 mmol) was dissolved in EtOH (150 ml), methylthiosemicarbazide (1.35 g, 2 eq) and 3 drops of H₂SO₄ were added. The stirred reaction mixture was heated to reflux for 4h and then maintained for 15h at rt. The solvent was evaporated in vacuo. The residue was dissolved in EtOAc and washed with aq.sat. NaHCO₃, water, dried over anh. Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, eluent DCM/MeOH 96:4). Yield 0.44 g (13.3%). LC-MS 1.31 min, m/z 515.3 [MH]⁺.

10 **Synthesis of Compound 127:**



Copper(II) chloride dihydrate (0.024 g, 1 eq) was added to a stirred solution of **INT-127** (0.073 g, 0.14 mmol) in ethanol. The mixture was stirred for 15h at rt. The formed complex precipitated as a red-brown powder. The precipitate was collected by filtration, washed with water, diethyl ether, and dried. Yield 0.057 g (69.7%).

Example 7: Efficacy of Copper Compounds in SOD1^{G93A} Mice

The SOD1^{G93A} transgenic mouse model of ALS has been the most widely used animal model since the 1990s. The mouse was genetically engineered to overexpress a mutant form of the human Cu/Zn superoxide dismutase 1 (SOD1) gene harboring an ALS-associated glycine to alanine mutation at amino acid position 93 (G93A). These mice replicate many of the features of ALS, such as motor neuron loss, muscle wasting, progressive paralysis and decreased survival. Additionally, the SOD1^{G93A} mouse model has shown to be ideal for drug screening because of early onset of the disease and moderate progression.

The mice were treated with vehicle, 10 mg/kg or 30 mg/kg CuATSM or one of the derivatives: Compound 25 (2% DMSO, 10% KolliphorHS15), Compound 9 (0.5% methylcellulose), Compound 24 (0.5% methylcellulose, 0.4% TWEEN-80), and Compound 37 (0.5% methylcellulose, 0.4% TWEEN-80). Measurements were taken to assess compound muscle action potential (CMAP), neuroscore, and disease onset and survival.

Methods:

Neuroscore

Neuroscore is a neurological scoring system based on visual observations of the hindlimb designed to assess the neuromuscular function of SOD1^{G93A} mice. The hindlimb is observed due to this being the earliest reported neurological sign of disease in SOD1^{G93A} mice. This method provides an unbiased assessment of onset of paresis (slight or partial paralysis) and the progression and severity of the paralysis. This method has also proven to be sensitive enough to identify drug-induced changes in disease progression. Neuroscore is assigned on a 0-4 scale corresponding to the following observations: NS0=the hindlimbs present with a normal splay; NS1=hindlimbs present with an abnormal splay; NS2=the hindlimbs show signs of paresis or are partially paralyzed; NS3=rigid paralysis in the hindlimbs; NS4=the mouse is unable to right itself up. These measurements were used in the current study to assess disease onset.

Disease Onset and Survival

It has been shown that SOD1^{G93A} mice have significantly shortened lifespans compared to wild-type mice. The onset of disease in the SOD1^{G93A} mice typically happens around age day 90-100, with mice eventually succumbing to the disease around age day 120-130. For comparison, a wild-type mouse of the same background may live up to 2 years. The onset of the disease in the current study was defined as the time to observe a neuroscore of NS2 in the mouse, while a neuroscore of a NS4 was considered to be the humane end-point. Reported p-values to illustrate statistical significant represent a log-rank test.

Compound Muscle Action Potential (CMAP)

Compound muscle action potential (CMAP) is an electrophysiological technique that assesses the functional integrity of motor axons. Male SOD1^{G93A} mice were treated with vehicle (control), 10 mg/kg, or 30 mg/kg every day for five weeks starting at about age day 50 via oral gavage. The response was measured in the innervated tibialis anterior (TA) muscle using an implanted recording electrode. To establish baseline CMAP measurements, the mice were anesthetized, and the sciatic nerve was stimulated using implanted microelectrodes which provided small electrical currents prior to treatment with the compound or vehicle. Mice were then randomized into each treatment cohort. After daily dosing and at the end of the experiment, CMAP data was recorded and compared to the baseline measurements to calculate change from baseline and % of baseline. Data was calculated and represented as a mean $\pm$ SEM, and statistics were calculated with a one-way ANOVA with Dunnett's Multiple Comparison Test vs. control mice; * p<0.05, ** p<0.01.

Results:

CuATSM

CuATSM has been used in clinical studies as an experimental treatment for ALS, but suffers from certain drawbacks that can limit its use as a therapeutic agent. CuATSM has been shown to possess a high affinity for copper, potentially causing this agent to be an inefficient delivery vehicle to bypass the distribution system that naturally limits copper transport into the central nervous system. Further, CuATSM has a compact, symmetric structure, which contributes to another limitation associated with this compound: its compact structure allows the ATSM ligand component to rapidly form extremely stable crystals, which causes several challenges in making and formulating this compound, hindering its ability to serve as suitable pharmacological agent.

Male SOD1^{G93A} mice were treated with 10 mg/kg (n=9) or 30 mg/kg CuATSM (n=8) or vehicle (0.5% methylcellulose, 0.4% TWEEN-80, 0.9% normal saline; n=9). Changes from baseline CMAP values were observed for each cohort of mice. After four weeks of daily dosing with CuATSM or vehicle, no differences in the changes from baseline (**FIG. 1A**) or percent of baseline CMAP (**FIG. 1B**) values were observed between the different cohorts.

Compound 25

SOD1^{G93A} mice treated with 10 mg/kg (n=9) or 30 mg/kg (n=9) of Compound 25 or vehicle (2% DMSO, 10% KolliphorHS15; n=8) daily for 15 days. Treatments were performed daily starting at about age 50 by oral gavage. Compound muscle action potential (CMAP) was recorded for each cohort of mice, as a change from baseline after five weeks of dosing. The mice administered either 10 mg/kg or 30 mg/kg Compound 25 exhibited significant change in CMAP measurements from baseline compared to control mice (**FIG. 2A**). **FIG. 2B** illustrates CMAP data as a percentage of baseline after 5 weeks of dosing. The mice who

received 10 mg/kg or 30 mg/kg Compound 25 demonstrated significantly less change than the mice receiving vehicle.

It was found that chronic daily dosing produced several beneficial effects which included a delayed disease onset (**FIG. 3A**) as measured by the onset of paresis and the neuroscore. Disease onset seen in mice receiving Compound 25 was more delayed compared to mice receiving vehicle, with mice receiving 30 mg/kg displaying significantly delayed onset (113 days) compared to the mice receiving 10 mg/kg (103 days) and the control mice receiving vehicle (98 days).

Survival was also observed based on the neuroscore testing, and once a mouse reached a neuroscore of NS4, it was determined the mouse had reached a humane end-point, and survival was recorded. Treatment with Compound 25 extended median survival by 7 days (126 days) for mice receiving 30 mg/kg and 6 days (125 days) for mice receiving 10 mg/kg, compared to the mice receiving vehicle (119 days) (**FIG. 3B**).

Due to the significant improvement of the mice that received Compound 25, additional measurements were observed in mice that were chronically dosed daily with 30 mg/kg of Compound 25 and compared to control mice. Overall, Compound 25 displayed benefits in a survival efficacy study based on the onset of definitive neurological disease measured as a proportion at onset (**FIG. 4A**), proportion of the cohort surviving as a function of age (**FIG. 4B**), change in body weight (**FIG. 4C**), and ordinal expected score by median age at the time the mice reached a neurological score of NS4 (**FIG. 4D**).

Compound 9

Like Compound 25, male SOD1^{G93A} mice were dosed with 10 mg/kg (n=8) or 30 mg/kg (n=8) of Compound 9, or vehicle (0.5% methylcellulose; n=9). Treatment began around age Day 50 via oral gavage and were administered to the mice daily. CMAP values were recorded for the cohorts after four weeks of dosing with Compound 9 or vehicle, and are illustrated as either change from baseline (**FIG. 5A**) or % of baseline (**FIG. 5B**). Disease onset (**FIG. 6A**) and survival (**FIG. 6B**), and there was no significant difference observed between the mice given either dose of Compound 9 or vehicle. Overall, Compound 9 did not significantly affect disease onset or survival in SOD1G93A mice.

Compound 24

Male SOD1^{G93A} mice were dosed with 10 mg/kg (n=9) or 30 mg/kg (n=9) Compound 24, or vehicle (0.5% methylcellulose, 0.4% TWEEN-80; n=9) daily starting around age Day 50 via oral gavage. CMAP values were recorded for the cohorts after five weeks of dosing with Compound 24 or with the vehicle. CMAP data is illustrated as either change from the baseline (**FIG. 7A**) or % of baseline (**FIG. 7B**). Mice treated with Compound 24 at either dose did not significantly improve CMAP values over the control mice.

Despite no significant improvement in CMAP values, mice administered 30 mg/kg Compound 24 daily experienced a significant delay in disease onset (**FIG. 8A**) and survival (**FIG. 8B**). Mice treated with 30 mg/kg of the compound saw an improvement of median disease onset by 16 days over the control (disease onset at day 124). The same mice saw extended survival by 11 days, with median survival at 137 days as compared to 126 days observed in the control mice.

Compound 37

Male SOD1^{G93A} mice were dosed with 10 mg/kg (n=9) or 30 mg/kg (n=9) Compound 37, or with vehicle as a control (0.5% methylcellulose, 0.4% TWEEN-80; n=9) daily starting around age Day 50 via oral gavage. CMAP values were measured after four weeks of dosing. CMAP data is illustrated as either change from baseline (**FIG. 9A**) or % of baseline (**FIG. 9B**). Treatment with Compound 37 did not attenuate the CMAP decline in ALS mice.

Similarly, when disease onset (**FIG. 10A**) and survival (**FIG. 10B**) were measured in mice treated with Compound 37 at either dose of 10 mg/kg or 30 mg/kg, neither dose significantly affected either parameters over mice treated with vehicle.

Example 8: In Vitro Activity of Cu Complexes

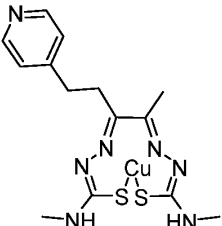
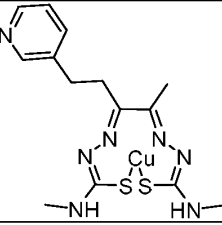
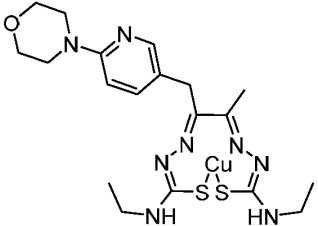
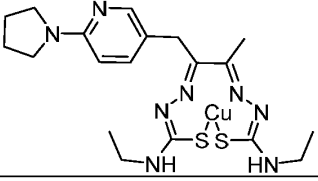
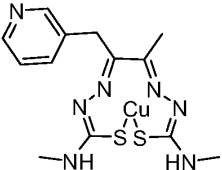
In vitro activity of the ligands and their Cu and Zn complexes was determined as their ability to promote viability of human neurogenic cells in a cell-based assay. Cells were treated with the compounds added to the culture medium for 7 days. Cell viability was determined at the end of the treatment period using the CellTiter Blue[®] cell viability assay (Promega). The corresponding EC₅₀ values were calculated using nonlinear regression fitting of the standard variable slope dose response model provided in the GraphPad Prism software.

Activity ranges of compounds of the disclosure are provided in Table 1 according to the following key:

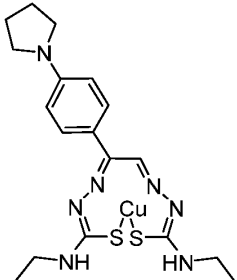
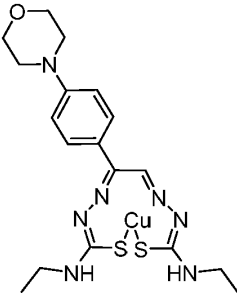
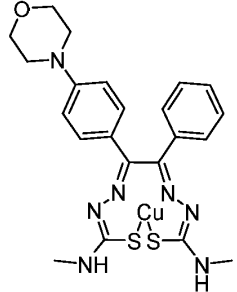
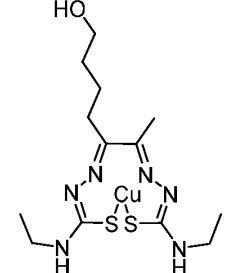
- A: EC₅₀ between 0.5 nM and 10 nM;
- B: EC₅₀ between 11nM and 25 nM;
- C: EC₅₀ between 26 nM and 50 nM;
- D: EC₅₀ between 51 nM and 100 nM; and
- E: EC₅₀ between 101 nM and 500 nM.

Table 1

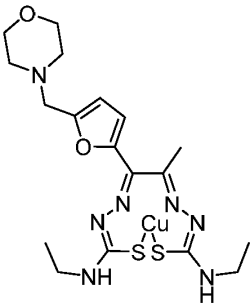
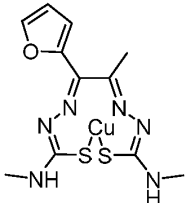
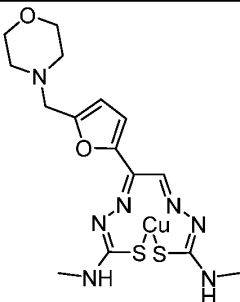
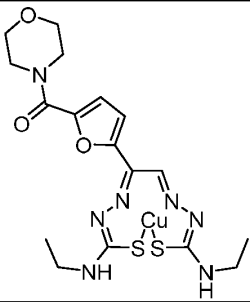
Cpd #	Structure	Activity
Cu-ATSM		D
Cu-PTSM		A
1		C
2		A
3		C
4		B

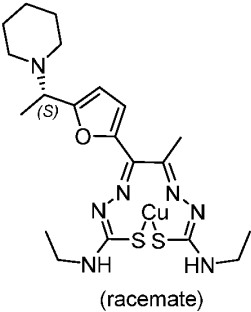
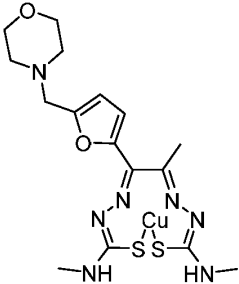
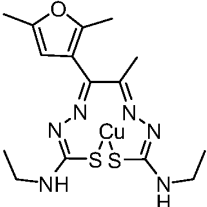
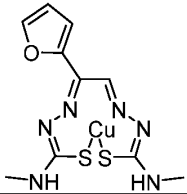
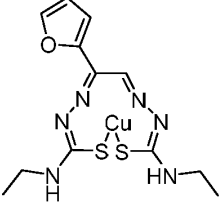
Cpd #	Structure	Activity
5		C
6		C
7		E
8		D
9		C

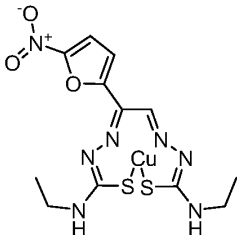
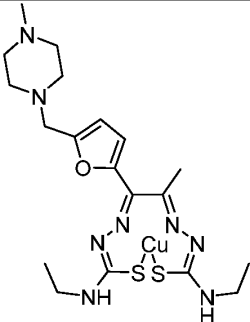
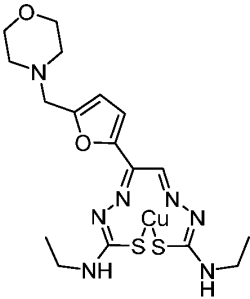
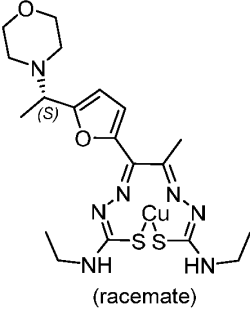
Cpd #	Structure	Activity
10		C
11		B
12		A
13		D

