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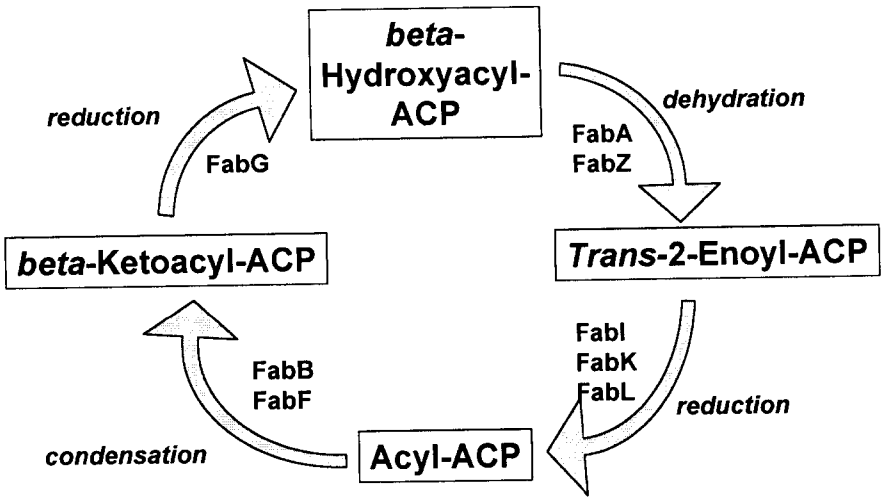
(54) **Title:** ACRYLAMIDE DERIVATIVES AS FAB I INHIBITORS



(57) **Abstract:** In part, the present invention is directed towards compounds with FAB I inhibiting properties. Such compounds may also inhibit other enzymes, including those similar to FAB I either structurally or functionally, for example FAB K. Said compounds and compositions thereof may be used to treat bacterial infections. Said compounds may also be used to disinfect an inanimate surface by contacting the antibacterial compound to the inanimate surface. Kits comprising said compositions that include the disclosed compounds are also provided, along with instructions for use thereof.

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THERAPEUTIC AGENTS, AND METHODS OF MAKING AND USING THE SAME

RELATED APPLICATIONS:

This application claims priority to provisional application U.S.S.N 60/60/832,058 filed July 20, 2006, which is hereby incorporated by reference in its entirety.

GOVERNMENT SUPPORT

This invention was made with support provided by the National Institute of Health; the government, therefore, has certain rights in the invention.

INTRODUCTION

Infections caused by or related to bacteria are a major cause of human illness worldwide, and the frequency of resistance to standard antibiotics has risen dramatically over the last decade. Hence, there exists an unmet medical need and demand for new agents acting against bacterial targets.

Examples of potential bacterial targets are those enzymes involved in fatty acid biosynthesis. While the overall pathway of saturated fatty acid biosynthesis is similar in all organisms, the fatty acid synthase (FAS) systems vary considerably with respect to their structural organization. It is believed that vertebrates and yeast possess a FAS in which all the enzymatic activities are encoded on one or two polypeptide chains, respectively, and the acyl carrier protein (ACP) is an integral part of the complex. In contrast, in bacterial FAS, it is known that each of the reactions is catalyzed by a distinct, mono-functional enzyme and the ACP is a discrete protein. Therefore, it may be possible to achieve selective inhibition of the bacterial system by appropriate agents.

One such potential bacterial target is the FabI protein. FabI (previously designated EnvM) is believed to function as an enoyl-ACP reductase in the final step of the four reactions involved in each cycle of bacterial fatty acid biosynthesis. It is believed that in this pathway, the first step is catalyzed by β-ketoacyl-ACP synthase, which condenses malonyl-ACP with acetyl-CoA (FabH, synthase III). It is believed that in subsequent rounds, malonyl-ACP is condensed with the growing-chain acyl-ACP (FabB

and FabF, synthases I and II, respectively). The second step in the elongation cycle is thought to be ketoester reduction by NADPH-dependent β-ketoacyl-ACP reductase (FabG). Subsequent dehydration by β-hydroxyacyl-ACP dehydrase (either FabA or FabZ) leads to trans-2-enoyl-ACP. Finally, in step four, trans-2-enoyl-ACP is converted to acyl-ACP by an NADH (or NADPH)-dependent enoyl-ACP reductase (Fab I). Further rounds of this cycle, adding two carbon atoms per cycle, would eventually lead to palmitoyl-ACP (16C), where upon the cycle is stopped largely due to feedback inhibition of Fab I by palmitoyl-ACP. Thus, Fab I is believed to be a major biosynthetic enzyme and is a key regulatory point in the overall synthetic pathway of bacterial fatty acid biosynthesis.

In some bacteria the final step of fatty acid biosynthesis is catalyzed by Fab I only, in others by FabK, an NADH and FMN dependent reductase, still others utilize both FabI and FabK. The present invention provides, in part, compounds and compositions with FabI inhibiting properties.

SUMMARY

In part, the present invention is directed towards compounds with FabI inhibiting properties as well as other enzymes. Other uses for the subject compounds and compositions will be readily discernable to those of skill in the art.

In part, the present invention is directed towards compounds that will affect multiple species, so-called "wide spectrum" anti-bacterials. Alternatively, subject compounds that are selective for one or more bacterial or other non-mammalian species, and not for one or more mammalian species (especially human), may be identified.

In part, the present invention is directed towards pharmaceutical compositions comprising a compound with FabI inhibiting properties.

The subject compositions may be administered by one of a variety of means known to those of skill in the art. The subject compounds may be prepared as described herein and as known to those of skill in the art.

Whole-cell antimicrobial activity for the antibacterial compositions of the present invention may be determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A5,

"Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compositions of the present invention may be tested, for example, in serial two-fold dilutions ranging from 0.06 to 32 mcg/mL. A panel of up to 12 or more bacterial strains may be evaluated in the assay. A panel may consist of, for example, the following laboratory strains: *Enterococcus faecalis* 29212, *Staphylococcus aureus* 29213, *Staphylococcus aureus* 43300, *Moraxella catarrhalis* 49143, *Haemophilus influenzae* 49247, *Streptococcus pneumoniae* 49619, *Staphylococcus epidermidis* 1024939, *Staphylococcus epidermidis* 1024961, *Escherichia coli* AG100 ($AcrAB^+$), *Escherichia coli* AG100A ($AcrAB^-$),, *Pseudomonas aeruginosa* K767 ($MexAB^+$, $OprM^+$), *Pseudomonas aeruginosa* K1119 ($MexAB^-$, $OprM^-$). The minimum inhibitory concentration (MIC) may then be determined as the lowest concentration of the subject composition that inhibited visible growth. A spectrophotometer may be used to assist in determining the MIC endpoint.

Non-limiting examples of bacteria that the antibacterial compounds or compositions of the present invention may be used to either destroy or inhibit the growth of include a member of the genus *Streptococcus, Staphylococcus, Bordetella, Corynebacterium, Mycobacterium, Neisseria, Haemophilus, Actinomycetes, Streptomycetes, Nocardia, Enterobacter, Yersinia, Francisella, Pasturella, Moraxella, Acinetobacter, Erysipelothrix, Branhamella, Actinobacillus, Streptobacillus, Listeria, Calymmatobacterium, Brucella, Bacillus, Clostridium, Treponema, Escherichia, Salmonella, Kleibsiella, Vibrio, Proteus, Erwinia, Borrelia, Leptospira, Spirillum, Campylobacter, Shigella, Legionella, Pseudomonas, Aeromonas, Rickettsia, Chlamydia, Borrelia, Propionibacterium acnes,* and *Mycoplasma*, and further including, but not limited to, a member of the species or group, Group A *Streptococcus,* Group B *Streptococcus,* Group C *Streptococcus,* Group D *Streptococcus,* Group G *Streptococcus, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus faecalis, Streptococcus faecium, Streptococcus durans, Neisseria gonorrheae, Neisseria meningitidis, coagulase negative Staphylococci, Staphylococcus aureus, Staphylococcus epidermidis, Corynebacterium diptheriae, Gardnerella vaginalis, Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium ulcerans, Mycobacterium leprae, Actinomyctes israelii, Listeria monocytogenes, Bordetella pertusis, Bordatella parapertusis, Bordetella bronchiseptica, Escherichia coli, Shigella dysenteriae, Haemophilus influenzae, Haemophilus aegyptius, Haemophilus*

parainfluenzae, Haemophilus ducreyi, Bordetella, Salmonella typhi, Citrobacter freundii, Proteus mirabilis, Proteus vulgaris, Yersinia pestis, Kleibsiella pneumoniae, Serratia marcessens, Serratia liquefaciens, Vibrio cholera, Shigella dysenterii, Shigella flexneri, Pseudomonas aeruginosa, Franscisella tularensis, Brucella abortis, Bacillus anthracis, Bacillus cereus, Clostridium perfringens, Clostridium tetani, Clostridium botulinum, Treponema pallidum, Rickettsia rickettsii, Helicobacter pylori or *Chlamydia trachomitis.*

In another aspect, the subject compounds or compositions may be used to treat bacterial infections.

In certain embodiments, the present invention provides antibacterial compositions of the present invention, and methods of using the same, for the reduction and abatement of at least one of the bacteria caused disorders or conditions based on a therapeutic regimen. In certain aspects, the present invention contemplates monitoring such disorders or conditions as part of any therapeutic regimen, which may be administered over the short-term and/or long-term. These aspects of the invention may be particularly helpful in preventive care regimes.

In another aspect of the present invention, the antibacterial compounds or compositions of the present invention may be used in the manufacture of a medicament to treat any of the foregoing bacteria related conditions or diseases. In certain embodiments, the present invention is directed to a method for formulating compounds of the present invention in a pharmaceutically acceptable carrier or excipient.

In part, the present invention also relates to inhibitors and compositions comprising inhibitors of enzymes similar to FabI either structurally or functionally, such as, for example, FabK which is also believed to play a role in bacterial fatty acid synthesis.

In another aspect of the present invention, the antibacterial compounds of the present invention may be used to disinfect an inanimate surface by administering the antibacterial compound to the inanimate surface.

For continuous intravenous infusion, e.g., drip or push, the antibacterial agent can be provided in a sterile dilute solution or suspension (collectively hereinafter "i.v. injectable solution"). The i.v. injectable solution may be formulated such that the amount of antibacterial agent (or antibacterial agents) provided in a 1L solution would provide a

dose, if administered over 15 minutes or less, of at least the median effective dose, or less than 100 times the ED_{50}, or less than 10 or 5 times the ED_{50}. The i.v. injectable solution may be formulated such that the total amount of antibacterial agent (or antibacterial agents) provided in 1L solution administered over 60, 90, 120 or 240 minutes would provide an ED_{50} dose to a patient, or less than 100 times the ED_{50}, or less than 10 or 5 times the ED_{50}. In other embodiments, a single i.v. "bag" provides about 0.25 mg to 5000 mg of antibacterial agent per liter i.v. solution, or 0.25 mg to 2500 mg, or 0.25 mg to 1250 mg.

In another embodiment of the invention it will be desirable to include monitoring or diagnostic regimes or kits with subject antibacterial compounds or methods based on FabI inhibitors described herein, and instructions for use of these compositions or methods.

In another aspect, the present invention also provides for kits containing at least one dose of a subject composition, and often many doses, and other materials for a treatment regimen. For example, in one embodiment, a kit of the present invention contains sufficient subject composition for from five to thirty days and optionally equipment and supplies necessary to measure one or more indices relevant to the treatment regiment. In another embodiment, kits of the present invention contain all the materials and supplies, including subject compositions, for carrying out any methods of the present invention. In still another embodiment, kits of the present invention, as described above, additionally include instructions for the use and administration of the subject compositions.

The dosage may be selected to modulate metabolism of the bacteria in such a way as to inhibit or stop growth of said bacteria or by killing said bacteria. The skilled artisan may identify this amount as provided herein as well as by using other methods known in the art.

As explained herein in greater detail, the invention will readily enable the design and implementation of trials in warm-blooded animals, including humans and mammals, necessary for easily determining or tailoring the form and dose for any composition of the present invention.

These embodiments of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, drawings and claims that follow.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 depicts the bacterial fatty acid biosynthesis cycle via a Type II or dissociated fatty acid synthase system.

Figure 2 depicts a simplified view of ene-amide core flanked by LHS (left-hand side) and RHS (right-hand side) moieties.

DETAILED DESCRIPTION

Introduction

The present invention is directed in part towards novel compositions that inhibit bacterial enzymes, and methods of making and using the same. In certain aspects, inhibitors and other compounds of the invention may be found by a structure-guided medicinal chemistry effort.

Bacterial fatty acid biosynthesis is believed to proceed via a Type II or dissociated fatty acid synthase system, in contrast to the mammalian Type I system. The overall process is believed to proceed in two stages – initiation and cyclical elongation. Enoyl-ACP reductase is part of the elongation cycle, in which malonyl-ACP is condensed with a growing acyl chain by b-ketoacyl-ACP synthase (FabB, FabF, FabH). The β-ketoester is reduced by β-ketoacyl-ACP reductase, which is then dehydrated to the trans-unsaturated acyl-ACP. The trans-unsaturated acyl-ACP is then reduced by enoyl-ACP reductase. (See Figure 1).

The enoyl-ACP reductase step is believed to be accomplished by FabI in *E. coli* and other gram negative organisms and *Staphylococci.* In certain gram-positive organisms, FabI paralogs exist. In *Streptococcus pneumoniae*, the enzymatic step is believed to be accomplished by the FabK protein, which has limited homology with the *S. aureus* FabI protein. In *B. subtilis* and *E. faecalis*, genes encoding both FabI and FabK exist. In *Mycobacterium tuberculosis* a FabI paralog termed InhA exists.

Enoyl-ACP reductase is believed to be the enzymatic target of the antimicrobial product triclosan.

In certain embodiments, the design of new analogs having FabI inhibiting properties is based on viewing the analogs as consisting of a central acrylamide flanked by two relatively hydrophobic groups, conveniently denoted as left-hand side (LHS) and right-hand side (RHS) as put forth in U.S. Provisional Patent Application 60/431,406. Schematically this is depicted in Figure 2, where a dumbbell like structure provides one way of viewing certain of the subject compositions (the central bond disconnections that is envisioned in a retrosynthetic sense are shown with dashed lines).

Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

The articles "a" and "an" are used herein to 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.

The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included.

The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

The term "FabI" is art-recognized and refers to the bacterial enzyme believed to function as an enoyl-acyl carrier protein (ACP) reductase in the final step of the four reactions involved in each cycle of bacterial fatty acid biosynthesis. This enzyme is believed to be widely distributed in bacteria and plants.

The term "enzyme inhibitor" refers to any compound that prevents an enzyme from effectively carrying out its respective biochemical roles. Therefore a "FabI inhibitor" is any compound that inhibits FabI from carrying out its biochemical role. The

amount of inhibition of the enzyme by any such compound will vary and is described herein and elsewhere.

The term "antibiotic agent" shall mean any drug that is useful in treating, preventing, or otherwise reducing the severity of any bacterial disorder, or any complications thereof, including any of the conditions, disease, or complications arising therefrom and/or described herein. Antibiotic agents include, for example, cephalosporins, quinolones and fluoroquinolones, penicillins, penicillins and beta lactamase inhibitors, carbepenems, monobactams, macrolides and lincosamines, glycopeptides, rifampin, oxazolidonones, tetracyclines, aminoglycosides, streptogramins, sulfonamides, and the like. Other general categories of antibiotic agents which may be part of a subject composition include those agents known to those of skill in the art as antibiotics and that qualify as (with defined terms being in quotation marks): "drug articles" recognized in the official United States Pharmacopoeia or official National Formulary (or any supplement thereto); "new drug" and "new animal drug" approved by the FDA of the U.S. as those terms are used in Title 21 of the United States Code; any drug that requires approval of a government entity, in the U.S. or abroad ("approved drug"); any drug that it is necessary to obtain regulatory approval so as to comply with 21 U.S.C. §355(a) ("regulatory approved drug"); any agent that is or was subject to a human drug application under 21 U.S.C. §379(g) ("human drug"). (All references to statutory code for this definition refer to such code as of the original filing date of this provisional application.) Other antibiotic agents are disclosed herein, and are known to those of skill in the art. In certain embodiments, the term "antibiotic agent" does not include an agent that is a FabI inhibitor, so that the combinations of the present invention in certain instances will include one agent that is a FabI inhibitor and another agent that is not.

The term "synergistic" is art recognized and refers to two or more components working together so that the total effect is greater than the sum of the effect of the components.

The term "illness" as used herein refers to any illness caused by or related to infection by an organism.

The term "bacterial illness" as used herein refers to any illness caused by or related to infection by bacteria.

The term "polynucleotide(s)" is art recognized and refers to any polyribonucleotide or polydeoxyribonucleotide, that may be unmodified RNA or DNA or modified RNA or DNA. "Polynucleotide(s)" include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions or single-, double- and triple-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded, or triple-stranded regions, or a mixture of single- and double-stranded regions. In addition, "polynucleotide" as used herein refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The strands in such regions may be from the same molecule or from different molecules. The regions may include all of one or more of the molecules, but more typically involve only a region of some of the molecules. One of the molecules of a triple-helical region often is an oligonucleotide. As used herein, the term "polynucleotide(s)" also includes DNAs or RNAs as described above that comprise one or more modified bases. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are "polynucleotide(s)" as that term is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as tritylated bases, to name just two examples, are polynucleotides as the term is used herein. It will be appreciated that a great variety of modifications have been made to DNA and RNA that serve many useful purposes known to those of skill in the art. The term "polynucleotide(s)" as it is employed herein embraces such chemically, enzymatically or metabolically modified forms of polynucleotides, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including, for example, simple and complex cells. "Polynucleotide(s)" also embraces short polynucleotides often referred to as oligonucleotide(s).

The term "polypeptide(s)" is art recognized and refers to any peptide or protein comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds. "Polypeptide(s)" refers to both short chains, commonly referred to as peptides, oligopeptides and oligomers and to longer chains generally referred to as proteins. Polypeptides may comprise amino acids other than the 20 gene encoded amino acids. "Polypeptide(s)" include those modified either by natural processes, such as

processing and other post-translational modifications, but also by chemical modification techniques. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature, and they are well known to those of skill in the art. It will be appreciated that the same type of modification may be present in the same or varying degree at several sites in a given polypeptide. Also, a given polypeptide may comprise many types of modifications. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains, and the amino or carboxyl termini. Modifications include, for example, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins, such as arginylation, and ubiquitination. See, for instance, *PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES*, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993) and Wold, F., Posttranslational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in *POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS*, B. C. Johnson, Ed., Academic Press, New York (1983); Seifter et al., *Meth. Enzymol. 182*:626-646 (1990) and Rattan et al., *Protein Synthesis: Posttranslational Modifications and Aging*, Ann. N.Y. Acad. Sci. 663: 48-62 (1992). Polypeptides may be branched or cyclic, with or without branching. Cyclic, branched and branched circular polypeptides may result from post-translational natural processes and may be made by entirely synthetic methods, as well.

The term "cis" is art-recognized and refers to the arrangement of two atoms or groups around a double bond such that the atoms or groups are on the same side of the double bond. Cis configurations are often labeled as (Z) configurations.

The term "trans" is art-recognized and refers to the arrangement of two atoms or groups around a double bond such that the atoms or groups are on the opposite sides of a double bond. Trans configurations are often labeled as (E) configurations.

The term "covalent bond" is art-recognized and refers to a bond between two atoms where electrons are attracted electrostatically to both nuclei of the two atoms, and the net effect of increased electron density between the nuclei counterbalances the internuclear repulsion. The term covalent bond includes coordinate bonds when the bond is with a metal ion.

The term "therapeutic agent" is art-recognized and refers to any chemical moiety that is a biologically, physiologically, or pharmacologically active substance that acts locally or systemically in a subject. Examples of therapeutic agents, also referred to as "drugs", are described in well-known literature references such as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics, and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. Antibiotic agents and Fab I/Fab K inhibitors are examples of therapeutic agents.

The term "therapeutic effect" is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and/or conditions in an animal or human. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art. For example,

certain compositions of the present invention may be administered in a sufficient amount to produce a at a reasonable benefit/risk ratio applicable to such treatment.

The terms "combinatorial library" or "library" are art-recognized and refer to a plurality of compounds, which may be termed "members," synthesized or otherwise prepared from one or more starting materials by employing either the same or different reactants or reaction conditions at each reaction in the library. There are a number of other terms of relevance to combinatorial libraries (as well as other technologies). The term "identifier tag" is art-recognized and refers to a means for recording a step in a series of reactions used in the synthesis of a chemical library. The term "immobilized" is art-recognized and, when used with respect to a species, refers to a condition in which the species is attached to a surface with an attractive force stronger than attractive forces that are present in the intended environment of use of the surface, and that act on the species. The term "solid support" is art-recognized and refers to a material which is an insoluble matrix, and may (optionally) have a rigid or semi-rigid surface. The term "linker" is art-recognized and refers to a molecule or group of molecules connecting a support, including a solid support or polymeric support, and a combinatorial library member. The term "polymeric support" is art-recognized and refers to a soluble or insoluble polymer to which a chemical moiety can be covalently bonded by reaction with a functional group of the polymeric support. The term "functional group of a polymeric support" is art-recognized and refers to a chemical moiety of a polymeric support that can react with an chemical moiety to form a polymer-supported amino ester.

The term "synthetic" is art-recognized and refers to production by in vitro chemical or enzymatic synthesis.

The term "meso compound" is art-recognized and refers to a chemical compound which has at least two chiral centers but is achiral due to a plane or point of symmetry.

The term "chiral" is art-recognized and refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. A "prochiral molecule" is a molecule which has the potential to be converted to a chiral molecule in a particular process.

The term "stereoisomers" is art-recognized and refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. In particular, "enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another. "Diastereomers", on the other hand, refers to stereoisomers with two or more centers of dissymmetry and whose molecules are not mirror images of one another.

Furthermore, a "stereoselective process" is one which produces a particular stereoisomer of a reaction product in preference to other possible stereoisomers of that product. An "enantioselective process" is one which favors production of one of the two possible enantiomers of a reaction product.

The term "regioisomers" is art-recognized and refers to compounds which have the same molecular formula but differ in the connectivity of the atoms. Accordingly, a "regioselective process" is one which favors the production of a particular regioisomer over others, e.g., the reaction produces a statistically significant increase in the yield of a certain regioisomer.

The term "epimers" is art-recognized and refers to molecules with identical chemical constitution and containing more than one stereocenter, but which differ in configuration at only one of these stereocenters.

The term "ED_{50}" is art-recognized. In certain embodiments, ED_{50} means the dose of a drug which produces 50% of its maximum response or effect, or alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations. The term "LD_{50}" is art-recognized. In certain embodiments, LD_{50} means the dose of a drug which is lethal in 50% of test subjects. The term "therapeutic index" is an art-recognized term which refers to the therapeutic index of a drug, defined as LD_{50}/ED_{50}.

The term "K_i" is art-recognized and refers to the dissociation constant of the enzyme-inhibitor complex.

The term "antimicrobial" is art-recognized and refers to the ability of the compounds of the present invention to prevent, inhibit or destroy the growth of microbes such as bacteria, fungi, protozoa and viruses.

The term "antibacterial" is art-recognized and refers to the ability of the compounds of the present invention to prevent, inhibit or destroy the growth of microbes of bacteria.

The term "microbe" is art-recognized and refers to a microscopic organism. In certain embodiments the term microbe is applied to bacteria. In other embodiments the term refers to pathogenic forms of a microscopic organism.

The term "prodrug" is art-recognized and is intended to encompass compounds which, under physiological conditions, are converted into the antibacterial agents of the present invention. A common method for making a prodrug is to select moieties which are hydrolyzed under physiological conditions to provide the desired compound. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal or the target bacteria.

The term "structure-activity relationship" or "(SAR)" is art-recognized and refers to the way in which altering the molecular structure of a drug or other compound alters its interaction with a receptor, enzyme, nucleic acid or other target and the like.

The term "aliphatic" is art-recognized and refers to a linear, branched, cyclic alkane, alkene, or alkyne. In certain embodiments, aliphatic groups in the present invention are linear or branched and have from 1 to about 20 carbon atoms.

The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chain, C_3-C_{30} for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure. The term "alkyl" is also defined to include halosubstituted alkyls.

Moreover, the term "alkyl" (or "lower alkyl") includes "substituted alkyls", which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a

phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain may themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls may be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CN, and the like.

The term "aralkyl" is art-recognized and refers to an alkyl group substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

Unless the number of carbons is otherwise specified, "lower alkyl" refers to an alkyl group, as defined above, but having from one to about ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

The term "heteroatom" is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium.

The term "aryl" is art-recognized and refers to 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "heteroaryl" or "heteroaromatics." The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl,

hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, $-CF_3$, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

The terms "heterocyclyl" or "heterocyclic group" are art-recognized and refer to 3- to about 10-membered ring structures, alternatively 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxanthene, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

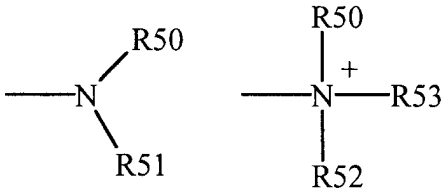
The terms "polycyclyl" or "polycyclic group" are art-recognized and refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle may be substituted with such substituents as

described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, $-CF_3$, -CN, or the like.

The term "carbocycle" is art-recognized and refers to an aromatic or non-aromatic ring in which each atom of the ring is carbon.

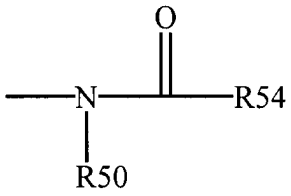
The term "nitro" is art-recognized and refers to $-NO_2$; the term "halogen" is art-recognized and refers to -F, -Cl, -Br or -I; the term "sulfhydryl" is art-recognized and refers to -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" is art-recognized and refers to $-SO_2^-$. "Halide" designates the corresponding anion of the halogens, and "pseudohalide" has the definition set forth on 560 of "Advanced Inorganic Chemistry" by Cotton and Wilkinson.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



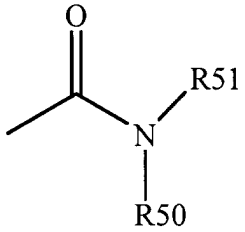
wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_m$-R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R50 or R51 may be a carbonyl, e.g., R50, R51 and the nitrogen together do not form an imide. In other embodiments, R50 and R51 (and optionally R52) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_m$-R61. Thus, the term "alkylamine" includes an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R50 and R51 is an alkyl group.

The term "acylamino" is art-recognized and refers to a moiety that may be represented by the general formula:



wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R61, where m and R61 are as defined above.

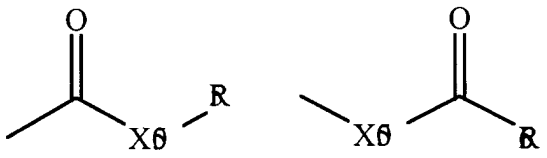
The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that may be represented by the general formula:



wherein R50 and R51 are as defined above. Certain embodiments of the amide in the present invention will not include imides which may be unstable.

The term "alkylthio" refers to an alkyl group, as defined above, having a sulfur radical attached thereto. In certain embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-$(CH_2)_m$-R61, wherein m and R61 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

The term "carbonyl" is art recognized and includes such moieties as may be represented by the general formulas:

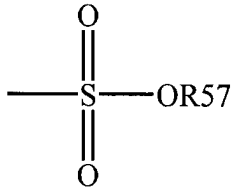


wherein X50 is a bond or represents an oxygen or a sulfur, and R55 and R56 represents a hydrogen, an alkyl, an alkenyl, -$(CH_2)_m$-R61or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R61, where m and R61 are defined above. Where X50 is an oxygen and R55 or R56 is not hydrogen, the formula represents an "ester". Where X50 is an oxygen, and R55 is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R55 is a hydrogen, the formula represents a "carboxylic acid". Where X50 is an oxygen, and R56 is hydrogen, the

formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiolcarbonyl" group. Where X50 is a sulfur and R55 or R56 is not hydrogen, the formula represents a "thiolester." Where X50 is a sulfur and R55 is hydrogen, the formula represents a "thiolcarboxylic acid." Where X50 is a sulfur and R56 is hydrogen, the formula represents a "thiolformate." On the other hand, where X50 is a bond, and R55 is not hydrogen, the above formula represents a "ketone" group. Where X50 is a bond, and R55 is hydrogen, the above formula represents an "aldehyde" group.

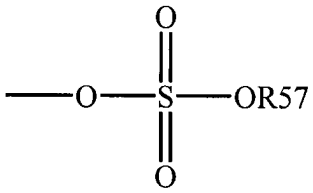
The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, *tert*-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O--$(CH_2)_m$-R61, where m and R61 are described above.

The term "sulfonate" is art recognized and refers to a moiety that may be represented by the general formula:



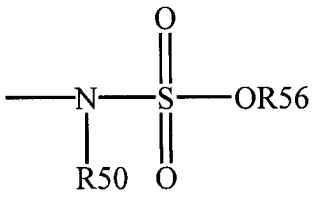
in which R57 is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

The term "sulfate" is art recognized and includes a moiety that may be represented by the general formula:



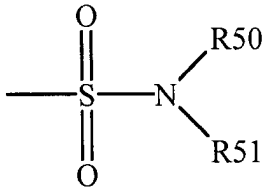
in which R57 is as defined above.

The term "sulfonamido" is art recognized and includes a moiety that may be represented by the general formula:



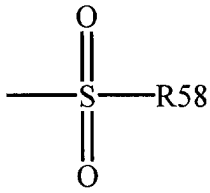
in which R50 and R56 are as defined above.

The term "sulfamoyl" is art-recognized and refers to a moiety that may be represented by the general formula:



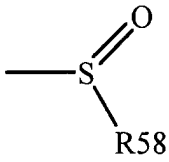
in which R50 and R51 are as defined above.

The term "sulfonyl" is art-recognized and refers to a moiety that may be represented by the general formula:



in which R58 is one of the following: hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

The term "sulfoxido" is art-recognized and refers to a moiety that may be represented by the general formula:



in which R58 is defined above.

Analogous substitutions may be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

The definition of each expression, e.g. alkyl, m, n, and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, *p*-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, *p*-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, *p*-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization

or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. Also for purposes of this invention, the term "hydrocarbon" is contemplated to include all permissible compounds having at least one hydrogen and one carbon atom. In a broad aspect, the permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds that may be substituted or unsubstituted.

The term "protecting group" is art-recognized and refers to temporary substituents that protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed by Greene and Wuts in Protective Groups in Organic Synthesis (2nd ed., Wiley: New York, 1991).

The term "hydroxyl-protecting group" is art-recognized and refers to those groups intended to protect a hydrozyl group against undesirable reactions during synthetic procedures and includes, for example, benzyl or other suitable esters or ethers groups known in the art.

The term "carboxyl-protecting group" is art-recognized and refers to those groups intended to protect a carboxylic acid group, such as the C-terminus of an amino acid or peptide or an acidic or hydroxyl azepine ring substituent, against undesirable reactions during synthetic procedures and includes. Examples for protecting groups for carboxyl groups involve, for example, benzyl ester, cyclohexyl ester, 4-nitrobenzyl ester, t-butyl ester, 4-pyridylmethyl ester, and the like.

The term "amino-blocking group" is art-recognized and refers to a group which will prevent an amino group from participating in a reaction carried out on some other functional group, but which can be removed from the amine when desired. Such groups are discussed by in Ch. 7 of Greene and Wuts, cited above, and by Barton, Protective Groups in Organic Chemistry ch. 2 (McOmie, ed., Plenum Press, New York, 1973). Examples of suitable groups include acyl protecting groups such as, to illustrate, formyl, dansyl, acetyl, benzoyl, trifluoroacetyl, succinyl, methoxysuccinyl, benzyl and substituted benzyl such as 3,4-dimethoxybenzyl, o-nitrobenzyl, and triphenylmethyl; those of the formula -COOR where R includes such groups as methyl, ethyl, propyl, isopropyl, 2,2,2-trichloroethyl, 1-methyl-1-phenylethyl, isobutyl, t-butyl, t-amyl, vinyl, allyl, phenyl, benzyl, p-nitrobenzyl, o-nitrobenzyl, and 2,4-dichlorobenzyl; acyl groups and substituted acyl such as formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, benzoyl, and p-methoxybenzoyl; and other groups such as methanesulfonyl, p-toluenesulfonyl, p-bromobenzenesulfonyl, p-nitrophenylethyl, and p-toluenesulfonyl-aminocarbonyl. Preferred amino-blocking groups are benzyl ($-CH_2C_6H_5$), acyl [C(O)R1] or $SiR1_3$ where R1 is C_1-C_4 alkyl, halomethyl, or 2-halo-substituted-(C_2-C_4 alkoxy), aromatic urethane protecting groups as, for example, carbonylbenzyloxy (Cbz); and aliphatic urethane protecting groups such as t-butyloxycarbonyl (Boc) or 9-fluorenylmethoxycarbonyl (FMOC).

The definition of each expression, e.g. lower alkyl, m, n, p and the like, when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The term "electron-withdrawing group" is art-recognized, and refers to the tendency of a substituent to attract valence electrons from neighboring atoms, i.e., the substituent is electronegative with respect to neighboring atoms. A quantification of the level of electron-withdrawing capability is given by the Hammett sigma (σ) constant. This well known constant is described in many references, for instance, March, Advanced Organic Chemistry 251-59 (McGraw Hill Book Company: New York, 1977). The Hammett constant values are generally negative for electron donating groups ($\sigma(P) = -0.66$ for NH_2) and positive for electron withdrawing groups ($\sigma(P) = 0.78$ for a nitro group), $\sigma(P)$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

The term "small molecule" is art-recognized and refers to a composition which has a molecular weight of less than about 2000 amu, or less than about 1000 amu, and even less than about 500 amu. Small molecules may be, for example, nucleic acids, peptides, polypeptides, peptide nucleic acids, peptidomimetics, carbohydrates, lipids or other organic (carbon containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays of the invention. The term "small organic molecule" refers to a small molecule that is often identified as being an organic or medicinal compound, and does not include molecules that are exclusively nucleic acids, peptides or polypeptides.

The term "modulation" is art-recognized and refers to up regulation (i.e., activation or stimulation), down regulation (i.e., inhibition or suppression) of a response, or the two in combination or apart.

The term "treating" is art-recognized and refers to curing as well as ameliorating at least one symptom of any condition or disease.

The term "prophylactic" or "therapeutic" treatment is art-recognized and refers to administration to the host of one or more of the subject compositions. If it is

administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate or maintain the existing unwanted condition or side effects therefrom).

A "patient," "subject" or "host" to be treated by the subject method may mean either a human or non-human animal.

The term "mammal" is known in the art, and exemplary mammals include humans, primates, bovines, porcines, canines, felines, and rodents (e.g., mice and rats).

The term "bioavailable" is art-recognized and refers to a form of the subject invention that allows for it, or a portion of the amount administered, to be absorbed by, incorporated to, or otherwise physiologically available to a subject or patient to whom it is administered.

The term "pharmaceutically-acceptable salts" is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds, including, for example, those contained in compositions of the present invention.

The term "pharmaceutically acceptable carrier" is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl

laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

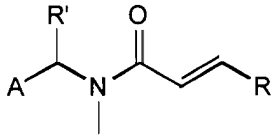
The terms "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" are art-recognized and refer to the administration of a subject composition, therapeutic or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

The terms "parenteral administration" and "administered parenterally" are art-recognized and refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articulare, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

Contemplated equivalents of the compositions described herein include compositions which otherwise correspond thereto, and which have the same general properties thereof (such as other compositions comprising FabI/Fab K inhibitors), wherein one or more simple variations of substituents or components are made which do not adversely affect the characteristics of the compositions of interest. In general, the components of the compositions of the present invention may be prepared by the methods illustrated in the general reaction schema as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

FabI Inhibitors

The FabI inhibitor compounds of the present invention include those depicted by formula **I**:

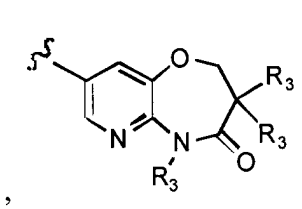


I

wherein, independently for each occurrence,

A is a monocyclic ring of 4-7 atoms containing 0-2 heteroatoms, a bicyclic ring of 8-12 atoms containing 0-4 heteroatoms or a tricyclic ring of 8-12 atoms containing 0-6 heteroatoms wherein the rings are independently aliphatic, aromatic, heteroaryl or heterocyclic in nature, the heteroatoms are selected from N, S or O and the rings are optionally substituted with one or more groups selected from C_{1-4} alkyl, OR", CN, OCF_3, F, Cl, Br, I; wherein R" is H, alkyl, aralkyl, or heteroaralkyl; R' is H or alkyl;

R is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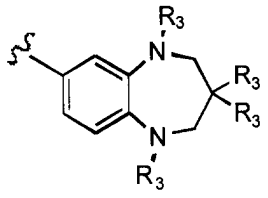
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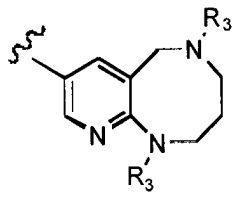
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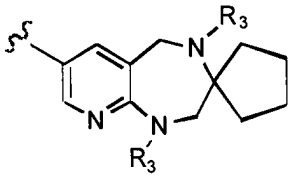
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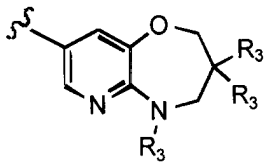
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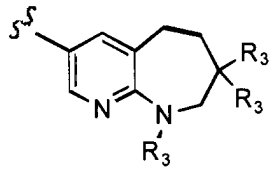
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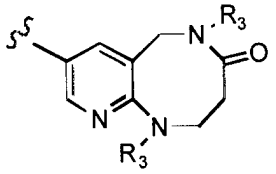
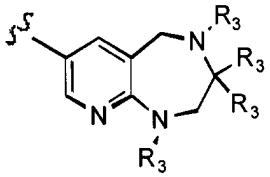

, or

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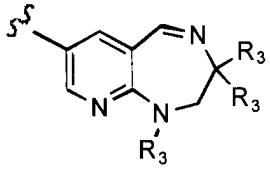
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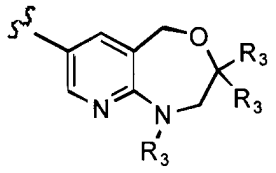
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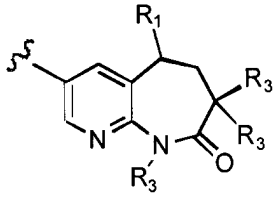
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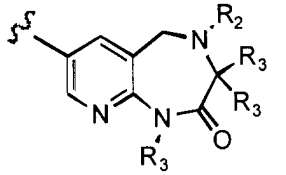
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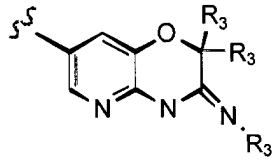


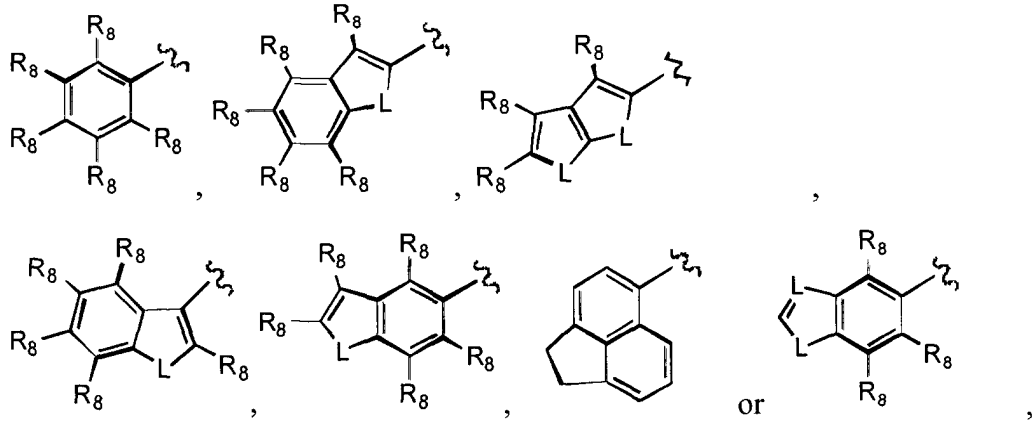
wherein, independently for each occurrence,

R_1 is H or OH;

R_2 is OH or -Ar; and

R_3 is each independently H, alkyl, carbonyl, sulfonyl, or aryl.

