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ANTIBIOTIQUES

(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING INHIBITORS OF FAB I AND FURTHER ANTIBIOTICS

(57) **Abrégé/Abstract:**

In part, the present invention is directed to antibacterial compositions comprising a FabI inhibitor and at least one other antibiotic agent. In part, the present invention is directed to antibacterial compositions comprising a compound of formulas I-III and at least one other antibacterial agent. In part, the present invention is directed to one of the preceding embodiments, wherein the antibacterial composition exhibits a synergistic antibacterial effect compared to its individual components.



Abstract

In part, the present invention is directed to antibacterial compositions comprising a FabI inhibitor and at least one other antibiotic agent. In part, the present invention is directed to antibacterial compositions comprising a compound of formulas **I-III** and at least
5 one other antibacterial agent. In part, the present invention is directed to one of the preceding embodiments, wherein the antibacterial composition exhibits a synergistic antibacterial effect compared to its individual components.

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PHARMACEUTICAL COMPOSITIONS
COMPRISING INHIBITORS OF FAB I AND FURTHER ANTIBIOTICS

Related Application Information

5 This application claims priority to U.S. Provisional Patent Application Nos.:
60/455,189, filed March 17, 2003, 60/476,970, filed June 9, 2003, and 60/488,379, filed
July 18, 2003. All three applications are incorporated herein in their entirety.

Introduction

10 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.

15 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
20 and the ACP is a discrete protein. Therefore, it may be possible to achieve selective
inhibition of the bacterial system by appropriate agents.

25 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
30 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 it is believed that 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, compositions with FabI inhibiting properties.

Summary of Invention

In part, the present invention is directed towards compositions comprising a FabI inhibitor and at least one other antibiotic agent. The ratio between the FabI inhibitor and the at least one other antibacterial agent may vary within relatively broad ranges and will be dependent on the intended use. It is contemplated that the compositions of the present invention may comprise a ratio in the range of about 0.01:1 to 1:100 between the FabI inhibitor and the antibiotic agent. In certain embodiments, the two or more agents in the subject compositions work synergistically.

In one embodiment, the present invention relates to antibacterial compositions comprising a compound of formulas I-III and at least one other antibacterial compound. In certain embodiments, the compound of formulas I-III and the at least one other antibacterial compound exhibit a synergistic antibacterial effect. That is, fractional amounts of the MIC of each compound are combined such that the total amount is still less than one times the MIC of either compound, and the antibacterial composition of the present invention still inhibits bacterial growth. As a non-limiting example, the antibacterial compositions of the present invention may comprise a compound of formula I at half its MIC and another antibacterial compound at a quarter of its MIC, with the combined composition inhibiting bacterial growth. Other examples using other fractional amounts can be envisioned by of ordinary skill in the art.

In one embodiment, the dosage amount of the at least one other antibiotic agent in the compositions of the present invention is about half the dosage amount when the FabI inhibitor is absent. In another embodiment, the amount of the at least one other antibiotic agent is less than about half of the amount in the dosage when the FabI inhibitor is absent. In another embodiment, the amount of the at least one other antibiotic agent is less than about a quarter of the amount in the dosage when the FabI inhibitor is absent. In another

embodiment, the amount of the at least one other antibiotic agent is less than about a tenth of the amount in the dosage when the FabI inhibitor is absent.

In part, the present invention is directed towards compositions that will affect multiple species, so-called "wide spectrum" anti-bacterials. Alternatively, subject
5 compositions 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 one embodiment, the dosage amount of the FabI inhibitor in the compositions of the present invention is about half the dosage amount when the at least one other antibiotic agent is absent. In another embodiment, the amount of the FabI inhibitor is less than about
10 half of the amount in the dosage when the at least one other antibiotic agent is absent. In another embodiment, the amount of the FabI inhibitor is less than about a quarter of the amount in the dosage when the at least one other antibiotic agent is absent. In another embodiment, the amount of the FabI inhibitor is less than about a tenth of the amount in the dosage when the at least one other antibiotic agent is absent.

15 The subject compositions may be administered by one of a variety of means 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-A4,
20 "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compositions of the present invention may be tested in serial two-fold dilutions ranging from, for example, 0.06 to 64 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: *Staphylococcus aureus* Oxford, *Streptococcus pneumoniae* R6, *Streptococcus*
25 *pyogenes* CN10, *Enterococcus faecalis* I, *Haemophilus influenzae* Q1, *Escherichia coli* DC0, *E. coli* ESS, *E. coli* 7623 (*AcrAB*⁺) *E. coli* 120 (*AcrAB*⁻) *Klebsiella pneumoniae* E70, *Pseudomonas aeruginosa* K799wt and *Candida albicans* GRI 681. The minimum inhibitory concentration (MIC) may then be determined as the lowest concentration of the subject composition that inhibited visible growth. A mirror reader may be used to assist in
30 determining the MIC endpoint.

In one embodiment, the antibacterial compositions of the present invention have a MIC of less than 256 µg/mL. In other embodiments, the antibacterial compositions of the

present invention may have a MIC value of less than 128 µg/mL, or even less than 64 µg/mL.

Non-limiting examples of bacteria that the antibacterial 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*,
 5 *Neisseria*, *Haemophilus*, *Actinomyces*, *Streptomyces*, *Nocardia*, *Enterobacter*, *Yersinia*, *Fancisella*, *Pasturella*, *Moraxella*, *Acinetobacter*, *Erysipelothrix*, *Branhamella*, *Actinobacillus*, *Streptobacillus*, *Listeria*, *Calymmatobacterium*, *Brucella*, *Bacillus*, *Clostridium*, *Treponema*, *Escherichia*, *Salmonella*, *Kleibsiella*, *Vibrio*, *Proteus*, *Erwinia*,
 10 *Borrelia*, *Leptospira*, *Spirillum*, *Campylobacter*, *Shigella*, *Legionella*, *Pseudomonas*, *Aeromonas*, *Rickettsia*, *Chlamydia*, *Borrelia* 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*,
 15 *Streptococcus faecalis*, *Streptococcus faecium*, *Streptococcus durans*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Corynebacterium diphtheriae*, *Gardnerella vaginalis*, *Mycobacterium tuberculosis*, *Mycobacterium bovis*, *Mycobacterium ulcerans*, *Mycobacterium leprae*, *Actinomyces israelii*, *Listeria monocytogenes*, *Bordetella pertussis*, *Bordatella parapertussis*, *Bordetella bronchiseptica*, *Escherichia coli*, *Shigella dysenteriae*, *Haemophilus influenzae*,
 20 *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 dysenteriae*, *Shigella flexneri*, *Pseudomonas aeruginosa*, *Franscisella tularensis*,
 25 *Brucella abortus*, *Bacillus anthracis*, *Bacillus cereus*, *Clostridium perfringens*, *Clostridium tetani*, *Clostridium botulinum*, *Treponema pallidum*, *Rickettsia rickettsii*, *Helicobacter pylori* or *Chlamydia trachomatis*.

Non-limiting examples of illnesses caused by a bacterial illness include otitis media, conjunctivitis, pneumonia, bacteremia, meningitis, sinusitis, pleural empyema and
 30 endocarditis, and meningitis, such as for example infection of cerebrospinal fluid.

In another aspect, the subject 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 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 compositions of the present invention in a pharmaceutically acceptable excipient.

In certain embodiments, the subject compositions formulated as a tablet, pill capsule or other appropriate ingestible formulation, 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 another embodiment of the invention it will be desirable to include monitoring or diagnostic regimes or kits with subject antibacterial compositions or methods based on FabI inhibitors and at least one other antibiotic agent 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 regimen. 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.

5 *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.

10 Figures 3a-f depict the structures of some of the compounds of the present invention from the representative list.

Figure 4 depicts a 96-well plate layout for assays of antimicrobial combinations.

Figure 5 depicts the compounds of the antibacterial compositions of the present invention used in the combination efficacy experiments.

15 *Detailed Description of Invention*

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.

20 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 β -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).

30 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. 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
5 relatively hydrophobic groups, conveniently denoted as left-hand side (LHS) and right-hand side (RHS). 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

10 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
15 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,
20 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 bacterial enzymes believed to function as an enoyl-acyl carrier protein (ACP) reductase in the final step of the four
25 reactions involved in each cycle of bacterial fatty acid biosynthesis. The 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 biochemical role(s). Therefore a "FabI inhibitor" is any compound that inhibits FabI from carrying out its biochemical role(s). The amount of
30 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, carbapenems, 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 components. One measure of synergism for antibacterial compounds and other enzyme inhibiting compounds is described under the section Method for Checkerboard Combination Studies.

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
5 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
10 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
15 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).

20 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.
25 "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
30 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 phosphatidylinositol, 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;

5 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 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

10 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

15 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

20 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

25 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

30 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 "ED₅₀" is art-recognized. In certain embodiments, ED₅₀ 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 "LD₅₀" is art-recognized. In certain embodiments, LD₅₀ 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 LD₅₀/ED₅₀.

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.

10 The term "agonist" is art-recognized and refers to a compound that mimics the action of natural transmitter or, when the natural transmitter is not known, causes changes at the receptor complex in the absence of other receptor ligands.

The term "antagonist" is art-recognized and refers to a compound that binds to a receptor site, but does not cause any physiological changes unless another receptor ligand is present.

The term "competitive antagonist" is art-recognized and refers to a compound or that binds to a receptor site; its effects may be overcome by increased concentration of the agonist.

20 The term "partial agonist" is art-recognized and refers to a compound or that binds to a receptor site but does not produce the maximal effect regardless of its concentration.

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., C₁-C₃₀ for straight chain, C₃-C₃₀ 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
5 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
10 (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.

15 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.

20 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
25 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,
30 pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" 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, -CF₃, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more
5 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
10 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,
15 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,
20 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,
25 carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -CN, or the like.

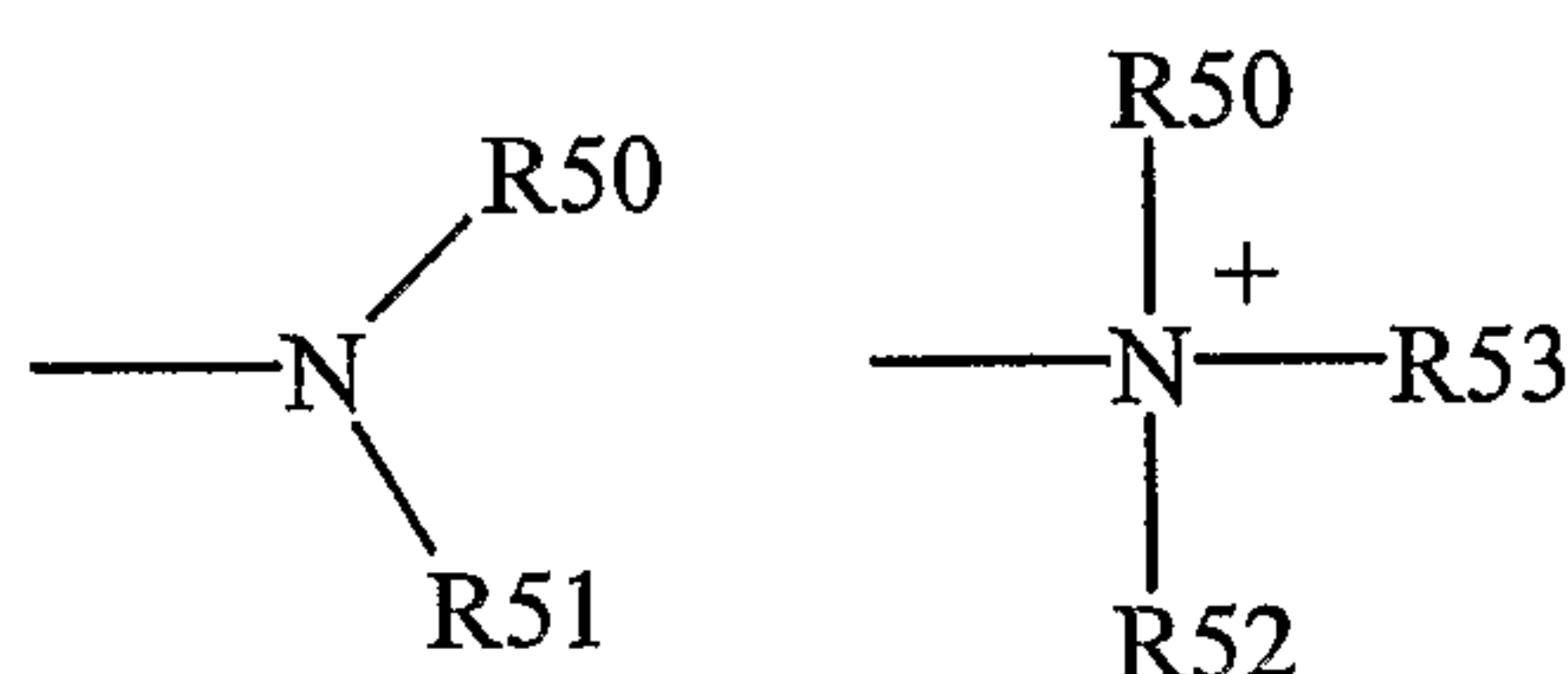
The terms "polycyclyl" or "polycyclic group" are art-recognized and refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused
30 rings". Rings that are joined through 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, -CF₃, -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.

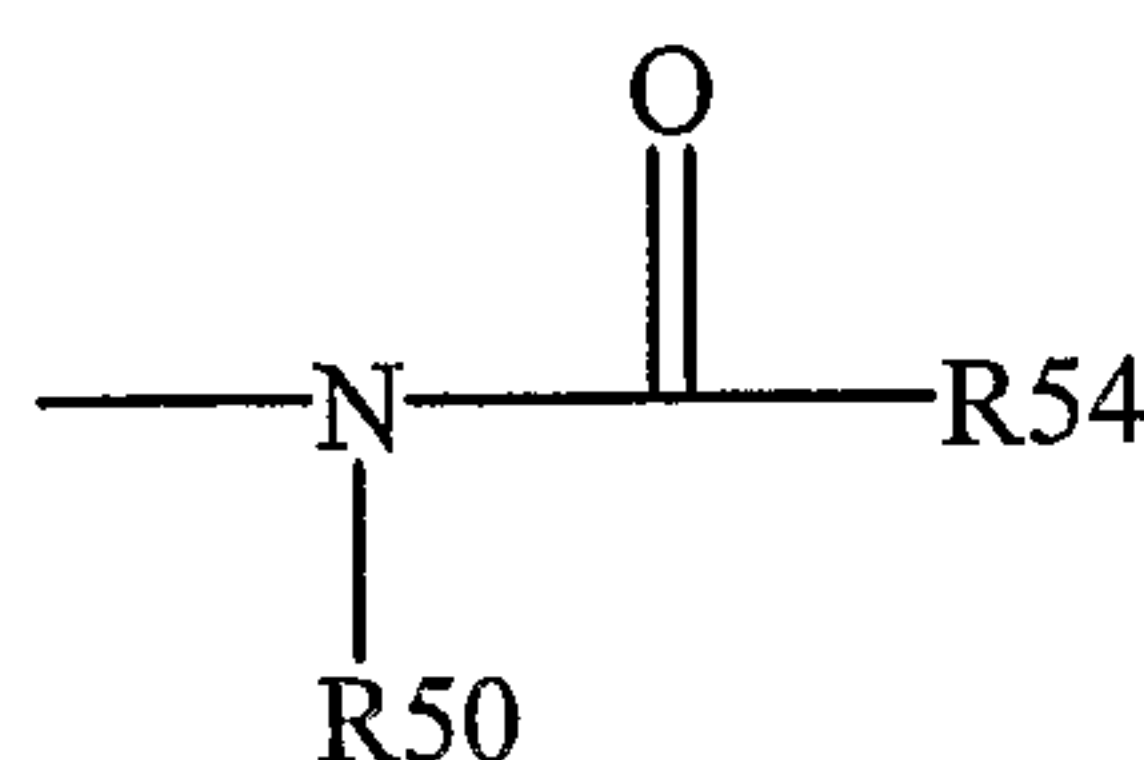
- 5 The term "nitro" is art-recognized and refers to -NO₂; the term "halogen" is art-recognized and refers to -F, -Cl, -Br or -I; the term "sulfhydryl" is art-recognized and refers to -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" is art-recognized and refers to -SO₂⁻. "Halide" designates the corresponding anion of the halogens, and "pseudohalide" has the definition set forth on 560 of "Advanced Inorganic Chemistry" by
 10 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:



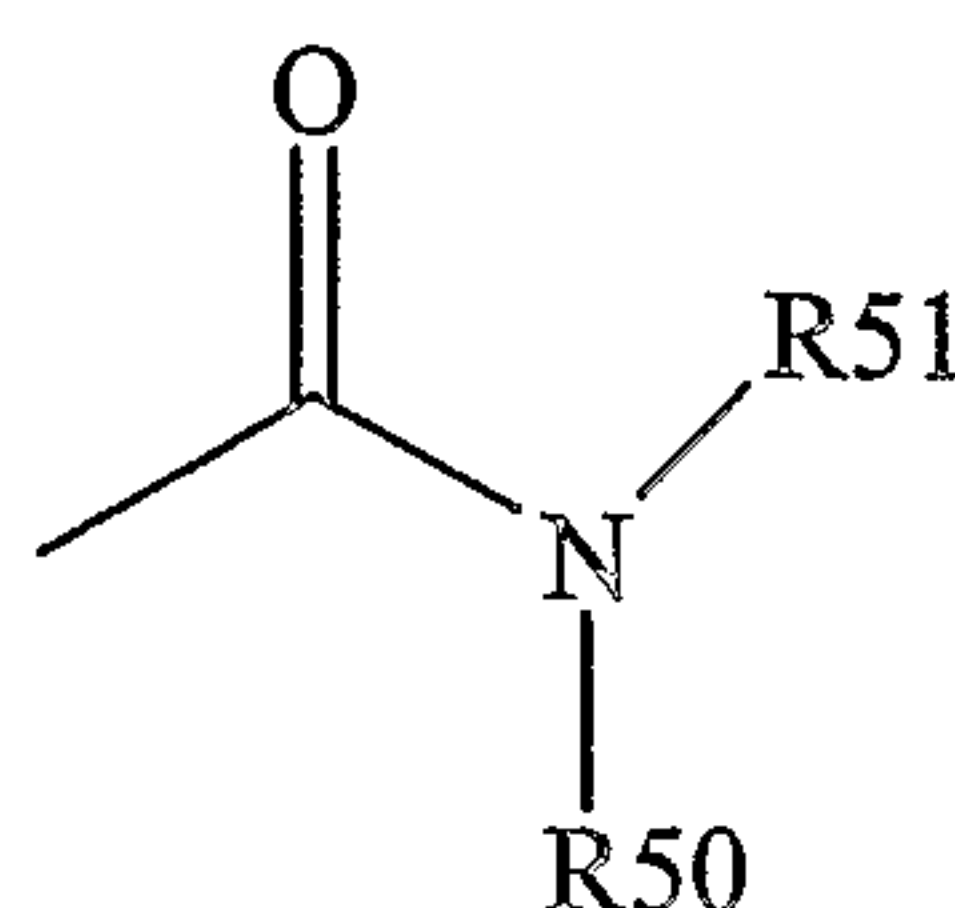
- wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, -
 15 (CH₂)_m-R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, 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
 20 and R51 (and optionally R52) each independently represent a hydrogen, an alkyl, an alkenyl, or -(CH₂)_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
 25 represented by the general formula:



wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or -
 (CH₂)_m-R61, where m and R61 are as defined above.