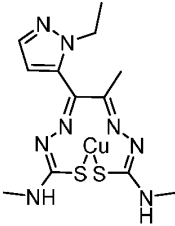
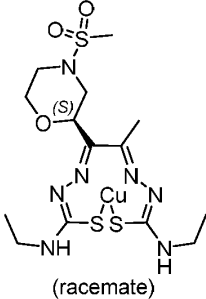
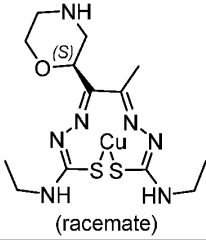
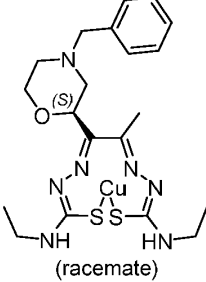
Cpd #	Structure	Activity
14		D
15		B
17		B
18		D

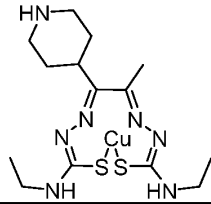
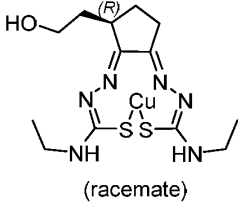
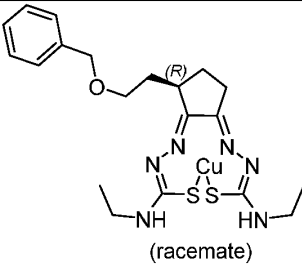
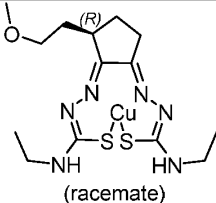
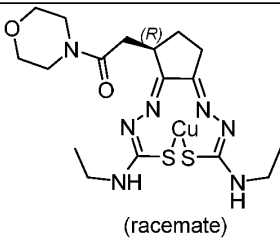
Cpd #	Structure	Activity
19		E
20		E
21		D

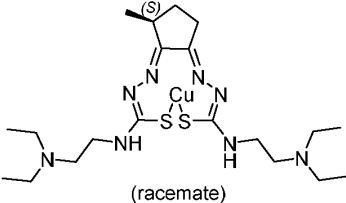
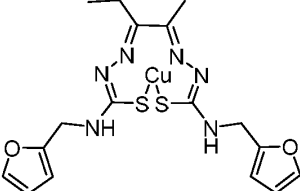
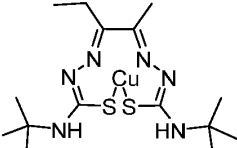
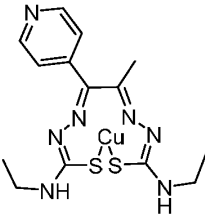
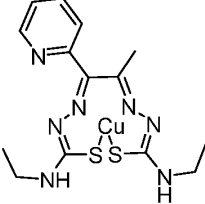
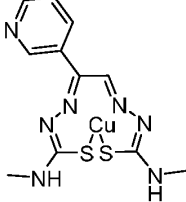
Cpd #	Structure	Activity
24		C
25		A
29		B
30		B

Cpd #	Structure	Activity
31	 (racemate)	C
32		A
33		C
34		A
35		B

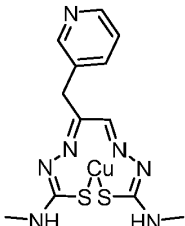
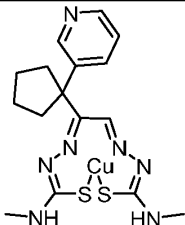
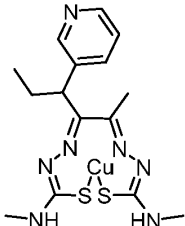
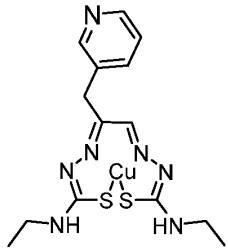
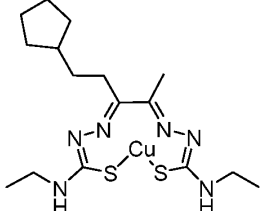
Cpd #	Structure	Activity
36		C
37		B
38		C
39	 (racemate)	D

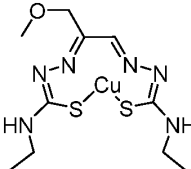
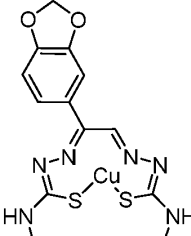
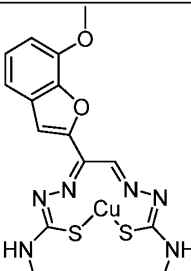
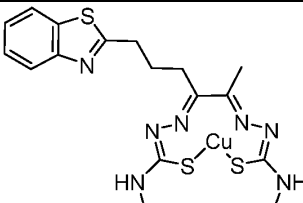
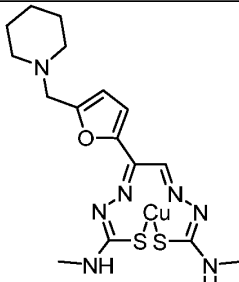
Cpd #	Structure	Activity
41		B
43	 (racemate)	B
44	 (racemate)	A
45	 (racemate)	C

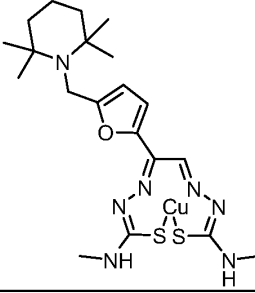
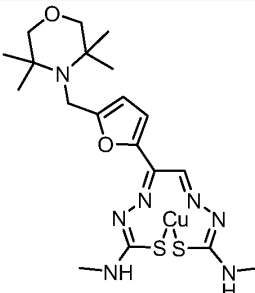
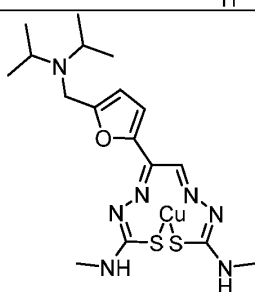
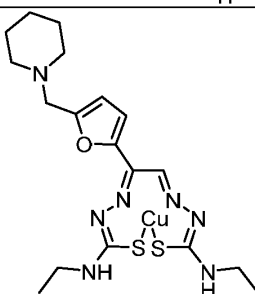
Cpd #	Structure	Activity
46		C
47	 (racemate)	E
48	 (racemate)	E
49	 (racemate)	D
50	 (racemate)	D

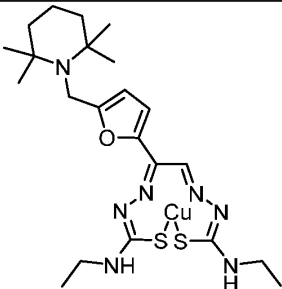
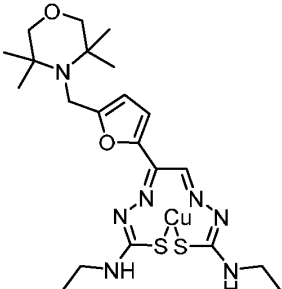
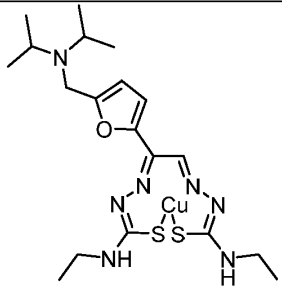
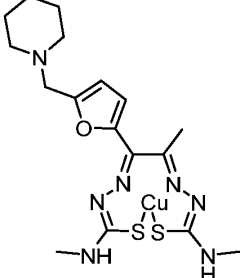
Cpd #	Structure	Activity
53	 (racemate)	C
54		A
55		C
56		B
58		B
59		A

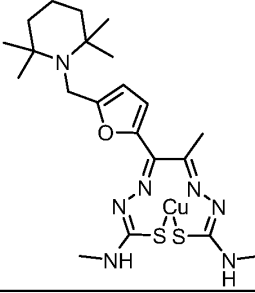
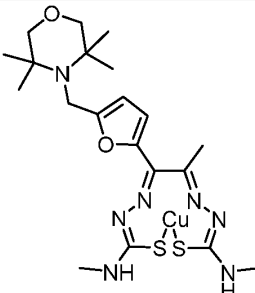
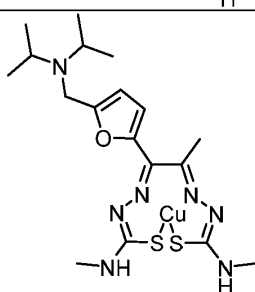
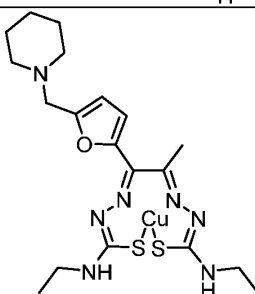
Cpd #	Structure	Activity
60		A
61		A
62		B
63		C
65		C

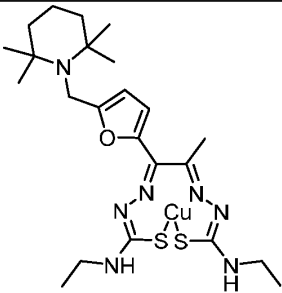
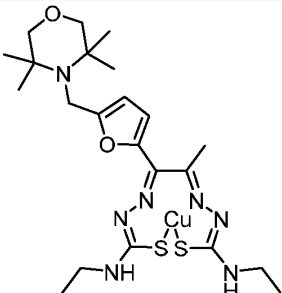
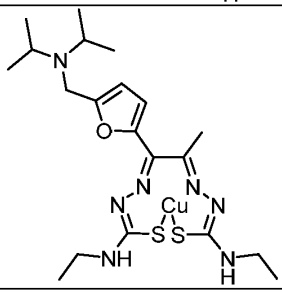
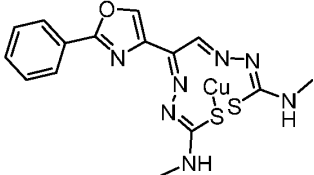
Cpd #	Structure	Activity
66		A
68		D
69		C
71		B
73		D

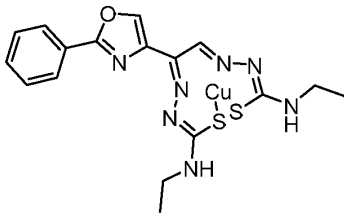
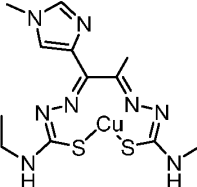
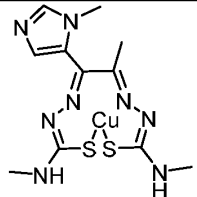
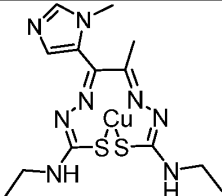
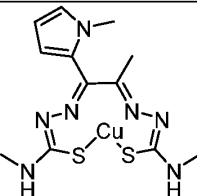
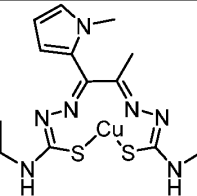
Cpd #	Structure	Activity
74		A
75		B
77		A
78		D
79		B

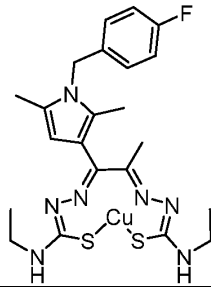
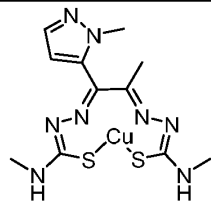
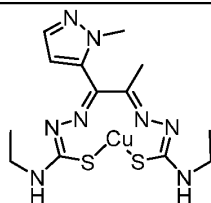
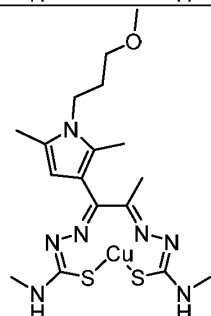
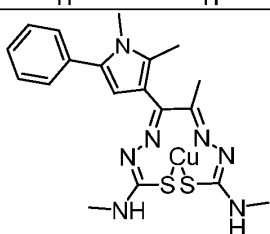
Cpd #	Structure	Activity
80		B
81		B
82		A
83		B

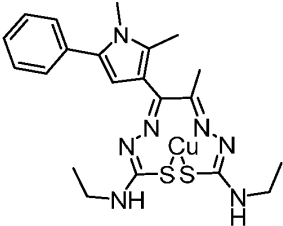
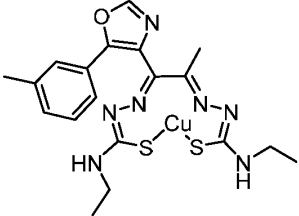
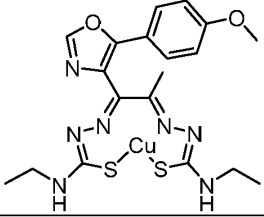
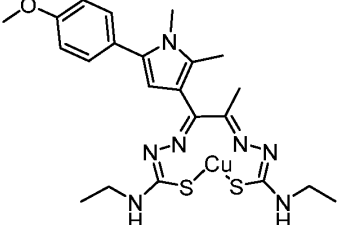
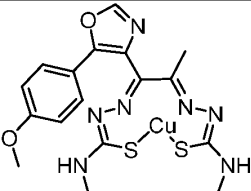
Cpd #	Structure	Activity
84		B
85		B
86		B
87		A

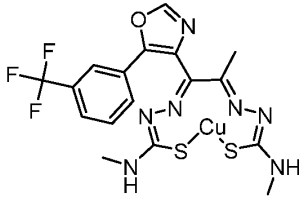
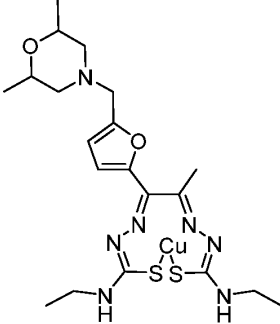
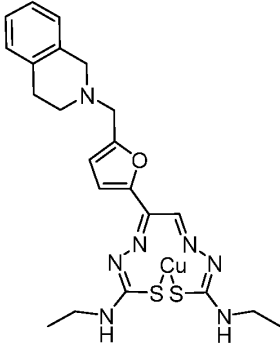
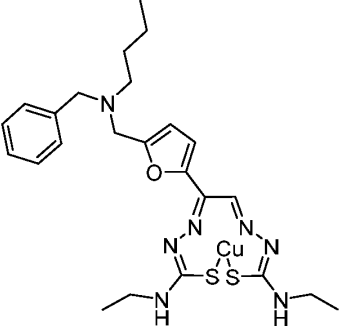
Cpd #	Structure	Activity
88		B
89		C
90		A
91		A

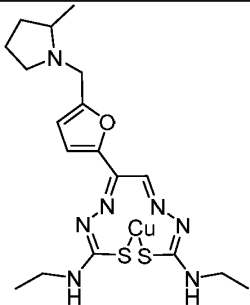
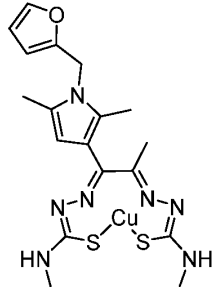
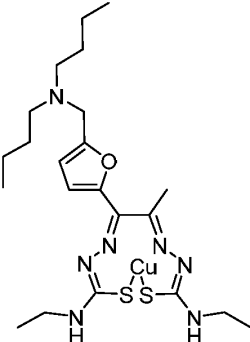
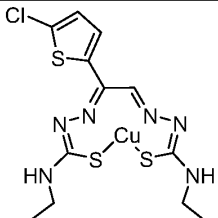
Cpd #	Structure	Activity
92		E
93		D
94		A
95		A

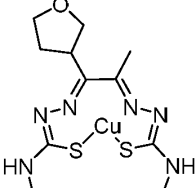
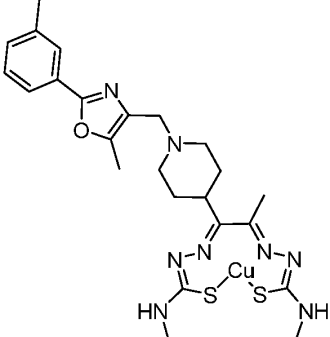
Cpd #	Structure	Activity
96		B
98		A
99		C
100		A
101		B
102		E

Cpd #	Structure	Activity
104		B
105		A
106		A
107		C
109		B

Cpd #	Structure	Activity
110		D
111		E
112		E
113		D
114		D

Cpd #	Structure	Activity
115		C
116		B
118		D
119		C

Cpd #	Structure	Activity
120		A
121		C
122		B
123		A

Cpd #	Structure	Activity
126		C
127		B

Example 9: Analysis of Compounds 25 and 34 in Mouse Plasma and Spinal Cord Tissue

Mouse spinal cord samples were homogenized by first thawing frozen tissues in an ice bath, where samples were kept when not actively being processed. Phosphate buffered saline (200 μ L), pH 7.4, was added to each tissue, which was homogenized by

5 ultrasonication with a microprobe at 40% output for approximately 15 sec. Homogenate samples were stored frozen at -70°C until analysis.