In a further embodiment, the present invention includes compounds of formula I and the attendant definitions, wherein A is selected from the following:

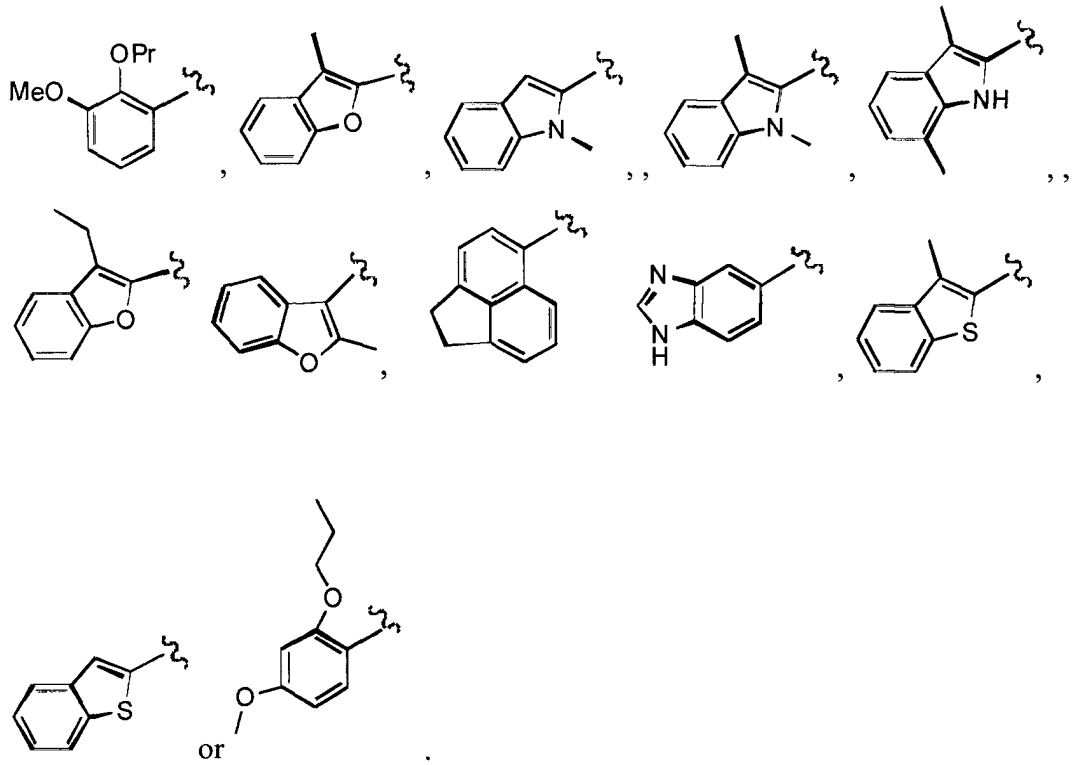


wherein, independently for each occurrence,

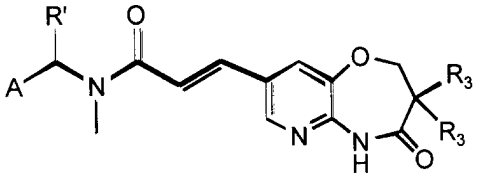
R_8 is H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkenyl, OR", CN, OCF_3, F, Cl, Br, I; wherein R" is H, alkyl, aralkyl, or heteroaralkyl; and

L is each independently O, S, or NR_3.

In a further embodiment, the present invention includes compounds of formula I and the attendant definitions, wherein A is selected from the following:



In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ia**:

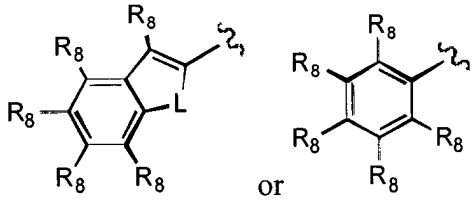


Ia

wherein,

R'and R_3 are as previously defined, and

A is selected from the following:

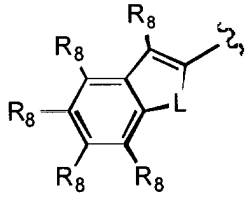


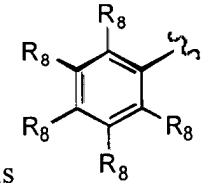
wherein L and R_8 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Ia and the attendant definitions, wherein R' is H.

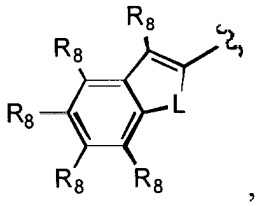
In a further embodiment, the present invention relates to compounds of formula Ia and the attendant definitions, wherein R' is methyl.

In a further embodiment, the present invention relates to compounds of formula Ia and the attendant definitions, wherein R_3 is methyl.

In a further embodiment, the present invention relates to compounds of formula Ia and the attendant definitions, wherein A is  .

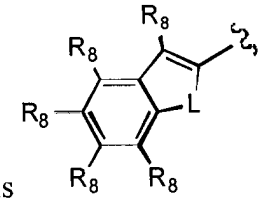
In a further embodiment, the present invention relates to compounds of formula Ia and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula Ia



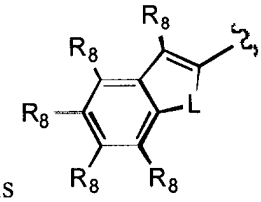
and the attendant definitions, wherein A is , and L is O.

In a further embodiment, the present invention relates to compounds of formula Ia



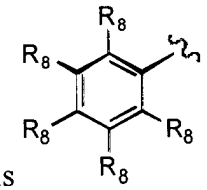
and the attendant definitions, wherein A is , and L is N.

In a further embodiment, the present invention relates to compounds of formula Ia



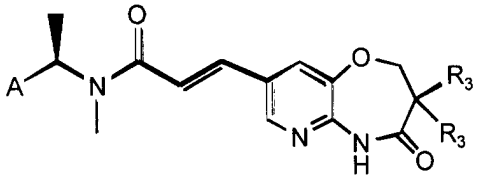
and the attendant definitions, wherein A is , L is O, N or S, and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula Ia



and the attendant definitions, wherein A is , wherein R_8 is OR" or H, and R" is alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ib**:

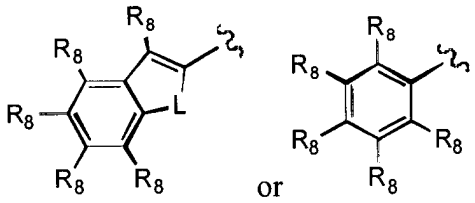


Ib

wherein,

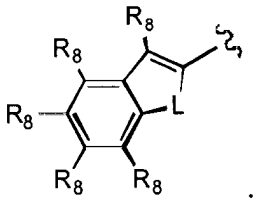
R_3 is as defined previously, and

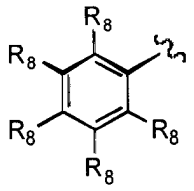
A is selected from the following:

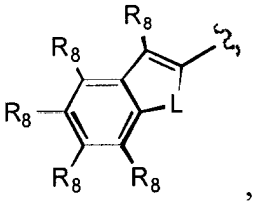


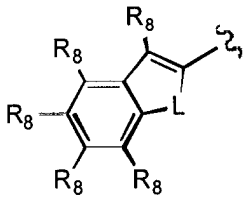
wherein L and R_8 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Ib and the attendant definitions, wherein R_3 is each independently H or alkyl.

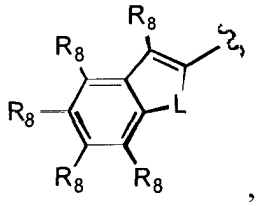
In a further embodiment, the present invention relates to compounds of formula Ib and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula Ib and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula Ib and the attendant definitions, wherein A is  , and L is O.

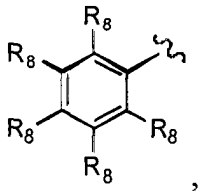
In a further embodiment, the present invention relates to compounds of formula Ib and the attendant definitions, wherein A is  , and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula Ib



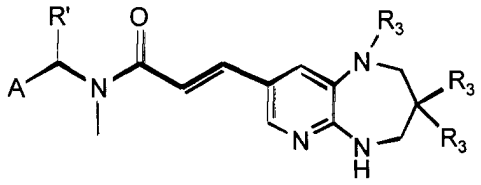
and the attendant definitions, wherein A is , L is O or S, and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula Ib



and the attendant definitions, wherein A is , R_8 is H or OR", and R" is alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ic**:

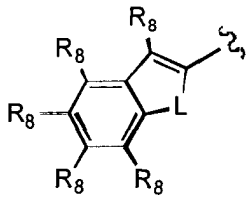


Ic

wherein,

R' and R_3 are as defined previously, and

A is:

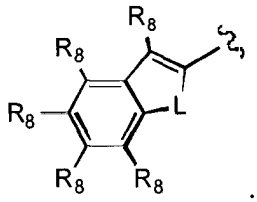


wherein L and R_8 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Ic and the attendant definitions, wherein R' is H.

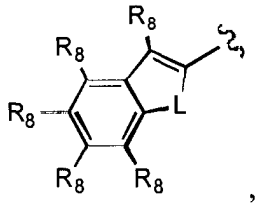
In a further embodiment, the present invention relates to compounds of formula Ic and the attendant definitions, wherein R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Ic



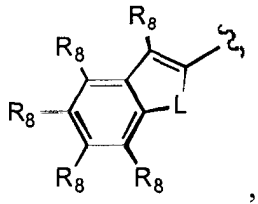
and the attendant definitions, wherein A is .

In a further embodiment, the present invention relates to compounds of formula Ic



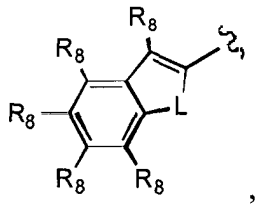
and the attendant definitions, wherein A is , and L is O.

In a further embodiment, the present invention relates to compounds of formula Ic



and the attendant definitions, wherein A is , and L is S.

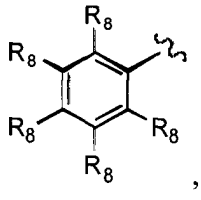
In a further embodiment, the present invention relates to compounds of formula Ic



and the attendant definitions, wherein A is , and R_8 is H, or alkyl.

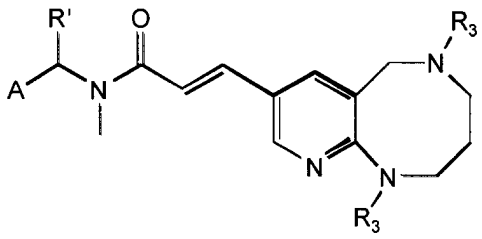
.

In a further embodiment, the present invention relates to compounds of formula Ic



and the attendant definitions, wherein A is , R_8 is H or OR", and R" is alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Id**:

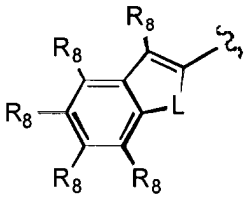
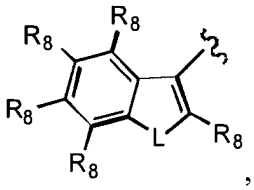
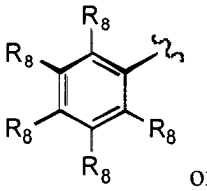


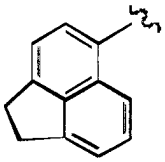
Id

wherein,

R' and R_3 are as defined previously, and

A is selected from the following:




or


;

wherein L and R_8 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein R' is H.

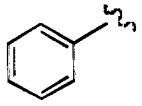
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein at least one nitrogen bonded R_3 is sulfonyl.

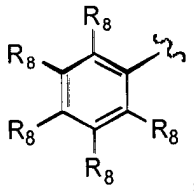
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein at least one nitrogen bonded R_3 is methyl.

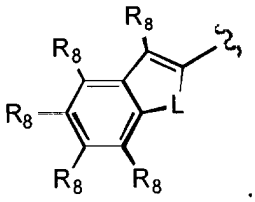
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein at least one R_3 is aryl.

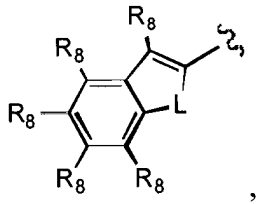
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein at least one nitrogen bonded R_3 is

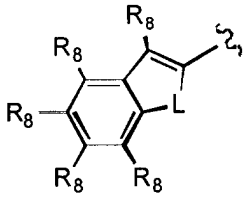


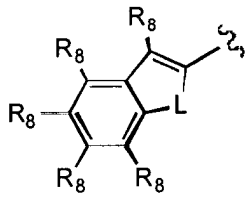
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein at least one R_3 is Boc.

In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein A is  , and R_8 is H or OR".

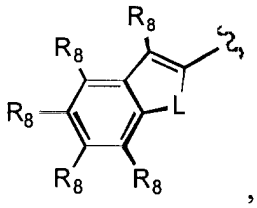
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein A is  , and L is O.

In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein A is  , and L is S.

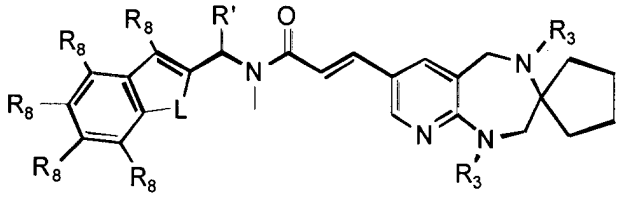
In a further embodiment, the present invention relates to compounds of formula Id and the attendant definitions, wherein A is  , and L is NMe.

In a further embodiment, the present invention relates to compounds of formula Id



and the attendant definitions, wherein A is , and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ie**:



Ie

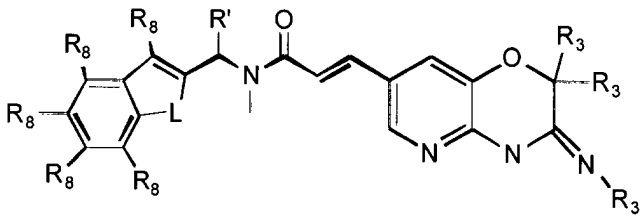
wherein R', R_3, R_8 and L are as defined previously.

In a further embodiment, the present invention relates to compounds of formula Ie and the attendant definitions, wherein R' is H.

In a further embodiment, the present invention relates to compounds of formula Ie and the attendant definitions, wherein L is O.

In a further embodiment, the present invention relates to compounds of formula Ie and the attendant definitions, wherein R_8 is H or Me.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **If**:



If

wherein R', R_3, R_8, and L are as defined previously.

In a further embodiment, the present invention relates to compounds of formula If and the attendant definitions, wherein R' is H.

In a further embodiment, the present invention relates to compounds of formula If and the attendant definitions, wherein R_3 is H.

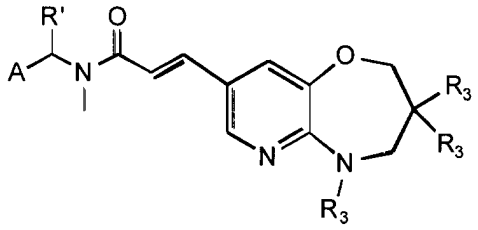
In a further embodiment, the present invention relates to compounds of formula If and the attendant definitions, wherein L is O.

In a further embodiment, the present invention relates to compounds of formula If and the attendant definitions, wherein L is S.

In a further embodiment, the present invention relates to compounds of formula If and the attendant definitions, wherein R_3 is alkyl.

In a further embodiment, the present invention relates to compounds of formula If and the attendant definitions, wherein R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ig**:

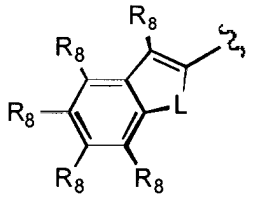


Ig

wherein,

R' and R_3, are as defined previously, and

A is:

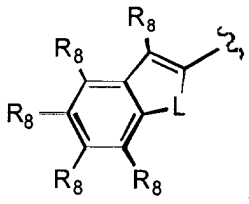


wherein L and R_8 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Ig and the attendant definitions, wherein R' is H.

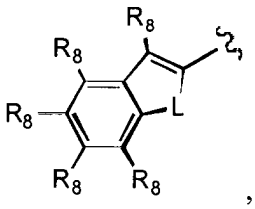
In a further embodiment, the present invention relates to compounds of formula Ig and the attendant definitions, wherein R_3 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula Ig



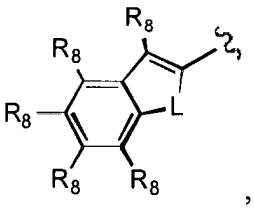
and the attendant definitions, wherein A is .

In a further embodiment, the present invention relates to compounds of formula Ig



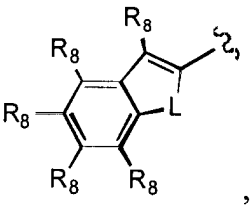
and the attendant definitions, wherein A is , and L is O.

In a further embodiment, the present invention relates to compounds of formula Ig



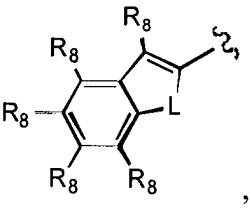
and the attendant definitions, wherein A is , and L is NMe.

In a further embodiment, the present invention relates to compounds of formula Ig



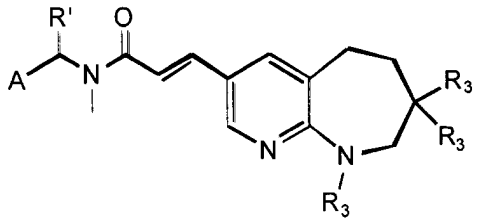
and the attendant definitions, wherein A is , and L is S.

In a further embodiment, the present invention relates to compounds of formula Ig



and the attendant definitions, wherein A is , and R_8 is H, or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ih**:

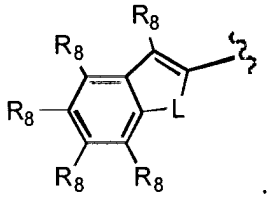


Ih

wherein,

R' and R_3 are as previously defined; and

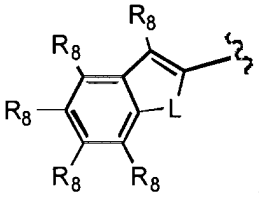
A is:

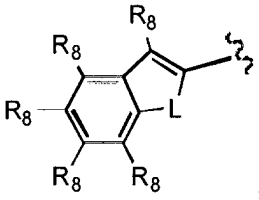


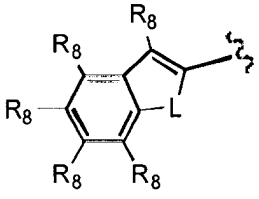
.

In a further embodiment, the present invention relates to compounds of formula Ih and the attendant definitions, wherein R' is H.

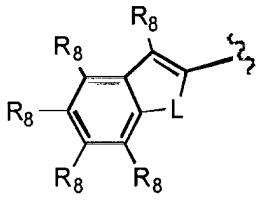
In a further embodiment, the present invention relates to compounds of formula Ih and the attendant definitions, wherein R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Ih and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula Ih and the attendant definitions, wherein A is  , and L is O.

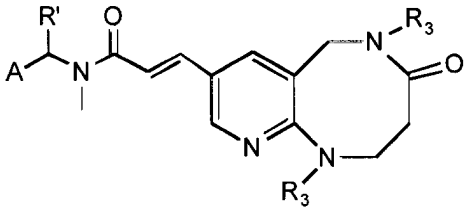
In a further embodiment, the present invention relates to compounds of formula Ih and the attendant definitions, wherein A is  , and L is S.

In a further embodiment, the present invention relates to compounds of formula Ih



and the attendant definitions, wherein A is , and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ii**:

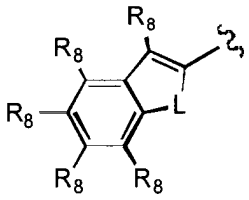


Ii

wherein,

R' and R_3 are as previously defined, and

A is:

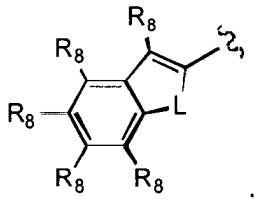


.

In a further embodiment, the present invention relates to compounds of formula Ii and the attendant definitions, wherein R' is H.

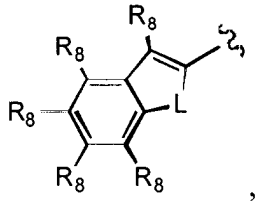
In a further embodiment, the present invention relates to compounds of formula Ii and the attendant definitions, wherein R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Ii



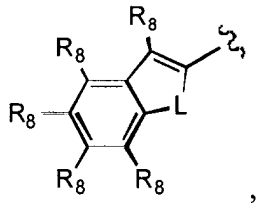
and the attendant definitions, wherein A is .

In a further embodiment, the present invention relates to compounds of formula Ii



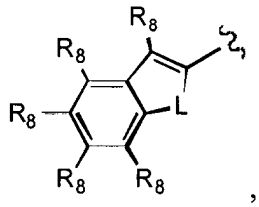
and the attendant definitions, wherein A is , and L is O.

In a further embodiment, the present invention relates to compounds of formula Ii



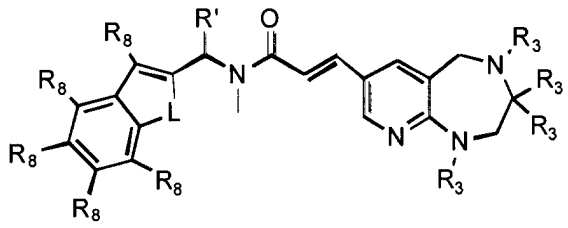
and the attendant definitions, wherein A is , and L is S.

In a further embodiment, the present invention relates to compounds of formula Ii



and the attendant definitions, wherein A is , and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ij**:



Ij

wherein,

R', R_3, R_8 and L are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein L is O.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein L is S.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein R' is H.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula Ij

and the attendant definitions, wherein at least one R_3 is 

.

In a further embodiment, the present invention relates to compounds of formula Ij

and the attendant definitions, wherein at least one R_3 is 

.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein L is O, and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein at each nitrogen bonded R_3 is H or alkyl.

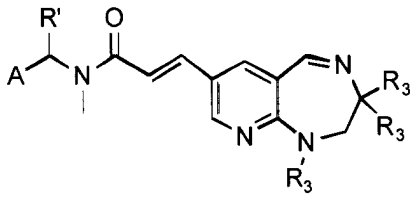
In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein each geminal R_3 is alkyl.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein at least one R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein the geminal R_3 are H and (*R*)-Me.

In a further embodiment, the present invention relates to compounds of formula Ij and the attendant definitions, wherein the geminal R_3 is H and (*S*)-Me.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Ik**:

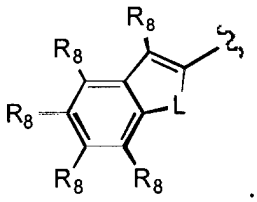


Ik

wherein,

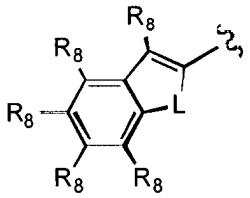
R' and R_3 are as defined previously, and

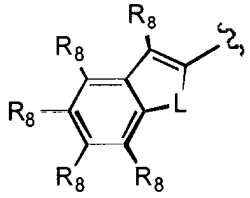
A is:

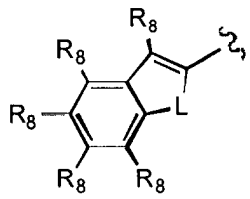


wherein R_8 and L are as defined previously.

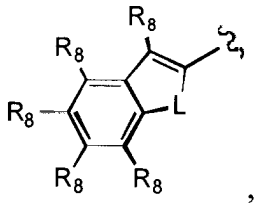
In a further embodiment, the present invention relates to compounds of formula Ik and the attendant definitions, wherein R' is H.

In a further embodiment, the present invention relates to compounds of formula Ik and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula Ik and the attendant definitions, wherein A is  , and L is O.

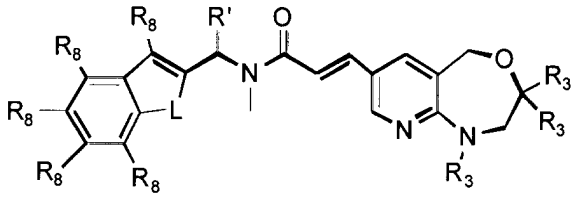
In a further embodiment, the present invention relates to compounds of formula Ik and the attendant definitions, wherein A is  , and L is NMe.

In a further embodiment, the present invention relates to compounds of formula Ik



and the attendant definitions, wherein A is , and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **II**:



II

wherein,

R',R_3, R_8, and L are as previously defined.

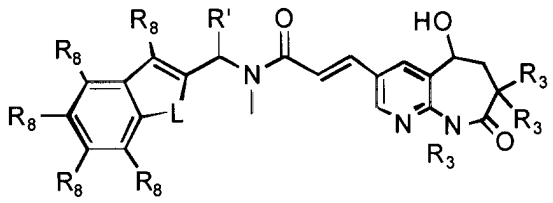
In a further embodiment, the present invention relates to compounds of formula II and the attendant definitions, wherein R_3 is H.

In a further embodiment, the present invention relates to compounds of formula II and the attendant definitions, wherein L is O.

In a further embodiment, the present invention relates to compounds of formula II and the attendant definitions, wherein R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula II and the attendant definitions, wherein R_3 is H, L is O, and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **Im**:



Im

wherein,

R', R_3, and R_8 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula Im and the attendant definitions, wherein R' is H.

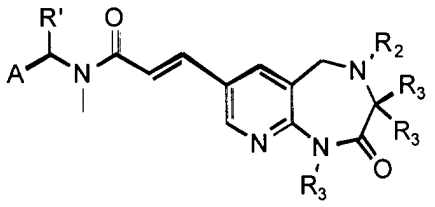
In a further embodiment, the present invention relates to compounds of formula Im and the attendant definitions, wherein the nitrogen bound R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Im and the attendant definitions, wherein the geminal R_3 are H.

In a further embodiment, the present invention relates to compounds of formula Im and the attendant definitions, wherein L is O.

In a further embodiment, the present invention relates to compounds of formula Im and the attendant definitions, wherein R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula I, wherein the compound has formula **In**:

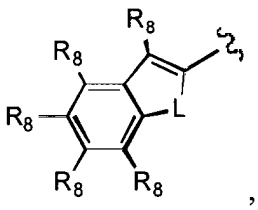


In

wherein,

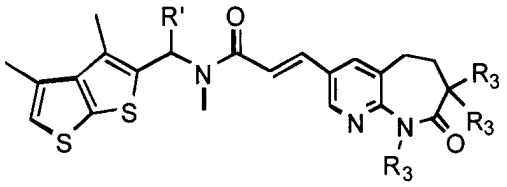
R', R_2 and R_3 are as defined previously, and

A is selected from the following:



wherein R_8 and L are as defined previously.

In an embodiment, compounds of formula **Io** contemplated:

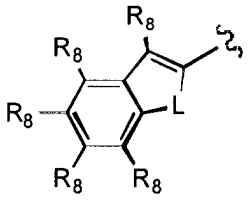


Io

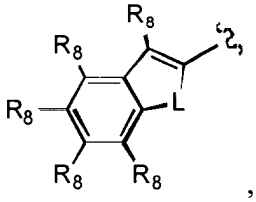
whre R' and R_3 are as previously defined.

In a further embodiment, the present invention relates to compounds of formula In and the attendant definitions, wherein R' is H.

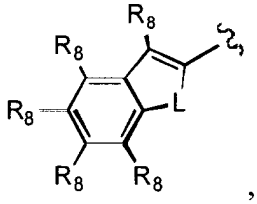
In a further embodiment, the present invention relates to compounds of formula In and the attendant definitions, wherein R_3 is H.

In a further embodiment, the present invention relates to compounds of formula Im and the attendant definitions, wherein A is  .

In a further embodiment, the present invention relates to compounds of formula In and the attendant definitions, wherein R_2 is phenyl.

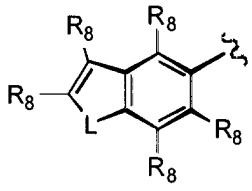
In a further embodiment, the present invention relates to compounds of formula In and the attendant definitions, wherein A is  , and L is N.

In a further embodiment, the present invention relates to compounds of formula In



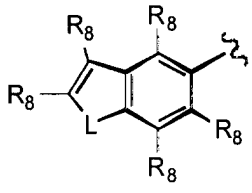
and the attendant definitions, wherein A is , and R_8 is H or alkyl.

In a further embodiment, the present invention relates to compounds of formula In



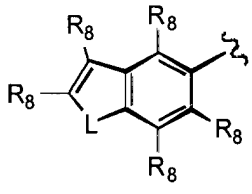
and the attendant definitions, wherein A is .

In a further embodiment, the present invention relates to compounds of formula In



and the attendant definitions, wherein A is , and L is NH.

In a further embodiment, the present invention relates to compounds of formula In



and the attendant definitions, wherein A is , and R_8 is H or alkyl.

The present invention relates to, but is not limited to, the compounds wherein the compound is selected from the following list:

(*E*)-3-(7,7-Dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-(3-methoxy-2-propoxy-benzyl)-*N*-methylacrylamide; (*E*)-3-(7,7-Dimethyl-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)acrylamide; 3-(7,7-dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-N-methyl-N-[1-(R)-(3-methyl-benzofuran-2-yl)-ethyl]acrylamide; (*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide; (*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride; (*E*)-7-{2-[Methyl-(3-methylbenzofuran-2-ylmethyl)carbamoyl]vinyl}-1,2,3,5-tetrahydropyrido[2,3-*e*][1,4]diazepine-4-carboxylic

acid *tert*-butyl ester; (*E*)-3-(4-Acetyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride; *N*-Methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide; *N*-Methyl-*N*-(1-methyl-1H-indol-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide; N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride; N-Methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride; (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride; (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride; (E)-tert-butyl 7-(3-(((1,2-dihydroacenaphthylen-5-yl)methyl)(methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate; (S,E)-3-(3-benzyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetate; (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride; (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride; (E)-3-(3,3-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide hydrochloride; (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride; (E)-3-(3-spirocyclopentyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid; E)-N-methyl-3-((S)-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methyl-3a,7a-dihydrobenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid; (R,E)-N-methyl-3-(3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid salt; (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide; (E)-N-methyl-N-((3-methyl-1H-indol-2-yl)methyl)-3-(1,2,3,5-

tetrahydropyrido[2,3-e][1,4]oxazepin-7-yl)acrylamide; (*E*)-3-(2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)-*N*-methyl-*N*-((3-methyl-1*H*-indol-2-yl)methyl)acrylamide; (*R*,*E*)-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)-*N*-(1(3-ethylbenzofuran-2-yl)ethyl)-*N*-methylacrylamide; (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide, di-methane sulfonic salt; (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide, di-methane sulfonic salt; (*R,E*)-3-(3,3-dimethyl-2-oxo-1,2,3,5-tetrahydropyrido[2,3-e][1,4]oxazepin-7-yl)-*N*-(1-(3-methoxy-2-propoxyphenyl)ethyl)-*N*-methylacrylamide; (*E*)-*N*-methyl-*N*-((3-methylbenoz[*b*]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylamide; (E)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride; (E)-N-(3-methoxy-2-propoxybenzyl)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide; (E)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide; (E)-3-(5-hydroxy-8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide; (E)-3-(1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide; (E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride; (E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide; *E*)-*N*-((1,3-dimethyl-1*H*-indol-2-yl)methyl)-*N*-methyl-3-(2-oxo-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide; (E)-*N*-methyl-*N*-((3-methylbenzofuran-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylamide.

Also included in the antibacterial compositions of the present invention are pharmaceutically acceptable addition salts and complexes of the FabI inhibitors. In cases wherein the inhibitors may have one or more chiral centers, unless specified, the present

invention comprises each unique racemic compound, as well as each unique nonracemic compound.

In cases in which the inhibitors have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein inhibitors may exist in tautomeric forms, such as keto-enol tautomers, such as  and  , each tautomeric form is contemplated as being included within this invention, whether existing in equilibrium or locked in one form by appropriate substitution with R'. The meaning of any substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Also included in the antibiotic compounds of the present invention are prodrugs of the FabI inhibitors.

A variety of subject compounds and intermediates of them may be made by a person of ordinary skill in the art using conventional reaction techniques. Non-limiting examples of compounds and methods of making them may be found in U.S. Patent Application Nos. 08/790,043, 10/009,219, 10/089,019, 09/968,129, 09/968,123, 09/968,236, 09/959,172, 09/979,560, 09/980,369, 10/089,755, 10/089,739, 10/089,740, and PCT Application Nos. PCT/US03/38706, WO 0027628 and WO 0210332.

Synthetic Routes to Compounds of Formula I

A generalized chemical approach to assembling compounds of formula I is based on viewing the analogs as consisting of a central ene-amide flanked by left-hand side (LHS) and right-hand side (RHS) moieties. Schematically, this is depicted in Figure 2. Two possible bond disconnections envisioned in a retrosynthetic sense are shown with dashed lines. The examples illustrate some of the methods that can be used in the synthesis of compounds of formula I wherein the final covalent bond formed is via a Heck coupling between an alkene and a suitably halogenated right hand side moiety, or via a dehydrative coupling between a left hand side alkyl amine and an ene-carboxylic acid. It will be recognized by one skilled in the art that other disconnections are possible resulting in alternative modes of assembly of the compounds of the invention.

It will be recognized by one skilled in the art that other methods of LHS and RHS synthesis can be employed in the preparation of said intermediates. Likewise other methods of amide and/or carbon-carbon bond formation may be used to assemble the

compounds of the inverntion. It is also apparent that combinations of LHS and RHS other than those described above can be envisioned to prepare compounds falling within the scope of the invention as represented by formula I. These possibilities are futher detailed in the preparations and examples section to follow.

Acid addition salts of the compounds of formula I can be prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. This is illustrated by the preparation of hydrochloric acid salts as a final step in several of the general schemes shown above. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts may be prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are some non-limiting examples of cations present in pharmaceutically acceptable salts.

Toxicology of Compounds

Acute toxicity can be assessed using increasing doses in mice and rodents. Exploratory acute toxicity in mice and/or rats after single dose may be undertaken to begin estimation of the therapeutic window of inhibitors and to identify the potential target organis of toxicity. As candidate selection nears, these studies may provide guidance for the selection of proper doses in multi-dose studies, as well as establish any species specific differences in toxicities. These studies may be combined with routine PK measurements to assure proper dosages were achieved. Generally 3-4 doses will be chosen that are estimated to span a range having no effect through to higher doses that cause major toxic, but non-lethal, effects. Animals will be observed for effects on body weight, behavior and food consumption, and after euthanasia, hematology, blood chemistry, urinalysis, organ weight, gross pathology and histopathology will be undertaken.

Resistance Frequencies and Mechanisms of Compounds

In vitro resistance frequencies in bacteria of interest can be estimated for compounds of formula I. Experiments can determine whether resistant isolates arise when challenged to grow on solid media at 1X, 2X and 4XMIC concentrations. For

example with respect to *S. aureus* or *E. coli*, the experiments may use several recent clinical isolates of methicillin-sensitive and methicillin-resistant *S. aureus* and a laboratory strain of *E. coli* with *acrA* efflux pump defect. In addition, experiments may use several characterized triclosan-resistant *S. aureus* strains. The MICs of resistant strains isolated in this manner can then be determined. Subsequent experiments can determine whether resistant strains arise after serial passage of the strains in 0.5XMIC concentrations of each lead compound.

Mechanism of resistance may be determined in *S. aureus* laboratory strain, RN450 and in an *E. coli* laboratory strain carrying an *acrA* efflux pump mutation. Both high dose challenge (4XMIC) and sub-MIC serial passage may be used to obtain spontaneously arising resistant isolates. If no isolates are obtained with reasonable frequencies, chemical and physical mutagenesis methods can be used to obtain resistant isolates. The *fabI* gene from the chromosome of resistant isolates may be PCR amplified, then may be sequenced to determine whether changes in the FabI protein caused resistance. Triplicate PCR amplifications and sequences may be performed to assure that the observed sequence changes are correct, and did not arise from PCR errors during amplification. Strains carrying resistance mutations outside of the gene of interest may be documented and saved, characterized for their effects on susceptibilities of other antibiotics as evidence of possible efflux-mediated resistance mechanisms, characterized for their ability to alter compounds characterized for their effects on the expression of the specific mRNA and FabI protein.

Assays

Many different assay methods can be used to determine the activity of the compounds of the present invention. These assay methods include, for example, the following but also include other methods known to one of ordinary skill in the art.

S. aureus FabI Enzyme Inhibition Assay (NADH)

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 50-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 1 mM NADH, and an appropriate dilution of *S. aureus* FabI. Inhibitors are typically varied over the range of 0.01-10 uM. The consumption of NADH is monitored for 20 minutes at 30 °C

by following the change in absorbance at 340 nm. Initial velocities are estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC_{50}'s are estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, may be included in an assay as a positive control. Compounds of this invention may have IC_{50}'s from about 5.0 micromolar to about 0.05 micromolar.

S. aureus FabI Enzyme Inhibition Assay (NADPH) (modified)

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 150-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 50 uM NADPH, and an appropriate dilution of *S. aureus* FabI. Inhibitors are typically varied over the range of 0.01-10 uM. The consumption of NADPH is monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities are estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC_{50}'s are estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control.

H. influenzae FabI Enzyme Inhibition Assay

Assays are carried out in half-area, 96-well microtiter plates. Compounds are evaluated in 150-uL assay mixtures containing 100 mM MES, 51 mM diethanolamine, 51 mM triethanolamine, pH 6.5 (MES = 2-(N-morpholino)ethanesulfonic acid), 4% glycerol, 25 uM crotonoyl-ACP, 50 uM NADH, and an appropriate dilution of *H. influenzae* FabI (approximately 20 nM). Inhibitors are typically varied over the range of 0.01-10 uM. The consumption of NADH is monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities are estimated from an exponential fit of the non-linear progress curves. IC_{50}'s are estimated from a fit of the initial velocities to a standard, 4-parameter model, and are typically reported as the mean ± S.D. of duplicate determinations. The apparent Ki is calculated assuming the inhibition is competitive with

crotonoyl-ACP. A proprietary lead compound is currently included in all assays as a positive control.