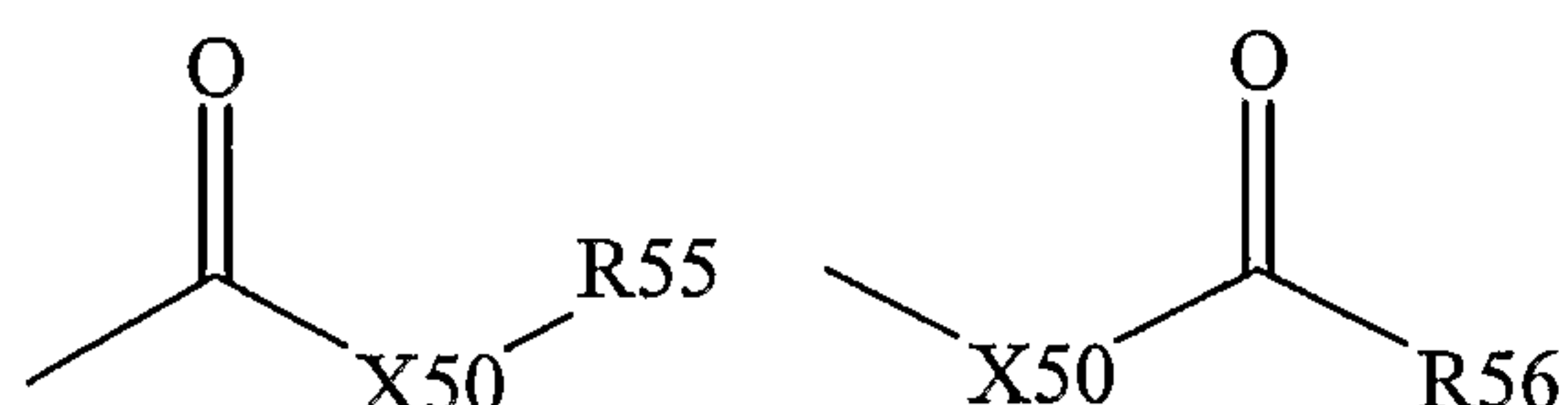
The term “amido” is art recognized as an amino-substituted carbonyl and includes a moiety that may be represented by the general formula:



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-(CH₂)_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:

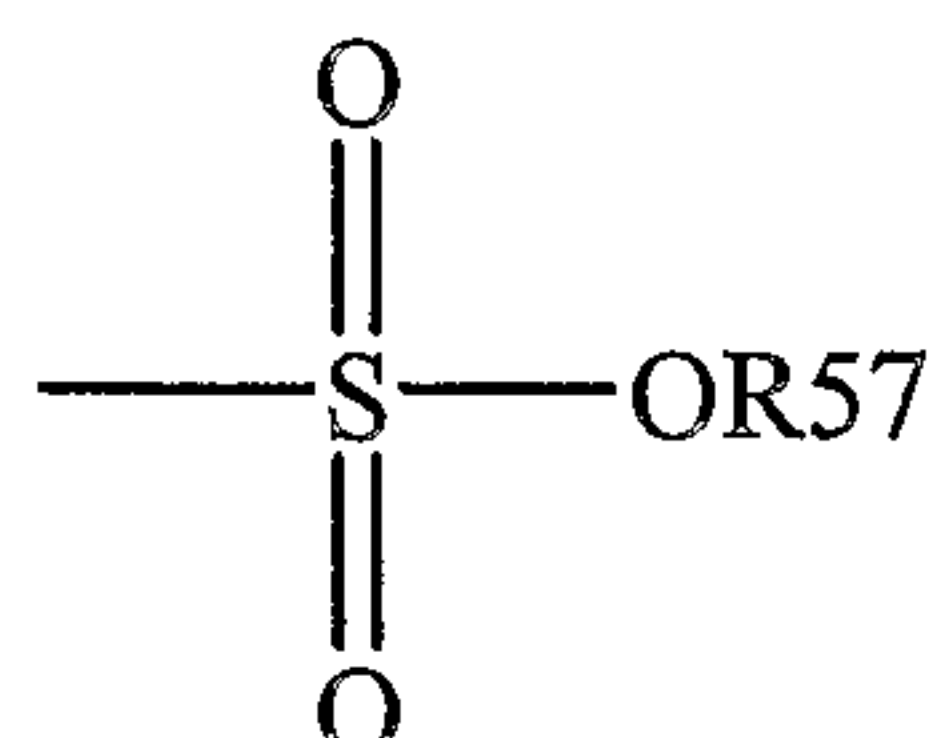


wherein X50 is a bond or represents an oxygen or a sulfur, and R55 and R56 represents a hydrogen, an alkyl, an alkenyl, -(CH₂)_m-R61 or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or -(CH₂)_m-R61, where m and R61 are defined above. Where X50 is an oxygen and R55 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

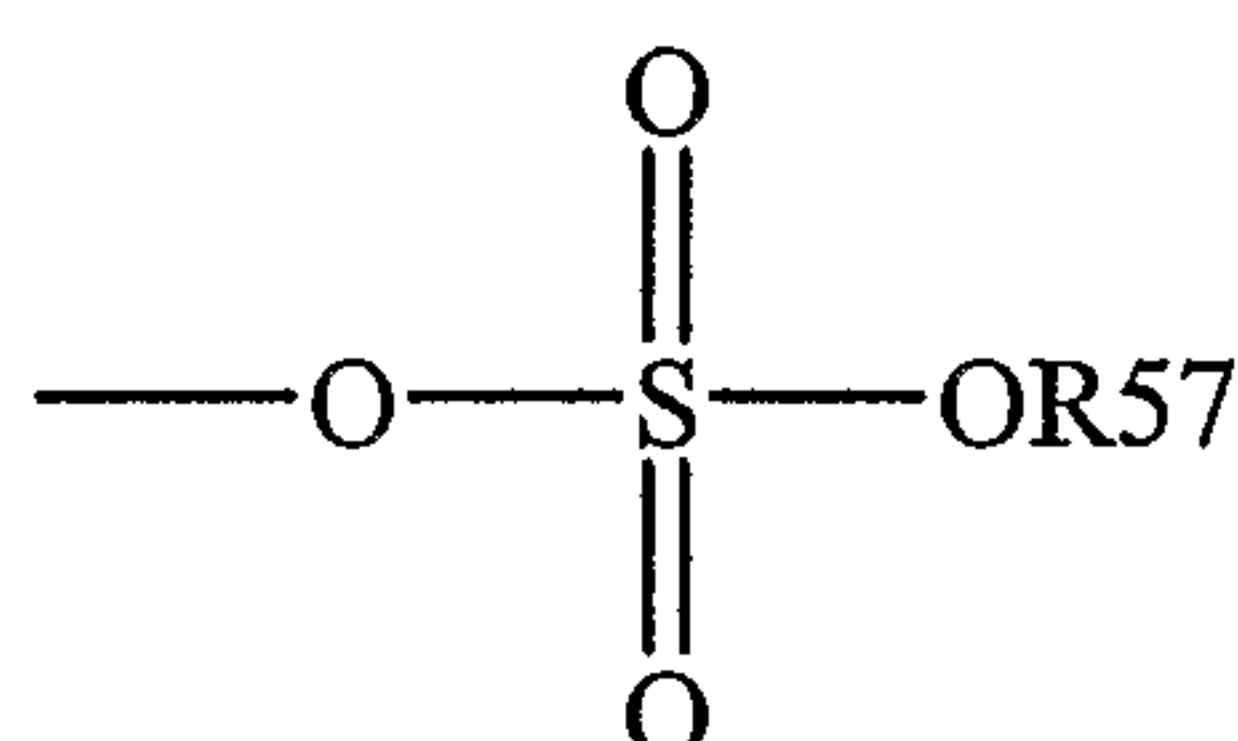
include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O--(CH₂)_m-R61, where m and R61 are described above.

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



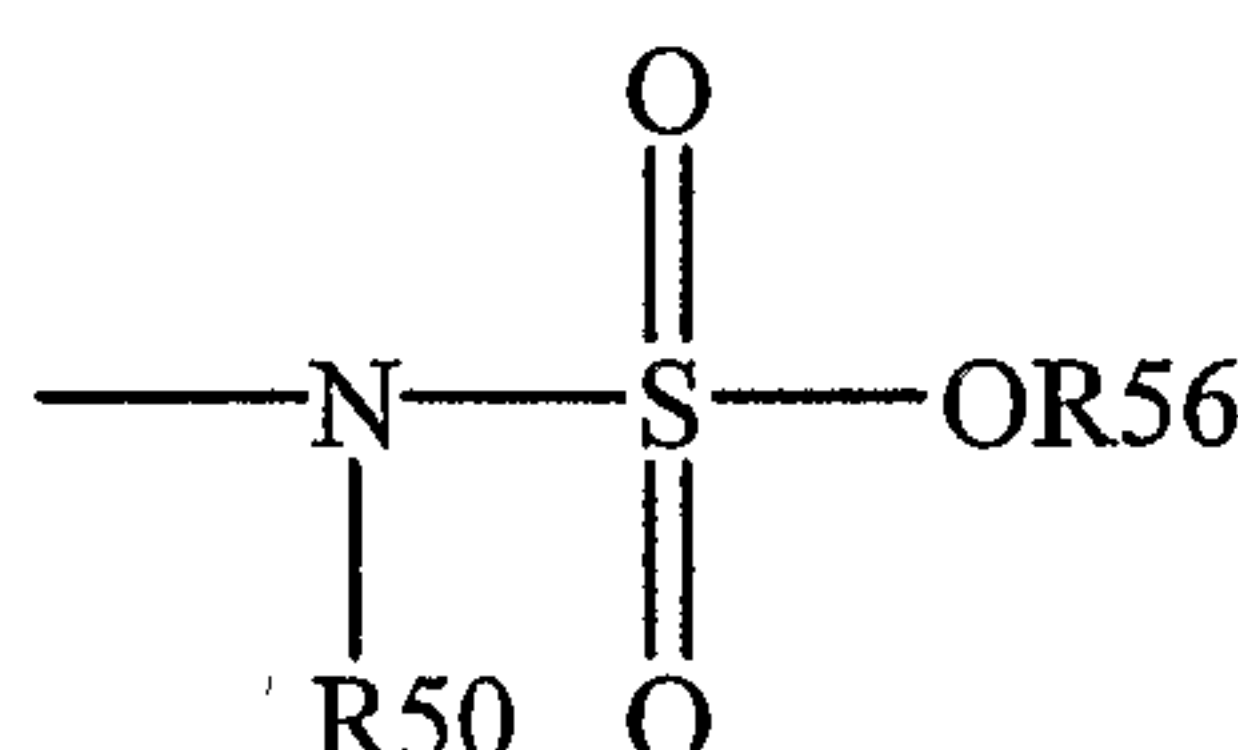
in which R57 is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

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



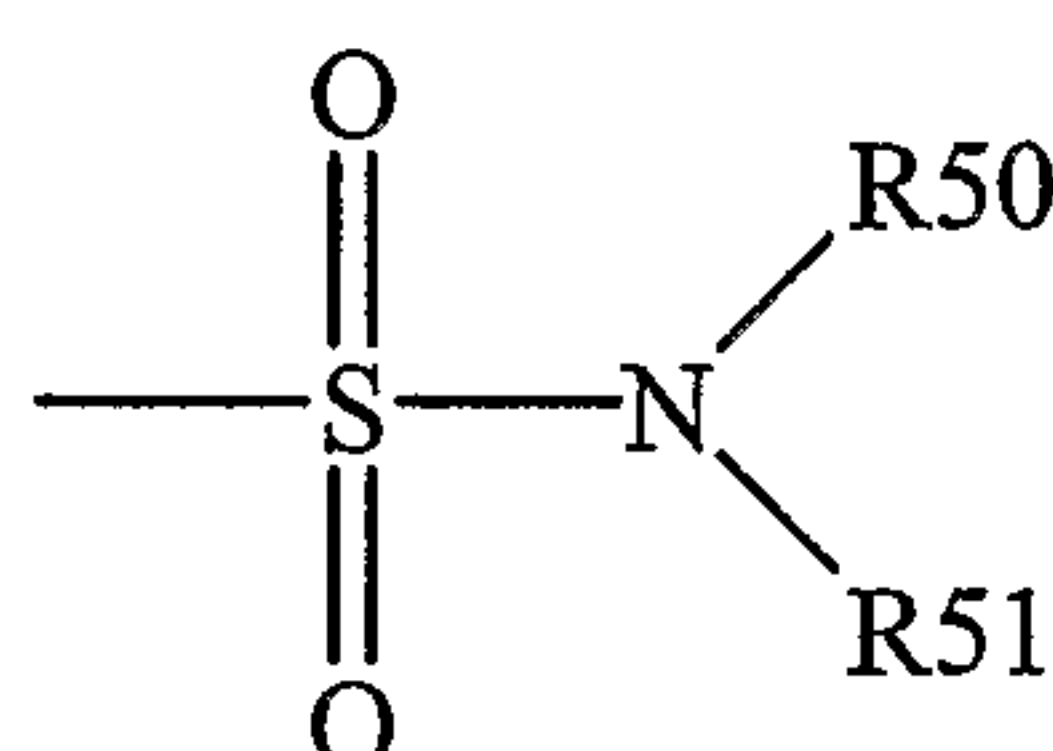
in which R57 is as defined above.

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



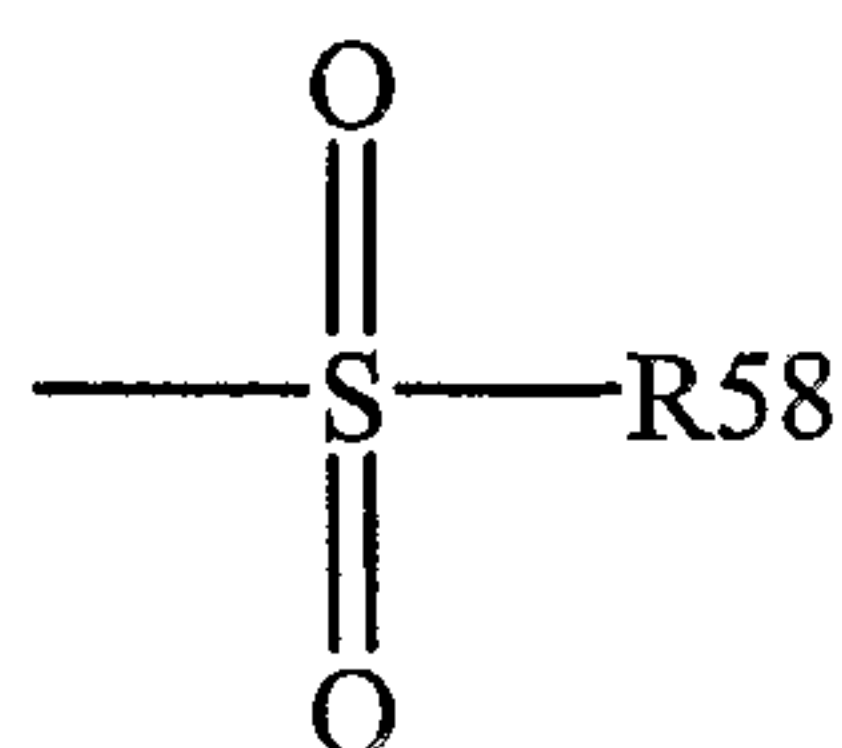
15 in which R50 and R56 are as defined above.

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



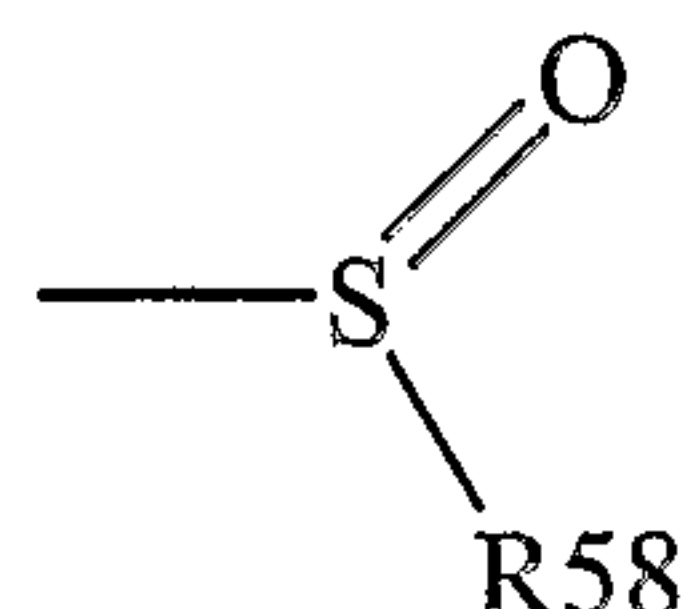
20 in which R50 and R51 are as defined above.

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



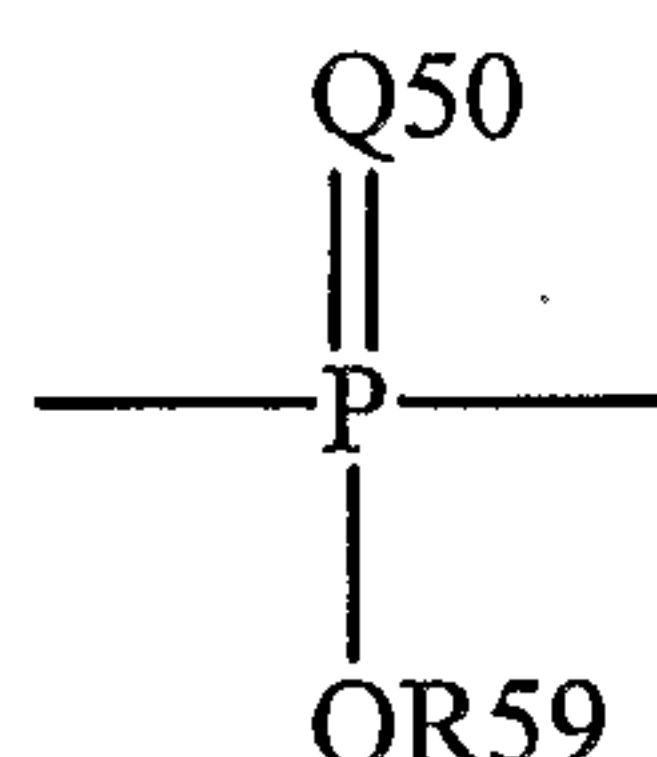
in which R58 is one of the following: hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

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



in which R58 is defined above.