Mouse plasma samples or spinal cord homogenate samples (20 μ L) were added to polypropylene test tubes containing 150 μ L of extraction buffer [ammonium phosphate dibasic:ammonium citrate tribasic:ammonium hydroxide:water (0.880:1.05:1.70:~98.3, w/w/v/v)]. Internal standard solution (10 μ L of 100 ng/mL) was added to each tube.

10 Compound 25 was the internal standard for Compound 34 and vice versa. All tubes were mixed by vortexing. The contents of each tube were transferred to appropriate wells of a Biotage Isolute SLE+ plate (200 μ L size; Uppsala, Sweden). Samples were briefly loaded

15 onto the plate with positive pressure (~1 psi) and allowed to rest for 5 minutes. Dichloromethane (1 mL) was added to each well and allowed to flow through via gravity. Brief positive pressure (~1 psi) was used to complete the elution process. All wells of the

receiver plate were supplemented with 25 μ L of 4% propylene glycol in isopropanol (v/v).

The solvent was evaporated under a stream of nitrogen, and the samples were reconstituted with 300 μ L of [0.2% formic acid, 10 mM ammonium formate in water]: [0.2% formic acid, 10 mM ammonium formate in acetonitrile:water (9:1, v/v)], (1:1, v/v). The plate was capped,
5 lightly vortex mixed, and stored at 10°C pending analysis.

Separate tubes for the calibrators were prepared similarly using blank mouse plasma (K₂EDTA) or blank spinal cord homogenate as appropriate.

The extracts were analyzed using an Agilent 1200 HPLC system (Agilent, Santa Clara, CA) coupled to an API5500 mass analyzer (SCIEX, Foster City, CA). Analytes were
10 chromatographically separated using a Kinetex® PhenylHexyl column (50 x 2.1 mm, 2.6 μ m; Phenomenex, Torrance, CA) using a mobile phase system consisting of Mobile Phase A (0.2% formic acid, 10 mM ammonium formate in water) and Mobile Phase B (0.2% formic acid, 10 mM ammonium formate in acetonitrile:water (9:1, v/v)). The following gradient profile was used.

Time (min)	Flow Rate (mL/min)	%A	%B
Initial	300	50	50
0.50	300	50	50
2.50	300	20	80
2.51	300	2	98
3.00	300	2	98
3.01	300	50	50
4.00	300	50	50

15

The mobile phase was nebulized using heated nitrogen in a Turbo-V source/interface set to electrospray positive ionization mode. The ionized compounds were detected using multiple reaction monitoring with transitions m/z 373.95 > 300.9 (Compound 25) and 360 > 286.9 (Compound 34).

20

The peak heights of Compounds 25 and 34 were acquired using Analyst v. 1.6.2 (SCIEX, Framingham, MA). The calibration curve was obtained by fitting the peak height ratios of the analyte/I.S. and the standard concentrations to a quadratic equation with $1/x^2$ weighting, using Analyst. The equation of the calibration curve was then used to interpolate the concentrations of the analyte in the samples using their peak height ratios. Results for
25 Compound 25 are depicted in FIGS. 11A, 11B, 12A, 12B. Results for Compound 34 are depicted in FIGS. 13A, 13B, 14A, 14B.

Example 10: Analysis of Compounds 32 and 29 in Mouse Plasma and Spinal Cord Tissue

Mouse spinal cord samples were homogenized by first thawing frozen tissues in an ice bath, where samples were kept when not actively being processed. Phosphate buffered saline (200 μ L), pH 7.4, was added to each tissue, which was homogenized by ultrasonication with a microprobe at 40% output for approximately 15 sec. Homogenate samples were stored frozen at -70°C until analysis.

Mouse plasma samples or spinal cord homogenate samples (20 μ L) were added to wells of a Biotage Isolute PPT+ plate (Uppsala, Sweden) containing 200 μ L of acetonitrile. Internal standard solution (20 μ L of 50 ng/mL) was added to each tube. Compound 32 was the internal standard for Compound 29 and vice versa. The samples were mixed gently by aspiration and dispensing using a multi-channel pipette, then they were allowed to rest for 5 min. Positive pressure was used to push the samples into the receiver plate. Deionized water (300 μ L) was added to each well, and the plate was capped and lightly vortex mixed prior to storage at 10°C pending analysis.

Separate tubes for the calibrators were prepared similarly using blank mouse plasma (K₂EDTA) or blank spinal cord homogenate as appropriate.

The extracts were analyzed using an Agilent 1200 HPLC system (Agilent, Santa Clara, CA) coupled to an API5500 mass analyzer (SCIEX, Foster City, CA). Analytes were chromatographically separated using an ACE Excel 2 C18-PFP column (100 x 2.1 mm, 2 μ m; Mac-Mod, Chadds Ford, PA) using a mobile phase system consisting of Mobile Phase A (0.2% formic acid, 10 mM ammonium formate in water) and Mobile Phase B (0.2% formic acid, 10 mM ammonium formate in acetonitrile:water (9:1, v/v)). The following gradient profile was used.

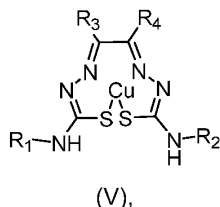
Time (min)	Flow Rate (mL/min)	%A	%B
Initial	300	60	40
0.50	300	60	40
2.50	300	10	90
3.00	300	10	90
3.01	300	60	40
4.00	300	60	40

The mobile phase was nebulized using heated nitrogen in a Turbo-V source/interface set to electrospray positive ionization mode. The ionized compounds were detected using multiple reaction monitoring with transitions m/z 473.05 > 385.9 (Compound 32) and 458.95 > 371.9 (Compound 29).

The peak heights of Compound 32 and Compound 29 were acquired using Analyst v. 1.6.2 (SCIEX, Framingham, MA). The calibration curve was obtained by fitting the peak height ratios of the analyte/I.S. and the standard concentrations to a quadratic equation with $1/x^2$ weighting, using Analyst. The equation of the calibration curve was then used to
5 interpolate the concentrations of the analyte in the samples using their peak height ratios. The peak heights used for the calculations were not rounded. Results for Compound 32 are depicted in FIGS. 15A, 15B, 16A, 16B. Results for Compound 29 are depicted in FIGS. 17A, 17B, 18A, 18B.

CLAIMS

1. A compound of Formula (V):



or pharmaceutically acceptable salts thereof, wherein:

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is 4- to 8-membered heterocycle or 5-membered heteroaryl, wherein the 4- to 8-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a}, and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkyl-(C₆-C₁₀ aryl), C₁-C₆ alkyl-(5- to 10-membered heteroaryl), S(O)₂H, S(O)₂-(C₁-C₆ alkyl), S(O)₂-(C₃-C₇ cycloalkyl), or S(O)₂-(C₆-C₁₀ aryl); wherein each heteroaryl is optionally further substituted one to four times with C₁-C₆ alkyl or C₆-C₁₀ aryl; and wherein each C₆-C₁₀ aryl is optionally further substituted one to four times with C₁-C₆ alkyl;

R_{3b} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ alkyl-N(R₅)₂, (C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), halo, nitro, cyano, C₆-C₁₀ aryl, C(O)-(4- to 8-membered heterocycle), C₁-C₆ alkyl-(C₆-C₁₀ aryl), C₁-C₆ alkyl-(5- to 10-membered heteroaryl), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C₆-C₁₀ aryl, and 5- to 10-membered heteroaryl are optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo;

R₄ is hydrogen or C₁₋₃ alkyl; and

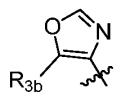
R₅ independently for each occurrence is hydrogen, C₁-C₆ alkyl, or C₁-C₃ alkyl-(C₆-C₁₀ aryl).

2. The compound of claim 1, wherein:

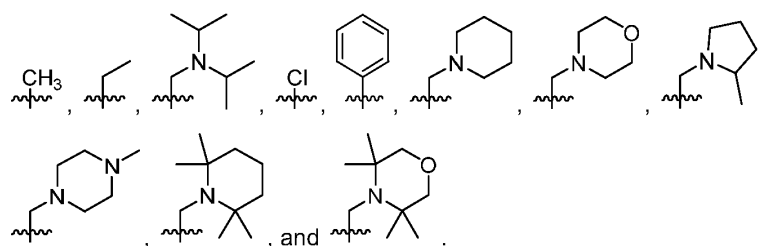
R₁ is C₁-C₆ alkyl optionally substituted with 5-membered heteroaryl; and

R₂ is C₁-C₆ alkyl optionally substituted with 5-membered heteroaryl.

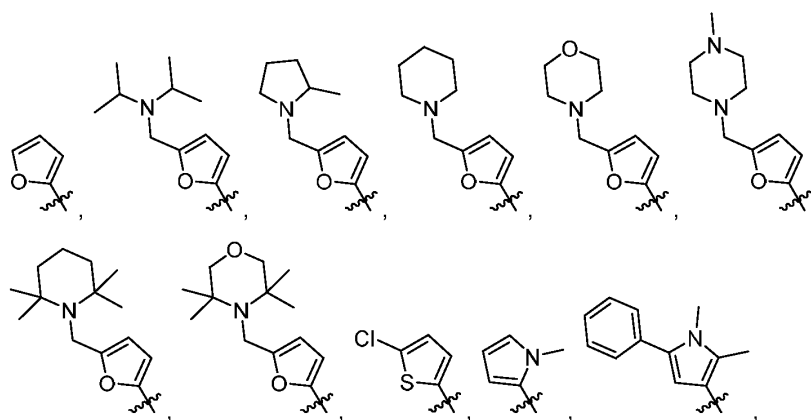
3. The compound of claim 1 or claim 2, wherein:
 R_1 is methyl or ethyl; and
 R_2 is methyl or ethyl.
4. The compound of any one of claims 1-3, wherein R_3 is tetrahydrofuranyl, morpholinyl, piperidinyl, furyl, thiophenyl, pyrrolyl, oxazolyl, pyrazolyl, or imidazolyl, wherein the tetrahydrofuranyl, morpholinyl, and piperidinyl are optionally substituted one, two, or three times with the group R_{3a} , and wherein the furyl, thiophenyl, pyrrolyl, oxazolyl, pyrazolyl, and imidazolyl are optionally substituted one, two, or three times with the group R_{3b} .
5. The compound of any one of claims 1-4, wherein R_3 is furyl, thiophenyl, oxazolyl, pyrazolyl, or imidazolyl optionally substituted one, two, or three times with the group R_{3b} .
6. The compound of any one of claims 1-6, wherein when R_3 is oxazolyl, R_3 does not have the following structure:

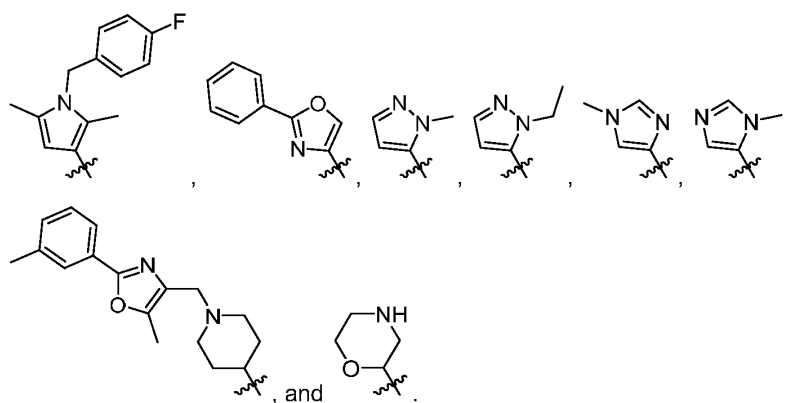


7. The compound of any one of claims 1-6, wherein when R_1 is not methyl, R_2 is not methyl, and R_4 is not hydrogen, then R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 alkyl- $N(R_5)_2$, (C_1 - C_6 alkyl)-O-(C_1 - C_6 alkyl), halo, nitro, cyano, C_6 - C_{10} aryl, C(O)-(4- to 8-membered heterocycle), C_1 - C_6 alkyl-(C_6 - C_{10} aryl), C_1 - C_6 alkyl-(5- to 10-membered heteroaryl), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle, C_6 - C_{10} aryl, and 5- to 10-membered heteroaryl are optionally further substituted one or two times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.
8. The compound of any one of claims 1-6, wherein R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl- $N(R_5)_2$, halo, C_6 - C_{10} aryl, C_1 - C_6 alkyl-(4- to 8-membered heterocycle), or C_1 - C_6 alkyl-(C_6 - C_{10} aryl), wherein each 4- to 8-membered heterocycle and C_6 - C_{10} aryl are optionally further substituted one to four times with C_1 - C_3 alkyl, C_1 - C_3 alkoxy, C_1 - C_3 haloalkyl, or halo.
9. The compound of any one of claims 1-7, wherein R_{3b} is selected from the group consisting of:

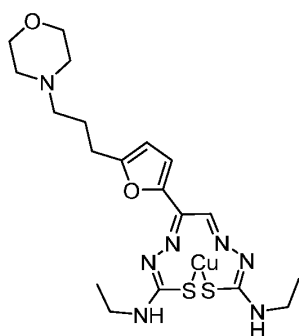


10. The compound of any one of claims 1-5 or 7, wherein R₃ is furyl optionally substituted one time with C₁-C₃ alkyl-N(C₁-C₄ alkyl)₂ or C₁-C₃ alkyl-(5- to 6-membered heterocycle), wherein the 5- to 6-membered heterocycle is optionally further substituted one to four times with C₁-C₃ alkyl.
11. The compound of any one of claims 1-7, wherein R₃ is thiophenyl, oxazolyl, pyrazolyl, or imidazolyl, optionally substituted one, two, or three times with C₁-C₆ alkyl, halo, C₆-C₁₀ aryl, or C₁-C₆ alkyl-(C₆-C₁₀ aryl), wherein each C₆-C₁₀ aryl is optionally further substituted one to four times with C₁-C₃ alkyl, C₁-C₃ alkoxy, C₁-C₃ haloalkyl, or halo.
12. The compound of any one of claims 1-4, wherein R₃ is selected from the group consisting of:

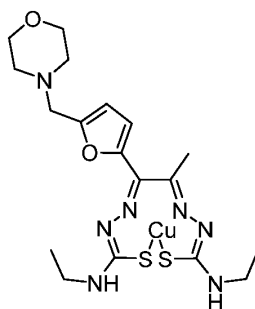




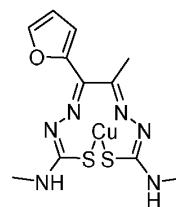
13. The compound of any one of claims 1-12, wherein R_4 is hydrogen or methyl.
14. The compound of any one of claims 1-8, 10, or 13, wherein R_5 is C_1 - C_4 alkyl or benzyl.
15. The compound of claim 1, selected from the group consisting of:



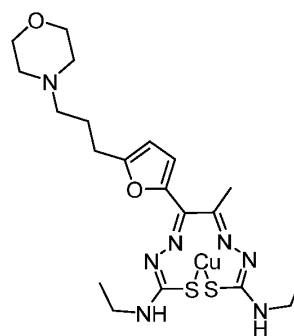
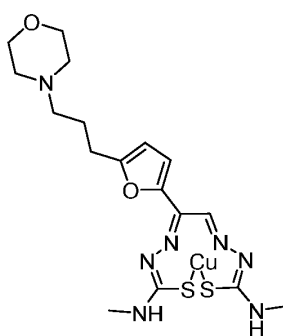
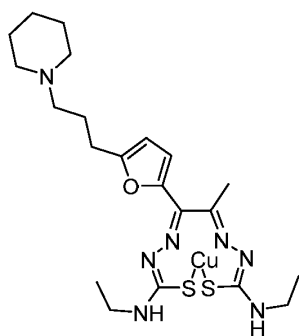
Compound 23



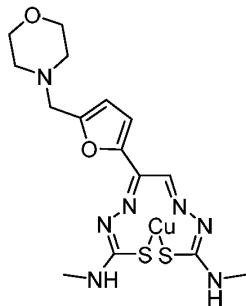
Compound 24



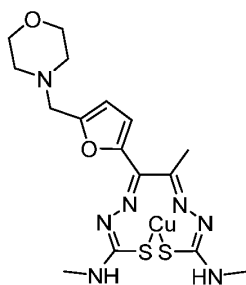
Compound 25



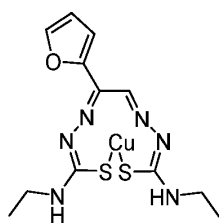
Compound 26



Compound 29

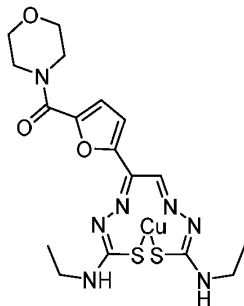


Compound 32

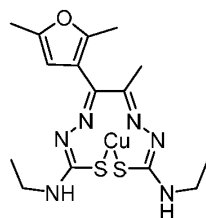


Compound 35

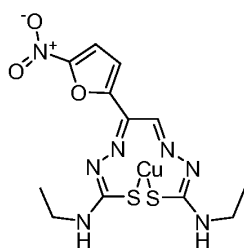
Compound 27



Compound 30

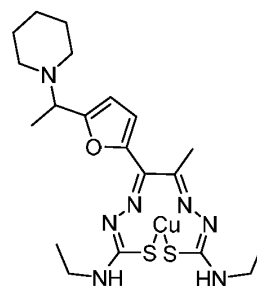


Compound 33

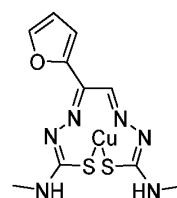


Compound 36

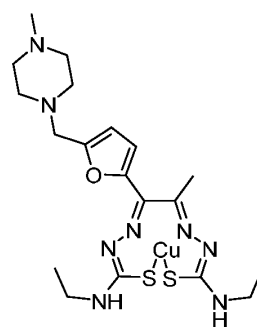
Compound 28



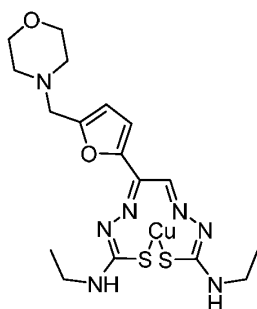
Compound 31



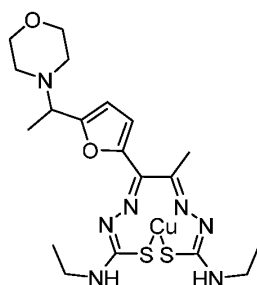
Compound 34



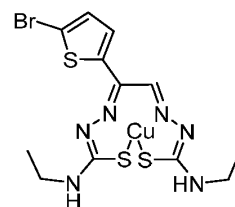
Compound 37



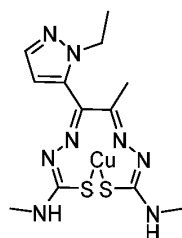
Compound 38



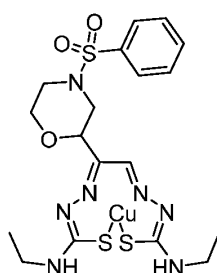
Compound 39



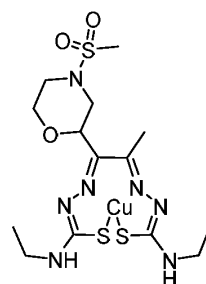
Compound 40



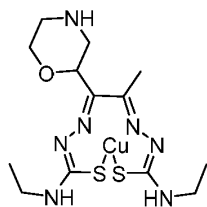
Compound 41



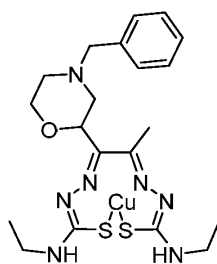
Compound 42



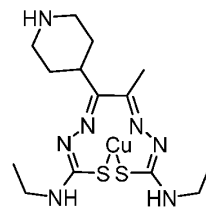
Compound 43



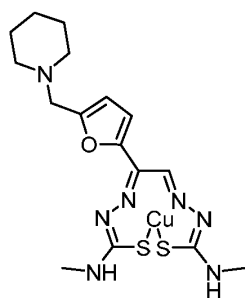
Compound 44



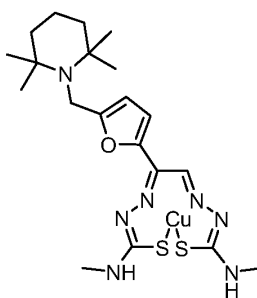
Compound 45



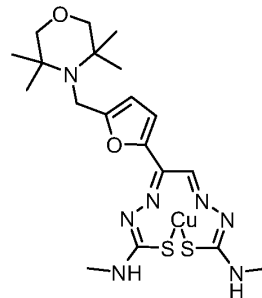
Compound 46.