E. coli FabI Enzyme Inhibition Assay

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 150-uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-[2-acetamido]-2-iminodiacetic acid), 4 % glycerol, 0.25 mM crotonoyl CoA, 50 uM NADH, and an appropriate dilution of *E. coli* FabI. Inhibitors are typically varied over the range of 0.01-10 uM. The consumption of NADH is monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities are estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC_{50}'s are estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean ± S.D. of duplicate determinations. Triclosan, a commercial antibacterial agent and inhibitor of FabI, is currently included in all assays as a positive control. Compounds of this invention have IC_{50}'s from about 100.0 micromolar to about 0.05 micromolar.

Preparation and purification of crotonoyl-ACP

Reactions contain 5 mg/mL *E. coli* apo-ACP, 0.8 mM crotonoyl-CoA (Fluka), 10 mM $MgCl_2$, and 30 uM *S. pneumoniae* ACP synthase in 50 mM NaHEPES, pH 7.5. The mixture is gently mixed on a magnetic stirrer at 23 °C for 2 hr, and the reaction is terminated by the addition of 15 mM EDTA and cooling on ice. The reaction mixture is filtered through a 0.2 micron filter (Millipore) and applied to a MonoQ column (Pharmacia) equilibrated with 20 mM Tris-Cl, pH 7.5. The column is washed with buffer until all non-adherent material is removed (as observed by UV detection), and the crotonoyl-ACP is eluted with a linear gradient of 0 to 400 mM NaCl.

S. aureus FabI Enzyme Inhibition Assay using crotonoyl-ACP

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 100 uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-(2-acetamido)-2-iminodiacetic acid), 4 % glycerol, 25 uM crotonoyl-ACP, 50 uM NADPH, and an appropriate dilution of *S. aureus* Fab I (approximately 20 nM). Inhibitors are typically varied over the range of 0.01-30 uM. The consumption of NADPH is monitored for 30 minutes at 30 °C by following the change in absorbance at 340 nm. Initial

velocities are estimated from a linear fit of the progress curves. IC_{50}'s are estimated from a fit of the initial velocities to a standard, 4-parameter model (Equation 1) and are typically reported as the mean ± S.D. of duplicate determinations. Compounds of this invention in this assay have IC_{50}'s from about 60.0 micromolar to about 0.01 micromolar. The apparent Ki is calculated from Equation 2 assuming the inhibition is competitve with crotonoyl-ACP. More specifically, measured IC_{50} values for 24 compounds of the present invention, as provided in the representative list above, ranged from less than about 0.02 μM to about 25 μM with 11 of these compounds having an IC_{50} of less than 1.

H. pylori FabI Enzyme Inhibition Assay using crotonoyl-ACP

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 100 uL assay mixtures containing 100 mM NaADA, pH 6.5 (ADA = N-(2-acetamido)-2-iminodiacetic acid), 4 % glycerol, 10 uM crotonoyl-ACP, 50 uM NADH, 100 mM ammonium acetate, and an appropriate dilution of *H. pylori* Fab I (approximately 15 nM). Inhibitors are typically varied over the range of 0.025-30 uM. The consumption of NADH is monitored for 30 minutes at 25 °C by following the change in absorbance at 340 nm. Initial velocities are estimated from a linear fit of the progress curves. IC50's are estimated from a fit of the initial velocities to a standard, 4-parameter model (Equation 1) and are typically reported as the mean ± S.D. of duplicate determinations. Compounds of this invention in this assay have IC_{50}'s from about 60.0 micromolar to about 0.01 micromolar. The apparent K_i is calculated from Equation 2 assuming the inhibition is competitve with crotonoyl-ACP.

Equation 1: $v = \text{Range}/(1+[I]/IC50)\ s + \text{Background}$

Equation 2: $Ki(app) = IC50/(1+[S]/Ks)$

S. pneumoniae FabK Enzyme Inhibition Assay using crotonoyl-ACP

Assays are carried out in half-area, 96-well microtitre plates. Compounds are evaluated in 100 uL assay mixtures containing 100 mM MES, 51 mM diethanolamine, 51 mM triethanolamine, pH 6.5 [MES = 2-(N-morpholino)ethanesulfonic acid], 4% glycerol buffer, 100 mM NH_4Cl, 25 μM crotonoyl-ACP, 50 μM NADH, and 15 nM *S. pneumoniae* FabK. Inhibitors are typically varied over the range of 0.025-30 uM. The consumption of NADH is monitored for 30 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities are estimated from a linear fit of the progress

curves. IC_{50}'s are estimated from a fit of the initial velocities to a standard, 4-parameter model (Equation 1) and are typically reported as the mean ± S.D. of duplicate determinations. Compounds of this invention in this assay have IC_{50}'s from about 60.0 micromolar to about 0.01 micromolar. The apparent K_i is calculated from Equation 2 assuming the inhibition is competitve with crotonoyl-ACP.

Antimicrobial Activity Assay

Whole-cell antimicrobial activity is determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A5, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compound is tested in serial two-fold dilutions ranging from 0.06 to 64 mcg/mL. A panel of 12 strains are evaluated in the assay. This panel consists of the following laboratory strains: *Enterococcus faecalis 29212, Staphylococcus aureus 29213, Staphylococcus aureus 43300, Moraxella catarrhalis 49143, Haemophilus influenzae 49247, Streptococcus pneumoniae 49619, Staphylococcus epidermidis 1024939, Staphylococcus epidermidis 1024961, Escherichia coli AG100 ($AcrAB^+$), Escherichia coli AG100A ($AcrAB^-$),, Pseudomonas aeruginosa K767 ($MexAB^+$, $OprM^+$), Pseudomonas aeruginosa K1119 ($MexAB^-$, $OprM^-$)*. The minimum inhibitory concentration (MIC) is determined as the lowest concentration of compound that inhibited visible growth. A spectrophotometer is used to assist in determining the MIC endpoint.

MIC assays may be performed using the microdilution method in a 96 well format.. The assays may be performed in 96 well plates with a final volume of 100 µl cation-adjusted Mueller Hinton broth containing 2 fold serial dilutions of compounds ranging from 32 to 0.06 µg/ml. Bacterial growth may be measured at 600nm using a Molecular Devices SpectraMax 340PC spectrophotometer. MICs can then be determined by an absorbance threshold algorithm and confirmed in some cases by inspecting the plates over a light box.

Minimum Bactericidal Concentration (MBC) may be determined by plating aliquots of MIC dilution series that did not show bacterial growth onto Petri plates containing appropriate semi-solid growth media. The lowest compound concentration

that resulted in >99% killing of bacterial cells (relative to initial bacterial inocula in MIC test) is defined as the MBC.

Several strain panels may be used at various points in the compound progression scheme. The primary panel may include single prototype strains of both community- and hospital-acquired pathogens for determining initial activities and spectra of activity. Secondary panel compositions will depend on the results of the primary panels, and will include 10-20 strains of relevant species that will include community acquired and antibiotic-resistant hospital acquired strains of *Staphylococcus aureus* and coagulase negative *Staphylococci* together with other strains that are sensitive to the new compounds, and negative control strains. The secondary panels will be used during optimization of lead chemical series. Tertiary panels will include 100-200 clinical strains of *S. aureus* and coagulase negative *Staphylococci* together with other relevant strains as for the secondary panels. The tertiary panels will be utilized during the compound candidate selection stage and preclinical studies to generate bacterial population efficacy parameters such as MIC_{50} and MIC_{90}.

Using the assay described above, measured MIC values against *Staphylococcus aureus* 29213 for 24 compounds of the present invention, as provided in the representative list above, ranged from less than about 0.06 μg/ml to greater than about 30 μg/ml with 9 of these compounds having an MIC of less than 1.

Franciscella tularensis in vitro efficacy studies

Routine MIC testing of *F. tularensis* may be undertaken on compounds that have demonstrated enzymatic activity inhibition against the *F. tularensis* FabI protein. The MIC testing of *F. tularensis* may be outsourced to a facility with BL3 capabilities, and with experience in handling *F. tularensis* cultures in the laboratory. The studies may be undertaken with the recommended methods for antimicrobial susceptibility testing of *F. tularensis*.

Helicobacter pylori in vitro efficacy studies

Routine MIC testing of *H. pylori* may be undertaken on compounds that have demonstrated enzymatic activity inhibition against the *H. pylori* FabI protein. The studies may be undertaken with the recommended methods for antimicrobial susceptibility testing of *H. pylori*.

Cytotoxicity assays

Cytotoxicity of the new compounds may be evaluated by the Alamar Blue assay according the manufacturers instructions. Human cell lines (e.g. Jurkat) grown in 96 well plates may be exposed to serial dilutions of the tested compounds. After adding Alamar Blue, cell viability may be determined by measuring the absorbance of the reduced and oxidized forms of Alamar Blue at 570 nm and 600 nm. Cytotoxicity may be reported as LD_{50}, the concentration that causes a 50% reduction in cell viability.

Dosages

The dosage of any compositions of the present invention will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration, and the form of the subject composition. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for the compositions of the present invention may be readily determined by techniques known to those of skill in the art or as taught herein.

In certain embodiments, the dosage of the subject compounds will generally be in the range of about 0.01 ng to about 10 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg.

An effective dose or amount, and any possible affects on the timing of administration of the formulation, may need to be identified for any particular composition of the present invention. This may be accomplished by routine experiment as described herein, using one or more groups of animals (preferably at least 5 animals per group), or in human trials if appropriate. The effectiveness of any subject composition and method of treatment or prevention may be assessed by administering the composition and assessing the effect of the administration by measuring one or more applicable indices, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment.

The precise time of administration and amount of any particular subject composition that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a subject composition, physiological condition of the patient (including age, sex, disease type and stage, general

physical condition, responsiveness to a given dosage and type of medication), route of administration, and the like. The guidelines presented herein may be used to optimize the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

Treatment may be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum therapeutic effect is attained.

The use of the subject compositions may reduce the required dosage for any individual agent contained in the compositions (e.g., the FabI inhibitor) because the onset and duration of effect of the different agents may be complimentary.

Toxicity and therapeutic efficacy of subject compositions may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} and the ED_{50}.

The data obtained from the cell culture assays and animal studies may be used in formulating a range of dosage for use in humans. The dosage of any subject composition lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For compositions of the present invention, the therapeutically effective dose may be estimated initially from cell culture assays.

Formulation

The antibacterial compositions of the present invention may be administered by various means, depending on their intended use, as is well known in the art. For example, if compositions of the present invention are to be administered orally, they may be formulated as tablets, capsules, granules, powders or syrups. Alternatively, formulations of the present invention may be administered parenterally as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositories. For application by the ophthalmic mucous membrane route, compositions of the present invention may be formulated as eyedrops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the compositions may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

In formulations of the subject invention, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the formulated agents.

Subject compositions may be suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of composition that may be combined with a carrier material to produce a single dose vary depending upon the subject being treated, and the particular mode of administration.

Methods of preparing these formulations include the step of bringing into association compositions of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association agents with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or

syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a subject composition thereof as an active ingredient. Compositions of the present invention may also be administered as a bolus, electuary, or paste.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Compositions and compounds of the present invention may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions.

Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating

materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

In certain embodiments, the subject compounds may be formulated as a tablet, pill capsule or other appropriate ingestible formulation (collectively hereinafter "tablet"), to provide a therapeutic dose in 10 tablets or fewer. In another example, a therapeutic dose is provided in 50, 40, 30, 20, 15, 10, 5 or 3 tablets.

In a certain embodiment, the antibacterial agent is formulated for oral administration as a tablet or an aqueous solution or suspension. In another embodiment of the tablet form of the antibacterial agent, the tablets are formulated such that the amount of antibacterial agent (or antibacterial agents) provided in 20 tablets, if taken together, would provide a dose of at least the median effective dose (ED_{50}), e.g., the dose at which at least 50% of individuals exhibited the quantal effect of inhibition of bacterial cell growth or protection (e.g., a statistically significant reduction in infection). In a further embodiment, the tablets are formulated such that the total amount of antibacterial agent (or antibacterial agents) provided in 10, 5, 2 or 1 tablets would provide at least an ED_{50} dose to a patient (human or non-human mammal). In other embodiments, the amount of antibacterial agent (or antibacterial agents) provided in 20, 10, 5 or 2 tablets taken in a 24 hour time period would provide a dosage regimen providing, on average, a mean plasma level of the antibacterial agent(s) of at least the ED_{50} concentration (the concentration for 50% of maximal effect of, e.g., inhibiting bacterial cell growth). In other embodiments less than 100 times, 10 times, or 5 times the ED50 is provided. In other embodiments, a single dose of tablets (1-20 tablets) provides about 0.25 mg to 1250 mg of an antibacterial agent(s).

Likewise, the antibacterial agents can be formulated for parenteral administration, as for example, for subcutaneous, intramuscular or intravenous injection, e.g., the antibacterial agent can be provided in a sterile solution or suspension (collectively hereinafter "injectable solution"). The injectable solution is formulated such that the amount of antibacterial agent (or antibacterial agents) provided in a 200cc bolus injection would provide a dose of at least the median effective dose, or less than 100 times the ED_{50}, or less than 10 or 5 times the ED_{50}. The injectable solution may be formulated such that the total amount of antibacterial agent (or antibacterial agents) provided in 100, 50,

25, 10, 5, 2.5, or 1 cc injections would provide an ED_{50} dose to a patient, or less than 100 times the ED_{50}, or less than 10 or 5 times the ED_{50}. In other embodiments, the amount of antibacterial agent (or antibacterial agents) provided in a total volume of 100cc, 50, 25, 5 or 2cc to be injected at least twice in a 24 hour time period would provide a dosage regimen providing, on average, a mean plasma level of the antibacterial agent(s) of at least the ED_{50} concentration, or less than 100 times the ED_{50}, or less than 10 or 5 times the ED_{50}. In other embodiments, a single dose injection provides about 0.25 mg to 1250 mg of antibacterial agent.

Efficacy of treatment

The efficacy of treatment with the subject compositions may be determined in a number of fashions known to those of skill in the art.

In one exemplary method, the median survival rate of the bacteria or bacteria median survival time or life span for treatment with a subject composition may be compared to other forms of treatment with the particular FabI inhibitor, or with other antibiotic agents. The decrease in median bacteria survival rate or time or life span for treatment with a subject composition as compared to treatment with another method may be 10, 25, 50, 75, 100, 150, 200, 300, 400% even more. The period of time for observing any such decrease may be about 3, 5, 10, 15, 30, 60 or 90 or more days. The comparison may be made against treatment with the particular FabI inhibitor contained in the subject composition, or with other antibiotic agents, or administration of the same or different agents by a different method, or administration as part of a different drug delivery device than a subject composition. The comparison may be made against the same or a different effective dosage of the various agents. The different regiments compared may use measurements of bacterial levels to assess efficacy.

Alternatively, a comparison of the different treatment regimens described above may be based on the effectiveness of the treatment, using standard indicies for bacterial infections known to those of skill in the art. One method of treatment may be 10%, 20%, 30%, 50%, 75%, 100%, 150%, 200%, 300% more effective, than another method.

Alternatively, the different treatment regimens may be analyzed by comparing the therapeutic index for each of them, with treatment with a subject composition as compared to another regimen having a therapeutic index two, three, five or seven times

that of, or even one, two, three or more orders of magnitude greater than, treatment with another method using the same or different FabI inhibitor.

As a non-limiting example, to determine if compounds are bactericidal or bacteriostatic at relevant concentrations, and to examine the kinetics of bacterial killing the following experiment may be performed with *S. aureus*, *S. epidermidis* and appropriate control strains and antibiotics. To fresh logarithmic cultures at 10^7 viable cells / ml, compound may be added to reach concentrations of X1, X2 or X4 the MIC. Control cultures will receive no compound. At 1 hour intervals, aliquots will be diluted and plated for determining viable counts. Plots of viable cells vs. time for up to 24 hours will reveal bactericidal/ bacteriostatic properties of the compounds, and also show the kill kinetics. These experiments are important to determine whether these inhibitors have time-dependent or concentration-dependent effects, and will be used to help set appropriate dosages *in vivo* in combination with pharmacokinetic and pharmacodynamic measurements.

In the practice of the instant methods, the antibacterial compositions of the present invention inhibit bacterial FabI with a K_i of 5 μM or less, 1 μM or less, 100 nM or less, 10 nM or less or even 1 nM or less. In treatment of humans or other animals, the subject method may employ FabI inhibitors which are selective for the bacterial enzyme relative to the host animals' enoyl CoA hydratase, e.g., the K_i for inhibition of the bacterial enzyme is at least one order, two orders, three orders, or even four or more orders of magnitude less than the K_i for inhibition of enoyl CoA hydratase from the human (or other animal). That is, the practice of the subject method *in vivo* in animals utilizes FabI inhibitors with therapeutic indexes of at least 10, 100 or 1000.

Similarly, in the practice of the instant method, the antibacterial compounds of the present invention inhibit FabI with an IC_{50} of 30 μM or less, 10 μM or less, 100 nM or less, or even 10 nM or less. In treatment of humans or other animals, the subject method may employ FabI inhibitors which are selective for the bacterial enzyme relative to the host animals' enoyl CoA hydratase, e.g., the IC_{50} for inhibition of the bacterial enzyme is at least one order, two orders, three orders, or even four orders of magnitude less than the IC_{50} for inhibition of enoyl CoA hydratase from the human (or other animal). That is, in

preferred embodiments, the practice of the subject method *in vivo* in animals utilizes FabI inhibitors with therapeutic indexes of at least 10, 100 or 1000.

Alternatively, bacterial inhibition by an antibacterial compound of the present invention may also be characterized in terms of the minimum inhibitory concentration (MIC), which is the highest concentration of compound required to achieve complete inhibition of bacterial cell growth. Such values are well known to those in the art as representative of the effectiveness of a particular antibacterial agent against a particular organism or group of organisms. In the practice of the instant methods, the antibacterial compositions of the present invention inhibit bacterial growth with MIC values of about 32 μg/mL, less than about 16 μg/mL, less than about 8 μg/mL, less than about 4 μg/mL, less than about 2 μg/mL, less than about 1 μg/mL, less than about 0.5 μg/mL, less than about 0.25 μg/mL, or even less than about 0.125 μg/mL. The value of MIC90, defined as the concentration of a compound required to inhibit the growth of 90% of bacterial strains within a given bacterial strain population, can also be used. In certain embodiments, the compounds of the present invention are selected for use based, *inter alia*, on having MIC90 values of less than about 32 μg/mL, less than about 16 μg/mL, less than about 8 μg/mL, less than about 4 μg/mL, less than about 2 μg/mL, less than about 1 μg/mL, less than about 0.5 μg/mL, less than about 0.25 μg/mL, or even less than about 0.125 μg/mL.

In other embodiments, the subject compounds are selected for use in animals, or animal cell/tissue culture based at least in part on having LD_{50}'s at least one order, or two orders, or three orders, or even four orders or more of magnitude greater than the ED_{50}. That is, in certain embodiments where the subject compounds are to be administered to an animal, a suitable therapeutic index is preferably greater than 10, 100, 1000 or even 10,000.

Kits

This invention also provides kits for conveniently and effectively implementing the methods of this invention. Such kits comprise any subject composition, and a means for facilitating compliance with methods of this invention. Such kits provide a convenient and effective means for assuring that the subject to be treated takes the appropriate active in the correct dosage in the correct manner. The compliance means of such kits includes any means which facilitates administering the actives according to a

method of this invention. Such compliance means include instructions, packaging, and dispensing means, and combinations thereof. Kit components may be packaged for either manual or partially or wholly automated practice of the foregoing methods. In other embodiments involving kits, this invention contemplates a kit including compositions of the present invention, and optionally instructions for their use.

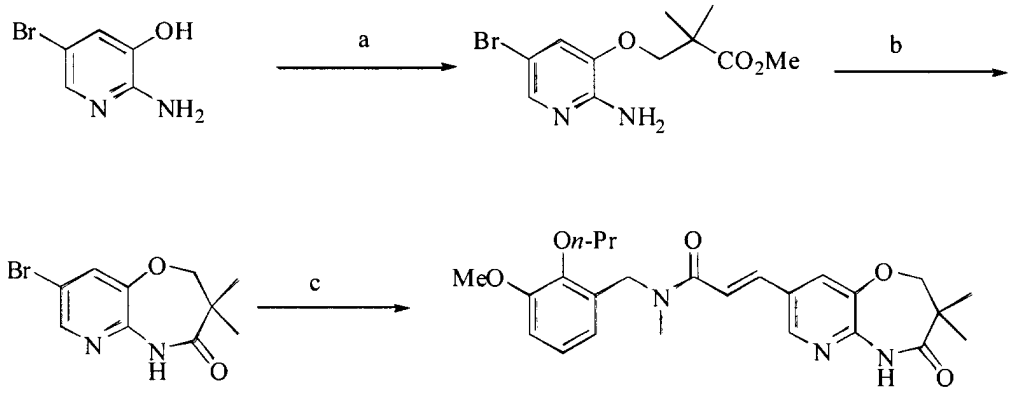
The examples which follow are intended in no way to limit the scope of this invention but are provided to illustrate how to prepare and use compounds of the present invention. Many other embodiments of this invention will be apparent to one skilled in the art.

Exemplification

General

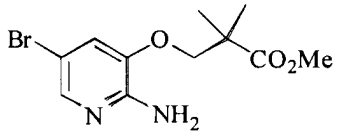
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at either 300 or 500 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS) or from deuterated solvent. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, CD_3OD is tetradeuteriomethanol and D_2O is deuterated oxide. Mass spectra were obtained using electrospray (ESI) ionization techniques. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical HPLC was performed on Varian chromatography systems. Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado. General abbreviations are as follows: EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole hydrate, (i-Pr)$_2$EtN = *N*, *N*-diisopropylethylamine, DMF = *N*, *N*-dimethylformamide, MeOH = methanol, EtOH = ethanol, THF = tetrahydrofuran, DMSO = dimethylsulfoxide, Et_2O = diethyl ether, Ar = argon, $Pd(OAc)_2$ = palladium(II)acetate, P(o-tol)$_3$ = tri-*ortho*-tolylphoshine, EtOAc = ethyl acetate, ACE-Cl = 1-chloroethyl chloroformate, satd = saturated, Et_3N = triethylamine, TFA = trifluoroacetic acid, $NaBH(OAc)_3$ = sodium triacetoxyborohydride, HOAc = acetic acid, EtCN = proprionitrile, CBzCl = benzyl chloroformate, MeCN = acetonitrile.

Example 1 Preparation of (*E*)-3-(7,7-Dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-(3-methoxy-2-propoxy-benzyl)-*N*-methylacrylamide



a) 2,2-dimethyl-3-hydroxypropionate, DEAD, PPh_3, THF, microwave; b) sodium hydride, DMSO; c) *N*-(3-methoxy-2-propoxy-benzyl)-*N*-methylacrylamide, $Pd(OAc)_2$, $P(o\text{-tol})_3$, $(i\text{-Pr})_2EtN$, EtCN, DMF.

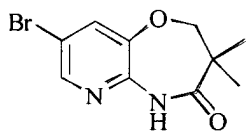
a) 3-(2-Amino-5-bromo-pyridin-3-yloxy)-2,2-dimethylpropionic acid methyl ester



$C_{11}H_{15}BrN_2O_3$
Exact Mass: 302.03

To a suspension of 2-amino-5-bromopyridin-3-ol (1.42 g, 7.51 mmol) in THF (40 mL) was added methyl 2,2-dimethyl-3-hydroxypropionate (1.2 mL, 9.0 mmol) and triphenyl phosphine (2.36 g, 9.00 mmol). The mixture was cooled to 0 °C, then treated with diethyl diazodicarboxylate (1.70 g, 9.75 mmol). The mixture was heated in microwave at 120 °C for 20 min. The solvent was concentrated, and the residue was purified by chromatography (silica gel, hexanes/EtOAc, 75:25 to 60:40) to give the title compound (0.88 g, 39%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, J = 2.1 Hz, 1H), 7.02 (d, J = 2.1 Hz, 1H), 4.65 (br s, 2H), 3.96 (s, 2H), 3.71 (s, 3H), 1.34 (s, 6H); ESI MS *m/e* 303 $(M + H)^+$.

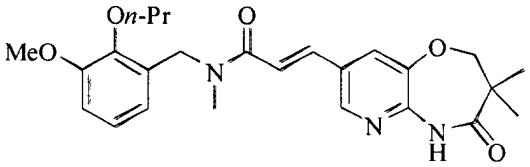
b) 3-Bromo-7,7-dimethyl-6,7-dihydro-9*H*-5-oxa-1,9-diaza-benzocyclohepten-8-one



$C_{10}H_{11}BrN_2O_2$
Exact Mass: 270.00

To a solution of 3-(2-amino-5-bromo-pyridin-3-yloxy)-2,2-dimethylpropionic acid methyl ester (880 mg, 2.90 mmol) in DMSO (40 mL) was added NaH (60% in oil, 139 mg, 3.48 mmol), and the mixture was stirred overnight at room temperature. The mixture was diluted with water (100 mL), and further stirred for 15 min. The resulting precipitate was collected by filtration to give the title compound (600 mg, 76%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 8.11 (d, J = 1.8 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 4.01 (s, 2H), 1.32 (s, 6H); ESI MS *m/e* 271 $(M + H)^+$.

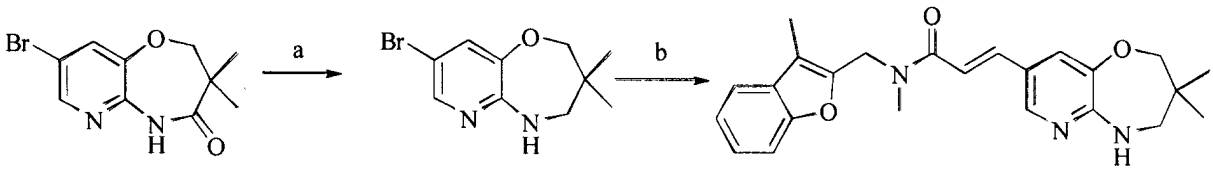
c) (*E*)-3-(7,7-Dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-(3-methoxy-2-propoxy-benzyl)-*N*-methylacrylamide



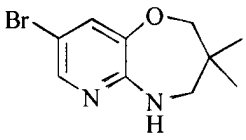
$C_{25}H_{31}N_3O_5$
Exact Mass: 453.23

To a solution of 3-bromo-7,7-dimethyl-6,7-dihydro-9H-5-oxa-1,9-diaza-benzocyclohepten-8-one (200 mg, 0.738 mmol) in propionitrile (24 mL) and DMF (6 mL) were added *N*-(3-methoxy-2-propoxy-benzyl)-*N*-methylacrylamide (253 mg, 0.959 mmol), (*i*-Pr)$_2$EtN (0.26 mL, 1.5 mmol), $Pd(OAc)_2$ (17 mg, 0.074 mmol) and P(*o*-tol)$_3$ (45 mg, 0.15 mmol), and the mixture was de-oxygenated with argon for 15 min. The mixture was heated to reflux overnight, allowed to cool and then diluted with water (60 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were washed with water and brine, dried (Na_2SO_4) and the solvent was removed in vacuo. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH, 97:3) then by slow precipitation from CH_2Cl_2/hexanes gave the title compound (150 mg, 45%) as a pale-yellow solid and as a mixture of amide rotamers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.12–10.10 (m, 1H), 8.28–8.22 (m, 1H), 7.95–7.85 (m, 1H), 7.54–7.47 (m, 1H), 7.33–7.27 (m, 1H), 7.07–6.93 (m, 2H), 6.68–6.61 (m, 1H), 4.80–4.63 (m, 2H), 4.08–4.04 (m, 2H), 3.91–3.84 (m, 2H), 3.79 (s, 3H), 3.10–2.73 (m, 3H), 1.74–1.67 (m, 2H), 1.20–1.17 (m, 6H), 1.01–0.93 (m, 3H); MS (ESI) *m/e* 454 $(M + H)^+$.

Example 2 Preparation of (*E*)-3-(7,7-Dimethyl-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)acrylamide



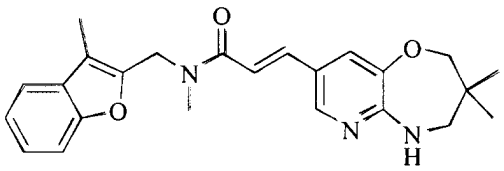
a) 1. BH3, THF; 2. NaOH, MeOH; b) N-methyl-N-(3-methyl-benzofuran-2-ylmethyl)acrylamide, Pd(OAc)2, P(o-tol)3. (i-Pr)2EtN, EtCN, DMF.



$C_{10}H_{13}BrN_2O$
Exact Mass: 256.02

a) 3-Bromo-7,7-dimethyl-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocycloheptene

To a solution of 3-bromo-7,7-dimethyl-6,7-dihydro-9H-5-oxa-1,9-diaza-benzocyclohepten-8-one (620 mg, 2.28 mmol) in THF (15 mL) was added BH3 (9.1 mL of a 1 M solution in THF, 9.1 mmol), and the mixture was heated to reflux overnight. After cooling, the solvent was removed in vacuo. The residue was dissolved in MeOH (15 mL) and 2 N NaOH (5 mL), and the mixture was heated to reflux for 4 h. Methanol was then removed in vacuo and the resulting precipitate was collected by filtration to give the title compound (260 mg, 44%) as a white solid: 1H NMR (300 MHz, CDCl3) δ 7.78 (d, J = 1.8 Hz, 1H), 7.19–7.18 (m, 1H), 4.60 (br s, 1H), 3.83 (s, 2H), 3.10 (d, J = 3.9 Hz, 2H), 1.03 (s, 6H); ESI MS *m/e* 257 (M + H)+.



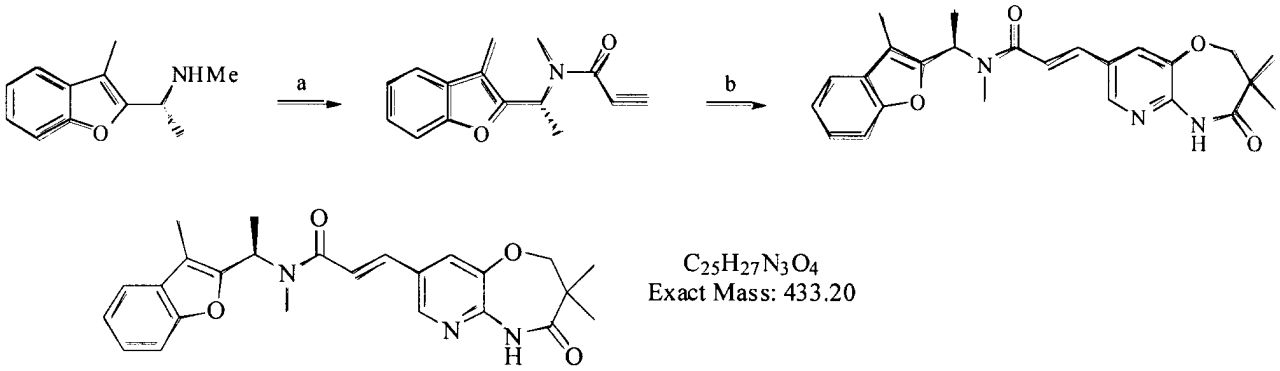
$C_{24}H_{27}N_3O_3$
Exact Mass: 405.21

b) (E)-3-(7,7-Dimethyl-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-N-methyl-N-(3-methyl-benzofuran-2-ylmethyl)acrylamide

To a solution of 3-bromo-7,7-dimethyl-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocycloheptene (250 mg, 0.972 mmol) in propionitrile (24 mL) and DMF (6 mL) were added N-methyl-N-(3-methyl-benzofuran-2-ylmethyl)acrylamide (290 mg, 1.26 mmol), (i-Pr)2EtN (0.34 mL, 1.94 mmol), Pd(OAc)2 (22 mg, 0.097 mmol) and P(o-tol)3 (59 mg, 0.19 mmol), and the mixture was de-oxygenated with argon for 15 min. The mixture was heated to reflux overnight, allowed to cool and then diluted with water (60 mL). The mixture was extracted with CH2Cl2 (3 x 50 mL). The combined extracts were

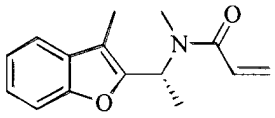
washed with water and brine, dried (Na2SO4) and the solvent was removed in vacuo. Purification by column chromatography (silica gel, CH2Cl2/MeOH, 97:4) and then by slow precipitation from CH2Cl2/hexanes gave the title compound (60 mg, 15%) as a pale yellow solid and as a mixture of amide rotamers: 1H NMR (300 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.60–7.55 (m, 2H), 7.50–7.38 (m, 2H), 7.31–6.96 (m, 3H), 6.68–6.65 (m, 1H), 4.96–4.76 (m, 2H), 3.77 (s, 2H), 3.15–2.91 (m, 5H), 2.26 (s, 3H), 0.96 (s, 6H); MS (ESI) m/e 406 (M + H)+.

Example 3 Preparation of 3-(7,7-dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-N-methyl-N-[1-(R)-(3-methyl-benzofuran-2-yl)-ethyl]acrylamide



$C_{25}H_{27}N_3O_4$
Exact Mass: 433.20

a) acryloyl chloride, Et3N, DMF; b) 3-bromo-7,7-dimethyl-6,7-dihydro-9H-5-oxa-1,9-diaza-benzocyclohepten-8-one, Pd(OAc)2, P(o-tol)3, (i-Pr)2EtN, EtCN, DMF

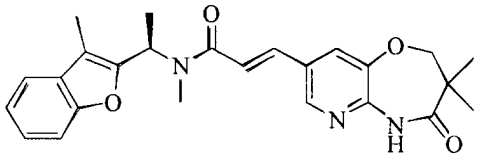


$C_{15}H_{17}NO_2$
Exact Mass: 243.13

a) (R)-N-methyl-N-[1-(3-methyl-benzofuran-2-yl)-ethyl]acrylamide

To an ice cold mixture of (R)-methyl-[1-(3-methyl-benzofuran-2-yl)-ethyl]amine (7.5 mL of a 0.46 M solution in DMF, 3.5 mmol) and Et3N (0.6 mL, 4.1 mmol) was added acryloyl chloride (0.3 mL, 3.8 mmol) drop-wise. The mixture was slowly warmed to room temperature and stirred overnight. The mixture was diluted with H2O and extracted with Et2O (3 ×). The combined organics were washed with H2O and satd

NaCl, dried (Na2SO4) and concentrated. Purification by column chromatography (silica gel, 7:3 hexanes/EtOAc) gave the title compound (630 mg, 75%) as a yellow oil: 1H NMR (300 MHz, DMSO-d_6) δ 7.50–7.47 (m, 1H),7.44–7.41 (m, 1H), 7.30–7.20 (m, 2H), 6.81–6.52 (m, 1H), 6.40–6.25 (m, 2H), 5.74–5.70 (m, 1H), 2.99–2.90 (m, 3H), 2.23 (s, 3H), 1.69–1.58 (m, 3H).

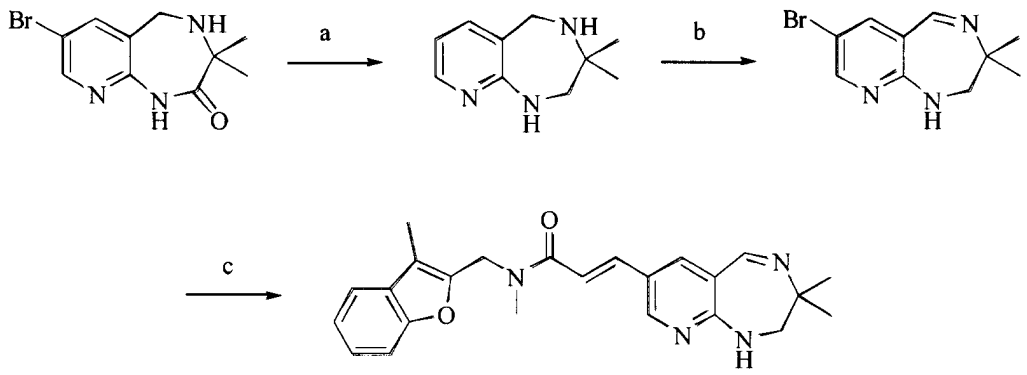


$C_{25}H_{27}N_3O_4$
Exact Mass: 433.20

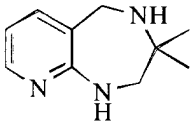
b) 3-(7,7-dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-N-methyl-N-[1-(R)-(3-methyl-benzofuran-2-yl)-ethyl]acrylamide

A suspension of (R)-N-methyl-N-[1-(3-methyl-benzofuran-2-yl)-ethyl]acrylamide (328 mg, 1.35 mmol), 3-bromo-7,7-dimethyl-6,7-dihydro-9H-5-oxa-1,9-diaza-benzocyclohepten-8-one (400 mg, 1.48 mmol), (o-tol)3P (132 mg, 0.43 mmol) and DIEA (0.3 mL, 1.6 mmol) in EtCN (10 mL) and DMF (5 mL) was deoxygenated with argon for 30 min. Pd(OAc)2 (50 mg, 0.22 mmol) was added, the mixture was deoxygenated again with argon for 20 min and the mixture was heated to reflux overnight. The mixture was cooled to room temperature and partitioned between EtOAc and water. The residue was suspended in Et2O and then sonicated to give a solid. The solid was collected by filtration. Purification by column chromatography (silica gel, 1:1 hexanes/EtOAc) and sonication in Et2O gave the title compound (150 mg, 26%) as a white solid: 1H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.27 (s, 1H), 8.01–7.89 (m, 1H),7.58–7.50 (m, 3H), 7.32–7.18 (m, 3H), 6.19–5.99 (m, 1H), 4.07 (s, 2H), 3.04–2.79 (m, 3H), 2.18 (s, 3H), 1.64–1.54 (m, 3H), 1.19 (s, 6H); MS (ESI) m/e 434 (M + H)+.

Example 4 Preparation of (*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide



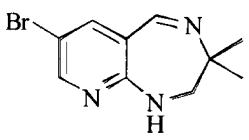
a) $LiAlH_4$, THF; b) Br_2, DMF; c) *N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide, $Pd(OAc)_2$, P(*o*-tol)$_3$, (*i*-Pr)$_2$EtN, EtCN, DMF



$C_{10}H_{15}N_3$
Exact Mass: 177.13
Mol. Wt.: 177.25

a) 3,3-Dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepine

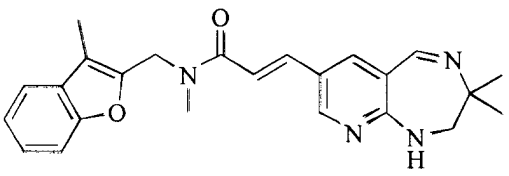
A suspension of 7-bromo-3,3-dimethyl-1,3,4,5-tetrahydropyrido[2,3-*e*][1,4]diazepin-2-one (0.50 g, 1.8 mmol) in THF (15 mL) was cooled in an ice bath and treated dropwise with $LiAlH_4$ (4.1 mL of a 1.0 M solution in THF, 4.1 mmol). After stirring for 30 min, the ice bath was removed and the solution was allowed to warm to room temperature. After heating to reflux overnight, the mixture was cooled in an ice bath. The reaction was quenched sequentially with H_2O (0.15 mL), 15% NaOH (0.15 mL) and H_2O (0.45 mL). After 5 min, the ice bath was removed and the mixture was stirred at room temperature for 1.5 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give the title compound (0.43 g, quantitative) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 6.61 (dd, *J* = 7.2, 4.9 Hz, 1H), 4.85 (br s, 1H), 3.91 (s, 2H), 3.22 (d, *J* = 4.5 Hz, 2H), 2.39 (br s, 1H), 1.20 (s, 6H); MS (ESI) *m/e* 178 $(M + H)^+$.