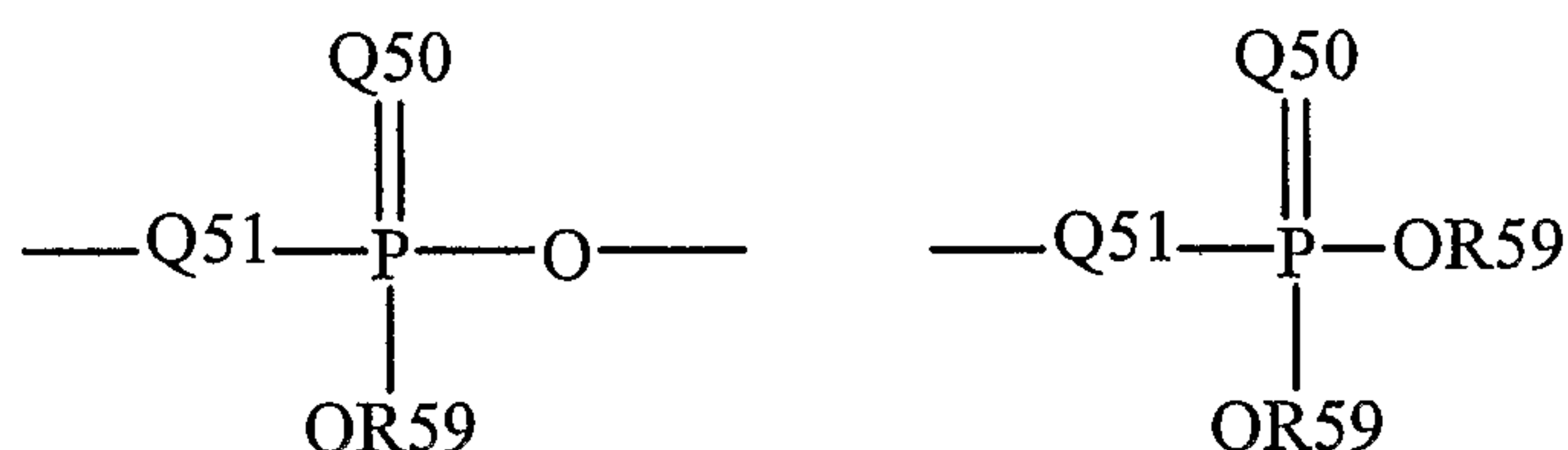
The term "phosphoryl" is art-recognized and may in general be represented by the formula:



10

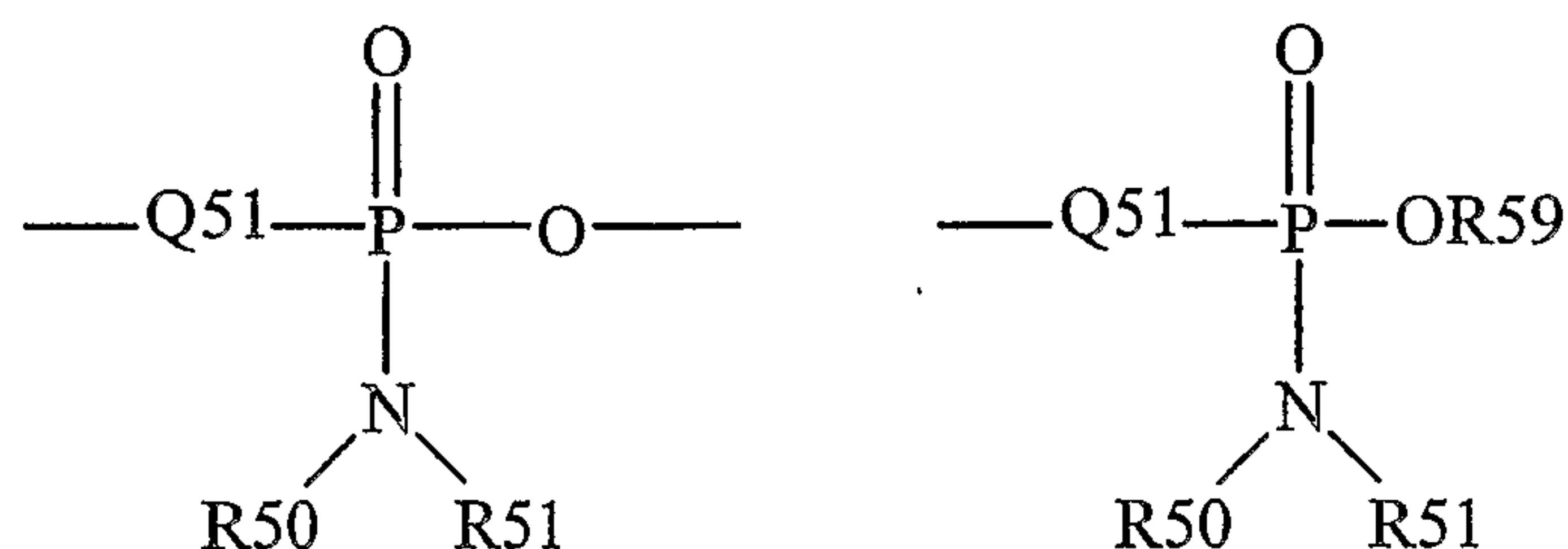
wherein Q50 represents S or O, and R59 represents hydrogen, a lower alkyl or an aryl.

When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



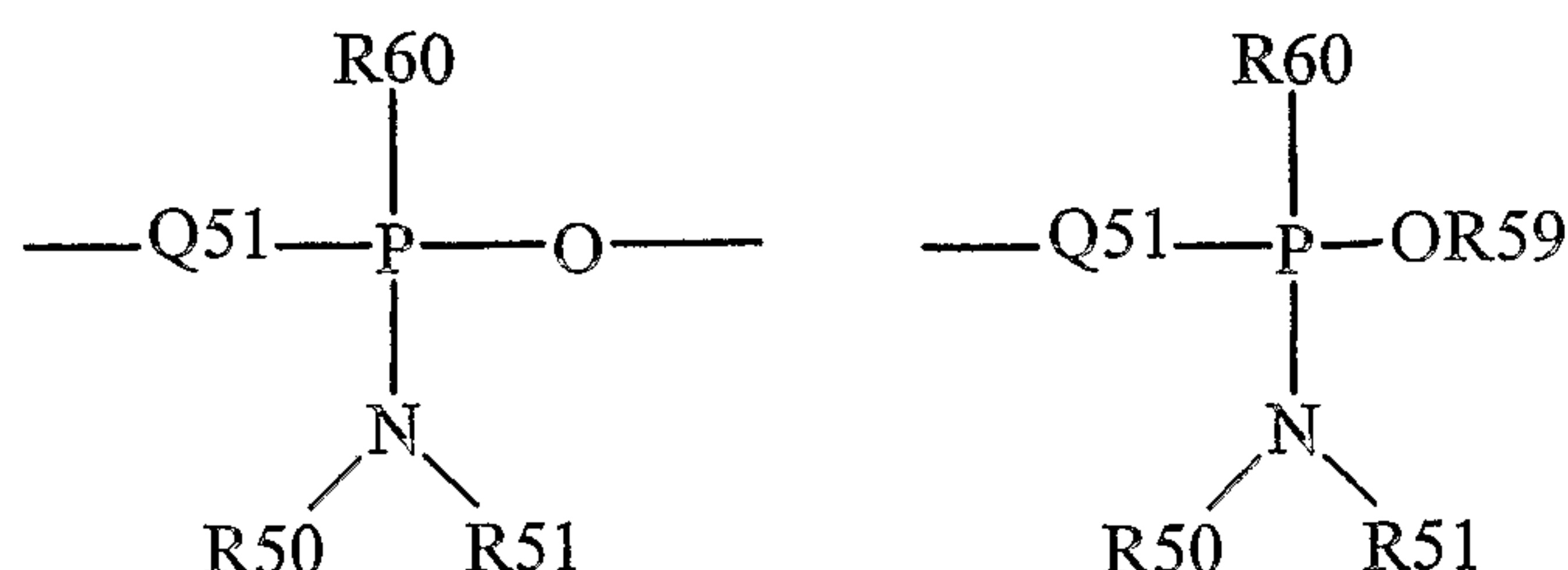
15 wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N. When Q50 is S, the phosphoryl moiety is a "phosphorothioate".

The term "phosphoramidite" is art-recognized and may be represented in the general formulas:



wherein Q51, R50, R51 and R59 are as defined above.

The term "phosphonamidite" is art-recognized and may be represented in the general formulas:



- 5 wherein Q51, R50, R51 and R59 are as defined above, and R60 represents a lower alkyl or an aryl.

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.

- 10 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 term "selenoalkyl" is art-recognized and refers to an alkyl group having a substituted seleno group attached thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-(CH₂)_m-R61, m and R61 being defined above.

- The terms triflyl, tosyl, mesyl, and nonafllyl 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
5 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
10 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
15 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,
20 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
25 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
30 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.

5 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
10 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 hydroxyl group against undesirable reactions during synthetic procedures and includes, for example, benzyl or other suitable esters or ethers groups known in the art.

15 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
20 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
25 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-
30 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 ($-\text{CH}_2\text{C}_6\text{H}_5$), acyl $[\text{C}(\text{O})\text{R}_1]$ or SiR_1_3 where R_1 is C_1 - C_4 alkyl, halomethyl, or 2-halo-substituted- $(\text{C}_2$ - 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.

10 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
15 Chemistry 251-59 (McGraw Hill Book Company: New York, 1977). The Hammett constant values are generally negative for electron donating groups ($\sigma(\text{P}) = -0.66$ for NH_2) and positive for electron withdrawing groups ($\sigma(\text{P}) = 0.78$ for a nitro group), $\sigma(\text{P})$ indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-
20 donating groups include amino, methoxy, and the like.

The term "amino acid" is art-recognized and refers to all compounds, whether natural or synthetic, which include both an amino functionality and an acid functionality, including amino acid analogs and derivatives.

25 The terms "amino acid residue" and "peptide residue" are art-recognized and refer to an amino acid or peptide molecule without the $-\text{OH}$ of its carboxyl group.

The term "amino acid residue" further includes analogs, derivatives and congeners of any specific amino acid referred to herein, as well as C-terminal or N-terminal protected amino acid derivatives (e.g. modified with an N-terminal or C-terminal protecting group).

30 The names of the natural amino acids are abbreviated herein in accordance with the recommendations of IUPAC-IUB.

A "reversed" or "retro" peptide sequence as disclosed herein refers to that part of an overall sequence of covalently-bonded amino acid residues (or analogs or mimetics thereof) wherein the normal carboxyl-to amino direction of peptide bond formation in the amino

acid backbone has been reversed such that, reading in the conventional left-to-right direction, the amino portion of the peptide bond precedes (rather than follows) the carbonyl portion. See, generally, Goodman et al. Accounts of Chem. Res. 12:423 (1979).

The reversed orientation peptides described herein include (a) those wherein one or more amino-terminal residues are converted to a reversed ("rev") orientation (thus yielding a second "carboxyl terminus" at the left-most portion of the molecule), and (b) those wherein one or more carboxyl-terminal residues are converted to a reversed ("rev") orientation (yielding a second "amino terminus" at the right-most portion of the molecule). A peptide (amide) bond cannot be formed at the interface between a normal orientation residue and a reverse orientation residue.

Therefore, certain reversed peptide compounds of the invention may be formed by utilizing an appropriate amino acid mimetic moiety to link the two adjacent portions of the sequences depicted above utilizing a reversed peptide (reversed amide) bond.

The reversed direction of bonding in such compounds will generally, in addition, require inversion of the enantiomeric configuration of the reversed amino acid residues in order to maintain a spatial orientation of side chains that is similar to that of the non-reversed peptide. The configuration of amino acids in the reversed portion of the peptides is usually (D), and the configuration of the non-reversed portion is usually (L). Opposite or mixed configurations are acceptable when appropriate to optimize a binding activity.

The term "nucleic acid" is art-recognized and refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single-stranded (such as sense or antisense) and double-stranded polynucleotides.

The terms "gene" or "recombinant gene" are art-recognized and refer to a nucleic acid comprising an open reading frame encoding a polypeptide, including both exonic and (optionally) intronic sequences.

The term "gene construct" is art-recognized and refers to a vector, plasmid, viral genome or the like which includes an "coding sequence" for a polypeptide or which is otherwise transcribable to a biologically active RNA (e.g., antisense, decoy, ribozyme, etc), can transfect cells, in certain embodiments mammalian cells, and may cause expression of the coding sequence in cells transfected with the construct.

The term "homology" is art-recognized and refers to sequence similarity between two peptides or between two nucleic acid molecules.

The term "operably linked" is art-recognized and refers to the relationship between two nucleic acid regions, means that they are functionally related to each other.

5 The term "antisense" nucleic acid is art-recognized and refers to oligonucleotides which specifically hybridize (e.g., bind) under cellular conditions with a gene sequence, such as at the cellular mRNA and/or genomic DNA level, so as to inhibit expression of that gene, e.g., by inhibiting transcription and/or translation. The binding may be by conventional base pair complementarily, or, for example, in the case of binding to DNA
10 duplexes, through specific interactions in the major groove of the double helix.

The term "host cell" is art-recognized and refers to a cell transduced with a specified transfer vector. The cell is optionally selected from in vitro cells such as those derived from cell culture, ex vivo cells, such as those derived from an organism, and in vivo cells, such as those in an organism. "Recombinant host cells" refers to cells which have been
15 transformed or transfected with vectors constructed using recombinant DNA techniques.

The terms "recombinant protein," "heterologous protein" and "exogenous protein" are art-recognized and are used interchangeably to refer to a polypeptide which is produced by recombinant DNA techniques, wherein generally, DNA encoding the polypeptide is inserted into a suitable expression vector which is in turn used to transform a host cell to
20 produce the heterologous protein. That is, the polypeptide is expressed from a heterologous nucleic acid.

The term "regulatory element" is art-recognized and refers to nucleotide sequences (such as DNA sequences) that induce or control transcription of protein coding sequences with which they are operably linked. Examples of regulatory elements categorized by
25 function include initiation signals, enhancers, promoters and the like. Exemplary regulatory elements are described in Goeddel; Methods in Enzymology 185 (1990). In certain embodiments, transcription of a gene or other DNA is under the control of a promoter sequence (or other regulatory element) which controls the expression of a coding sequence in a cell-type in which expression is intended. A variety of promoters categorized by
30 function are known. The term "tissue-specific promoter" means a DNA sequence that serves as a promoter, i.e., regulates expression of a selected DNA sequence operably linked to the promoter, and which effects expression of the selected DNA sequence in specific cells of a tissue, such as cells of a urogenital origin, e.g., renal cells, or cells of a neural

origin, e.g., neuronal cells. The term also covers so-called "leaky" promoters, which regulate expression of a selected DNA primarily in one tissue, but cause expression in other tissues as well. The term "inducible" promoter refers to a promoter which is under environmental or developmental regulation. The term "constitutive" promoter refers to a promoter which is active under most environmental and developmental conditions.

The term "transfection" is art-recognized and refers to the introduction of a nucleic acid, e.g., an expression vector, into a recipient cell, which in certain embodiments may be by nucleic acid-mediated gene transfer. "Transformation," as used with respect to transfected nucleic acid, is an art-recognized term and refers to a process in which a cell's genotype is changed as a result of the cellular uptake of exogenous nucleic acid.

The term "transfer vector" is art-recognized and refers to a first nucleic acid molecule to which a second nucleic acid has been linked, and includes for example plasmids, cosmids or phages (as discussed in greater detail below). In certain embodiments of the present invention, the therapeutic agent is the second nucleic acid. One type of transfer vector is an episome, i.e., a nucleic acid capable of extra-chromosomal replication.

In certain embodiments, a transfer vector may be an "expression vector," which refers to a replicable DNA construct used to express DNA which encodes the desired protein and which includes a transcriptional unit comprising an assembly of (i) genetic element(s) having a regulatory role in gene expression, for example, promoters, operators, or enhancers, operatively linked to (ii) a DNA sequence encoding a desired protein which is transcribed into mRNA and translated into protein, and (iii) appropriate transcription and translation initiation and termination sequences. In certain embodiments, the therapeutic agent is the DNA sequence. The choice of promoter and other regulatory elements generally varies according to the intended host cell. In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids," which refer to circular double stranded DNA loops which, in their vector form are not bound to the chromosome. The invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

Certain transfer vectors may contain regulatory elements for controlling transcription or translation, which may be generally derived from mammalian, microbial, viral or insect genes. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants, may additionally be incorporated.

The design of any transfer vector may depend on such factors as the choice of the host cell to be transformed and/or the type of protein desired to be expressed. Moreover, the vector's copy number, the ability to control that copy number and the expression of any other proteins encoded by the vector, such as antibiotic markers (e.g., ampicillin), may also
5 be considered.

The term "transgenic animal" is art-recognized and refers to any animal, often a non-human mammal, a bird or an amphibian, in which one or more of the cells of the animal contain nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. Such nucleic acid may be referred to as a "transgene."
10 The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. This molecule may be integrated within a chromosome, or
15 it may be extrachromosomally replicating DNA. A transgene may be partly or entirely heterologous, i.e., foreign, to the transgenic animal or cell into which it is introduced, or, is homologous to an endogenous gene of the transgenic animal or cell into which it is introduced, but which is designed to be inserted, or is inserted, into the animal's genome in such a way as to alter the genome of the cell into which it is inserted (e.g., it is inserted at a
20 location which differs from that of the natural gene or its insertion results in a knockout). A transgene may also be present in a cell in the form of an episome. A transgene may include one or more regulatory elements and any other nucleic acid, such as introns, that may be necessary for optimal expression of a selected nucleic acid. In certain embodiments, a transgene comprises a nucleic acid sequence of interest and one or more regulatory
25 elements for controlling transcription of the nucleotide sequence encoded by such nucleic acid sequence, e.g., the regulatory element is operably linked to a nucleic acid.

In certain embodiments, the transgene or other therapeutic agent may be a "gene therapy construct," which is an expression vector which may alter the phenotype of a cell when taken up by the cell, or a gene construct. In certain embodiments, the gene therapy
30 construct may be a "recombinant coding sequence" which encodes a polypeptide, or is transcribable to an antisense nucleic acid, a ribozyme, or any other RNA product which alters the phenotype of the cell in which it is produced. "Recombinant gene" refers to a genetic construct including a "recombinant coding sequence."

The term "antibody" is art-recognized and refers to whole antibodies, e.g., of any isotype (IgG, IgA, IgM, IgE, etc.), and includes fragments thereof which are also specifically reactive with a vertebrate, e.g., mammalian, protein. Antibodies may be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. Thus, the term includes segments of proteolytically-cleaved or recombinantly-prepared portions of an antibody molecule that are capable of selectively reacting with a certain protein. Non-limiting examples of such proteolytic and/or recombinant fragments include Fab, F(ab')₂, Fab', Fv, and single chain antibodies (scFv) containing a V[L] and/or V[H] domain joined by a peptide linker. The scFv's may be covalently or non-covalently linked to form antibodies having two or more binding sites. The subject invention includes polyclonal, monoclonal or other purified preparations of antibodies and recombinant antibodies.

"Human monoclonal antibodies" or "humanized" murine antibodies, as the terms are used herein, refer to murine monoclonal antibodies "humanized" by genetically recombining the nucleotide sequence encoding the murine Fv region (i.e., containing the antigen binding site) or the complementarity-determining regions thereof with the nucleotide sequence encoding at least a human constant domain region and an Fc region, e.g., in a manner similar to that disclosed in European Patent Application Publication No. 0,411,893 A3. Some additional murine residues may also be retained within the human variable region framework domains to ensure proper target site binding characteristics. In certain embodiments, humanized antibodies may decrease the immunoreactivity of the antibody or polypeptide in the host recipient, permitting an increase in the half-life and a reduction in the possibility of adverse immune reactions.

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.

A "target" shall mean a site to which targeted constructs bind. A target may be either in vivo or in vitro. In certain embodiments, a target may be a tumor (e.g., tumors of the brain, lung (small cell and non-small cell), ovary, prostate, breast and colon as well as other carcinomas and sarcomas). In other embodiments, a target may be a site of infection (e.g., by bacteria, viruses (e.g., HIV, herpes, hepatitis) and pathogenic fungi (Candida sp.)). In still other embodiments, a target may refer to a molecular structure to which a targeting moiety binds, such as a hapten, epitope, receptor, dsDNA fragment, carbohydrate or enzyme. Additionally, a target may be a type of tissue, e.g., neuronal tissue, intestinal tissue, pancreatic tissue etc.

10 The term "targeting moiety" refers to any molecular structure which assists the construct in localizing to a particular target area, entering a target cell(s), and/or binding to a target receptor. For example, lipids (including cationic, neutral, and steroidal lipids, virosomes, and liposomes), antibodies, lectins, ligands, sugars, steroids, hormones, nutrients, and proteins may serve as targeting moieties.

15 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.

20 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.

30 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
5 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
10 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
15 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)
20 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
25 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.