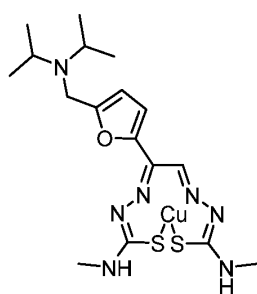
Compound 79



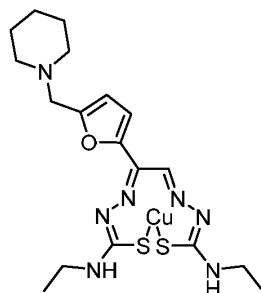
Compound 80



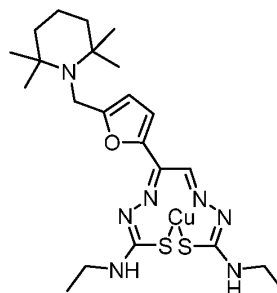
Compound 81



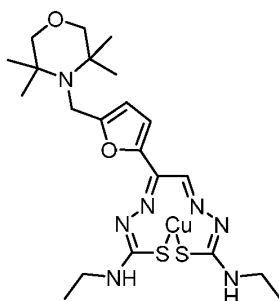
Compound 82



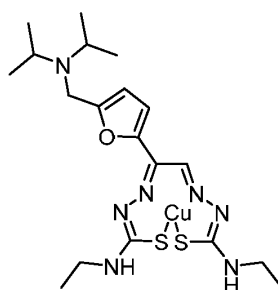
Compound 83



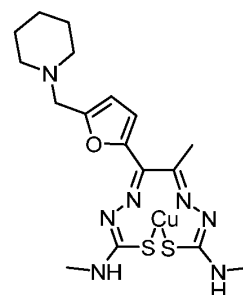
Compound 84



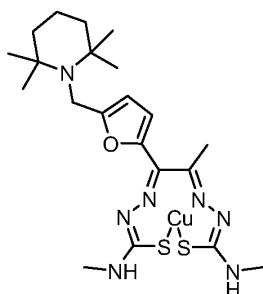
Compound 85



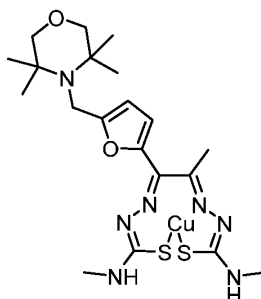
Compound 86



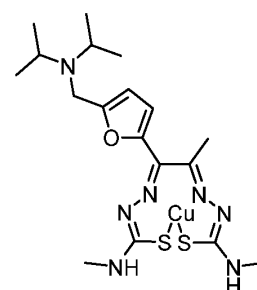
Compound 87



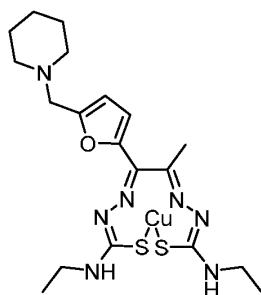
Compound 88



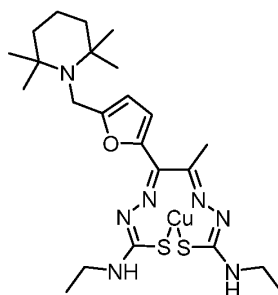
Compound 89



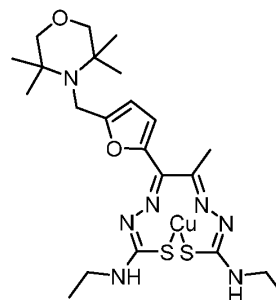
Compound 90



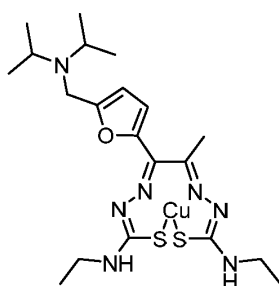
Compound 91



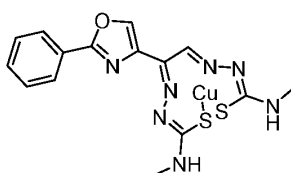
Compound 92



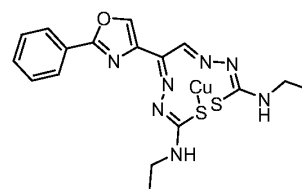
Compound 93



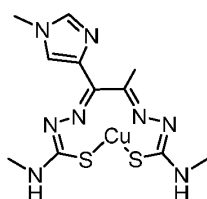
Compound 94



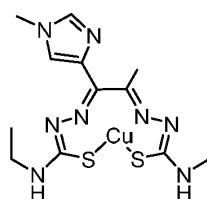
Compound 95



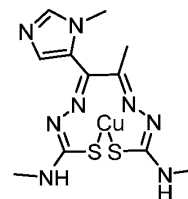
Compound 96



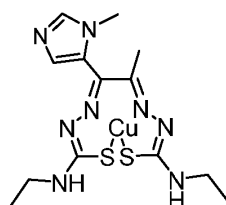
Compound 97



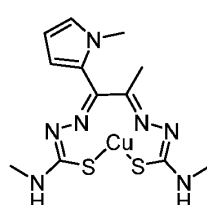
Compound 98



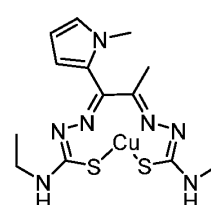
Compound 99



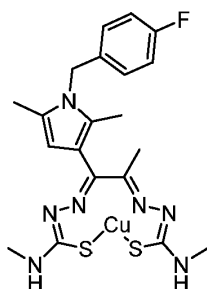
Compound 100



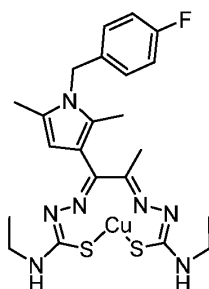
Compound 101



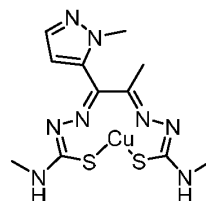
Compound 102



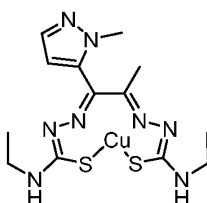
Compound 103



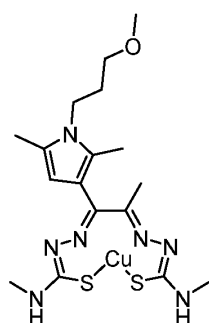
Compound 104



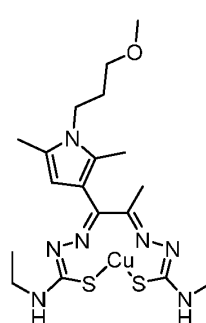
Compound 105



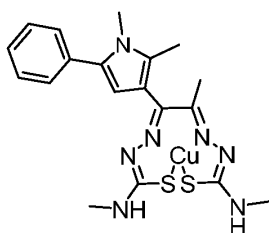
Compound 106



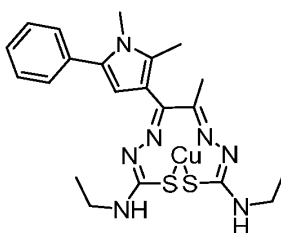
Compound 107



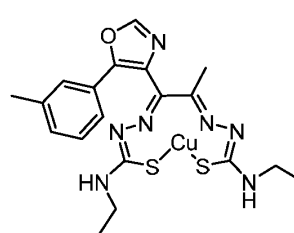
Compound 108



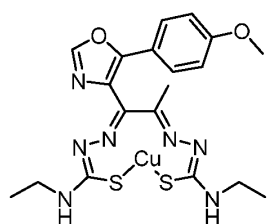
Compound 109



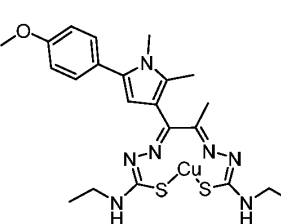
Compound 110



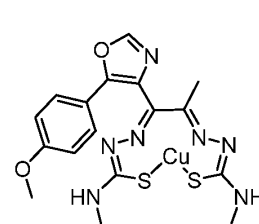
Compound 111



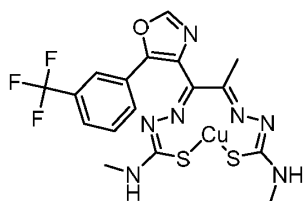
Compound 112



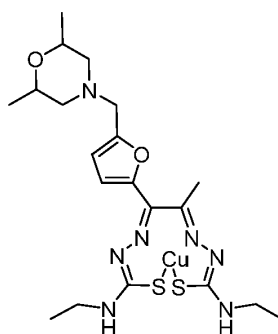
Compound 113



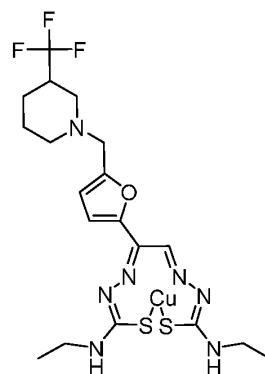
Compound 114



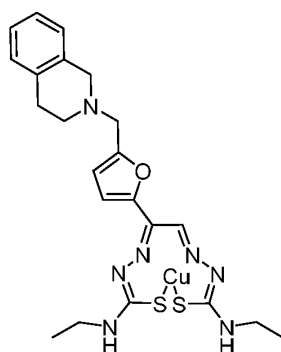
Compound 115



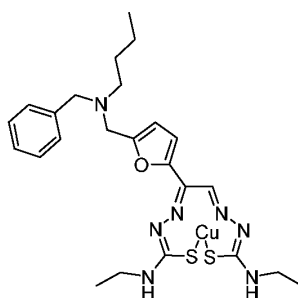
Compound 116



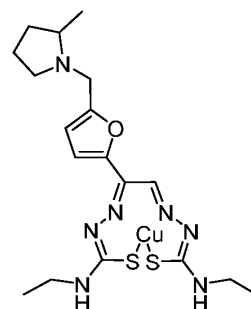
Compound 117



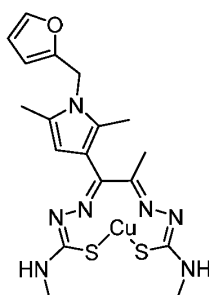
Compound 118



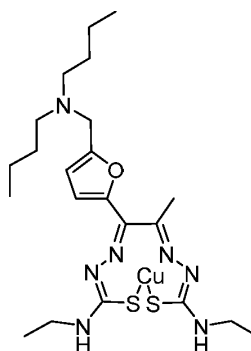
Compound 119



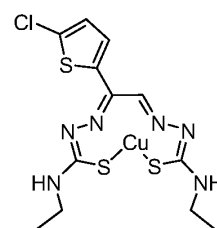
Compound 120



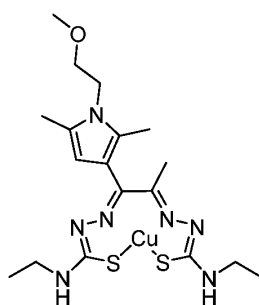
Compound 121



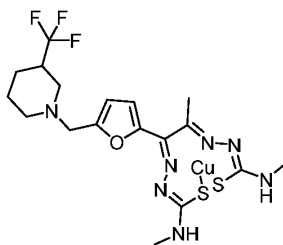
Compound 122



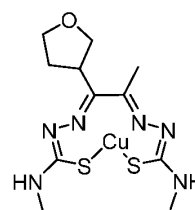
Compound 123



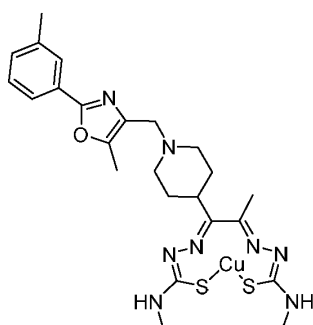
Compound 124



Compound 125



Compound 126

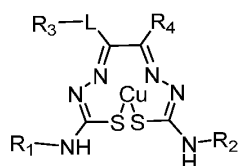


Compound 127

or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, selected from the group consisting of Compounds 25, 29, 32, 34, 41, 43, 44, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 90, 91, 94, 95, 96, 98, 100, 104, 105, 106, 120, and 123, or a pharmaceutically acceptable salt thereof.

17. A compound of Formula (IV):



(IV),

or pharmaceutically acceptable salts thereof, wherein:

L is C₃-C₇ cycloalkyl, C₁-C₆ alkyl, or absent;

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C₃-C₁₀ cycloalkyl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₆-C₁₀ aryl is substituted one, two, or three times with the group R_{3a}, and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₃-C₇ cycloalkyl or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl;

R_{3b} independently for each occurrence is C₁-C₃ alkyl, C₁-C₃ alkoxy, C₃-C₇ cycloalkyl, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

R₄ is hydrogen, C₁-C₃ alkyl, or C₆-C₁₀ aryl;

provided that when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}; or when L is absent, R₃ is 6- to 10-membered heteroaryl optionally substituted one, two, or three times with the group R_{3b}, and R₄ is H.

18. The compound of claim 17, wherein:

R₁ is C₁-C₆ alkyl optionally substituted with 5-membered heteroaryl; and

R₂ is C₁-C₆ alkyl optionally substituted with 5-membered heteroaryl.

19. The compound of claim 17 or claim 18, wherein:

R₁ is methyl or ethyl; and

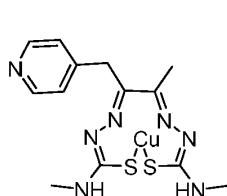
R₂ is methyl or ethyl.

20. The compound of any one of claims 17-19, wherein R₃ is phenyl, pyrazolyl, pyridinyl, benzofuranyl, benzothiazolyl, benzodioxolyl, C₃-C₆ cycloalkyl, adamantyl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the phenyl is substituted one, two, or three times with the group R_{3a}; and wherein the pyrazolyl, pyridinyl, benzofuranyl, benzothiazolyl, and benzodioxolyl are optionally substituted one, two, or three times with the group R_{3b}.

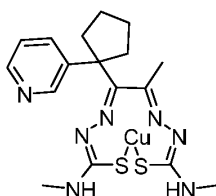
21. The compound of any one of claims 17-20, wherein L is C₁-C₆ alkyl, and R₃ is C₁-C₆ alkoxy.

22. The compound of any one of claims 17-20, wherein when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}.

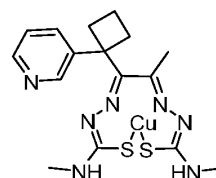
23. The compound of claim 17, selected from the group consisting of:



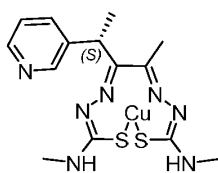
Compound 1



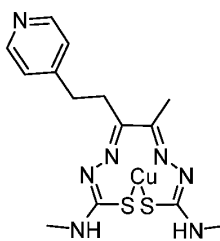
Compound 2



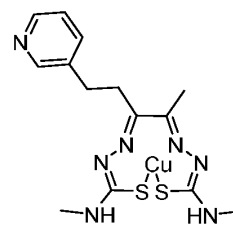
Compound 3



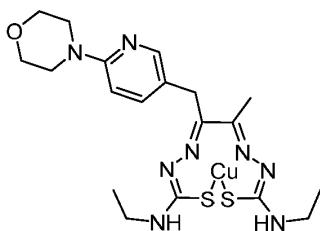
Compound 4



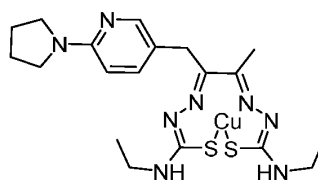
Compound 5



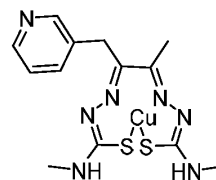
Compound 6



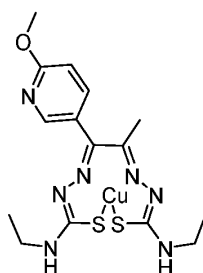
Compound 7



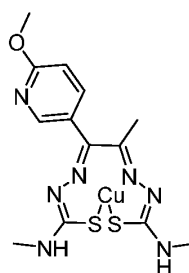
Compound 8



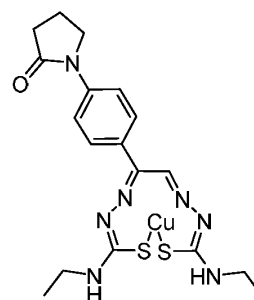
Compound 9



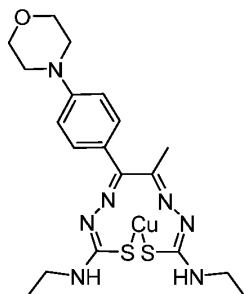
Compound 10



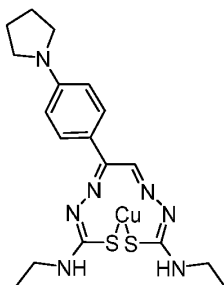
Compound 11



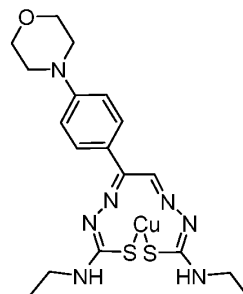
Compound 12



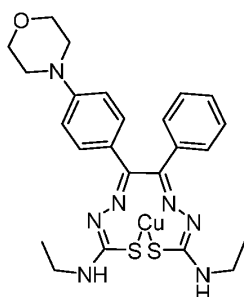
Compound 13



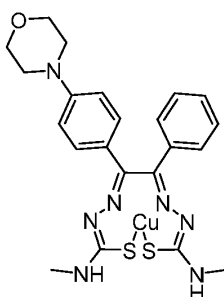
Compound 14



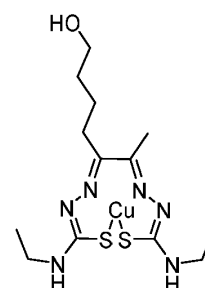
Compound 15



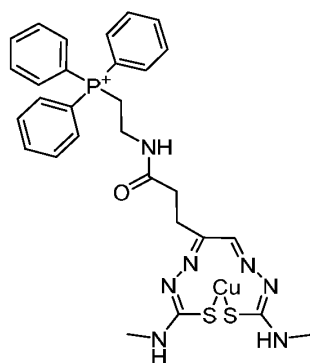
Compound 16



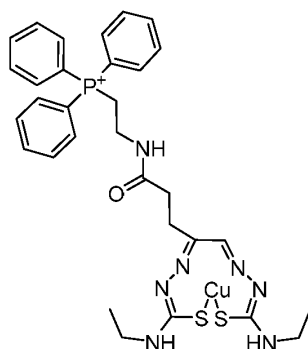
Compound 17



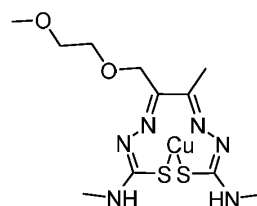
Compound 18



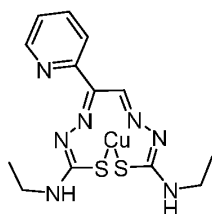
Compound 19



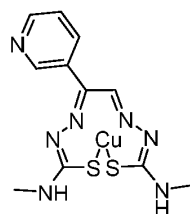
Compound 21



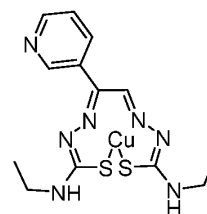
Compound 22



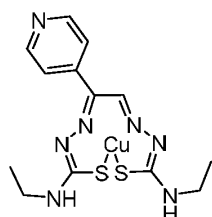
Compound 57



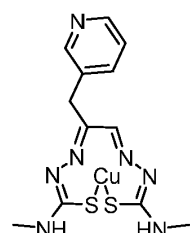
Compound 59



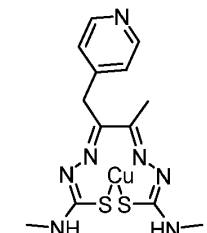
Compound 60



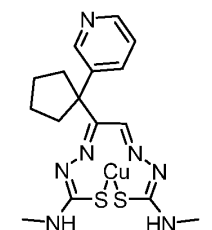
Compound 61



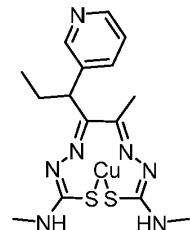
Compound 66



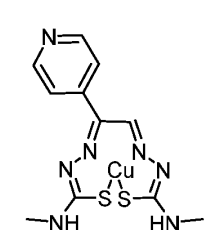
Compound 67



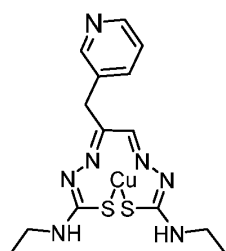
Compound 68



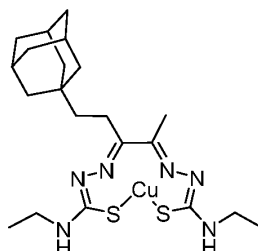
Compound 69



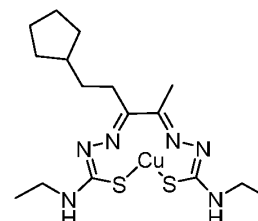
Compound 70



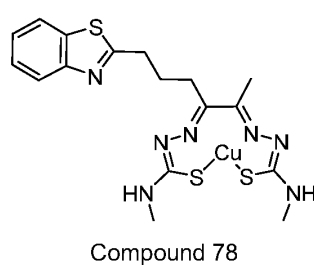
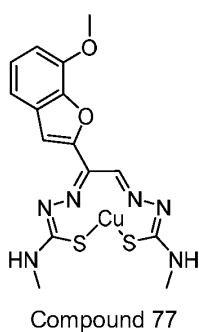
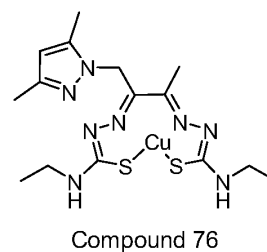
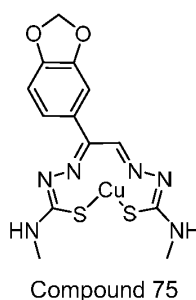
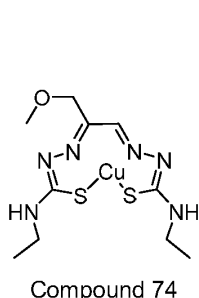
Compound 71



Compound 72



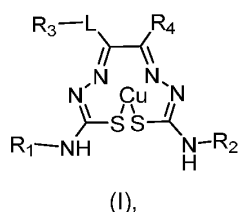
Compound 73



or a pharmaceutically acceptable salt thereof.

24. The compound of claim 23, selected from the group consisting of Compounds 2, 12, 15, 17, 59, 60, 61, 66, 74, and 77, or a pharmaceutically acceptable salt thereof.

25. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

L is C₃-C₇ cycloalkyl, C₁-C₆ alkyl, or absent

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₆-C₁₀ aryl is substituted one,

two, or three times with the group R_{3a}, and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₃-C₇ cycloalkyl or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl;

R_{3b} independently for each occurrence is C₁-C₃ alkoxy, C₃-C₇ cycloalkyl, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

R₄ is hydrogen, C₁-C₃ alkyl, or C₆-C₁₀ aryl;

provided that when L is absent, R₃ is C₆-C₁₀ aryl substituted one, two, or three times with the group R_{3a}; or when L is absent, R₃ is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b}.

26. The compound of claim 25, wherein R₃ is C₆-C₁₀ aryl, 6- to 10-membered heteroaryl, C(O)NH-(C₁-C₆ alkyl)-PPh₃, hydroxy, C₁-C₆ alkoxy, or O-(C₁-C₆ alkyl)-O-(C₁-C₆ alkyl), wherein the C₆-C₁₀ aryl is substituted one, two, or three times with the group R_{3a}, and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b}.

27. The compound of claim 25 or claim 26, wherein L is C₃-C₅ cycloalkyl or C₁-C₃ alkyl.

28. The compound of any one of claims 25-27, wherein R₃ is pyridinyl optionally substituted one, two, or three times with C₁-C₃ alkoxy or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally substituted one time with C₁-C₃ alkyl.

29. The compound of claim 25 or claim 26, wherein L is absent and R₃ is pyridinyl substituted one, two, or three times with C₁-C₃ alkoxy.

30. The compound of claim 25 or claim 26, wherein L is absent and R₃ is phenyl substituted with 4- to 8-membered heterocycle.