$C_{10}H_{12}BrN_3$
Exact Mass: 253.02
Mol. Wt.: 254.13

b) 7-Bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine

A solution of 3,3-dimethyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepine (0.43 g, 1.8 mmol) in DMF (20 mL) was cooled in an ice bath and treated drop-wise with Br_2 (0.19 mL, 3.7 mmol). After stirring in the ice bath for 2.5 h, the reaction was quenched with H_2O (25 mL) and $NaHCO_3$ (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O (2 x 50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated to an orange oil. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 98:2 to 96:4) gave the title compound (0.26 g, 54%) as a yellow solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (d, J = 2.3 Hz, 1H), 8.03 (s, 1H), 7.73 (d, J = 2.3 Hz, 1H), 5.93 (br s, 1H), 3.09 (d, J = 4.9 Hz, 2H), 1.30(s, 6H); MS (ESI) *m/e* 254 $(M + H)^+$.



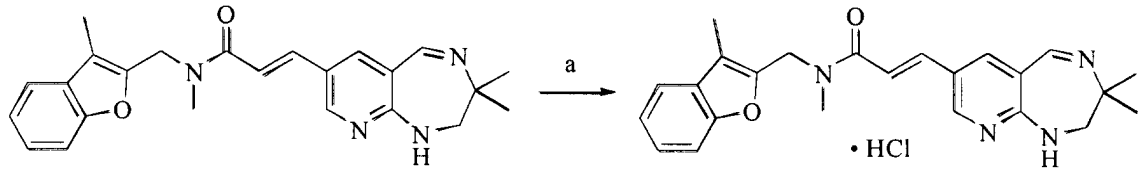
$C_{24}H_{26}N_4O_2$
Exact Mass: 402.21
Mol. Wt.: 402.49

c) (*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide

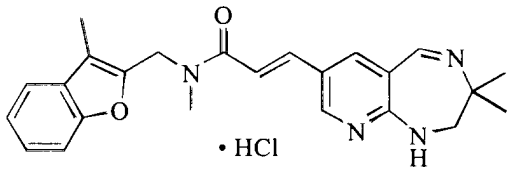
A suspension of 7-bromo-3,3-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepine (255 mg, 1.00 mmol) and *N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide (0.28 g, 1.2 mmol) in propionitrile (5.0 mL) and DMF (1.3 mL) was de-oxygenated with Ar for 10 min. The mixture was treated with $(i\text{-Pr})_2$EtN (0.38 mL, 2.2 mmol) and was de-oxygenated with Ar for 5 min. $Pd(OAc)_2$ (22 mg, 0.10 mmol) and P(*o*-tol)$_3$ (63 mg, 0.21 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 5 min. The mixture was heated to reflux overnight, then allowed to cool. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to an orange oil. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 96:4) followed by trituration with Et_2O gave the title compound (85 mg, 21%) as a yellow powder and as a mixture of amide rotamers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44–8.43

(m, 1H), 8.25 (s, 1H), 8.19–8.15 (m, 1H), 8.06 (s, 1H), 7.58–7.08 (m, 6H), 4.99–4.79 (m, 2H), 3.18–2.92 (m, 5H), 2.27 (s, 3H), 1.16 (s, 6H); MS (ESI) *m/e* 403 $(M + H)^+$.

Example 5 Preparation of (*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride



a) HCl in Et_2O, CH_2Cl_2

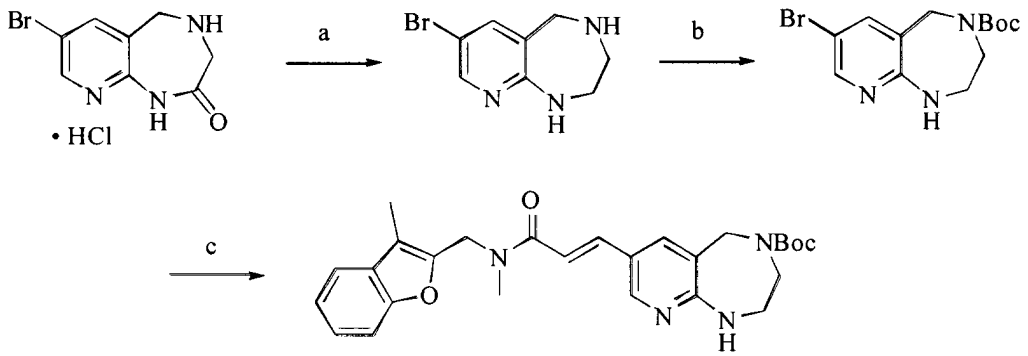


$C_{24}H_{27}ClN_4O_2$
Exact Mass: 438.18
Mol. Wt.: 438.95

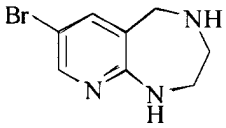
a) (*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride

A solution of (*E*)-3-(3,3-dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide (0.11 g, 0.27 mmol) in CH_2Cl_2 (10 mL) was treated with anhydrous HCl (0.27 mL of a 1.0 M solution in Et_2O, 0.27 mmol). After stirring for 15 min, the mixture was diluted with Et_2O (50 mL) and allowed to stir for 3 h. The solid was isolated by filtration, washed with Et_2O, and dried under vacuum at 50 °C overnight to give the title compound (0.10 g, 86%) as a yellow powder and as a mixture of amide rotamers: ^1H NMR (300 MHz, DMSO-d_6) δ 13.16–13.13 (m, 1H), 9.67–9.65 (m, 1H), 8.96–8.92 (m, 1H), 8.69 (s, 1H), 8.64–8.61 (m, 1H), 7.58–7.24 (m, 6H), 5.00–4.80 (m, 2H), 4.54 (br s, 2H), 3.19–2.92 (m, 3H), 2.27 (s, 3H), 1.36 (br s, 6H); MS (ESI) *m/e* 403 $(M + H)^+$.

Example 6 Preparation of (*E*)-7-{2-[Methyl-(3-methylbenzofuran-2-ylmethyl)carbamoyl]vinyl}-1,2,3,5-tetrahydropyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid *tert*-butyl ester



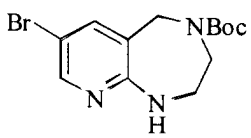
a) $LiAlH_4$, THF; b) $(Boc)_2O$, Et_3N, CH_2Cl_2; c) *N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide, $Pd(OAc)_2$, P(*o*-tol)$_3$, (*i*-Pr)$_2$EtN, EtCN, DMF



$C_8H_{10}BrN_3$
Exact Mass: 227.01
Mol. Wt.: 228.09

a) 7-Bromo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepine

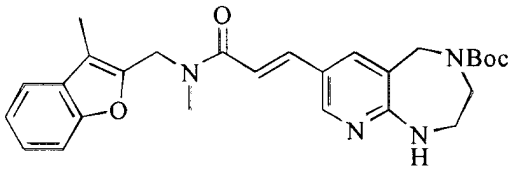
A suspension of 7-bromo-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one hydrochloride (1.16 g, 4.16 mmol) in THF (35 mL) was cooled in an ice bath and treated dropwise with $LiAlH_4$ (8.4 mL of a 1.0 M solution in THF, 8.4 mmol). After stirring for 30 min, the ice bath was removed and the solution was allowed to warm to room temperature. After heating to reflux overnight, the mixture was cooled in an ice bath. The reaction was quenched sequentially with H_2O (0.3 mL), 15% NaOH (0.3 mL) and H_2O (0.9 mL). After 5 min, the ice bath was removed and the mixture was stirred at room temperature for 2.5 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give a yellow syrup. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5 to 90:10) gave the title compound (0.42 g, 44%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 2.3 Hz, 1H), 7.44 (d, J = 2.0 Hz, 1H), 4.96 (br s, 1H), 3.82 (s, 2H), 3.22–3.15 (m, 2H), 3.08–3.05 (m, 2H), 1.97 (br s, 1H); MS (ESI) *m/e* 228 $(M + H)^+$.



$C_{13}H_{18}BrN_3O_2$
Exact Mass: 327.06
Mol. Wt.: 328.20

b) 7-Bromo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid *tert*-butyl ester

A solution of 7-bromo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepine (0.42 g, 1.8 mmol) in CH_2Cl_2 (20 mL) was treated with Et_3N (0.34 mL, 2.4 mmol) followed by di-*tert*-butyl-dicarbonate (0.44 g, 2.0 mmol). After stirring for 1 h, the reaction was concentrated to a white solid. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 99:1) gave the title compound (0.55 g, 91%) as a white solid and as a mixture of rotamers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 8.59–8.45 (m, 1H), 4.90 (s, 1H), 4.35–4.27 (m, 2H), 3.66–3.65 (m, 2H), 3.29–3.24 (m, 2H), 1.42 (s, 9H); MS (ESI) *m/e* 328 $(M + H)^+$.



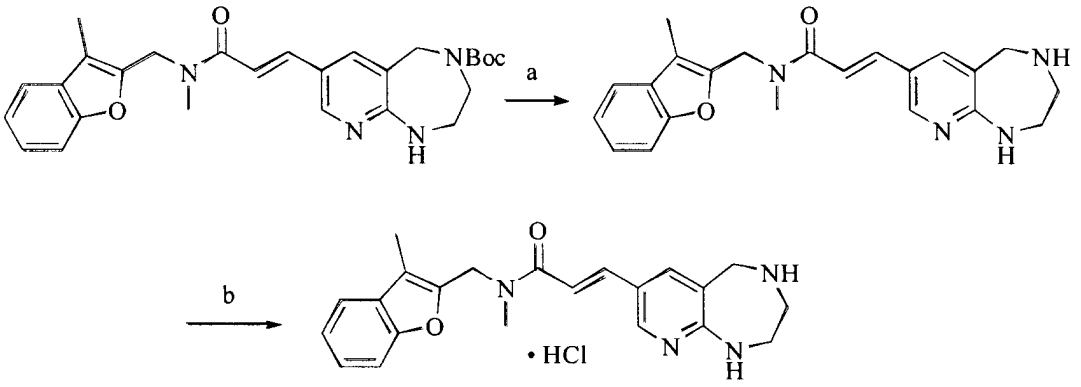
$C_{27}H_{32}N_4O_4$
Exact Mass: 476.24
Mol. Wt.: 476.57

c) (*E*)-7-{2-[Methyl-(3-methylbenzofuran-2-ylmethyl)carbamoyl]vinyl}-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid *tert*-butyl ester

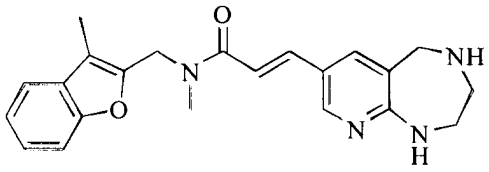
A solution of 7-bromo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid *tert*-butyl ester (0.53 g, 1.6 mmol) and *N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide (0.41 g, 1.8 mmol) in propionitrile (8.0 mL) and DMF (2.0 mL) was de-oxygenated with Ar for 10 min. The mixture was treated with $(i\text{-Pr})_2$EtN (0.62 mL, 3.5 mmol) and was de-oxygenated with Ar for 5 min. $Pd(OAc)_2$ (36 mg, 0.16 mmol) and P(*o*-tol)$_3$ (100 mg, 0.33 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 10 min. The mixture was heated to reflux for 6 h, then allowed to cool. The mixture was diluted with EtOAc (100 mL) and washed with H_2O (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to an orange oil. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 98:2) gave the title compound (0.48 g, 62%) as a white powder and as a mixture of amide rotamers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15–8.10 (m, 1H), 7.87–7.74 (m, 1H), 7.57–7.42 (m, 3H), 7.32–6.77 (m, 4H), 4.97–4.78 (m, 2H), 4.51–4.42 (m, 2H), 3.59–3.57

(m, 2H), 3.43–3.41 (m, 2H), 3.17–2.92 (m, 3H), 2.26 (s, 3H), 1.38–1.24 (m, 9H); MS (ESI) *m/e* 477 $(M + H)^+$.

Example 6 Preparation of (*E*)-*N*-Methyl-*N*-(3-methylbenzofuran-2-ylmethyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride



a) TFA, CH_2Cl_2; b) HCl in Et_2O, CH_2Cl_2

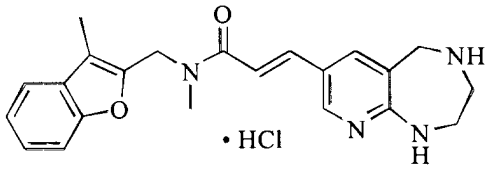


$C_{22}H_{24}N_4O_2$
Exact Mass: 376.19
Mol. Wt.: 376.45

a) (*E*)-*N*-Methyl-*N*-(3-methylbenzofuran-2-ylmethyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide

A solution of (*E*)-7-{2-[methyl-(3-methylbenzofuran-2-ylmethyl)carbamoyl]vinyl}-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid *tert*-butyl ester (0.38 g, 0.80 mmol) in CH_2Cl_2 (4 mL) was cooled in an ice bath and then treated with TFA (4 mL). After stirring for 2 h, the mixture was concentrated under vacuum. The residue was treated with saturated $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2/MeOH (4 x 50 mL of a 98:2 mixture). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to a light yellow solid. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 92:8) gave the title compound (0.21 g, 70%) as a white powder and as a mixture of amide rotamers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (br s, 1H), 7.68–7.63 (m, 1H), 7.50–7.40 (m, 3H), 7.26–7.20 (m, 2H),

7.04–6.72 (m, 1H), 5.10 (s, 1H), 4.83–4.72 (m, 2H), 3.89 (s, 2H), 3.30–3.26 (m, 2H), 3.22–3.04 (m, 5H), 2.31 (s, 3H), 1.70 (br s, 1H); MS (ESI) *m/e* 377 $(M + H)^+$.

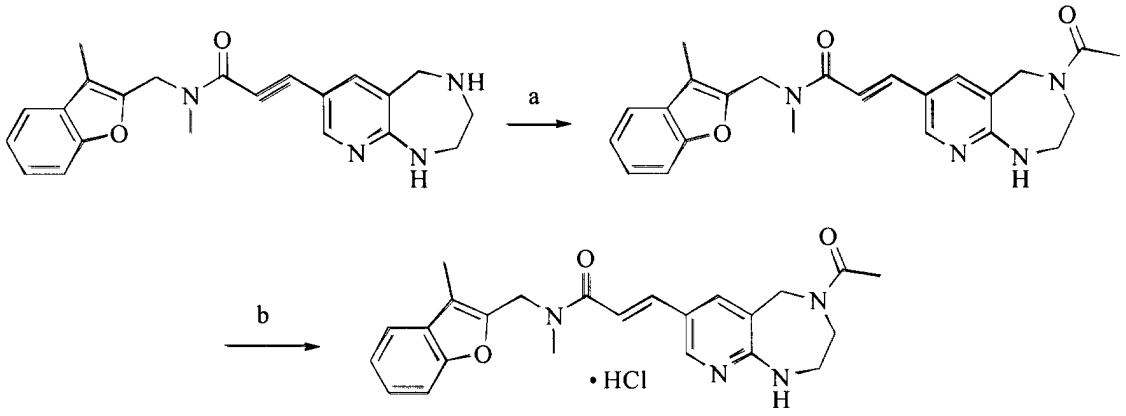


$C_{22}H_{25}ClN_4O_2$
Exact Mass: 412.17
Mol. Wt.: 412.91

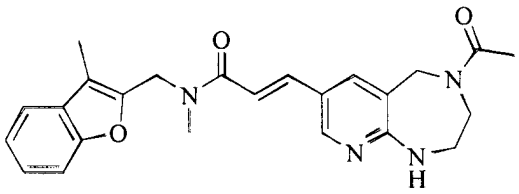
b) (*E*)-*N*-Methyl-*N*-(3-methylbenzofuran-2-ylmethyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

A solution of (*E*)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide (0.21 g, 0.56 mmol) in CH_2Cl_2 (5 mL) was treated with anhydrous HCl (0.56 mL of a 1.0 M solution in Et_2O, 0.56 mmol). After stirring for 5 min, the mixture was diluted with Et_2O (50 mL), allowed to stir for 30 min and sonicated for 5 min. The solid was isolated by filtration, washed with Et_2O, and dried under vacuum at 50 °C for 4 days to give the title compound (0.22 g, 97%) as an off-white powder and as a mixture of amide rotamers: ^1H NMR (300 MHz, DMSO-d_6) δ 9.66 (br s, 2H), 8.36–8.33 (m, 1H), 8.14 (s, 1H), 7.58–7.07 (m, 7H), 4.98–4.79 (m, 2H), 4.26 (s, 2H), 3.51 (s, 2H), 3.33 (s, 2H), 3.17–2.91 (m, 3H), 2.27 (s, 3H); MS (ESI) *m/e* 377 $(M + H)^+$.

Example 7 Preparation of (*E*)-3-(4-Acetyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride



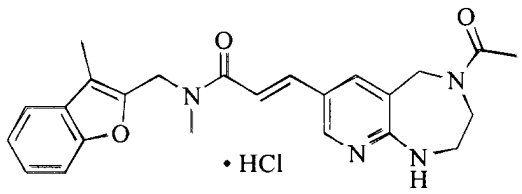
a) Ac_2O, Et_3N, CH_2Cl_2; b) HCl in Et_2O, CH_2Cl_2



$C_{24}H_{26}N_4O_3$
Exact Mass: 418.20
Mol. Wt.: 418.49

a) (*E*)-3-(4-Acetyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide

A solution of (*E*)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide (105 mg, 0.280 mmol) in CH_2Cl_2 (6 mL) was treated with Et_3N (0.05 mL, 0.36 mmol) followed by acetic anhydride (27 μL, 0.29 mmol). After stirring for 1.5 h, the mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to a tan residue. Purification by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 96:4) gave the title compound (89 mg, 76%) as a colorless residue and as a mixture of amide rotamers: MS (ESI) *m/e* 419 $(M + H)^+$.

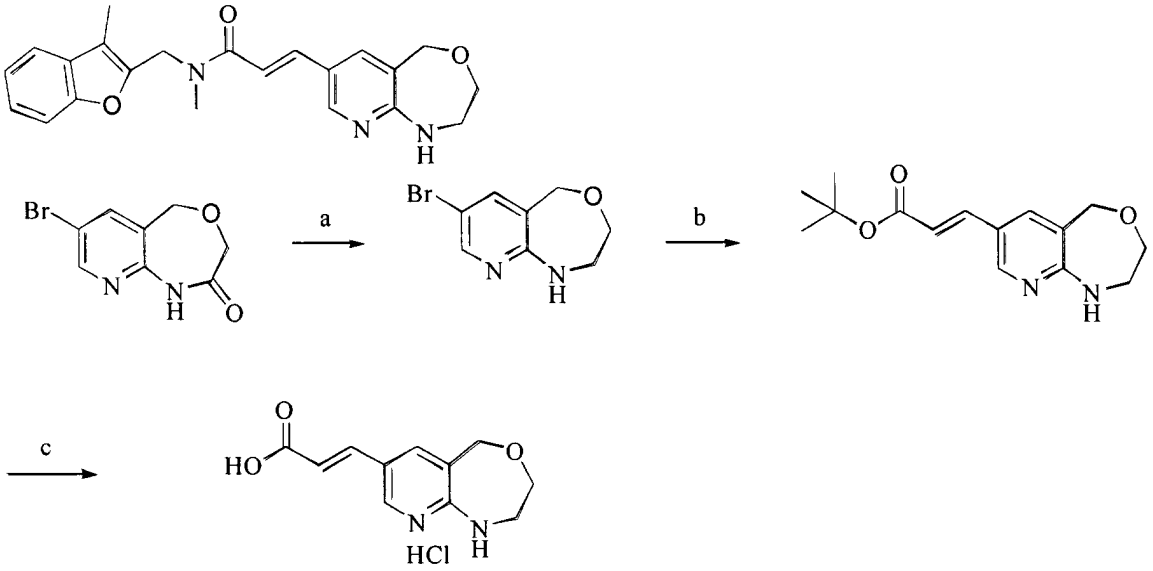


$C_{24}H_{27}ClN_4O_3$
Exact Mass: 454.18
Mol. Wt.: 454.95

b) (*E*)-3-(4-Acetyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride

A solution of (*E*)-3-(4-acetyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide (89 mg, 0.21 mmol) in CH_2Cl_2 (4 mL) was treated with anhydrous HCl (0.21 mL of a 1.0 M solution in Et_2O, 0.21 mmol). After stirring for 15 min, the mixture was diluted with Et_2O (25 mL) and allowed to stir for 2 h. The solid was isolated by filtration, washed with Et_2O, and dried under vacuum at 50 °C for 3 days to give the title compound (83 mg, 88%) as a white powder and as a mixture of amide rotamers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.46–8.23 (m, 3H), 7.58–7.22 (m, 6H), 5.02–4.80 (m, 4H), 3.87–3.74 (m, 4H), 3.19–2.90 (m, 3H), 2.26 (s, 3H), 2.03–1.99 (m, 3H); MS (ESI) *m/e* 419 $(M + H)^+$.

Example 8 Preparation of *N*-Methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide



(a)) BH_3•THF complex, THF, reflux; (b) *tert*-butyl acrylate, $Pd(OAc)_2$, P(*o*-tol)$_3$, (*i*-Pr)$_2$EtN, DMF; (c) i. TFA, CH_2Cl_2; ii. 4 M HCl/dioxane

a) 3-Bromo-5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocycloheptene

To a solution of 3-Bromo-5,9-dihydro-6-oxa-1,9-diazabenzocyclohepten-8-one (1.0 g, 4.13 mmol) in THF (40 mL) at 0 °C was added BH_3 (30 mL of a 1.0 M solution in THF, 30.0 mmol). The solution was heated to reflux. After 18 h, the solution was cooled

to 0 °C and the reaction quenched with H_2O (2.5 mL). The mixture was concentrated and the resulting off-white solid was dissolved in MeOH (30 mL) and NaOH (15 mL of a 2 N solution). The mixture was heated at reflux for 4 h. The MeOH was removed under reduced pressure. The resulting precipitate was collected by filtration and washed with H_2O (20 mL). The white solid was dried to give the title compound (0.360 g, 38%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.06 (d, J = 2.3 Hz, 1H), 7.71 (d, J = 2.3 Hz, 1H), 6.55 (br s, 1H), 4.47 (s, 2H), 3.74 – 3.70 (m, 2H), 3.16 – 3.12 (m, 2H); ESI MS *m/z* 229 (100%); 231(100%)$[C_8H_9BrN_2O + H]^+$.

b) 3-(5,7,8,9-Tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid tert-butyl ester

A solution of 3-Bromo-5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocycloheptene (0.5 g, 2.2 mmol), *tert*-butyl acrylate (1.6 mL, 10.9 mmol) and $(i\text{-Pr})_2EtN$ (1.1 mL, 6.5 mmol) in propionitrile/DMF (20mL/5 mL) was de-oxygenated with Ar for 30 min. The mixture was treated with $Pd(OAc)_2$ (49 mg, 0.22 mmol) and $P(o\text{-tol})_3$ (133 mg, 0.44 mmol) then heated to 100 °C for 16 h. The hot mixture was filtered through a pad of celite. The filtrate was diluted with H_2O (100 mL) then extracted with dichloromethane (2 x 75 mL). The combined organic fractions were treated with brine (100 mL), dried over Na_2SO_4 and concentrated to give a yellow residue. This was subjected to flash chromatography on silica gel using 1.3% methanol:dichloromethane. The appropriate fractions were collected and concentrated to give a cream solid. Yield: 0.4g (67%); ^1H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 16.0 Hz, 1H), 6.87 (br s, 1H), 6.33 (d, J = 16.0 Hz, 1H), 4.50 (s, 2H), 3.75 – 3.72 (m, 2H), 3.22 – 3.20 (m, 2H), 1.47 (s, 9H); ESI MS *m/z* 277 $[C_{15}H_{20}N_2O_3 + H]^+$

c) 3-(5,7,8,9-Tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid hydrochloride

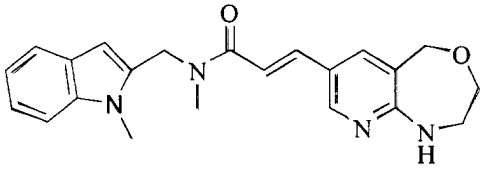
A suspension of 3-(5,7,8,9-Tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid tert-butyl ester (0.14 g, 0.49 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After stirring at room temperature for 30 min, the clear tan solution was concentrated in vacuo. The resulting oil was triturated with hexanes (20 mL) until the oil was converted to a fine off-white solid. The solid was then suspended in anhydrous HCl

in dioxane (2 mL, 4.0 M), sonicated and concentrated to about 1 mL. The suspension was treated with Et_2O (20 mL), sonicated, isolated by filtration and dried under vacuum. Yield: 0.11g (87%); ^1H NMR (300 MHz, DMSO-d_6) δ 8.40 (br s, 3H), 8.31 – 8.29 (m, 2H), 7.53 (d, J = 16.0 Hz, 1H), 6.51 (d, J = 16.0 Hz, 1H), 4.76 (s, 2H), 3.96 – 3.92 (m, 2H), 3.71 – 3.67 (m, 2H); ESI MS *m/z* 221 $[C_{11}H_{12}N_2O_3 + H]^+$

d) N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide

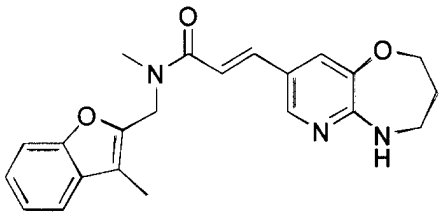
EDC (0.10 g, 0.52 mmol) was added to a solution of 3-(5,7,8,9-Tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid hydrochloride (0.11 g, 0.43 mmol), HOBt (64 mg, 0.47 mmol), Methyl-(3-methyl-benzofuran-2-ylmethyl)-amine (91 mg, 0.52 mmol) and (*i*-Pr)$_2$EtN (0.44 mL, 2.58 mmol) in DMF (6 mL). The mixture was allowed to stir overnight at 35 °C. The mixture was cooled to 0 °C and diluted with H_2O (15 mL) with rapid stirring. The resulting precipitate was filtered, washed with H_2O (30 mL) then dried under high vacuum. The solid was triturated with Et_2O (30mL), stirred for 20 min then filtered to give a beige solid as a mixture of amide rotamers. Yield: 0.10g (62%); ^1H NMR (300 MHz, DMSO-d_6) δ 8.25 (s, 1H), 7.94 (s, 1H), 7.59 – 7.03 (m, 6H), 6.79 (br s, 1H), 4.98 and 4.79 (2 x s, 2H), 4.53 (s, 2H), 3.77 – 3.73 (m, 2H), 3.25 – 3.19 (m, 2H), 3.17 and 2.93 (2 x s, 3H), 2.28 (s, 3H); ESI MS *m/z* 378 $[C_{22}H_{23}N_3O_3 + H]^+$

Example 9 Preparation of *N*-Methyl-*N*-(1-methyl-1H-indol-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide

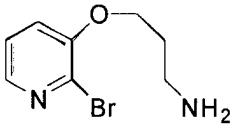


EDC (0.10 g, 0.52 mmol) was added to a solution of 3-(5,7,8,9-Tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid hydrochloride (0.11 g, 0.43 mmol), HOBt (64 mg, 0.47 mmol), Methyl-(1-methyl-1H-indol-2-ylmethyl)-amine (128 mg, 0.47 mmol) and (*i*-Pr)$_2$EtN (0.36 mL, 2.15 mmol) in DMF (6 mL). The mixture was allowed to stir overnight at 35 °C. The mixture was cooled to 0 °C and diluted with H_2O (15 mL) with rapid stirring. The resulting gummy precipitate was filtered, washed with H_2O (30 mL) then with Et_2O (20 mL). The solid was dissolved in dichloromethane (100 mL), washed with H_2O(50 mL), brine (50 mL), dried over $MgSO_2$, and treated with charcoal. The mixture was filtered and the filtrate was passed through a plug of silica gel. The silica gel was washed with ethyl acetate (50 mL) then with 5% methanol: dichloromethane (50 mL). The combined organic fractions were concentrated to give an oil. The resulting oil was triturated with ether:hexanes (20 mL) until the oil was converted to a beige solid. Yield: 40 mg (25%) as a mixture of amide rotamers; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (br s, 1H), 7.92 and 7.85 (2 x s, 1H), 7.50 - 7.39 (m, 3H), 7.18 – 6.92 (m, 3H), 6.78 (br s, 1H), 6.41 and 6.20 (2 x s, 1H), 5.07 and 4.83 (2 x s, 2H), 4.52 and 4.45 (2 x s, 2H), 3.71 - 3.61 (m, 5H), 3.50 – 3.40 (m, 2H), 3.10 and 2.95 (2 x s, 3H); ESI MS *m/z* 377 $[C_{22}H_{24}N_4O_2 + H]^+$

Example 9 Preparation of N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamid hydrochloride



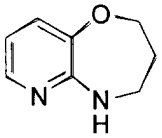
a) Preparation of 3-(2-bromo-pyridin-3-yloxy)-propylamine



Diisopropyl azodicarboxylate (4.65 mL, 24 mmol) was added slowly to a dioxane (200 mL) solution of 2-bromo-pyridin-3-ol (3.50 g, 20 mmol), 3-aminopropanol (1.67 mL, 22 mmol) and triphenylphosphine (6.30 g, 24 mmol) at 10 °C. After stirring the

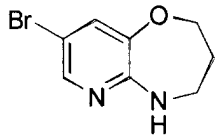
mixture for 30 min at this temperature, it was refluxed for 18 h Upon cooling, the volatiles were evaporated and the residue was purified by chromatography (silica, 3% MeOH in CH_2Cl_2 then 5% (2M NH_3 in MeOH) in CH_2Cl_2 to afford the title compound (3.19 g, 69%). ^1H NMR (300 MHz, $CDCl_3$, δ): 7.98 (dd, *J* =4.5, 1.8 Hz, 1H), 7.23 (dd, *J* =4.5, 8.2 Hz, 1H), 7.15 (dd, *J* =1.8, 8.2 Hz, 1H), 4.15 (t, *J* =6.0 Hz, 2H), 2.98 (t, *J* =6.6 Hz, 2H), 2.00 (m, 2H). MS (ESI): *m/e* 231 and 233 $(M+H)^+$.

b) Preparation of 6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocycloheptene



Potassium tert-butoxide (18 mL, 18 mmol) was added to a THF (120 mL) solution of 3-(2-bromo-pyridin-3-yloxy)-propylamine (2.75 g, 11.9 mmol). The solution was purged with an Ar stream for 10 min, bis(dibenzylideneacetone)palladium (342 mg, 0.6 mmol) and tri-tert-butylphosphine (2.1 mL, 0.7 mmol, 10% in hexane) were added and the mixture was stirred at 60 °C for 5 h. The solvent was evaporated, the residue was dissolved in CH_2Cl_2. This solution was washed with water, dried and evaporated. Chromatographic purification (silica, 0-2% MeOH in CH_2Cl_2) afforded 0.75 g (42%) of the title compound. ^1H NMR (300 MHz, DMSO-d_6, δ): 7.70 (dd, *J* =4.8, 1.4 Hz, 1H), 7.09 (dd, *J* =7.7, 1.4 Hz, 1H), 6.60 (dd, *J* =4.8, 7.7 Hz, 1H), 6.02 (s, br, 1H), 4.06 (t, *J* =5.5 Hz, 2H), 3.21 (m, 2H), 1.90 (m, 2H).

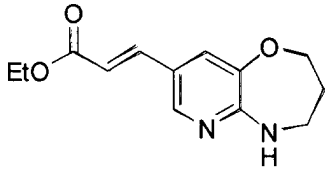
c) Preparation of 3-bromo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocycloheptene



A solution of bromine (960 mg, 6 mmol) in CH_2Cl_2 (50 mL) was added dropwise at 0 °C to a CH_2Cl_2 (50 mL) suspension of 6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocycloheptene (750 mg, 5 mmol) and solid K_2CO_3 (1 g). The mixture was stirred for 30 min at 20 °C, then the excess bromine was quenched with a saturated solution of aqueous $NaHSO_3$. The basic aqueous phase was separated, extracted with CH_2Cl_2, the combined organic layers were dried and evaporated to afford the title compound (1.10 g, 96%). ^1H NMR (300 MHz, DMSO-d_6, δ): 7.78 (d, *J* =1.8 Hz, 1H), 7.30 (d, *J* =1.9 Hz,

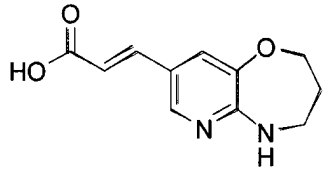
1H), 6.35 (s, br, 1H), 4.10 (t, *J* =5.7 Hz, 2H), 3.24 (m, 2H), 1.92 (m, 2H). MS (ESI): *m/e* 229 and 231 $(M+H)^+$.

d) Preparation of (6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid ethyl ester



A solution of 3-bromo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocycloheptene (1.1 g, 4.80 mmol), ethyl acrylate (1.5 mL, 14.4 mmol) and diisopropylethylamine (2.5 mL, 14.4 mmol) in propionitrile (100 mL) was purged with an Argon stream for 10 min. $Pd(OAc)_2$ (108 mg, 048 mmol) and $P(o\text{-}Tol)_3$ (292 g, 0.96 mmol) were added and the Argon purge was repeated. The mixture was stirred at 100 °C for 8 h under Argon. Upon cooling, the resultant mixture was filtered through celite; the filtrate was evaporated. The crude product was purified by chromatography (silica, 0-2% MeOH in CH_2Cl_2) to afford the title compound (0.753 g, 63%). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.98 (d, *J*=1.9Hz, 1H), 7.52 (d, *J*=1.9Hz, 1H), 7.51 (d, *J*=16 Hz, 1H), 6.83 (s, br, 1H), 6.42 (d, *J* = 16Hz, 1H), 4.15 (m, 4H), 3.34 (m, 2H), 1.98 (m, 2H), 1.25 (t, *J*=7.2Hz, 3H).

e) Preparation of 3-(6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid



A solution of (6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid ethyl ester (0.75 g, 3 mmol) in MeOH (30 mL) and aqueous NaOH (2 mL, 8 mmol, 4N) was refluxed for 23 hours. Upon cooling and addition of water (10 mL), the volatiles were evaporated; the aqueous solution was washed with CH_2Cl_2 and neutralized (1N HCl). The precipitate was filtered and dried to afford title product (55 mg, 8%). An additional 46 mg (7%) was obtained by extracting the aqueous filtrate with EtOAc. ^{1}H NMR (300 MHz, DMSO-d_6, δ): 12.10 (s, br 1H), 7.93 (d, *J*=1.9Hz, 1H), 7.46 (d,

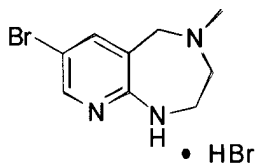
J=1.9Hz, 1H), 7.43 (d, *J*=16 Hz, 1H), 6.75 (t, br, *J*=3.4Hz, 1H), 6.29 (d, *J*=16Hz, 1H), 4.13 (t, *J*=6Hz, 1H), 3.35 (m, 2H), 1.96 (m, 2H).

f) Preparation of N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamid hydrochloride

EDC (108 mg, 0.56 mmol) was added to a solution of 3-(6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylic acid (95 mg, 0.43 mmol), methyl-(3-methyl-benzofuran-2-ylmethyl)-amine (100 µL, 0.52 mmol), HOBt · H_2O (64 mg, 0.47 mmol) and DIPEA (225 µL, 1.29 mmol) in dry DMF (4 mL). After stirring for 23 hr, the mixture was cooled (10 °C) and treated with water (50 mL). The precipitated crude product was separated by decantation and purified by chromatography (silica, EtOAc). The clean fractions of the free base were collected, concentrated to 10 mL and treated with HCl (0.7 mL, 1.4 mmol, 2M in Et_2O). The resulting precipitate was collected by filtration, washed with EtOAc and hexanes to afford the title compound (123 mg, 57%). ^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.07 (m, 2H), 7.58-7.41 (m, 3H), 7.36-7.15 (m, 3H), 4.99 and 4.77 (rotamers, 2s, 2H), 4.28 (m, 2H), 3.57 (m, 2H), 3.16 and 2.90 (rotamers, 2s, 3H), 2.25 (s, 3H), 2.11 (m, 2H). MS (ESI): *m/e* 378 $(M+H)^+$.

Example 10 Preparation of N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride

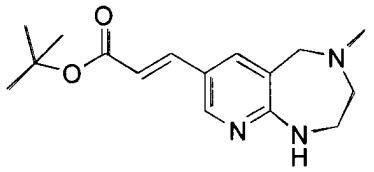
a) 7-Bromo-4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine hydrobromide



7-bromo-4-methyl-1,3,4,5-tetrahydro-pyrido[e][1,4]diazepin-2-one (1.67 g, 6.55 mmol) was reduced to give a 1:1 mixture of the title compound and 4-methyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4] diazepine. The mixture was dissolved in acetic acid (12 mL), treated with bromine (1.04 g, 6.5 mmol) and stirred at room temperature overnight. Ether (100 mL) was added and the precipitate was isolated by filtration to yield the title

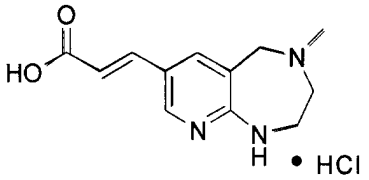
compound as an orange solid (2.04 g, 95%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, 1H) 8.16 (d, J = 2.3 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 6.89 (s, 1H), 4.25-4.48 (m, 2H), 3.54-3.58 (m, 2H), 3.28–3.35 (m, 2H), 2.86-2.87 (m, 3H); MS (ESI) *m/e* 242 ($C_9H_{12}BrN_3$ + H)$^+$.

b) 3-(4-Methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylic acid tert-butyl ester



7-bromo-4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine hydrobromide (2.0 g, 6.2 mmol) was subjected to Heck coupling with *tert*–butyl acrylate to give crude product. Purification by silica gel chromatography (CH_2Cl_2:MeOH:NH_4OH/ 95:4.95:0.05) gave the title compound as a brown oil (970 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) 8.11 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 2.2 Hz, 1H), 7.47 (d, J = 16.0 Hz, 1H) 6.22 (d, J = 16.0 Hz, 1H), 3.64 (s, 2H), 3.27-3.31 (m, 2H), 2.83-2.88 (m, 2H), 2.44 (s, 3H), 1.52 (s, 9H); MS (ESI) *m/e* 290 ($C_{16}H_{23}N_3O_2$ + H)$^+$.