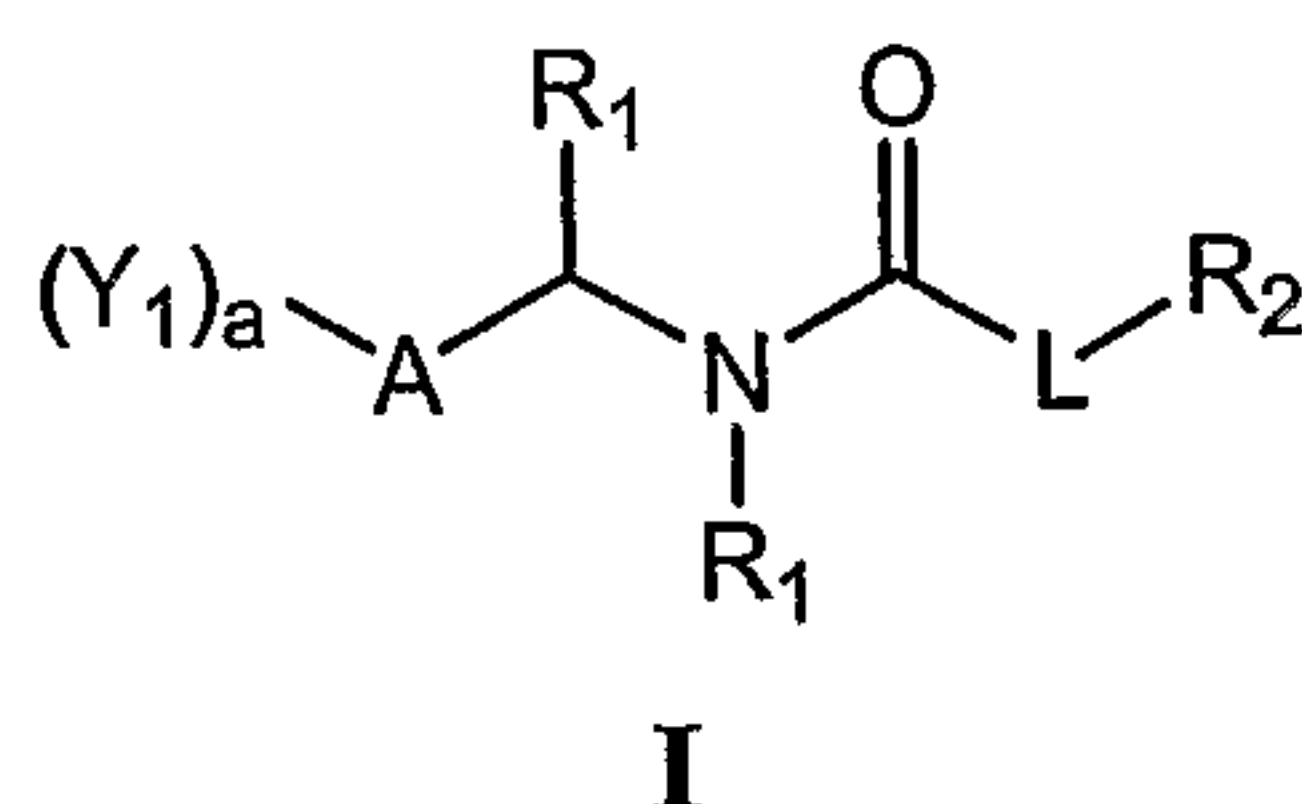
The terms "parenteral administration" and "administered parenterally" are art-
30 recognized and refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal,

intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, 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

In one embodiment, the enzyme inhibiting compositions of the present invention comprise a compound depicted by formula I:



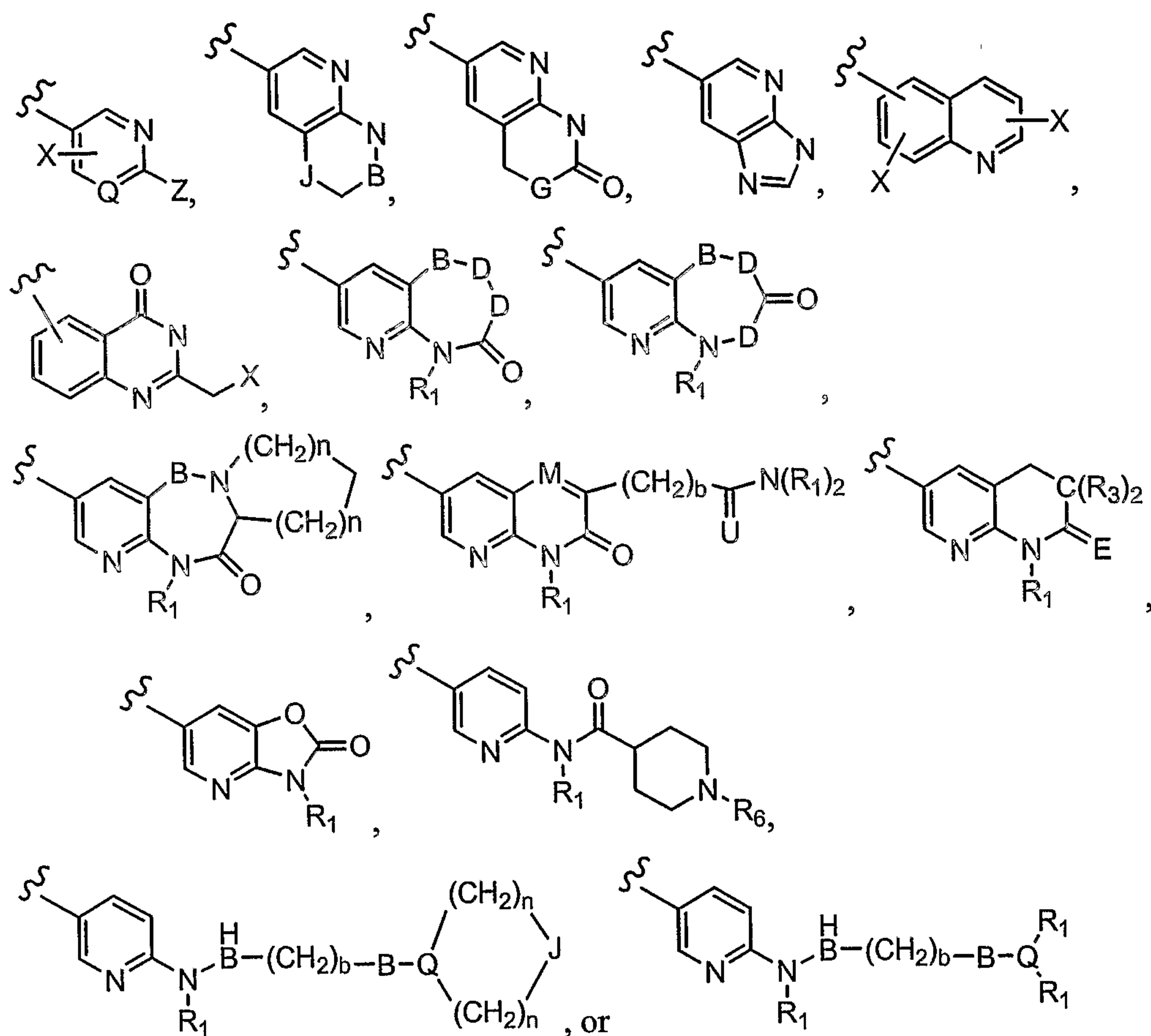
wherein, independently for each occurrence,

L is a bond, or L is alkyl, alkenyl, or cycloalkyl which may be substituted with one or more R₁;

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 C₁₋₄ alkyl, CH₂OH, OR'', SR'', CN, N(R'')₂, CH₂N(R'')₂, NO₂, CF₃, CO₂R'', CON(R'')₂, COR'', NR''C(O)R'', F, Cl, Br, I and -S(O)_rCF₃; wherein R'' is H, alkyl or alkaryl;

R₁ is, independently for each occurrence, H, alkyl, cycloalkyl, aryl, or aralkyl;

R₂ is



wherein, independently for each occurrence,

B is a bond, $C(R_1)_2$ or $C=O$;

E is O or S;

D is $C(R_1)_2$, NR_1 , $C=O$, or $N-B-(CH_2)_b-B-Q$;

$N-B-(CH_2)_b-B-Q$ providing that the two Ds are different;

$N-B-(CH_2)_b-B-Q$ or $N-B-(CH_2)_b-B-Q$;

G is O, NR_1 ,

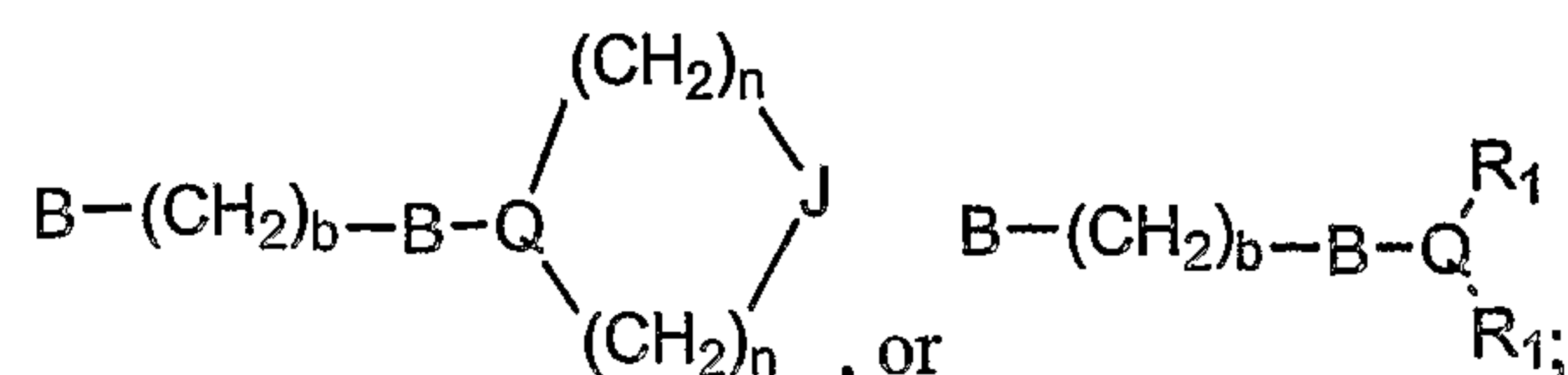
J is NR_1 , CH_2 , CH_2CH_2 , or O;

M is CR_1 or N;

Q is N or CH;

U is O, H_2 , or CH_2 ;

X is H, C₁₋₄ alkyl, CH₂OH, OR₁, SR₁, CN, N(R₁)₂, CH₂N(R₁)₂, NO₂, CF₃, CO₂R₁, CON(R₁)₂, COR₁, NR₁C(O)R₁, F, Cl, Br, I, -S(O)_rCF₃,



Z is H, C₁₋₄ alkyl, N(R₁)₂, NHC(O)R₁, NHCH₂C(O)R₁ or

5 NHC(O)CH=CHR₁;

r is 0, 1, or 2;

R₆ is C(O)OR₁;

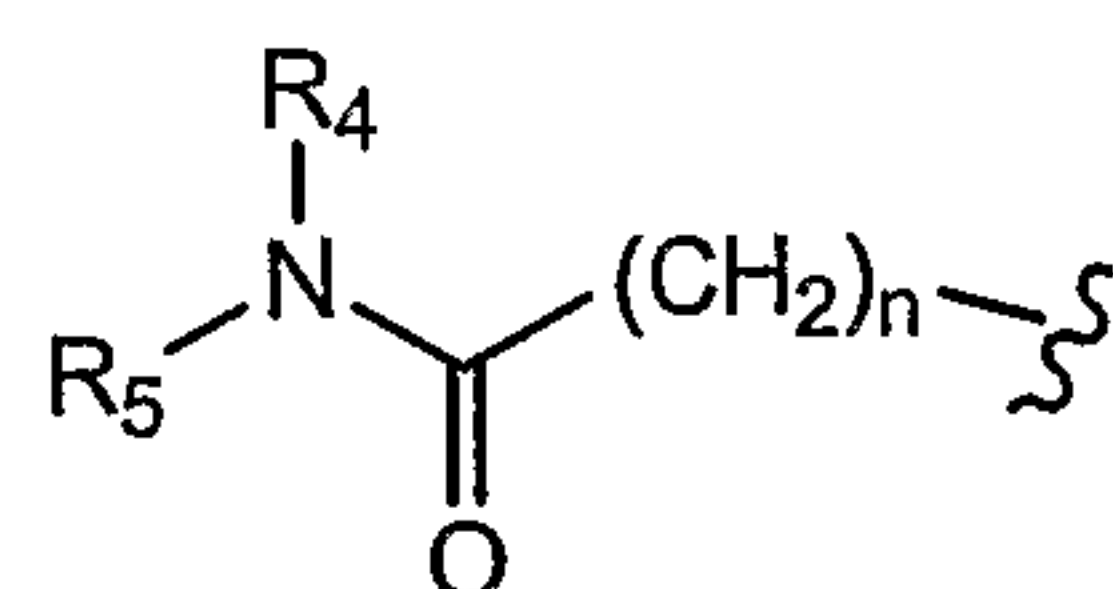
R₁ is as previously defined; and

b is an integer from 0-4;

10 R₃ is alkyl or cycloalkyl;

a is an integer from 0-4; and

Y₁ is



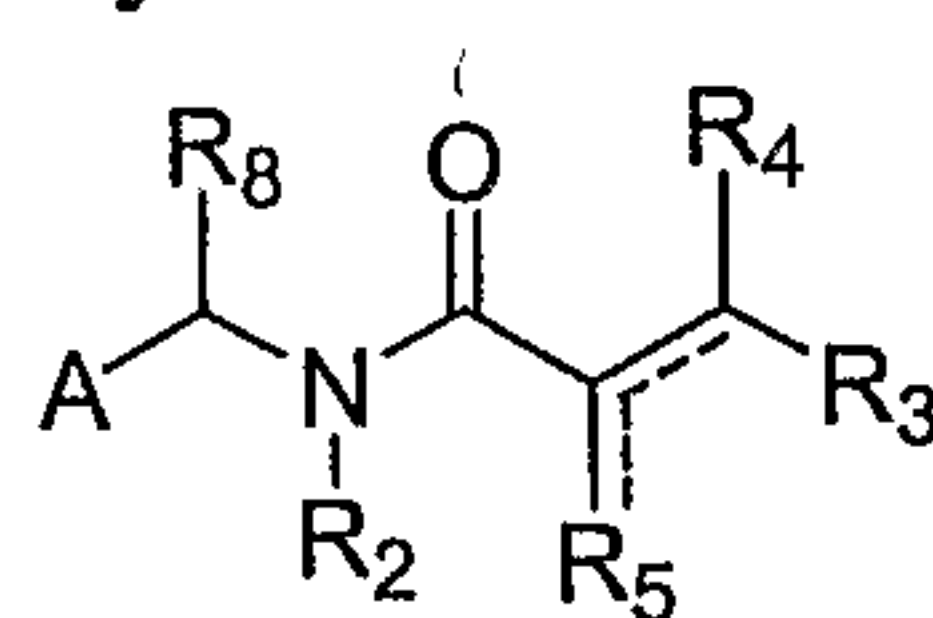
wherein,

15 R₄ is a water solubilizing group;

R₅ is H, alkyl, or cycloalkyl; and

n is an integer from 0 to 4, or pharmaceutically acceptable salts thereof.

In another embodiment, the enzyme inhibiting compositions of the present invention may comprise a compound depicted by formula II:



II

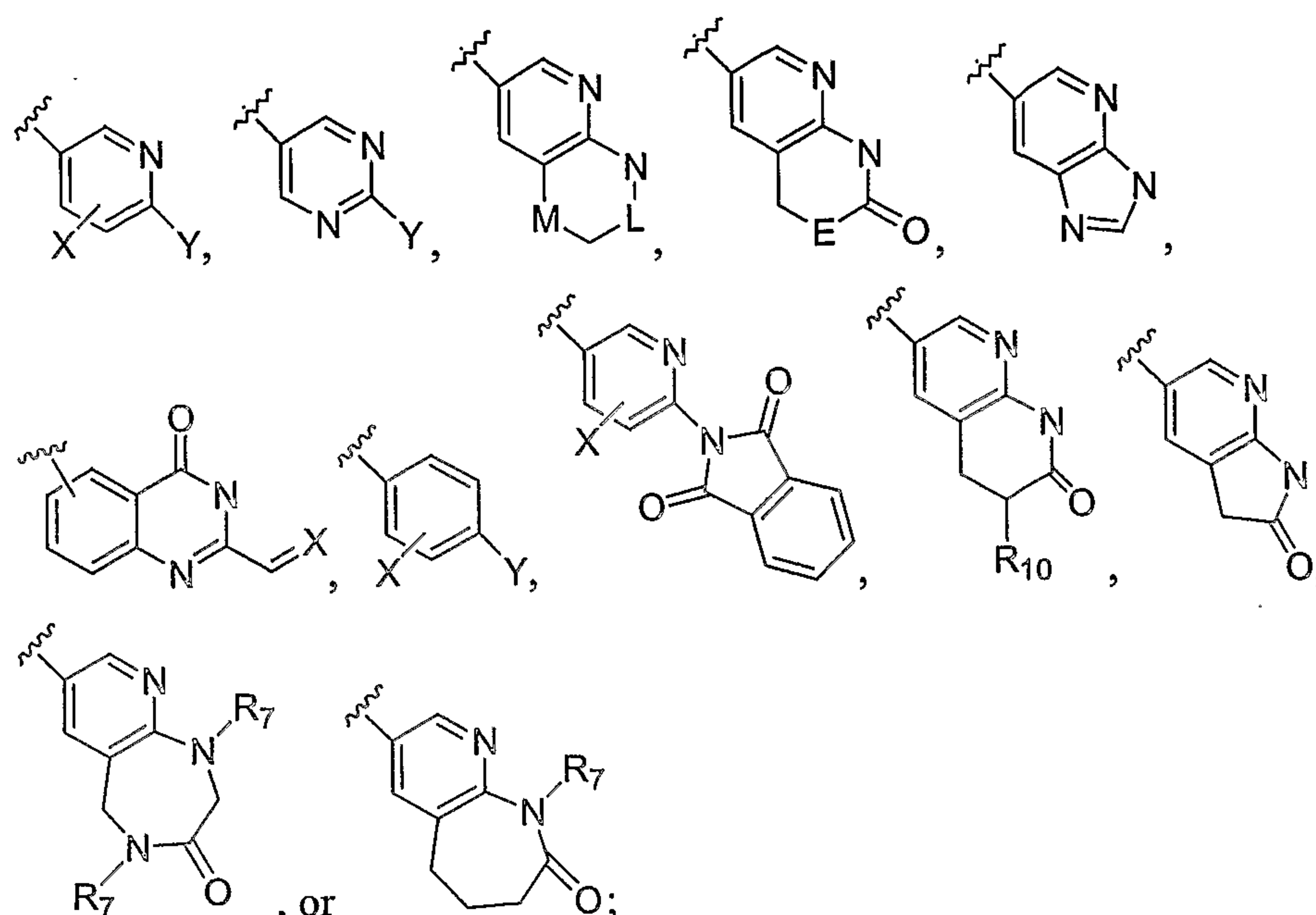
wherein, independently for each occurrence:

A is a bicyclic or tricyclic heteroaryl ring system of 8-12 atoms, wherein said bicyclic or tricyclic heteroaryl ring system contains 1-4 heteroatoms selected from

25 N, S, and O;

R₂ is alkyl or cycloalkyl;

R₃ is one of the following:



R_4 is H or C_{1-4} alkyl;

- 5 R_5 is CH_2 when the bond to which it is attached is a double bond; or R_5 is H or C_{1-4} alkyl when the bond to which it is attached is a single bond;

R_7 each independently is H, C_{1-4} alkyl, $-C_{0-6}$ alkyl-Ar, $-(CH_2)_{1-3}N(R')_2$, or $-(CH_2)_{1-3}O(R')$;

R_8 is H or C_{1-4} alkyl;

- 10 R_{10} is C_{1-4} alkyl, $N(R')_2$, $NHC(O)R'$, $NHCH_2C(O)R'$ or $NHC(O)CH=CHR'$

 indicates that one of two designated bonds is a double bond and the other a single bond;

Y is independently for each occurrence H, C_{1-4} alkyl, $N(R')_2$, $NHC(O)R'$, $NHCH_2C(O)R'$ or $NHC(O)CH=CHR'$;

- 15 X is H, C_{1-4} alkyl, CH_2OH , OR' , SR' , CN, $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I or $-S(O)_rCF_3$;

M is CH_2 , $-CH_2-CH_2-$, or O;

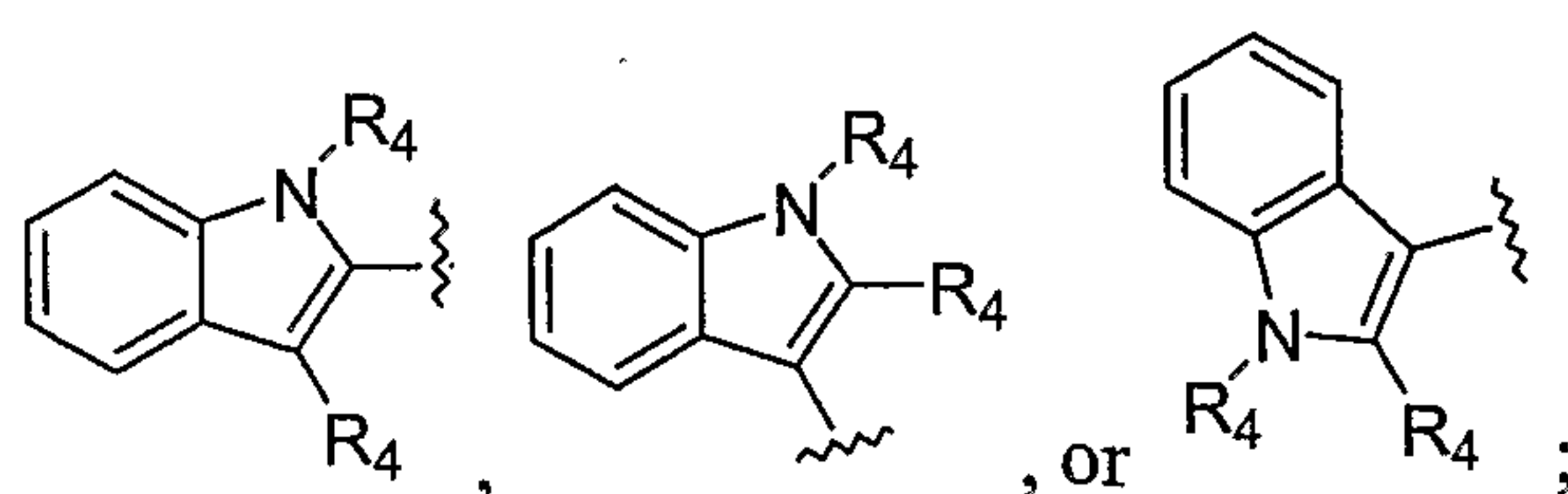
L is CH_2 or $C(O)$;