31. The compound of any one of claims 25-30, wherein
R₁ is C₁-C₆ alkyl, and
R₂ is C₁-C₆ alkyl.

32. The compound of any one of claims 25-31, wherein
R₁ is methyl or ethyl, and

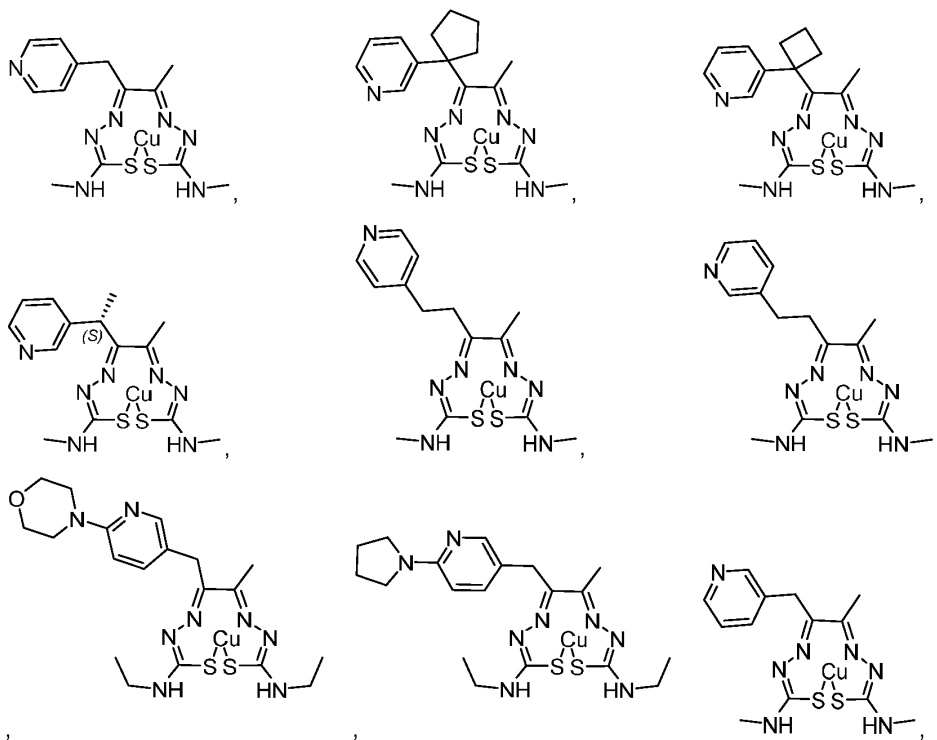
R₂ is methyl or ethyl.

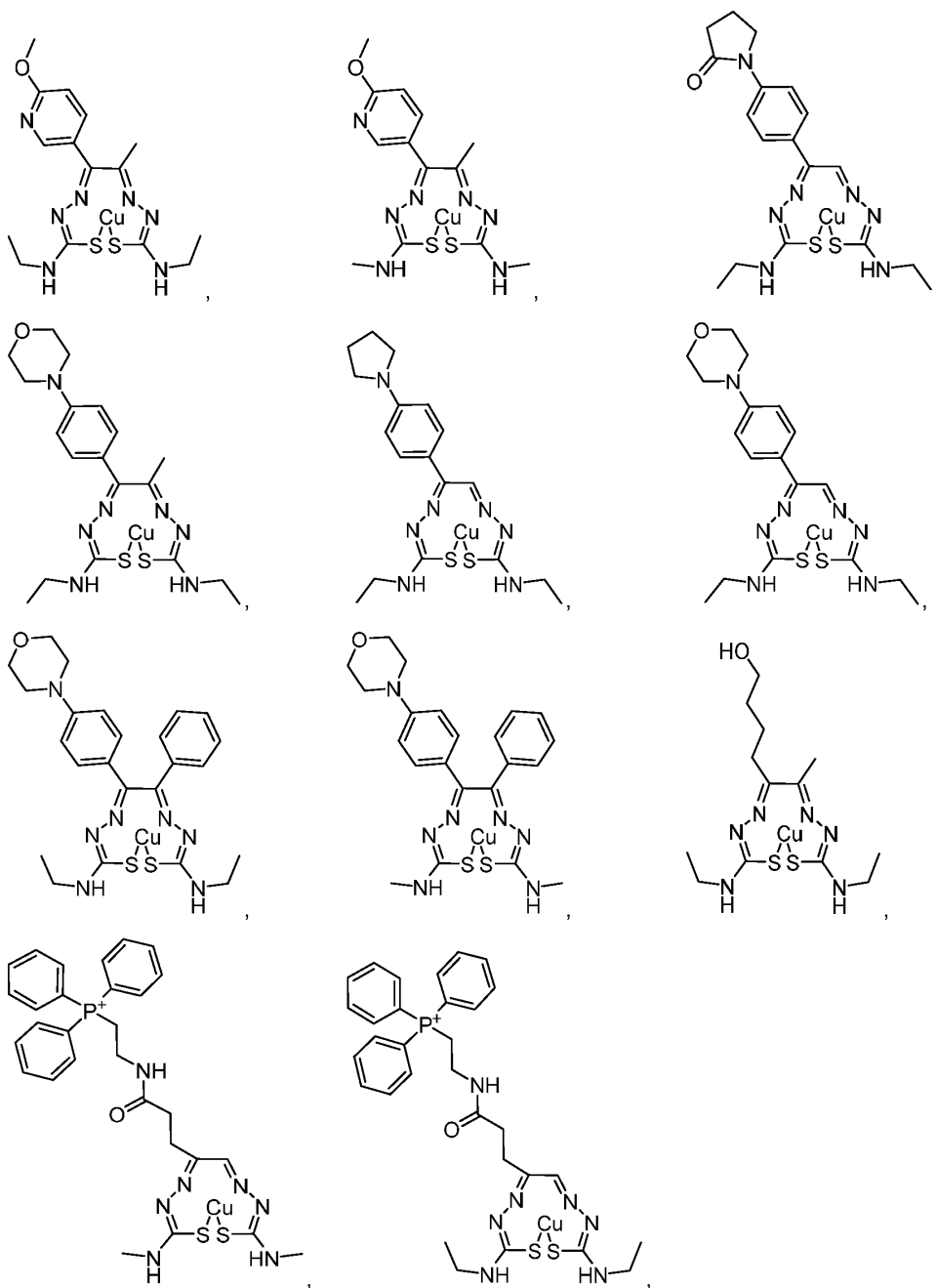
33. The compound of any one of claims 25-32, wherein R₁ and R₂ are identical.

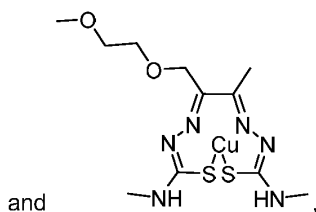
34. The compound of any one of claims 25-33, wherein R₄ is hydrogen, methyl, or phenyl.

35. The compound of claim 25 or claim 26, wherein L is C₃-C₅ cycloalkyl or C₁-C₃ alkyl; R₃ is pyridinyl optionally substituted one, two, or three times with 4- to 8-membered heterocycle; and R₄ is methyl.

36. The compound of claim 25 or claim 26, selected from the group consisting of:

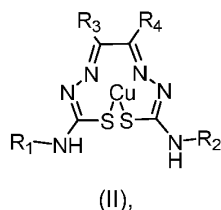






or a pharmaceutically acceptable salt thereof.

37. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is 4- to 8-membered heterocycle or 5-membered heteroaryl, wherein the 4- to 8-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a}, and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b};

R_{3a} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkyl-(C₆-C₁₀ aryl), S(O)₂H, S(O)₂-(C₁-C₆ alkyl), S(O)₂-(C₃-C₇ cycloalkyl), or S(O)₂-(C₆-C₁₀ aryl);

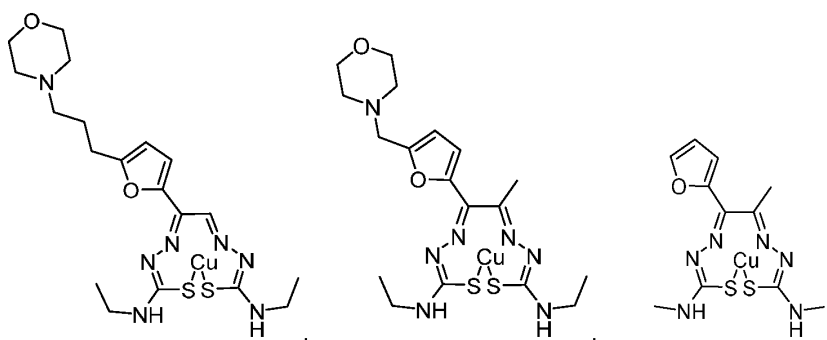
R_{3b} independently for each occurrence is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, halo, nitro, cyano, C(O)-(4- to 8-membered heterocycle), or C₁-C₆ alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C₁-C₃ alkyl; and

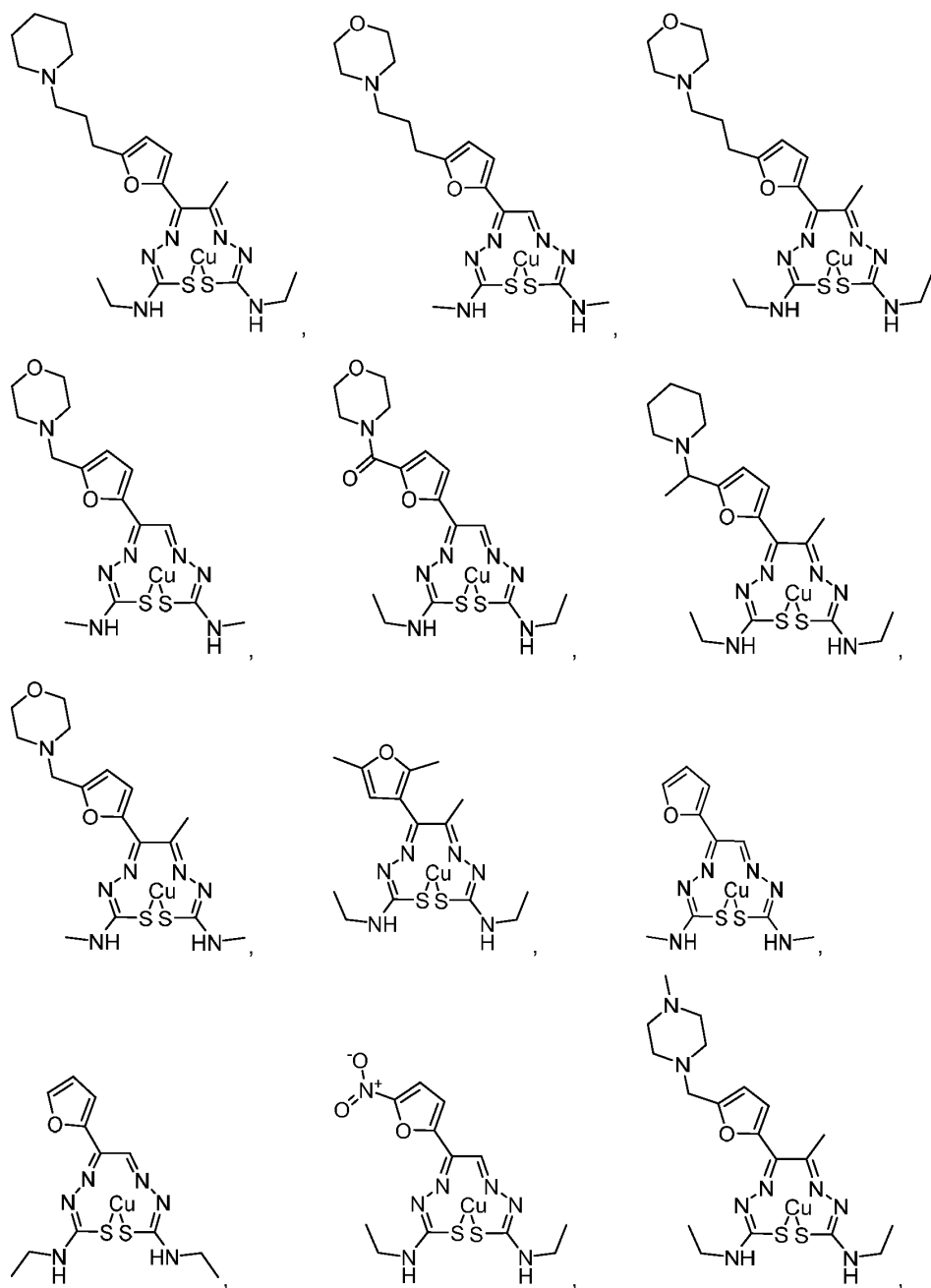
R₄ is hydrogen or C₁₋₃ alkyl.

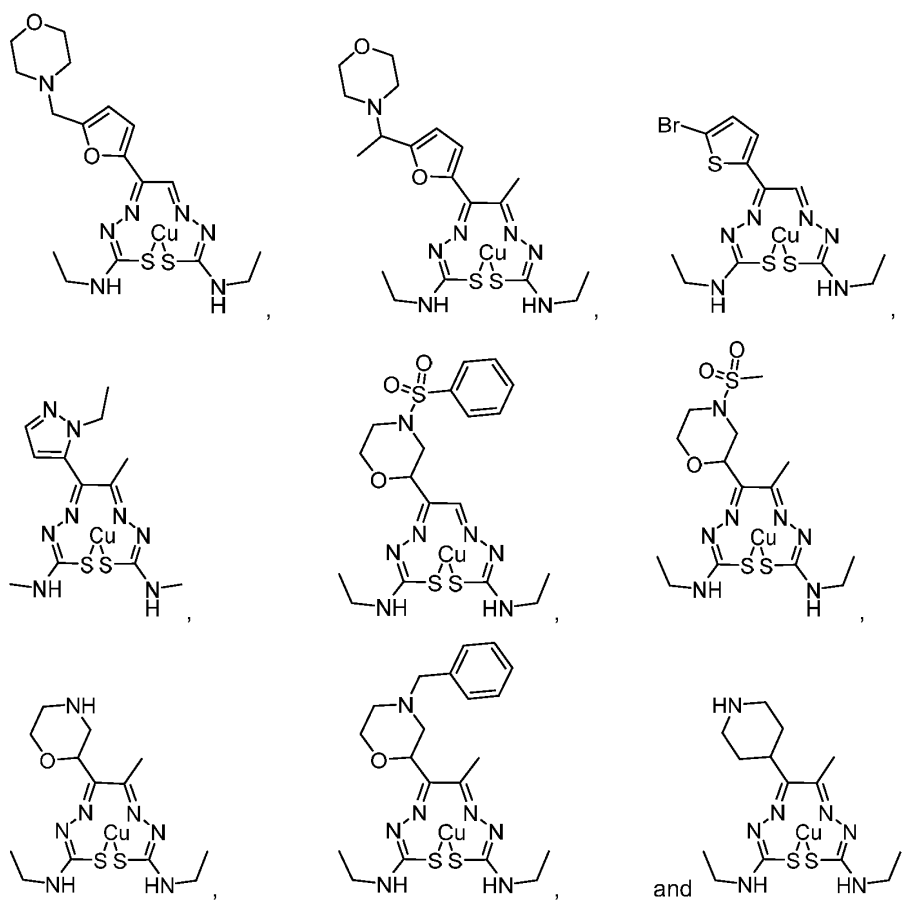
38. The compound of claim 37, wherein R₃ is furyl, thiophenyl, or pyrazolyl optionally substituted one, two, or three times with the group R_{3b}.

39. The compound of claim 37 or claim 38, wherein R₃ is furyl, thiophenyl, or pyrazolyl substituted one, two, or three times with the group R_{3b}.

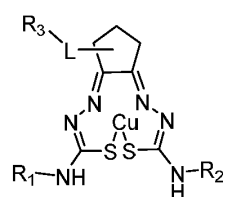
40. The compound of claim 37 or claim 38, wherein R_3 is furyl optionally substituted one, two, or three times with the group R_{3b} .
41. The compound of any one of claims 37, 38, and 40, wherein R_3 is furyl substituted one, two, or three times with the group R_{3b} .
42. The compound of claim 37, wherein R_3 is morpholinyl or piperidinyl optionally substituted one, two, or three times with the group R_{3a} .
43. The compound of any one of claims 37-42, wherein
 R_1 is C_1 - C_6 alkyl, and
 R_2 is C_1 - C_6 alkyl.
44. The compound of any one of claims 37-43, wherein
 R_1 is methyl or ethyl, and
 R_2 is methyl or ethyl.
45. The compound of any one of claims 37-44, wherein R_1 and R_2 are identical.
46. The compound of any one of claims 37-45, wherein R_4 is hydrogen or methyl.
47. The compound of claim 37, selected from the group consisting of:







48. A compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, wherein:

L is C₁-C₆ alkyl or absent

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₃ is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, halo, hydroxy, C(O)NH₂, C(O)NH(C₁-C₆ alkyl), C(O)N(C₁-C₆ alkyl)₂, or C(O)-(4- to 8-membered heterocycle), wherein the C₁-C₆ alkyl and the C₁-C₆ alkoxy are optionally substituted one, two, or three times with C₆-C₁₀ aryl, and wherein the C(O)-(4- to 8-membered heterocycle) is optionally substituted one, two, or three times with C₁-C₃ alkyl.