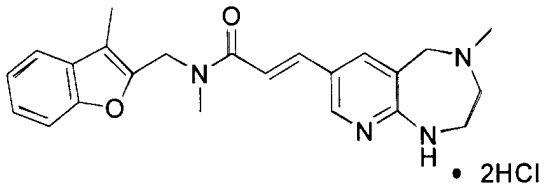
c) 3-(4-Methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylic acid hydrochloride



3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-y)-acrylic acid tert-butyl ester (576 mg, 2.1 mmol) was converted to the title compound which was obtained as a yellow solid (542 mg, 96%). ^{1}H NMR (300 MHz, DMSO-d_6) 8.35 (s, 1H),

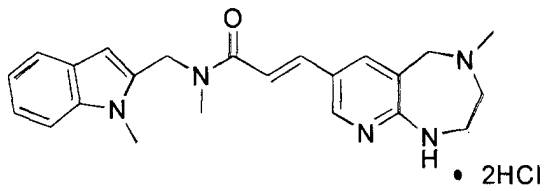
8.17-8.22 (m, 1H), 7.51 (d, J = 16.1 Hz, 1H), 6.40 (d, J = 16.1 Hz, 1H), 4.25-4.48 (m, 2H), 3.60-3.75 (m, 2H), 3.30–3.45 (m, 2H), 2.68 (s, 3H).

d) N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride



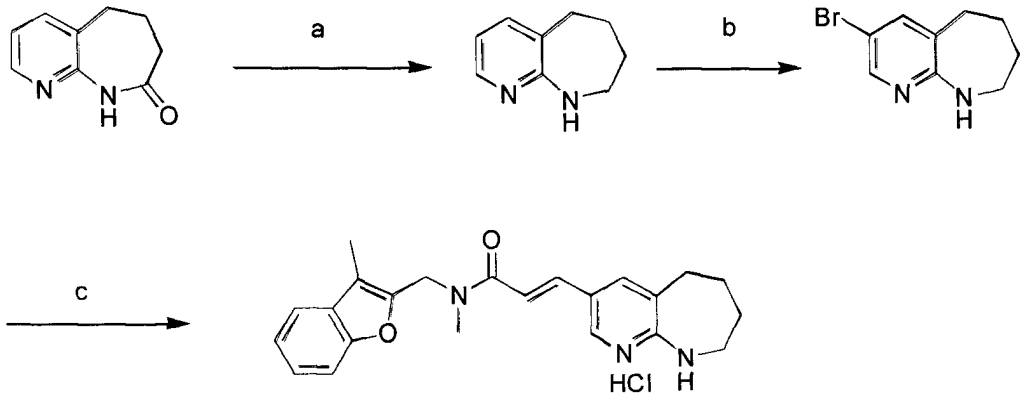
EDC (0.21 g, 1.1 mmol) was added to a suspension of methyl-(2-methyl-benzofuran-3-ylmethyl)-amine (158 mg, 0.9 mmol) and 3-(4-Methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylic acid hydrochloride (201 mg, 0.75 mmol). The mixture was allowed to stir overnight at 40 °C. The mixture was cooled to 0 °C and diluted with H2O (60mL) with rapid stirring. The resulting precipitate was filtered, washed with H_2O (20 mL) then dried under high vacuum. The solid was then subjected to flash chromatography on silicia gel using 5% methonal:dichloromethane. The fractions were collected and treated with 5 mL of 2.0M HCL in Et_2O. The suspension was concentrated, triturated with Et_2O (50 Ml then filtered to give a coupled solid. The resulting solid was dissolved in methylene chloride (5 mL) and treated with 2M HCl in ether (0.75 mL, 1.5 mmol). The resultant yellow precipitate was filtered, triturated with diethyl ether and dried under high vacuum to afford the title compound as a white solid (186 mg, 53%) and a mixture of amide rotomers. ^{1}H NMR (300 MHz, DMSO-d_6) 11.80 (bs, 1H) 8.45-8.17 (m, 2H), 7.56-7.46 (m, 3H), 7.29-7.14 (m, 3H), 4.82-4.97 (m, 2H), 4.60-4.70 (m, 1H), 4.30-4.40 (m, 1H), 3.65-3.75 (m, 3H), 3.33-3.45 (m, 1H), 2.89-2.78 (m, 2H) 2.82 (s, 3H), 2.25 (s, 3H); MS (ESI) *m/e 391* ($C_{23}H_{26}N_4O_2$ + H)$^+$.

Example 11 N-Methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride



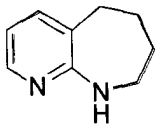
EDC (0.21 g, 1.1 mmol) was added to a suspension of methyl-(2-methyl-benzofuran-3-ylmethyl)-amine (158 mg, 0.9 mmol) and 3-(4-Methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylic acid hydrochloride (201 mg, 0.75 mmol). The mixture was allowed to stir overnight at 40 °C. The mixture was cooled to 0 °C and diluted with H_2O (60mL) with rapid stirring. The resulting precipitate was filtered, washed with H_2O (20 mL) then dried under high vacuum. The solid was then subjected to flash chromatography on silicia gel using 5% methonal:dichloromethane. The fractions were collected and treated with 5 mL of 2.0M HCL in Et_2O. The suspension was concentrated, triturated with Et_2O (50 Ml then filtered to give a coupled solid. were coupled. The resulting solid was dissolved in methylene chloride (5 mL) and treated with 2M HCl in ether (0.75 mL, 1.5 mmol). The yellow precipitate was filtered, triturated with diethyl ether and dried under high vacuum to afford the title compound as a white solid (138 mg, 42%). ^{1}H NMR (300 MHz, DMSO-d_6) 11.92 (bs, 1H) 8.43-8.17 (m, 2H), 7.53-7.38 (m, 3H), 7.29-6.98 (m, 3H), 6.40 (s, 1H), 5.05-4.84 (m, 2H), 4.55-4.63 (m, 1H), 4.31-4.38 (1H), 3.64-3.80 (m, 6H), 3.33-3.45 (m, 1H), 2.97-2.93 (m, 2H) 2.82-2.79 (m, 3H); MS (ESI) *m/e 390* $(C_{23}H_{27}N_5O + H)^+$.

Example 12 Preparation of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride.



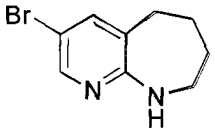
(a) $LiAlH_4$, THF; (b) Br_2, Acetic Acid; (c) N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF.

(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine)



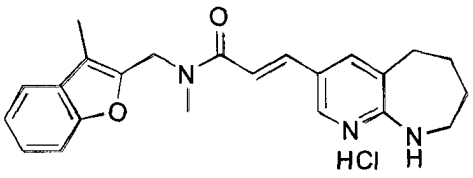
Prepared according to the standard procedure. The title compound (6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine) (400 mg, 87%) was obtained as a brown oil: ^1H NMR (400 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.34-7.33 (m, 1H), 6.63-6.62 (m, 1H), 5.75 (s, 1H), 3.04 (bs, 2H), 2.62 (bs, 2H), 1.69-1.64 (m, 4H).

(3-bromo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine)



Prepared according to a standard procedure. The title compound (3-bromo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine) (493 mg, 80%) was obtained as a brown oil: ^1H NMR (400 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.55 (s, 1H), 3.07-3.06 (m, 2H), 2.65-2.64 (m, 2H), 1.71-1.64 (m, 4H).

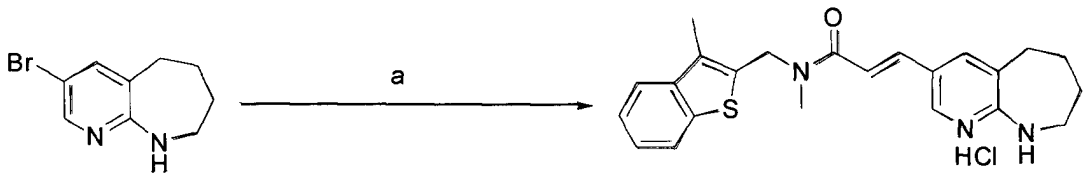
E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride



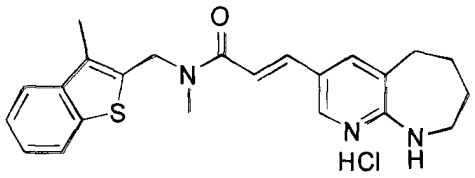
A solution of 3-bromo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine (150 mg, 0.661 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (227 mg, 0.991

mmol) and DIPEA (0.98 mL, 5.63 mmol) in anhydrous DMF (4.0 mL) was prepared. Argon was bubbled into the mixture with stirring for 30 min. Next P(*o*-tol)$_3$ (40.2 mg, 0.132 mmol) and Pd(OAc)$_2$ (14.8 mg, 0.0661 mmol) were added to the mixture and argon was bubbled into the reaction for an additional 5 min. The reaction was sealed and treated under microwave irradiation for 5 min at 160°C. The reaction was cooled to room temperature and diluted with water (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (4x 10 mL). The combined organic layers were washed with brine (20mL), dried over Na_2SO_4, filtered and concentrated to give a brown oil. Purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) gave the desired product as a white solid which was dissolved in CH_2Cl_2 (5.0 mL). To the mixture was added HCl (540 µl of 1M solution in ether, 0.540 mmol) and the mixture was stirred for 5 min at room temperature. After concentrating under high vacuum the title compound ((E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride) (200 mg, 80%) was obtained as a yellow solid and a mixture of amide rotomers: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29-8.26 (m, 2H), 8.20-8.18 (m, 1H), 7.57-7.55 (m, 1H), 7.49-7.43 (m, 2H), 7.30-7.17 (m, 3H), 4.99-4.78 (m, 2H), 3.58 (bs, 2H), 3.17-2.90 (m, 5H), 2.26 (s, 3H), 1.92 (bs, 4H); ESI MS *m/z* 376 $[C_{23}H_{25}N_3O_2+H]^+$.

Example 13 Preparation of (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride

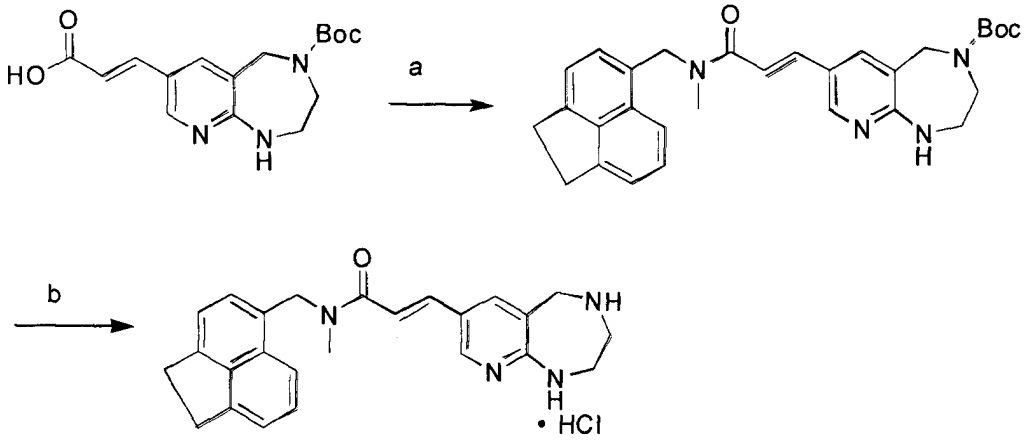


(a) N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide, DIPEA, Pd(OAc)$_2$, P(o-tol)$_3$, DMF.



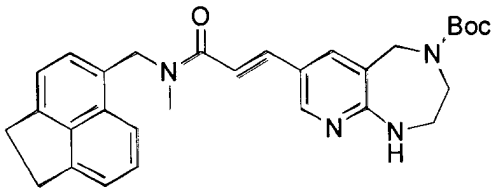
Prepared according to a standard procedure. After purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) the desired product was dissolved in CH_2Cl_2 (2.0 mL). To the mixture was added HCl (172 µl of 1M solution in ether, 0.172 mmol) and the mixture was stirred for 5 min at room temperature. After concentrating under high vacuum the title compound ((E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride) (70.0 mg, 60%) was obtained as a brown solid and a mixture of amide rotomers: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27-8.19 (m, 3H), 7.87-7.72 (m, 2H), 7.50-7.18 (m, 4H), 5.11-4.88 (m, 2H), 3.58 (bs, 2H), 3.14-2.91 (m, 5H), 2.41 (s, 3H), 1.91 (bs, 4H); ESI MS *m/z* 392 $[C_{23}H_{25}N_3OS+H]^+$.

Example 14 Preparation of (E)-tert-butyl 7-(3-(((1,2-dihydroacenaphthylen-5-yl)methyl)(methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate



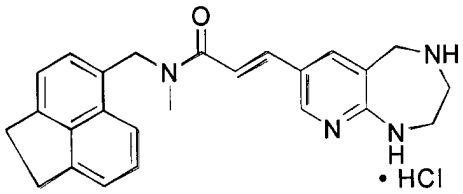
(a) 1,2-dihydroacenaphthylen-5-yl)-N-methylmethanamine, EDC, HOBt, DIPEA, DMF (b) i) TFA, CH_2Cl_2 ii) HCl, ether

(E)-tert-butyl 7-(3-(((1,2-dihydroacenaphthylen-5-yl)methyl)(methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate



Prepared according to a standard procedure. The compound was purified by silica gel chromatography (4% MeOH in CH_2Cl_2) to give a white solid (142 mg, 92%).
ESI MS *m/z* 499 $[C_{30}H_{34}N_4O_3+H]^+$.

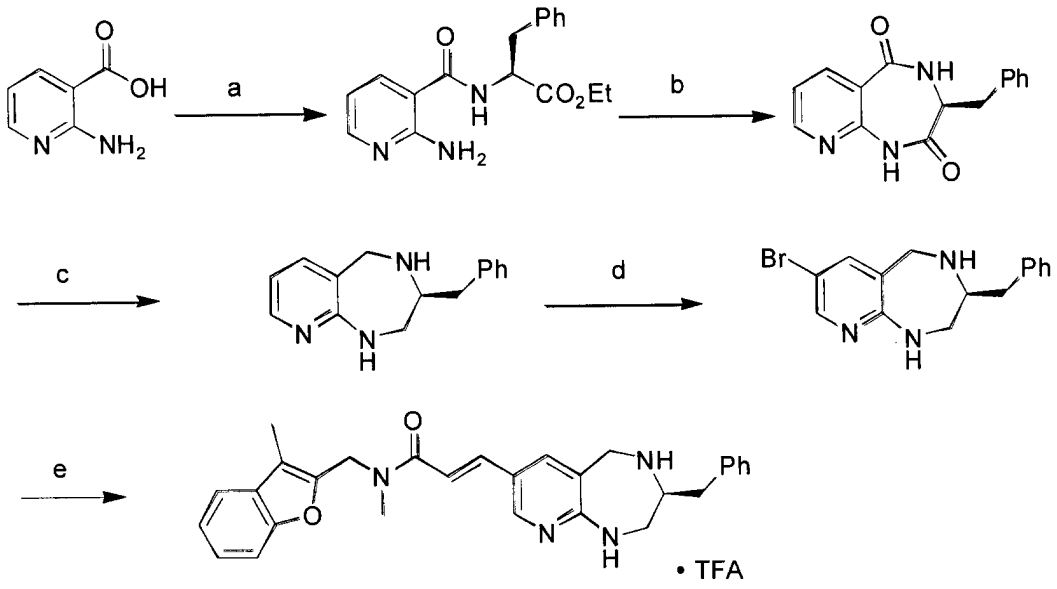
(E)-tert-butyl 7-(3-(((1,2-dihydroacenaphthylen-5-yl)methyl)(methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate



To a solution of (E)-tert-butyl 7-(3-(((1,2-dihydroacenaphthylen-5-yl)methyl)(methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate (142 mg, 0.28 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL). The mixture was stirred at room temperature for 1 h. The solvents were removed in vacuo and dissolved in to CH_2Cl_2 (100 mL) and washed with sat. Na_2CO_3 (2 mL) dried over MgSO4 and concentrated. The residue was dissolved in CH_2Cl_2 (2 mL) and HCl in ether (0.28 mL of a 1M solution) was added. The solvents were removed in vacuo and the residue was dissolved into H_2O (10 mL) and lyophilized to give the title compound as a yellow solid (84 mg, 60%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79-9.65 (m, 1H), 8.39-8.26 (m, 1H), 8.25-8.05 (m, 1H), 7.87-7.67 (m, 1H), 7.87-7.05 (m, 7H),

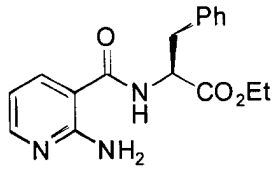
5.21-5.00 (2s, rotomers, 2H), 4.38-4.21 (m, 2H), 3.68-3.51 (m, 2H), 3.44-3.23 (m, 7H), 3.01-2.92 (2s, rotomers, 3H); ESI MS *m/z* 399 $[C_{25}H_{26}N_4O+H]^+$.

Example 15 (S,E)-3-(3-benzyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetate



a) L-phenylalanine ethyl ester, EDC, HOBt, TEA, DMF b) NaH, THF, c) LAH, dioxane, THF, d) Br_2, acetic acid e) N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF, propionitrile.

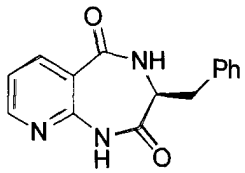
(S)-ethyl 2-(2-aminonicotinamido)-3-phenylpropanoate



To a solution of aminonicotinic acid (2.74 g, 20 mmol) in anhydrous DMF (100 mL) was added EDC (4.2 g, 22 mmol), HOBt (2.97 g, 22 mmol) and triethylamine (8.2 mL, 60 mmol). L-phenylalanine ethyl ester (4.97 g, 22 mmol) was added and the reaction was

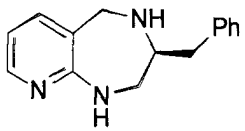
stirred overnight. Water (100 mL) was added and the mixture was extracted with methylene chloride (4 x 100 mL), dried over $MgSO_4$ and concentrate. The compound was purified by silica gel chromatography (gradient CH_2Cl_2 to 10% MeOH/CH_2Cl_2) to afford the title compound as a yellow oil (6.2 g, 98%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 5.0 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.31-7.18 (m, 5H), 6.96 (s, 2H), 6.60 (dd, J = 7.7 Hz, 4.7 Hz, 1H), 4.63-4.56 (m, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.15-3.09 (m, 2H), 1.05 (t, J = 7.0 Hz, 3H); ESI MS *m/z* 314 $[C_{17}H_{19}N_3O_3+H]^+$

(S)-3-benzyl-3,4-dihydro-1H-pyrido[2,3-e][1,4]diazepine-2,5-dione



(S)-Ethyl 2-(2-aminonicotinamido)-3-phenylpropanoate (5.7 g, 18.1 mmol) was dissolved into THF (125 mL) under argon. Sodium hydride (1.07 g, 60% dispersion in oil, 26.8 mmol) was added and the reaction was stirred overnight. Water (5 mL) was carefully added and the resulting white precipitate was collected. The precipitate was dissolved into ethyl acetate (200 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated to a yellow solid (2.1 g, 44%): ESI MS *m/z* 268 $[C_{15}H_{13}N_3O_2+H]^+$.

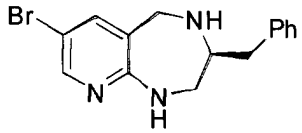
(S)-3-benzyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine



(S)-3-Benzyl-3,4-dihydro-1H-pyrido[2,3-e][1,4]diazepine-2,5-dione (1.6 g, 6 mmol) was dissolved into anhydrous THF (80 mL) under argon. Lithium aluminum hydride (30 mL of 1M in THF) was added and the reaction was heated to reflux for 16 h. The mixture

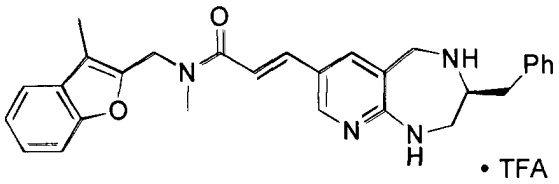
was cooled to room temperature. Water (0.25 mL), 4 N NaOH (0.25 mL) and water (0.75 mL) were carefully added sequentially. The resulting sludge was filtered through celite and the filter cake was washed with ethyl acetate. The filtrate was concentrated to give the monoreduced product (880 mg), which was dissolved into dioxane (50 mL) under argon. Lithium aluminum hydride (17 .3 mL of a 1 M solution in THF) was added and the reaction was heated to 95°C for 36 h. The reaction was cooled to room temperature and carefully quenched with water (0.14 mL), 4N NaOH (0.14 mL) and water (0.42 mL) and filtered through celite. The residue was preabsorbed onto silica gel and eluted with 95:5 CH_2Cl_2/(1%NH_4OH in MeOH) to give the title compound as a yellow solid (60 mg, 7%): ESI MS *m/z* 240 $[C_{15}H_{17}N_3+H]^+$.

(S)-3-benzyl-7-bromo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine



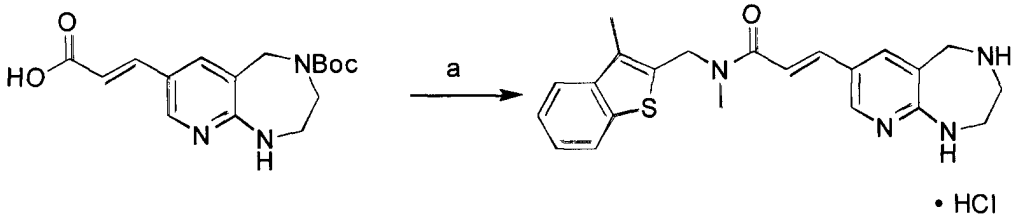
(S)-3-Benzyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine (60 mg, 0.25 mmol) was dissolved into acetic acid (1 mL). Bromine (15 μL, 0.3 mmol) was added and the reaction was stirred overnight. Methylene chloride (10 mL) was added and the solution was washed with 1 N NaOH (1 mL) and brine (1 mL), dried over $MgSO_4$ and concentrated. The residue was dissolved in CH_2Cl_2 (3 mL) and precipitated with diethyl ether. The title compound was collected as an orange solid (80 mg, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.42 (s, 1H), 7.37-7.17 (m, 5H), 5.42-5.00 (bs, 2H), 3.96-3.75 (m, 2H), 3.45-3.40 (m, 1H), 3.30-3.20 (m, 1H), 2.98-2.91 (m, 1H), 2.87-2.73 (m, 2H).

(S,E)-3-(3-benzyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetate



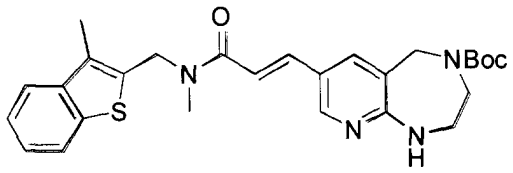
The title compound was prepared according to the standard method and isolated by preparatory HPLC as the trifluoroacetate salt (25 mg, 15%): ^{1}H NMR (400 MHz, CD_3OD) δ 10.35 (s, 1H), 9.95 (s, 1H), 9.15 (s, 1H), 8.86 (s, 1H), 8.40-8.07 (m, 11H), 7.88 (s, 1H), 5.79-5.61 (2s, rotomers, 2H), 5.22-5.15 (m, 2H), 4.61 (s, 1H) 4.40-4.36 (m, 1H), 4.00 (s, 2H), 3.87-3.74 (m, 4H), 3.03-2.52 (2s, rotomers, 2H); ESI MS *m/z* 467 $[C_{29}H_{30}N_4O_2+H]^+$.

Example 16 (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

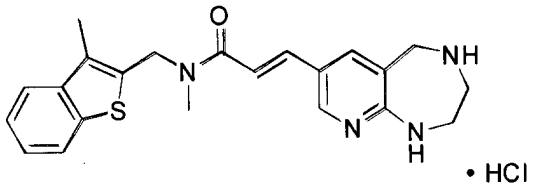


a) N-methyl(3-methylbenzo[b]thiophen-2-yl)methanamine, EDC, HOBt, DIPEA, DMF, b) TFA, CH_2Cl_2

(E)-tert-butyl 7-(3-(methyl((3-methylbenzo[b]thiophen-2-yl)methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate

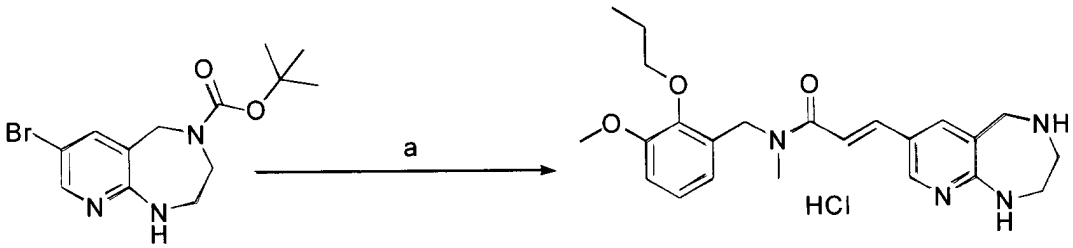


The title compound was prepared using the standard method. The product was obtained as a yellow powder (240 mg, 81%): ESI MS *m/z* 493 $[C_{27}H_{32}N_4O_3S+H]^+$.

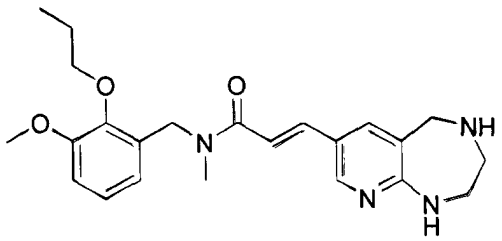


(E)-tert-butyl 7-(3-(methyl((3-methylbenzo[b]thiophen-2-yl)methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate (240 mg, 0.48 mmol) was dissolved into methylene chloride (10 mL) and treated with TFA (1 mL). The solvents were removed and the residue was dissolved into methylene chloride (150 mL), washed with 1 N NaOH (3 mL), brine (10 mL), dried over $MgSO_4$ and concentrated to a yellow oil. The oil was dissolved into methylene chloride (10 mL) and treated with 1M HCl in ether (0.4 mL). The precipitate was collected and triturated with ether to give the title compound as a yellow solid (125 mg, 50%): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (bs, 2H), 8.36-8.35 (m, 1H), 8.22 (bs, 1H), 7.88-7.82 (m, 1H), 7.75-7.72 (m, 1H), 7.68-7.32 (m, 4H), 7.15-7.10 (m, 1H) 5.10-4.88 (2s, rotomers, 2H), 4.31 (bs, 2H), 3.60 (bs, 2H), 3.38 (bs, 2H), 3.14-2.92 (2s, rotomers, 3H), 2.46 (s, 3H); ESI MS *m/z* 393 $[C_{22}H_{24}N_4OS+H]^+$.

Example 17 Preparation of (E)-N-(3-methoxy-2-propoxybenzyl)-N-methyl-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride.

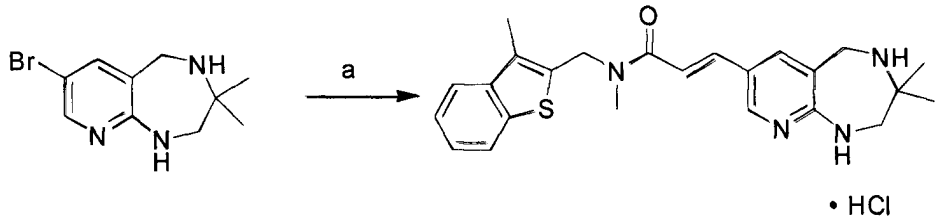


(a) N-(3-methoxy-2-propoxybenzyl)-N-methylacrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF, propionitrile.

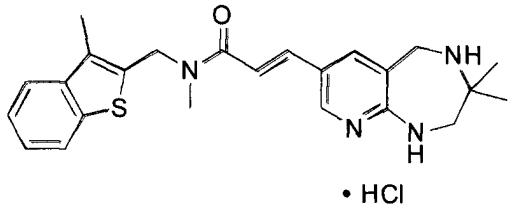


A solution of tert-butyl 7-bromo-2-oxo-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate (310 mg, 0.943 mmol), N-(3-methoxy-2-propoxybenzyl)-N-methylacrylamide (393 mg, 1.49 mmol) and DIPEA (0.33 mL, 1.89 mmol) in anhydrous DMF (2.0 mL) and propionitrile (6.0 mL) was prepared in a pressure flask. Argon was bubbled into the mixture with stirring for 30 min. Next P(*o*-tol)$_3$ (57.4 mg, 0.189 mmol) and Pd(OAc)$_2$ (21.2 mg, 0.0944 mmol) were added to the mixture and argon was bubbled into the reaction for an additional 5 min. The reaction was then sealed and was left to stir for 12 h at 110°C. The reaction was then allowed to cool to room temperature and was filtered through celite. The filter cake was washed with EtOAc (80 mL) and the filtrate was washed with water (50 mL) and brine (500 mL), dried over Na_2SO_4 and concentrated to give a brown oil. The crude product was dissolved in CH_2Cl_2 (6.5 mL) and TFA (6.5 mL) and was left to stir at room temperature for 1 h. The mixture was concentrated and the resulting brown oil was dissolved in EtOAc (20 mL) and washed with sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentration. Purification by column chromatography (silica, gradient elution of CH_2Cl_2 to 15% MeOH/CH_2Cl_2) gave the desired product as a brown solid which was dissolved in CH_2Cl_2 (20 mL) and EtOAc (5 mL). To the mixture was added HCl (413 µl of 1M solution in ether, 0.413 mmol) and the mixture was stirred for 5 minutes and then concentrated. The resulting solid was triturated with ether and left under high vacuum overnight to give the title compound ((E)-N-(3-methoxy-2-propoxybenzyl)-N-methyl-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride) (134 mg, 32%) as a brown solid and a mixture of amide rotomers: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.35-8.23 (m, 2H), 7.51-7.42(m, 1H), 7.21-7.16 (m, 1H), 7.06-6.93 (m, 2H), 6.66-6.53 (m, 1H), 4.77-4.62 (m, 2H), 4.37-4.30 (m, 2H), 3.90-3.83 (m, 2H), 3.78 (s, 3H), 3.68-3.62 (m, 2H), 3.38-3.36 (m, 2H), 3.08-2.83 (m, 3H), 1.73-1.64 (m, 2H), 0.99-0.94 (m, 3H); ESI MS *m/z* 411 $[C_{23}H_{30}N_4O_3+H]^+$.

Example 18 (E)-3-(3,3-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide hydrochloride



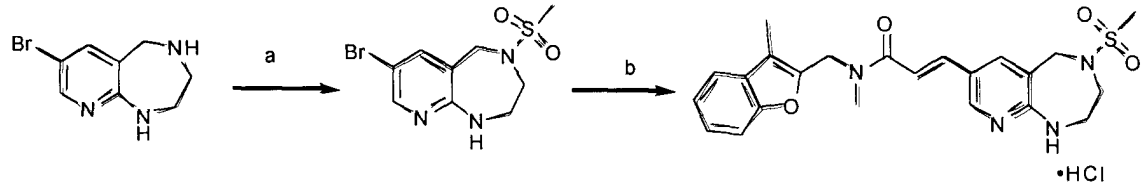
a) N-methyl-N-((3-methylbenzothiophene-2-yl)methyl)acrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF, propionitrile.



N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (147 mg, 0.6 mmol) and 7-bromo-3,3-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine hydrobromide (166 mg, 0.5 mmol) were dissolved into DMF (3 mL). Diisopropylethylamine (0.26 mL, 1.5 mmol) was added and the solution was degassed with argon. Palladium acetate (11 mg, 0.05 mmol) and tri-o-tolylphosphine (30 mg) were added and the mixture was heated under microwave irradiation at 200 °C for 5 min. The reaction mixture was cooled to room temperature and filtered through celite. The filter cake was washed with ethyl acetate. The organic phase was washed with water (2 x 50 mL), sat. sodium bicarbonate (25 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated to a brown oil. The compound was purified using a biotage silica cartridge (gradient, 95:5 CH_2Cl_2/(1%NH_4OH in MeOH) to 90:10). The compound was isolated as a yellow solid. The residue was dissolved in CH_2Cl_2 (3 mL) and HCl in ether was added. The precipitate was collected and triturated with ether. The title compound was isolated as a yellow solid (57 mg, 25%): ^1H NMR (300 MHz, DMSO-d_6) δ 9.77 (bs, 2H) 8.33 (s, 2H), 7.84-7.71 (m, 3H), 7.52-7.48 (m, 1H), 7.40-7.13 (m, 3H), 5.09-4.87 (2s, rotomers, 2H), 4.37-4.30

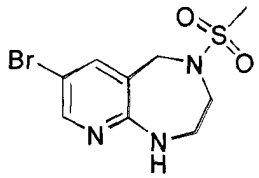
(m, 2H), 3.48 (bs, 2H), 3.14-2.91 (2s, rotomers, 3H), 2.41 (s, 3H), 1.39 (s, 6H); ESI MS *m/z* 421 $[C_{24}H_{28}N_4OS+H]^+$.

Example 19 Preparation of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride.

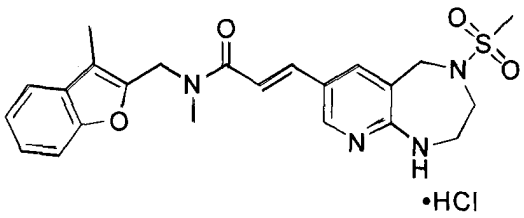


(a) Methanesulfonyl chloride, TEA, CH_2Cl_2; (b) N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF, propionitrile.

(7-bromo-4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine)

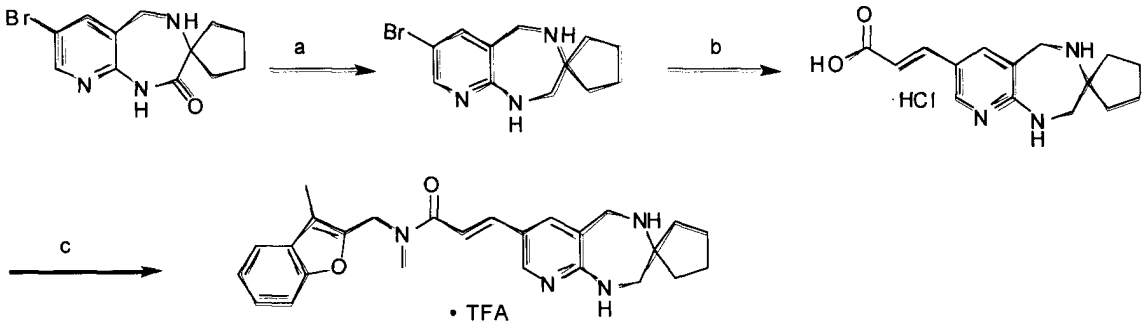


To a solution of 7-bromo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine (432 mg, 1.89 mmol) and TEA (0.28 mL, 2.02 mmol) in anhydrous CH_2Cl_2 (20 mL) under argon was added methanesulfonyl chloride (0.16mL, 2.06 mmol). The mixture was stirred for 12 h at room temperature. Mixture was then concentrated to a brown solid and redissolved in a 2:1 MeOH:DMSO mixture. Purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) gave the title compound (7-bromo-4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine) (281 mg, 48%) as a yellow solid: ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.68 (s, 1H), 4.39 (s, 2H), 3.48 (s, 2H), 3.39 (s, 2H), 2.79 (s, 3H).



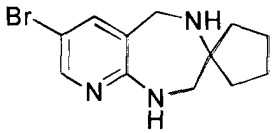
A solution of 7-bromo-4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine (281 mg, 0.917 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (327 mg, 1.42 mmol) and DIPEA (0.32 mL, 1.84 mmol) in anhydrous DMF (2.1 mL) and propionitrile (6.3 mL) was prepared in a pressure flask. Argon was bubbled into the mixture with stirring for 30 min. Next P(*o*-tol)$_3$ (55.8 mg, 0.183 mmol) and Pd(OAc)$_2$ (20.6 mg, 0.0917 mmol) were added to the mixture and argon was bubbled into the reaction for an additional 5 min. The reaction was then sealed and was left to stir for 12 h at 110 °C. The reaction was then allowed to cool to room temperature and was filtered through celite. The filter cake was washed with EtOAc (80 mL) and the filtrate was washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated to give a brown oil. Purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) gave the desired product as a yellow solid which was dissolved in CH_2Cl_2 (2.0 mL). To the mixture was added HCl (440 µl of 1M solution in ether, 0.142 mmol) and the mixture was stirred for 5 min and then concentrated under high vacuum to give the title compound ((E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride) (188 mg, 42%) as a yellow solid and a mixture of amide rotomers: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40-8.28 (m, 2H), 7.56-7.44(m, 4H), 7.29-7.20 (m, 2H), 4.99-4.69 (m, 4H), 3.81 (m, 2H), 3.64-3.63 (m, 2H), 3.17-2.88 (m, 6H), 2.25 (s, 3H); ESI MS *m/z* 455 $[C_{23}H_{26}N_4O_4S+H]^+$.

Example 20 (E)-3-(3-spirocyclopentyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid



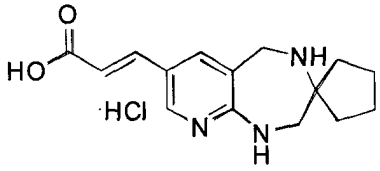
a) LAH, THF b) i) tert-butyl acrylate, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, DIPEA, EtCN, DMF ii) TFA, CH_2Cl_2 iii) HCl, dioxane

Spiro[7-bromo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-3,1'-cyclopentane]

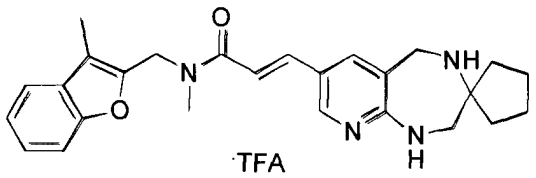


To a cooled solution of spiro[7-bromo-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-3,1'-cyclopentane] (850 mg, 2.87 mmol) in THF (10 mL) was added LAH (1M in THF, 3.16 mL, 3.16 mmol) drop wise over 20 min. The solution was stirred for 5h at room temperature. The solution is cooled in an ice bath and carefully quenched with sat. $NaHCO_3$ (15 mL) and extracted with ethyl acetate (3 x 15 mL), the organic layers combined, dried over sodium sulfate and concentrated to yield the title compound as a colorless oil (736 mg, 91%): ^1H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 4.0Hz, 1H), 7.38 (d, J = 4.0Hz, 1H), 3.73 (s, 2H), 3.17 (s, 2H), 1.41-1.75 (m, 8H).