E is O or NR' ;

- 20 R' is independently for each occurrence H, C_{1-6} alkyl, $-C_{0-6}$ alkyl-Het or $-C_{0-6}$ alkyl-Ar; and

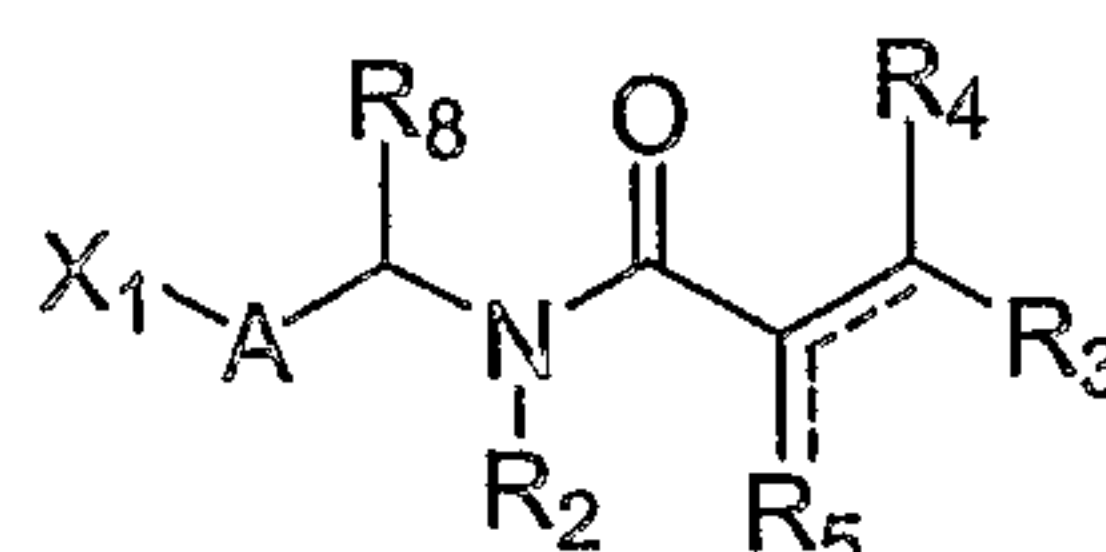
r is 0, 1 or 2; or pharmaceutically acceptable salts thereof.

In certain embodiments, A may be one of the following:



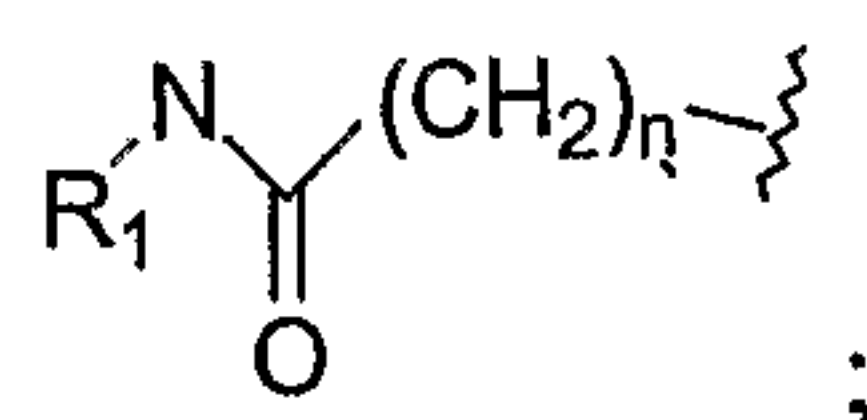
where R_4 is independently for each occurrence H, C_{1-4} alkyl, or $-N(R')_2$. In other embodiments, A is an indole moiety.

In another embodiment, the enzyme inhibiting compositions of the present invention may comprise is a compound depicted by formula III:



III

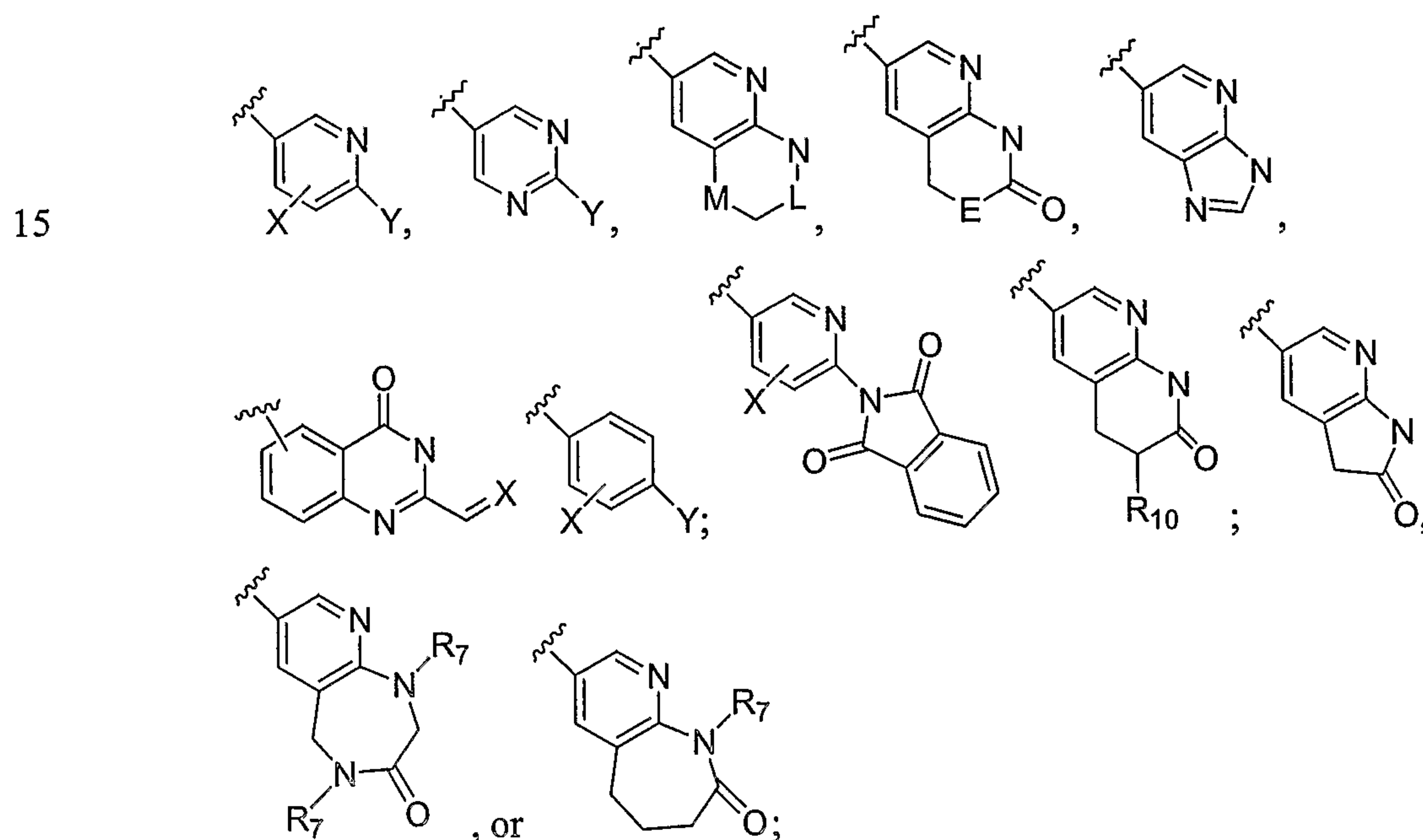
wherein X_1 is



A is a bicyclic or tricyclic heteroaryl ring system of 8-12 atoms, wherein said bicyclic or tricyclic heteroaryl ring system contains 1-4 heteroatoms selected from N, S, and O;

R_2 is alkyl or cycloalkyl;

R_3 is one of the following:



R_4 is H or C_{1-4} alkyl;

R_7 each independently is H, C_{1-4} alkyl, $-C_{0-6}$ alkyl-Ar, $-(CH_2)_{1-3}N(R')_2$, or $-(CH_2)_{1-3}O(R')$;

R_8 is H or C_{1-4} alkyl;

R_{10} is C_{1-4} alkyl, $N(R')_2$, $NHC(O)R'$, $NHCH_2C(O)R'$ or $NHC(O)CH=CHR'$

5  indicates that one of two designated bonds is a double bond and the other a single bond;

Y is independently for each occurrence H, C_{1-4} alkyl, $N(R')_2$, $NHC(O)R'$, $NHCH_2C(O)R'$ or $NHC(O)CH=CHR'$;

10 X is H, C_{1-4} alkyl, CH_2OH , OR' , SR' , CN , $N(R')_2$, $CH_2N(R')_2$, NO_2 , CF_3 , CO_2R' , $CON(R')_2$, COR' , $NR'C(O)R'$, F, Cl, Br, I or $-S(O)_rCF_3$;

M is CH_2 , $-CH_2-CH_2-$, or O;

L is CH_2 or $C(O)$;

E is O or NR' ;

15 R' is independently for each occurrence H, C_{1-6} alkyl $-C_{0-6}$ alkyl-Het or $-C_{0-6}$ alkyl-Ar;

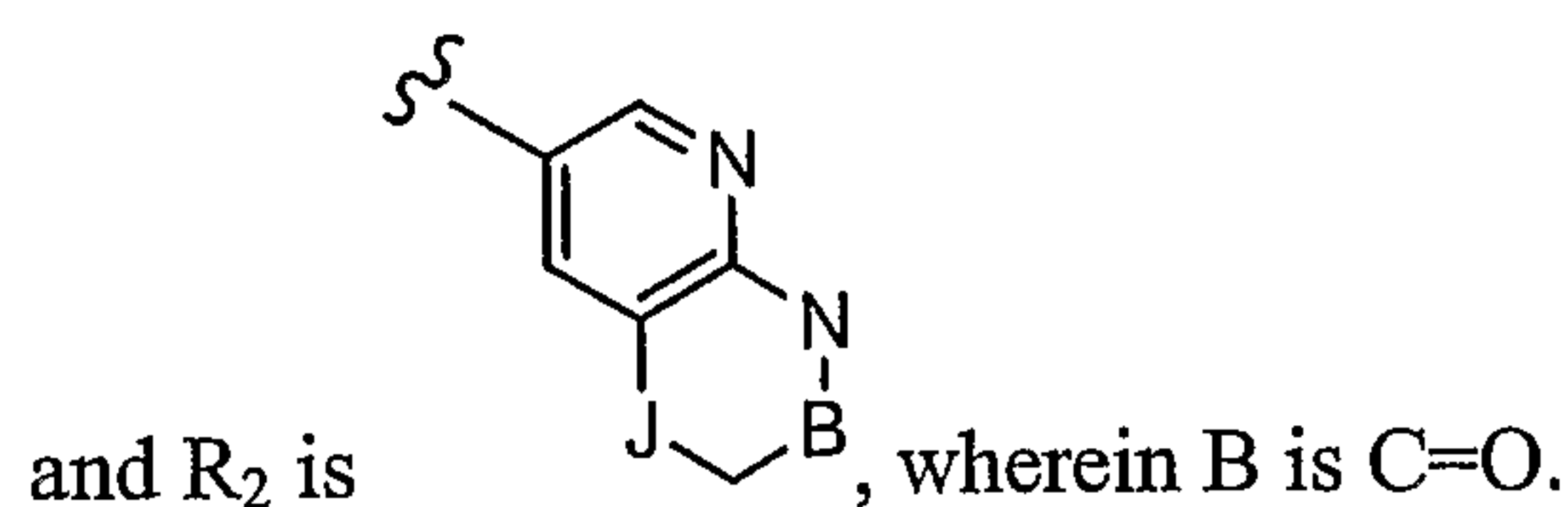
R_1 is a water solubilizing group;

n is an integer in the range 0 to 4;

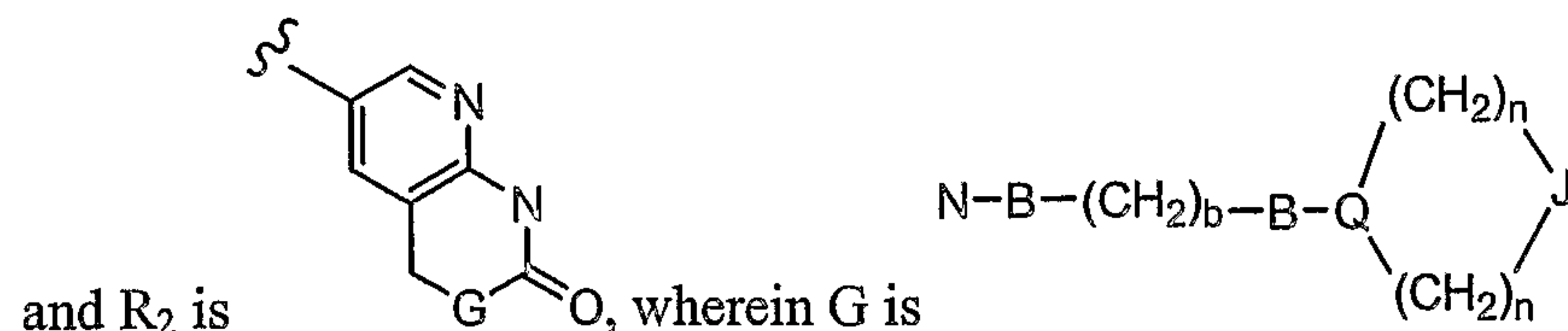
r is 0, 1 or 2; or pharmaceutically acceptable salts thereof.

20 In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C_2 alkenyl.

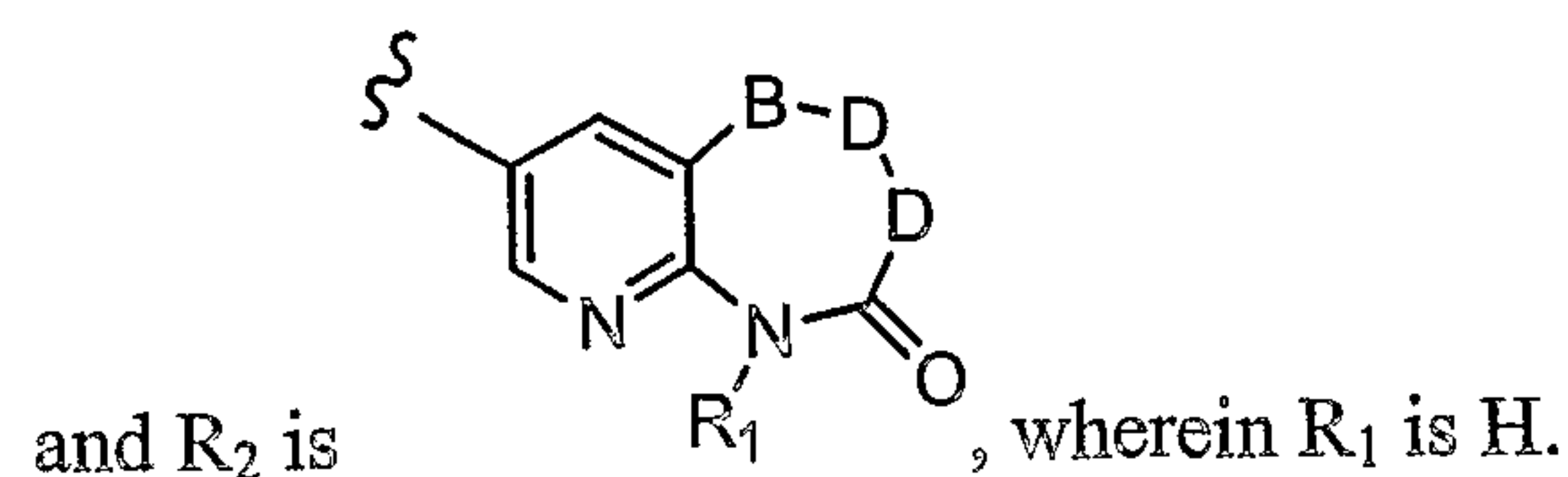
In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C_2 alkenyl



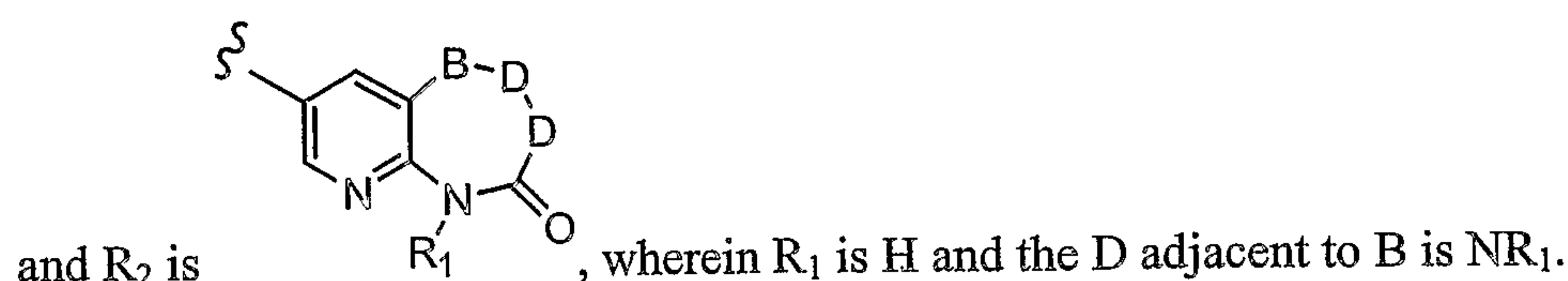
25 In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C_2 alkenyl



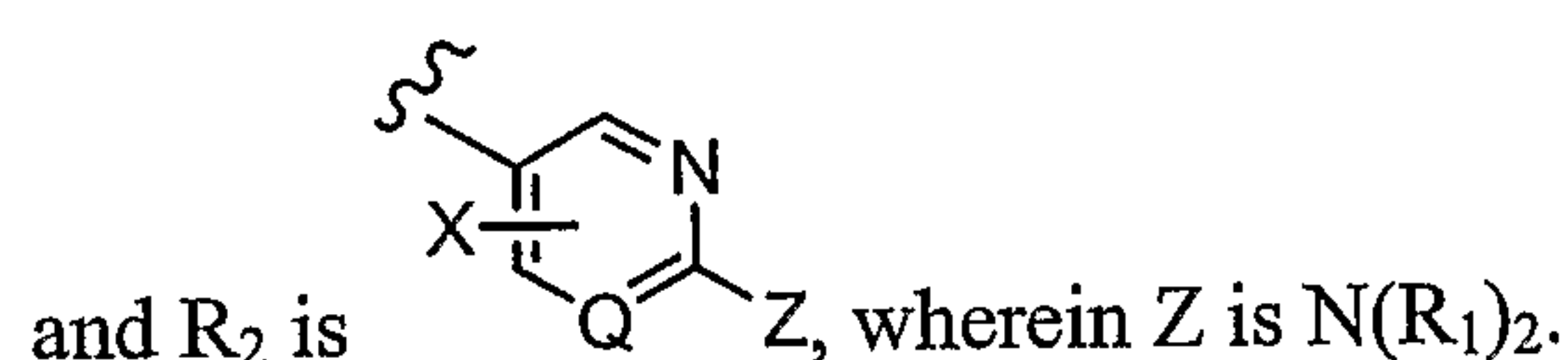
In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C₂ alkenyl



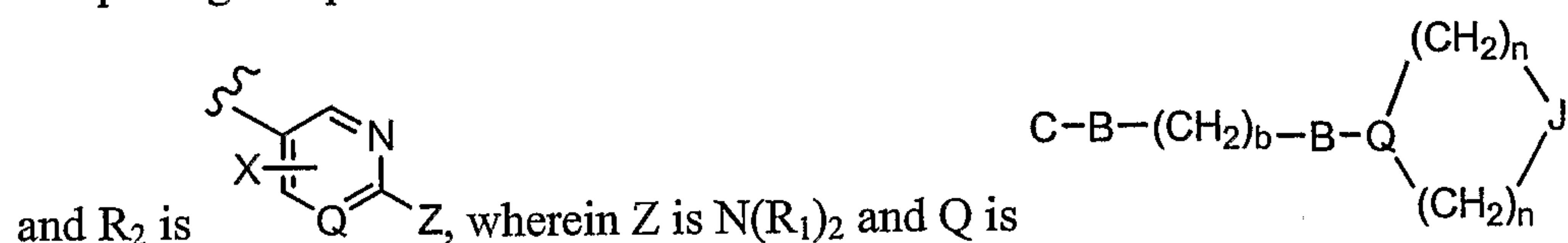
In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C₂ alkenyl



In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C₂ alkenyl



In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein L is a C₂ alkenyl



In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A is a 6 membered monocyclic aryl.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A is a 10 membered bicyclic aryl.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A is a 12 membered tricyclic aryl.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A is an 8 membered bicyclic heteroaryl.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A is a 9 membered bicyclic heteroaryl.