49. The compound of claim 48, wherein L is C₁-C₃ alkyl.

50. The compound of claim 48, wherein L is absent and R₃ is C₁-C₆ alkyl.

51. The compound of claim 48 or claim 49, wherein R₃ is C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, or C(O)-(4- to 8-membered heterocycle), wherein the C₁-C₆ alkyl and the C₁-C₆ alkoxy are optionally substituted one time with C₆-C₁₀ aryl and wherein the C(O)-(4- to 8-membered heterocycle) is optionally substituted one time with C₁-C₃ alkyl.

52. The compound of any one of claims 48-51, wherein

R₁ is C₁-C₆ alkyl optionally substituted with NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂, and

R₂ is C₁-C₆ alkyl optionally substituted with NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂.

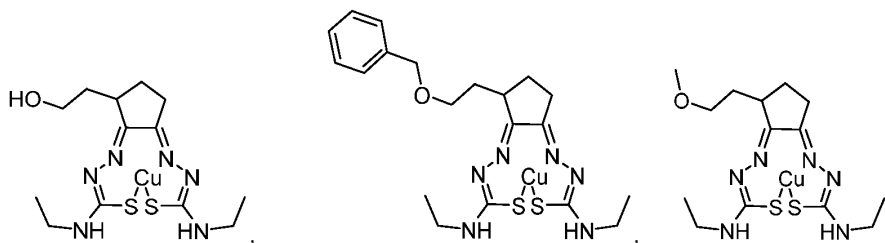
53. The compound of any one of claims 48-52, wherein

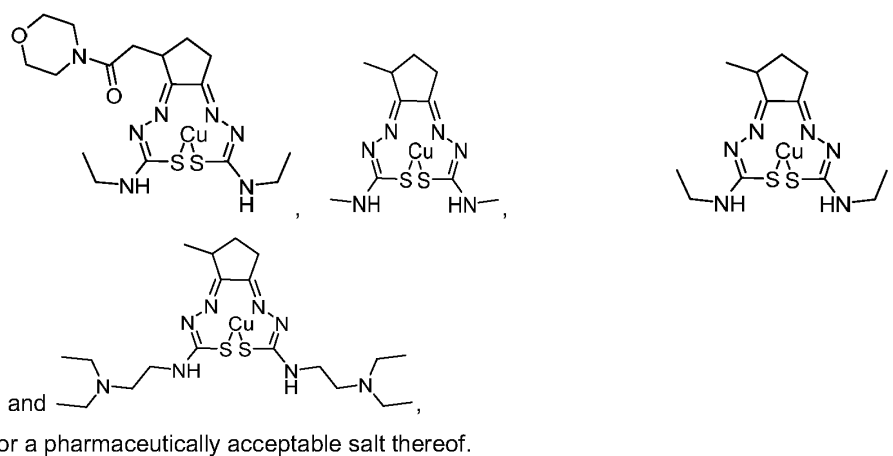
R₁ is C₁-C₆ alkyl optionally substituted with N(C₁-C₆ alkyl)₂, and

R₁ is C₁-C₆ alkyl optionally substituted with N(C₁-C₆ alkyl)₂.

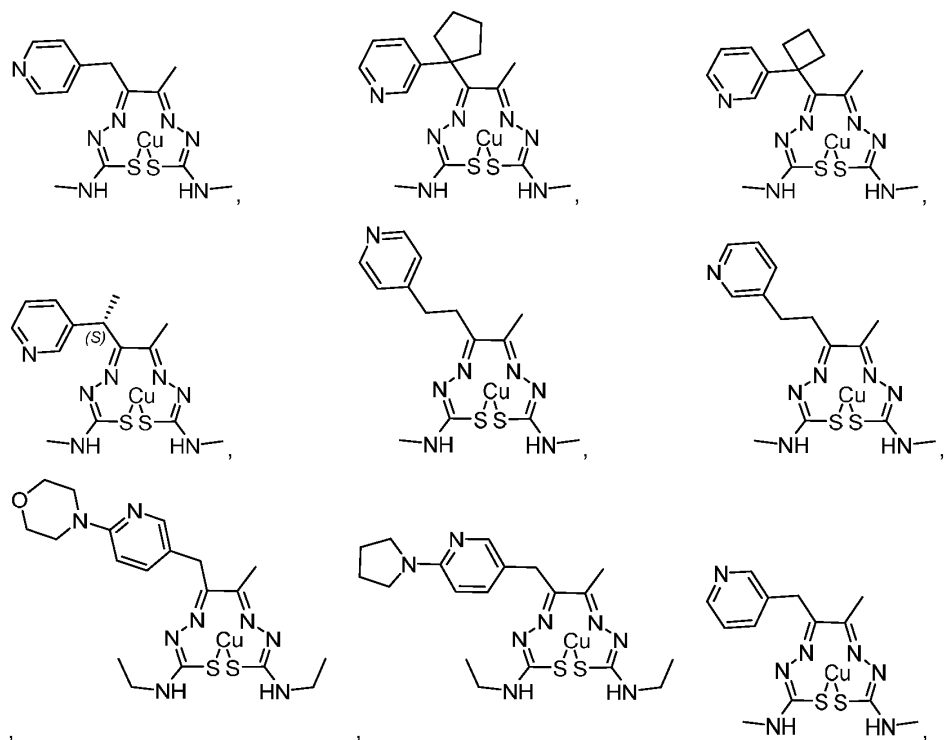
54. The compound of any one of claims 48-53, wherein R₁ and R₂ are identical.

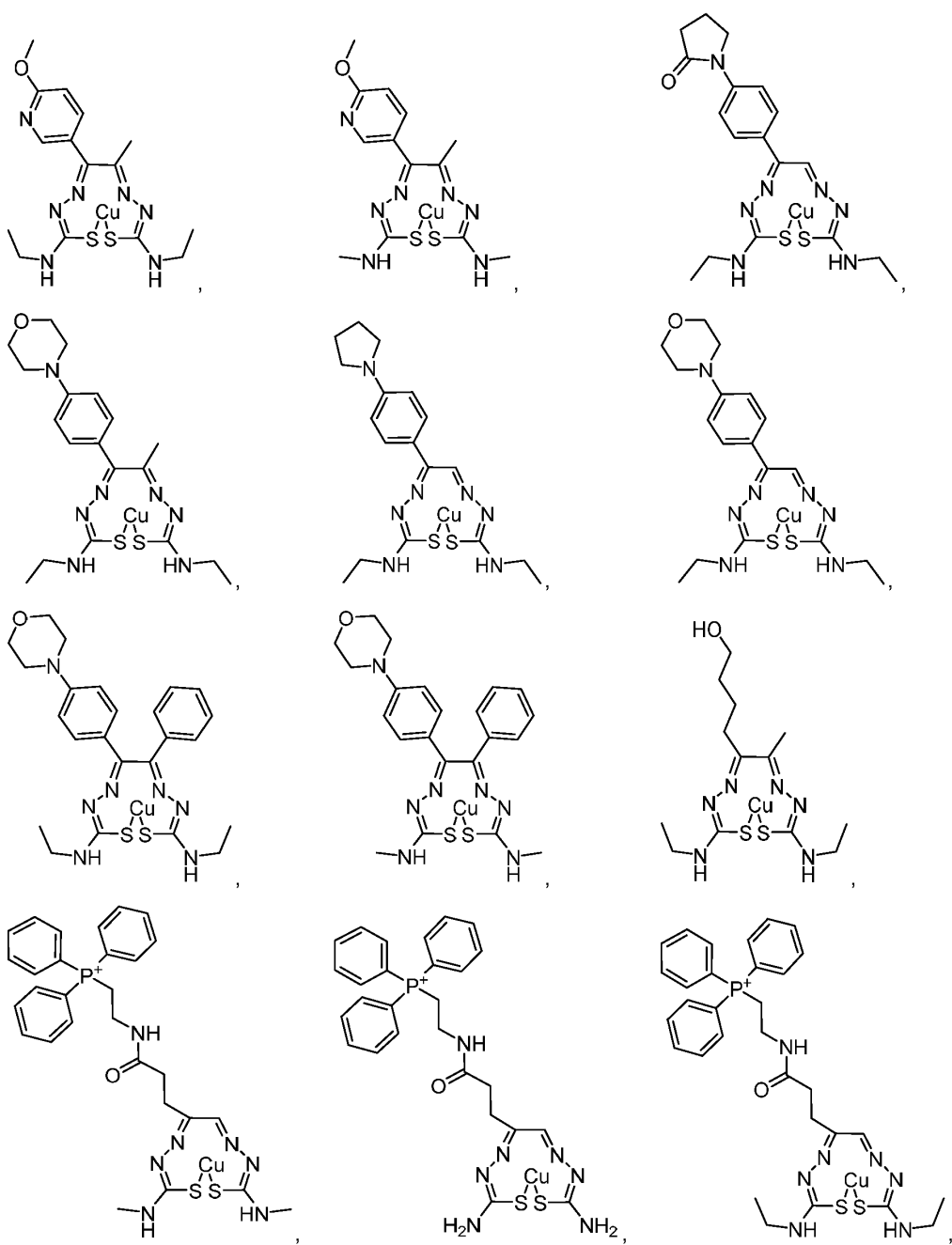
55. The compound of claim 48, selected from the group consisting of:

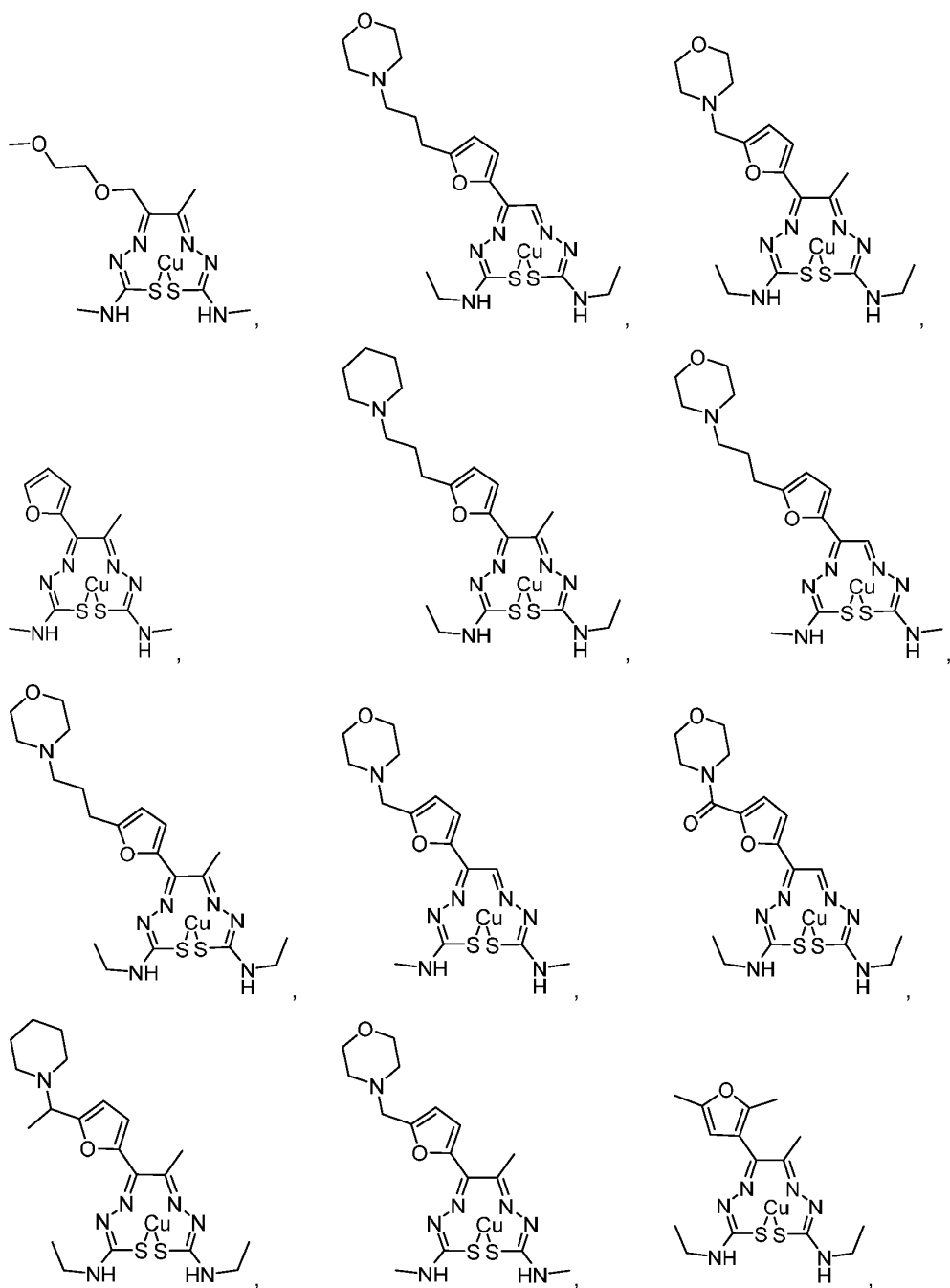


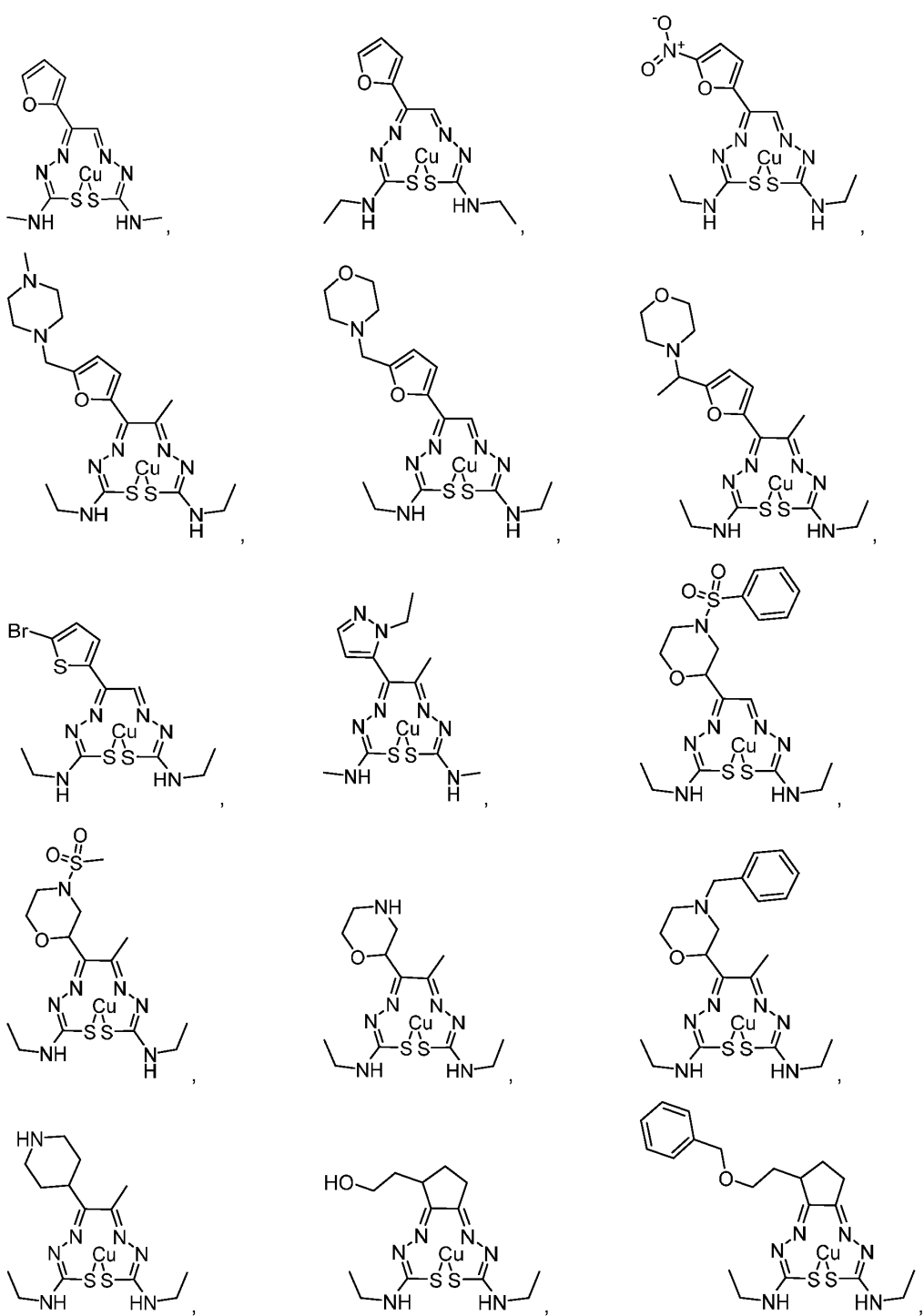


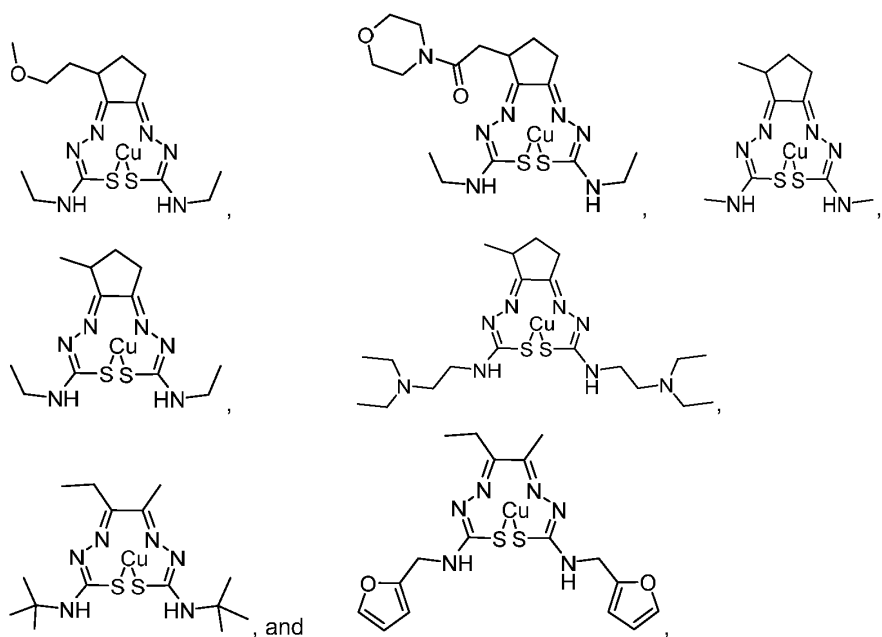
56. A compound selected from the group consisting of:





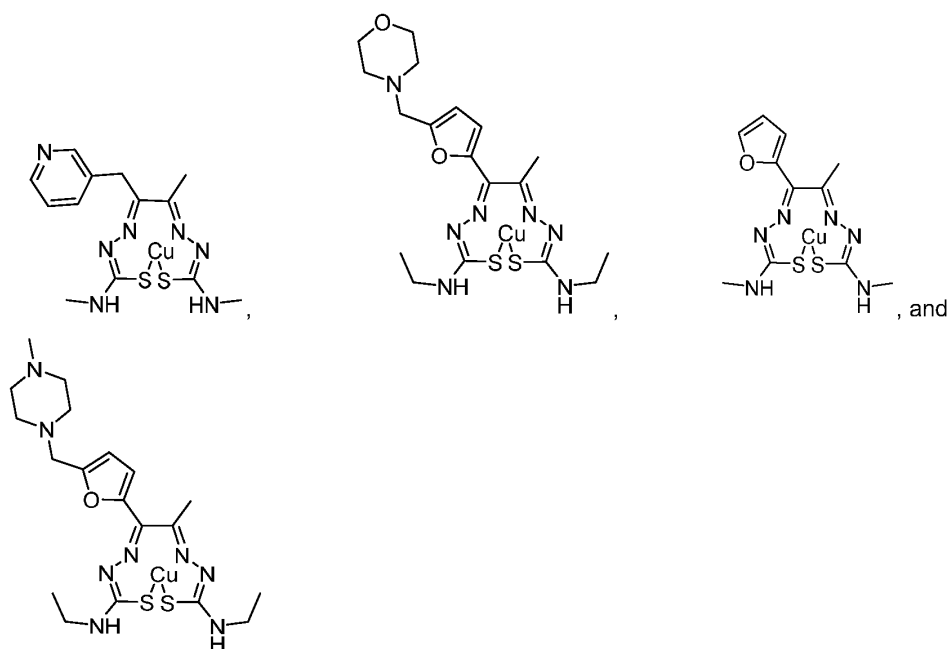






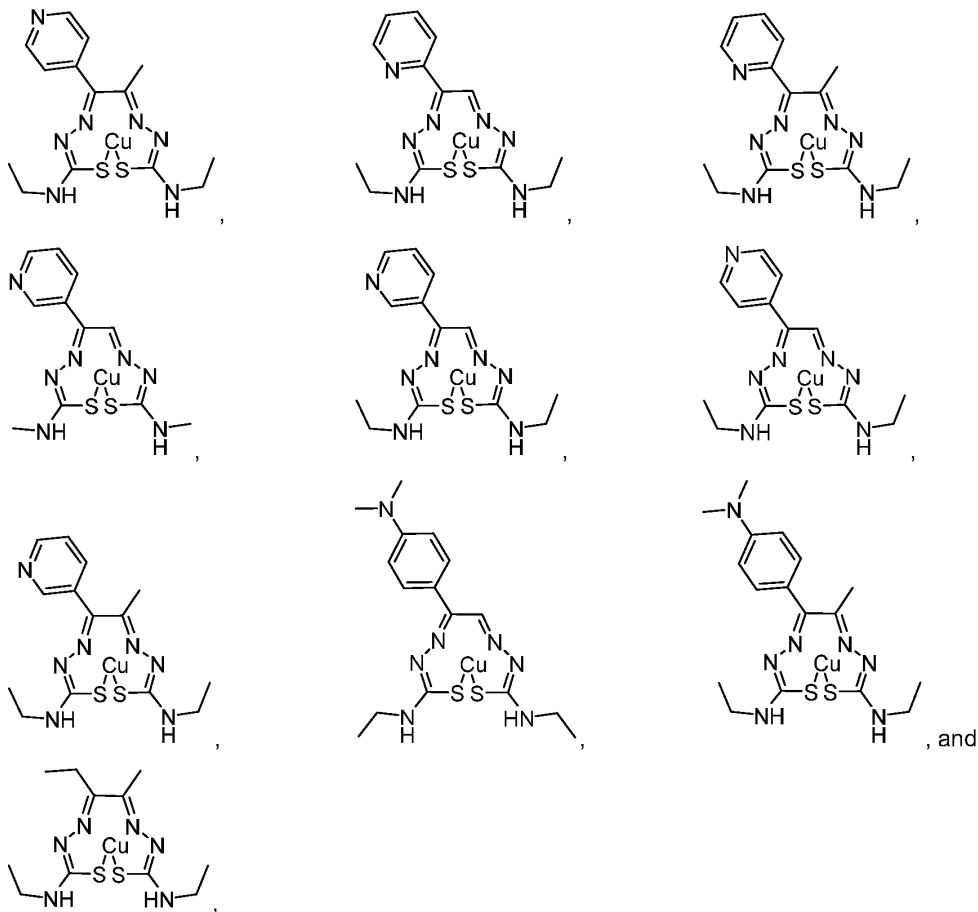
or a pharmaceutically acceptable salt thereof.

57. A compound selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

58. A compound selected from the group consisting of:

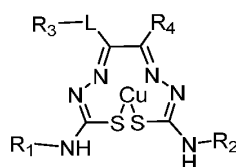


or a pharmaceutically acceptable salt thereof.

59. A pharmaceutical composition comprising a compound of any one of claims 1-58, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, diluent, or carrier.

60. A method of treating or preventing a neurodegenerative disease in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1-58.

61. The method of claim 60, wherein the neurodegenerative disease is amyotrophic lateral sclerosis (ALS), frontal temporal dementia (FTD), Parkinson's disease, Huntington's disease, and Alzheimer's disease.
62. The method of claim 60 or claim 61, wherein the neurodegenerative disease is ALS.
63. The method of claim 60, wherein the ALS is familial or sporadic.
64. The method of any one of claims 60-63, wherein the subject in need thereof is treatment naïve.
65. The method of any one of claims 60-63, wherein the subject in need thereof has received previous treatment for ALS.
66. The method of any one of claims 60-65, wherein the subject in need thereof is human, and the human has a genetic mutation associated with ALS.
67. The method of claim 66, wherein the genetic mutation associated with ALS comprises a mutation in the *SOD1* gene.
68. The method of any one of claims 60-66, wherein the compound is administered to the subject in combination with an additional ALS treatment therapy.
69. A method of making a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein:

L is C₃-C₇ cycloalkyl, C₁-C₆ alkyl, or absent

R₁ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R₂ is C₁-C₆ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH₂, NH(C₁-C₆ alkyl), or N(C₁-C₆ alkyl)₂;

R_3 is C_6 - C_{10} aryl, 5- to 10-membered heteroaryl, $C(O)NH$ -(C_1 - C_6 alkyl)- PPh_3 , hydroxy, C_1 - C_6 alkoxy, or O -(C_1 - C_6 alkyl)- O -(C_1 - C_6 alkyl), wherein the C_6 - C_{10} aryl is substituted one, two, or three times with the group R_{3a} , and wherein the 5- to 10-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b} ;

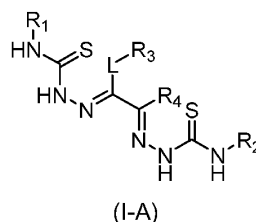
R_{3a} independently for each occurrence is C_3 - C_7 cycloalkyl or 4- to 8-membered heterocycle, wherein the 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl;

R_{3b} independently for each occurrence is C_1 - C_3 alkoxy, C_3 - C_7 cycloalkyl, or 4- to 8-membered heterocycle, wherein the heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl; and

R_4 is hydrogen, C_1 - C_3 alkyl, or C_6 - C_{10} aryl;

provided that when L is absent, R_3 is C_6 - C_{10} aryl substituted one, two, or three times with the group R_{3a} ; or when L is absent, R_3 is 6- to 10-membered heteroaryl substituted one, two, or three times with the group R_{3b} ;

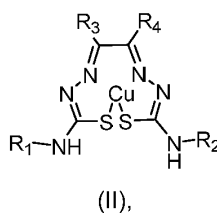
the method comprising mixing a compound of Formula (I-A):



with a copper (II) salt to form the compound of Formula (I).

70. The method of claim 69, wherein the copper (II) salt is $CuCl_2$ or $Cu(OAc)_2$, or a hydrate thereof.

71. A method of making a compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is C_1 - C_6 alkyl optionally substituted with 5- to 10-membered heteroaryl, NH_2 , $NH(C_1$ - C_6 alkyl), or $N(C_1$ - C_6 alkyl) $_2$;

R_2 is C_1 - C_6 alkyl optionally substituted with 5- to 10-membered heteroaryl, NH_2 , $NH(C_1-C_6 \text{ alkyl})$, or $N(C_1-C_6 \text{ alkyl})_2$;

R_3 is 4- to 8-membered heterocycle or 5-membered heteroaryl, wherein the 4- to 8-membered heterocycle is optionally substituted one, two, or three times with the group R_{3a} , and wherein the 5-membered heteroaryl is optionally substituted one, two, or three times with the group R_{3b} ;

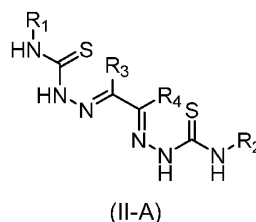
R_{3a} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkyl- $(C_6-C_{10} \text{ aryl})$, $S(O)_2H$, $S(O)_2(C_1-C_6 \text{ alkyl})$, $S(O)_2(C_3-C_7 \text{ cycloalkyl})$, or $S(O)_2(C_6-C_{10} \text{ aryl})$;

R_{3b} independently for each occurrence is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, halo, nitro, cyano, $C(O)$ -(4- to 8-membered heterocycle), or C_1 - C_6 alkyl-(4- to 8-membered heterocycle), wherein each 4- to 8-membered heterocycle is optionally further substituted one, two, or three times with C_1 - C_3 alkyl; and

R_4 is hydrogen or C_{1-3} alkyl;

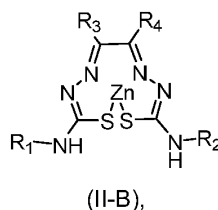
the method comprising:

(i) mixing a compound of Formula (II-A):



with a copper (II) salt to form the compound of Formula (II); or

(ii) mixing a compound of Formula (II-A) with a zinc salt to form a compound of Formula (II-B):

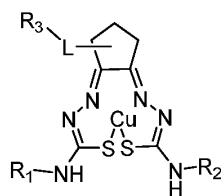


and mixing the compound of Formula (II-B) with a copper (II) salt to form the compound of Formula (II).

72. The method of claim 71, wherein the copper (II) salt is $CuCl_2$ or $Cu(OAc)_2$, or a hydrate thereof.

73. The method of claim 71 or claim 72, wherein the zinc salt is $\text{Zn}(\text{OAc})_2$ or a hydrate thereof.

74. A method of making a compound of Formula (III):



(III),

or a pharmaceutically acceptable salt thereof, wherein:

L is $\text{C}_1\text{-C}_6$ alkyl or absent

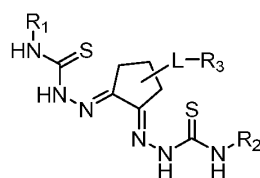
R_1 is $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH_2 , $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, or $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$;

R_2 is $\text{C}_1\text{-C}_6$ alkyl optionally substituted with 5- to 10-membered heteroaryl, NH_2 , $\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, or $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$;

R_3 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ haloalkyl, halo, hydroxy, $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NH}(\text{C}_1\text{-C}_6 \text{ alkyl})$, $\text{C}(\text{O})\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$, or $\text{C}(\text{O})$ -(4- to 8-membered heterocycle), wherein the $\text{C}_1\text{-C}_6$ alkyl and the $\text{C}_1\text{-C}_6$ alkoxy are optionally substituted one, two, or three times with $\text{C}_6\text{-C}_{10}$ aryl, and wherein the $\text{C}(\text{O})$ -(4- to 8-membered heterocycle) is optionally substituted one, two, or three times with $\text{C}_1\text{-C}_3$ alkyl;

the method comprising:

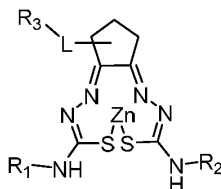
(i) mixing a compound of Formula (III-A):



(III-A)

with a copper (II) salt to form the compound of Formula (III); or

(ii) mixing a compound of Formula (III-A) with a zinc salt to form a compound of Formula (III-B):



(III-B),

and mixing the compound of Formula (III-B) with a copper (II) salt to form the compound of Formula (III).

75. The method of claim 74, wherein the wherein the copper (II) salt is CuCl_2 or $\text{Cu}(\text{OAc})_2$, or a hydrate thereof.

76. The method of claim 74 or claim 75, wherein the zinc salt is $\text{Zn}(\text{OAc})_2$ or a hydrate thereof.