(E)-tert-butyl 3-(3-spirocyclopentyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride



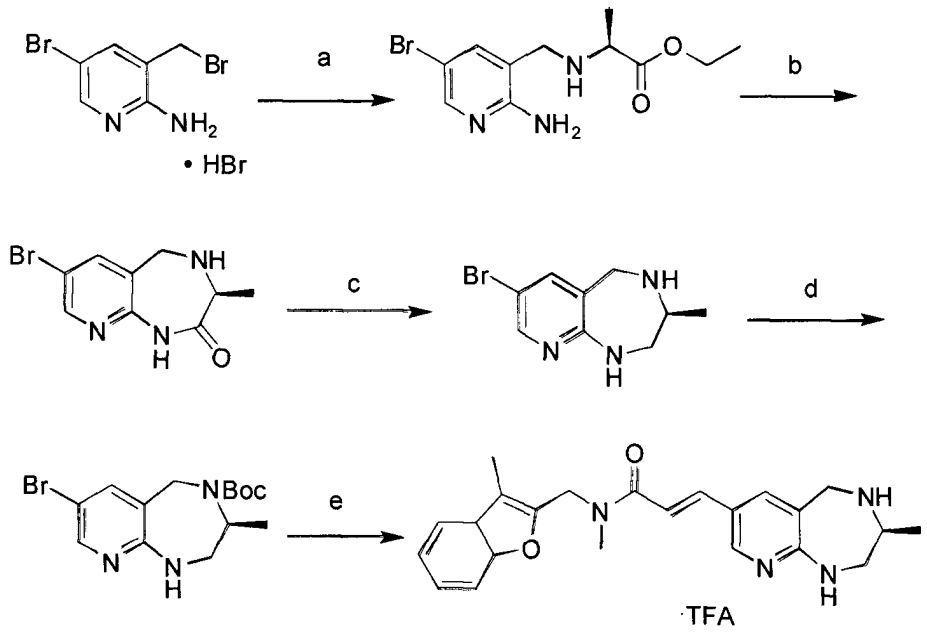
To a solution of spiro[7-bromo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-3,1'-cyclopentane] (736 mg, 2.61 mmol), tri(o-tolyl)phosphine (159 mg, 0.52 mmol), diisopropylethylamine (1.4 mL, 7.8 mmol), tert-butyl acrylate (1.9 mL, 13 mmol) in DMF (5 mL) was added palladium acetate (64 mg, 0.26 mmol) and the reaction heated to 90°C overnight. The reaction was cooled to room temperature and passed through a pad of celite. The filter cake was washed with ethyl acetate (20 mL). The reaction was washed with water (20 mL) and extracted with ethyl acetate (2 x 25 mL), dried over sodium sulfate and concentrated. This solution was then re-solvated in dichloromethane (5 mL) to which trifluoroacetic acid (2 mL) was added and the reaction was stirred at room temperature overnight. The reaction was concentrated and re-solvated in dichloromethane (2 mL) to which 4M HCl in dioxane (1 mL) was added, the product precipitated out with the addition of ether (5 mL) and was further washed with ether (10 mL) and dried to yield title compound (as the HCl salt) as a white solid (560 mg, 62%): ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (s, 1H), 8.30 (s, 1H), 7.60 (d, 1H, J=16.0Hz), 6.59 (d, 1H, J=16.0Hz), 4.69 (s, 2H), 3.88 (s, 2H), 2.08-1.83 (m, 8H).



To a solution of methyl-(2-methyl-benzofuran-3-ylmethyl)-amine (68 mg, 0.39 mmol) in DMF (3 mL) were added in sequential order (E)-tert-butyl 3-(3-spirocyclopentyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride (110 mg, 0.35 mmol), 1-hydroxybenzotriazole (54 mg, 0.39 mmol), diisopropylethylamine (240 uL, 1.4 mmol), and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (78 mg, 0.39 mmol). The mixture was stirred at room temperature overnight, cooled in an ice bath and water added with rapid stirring. The product was extracted with ethyl acetate (3 x 10 mL), dried with sodium sulfate, filtered and concentrated. The product was purified using a reverse phase preparative HPLC to give the TFA salt of the title compound as a white solid (72mg, 46%): ^{1}H NMR (400 MHz,

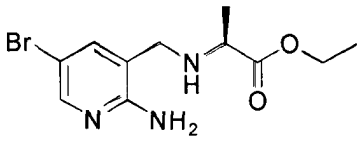
DMSO-d_6) δ 9.26 (1s, 1H), 8.31 (s, 1H), 8.04 (s, 1H), 7.60 (d, J = 8.0Hz, 1H), 7.50-7.45 (m, 2H), 7.31-7.26 (m, 2H), 7.15 (s, 1H), 4.94-4.79 (rotamers, 2s, 2H), 4.31 (s, 3H), 3.40 (d, J = 4.4Hz, 2H), 3.17 (s, 3H), 2.26 (s, 3H), 1.88-1.64 (m, 8H); MS (ESI) *m/e 431* $(C_{26}H_{30}N_4O_2 + H)^+$.

Example 21 E)-N-methyl-3-((S)-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methyl-3a,7a-dihydrobenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid



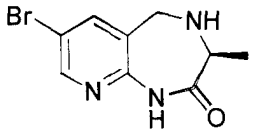
a) TEA, DMF b) NaH, DMSO c) LAH, THF, d) di-tert-butyl dicarbonate, TEA, CH_3CN e) N-methyl-N-((3-methyl-3a,7a-dihydrobenzofuran-2-yl)methyl)acrylamide, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, DIPEA, DMF, EtCN

(S)-ethyl 2-((2-amino-5-bromopyridin-3-yl)methylamino)propanoate



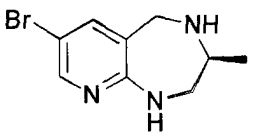
To a solution of 5-bromo-3-(bromomethyl)pyridin-2-amine hydrobromide (2.5 g, 7.3 mmol) in DMF (10 mL) is added L-alanine ethyl ester hydrochloride (1.67 g, 10.9 mmol) and triethylamine (5 mL, 36 mmol) and the reaction was stirred at room temperature overnight. The reaction was quenched with water (20 mL) and the product extracted with ethyl acetate (4 x 20 mL), the combined organic layers are dried over sodium sulfate and concentrated. The crude reaction mixture is purified using preparative HPLC to give the final product as a white solid (530 mg, 25%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.91 (s, 1H), 7.47 (s, 1H), 6.20 (b, 1H), 4.15-4.07 (m, 2H), 3.49 (b, 2H), 3.27 (m, 1H), 3.34 (s, 2H), 1.17-1.24 (m, 6H).

(S)-7-bromo-3-methyl-4,5-dihydro-1H-pyrido[2,3-e][1,4]diazepin-2(3H)-one



To a solution of (S)-ethyl 2-((2-amino-5-bromopyridin-3-yl)methylamino) propanoate (530 mg, 1.75 mmol) in DMSO (10 mL) is added NaH (42 mg, 1.75 mmol) and the reaction was stirred at room temperature overnight under argon. The mixture was diluted with water (5 mL) and the product extracted with ethyl acetate (4 x 10 mL), dried over sodium sulfate and concentrated to yield the title compound as light brown solid (375 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.44 (s, 1H), 3.76-3.69 (m, 2H), 3.66 (m, 1H), 1.36 (d, 3H, J=6.4Hz).

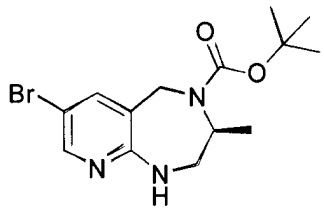
(S)-7-bromo-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine



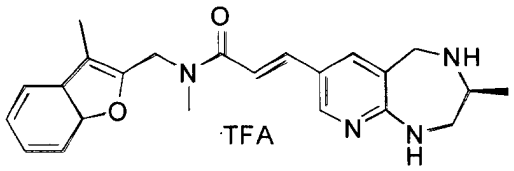
To a solution of LAH (2.5mL, 2.52mmol) was added a solution of (S)-7-bromo-3-methyl-4,5-dihydro-1H-pyrido[2,3-e][1,4]diazepin-2(3H)-one (375 mg, 1.26 mmol) in

THF (10 mL) at 0 °C. The reaction was warmed to room temperature and stirred over night. Once the reaction was complete, it was cooled to 0 °C and carefully quenched with water (10 mL), and extracted with ethyl acetate (4 x 15 mL), dried over sodium sulfate and concentrated. Preparative HPLC was used to purify the title compound as a white solid (166 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 2.4Hz, 1H), 7.75 (d, J = 2.4Hz, 1H), 4.36 (2s, 2H), 4.21 (d, J = 14.3Hz, 1H), 6.33-3.61 (m, 2H), 3.26-3.13 (m, 1H), 1.36 (d, J = 6.4Hz, 3H).

(S)-tert-butyl 7-bromo-3-methyl-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate

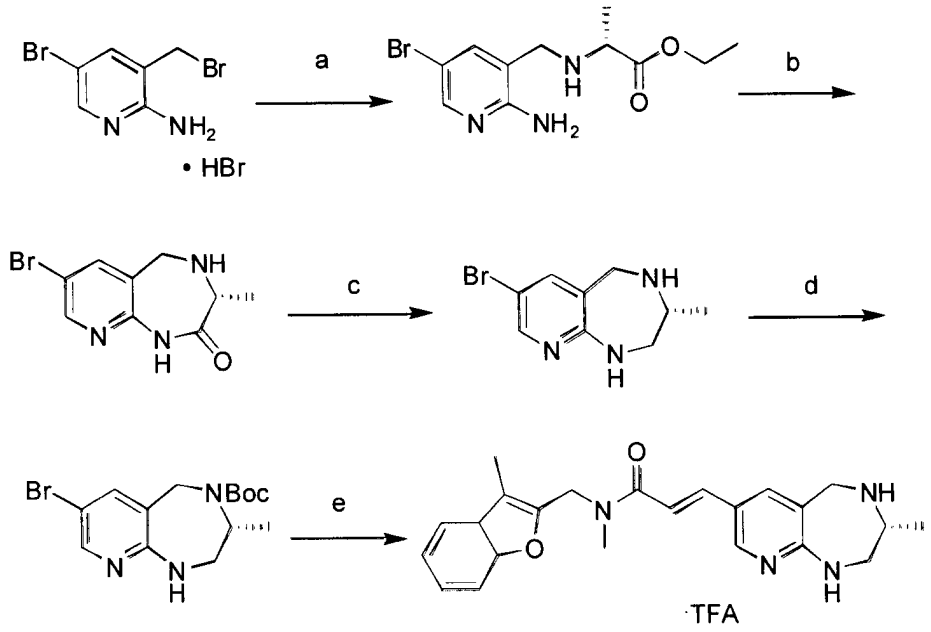


To a solution of (S)-7-bromo-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine (166 mg, 0.69 mmol) in MeCN (10 mL) and triethylamine (144 uL, 1.03 mmol) was added di-tert-butyl dicarbonate (151 mg, 0.69 mmol) and the reaction was stirred at room temperature for 1h. The reaction mixture was concentrated and re-solvated in dichloromethane (20 mL), washed with water (15 mL), dried over sodium sulfate and concentrated to give the title compound as a white solid (180 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.45 (s, 1H), 4.38-4.34 (2s, 2H), 4.23 (s, 1H), 6.33-3.61 (m, 2H), 3.26-3.13 (m, 1H), 1.35 (s, 9H), 1.36 (d, J = 6.4Hz, 3H).



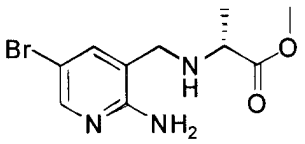
To a solution of (S)-tert-butyl 7-bromo-3-methyl-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate (180 mg, 0.53 mmol), tri(o-tolyl)phosphine (32 mg, 0.106 mmol), diisopropylethylamine (200 uL, 1.06 mmol), N-methyl-N-((3-methyl-3a,7a-dihydrobenzofuran-2-yl)methyl)acrylamide (243 mg, 1.06 mmol) in DMF (5 mL) is added palladium acetate (13 mg, 0.053 mmol) and the reaction was heated to 90°C overnight. The reaction was cooled to room temperature and passed through a pad of celite. The filter cake was washed with ethyl acetate (10 mL). The filtrate was washed with water (10 mL) and extracted with ethyl acetate (2 x 15 mL), dried over sodium sulfate and concentrated. The resultant solution was then re-dissolved in methylene chloride (5 mL) and cooled to 0 °C. Trifluoroacetic acid (1 mL) was added and reaction stirred at room temperature for 1h. The solution was concentrated and purified using preparative HPLC to yield the title compound as a yellow solid (49 mg, 24%): ^{1}H NMR (400 MHz, DMSO-d6) δ 9.43 (bs, 1H), 8.90 (bs, 1H), 8.33 (s, 1H), 8.05 (s, 1H), 7.57-7.46 (m, 3H), 7.30-7.22 (m, 2H), 7.06 (s, 1H), 4.96-4.79 (2s, 2H, rotamers), 4.35-4.21 (m, 2H), 3.62-3.58 (m, 3H), 3.17 (s, 3H), 2.26 (s, 3H), 1.28 (d, J = 6.4Hz, 3H). MS (ESI) *m/e* 391 $(C_{23}H_{26}N_4O_2 + H)^+$.

Example 22 (R,E)-N-methyl-3-(3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid salt



a) TEA, DMF b) NaH, DMSO c) LAH, THF, d) di-tert-butyl dicarbonate, TEA, CH_3CN e) N-methyl-N-((3-methyl-3a,7a-dihydrobenzofuran-2-yl)methyl)acrylamide, $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, DIPEA, DMF, EtCN

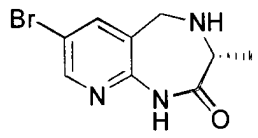
(R)-methyl 2-((2-amino-5-bromopyridin-3-yl)methylamino)propanoate



To a solution of 5-bromo-3-(bromomethyl)pyridin-2-amine hydrobromide (2.5 g, 7.3 mmol) in DMF (10 mL) was added D-alanine methyl ester hydrochloride (1.67 g, 10.9 mmol) and triethylamine (5 mL, 36 mmol) and the reaction was stirred at room temperature overnight. The reaction is quenched with water (20 mL) and the product was extracted with ethyl acetate (4 x 20 mL), the combined organic layers dried over sodium sulfate and concentrated. The crude reaction mixture was purified using a silica gel column eluting with ethyl acetate to give the final product as a white solid (1 g, 50%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.35 (s, 1H), 5.54 (bs, 2H), 3.73 (d, 1H,

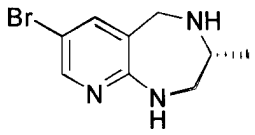
J=13.2Hz), 3.54 (d, 1H, J=13.2Hz), 3.36-3.34 (m, 1H), 2.96 (s, 3H), 1.35 (d, 3H, J=6.8Hz).

(R)-7-bromo-3-methyl-4,5-dihydro-1H-pyrido[2,3-e][1,4]diazepin-2(3H)-one



To a solution of (R)-methyl 2-((2-amino-5-bromopyridin-3-yl)methylamino) propanoate (1 g, 3.5 mmol) in DMSO (10 mL) was added NaH (174 mg, 3.9 mmol) portion wise and the reaction is stirred at room temperature overnight under argon. The mixture was diluted with water (5 mL) and the product extracted with ethyl acetate (4 x 10 mL), dried over sodium sulfate and concentrated to yield title compound as light brown solid (750 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (bs, 1H), 8.31 (d, 1H, J=2.4Hz), 7.59 (d, 1H, J=2.4Hz), 4.07-3.96 (m, 2H), 3.72-3.70 (m, 1H), 1.43 (d, 3H, J=7.2Hz).

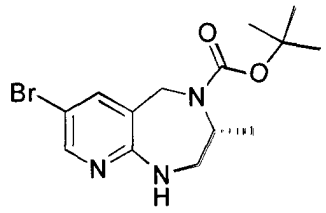
(R)-7-bromo-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine



To a cooled solution (0°C) of LAH (1M in THF, 4.4 mL, 4.4 mmol) was added a solution of (R)-7-bromo-3-methyl-4,5-dihydro-1H-pyrido[2,3-e][1,4]diazepin-2(3H)-one (750 mg, 2.9 mmol) in THF (20 mL). The reaction was warmed to room temperature and stirred over night. Once the reaction was complete, it was cooled to 0°C and carefully quenched with water (10 mL), extracted with ethyl acetate (4 x 15 mL), dried over sodium sulfate and concentrated. The product was isolated by column chromatography (10% MeOH in CH_2Cl_2) to give the title compound as a light yellow solid (161 mg, 23%): ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (s, 1H), 7.55 (s, 1H), 3.93-3.89 (d, J =

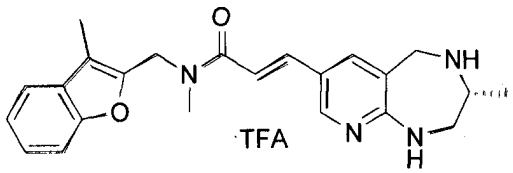
15.6Hz, 1H), 3.74-3.70 (d, J = 15.2Hz, 1H), 3.43-3.39 (d, J = 13.6Hz, 1H), 3.02 (m, 1H), 2.81-2.76 (m, 1H), 1.14-1.12 (d, J = 6.8Hz, 3H).

(R)-tert-butyl 7-bromo-3-methyl-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate



To a solution of (R)-7-bromo-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine (161 mg, 0.66 mmol) in MeCN (10 mL) and triethylamine (140 uL, 0.99 mmol) was added di-tert-butyl dicarbonate (144 mg, 0.66 mmol) and the reaction stirred at room temperature for 1h. The reaction mixture was concentrated and re-solvated in dichloromethane (20 mL), washed with water (15 mL), dried over sodium sulfate and concentrated to give the title compound as a white solid (218 mg, 96%): ^{1}H NMR (400 MHz, CDCl3) δ 7.96 (s, 1H), 7.46 (s, 1H), 4.36 (d, 2H, J= 14.3Hz), 4.21 (d, 1H, J=14.3Hz), 6.33-3.61 (m, 2H), 3.26-3.13 (m, 1H), 1.35-1.34 (s, 9H), 1.37-1.35 (d, 3H, J=6.4Hz).

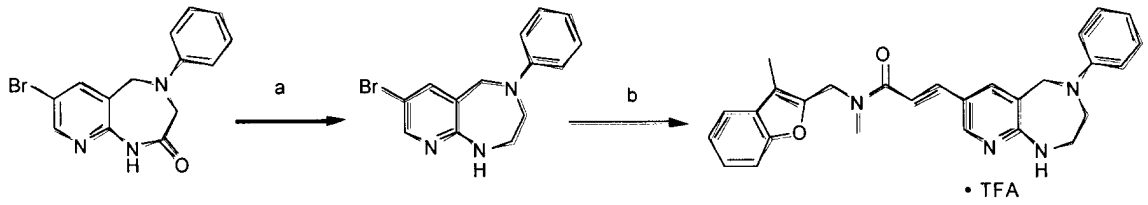
(R,E)-N-methyl-3-(3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid salt



To a solution of (R)-tert-butyl 7-bromo-3-methyl-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate (218 mg, 0.64 mmol), tri(o-tolyl)phosphine (39 mg, 0.128 mmol), diisopropylethylamine (360 uL, 1.92 mmol), N-methyl-N-((3-methyl-3a,7a-

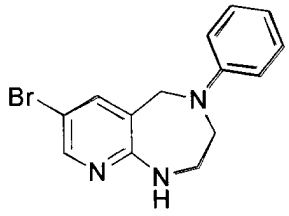
dihydrobenzofuran-2-yl)methyl)acrylamide (293 mg, 1.28 mmol) in DMF (5 mL) is added palladium acetate (16 mg, 0.064 mmol) and the reaction was heated to 90°C overnight. The reaction was cooled to room temperature and passed through a pad of celite, washing the filter cake with ethyl acetate (10 mL). The reaction was washed with water (10 mL) and extracted with ethyl acetate (2 x 15 mL), dried over sodium sulfate and concentrated. The residue was then re-dissolved in methylene chloride (5 mL) and cooled to 0°C. Trifluoroacetic acid (1 mL) was added and reaction stirred at room temperature for 1h. The solution was concentrated and purified using preparative HPLC to yield a yellow solid (8 mg, 4%) as the TFA salt: ^{1}H NMR (400 MHz, CD_3OD) δ 8.35-8.32 (m, 1H), 8.00 (s, 1H), 7.58-7.53 (m, 2H), 7.40-7.21 (m, 4H), 4.92-4.77 (2s, 2H, rotamers), 4.56-4.44 (m, 2H), 3.76 (m, 1H), 3.22-3.18 (m, 2H), 2.88 (s, 3H), 2.08 (s, 3H), 1.58-1.57 (m, 3H). MS (ESI) *m/e 391* $(C_{23}H_{26}N_4O_2 + H)^+$.

Example 23 Preparation of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide.



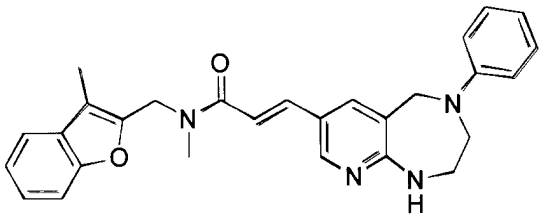
(a) $LiAlH_4$, THF; (b) N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF, propionitrile.

(7-bromo-4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine)



Prepared according to a standard procedure. The title compound (7-bromo-4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepine) (65.6 mg, 14%) was obtained as a yellow oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92-7.89 (m, 2H), 7.15-7.11 (m, 2H), 6.80-6.78 (m, 2H), 6.60-6.56 (m, 1H), 6.45 (bs, 1H), 4.55 (s, 2H), 3.66-3.63 (m, 2H), 3.40-3.29 (m, 2H).

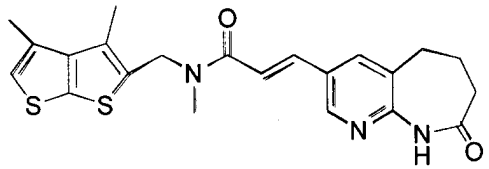
(E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide



• TFA

Prepared according to a standard procedure. Purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) gave the title compound ((E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide)(trifluoroacetic acid salt) (42.1 mg, 37%) as an orange solid and a mixture of amide rotomers: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40-8.14 (m, 2H), 7.58-7.45 (m, 4H), 7.31-7.23 (m, 2H), 7.16-7.12 (m, 3H), 6.79-6.77 (m, 2H), 6.63-6.61 (m, 1H), 5.00-4.71 (m, 4H), 3.73-3.68 (m, 4H), 3.21-2.95 (m, 3H), 2.27 (s, 3H); ESI MS *m/z* 453 $[C_{28}H_{28}N_4O_2+H]^+$.

Example 24 Preparation of (E)-N-((3,4-dimethylthieno[2,3-b]thiophen-2-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide



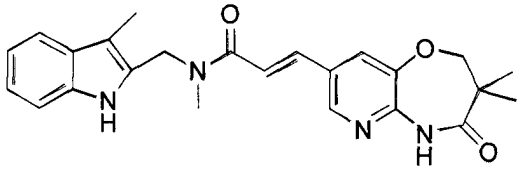
The title compound is prepared according to one of two standard procedures:

In the amide coupling reaction (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylic acid hydrochloride (1 equivalent) is treated with EDC (1.2 equivalents), HOBt (1.1 equivalents), and (*i*-Pr)$_2$EtN (5 equivalents) and the appropriate *N*-methyl-*N*-(arylmethyl)-amine (1 equivalent) in DMF. The mixture is stirred overnight at 40 °C, cooled to ambient temperature and worked up in the standard fashion.

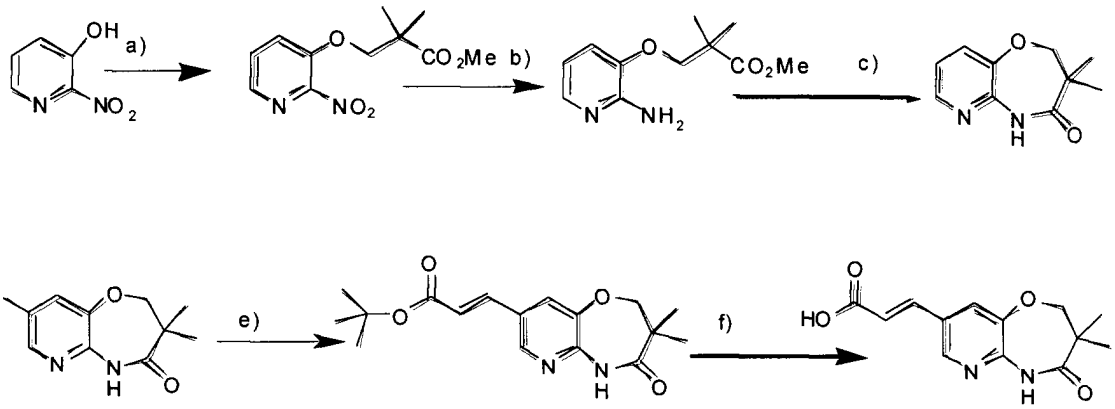
In the Heck coupling reaction, to a solution of 3-bromo-6,7-dihydro-5H-pyrido[2,3-b]azepin-8(9H)-one (2 equivalents) in propionitrile and DMF (2:1) is added the appropriate *N*-arylmethyl-*N*-methylacrylamide (2.60 equivalent), (*i*-Pr)$_2$EtN (4.0 equivalents), Pd(OAc)$_2$ (0.20 equivalents) and P(*o*-tol)$_3$ (0.40 equivalents), and the mixture is de-oxygenated with argon for 15 min. The mixture is heated to reflux overnight, cooled and then filtered through a pad of diatomaceous earth. The filtrate is concentrated and the residue is worked up in the standard fashion.

Purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) gave the title compound (94 mg, >95% by HPLC) as a white solid and a mixture of amide rotomers: ESI MS *m/z* 426 $[C_{22}H_{23}N_3O_2S_2+H]^+$.

Example 25 Preparation of (*E*)-3-(2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)-*N*-methyl-*N*-((3-methyl-1*H*-indol-2-yl)methyl)acrylamide



Preparation of (*E*)-3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazin-8-yl) acrylic acid



Reagents and conditions: a) methyl2,2-dimethyl-3-hydroxypropionate, DIAD, PPh_3, dioxane. b) Zn, AcOH. c) NaH, DMSO. d) Br_2, CH_2Cl_2. e) t-butylacrylate, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, DMF, propionitrile. f) TFA, CH_2Cl_2, HCL/dioxane (4M)

a) methyl 2,2-dimethyl-3-(2-nitropyridin-3-yloxy)propanoate:

3-Hydroxynitropyridine (10.0g, 64 mmol), methyl 2,2-dimethyl-3-hydroxypropionate (9.29 g, 70.4.0 mmol) and PPH_3 (15.15g, 76.8 mmol) were dissolved in dioxane (500 mL). DIAD (14.5 mL, 76.8 mmol) was added at 0 °C over 5 min and the mixture was stirred at rt for 4h then refluxed overnight. The mixture was evaporated, dissolved in ethyl acetate, washed with water, dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound (9.1g, 61%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.22 (d, J = 1.4Hz, 1H), 7.98 (d, J = 2.0Hz, 1H), 7.70 (m, 1H), 4.43 (s, 2H), 3.59 (s, 3H), 1.17 (s, 6H)

b) methyl 2,2-dimethyl-3-(2-aminopyridin-3-yloxy)propanoate:

A suspension of methyl 2,2-dimethyl-3-(2-nitropyridin-3-yloxy)propanoate (9.1g, 6mmol) and Pd/C (800 mg) in methanol (500 mL) was stirred at rt overnight under hydrogen. The cooled mixture was filtered through celite, washed with methanol and evaporated *in vacuo* to afford the title compound (8.23 g, 100%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (d, J = 1.3 Hz, 1H), 7.03 (d, J = 1.3 Hz, 1H), 6.47 (m, 1H), 5.47 (s, 2H), 3.94 (s, 2H), 3.62 (s, 3H), 1.17 (s, 6H)

c) 3,3-dimethyl-2,3-dihydropyrido[3,2-*b*][1,4]oxazepin-4(5*H*)-one:

NaH (60% in oil 533 mg) was added to a solution of methyl 2,2-dimethyl-3-(2-aminopyridin-3-yloxy)propanoate (8.04, 37 mmol) in DMSO (400 mL) and the mixture stirred overnight at rt. The mixture was diluted with water and separated. The aqueous layer was washed with ethyl acetate and the combined organic phases were dried over magnesium sulfate and evaporated *in vacuo* to afford the title compound (6.5g, 94%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.83 (s, 1H), 7.96 (d, J = 4.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 6.98 (m, 1H), 4.02 (s, 2H), 1.47 (s, 6H)

d) 8-bromo-3,3-dimethyl-2,3-dihydropyrido[3,2-*b*][1,4]oxazepin-4(5*H*)-one:

Bromine (13.3 mL, 83.2 mmol) was added slowly to a cooled solution of 3-dimethyl-2,3-dihydropyrido[3,2-*b*][1,4]oxazepin-4(5*H*)-one (4g, 20.8 mmol) in CH_2Cl_2 (400 mL) with Na_2CO_3 (1g). The mixture was stirred at rt overnight and poured into saturated $NaHSO_3$ (200 mL). The mixture was separated and the aqueous layer washed with CH_2Cl_2. The

combined organic phases were dried and evaporated *in vacuo* to afford the title compound (4.21g, 78%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.16 (s, 1H), 7.77 (s, 1H), 4.05 (s, 2H), 1.47 (s, 6H)

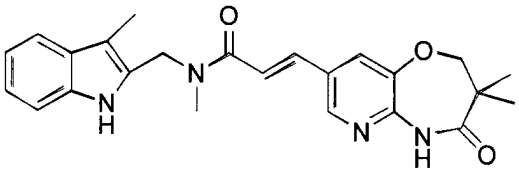
e) (*E*)-tert-butyl 3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)acrylate:

A solution of 8-bromo-3,3-dimethyl-2,3-dihydropyrido[3,2-*b*][1,4]oxazepin-4(5*H*)-one (1g, 3.6 mmol), t-butyl acrylate (1.38 g, 10.8 mmol) and DIPEA (1.86 mL, 10.1 mmol) in DMF (10 mL) was purged with Ar for 10 min. $Pd(OAc)_2$ (81 mg, 0.36 mmol) and $P(o\text{-}tol)_3$ (218 mg, 0.72 mmol) were added and the mixture purged again then refluxed overnight. The crude mixture was evaporated *in vacuo* and chromatographed over silica eluting with methanol/dichloromethane to afford the title compound (1.0 g, 87%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, 1H), 8.26 (s, 1H), 7.77 (s, 1H), 7.47 (d, J = 16.1 Hz, 1H), 6.53 (d, J = 16.1 Hz, 1H), 4.05 (s, 2H), 1.53 (s, 9H), 1.47 (s, 6H)

f) (*E*)- 3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)acrylic acid:

TFA (3mL) was added to a cooled solution of (*E*)-tert-butyl 3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)acrylate (1g, 3 mmol) in CH_2Cl_2 (5 mL) and stirred for 30 min at rt. The mixture was evaporated and HCl/dioxane (4M, 5mL) was added. The precipitate that formed was washed with ether and dried to afford the title compound (530 mg, 66%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.28 (s, 1H), 7.82 (d, J = 15.5 Hz, 1H), 6.84 (d, J = 20 Hz, 1H), 4.05 (s, 2H), 1.47 (s, 6H).

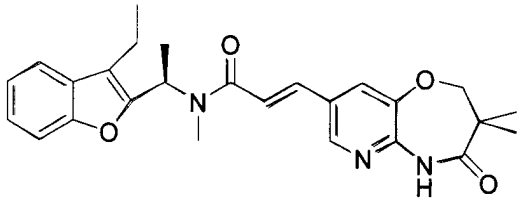
Preparation of (*E*)-3-(2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)-*N*-methyl-*N*-((3-methyl-1*H*-indol-2-yl)methyl)acrylamide



EDC (402 mg, 1.0mmol) was added to a solution of *N*-methyl(3-methyl-1*H*-indol-2-yl)methanamine (135 mg, 0.7 mmol), (*E*)-3-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)acrylic acid hydrochloride (240 mg, 0.8 mmol), HOBT•H_2O (101 mg, 0.7 mmol) and DIPEA (0.58 mL, 2.7 mmol) in dry DMF (

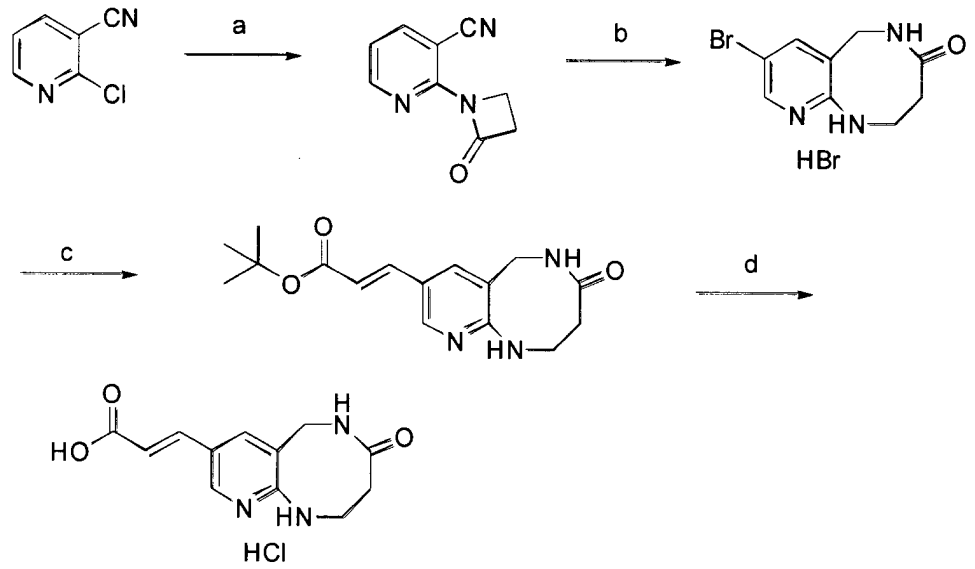
5 mL). After stirring overnight, water was added. The precipitate that formed was washed with ethyl acetate and dried to afford the title compound (234 mg, 79%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.62 - 10.58 (rotamers, s, 1H), 10.09 (s, 1H), 8.26 (s, 1H), 7.89 (s, 1H), 7.51 - 7.49 (m, 2H), 7.28 (t, J = 8.0 Hz, 1H), 7.03 – 6.90 (m, 3H), 4.90 - 4.73 (rotamers, s, 2H), 4.05 (s, 3H), 2.23 (s, 3H), 1.17(s, 6H); MS (ESI): *m/e* 419.4 ($C_{24}H_{26}N_4O_3$ + H)$^+$.

Example 26 Preparation of (*R*,*E*)-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)-*N*-(1(3-ethylbenzofuran-2-yl)ethyl)-*N*-methylacrylamide



EDC (557 mg, 1.4mmol) was added to a solution of (*R*)-1-(3-ethylbenzofuran-2-yl)-*N*-methylethananamine (225 mg, 1.1 mmol), (*E*)-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)acrylic acid hydrochloride (318 mg, 1.2 mmol), HOBT•H_2O (148 mg, 1.1 mmol) and DIPEA (1.1 mL, 4.4 mmol) in dry DMF (5 mL). After stirring overnight, water was added. The precipitate that formed was washed with ethyl acetate and dried to afford the title compound (231 mg, 46%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.33 (s, 1H), 8.00 (s, 1H), 7.84 (d, *J* = 7.4Hz, 1H), 7.65 (d, *J* = 7.1Hz, 1H), 7.41 – 7.34 (m, 2H), 7.10 - 6.98 (m, 2H), 6.29 (m, 1H), 4.14 – 3.99 (m, 2H), 3.09 (s, 2H), 1.73 (m, 3H), 1.43 (s, 6H); MS (ESI): *m/e* 448.3 ($C_{26}H_{29}N_3O_4$ + H)$^+$.

Example 27 Preparation of (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide, di-methane sulfonic salt



(a) Azetidin-2-one, Pd(dba), Xantphos, $Cs_2(CO_3)$, Toluene, 90 °C; (b) (i) Pd/C, HOAc; (ii) Br_2 (c) *tert* -butyl acrylate, $Pd(OAc)_2$, P(*o*-tol)$_3$, (*i*-Pr)$_2$EtN, DMF, 100 °C; (d) i. TFA, CH_2Cl_2; ii. 4 M HCl/dioxane.

Preparation of 2-(2-oxoazetidin-1-yl)nicotinonitrile

Step A. An oven dried round bottom flask was purged with argon then charged with 2-chloronicotinonitrile (277 mg, 2.0 mmol), azetidin-2-one (142 mg, 2.0 mmol), Palladium dibenzylideneacetone (115 mg, 0.1 mmol), Xantphos (174 mg, 0.3 mmol) and cesium carbonate (1.3g, 4.0 mmol) followed by toluene (10 mL). The suspension was heated at 90 °C for 16 hours (overnight). After cooling, the yellow suspension was filtered through a pad of celite and the filter cake was rinsed with CH_2Cl_2. The filtrate was concentrated and subjected to flash chromatography on silica gel using 5% MeOH:95% CH_2Cl_2 to give a yellow solid. Yield: 100 mg (28.9%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.65 (dd, 1H, J = 1.6 Hz, 3.2 Hz), 8.30 (dd, 1H, J = 6.0 Hz, 2.0 Hz), 7.35 (m, 1H), 3.88 (t, 2H, J = 5.2 Hz), 3.18 (t, 2H, J = 5.2 Hz).