5 In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A comprises at least 1 heteroatom.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A comprises at least 2 heteroatoms.

10 In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A comprises at least 1 nitrogen atom.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A comprises at least 1 oxygen atom.

In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A comprises at least 1 sulfur atom.

20 In a further embodiment, the present invention includes antibacterial compositions comprising compounds of formula I and the attendant definitions, wherein A comprises at least 2 sulfur atoms.

The antibacterial compositions of the present invention comprise, but are not limited to, the following compounds:

25 (E)-3-(6-aminopyridin-3-yl)-N-(4,6-dichloro-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide;

(E)-3-(2-aminopyrimidin-5-yl)-N-(2-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-3-(6-aminopyridin-3-yl)-N-(1-ethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-3-(6-aminopyridin-3-yl)-N-(1-isopropyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

30 (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-[6-(pyridin-2-ylamino)pyridin-3-yl]acrylamide;

(E)-3-(6-aminopyridin-3-yl)-N-(1,4-dimethyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;

(E)-3-(6-aminopyridin-3-yl)-N-(3,3-dimethyl-3*H*-indene-1-ylmethyl)-N-methylacrylamide;

- (E)-3-(2-aminopyrimidin-5-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)acrylamide;
- (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 5 (E)-N-methyl-N-(2-methylbenzo[*b*]thiophen-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide;
- (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- 10 (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- (E)-N-(1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 15 (E)-3-(6-aminopyridin-3-yl)-N-(5-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(4-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(1*H*-indol-3-ylmethyl)-N-methylacrylamide
- 20 (E)-3-(6-aminopyridin-3-yl)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-[N-(methylaminocarbonylmethyl)amino]pyridin-3-yl]acrylamide;
- (E)-3-(6-amino-5-(methoxycarbonyl)pyridin-3-yl)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-
- 25 methylacrylamide;
- (E)-N-(1-benzyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(7-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- 30 (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide;
- (E)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)acrylamide;

- (E)-N-[1-(2-dimethylaminoethyl)-1*H*-indol-3-ylmethyl]-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 5 (E)-3-[6-amino-5-[[N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)amino]carbonylethyl]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- (E)-N-(2,3-dihydro-1*H*-3a-azacyclopenta[*a*]indene-8-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 10 (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)acrylamide;
- (E)-N-(1-ethyl-5-fluoro-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(7-chloro-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-
- 15 naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(6-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-N-(5-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 20 (E)-N-(6-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(7-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(7-hydroxy-1-methyl-1*H*-indol-3-ylmethyl)-N-
- 25 methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(6-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(5-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- 30 (E)-3-(6-aminopyridin-3-yl)-N-(4-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-N-methyl-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylamide;

- (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- (E)-3-[6-[N-(carboxymethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- 5 (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-[6-[N-(methylaminocarbonylmethyl)amino]pyridin-3-yl]acrylamide;
- (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methylacrylamide;
- (E)-2,N-dimethyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 10 (E)-3-[6-[N-(carboxymethyl)amino]pyridin-3-yl]-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-[6-[N-(methylaminocarbonylmethyl)amino]pyridin-3-yl]acrylamide;
- 15 (E)-3,N-dimethyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(4-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(5-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- 20 (E)-3-(6-aminopyridin-3-yl)-N-(7-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(7-methoxycarbonyl-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- 25 (E)-3-(6-aminopyridin-3-yl)-N-(7-fluoro-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)acrylamide;
- (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(7-chloro-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- 30 (E)-3-(6-aminopyridin-3-yl)-N-(2-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-N-(2-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;

- (E)-N-(5-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(4-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 5 (E)-N-(6-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(4-fluoro-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(7-carboxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- 10 (E)-N-(1,7-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(1,6-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(1,4-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-
- 15 naphthyridin-3-yl)acrylamide;
- (E)-N-(3,3-dimethyl-3*H*-indene-1-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(1,5-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 20 (E)-N-(7-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(7-hydroxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- N-Methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-
- 25 pyrido[2,3-*e*]-1,4-diazepin-7-yl)acrylamide;
- (E)-N-[1-(2-hydroxyethyl)-1*H*-indol-3-ylmethyl]-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(4-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 30 (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylamide;
- (E)-N-(4-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;

- (E)-N-(5-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(6-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 5 (E)-N-(naphthalen-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(quinolin-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(6-amino-7-oxo-5,6,7,8-tetrahydro-1,8-
- 10 naphthyridin-3-yl)acrylamide;
- (E)-N-(1-ethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-(naphthalen-1-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 15 (E)-N-(benzofuran-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(6-methoxycarbonyl-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide;
- (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-[3-(2-methoxyethyl)-2-oxo-1,2,3,4-
- 20 tetrahydropyrido[2,3-*d*]pyrimidin-6-yl]acrylamide;
- (E)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-[6-(methoxycarbonyl)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-N-methylacrylamide;
- 25 (E)-N-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-3-ylmethyl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-3-
- 30 ylmethyl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-ylmethyl)acrylamide;

- (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 5 (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-(benzofuran-3-ylmethyl)-N-methylacrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(3-methylbenzofuran-2-ylmethyl)acrylamide;
- (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(2-methylbenzofuran-3-ylmethyl)acrylamide;
- 10 (E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-methyl-N-(3-methylbenzofuran-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (E)-N-methyl-N-(2-methylbenzofuran-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-
- 15 naphthyridin-3-yl)acrylamide;
- (E)-(6-aminopyridin-3-yl)-N-methyl-N-[1-(1-methyl-1*H*-indol-2-yl)ethyl]acrylamide;
- (E)-(6-aminopyridin-3-yl)-N-methyl-N-[1-(1-methyl-1*H*-indol-3-yl)ethyl]acrylamide;
- (E)-N-methyl-N-[1-(1-methyl-1*H*-indol-2-yl)ethyl]-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- 20 (E)-N-methyl-N-[1-(1-methyl-1*H*-indol-3-yl)ethyl]-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
- (*E*)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-N-(1-propyl-naphthalen-2-ylmethyl)acrylamide hydrochloride;
- (*E*)-3-(3,3-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-N-
- 25 methyl-N-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride;
- (*E*)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-N-naphthalen-2-ylmethyl-acrylamide hydrochloride;
- (*E*)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-N-naphthalen-1-ylmethyl-acrylamide hydrochloride;
- 30 (*E*)-N-(4-Acetylamino-benzyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- (*E*)-N-(4-Methanesulfonyl-benzyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;

- (*E*)-*N*-(2-Methoxy-naphthalen-1-ylmethyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- (*E*)-*N*-Methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- 5 (*E*)-*N*-(2,3-Dimethyl-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- (*E*)-*N*-(4-Isopropyl-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- (*E*)-*N*-Indan-5ylmethyl-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- 10 (*E*)-*N*-Indan-5ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 15 (*E*)-*N*-(3,5-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-
- 20 *N*-(2,4,5-trimethoxy-benzyl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-phenanthren-9-ylmethyl-acrylamide hydrochloride;
- (*E*)-*N*-Acenaphthen-5-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 25 (*E*)-*N*-(4-Methoxy-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2,5-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-
- 30 pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-quinolin-4-ylmethyl-acrylamide hydrochloride;

- (*E*)-*N*-(4-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 5 (*E*)-*N*-(3,4-Dimethyl-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(2,4,6-trimethyl-benzyl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-
 10 *N*-(2,4,5-trimethyl-benzyl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-quinolin-3-ylmethyl-acrylamide hydrochloride;
- (*E*)-*N*-(3,4-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 15 (*E*)-*N*-Benzofuran-2-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(2-methyl-naphthalen-1-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Biphenyl-2-ylmethyl-methyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-
 20 pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Biphenyl-3-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2-Ethoxy-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 25 (*E*)-*N*-(2-Ethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(2,3,4-trimethoxy-benzyl)acrylamide hydrochloride;
- (*E*)-*N*-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-
 30 tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2,3-Diethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;

- (*E*)-*N*-(3-Ethoxy-2-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2-Ethoxy-3-methyl-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 5 (*E*)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-quinolin-5-ylmethyl-acrylamide hydrochloride;
- (*E*)-*N*-(3-Methoxy-2-propoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(3-Methoxy-2-isopropoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 10 (*E*)-*N*-methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(3-Chloro-2-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 15 (*E*)-*N*-(3-Chloro-2-ethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(4,5-Dimethyl-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 20 (*E*)-*N*-Methyl-*N*-(2-methyl-benzofuran-3-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-*N*-quinolin-5-ylmethyl-acrylamide hydrochloride;
- 25 (*E*)-*N*-benzyl-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- (*E*)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-(7-{2-[Methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid ethyl ester hydrochloride;
- 30 (*E*)-*N*-(2,3-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;

- (*E*)-*N*-(2-Methoxy-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
 I-(+)-(*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(1-naphthalen-1-yl-ethyl)acrylamide hydrochloride;
- 5 (*S*)-(-)-(*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(1-naphthalen-1-yl-ethyl)acrylamide hydrochloride;
 (*E*)-*N*-Benzo[*b*]thiophen-2-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
 (*E*)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-
 10 (3-trifluoromethyl-benzyl)acrylamide hydrochloride;
 (*E*)-*N*-(2-Chloro-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
 (*E*)-*N*-Methyl-*N*-(4-methyl-benzyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 15 (*R*)-(-)-(*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10^a-hexahydro-1*H*-3^a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride;
 (*S*)-(+)-(*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10^a-hexahydro-1*H*-3^a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride;
 (*E*)-3-[4-(4-Methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-
 20 yl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide hydrochloride;
 (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
 (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[4-(2-morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride;
- 25 (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylamide hydrochloride;
 (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride;
- 30 (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylamide hydrochloride;

- (*S*)-(+)-(*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10^a-hexahydro-1*H*-3^a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride;
- (*R*)-(-)-(*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10^a-hexahydro-1*H*-3^a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride;
- 5 (*E*)-*N*-(4-Fluoro-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(4-Chloro-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-
- 10 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride;
- (*E*)-*N*-(2-Isopropoxy-3-methoxy-benzyl)-*N*-methyl-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-{4-[3-(4-methyl-piperazin-1-yl)propyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylamide
- 15 hydrochloride;
- (*E*)-*N*-Methyl-*N*-(2-methyl-benzofuran-3-ylmethyl)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride;
- (*E*)-*N*-(3-Chloro-benzo[*b*]thiophen-2-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- 20 (*E*)-*N*-(5-Chloro-1-methyl-1*H*-indol-2-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(1,7-Dimethyl-1*H*-indol-2-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(5-Fluoro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-
- 25 2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-*N*-(5-Chloro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-(1,7-dimethyl-1*H*-indol-2-ylmethyl)-*N*-methyl-acrylamide hydrochloride;
- 30 (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-(2-ethoxy-3-methoxy-benzyl)-*N*-methyl-acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide;

- (*E*)-7-{2-[Methyl-(1-methyl-1*H*-indol-3-ylmethyl)-carbamoyl]-vinyl}-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester;
- (*E*)-3-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- 5 (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridin-6-yl)acrylamide;
- (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridin-6-yl)acrylamide;
- (*E*)-3-(6-Amino-5-{2-[methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]ethyl}pyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 10 (*E*)-3-(6-Amino-5-piperidin-1-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (*E*)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide hydrochloride;
- 15 (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide hydrochloride;
- (*E*)-3-[6-Amino-5-(4-benzyl-piperidin-1-ylmethyl)pyridin-3-yl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide hydrochloride;
- (*E*)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-naphthalen-2-ylmethyl-
- 20 acrylamide hydrochloride;
- (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride;
- (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)acrylamide hydrochloride;
- 25 (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride;
- (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-(3,4-dimethyl-thieno[2,3-*b*]thiophen-2-ylmethyl)-*N*-methyl-acrylamide hydrochloride;
- (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-(2-ethoxy-3-methoxy-
- 30 benzyl)-*N*-methyl-acrylamide hydrochloride;
- (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)acrylamide hydrochloride;

- (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-benzofuran-2-ylmethyl-*N*-methyl-acrylamide hydrochloride;
- (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-(3-methoxy-2-propoxy-benzyl)-*N*-methyl-acrylamide hydrochloride;
- 5 (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-(2-ethoxy-3-methyl-benzyl)-*N*-methyl-acrylamide hydrochloride;
- (*E*)-*N*-(3-Methoxy-2-propoxy-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2-Isopropoxy-3-methoxy-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-
- 10 [1,8]naphthyridin-3-yl)acrylamide hydrochloride;
- (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide hydrochloride;
- (*E*)-3-[6-(2,5-Dioxo-pyrrolidin-1-yl)pyridin-3-yl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- 15 (*E*)-*N*-(5-{2-[Methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}pyridin-2-yl)succinamide;
- (*E*)-*N*-(5-{2-[Methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}pyridin-2-yl)-4-(4-methyl-piperazin-1-yl)-4-oxo-butyramide;
- (*E*)-*N*-(5-{2-[Methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}pyridin-2-yl)-4-
- 20 morpholin-4-yl-4-oxo-butyramide;
- (*E*)-1-Methyl-piperidine-4-carboxylic acid (5-{2-[methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}pyridin-2-yl)amide;
- (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-(2-pyridin-4-yl-acetylamino)pyridin-3-yl]acrylamide;
- 25 (*E*)-1-Acetyl-piperidine-4-carboxylic acid (5-{2-[methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}pyridin-2-yl)amide;
- (*E*)-3-(6-Amino-pyridin-3-yl)-*N*-(2,3-dimethoxy-benzyl)-*N*-methyl-acrylamide;
- (*E*)-*N*-(4-Acetylamino-benzyl)-3-(6-amino-pyridin-3-yl)-*N*-methyl-acrylamide;
- (*E*)-3-[3-(2-Dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]-
- 30 *N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide;
- (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;

- (*E*)-*N*-Methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-Acenaphthen-5-ylmethyl-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- 5 (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-(6-{2-[Methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}-2-oxo-1,4-dihydro-10 2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)acetic acid;
- Sodium (*E*)-(6-{2-[methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)acetate;
- Sodium (*E*)-(6-{2-[methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)carbamoyl]vinyl}-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)acetate;
- 15 (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-{3-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl}acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-{3-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl}acrylamide hydrochloride;
- 20 (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-{3-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl}acrylamide hydrochloride;
- (*E*)-2-Amino-5-{2-[methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}-*N*-(2-morpholin-4-yl-ethyl)nicotinamide hydrochloride;
- 25 (*E*)-*N*-(3-Methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[3-(3-morpholin-4-yl-propyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-[3-(3-morpholin-4-yl-propyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-(5-{2-[Methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)carbamoyl]vinyl}pyridin-2-30 yl)-4-(4-methyl-piperazin-1-yl)-4-oxo-butyramide;
- (*E*)-*N*-(2,3-Diethoxy-benzyl)-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;

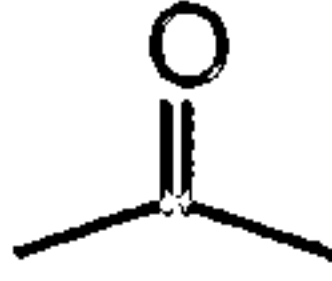
- (*E*)-*N*-(2-Isopropoxy-3-methoxy-benzyl)-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-(3-Methoxy-2-propoxy-benzyl)-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- 5 (*E*)-*N*-Methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-Methyl-*N*-(2-methyl-benzofuran-3-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-(3-Chloro-2-ethoxy-benzyl)-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- 10 (*E*)-*N*-(4-Fluoro-naphthalen-1-ylmethyl)-*N*-methyl-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylamide hydrochloride;
- (*E*)-*N*-(2,3-Dimethoxy-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide;
- 15 (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide;
- (*E*)-3-(6-Amino-pyridin-3-yl)-*N*-methyl-*N*-thieno[3,2-*c*]pyridin-2-ylmethyl-acrylamide;
- (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-thieno[3,2-*c*]pyridin-2-ylmethyl-acrylamide;
- 20 (*E*)-*N*-Methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-*N*-thieno[3,2-*c*]pyridin-2-ylmethyl-acrylamide;
- (*E*)-3-(6-Amino-pyridin-3-yl)-*N*-(2-ethoxy-3-methoxy-benzyl)-*N*-methyl-acrylamide hydrochloride;
- (*E*)-3-(6-Amino-pyridin-3-yl)-*N*-(2-propoxy-3-methoxy-benzyl)-*N*-methyl-acrylamide
- 25 hydrochloride;
- (*E*)-3-(6-amino-pyridin-3-yl)-*N*-(2-isopropoxy-3-methoxy-benzyl)-*N*-methyl-acrylamide hydrochloride;
- (*E*)-*N*-Acenaphthen-5-ylmethyl-3-(6-amino-pyridin-3-yl)-*N*-methyl-acrylamide hydrochloride;
- 30 (*E*)-*N*-(1*H*-Indol-5-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide;
- (*E*)-*N*-Methyl-*N*-(1-methylindol-5-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide;

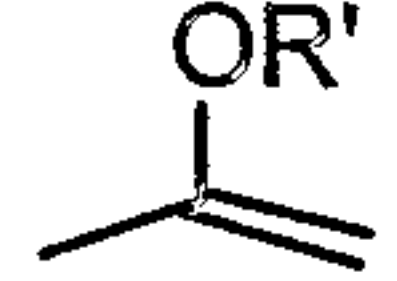
- (*E*)-*N*-(1*H*-Indol-7-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide;
- (*E*)-*N*-Methyl-*N*-(1-methylindol-7-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide;
- 5 (*E*)-*N*-(1*H*-Indol-6-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide;
- (*E*)-*N*-3-(6-Amino-pyridin-3-yl)-*N*-methyl-*N*-(2-methyl-benzofuran-3-ylmethyl)-acrylamide hydrochloride;
- (*E*)-3-(3,3-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)acrylamide hydrochloride;
- 10 (*E*)-*N*-Methyl-*N*-(3-methyl-1*H*-inden-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride;
- (*E*)-3-(6-{2-[Methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)carbamoyl]vinyl}-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)propionic acid ethyl ester;
- 15 (*E*)-3-(6-amino-5-cyano-pyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-acrylamide hydrochloride;
- (*E*)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-1,2,3,4-tetrahydro-pyrido-[2,3-*b*]pyrazin-7-yl)-acrylamide;
- N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-
- 20 [1,8]naphthyridin-3-yl)-acrylamide;
- N*-Methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-acrylamide;
- N*-Methyl-*N*-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-acrylamide;
- 25 *N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide;
- N*-Acenaphthen-5-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylamide; or
- N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]-acrylamide.
- 30

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

5 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.