Preparation of 8-bromo-2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one hydrobromide

Step B. A round bottom flask was purged with argon and charged with 2-(2-oxoazetidin-1-yl)nicotinonitrile (600 mg, 3.46 mmol) and palladium (10%) on activated carbon (250 mg, 0.23 mmol) followed by acetic acid (15 mL). The flask was stirred under a hydrogen balloon overnight. A TLC analysis indicated that the starting material has been consumed. The mixture was filtered through a pad of celite and the filtrate was treated with bromine (0.27 mL, 5.19 mmol) dropwise over 20 minutes. The yellow-orange suspension was stirred for 3.5 hours at room temperature. The suspension was then treated with 150 mL Et2O and stirred rapidly then sonicated. The solvent was decanted and the solid was filtered and washed with 200 mL Et_2O. The solid was collected and dried under reduced pressure. Yield: 600 mg (51.3%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.06 (d, 1H, J = 2.4 Hz), 7.75 (d, 1H, J = 2.4 Hz), 7.43 (t, 1H, J = 7.6 Hz), 4.48 (d, 2H, J = 7.6 Hz), 3.65 (t, 2H, J = 8.0 Hz), 2.74 (t, 2H, J = 8.0 Hz)

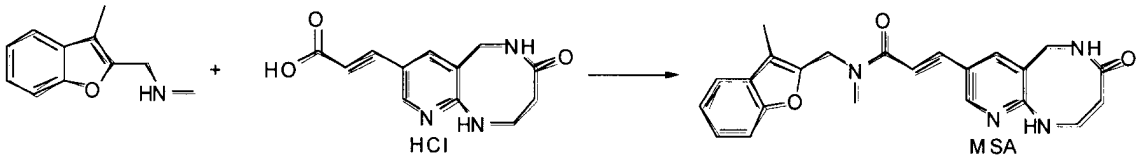
Preparation of (E)-tert-butyl 3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylate

Step C. A round bottom flask was charged with 8-bromo-2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one hydrobromide (0.5g, 1.48 mmol), *tert*-butyl acrylate (1.1 mL, 7.42 mmol), and (*i*-Pr)$_2$EtN (1.5 mL, 8.88 mmol) followed by 15 mL DMF. The solution was de-oxygenated with argon for 20 minutes. The mixture was treated with $Pd(OAc)_2$ (17 mg, 0.07 mmol) and P(*o*-tol)$_3$ (45 mg, 0.15 mmol) then heated to 100 °C for 18 hours (overnight). After cooling, the dark mixture was treated with activated charcoal (100 mg) and filtered through celite. The filtrate was partitioned between 150 mL CH_2Cl_2 and 50 mL H_2O in a separatory funnel. The organic layer was separated and treated with 3 x 50 mL saturated sodium chloride solution then dried over $MgSO_4$ and concentrated to give a brown residue. This residue was triturated with 20% Et_2O:hexanes to give a solid. The solid was collected and subjected to flash chromatography on silica gel using 5% MeOH:95% CH_2Cl_2. Yield: 200 mg (44.5 %); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.12 (d, 1H, J = 2.4 Hz), 7.74 (d, 1H, J = 2.4 Hz), 7.44 (m, 1H), 7.41 (d, 1H, J = 16.0 Hz), 6.94 (t, 1H, J = 6.4 Hz), 6.29 (d, 1H, J = 15.6 Hz), 4.46(d, 2H, J = 7.6Hz), 3.61(m, 2H), 2.73(t, 2H, J = 7.2 Hz), 1.46 (s, 9H); ESI MS *m/z* 304 $[C_{16}H_{21}N_3O_3 + H]^+$

Preparation of (E)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylic acid hydrochloride

Step D. A suspension of (E)-tert-butyl 3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylate(175 mg, 0.58 mmol) in 3 mL CH_2Cl_2 was treated with 3 mL of trifluoroacetic acid. The mixture became homogeneous and it was stirred at room temperature for 20 minutes. The solution was concentrated to dryness and treated with 1 mL 4M HCl in dioxane to give a creamish solid. The suspension was diluted with 10 mL Et_2O and sonicated . The solid was filtered and dried under reduced pressure overnight. Yield: 165 mg (100%) ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.28 – 8.27 (2 x s, 2H), 8.26 (br s, 1H), 7.60 (t, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 16.0 Hz), 6.50 (d, 1H, J = 16.0 Hz), 4.62 (br s, 2H), 3.85 (br s, 2H), 2.79(t, 2H, J = 7.2 Hz)

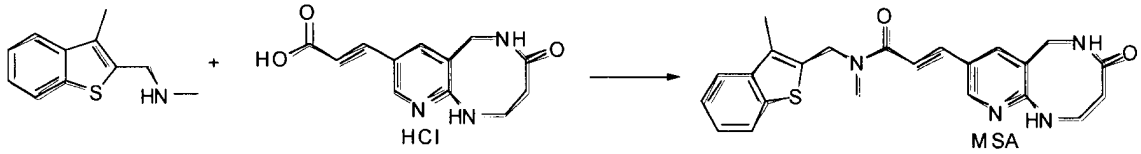
Preparation of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide di-methane sulfonic acid salt



Conditions: (i) EDC, HOBt, (*i*-Pr)$_2$EtN, DMF, 40 °C; (ii) Methanesulfonic acid, CH_2Cl_2, iPrOH.

The amide was prepared according to the general coupling procedure in a yield of 63%. To a cooled solution of (E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide (70 mg, 0.17 mmol) in 10 mL CH_2Cl_2 / 2 mL isopropanol mixture was added methanesulfonic acid (45 µL, 0.69 mmol). The solution was stirred for 1 hour at 0 °C then treated with 20 mL Et_2O with rapid stirring. A precipitate formed and it was filtered, washed with Et_2O (20 mL), collected and dried under reduced pressure to give a beige solid. Yield: 100 mg (99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 – 8.28 (m, 2H), 7.70 – 7.22(m, 6H), 4.79 and 4.66 (2 x s, 2H), 4.55 (br s, 2H), 3.88 (br s, 2H), 3.19 and 2.93 (2 x s, 3H), 2.81 (br s, 2H), 2.37 (s, 6H), 2.20 (s, 3H); ESI MS *m/z* 405 $[C_{23}H_{24}N_4O_3 + H]^+$

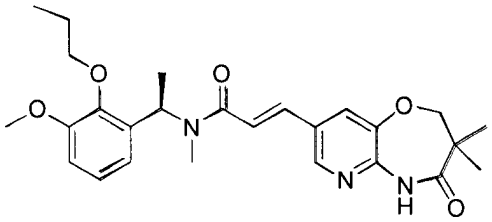
Example 28 Preparation of (E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide, di-methane sulfonic salt



Conditions: (i) EDC, HOBt, (*i*-Pr)$_2$EtN, DMF, 40 °C; (ii) Methanesulfonic acid, CH_2Cl_2, iPrOH

Prepared according to the procedure for the preparation of Example 27. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 7.21 (m, 8H), 5.11 and 4.89 (2 x s, 2H), 4.62 (br s, 2H), 3.85 (br s, 2H), 3.15 and 2.92 (2 x s, 3H), 2.80 (br s, 2H), 2.44 (s, 3H), 2.34 (s, 6H); ESI MS *m/z* 421 $[C_{23}H_{24}N_4O_2S + H]^+$

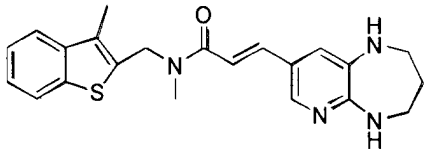
Example 29 Preparation of (*R*,*E*)-3-(3,3-dimethyl-2-oxo-1,2,3,5-tetrahydropyrido[2,3-e][1,4]oxazepin-7-yl)-*N*-(1-(3-methoxy-2-propoxyphenyl)ethyl)-*N*-methylacrylamide



EDC (0.14 g, 0.73 mmol) was added to a suspension of (*E*)-3-(3,3-dimethyl-2-oxo-1,2,3,5-tetrahydropyrido[2,3-e][1,4]oxazepin-7-yl)acrylic acid hydrochloride (0.16 g, 0.61 mmol), HOBt (0.091 g, 0.67 mmol), (*R*)-1-(3-methoxy-2-propoxyphenyl)-N-methylethanamine (0.15 g, 0.67 mmol) and (*i*-Pr)$_2$EtN (0.62 mL, 3.7 mmol) in DMF (5 mL). The mixture was allowed to stir overnight at 35 °C. The mixture was cooled to 0 °C and diluted with H_2O (30 mL) with rapid stirring. The resulting precipitate was filtered, washed with H_2O (20 mL) then dried under high vacuum. The solid was then triturated with Et_2O, and the resultant solid was collected, to yield 125 mg (44 %); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.25 (s, 1H), 7.92 and 7.86 (2 x s, 1H), 7.47-6.97 (m, 5H), 6.01 and 5.77 (2 x s, 1H), 4.07 (s, 2H), 3.83 and 3.73 (2 x m, 2H), 3.78

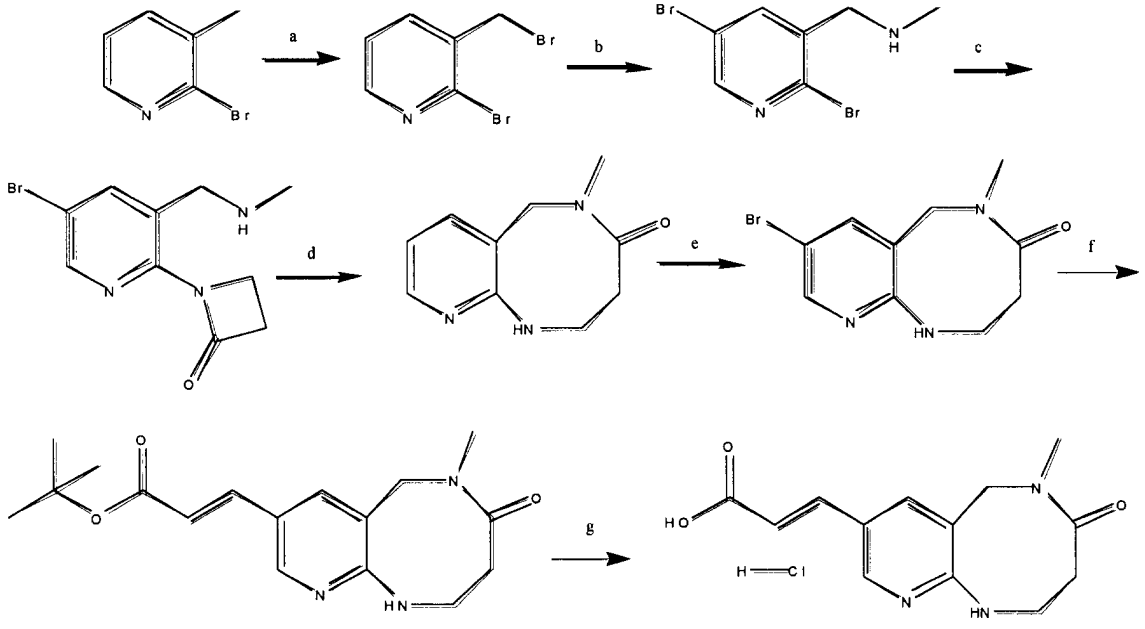
(s, 3H), 2.81 and 2.58 (2 x s, 3H), 1.65-1.38 (m, 5H), 1.19 (s, 6H), 0.86 and 0.77 (2 x m, 3H); ESI MS *m/z* 468 $[C_{26}H_{33}N_3O_5+ H]^+$

Example 30 (*E*)-*N*-methyl-*N*-((3-methylbenoz[*b*]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylamide



A solution of 8-bromo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepine (0.075 g, 0.31 mmol), N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide (0.15 g, 0.62 mmol), (*i*-Pr)$_2$EtN (0.16 mL, 0.93 mmol) in DMF (1.5 mL) and EtCN (1.5 mL) was de-oxygenated with Ar for 30 min. $Pd(OAc)_2$ (7 mg, 0.031 mmol) and P(*o*-tol)$_3$ (19 mg, 0.062 mmol) was added and the solution was de-oxygenated for an additional 15 min. The reaction was heated to 100 °C for 18 hrs at which time the reaction was cooled to room temperature and then filtered through a short column of silica washing with EtOAc (20 mL). The filtrate was washed with brine (2 x 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (silica gel, CH_2Cl_2/MeOH, 98:2) gave the title compound (27 mg, 22%) as a yellow powder; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, *J* = 7.5, 1H), 7.75-7.72 (m, 2H), 7.47-7.23 (m, 4H), 6.94 and 6.82 (2 x d, *J* = 14 Hz, 1H), 6.22 (s, 1H), 5.24 (s, 1H), 5.03 and 4.85 (2 x m, 2H), 3.18-2.90 (m, 7H), 2.45 (s, 3H), 1.68 (s, 2H); ESI MS *m/z* 393 $[C_{22}H_{24}N_4OS+ H]^+$

Example 31 Preparation of (E)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride



(a)NBS, BPO, $CHCl_3$; (b) $MeNH_2$, $MeOH/H_2O$; (c) CuI, N,N^1-dimethyldiamine, K_2CO_3, tol; (d) $Ti(o\text{-}iPr)_4$, tol; (e) Br_2, acetic acid; (f) *tert*-butyl acrylate, $Pd(OAc)_2$, P(*o*-tol)$_3$, (*i*-Pr)$_2$EtN, DMF; (g) (i). TFA, CH_2Cl_2; (ii). 4 M HCl/dioxane.

Preparation of 2-bromo-3-(bromomethyl)pyridine

Step A: A solution of 2-bromo-3-methylpyridine (1.0 mL, 8.98 mmol), benzoyl peroxide (217 mg, 0.90 mmol), and N-bromosuccinimide (1.76 g, 9.88 mmol) in 40 mL of chloroform was heated at reflux for 18h. At which point the solution was cooled to room temperature and the solution was diluted with 100 mL of water. The separated organic layer was then washed with $NaCO_3$(aq) and brine, dried over $MgSO_4$, and concentrated in vacuo. The orange oil crude product is used directly in the next step without further purification.

Preparation of (2,5-dibromopyridin-3-yl)-N-methylmethanamine

Step B: A solution of previously made 2-bromo-3-(bromomethyl)pyridine (8.98 mmol) in 5 mL of methanol was added dropwise to a solution of methyl amine (excess) in 5 mL methanol:water, 1:1 ratio. The resulting solution was let stir for 19h at room temperature. The solution was concentrated down in vacuo to ~5 mL and diluted with dichloromethane (25mL) and water (25 mL). The organic layer was dried over $MgSO_4$, and concentrated in vacuo to yield the crude orange oil product. This oil was subjected to flash chromatography on silica gel using 50% ethyl acetate:hexanes to give the title compound as an orange oil. Yield 1.1g (61% for 2 steps); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.33 (d, J=4.8 Hz, 1H), 7.93 (d, J=7.3 Hz, 1H), 7.50 (m, 1H), 3.93 (s, 2H), 2.46 (s, 3H); ESI MS *m/z* 201, 203 $[C_7H_9N_2Br + H]^+$

Preparation of 2-(5-bromo-3-((methylamino)methyl)pyridin-2-yl)cyclobutanone

Step C: A solution of (2,5-dibromopyridin-3-yl)-N-methylmethanamine(95 mg, 0.47 mmol), azetidinone (34 mg, 0.47 mmol), Cs_2CO_3 (308 mg, 0.94 mmol) in 5 mL of toluene was degassed with bubbling argon for 30 min followed by the addition of $Pd_2(dba)_3$ (6 mg, 0.01 mmol) and Xantphos (12 mg, 0.02 mmol). The resulting yellow solution was then stirred at 90°C 18h. The dark coloured solution was removed from the heat and poured over a pad of celite washing with 50 mL of ethyl acetate. The filtrate was diluted with 50 mL of water , the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified using flash chromatography on silica gel using 95% dichloromethane:methanol to obtain the product as a orange sticky solid. Yield 66 mg (73%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J=4.8 Hz, 1H), 7.28 (d, J=7.2 Hz, 1H), 6.78 (m, 1H), 4.92 (bs, 1H), 4.51 (s, 2H), 3.58 (q, J=6.0 Hz, 2H), 3.04 (t, J=6.8 Hz, 2H), 2.84 (s, 3H); ESI MS *m/z* 192 $[C_{10}H_{13}N_3O + H]^+$

Preparation of 5-methyl-2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one

Step D: A solution of 2-(5-bromo-3-((methylamino)methyl)pyridin-2-yl)cyclobutanone (66 mg, 0.35 mmol) and Ti(o-iPr)$_4$ (50 μL, 0.17 mmol) in toluene under argon was stirred at 110°C for 20h. The yellow solution was cooled to room temperature and concentrated in vacuo. The crude mixture was then redissolved in 10 mL of DCM:methanol (90:10) and passed through a silica gel plug and rinsed with a further 40 mL of the DCM/methanol solution to obtain the product as an off-white solid. Yield 63 mg (96%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J=4.8 Hz, 1H), 7.70 (d, 7.2 Hz, 1H), 6.77 (m,

1H), 4.96 (bs, 1H), 4.50 (s, 2H), 3.57 (q, J=6.4 Hz, 2H), 3.03 (t, J=6.8 Hz, 2H), 2.84 (s, 3H); ESI MS *m/z* 192 $[C_{10}H_{13}N_3O+ H]^+$

Preparation of 8-bromo-5-methyl-2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one

Step E: Bromine (189μL, 3.7 mmol) was added to a solution of 5-methyl-2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one (460 mg, 2.4 mmol) in 10 mL of acetic acid and stirred at room temperature for 17h. Add 30 mL of diethyl ether and collect orange solid product via suction filtration. Redissolve the solid in DCM and wash with $NaHCO_3$, dry the organic layer over $MgSO_4$, and concentrate in vacuo to obtain orange solid product. Yield 670 mg (quant); ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J=2.0 Hz, 1H), 7.50 (d, J=2.4 Hz, 1H), 5.17 (bs, 1H), 4.49 (s, 2H), 3.59 (bm, 2H), 3.04 (t, J=6.8 Hz, 2H), 2.85 (s, 3H); ESI MS *m/z* 270, 272 $[C_{10}H_{12}N_3OBr+ H]^+$

Preparation of (E)-tert-butyl 3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylate

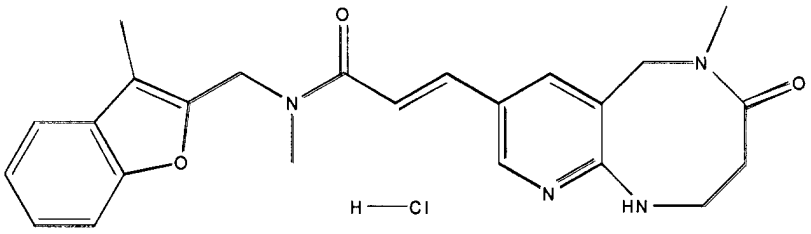
Step F: A suspension of 8-bromo-5-methyl-2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one (670 mg, 2.48 mmol), *tert*-butyl acrylate (1.8mL, 12.4 mmol) and $(i\text{-Pr})_2EtN$ (1.3 mL, 7.44 mmol) in 30 mL of DMF:Propionitriole (4:1) was de-oxygenated with Ar for 30 min. The mixture was treated with $Pd(OAc)_2$ (19.4 mg, 0.09 mmol) and $P(o\text{-tol})_3$ (51.7 mg, 0.18 mmol) then heated to 110 °C for 16 h. The hot mixture was filtered through a pad of celite. The filtrate was diluted with 100 mL H_2O then extracted with 2 x 100 mL ethyl acetate. The resulting brown solid was triturated with a solution of hexanes:ethyl acetate (4:1) followed by filtration to yield the brown solid product. Yield 391 mg (50%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.51 (s, 1H), 7.49 (d, J=16.4 Hz, 1H), 6.26 (d, J=16.0 Hz, 1H), 5.22 (bm, 1H), 4.55 (s, 2H), 3.66 (q, J=7.2 Hz, 2H), 3.07 (t, J=7.2 Hz, 2H), 2.81 (s, 3H), 1.55 (s, 9H); ESI MS *m/z* 318 $[C_{17}H_{23}N_3O_3+ H]^+$

Preparation of (E)-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylic acid hydrochloride

Step G: A suspension of (E)-tert-butyl 3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylate (391 mg, 1.23 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (10 mL). After stirring at room temperature for 2h, the solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl in dioxane (4 mL, 4.0 M) and sonicated until the oil was converted to a fine off-white solid.

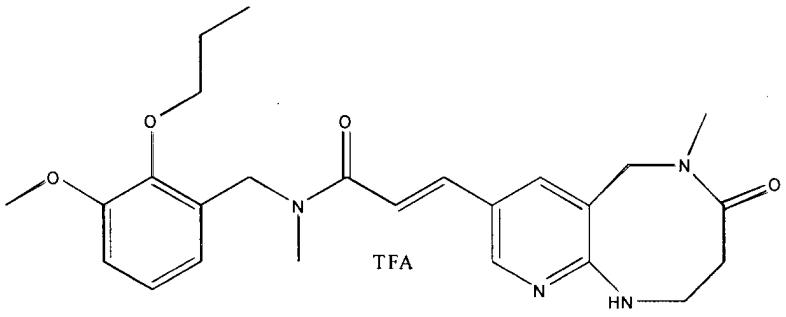
After stirring for 20 min, the suspension was concentrated. The solid was washed with Et_2O, isolated by filtration and dried under vacuum. Yield: 388 mg (quant); ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.04 (s, 1H), 7.48 (d, J=16.0 Hz, 1H), 6.48 (d, J=16.0 Hz, 1H), 4.78 (bs, 1H), 3.90 (s, 2H), 2.99 (s, 2H), 2.79 (s, 2H), 2.58 (s, 3H); ESI MS *m/z* 298 $[C_{13}H_{15}N_3O_3+ H]^+$

(E)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride



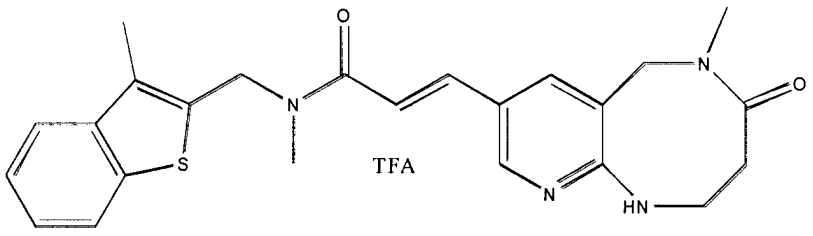
EDC (116 mg, 0.61 mmol) was added to a suspension of (E)-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylic acid hydrochloride (150 mg, 0.50 mmol), HOBt (75 mg, 0.55 mmol), methyl-(3-methyl-benzofuran-2-ylmethyl)-amine (97 mg, 0.55 mmol) and (*i*-Pr)$_2$EtN (0.43 mL, 2.5 mmol) in DMF (8 mL). The mixture was allowed to stir for 18h at 40 °C. The mixture was cooled to room temperature and diluted with ethyl acetate (40 mL) and washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$ and dried under high vacuum. The solid was then subjected to flash chromatography on silica gel using 5% methanol:dichloromethane to obtain 120 mg of yellow oil product. The product is redissolved in DCM followed by the addition of 1M HCl in diethyl ether (287 μL, 0.29 mmol) and sonicate for 5 min. Concentrate the suspension in vacuo to obtain the beige solid product. Yield: 130 mg (57%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.22 (bs, 1H), 7.65 (d, J=14.2 Hz, 1H), 7.50 (s, 1H), 7.41 (d, J=7.6 Hz, 1H), 7.25 (m, 2H), 7.03-6.79 (m, 1H), 5.22 (bm, 1H), 4.83 (s, 2H), 4.55 (s, 2H), 3.65 (q, J=7.6 Hz, 2H), 3.24 (s, 3H), 3.06 (t, J=7.2 Hz, 2H), 2.82 (s, 3H), 2.32 (s, 3H); ESI MS *m/z* 419 $[C_{24}H_{26}N_4O_3+ H]^+$

Example 32 Preparation of (E)-N-(3-methoxy-2-propoxybenzyl)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide



EDC (54 mg, 0.28 mmol) was added to a suspension of (E)-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylic acid hydrochloride (70 mg, 0.23 mmol), HOBt (34 mg, 0.25 mmol), (3-methoxy-2-propoxyphenyl)-N-methylmethanamine (52 mg, 0.25 mmol) and (i-Pr)$_2$EtN (0.20 mL, 1.2 mmol) in 5 mL of DMF:propionitrile (4:1). The mixture was allowed to stir for 17h at 40 °C. The mixture was cooled to room temperature and diluted with ethyl acetate (40 mL) and washed with water (50 mL) and $NaHCO_3$ (50 mL), dried over $MgSO_4$ and dried under high vacuum. The solid was then subjected to purification on Prep HPLC to obtain the product as a fluffy white solid. Yield 64 mg (62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.73 (s, 1H), 7.50 (m, 2H), 7.05 (m, 1H), 6.86 (m, 2H), 6.73 (d, J=7.6 Hz, 1H), 4.72 (s, 3H), 4.00 (m, 2H), 3.89 (s, 5H), 3.14 (m, 5H), 2.83 (s, 3H), 1.82 (q, J=6.8 Hz, 2H), 1.06 (t, J=7.6 Hz, 3H); ESI MS *m/z* 453 $[C_{25}H_{32}N_4O_4+ H]^+$

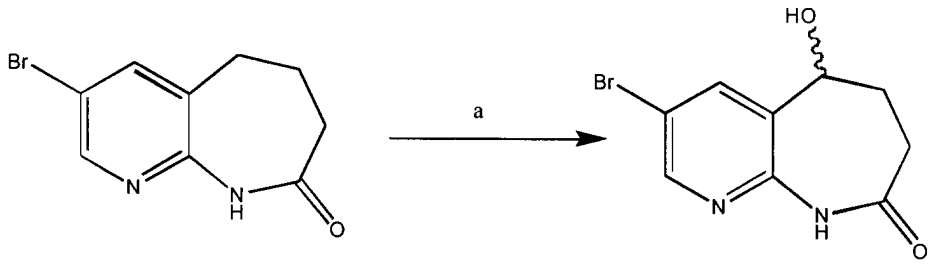
Example 33 Preparation of (E)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide



EDC (54 mg, 0.28 mmol) was added to a suspension of (E)-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylic acid hydrochloride (70 mg, 0.23 mmol), HOBt (34 mg, 0.25 mmol), N-methyl(3-methylbenzo[b]thiophen-2-yl)methanamine (48 mg, 0.25 mmol) and (i-Pr)$_2$EtN (0.20 mL, 1.2 mmol) in 5 mL of

DMF:propionitrile (4:1). The mixture was allowed to stir for 17h at 40 °C. The mixture was cooled to room temperature and diluted with ethyl acetate (40 mL) and washed with water (50 mL) and $NaHCO_3$ (50 mL), dried over $MgSO_4$ and dried under high vacuum. The solid was then subjected to purification on Prep HPLC to obtain the product as a fluffy white solid. Yield 54 mg (54%); ^1H NMR (400 MHz, $CDCl_3$) δ 10.41 (bs, 1H), 8.08 (s, 1H), 7.79-7.68 (m, 3H), 7.59 (d, J=15.2 Hz, 1H), 7.40 (m, 2H), 6.95-6.86 (m, 1H), 4.96 (s, 2H), 4.72 (bs, 2H), 3.90 (s, 2H), 3.15 (m, 5H), 2.84 (s, 3H), 2.46 (s, 3H); ESI MS *m/z* 435 $[C_{24}H_{26}N_4O_2S+ H]^+$

Example 34 Preparation of (E)-3-(5-hydroxy-8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide

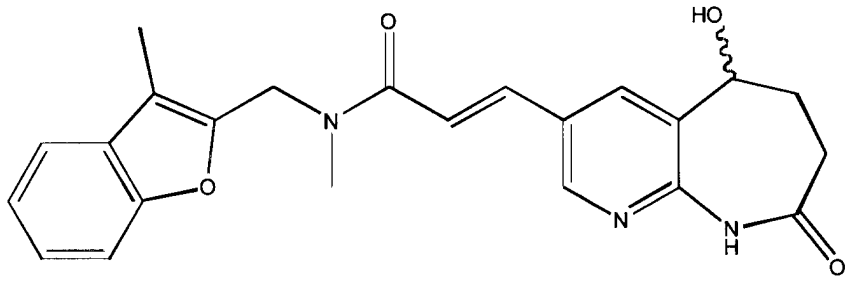


(a) NBS, BPO, $CHCl_3$, reflux

Preparation of 3-bromo-5-hydroxy-6,7-dihydro-5H-pyrido[2,3-b]azepin-8(9H)-one

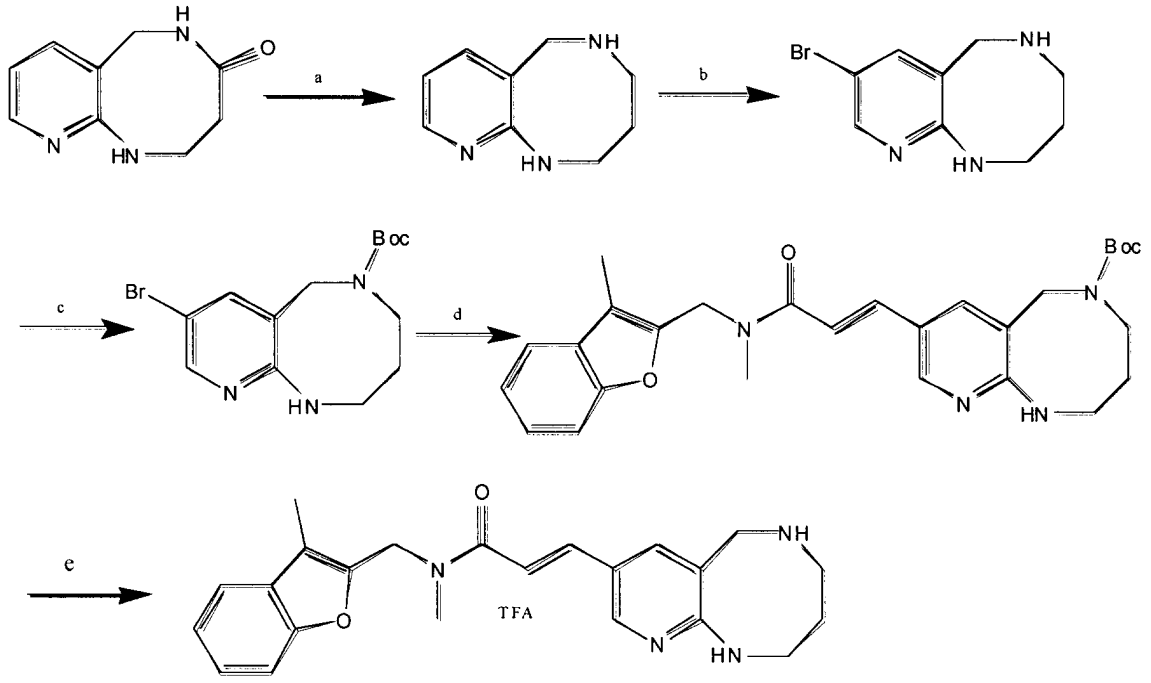
Step A: A solution of benzoyl peroxide (46 mg, 0.189 mmol), N-bromosuccinimide (251 mg, 1.42 mmol), and 3-bromo-6,7-dihydro-5H-pyrido[2,3-b]azepin-8(9H)-one (228 mg, 0.946 mmol) in 20 mL of chloroform is set at reflux temperature and stirred for 19h. The reaction is then cooled to room temperature, diluted with 20 mL DCM, washed with water and saturated sodium bicarbonate, organic layer dried over magnesium sulphate, and concentrated in vacuo. The resulting crude product was purified via prep column HPLC to obtain 150 mg of white powder product (>90% pure). A second prep HPLC afforded the pure compound as a fluffy white solid. Yield 46 mg (15%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.84 (s, 1H), 5.46 (m, 1H), 2.79-2.72 (m, 3H), 2.30 (m, 1H), 2.02 (s, 1H); ESI MS *m/z* 257, 259 $[C_9H_9N_2O_2Br+ H]^+$

Preparation of (E)-3-(5-hydroxy-8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide



A suspension of 3-bromo-5-hydroxy-6,7-dihydro-5H-pyrido[2,3-b]azepin-8(9H)-one (40 mg, 0.16 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (71 mg, 0.31 mmol) and (*i*-Pr)$_2$EtN (0.14 mL, 0.78 mmol) in 3 mL of DMF) was de-oxygenated with Ar for 30 min in a microwave reaction vial. The mixture was treated with Pd(OAc)$_2$ (4.0 mg, 0.02 mmol) and P(*o*-tol)$_3$ (9.0 mg, 0.04 mmol) then heated to 130 °C for 5 min in the microwave. The hot mixture was filtered through a pad of celite and washed liberally with ethyl acetate. The filtrate was diluted with 20 mL H_2O then extracted with 2 x 20 mL ethyl acetate. The resulting crude product was subjected to prep HPLC purification to yield 47 mg of product (75% pure). A seond prep HPLC purification was performed to obtain pure product as a fluffy white powder. Yield 5.1 mg (8%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.09 (s, 1H), 7.56 (d, J=7.4 Hz, 1H), 7.47 (m, 2H), 7.35-7.21 (m, 3H), 7.14 (d, J=15.2 Hz, 1H), 5.60 (s, 1H), 4.77 (s, 2H), 3.17 (s, 3H), 2.65 (s, 3H), 2.26 (m, 4H); ESI MS *m/z* 406 $[C_{23}H_{23}N_3O_4+ H]^+$

Example 35 Preparation of (E)-3-(1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamid



(a) LAH, THF, reflux,20h; (b) bromine, acetic acid, R.T., 20h; (c) Boc_2O, NEt_3, DCM, R.T., 20h; (d) R.H.S., $Pd(OAc)_2$, $P(o\text{-tol})_3$, $(i\text{-Pr})_2EtN$, DMF, 110°C, 20h; (e) TFA, DCM, R.T., 1h.

Preparation of 1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocine

Step A: A solution of 2,3,5,6-tetrahydropyrido[2,3-b][1,5]diazocin-4(1H)-one (400 mg, 33.5 mmol) in 30 mL THF was added dropwise to 22.6 mL of a 1M solution of lithium aluminum hydride in THF at 0°C. The resulting solution was heated to reflux and allowed to stir for 24h. The reaction was cooled to R.T. and the reaction was quenched with 1 mL of water, followed by 3 mL of 2M NaOH, and 3 mL water. The resulting slurry was poured through celite and washed with 100 mL ethyl acetate. The filtrate was concentrated in vacuo to yield the pure product as a white solid. Yield 180 mg (49%); %); ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J=5.2 Hz, 1H), 7.22 (d, J=7.6 Hz, 1H), 6.55

(m, 1H), 4.12 (s, 2H), 3.68 (t, J=6.0 Hz, 2H), 2.94 (m, 2H), 1.90 (m, 2H); ESI MS *m/z* 164 $[C_9H_{13}N_3+ H]^+$

Preparation of 8-bromo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocine

Step B: Bromine (33μL, 0.63 mmol) was added to a solution of 1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocine (69 mg, 0.42 mmol) in 5 mL of acetic acid and stirred at room temperature for 19h. Dilute with DCM and wash with satura ted $NaHCO_3$, wash the organic layer with brine, separate, dry over $MgSO_4$, and concentrate in vacuo to obtain orange solid product. Yield 91 mg (90%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.54 (s, 1H), 4.44 (s, 2H), 3.68 (s, 2H), 3.33 (m, 2H), 2.05 (m, 2H); ESI MS *m/z* 242, 244 $[C_9H_{12}N_3Br+ H]^+$

Preparation of tert-butyl 8-bromo-1,2,3,4-tetrahydropyrido[2,3-b][1,5]diazocine-5(6H)-carboxylate

Step C: NEt_3 (0.04 mL, 0.30 mmol) was added to a solution of 8-bromo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocine (55 mg, 0.23 mmol) in 3 mL of DCM under argon, followed by the addition of Boc_2O (57 mg, 0.25 mmol). The solution was stirred for 20h and then concentrated to dryness in vacuo. The crude mixture was then subjected to flash column chromatography on Silica gel with a solvent system of 95:5 (DCM:2M NH_3 in methanol) to yield the pure product as a yellow oil. Yield 49 mg (64%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.45 (s, 1H), 5.12 (bs, 1H), 4.43 (s, 2H), 3.46 (bs, 4H), 1.91 (bs, 2H), 1.37 (s, 9H); ESI MS *m/z* 342, 344 $[C_{12}H_{20}N_3O_2Br+ H]^+$

Preparation of (E)-tert-butyl 8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-enyl)-1,2,3,4-tetrahydropyrido[2,3-b][1,5]diazocine-5(6H)-carboxylate

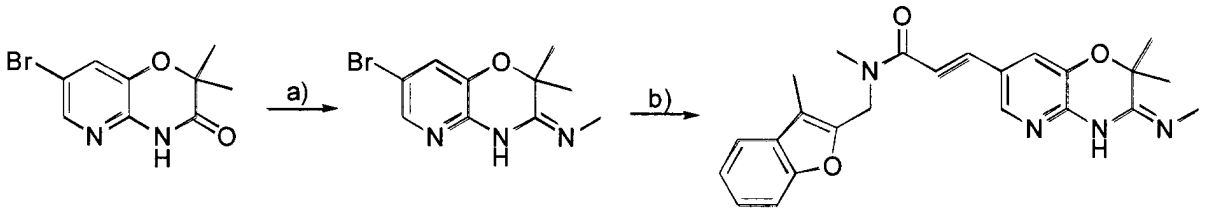
Step D: A suspension of tert-butyl 8-bromo-1,2,3,4-tetrahydropyrido[2,3-b][1,5]diazocine-5(6H)-carboxylate (45 mg, 0.13 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (90 mg, 0.39 mmol) and $(i\text{-}Pr)_2EtN$ (0.11 mL, 0.66 mmol) in 3.75 mL of DMF:propionitrile (4:1) was de-oxygenated with Ar for 30 min. The mixture was treated with $Pd(OAc)_2$ (3.0 mg, 0.013 mmol) and $P(o\text{-}tol)_3$ (8.0 mg, 0.026 mmol) then heated to 110 °C for 20h. The hot mixture was filtered through a pad of celite and washed with ethyl acetate 2 x 20 mL. The filtrate was concentrated in vacuo to obtain crude brown oil product. The resulting crude product was subjected to

prep HPLC purification to obtain pure product as an off-white solid. Yield 39 mg (60%); ESI MS *m/z* 491 $[C_{28}H_{34}N_4O_4+ H]^+$

Preparation of (E)-3-(1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide

Step E: (E)-tert-butyl 8-(3-(methyl((3-methylbenzofuran-2-yl)methyl)amino)-3-oxoprop-1-enyl)-1,2,3,4-tetrahydropyrido[2,3-b][1,5]diazocine-5(6H)-carboxylate (49 mg, 0.1 mmol) was dissolved in 5 mL of DCM followed by the addition of trifluoroacetic acid (5 mL). The solution was stirred for 1.5h, then concentrated in vacuo, and subjected to prep HPLC purification to obtain the product as a white solid. Yield 25 mg (64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (bs, 1H), 8.01 (m, 2H), 7.50-7.22 (m, 6H), 6.86 (d, J=16.0 Hz, 1H), 4.79 (s, 2H), 4.66 (s, 2H), 3.88 (s, 2H), 3.25 (s, 2H), 3.10 (s, 3H), 2.29 (bs,5H); ESI MS *m/z* 391 $[C_{23}H_{26}N_4O_2+ H]^+$

Example 36 Preparation of (E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride



Reagents and conditions: a) PCl_5, μwave then NH_2Me. b) N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide, DIPEA, $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, DMF, then HCl.

a) (E)-N-(7-bromo-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-ylidene)methanamine:

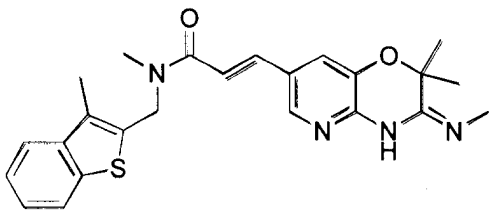
A dichloroethane (5 mL) solution of 7-bromo-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-one (520 mg, 2 mmol) and phosphorus pentachloride (840 mg, 4 mmol) was irradiated in a microwave oven for 10 min at 160 °C. The solution was cooled to -78 °C and methylamine (2M in THF) was added it slowly until it became permanently basic. The mixture was diluted with CH_2Cl_2, washed with dilute solution of NaOH, dried and

evaporated. Crystallization from CH_2Cl_2/hexane afforded 480 mg (89%) of the title compound. ^1H NMR (300 MHz, $CDCl_3$, δ) 8.07 (d, J=2.1 Hz, 1H), 7.21 (d, J=2.1 Hz, 1H), 4.9 (s, br, 1H), 3.06 (d, J=4.5 Hz, 3H), 1.46 (s, 6H). MS (ESI) *m/e* 270 $(M + H)^+$.

b) (E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride:

A DMF (3 mL) solution of (E)-N-(7-bromo-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-ylidene)methanamine (271 mg, 1 mmol), N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide (345 mg, 1.5 mmol) and diisopropylethylamine (0.52 mL, 3 mmol) was purged with Argon for 10 min. $Pd(OAc)_2$ (24 mg, 0.1 mmol) and $P(o\text{-}Tol)_3$ (61 mg, 0.2 mmol) was added and then the Argon purge was repeated. The mixture was irradiated in a microwave oven for 10 min at 160 °C under Argon. Upon cooling, the mixture was diluted with water and extracted with EtOAc. The crude product was purified by chromatography (silica, 0-4% MeOH in CH_2Cl_2). The free base was turned into the HCl salt by addition of HCl (1 mL, 1M in Et_2O) to its CH_2Cl_2 solution and evaporation to afford 230 mg (55%) of the title compound. as a mixture of amide rotamers. ^1H NMR (300 MHz, $CDCl_3$, δ, free base) 8.20 (s, 1H), 7.69 and 7.85 (2s, 1H), 7.5-6.7 (m, 6H), 5.14 (s, br, 1H), 4.83 and 4.71 (2s, 2H), 3.21 and 3.10 (2s, 3H), 3.09 (d, J=4.8 Hz, 3H), 2.31 (s, 3H), 1.49 (s, 6H). MS (ESI) *m/e* 419 $(M + H)^+$.