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

It is believed that the compositions of the present invention comprising compounds of formulas I-III are antibacterial because the compounds inhibit FabI, FabK, or both. It may be, however, that for some or all of the compounds, they inhibit other enzymes in
15 addition or inhibit completely different enzymes. The exact mechanism by which the compositions of the present invention achieve their antibacterial properties is not meant to be limiting.

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
20 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, PCT Published Patent Application Nos. WO 0027628 and WO 0210332; and PCT Patent Application PCT/US03/38706.

25 Synthetic Routes to Compounds of Formula I

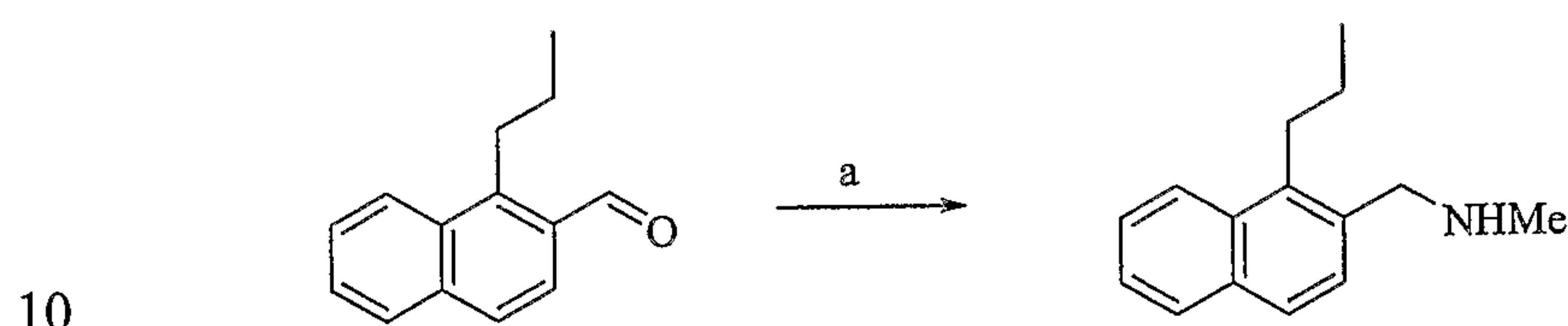
A generalized chemical approach to assembling compounds of formula I is based on viewing the analogs as consisting of a central ene-amide flanked left-hand side (LHS) and right-hand side (RHS) moieties. Schematically, this is depicted in Figure 2. Two possible bond disconnections envisioned in a retrosynthetic sense are shown with dashed lines.

30 Schemes I to XXXV illustrate some of the general methods that can be used in the synthesis of compounds of formula I. 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.

Schemes I to VIII disclose the basic chemistry involved in the synthesis of the left hand side moieties of formula I wherein the requisite LHS coupling partners are amines and the late stage chemistry involves formation of the amide linkage. The amines are typically arylalkyl-amines which are most conveniently prepared from commercially available arylcarbaldehydes by the action of a reducing agent such as sodium borohydride in the presence of an alkyl amine such as methyl amine (Scheme I).

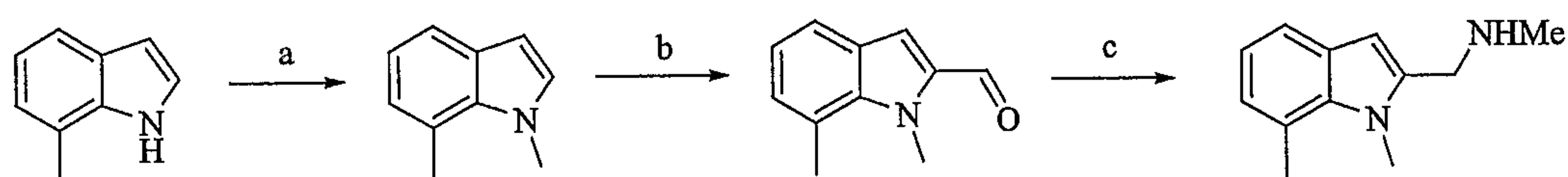
Scheme I



(a) i. MeNH₂, MeOH; ii. NaBH₄, EtOH

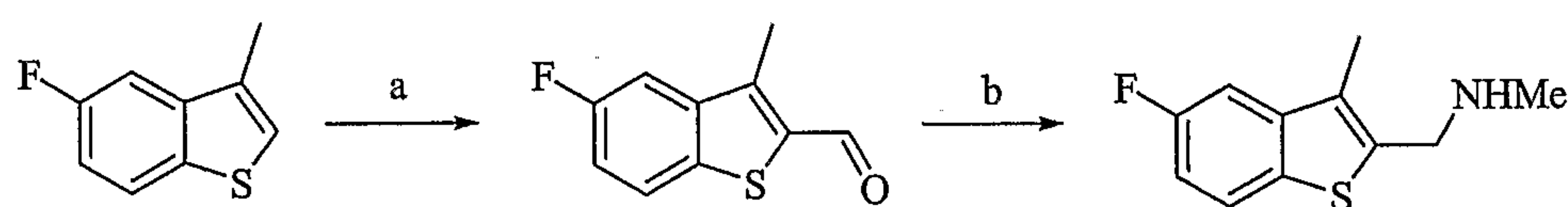
When the arylcarbaldehydes are not commercially available their synthesis can be effected by a number of general methods including the action of dimethylformamide on the lithium salt of aryl anions (Scheme Iib and IIIa).

15 Scheme II



(a) NaH, CH₃I, DMF; (b) *n*-BuLi, TMEDA, Et₂O, DMF; (c) i. CH₃NH₂, MeOH; ii. NaBH₄, EtOH

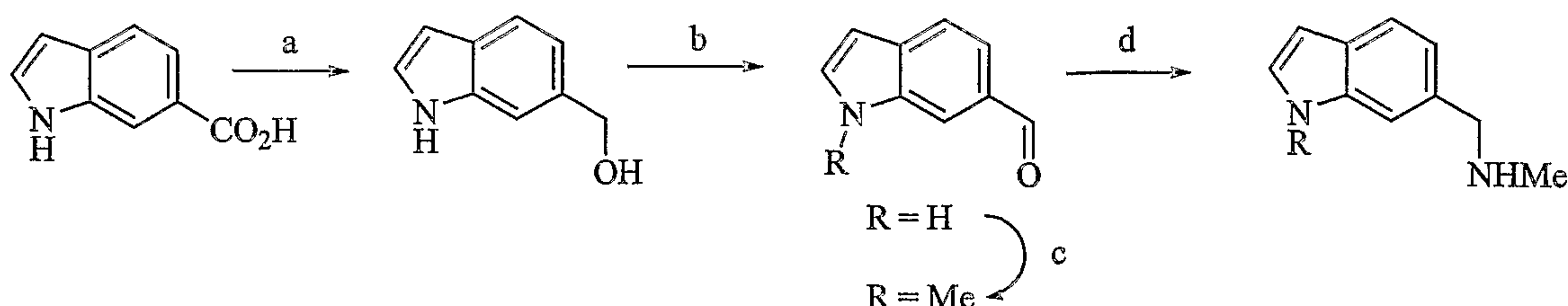
20 Scheme III



(a) *n*-BuLi, THF, DMF; (c) i. CH₃NH₂, MeOH; ii. NaBH₄, EtOH

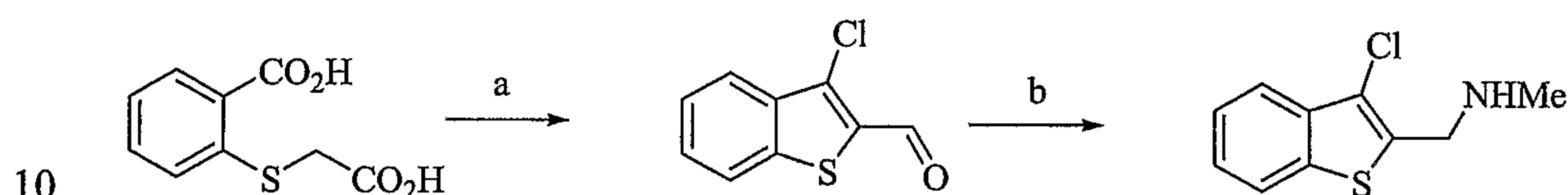
Other methods of obtaining the desired arylcarbaldehydes include the widely employed oxidation of alcohols (Scheme Ivb) and a variety of miscellaneous methods (Scheme Va and Via).

5 Scheme IV



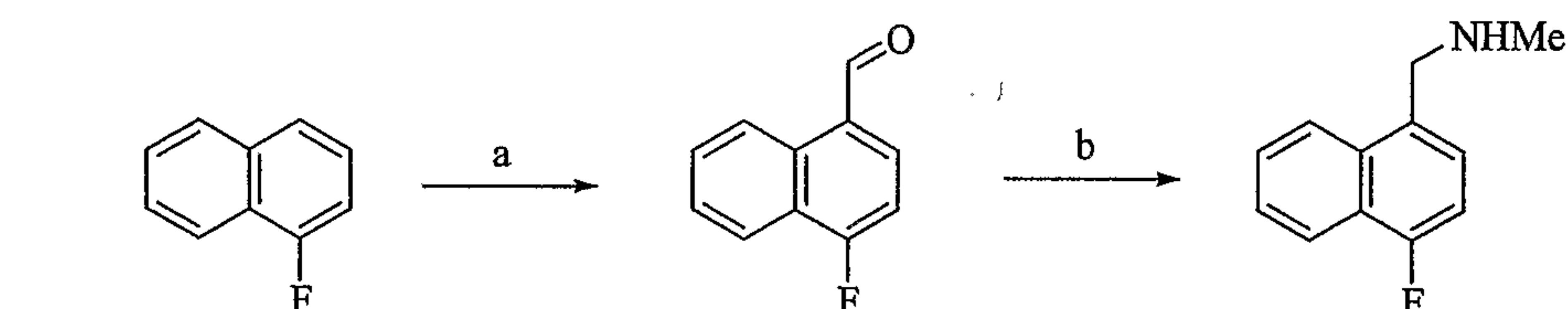
(a) LAH, THF; (b) Dess-Martine periodinane, CH_2Cl_2 , DMF; (c) NaH, CH_3I , DMF (d) i. CH_3NH_2 , MeOH; ii. NaBH_4 , EtOH

Scheme V



(a) POCl_3 , DMF; (b) i. CH_3NH_2 , MeOH; ii. NaBH_4 , EtOH

Scheme VI

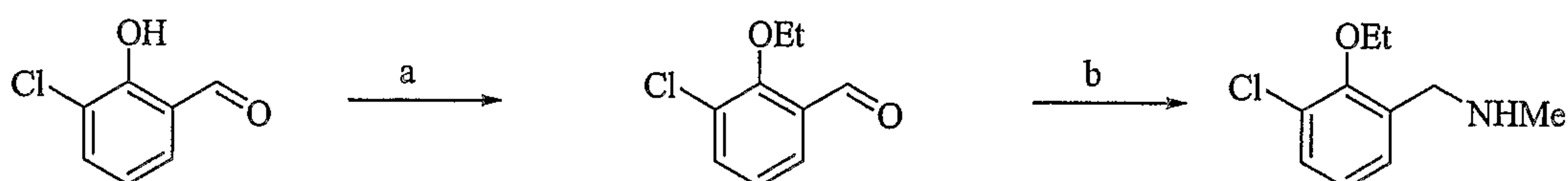


(a) $\text{CH}_3\text{OCHCl}_2$, SnCl_4 , CH_2Cl_2 ; (b) i. MeNH_2 , MeOH; ii. NaBH_4 , EtOH

During the course of these syntheses it may be desirable to alkylate indole-like nitrogens. This can be accomplished either prior to (Scheme IIa) or after formation of said carbaldehydes (Scheme Ivc) by the action of strong bases such as sodium hydride and the addition of alkylating agents such as alkyl halides. Likewise oxygen atoms appended to the aromatic systems (e.g. phenols) can be alkylated by the action of base (potassium carbonate) and an alkylhalide (Scheme VIIa).

20

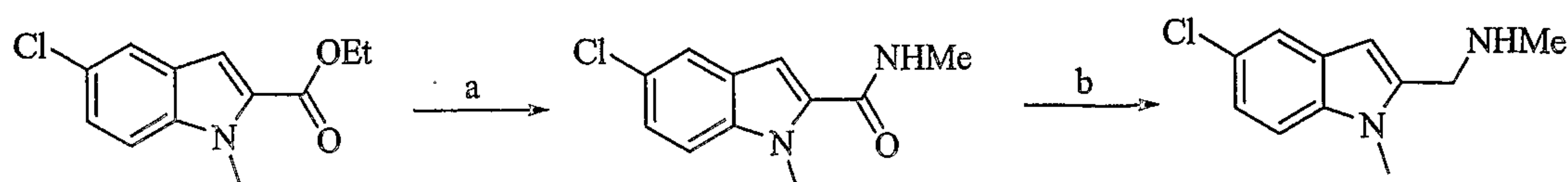
Scheme VII



(a) Iodoethane, K_2CO_3 , DMF; (b) i. MeNH_2 , MeOH; ii. NaBH_4 , EtOH

Yet another approach to the formation of the desired amines can be from the reduction of precursor amides (Scheme VIII)

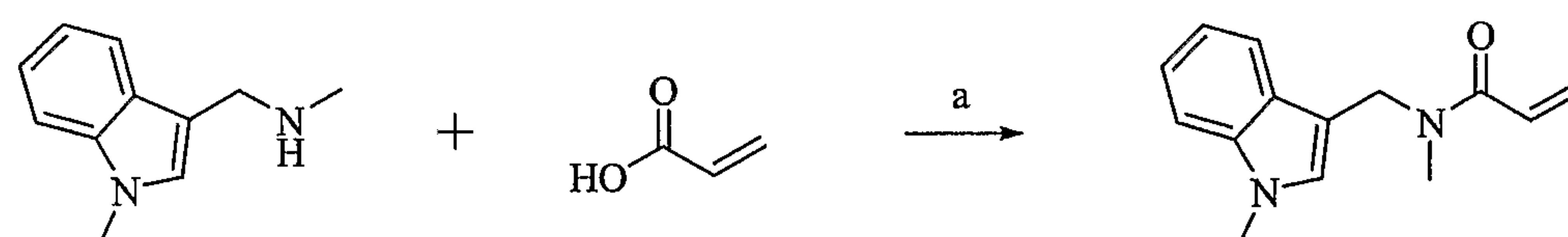
Scheme VIII



5 (a) $\text{CH}_3\text{Al}(\text{Cl})\text{NHCH}_3$, toluene; (b) LiAlH_4 , THF

Scheme IX describes the basic chemistry involved in the synthesis of the left hand side moieties of formula I wherein the requisite LHS coupling partners are ene-amides and the late stage chemistry involves formation of a carbon-carbon bond. The carbon-carbon bond formation is usually accomplished by Heck type chemistry which will be described subsequently. The ene-amide is prepared by activation of acrylic acid to undergo coupling reaction (with an amine) by any one of the known methods for amide bond formation. One typically used procedure is to treat acrylic acid with a solution of a tertiary amine in DMF followed by the addition of 1-hydroxybenzotriazole hydrate and a carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride. The reaction mixture is then treated with the desired arylalkylamine such as methyl-(1-methyl-1*H*-indol-3-ylmethyl)-amine (Scheme IX).

Scheme IX



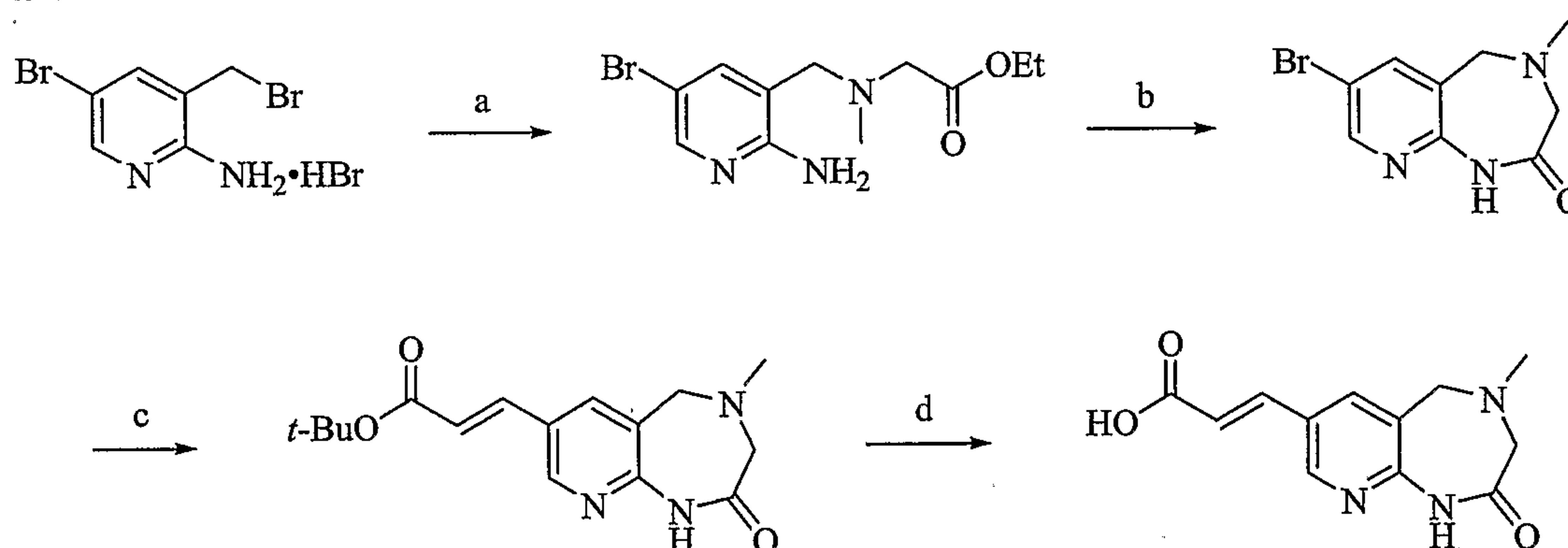
20 (a) $(i\text{-Pr})_2\text{EtN}$, EDC, HOBT, DMF

Schemes X to XXIV disclose the basic chemistry involved in the synthesis of the right hand side moieties of formula I wherein the requisite RHS coupling partners are carboxylic acids and the late stage chemistry involves formation of the amide linkage. The carboxylic acids are typically arylalkenyl carboxylic acids whose preparation is illustrated by the schemes described below. A common starting material, 5-bromo-3-bromomethylpyridin-2-ylamine hydrobromide, is used in the construction of the right hand side moieties described in Schemes X-XVII. In some embodiments of the invention, this material is reacted with a commercial secondary amine (Schemes X-XII) or reacted with a secondary amine which is prepared in the manner illustrated (Schemes XIII-XIV). In either case, a

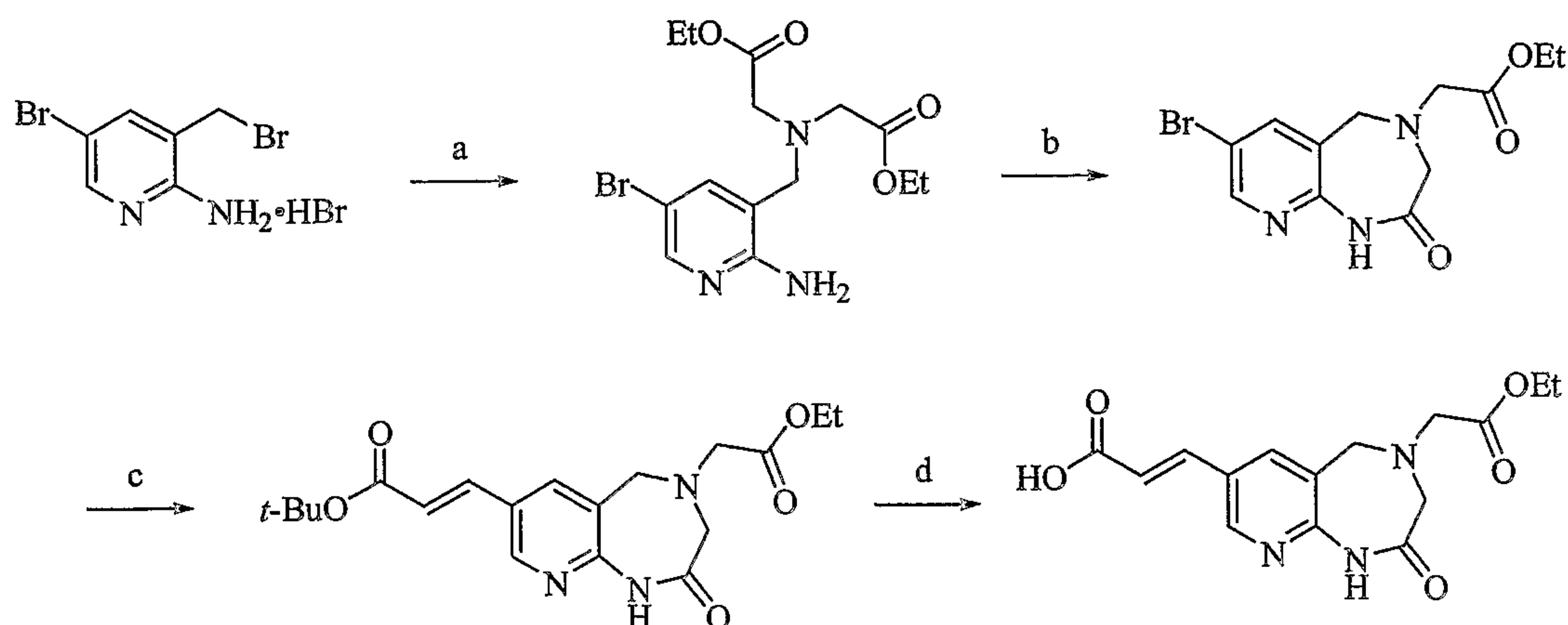
tertiary base is employed. A common feature of the resultant products are compounds incorporating a pendent alkyl ester and an aminopyridine moiety which react in the presence of a base like sodium hydride to form the pyridodiazepinone bicyclic unit.