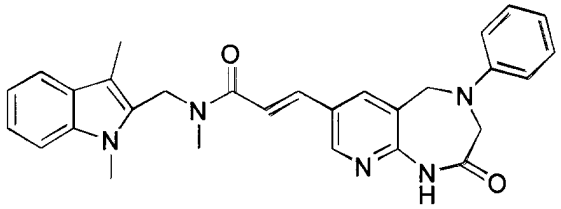
Example 37 Preparation of (E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide



A DMF (3 mL) solution of (E)-N-(7-bromo-2,2-dimethyl-2H-pyrido[3,2-b][1,4]oxazin-3(4H)-ylidene)methanamine (271 mg, 1 mmol), N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acryl-amide (367 mg, 1.5 mmol) and

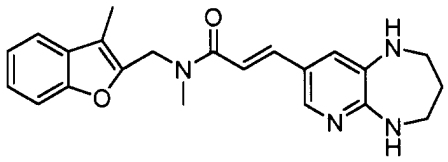
diisopropylethylamine (0.52 mL, 3 mmol) was purged with Argon for 10 min. $Pd(OAc)_2$ (24 mg, 0.1 mmol) and $P(o\text{-}Tol)_3$ (61 mg, 0.2 mmol) was added and then the Argon purge was repeated. The mixture was irradiated in a microwave oven for 10 min at 160 °C under Argon. Upon cooling, the mixture was diluted with water and extracted with EtOAc. The crude product was purified by chromatography (silica, 0-4% MeOH in CH_2Cl_2). The free base was turned into the HCl salt by addition of HCl (1 mL, 1M in Et_2O) to its CH_2Cl_2 solution and evaporation to afford 287 mg (66%) of the title compound. as a mixture of amide rotamers. ^1H NMR (300 MHz, $CDCl_3$, δ, free base) 8.21 (s, 1H), 7.8-7.6 (m, 3H), 7.4-7.2 (m, 3H), 6.9-6.7 (m, 1H), 5.30 (s, br, 1H), 4.95 and 4.88 (2s, 2H), 3.10 (m, 6H), 2.43 (s, 3H), 1.49 (s, 6H). MS (ESI) *m/e* 435 $(M + H)^+$.

Example 38 *E*)-*N*-((1,3-dimethyl-1*H*-indol-2-yl)methyl)-*N*-methyl-3-(2-oxo-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide



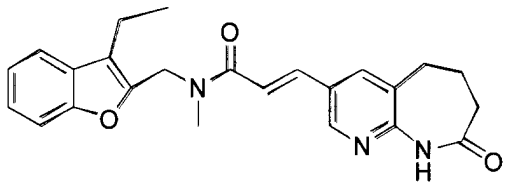
A solution of *N*-((1,3-dimethyl-1*H*-indol-2-yl)methyl)-N-methylacrylamide (92 mg, 0.3 mmol) and DIPEA (0.16 mL, 0.9 mmol) in DMF (5 mL) was purged with argon for 10 min. $Pd(oAC)_2$ (6 mg, 0.03 mmol) and $P(o\text{-}Tol)_3$ (18 mg, 0.06 mmol) were added and the mixture was purged with argon and heated to 100 °C. The crude mixture was filtered and water was added. The precipitate that formed was washed with ethyl acetate and dried to afford the title compound (144 mg, 74%). ^1H NMR (400 MHz, DMSO-d_6) δ 10.06 – 9.95 (rotamers, s, 1H), 8.32 (d, *J* = 8.0Hz, 2H), 7.57 (s, 1H), 7.50 (t, *J* = 7.6Hz, 2H), 7.38 (m, 3H), 7.12 (t, *J* = 7.6Hz, 2H), 7.03 (t, *J* = 7.6Hz, 1H), 6.84 – 6.35 (m, 2H), 4.90 – 4.80 (rotamers, s, 2H), 4.80 (s, 2H), 4.50 (s, 3H), 3.63 (s, 3H), 2.98 (s, 2H), 2.32 (s, 3H); MS (ESI): *m/e* 480.2 $(C_{29}H_{29}N_5O_2 + H)^+$.

Example 39 (E)-*N*-methyl-*N*-((3-methylbenzofuran-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylamide



A solution of 8-bromo-2,3,4,5-tetrahydro-1H-pyrido[2,3-b][1,4]diazepine (0.15 g, 0.66 mmol), N-methyl-N-((3-methyl benzofuran-2-yl)methyl)acrylamide (0.30 g, 1.32 mmol), $(i\text{-Pr})_2$EtN (0.34 mL, 2.0 mmol) in DMF (7 mL) was de-oxygenated with Ar for 30 min. $Pd(OAc)_2$ (15 mg, 0.066 mmol) and P(*o*-tol)$_3$ (40 mg, 0.13 mmol) was added and the solution was de-oxygenated for an additional 15 min. The reaction was heated to 100 °C for 18 hrs at which time the reaction was cooled to room temperature and then filtered through a short column of silica washing with EtOAc (20 mL). The filtrate was washed with brine (2 x 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo.* Purification by column chromatography (silica gel, CH_2Cl_2/MeOH, 99:1) gave the title compound (111 mg, 45%) as a yellow powder; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6, 1H), 7.43 and 7.39 (2 x s, 1H), 7.35-7.22 (m, 3H), 7.08 and 6.82 (2 x d, J = 15, 1H), 6.22 (s, 1H), 5.25 (s, 1H), 4.90 and 4.78 (2 x s, 2H), 3.14-2.93 (m, 7H), 2.26 (s, 3H), 1.68 (m, 2H); ESI MS *m/z* 377 $[C_{22}H_{24}N_4O_2 + H]^+$

Example 40 (E)-N-((3-ethylbenzofuran-2-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide



Using methods described above the title compound was prepared. Purification by preparative HPLC (water/acetonitrile/0.05% TFA mixture) gave the title compound (70

mg, >95% by HPLC) as a white solid and a mixture of amide rotomers: ESI MS *m/z* 4o4 $[C_{24}H_{25}N_3O_3+H]^+$.

References

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Heath, *et al. Nature* 406: 145 **2000**; Bergler, et al, **1994**, *J.Biol.Chem. 269*, 5493-5496; Heath, et al, **1996**, *J.Biol.Chem. 271*, 1833-1836; Grassberger, *et al* ,**1984** *J. Med Chem 27* 947-953; Turnowsky, *et al*, **1989**, *J.Bacteriol., 171*, 6555-6565; McMurry, et al, **1998** *Nature 394,* 531-532; Levy, et al, **1999** *Nature 398*, 383-384; Ward, et al ,**1999** *Biochem. 38,* 12514-12525; Heck, *Org. Reactions* **1982**, *27*, 345; *J. Het. Chem.* **1978**, *15*, 249-251; Morb. Mortal Wkly Rep. **1998**; 46:71-80; Standards, N.C.f.C.L., Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard - Fifth Edition. 2000; Baxter, D.F., et al., A novel membrane potential-sensitive fluorescent dye improves cell-based assays for ion channels. J Biomol Screen, **2002** 7(1): p. 79-85; Ahmed, S.A., R.M. Gogal, Jr., and J.E. Walsh, A new rapid and simple non-radioactive assay to monitor and determine the proliferation of lymphocytes: an alternative to [3H]thymidine incorporation assay. J Immunol Methods, **1994** 170(2) : p. 211-24 ; http ://bbrp.llnl.gov/bbrp/html/microbe.html ; http ://artedi.ebc.uu.se/Projects/Francisella/ ; U.S. Patent Application Nos. 08/790,043 ; 10/009,219, 10/089,019 ; 09/968,129 ; 09/968,123 ; 09/968,236 ; 09/959,172 ; 09/979,560 ; 09/980,369 ; 10/089,755 ; 10/089,739 ; 10/089,740 ; PCT Application Nos. PCT/US03/38706; WO 0027628; WO 0210332; U.S. Provisional Application Nos. 60/431,406; 60/465,583; U.S. Patent Nos. 6,531,126; 6,527,759; 6,518,270; 6,518,239; 6,517,827; 6,461,829; 6,448,054; 6,423,341; 6,495,551; 6,486,149; 6,441,162; 6,436,980; 6,399,629; 6,518,263; 6,503,881; 6,503,881; 6,486,148; 6,465,429; 6,388,070; 6,531,649; 6,531,465; 6,528,089; 6,521,408; 6,518,487; 6,531,508; 6,514,962; 6,503,953; 6,492,351; 6,486,148; 6,461,607; 6,448,054; 6,495,161; 6,495,158; 6,492,351; 6,486,165; 6,531,465; 6,514,535; 6,489,318; 6,497,886; 6,503,953; 6,503,539, 6,500,459; 6,492,351; 6,500,463; 6,461,829; 6,448,238; 6,432,444; 6,333,045; 6,291,462; 6,221,859; 6,514,986; 6,340,689;

6,309,663; 6,303,572; 6,277,836; 6,367,985; 6,468,964; 6,461,607; 6,448,449; 6,436,980; 6,423,741; 6,406,880; 6,395,746; 6,346,391; 6,294,192; 6,267,985; 6,235,908; 6,515,113; 6,509,327; 6,503,955; 6,525,066; 6,531,291; 6,517,827; 6,514,953; 6,514,541; 6,428,579; 6,451,339; 6,461,607; 6,461,829; 6,503,906; 6,518,239; 6,133,260; 6,174,878; 6,184,380; 6,187,341; 6,194,429; 6,194,441; 6,198,000; 6,221,859; 6,221,864; 6,239,113; 6,239,141; and 6,248,363.

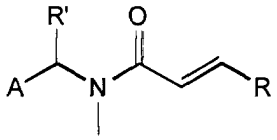
Equivalents

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

What is claimed is:

1. A compound of formula **I**:



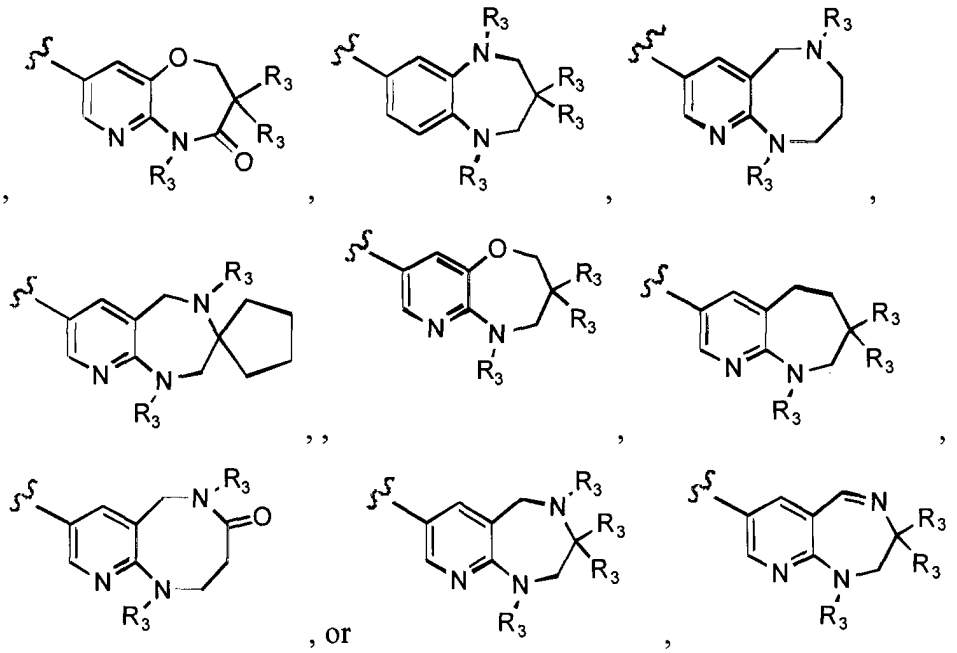
I

wherein, independently for each occurrence,

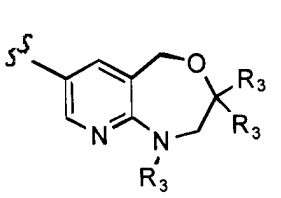
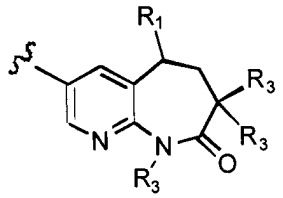
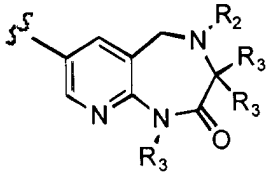
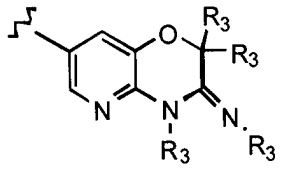
A is a monocyclic ring of 4-7 atoms containing 0-2 heteroatoms, a bicyclic ring of 8-12 atoms containing 0-4 heteroatoms or a tricyclic ring of 8-12 atoms containing 0-6 heteroatoms wherein the rings are independently aliphatic, aromatic, heteroaryl or heterocyclic in nature, the heteroatoms are selected from N, S or O and the rings are optionally substituted with one or more groups selected from C_{1-4} alkyl, OR", CN, OCF_3, F, Cl, Br, I; wherein R" is H, alkyl, aralkyl, or heteroaralkyl;

R' is H or alkyl;

R is



, or

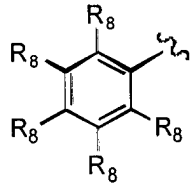
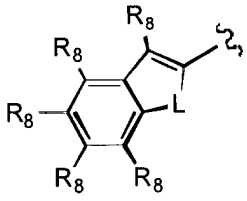
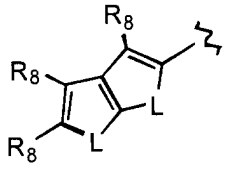
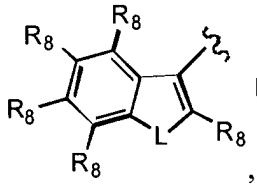
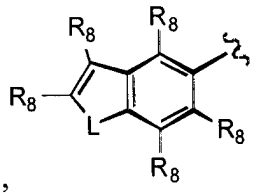
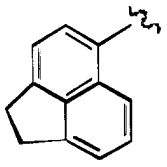
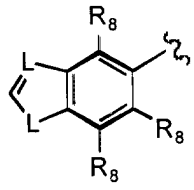
wherein, independently for each occurrence,

R_1 is H or OH;

R_2 is OH or -Ar; and

R_3 is each independently H, alkyl, carbonyl, sulfonyl, or aryl; and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein A is selected from the following:

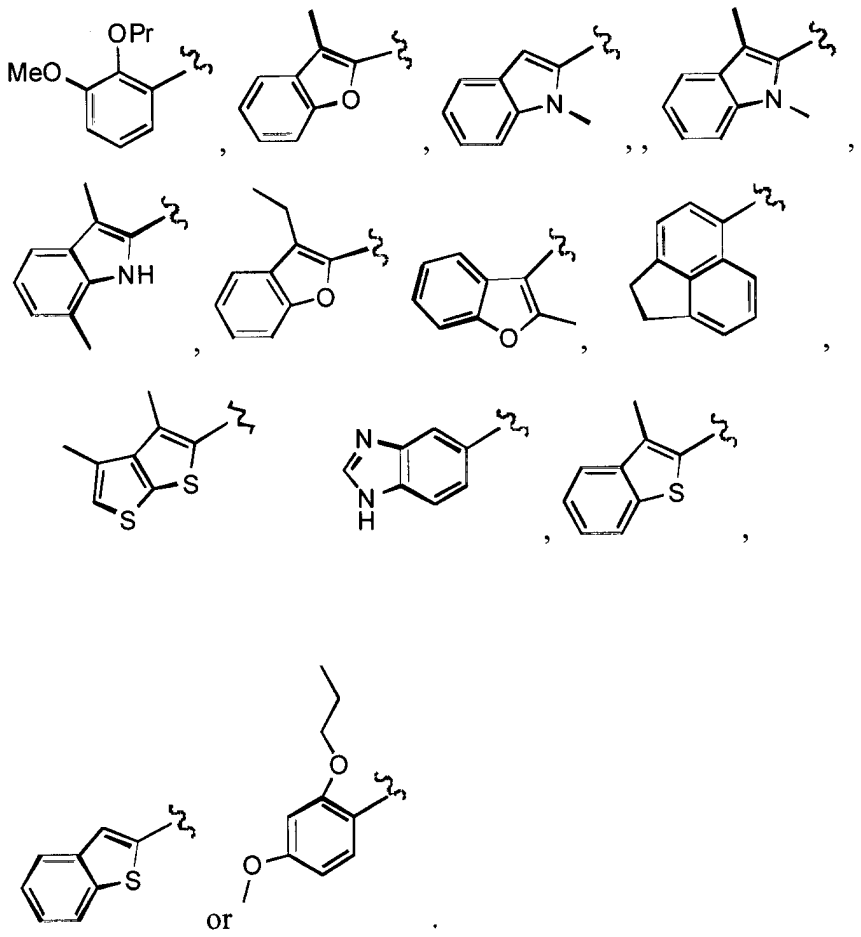






or


wherein, independently for each occurrence,

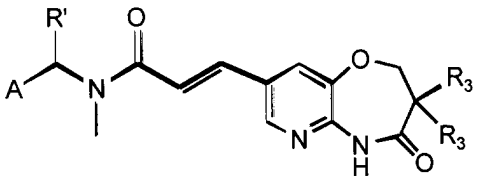
R_8 is H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkenyl, OR", CN, OCF_3, F, Cl, Br, I; wherein R" is H, alkyl, aralkyl, or heteroaralkyl; and

L is each independently O, S, or NR_3.

3. The compound of claim 1, wherein A is selected from the following:



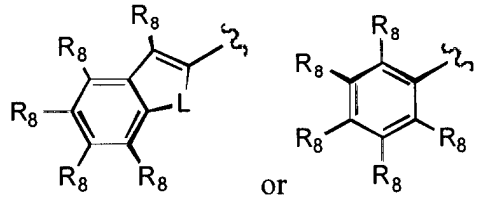
4. The compound of claim 2, wherein the compound has formula **Ia**:



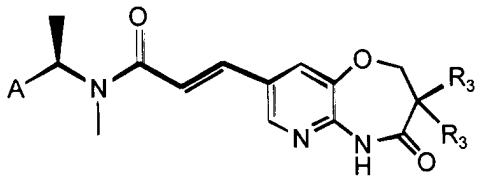
Ia

wherein R_3 is defined previously; and

A is selected from the following:



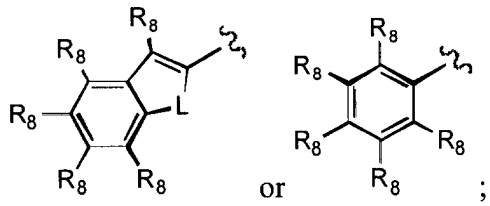
5. The compound of claim 2, wherein the compound has formula **Ib**:



Ib

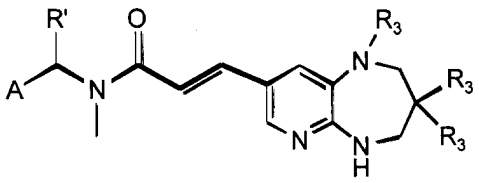
wherein,

A is selected from the following:



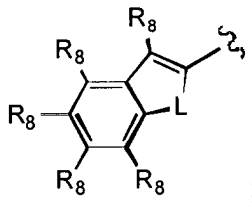
and wherein R_3 and R_8 are defined previously.

6. The compound of claim 2, wherein the compound has formula **Ic**:



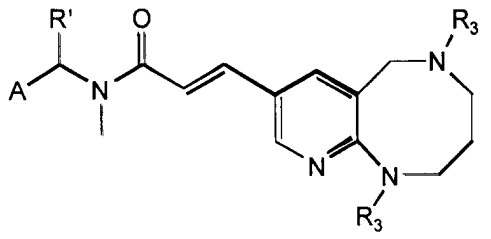
Ic

wherein A is:



and wherein R_3 and R_8 are defined previously.

7. The compound of claim 2, wherein the compound has formula **Id**:

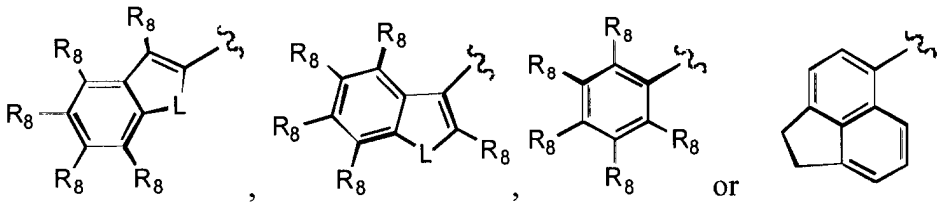


Id

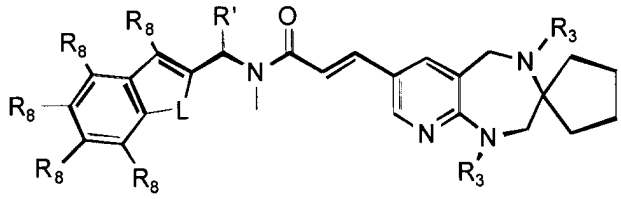
wherein,

R' and R_3 are as defined previously, and

A is selected from the following:



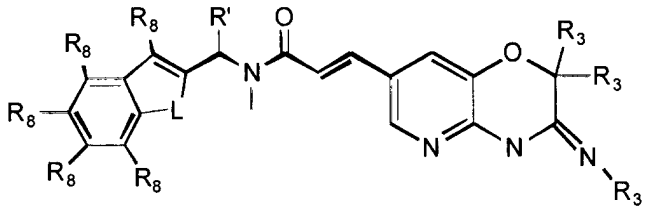
8. The compound of claim 2, wherein the compound has formula **Ie**:



Ie

and wherein R', R_3 and R_8 are defined previously.

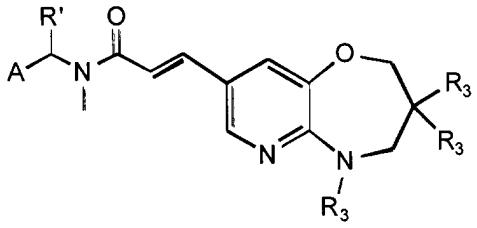
9. The compound of claim 2, wherein the compound has formula **If**: :



If

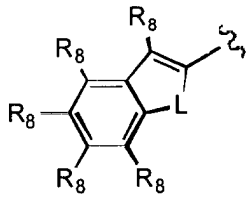
and wherein R', R_3 and R_8 are defined previously

10. The compound of claim 2, wherein the compound has formula **Ig**:



Ig

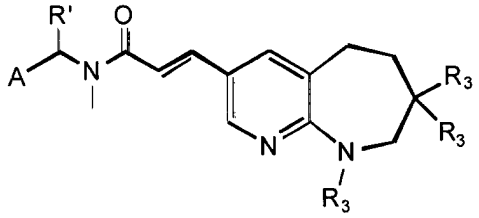
wherein A is:



;

and wherein R', R_3 and R_8 are defined previously.

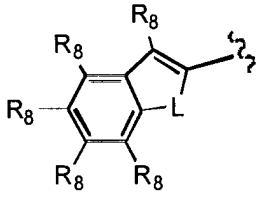
11. The compound of claim 2, wherein the compound has formula **Ih**:



Ih

wherein,

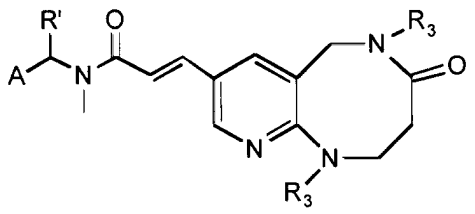
A is:



;

and R_8, R' and R_3 are as previously defined.

12. The compound of claim 2, wherein the compound has formula **Ii**:

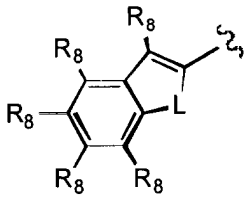


Ii

wherein,

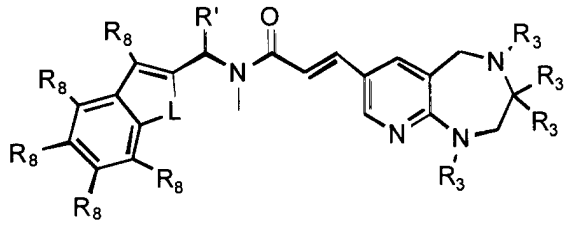
R' and R_3 are as previously defined, and

A is:



; wherein R_8 is previously defined.

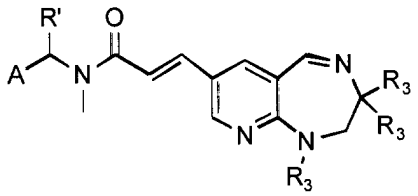
13. The compound of claim 2, wherein the compound has formula **Ij**:



Ij

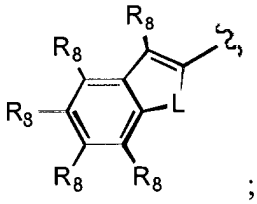
and R_8, R' and R_3 are as previously defined.

14. The compound of claim 2, wherein the compound has formula **Ik**:



Ik

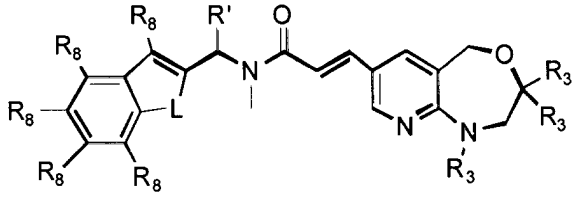
wherein A is:



;

and R_8, R' and R_3 are as previously defined.

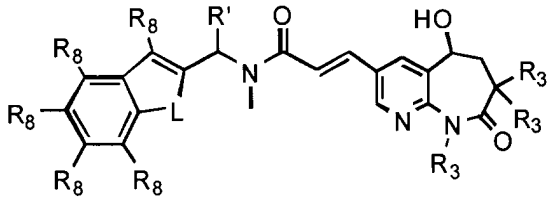
15. The compound of claim 2, wherein the compound has formula **II**:



II

and R_8, R' and R_3 are as previously defined.

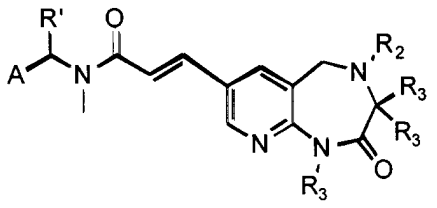
16. The compound of claim 2, wherein the compound has formula **Im**:



Im

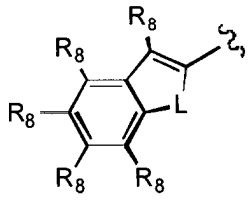
and R_8, R' and R_3 are as previously defined.

17. The compound of claim 2, wherein the compound has formula **In**:



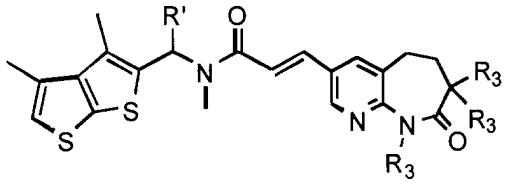
In

wherein A is selected from the following:



and R_8, R_2, R' and R_3 are as previously defined.

18. The compound of claim 2, wherein the compound has formula **Io**:



Io

and R' and R_3 are as previously defined.

19. The compound of claim 1, wherein the compound is selected from the following:

(*E*)-3-(7,7-Dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-(3-methoxy-2-propoxy-benzyl)-*N*-methylacrylamide;

(*E*)-3-(7,7-Dimethyl-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-*N*-methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)acrylamide;

3-(7,7-dimethyl-8-oxo-6,7,8,9-tetrahydro-5-oxa-1,9-diaza-benzocyclohepten-3-yl)-N-methyl-N-[1-(R)-(3-methyl-benzofuran-2-yl)-ethyl]acrylamide;

(*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide;

(*E*)-3-(3,3-Dimethyl-2,3-dihydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride;

(*E*)-7-{2-[Methyl-(3-methylbenzofuran-2-ylmethyl)carbamoyl]vinyl}-1,2,3,5-tetrahydropyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid *tert*-butyl ester;

(*E*)-3-(4-Acetyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methylbenzofuran-2-ylmethyl)acrylamide hydrochloride;

N-Methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide;

N-Methyl-*N*-(1-methyl-1H-indol-2-ylmethyl)-3-(5,7,8,9-tetrahydro-6-oxa-1,9-diaza-benzocyclohepten-3-yl)-acrylamide;

N-Methyl-N-(3-methyl-benzofuran-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride;

N-Methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(4-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide dihydrochloride;

(E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride;

(E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide hydrochloride;

(E)-tert-butyl 7-(3-(((1,2-dihydroacenaphthylen-5-yl)methyl)(methyl)amino)-3-oxoprop-1-enyl)-2,3-dihydro-1H-pyrido[2,3-e][1,4]diazepine-4(5H)-carboxylate;

(S,E)-3-(3-benzyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetate;

(E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride;

(E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride;

(E)-3-(3,3-dimethyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide hydrochloride;

(E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-(methylsulfonyl)-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride;
(E)-3-(3-spirocyclopentyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid;
(E)-N-methyl-3-((S)-3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methyl-3a,7a-dihydrobenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid;
(R,E)-N-methyl-3-(3-methyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide trifluoroacetic acid salt;
(E)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)-3-(4-phenyl-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide;
(E)-N-methyl-N-((3-methyl-1H-indol-2-yl)methyl)-3-(1,2,3,5-tetrahydropyrido[2,3-e][1,4]oxazepin-7-yl)acrylamide; (*E*)-3-(2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)-*N*-methyl-*N*-((3-methyl-1*H*-indol-2-yl)methyl)acrylamide;
(*R*,*E*)-(3,3-dimethyl-4-oxo-2,3,4,5-tetrahydropyrido[3,2-*b*][1,4]oxazepin-8-yl)-*N*-(1(3-ethylbenzofuran-2-yl)ethyl)-*N*-methylacrylamide;
(E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide, di-methane sulfonic salt;
(E)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)-3-(4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide, di-methane sulfonic salt;
(*R,E*)-3-(3,3-dimethyl-2-oxo-1,2,3,5-tetrahydropyrido[2,3-e][1,4]oxazepin-7-yl)-*N*-(1-(3-methoxy-2-propoxyphenyl)ethyl)-*N*-methylacrylamide;
(*E*)-*N*-methyl-*N*-((3-methylbenoz[*b*]thiophen-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylamide;
(E)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride;
(E)-N-(3-methoxy-2-propoxybenzyl)-N-methyl-3-(5-methyl-4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)acrylamide; (E)-N-methyl-3-(5-methyl-

4-oxo-1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide;
(E)-3-(5-hydroxy-8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide;
(E)-3-(1,2,3,4,5,6-hexahydropyrido[2,3-b][1,5]diazocin-8-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide; (E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzofuran-2-yl)methyl)acrylamide hydrochloride;
(E)-3-((E)-2,2-dimethyl-3-(methylimino)-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-7-yl)-N-methyl-N-((3-methylbenzo[b]thiophen-2-yl)methyl)acrylamide;
E)-*N*-((1,3-dimethyl-1*H*-indol-2-yl)methyl)-*N*-methyl-3-(2-oxo-4-phenyl-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide;
(E)-*N*-methyl-*N*-((3-methylbenzofuran-2-yl)methyl)-3-(2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*b*][1,4]diazepin-8-yl)acrylamide; (E)-N-((3,4-dimethylthieno[2,3-b]thiophen-2-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide; (E)-N-((3-ethylbenzofuran-2-yl)methyl)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylamide.

20. The compound of claim 1, wherein the compound inhibits FabI with a K_i of about 5 μM or less, about 1 μM or less, about 100 nM or less, about 10 nM or less, or about 1 nM or less.

21. The compound of claim 1, wherein the compound inhibits FabI with an IC_{50} of about 30 μM or less, about 1 μM or less, about 100 nM or less, or about 10 nM or less.

22. The compound of claim 1, wherein the compound inhibits FabI with an MIC of about 32 μg/mL or less, about 16 μg/mL or less, or about 8 μg/mL or less, about 4 μg/mL or less, about 2 μg/mL or less, about 1 μg/mL or less, about 0.5 μg/mL or less, about 0.25 μg/mL or less, or about 0.125 μg/mL or less.

23. A pharmaceutical composition comprising a compound of any one of claims 1-19 and a pharmaceutically acceptable carrier or excipient.

24. The composition of claim 23, wherein the composition is formulated for one of: intraveneous administration, injectable administration, topical application, as a suppository, or systemic administration.

25. The composition of claim 23, wherein the composition is formulated for oral administration.

26. The composition of claim 25, wherein the composition is formulated in tablets such that the amount of compound provided in 20 tablets, if taken together, provides a dose of at least the ED_{50} but no more than ten times the ED_{50}.

27. The composition of claim 26, wherein the composition is formulated for parenteral administration such that the amount of compound provided in 20 cc bolus injection provides a dose of at least the ED_{50} but no more that ten times the ED_{50}.

28. The composition of claim 24, wherein the composition is formulated for intravenous infusion such that the amount of compound provided in one liter of intravenous injectable solution provides a dose of at least the ED_{50} but no more that ten times the ED_{50}.

29. A pill for reducing bacterial levels in a subject with a bacteria related illness, comprising a compound of claim 1, wherein the pill provides effective bacterial treatment for at least about 8 hours, for at least about 12 hours, for at least about 24 hours, and/or for at least about one week.

30. A pack of pills in number sufficient for treatment of a bacterial illness, comprising a plurality of pills wherein each pill comprises a compound of claim 1.

31. The pack of pills of claim 30, wherein the pack contains at least 5 pills, at least 10 pills, or at least 20 pills.

32. A method of treating a subject with a bacterial illness comprising administering to the subject the pharmaceutical composition of claim 23.

33. The method of claim 32, wherein the compound inhibits the Fab I activity of a microbe with an IC_{50} at least 1 order of magnitude lower than the IC_{50} for inhibiting enoyl CoA hydratase of a mammal.

34. The method of claim 33, wherein the mammal is a human.

35. A method of disinfecting an inanimate surface comprising administering to the inanimate surface a compound of any one of claims 1-19.

36. A kit comprising the pharmaceutical composition of claim 23 and instructions for use thereof.

5

Figure 1.

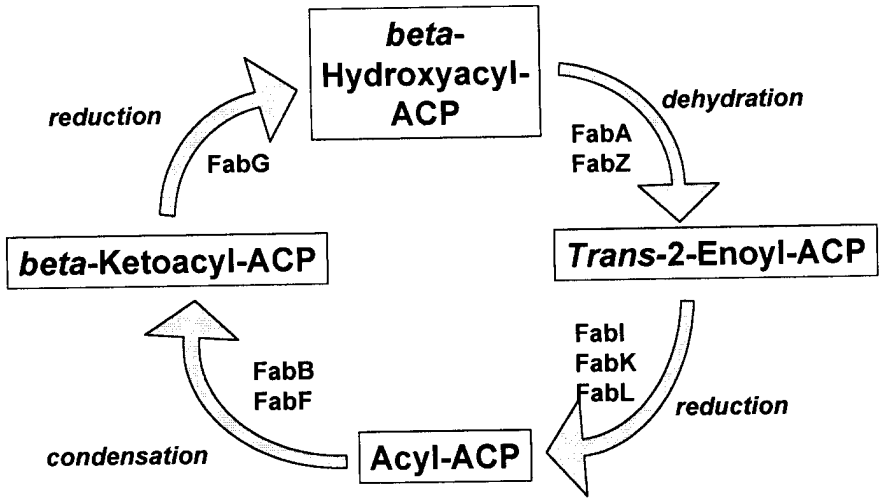
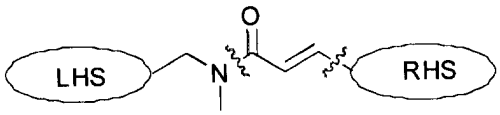

beta-Hydroxyacyl-ACP
dehydration
FabA
FabZ
Trans-2-Enoyl-ACP
FabI
FabK
FabL
reduction
Acyl-ACP
FabB
FabF
condensation
beta-Ketoacyl-ACP
reduction
FabG

Figure 2.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2007/001277

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***C07D 519/00*** (2006.01) , ***A61K 31/55*** (2006.01) , ***A61P 31/04*** (2006.01) , ***C07D 471/04*** (2006.01) , ***C07D 498/04*** (2006.01)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: ***C07D 519/00*** (2006.01) , ***A61K 31/55*** (2006.01) , ***A61P 31/04*** (2006.01) , ***C07D 471/04*** (2006.01) , ***C07D 498/04*** (2006.01)

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

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

STN (chemical structure), Scopus, Delphion, Canadian Patent Database: FAB I inhibitor, antibacterial

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA2,568,914 A1 (AFFINIUM PHARMACEUTICALS, INC.) 04 December 2005 (04-12-2005) whole document, also see examples 77 and 86	1-3, 17 and 19-36
X	WO 03/088897 A2 (AFFINIUM PHARMACEUTICALS, INC.) 30 October 2003 (30-10-2003) whole document, also see examples on page 12 and page 22, compound 10	1-3, 18-34 and 36
X	US2006/0142265 A1 (AFFINIUM PHARMACEUTICALS, INC.) 29 June 2006 (29-06-2006) whole document	1-3, 17, 19, 23-25 and 36
X	WO 04/052890 A1 (AFFINIUM PHARMACEUTICALS, INC.) 24 June 2004 (24-06-2004) whole document	1-3 and 17-36
P, X	WO 07/067416 A2 (AFFINIUM PHARMACEUTICALS, INC.) 14 June 2007 (14-06-2007) whole document	1-4 and 19-36

[ ] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2007 (02-10-2007)	26 October 2007 (26-10-2007)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer

Marie-Claire Wilson 819- 934-3595

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

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

1. [X] Claim Nos. : 32-34

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 32-34 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 32-34.

2. [ ] Claim Nos. :

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

3. [ ] Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

[ ] No protest accompanied the payment of additional search fees.

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2568914	04-12-2005	EP1828167 A2	05-09-2007
		WO2007053131 A2	10-05-2007
WO03088897	30-10-2003	AU2002367773 A1	03-11-2003
		CA2444597 A1	06-10-2002
		EP1560584 A2	10-08-2005
		JP2005519984T T	07-07-2005
		US7049310 B2	23-05-2006
		US7250424 B2	31-07-2007
US2006142265	29-06-2006	CA2519429 A1	30-09-2004
		EP1608377 A2	28-12-2005
		JP2006523207T T	12-10-2006
		WO2004082586 A2	30-09-2004
WO2004052890	24-06-2004	AU2003298937 A1	30-06-2004
		CA2508792 A1	24-06-2004
		EP1575951 A1	21-09-2005
		JP2006513262T T	20-04-2006
		US2006183908 A1	17-08-2006
WO2007067416	14-06-2007	NONE	