- 5 The pyridodiazepinones prepared in this manner have in common a bromine substitution in the pyridine ring. As will be seen from inspection of the Schemes X-XIV synthesis of arylalkenyl acids proceeds from intermediary bromo-pyridodiazepinones via Heck chemistry (e.g. Scheme Xc). Heck chemistry is carried out by admixture of an arylbromide with an alkylacrylate, such as *tert*-butylacrylate, in the presence of a palladium catalyst ($\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$) and a tertiary base such as di-(isopropyl)ethylamine in an appropriate solvent or solvents (e.g. DMF and EtCN). The desired carboxylic acid is
- 10 obtained by acid-catalysed hydrolysis of the *tert*-butyl ester (e.g. Scheme Xd).

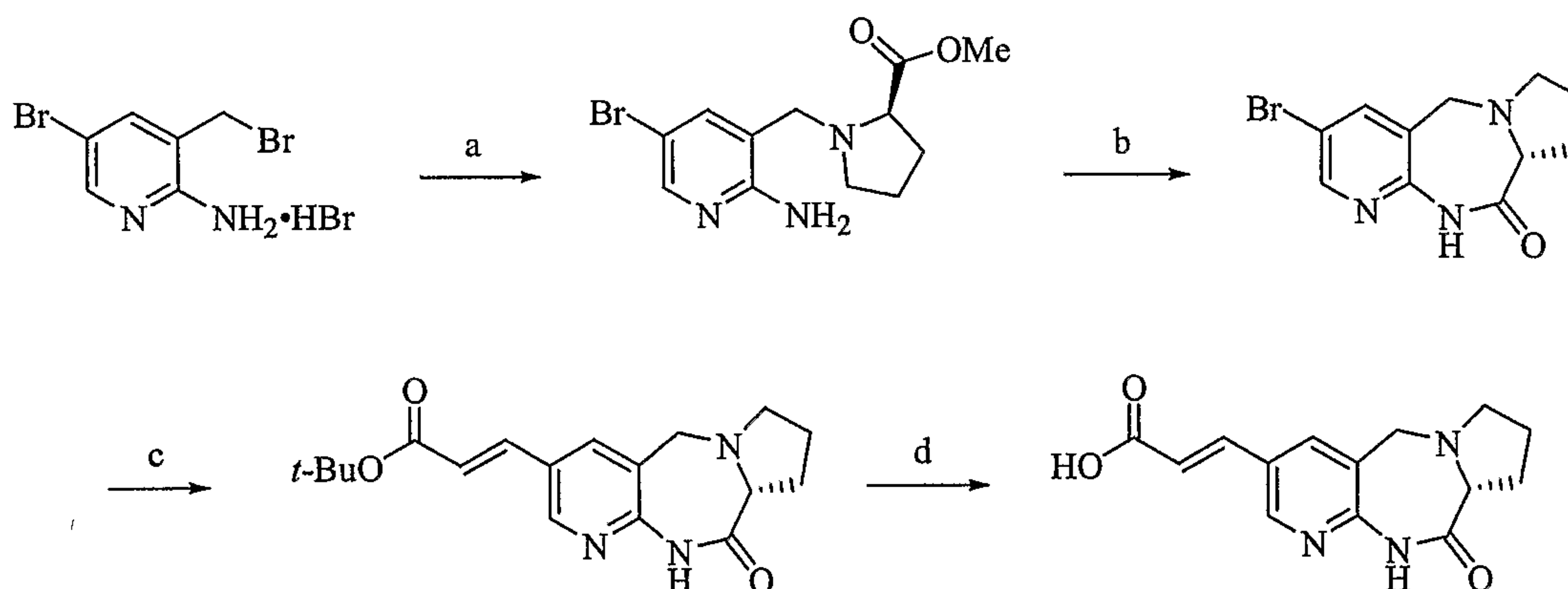
Scheme X



- 15 (a) sarcosine ethyl ester hydrochloride, Et_3N , DMF; (b) NaH, DMSO; (c) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{EtN}$, EtCN, DMF; (d) i. TFA, CH_2Cl_2 ; ii. 4 N HCl/dioxane

Scheme XI

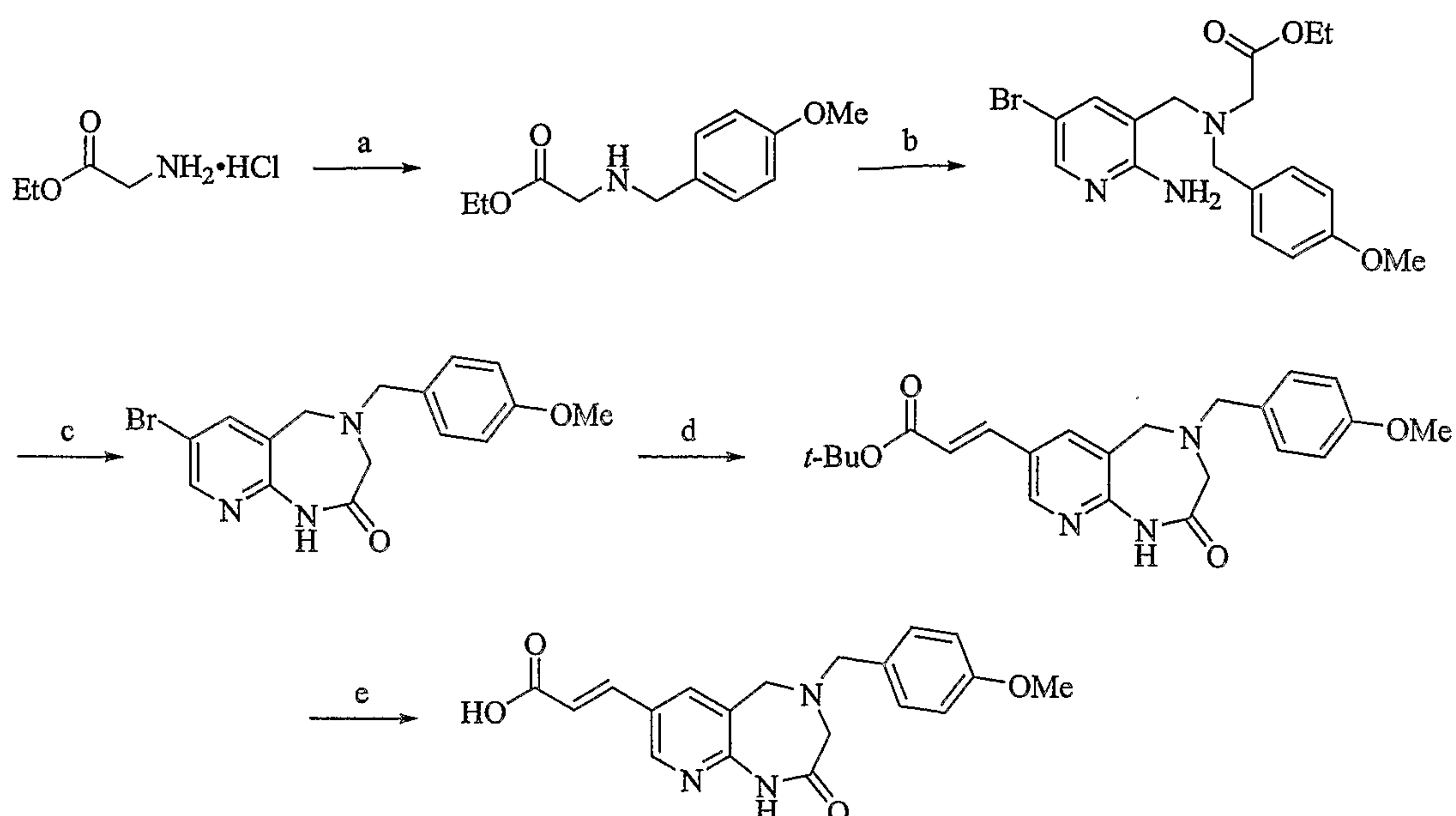
- 5 (a) diethyl iminodiacetate, Et_3N , CH_3CN ; (b) NaH , DMSO ; (c) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(I\text{-Pr})_2\text{EtN}$, EtCN , DMF ; (d) i. TFA , CH_2Cl_2 ; ii. 4 N HCl /dioxane

Scheme XII

10

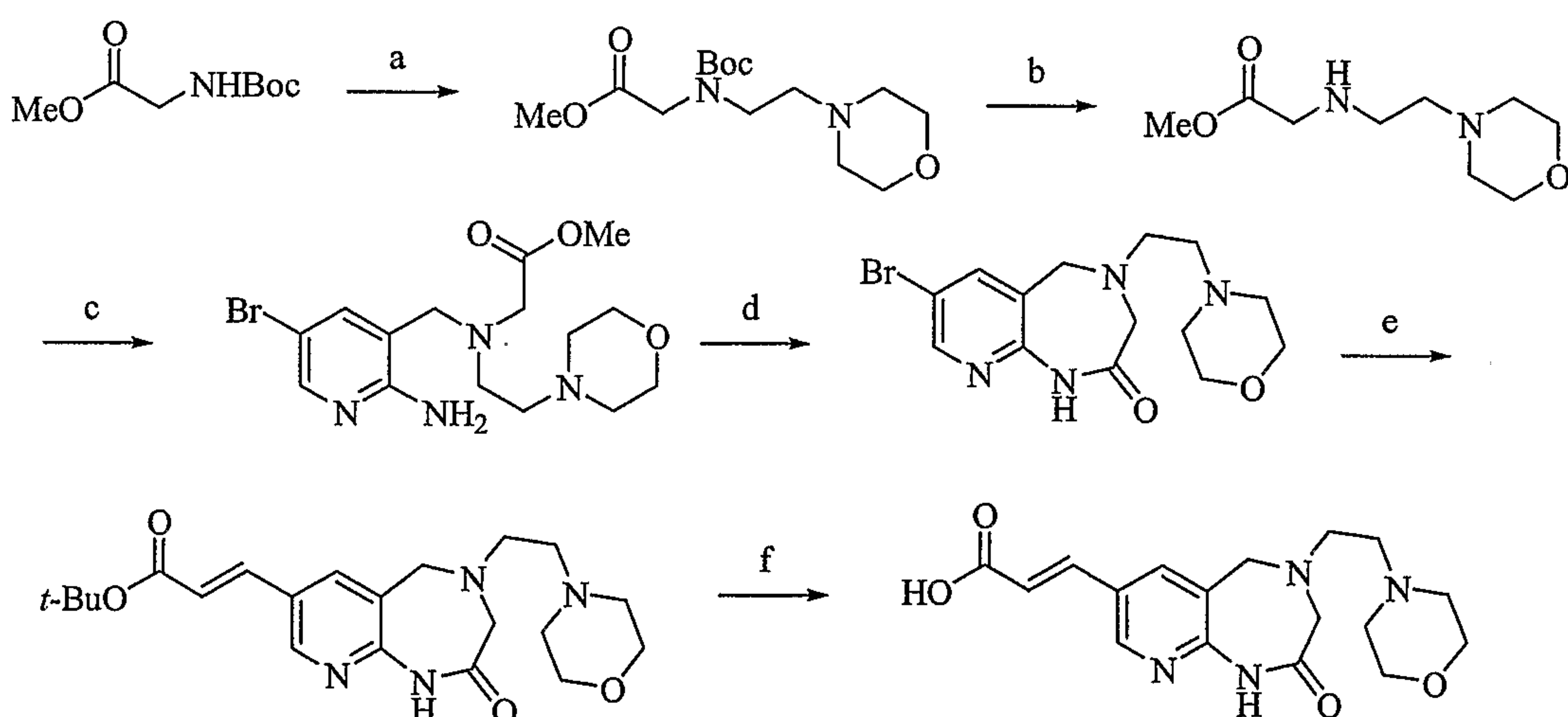
- (a) D-proline methyl ester hydrochloride, Et_3N , DMF ; (b) NaH , DMSO ; (c) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(I\text{-Pr})_2\text{EtN}$, EtCN , DMF ; (d) i. TFA , CH_2Cl_2 ; ii. 4 N HCl /dioxane

Scheme XIII



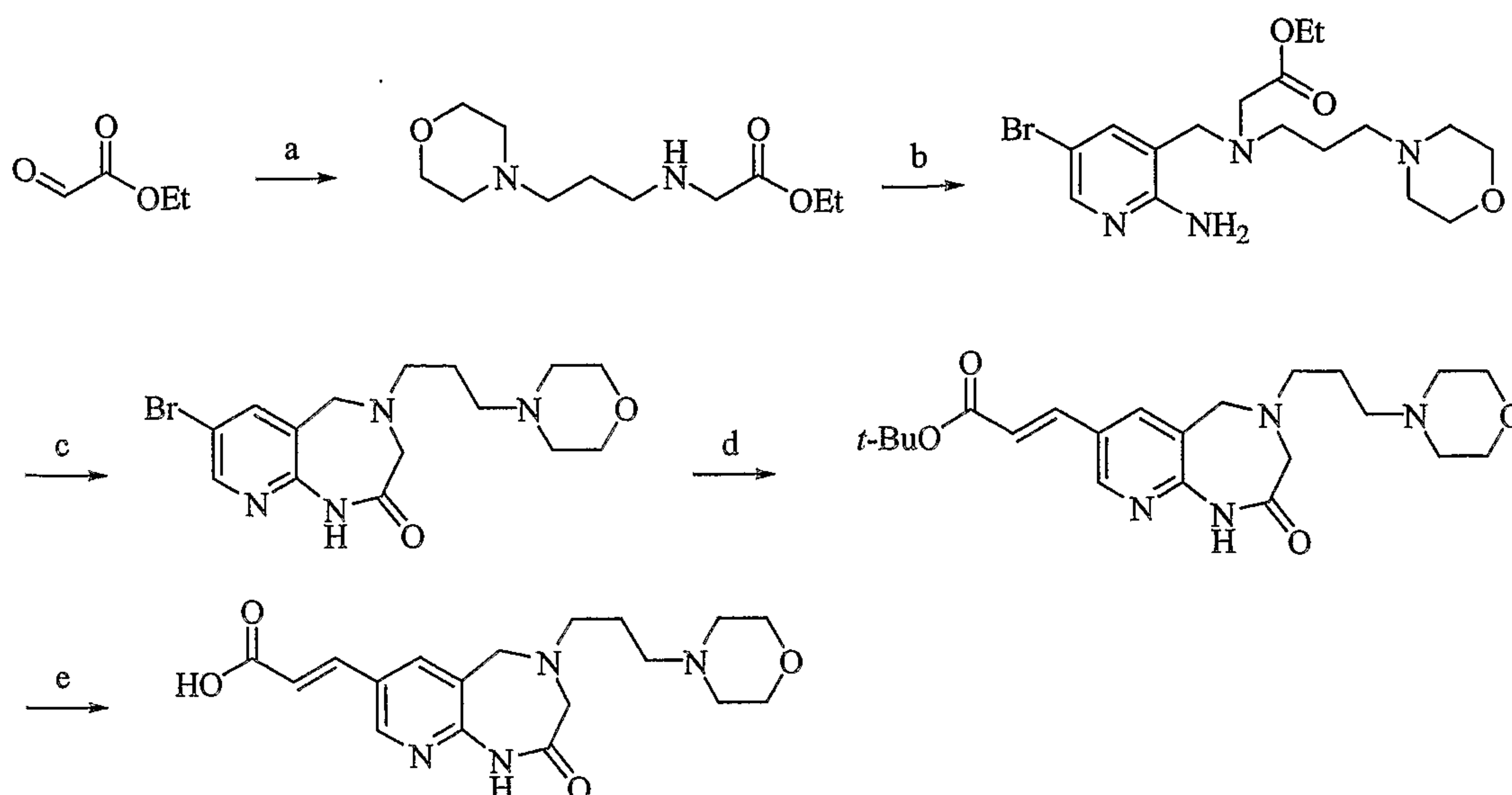
- (a) *p*-anisaldehyde, NaBH₃CN, MeOH; (b) 5-bromo-3-(4-methoxybenzyl)pyridin-2-ylamine hydrobromide, Et₃N, DMF; (c) NaH, DMSO; (d) *tert*-butyl acrylate, Pd(OAc)₂, P(*o*-tol)₃, (*I*-Pr)₂EtN, EtCN, DMF; (e) i. TFA, CH₂Cl₂; ii. 4 N HCl/dioxane

Scheme XIV



- (a) *N*-(2-chloroethyl)morpholine, NaH, DMF; (b) TFA, CH₂Cl₂; (c) 5-bromo-3-(2-(4-methoxybenzyl)pyridin-2-yl)pyridin-2-ylamine hydrobromide, Et₃N, DMF; (d) NaH, DMSO; (e) *tert*-butyl acrylate, Pd(OAc)₂, P(*o*-tol)₃, (*I*-Pr)₂EtN, EtCN, DMF; (f) i. TFA, CH₂Cl₂; ii. 4 N HCl/dioxane

Scheme XV

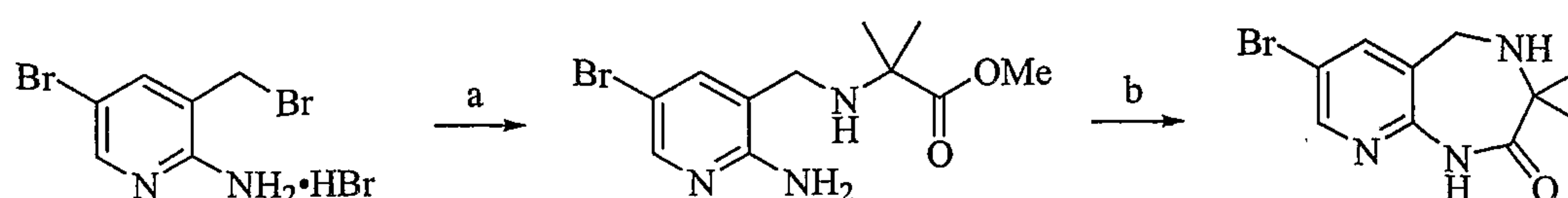


- (a) 4-(3-aminopropyl)morpholine, NaBH_3CN , AcOH , MeOH ; (b) 5-bromo-3-bromomethylpyridin-2-ylamine, Et_3N , DMF ; (c) NaH , DMSO ; (d) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{EtN}$, EtCN , DMF ; (e) i. TFA , CH_2Cl_2 ; ii. 4 N HCl /dioxane

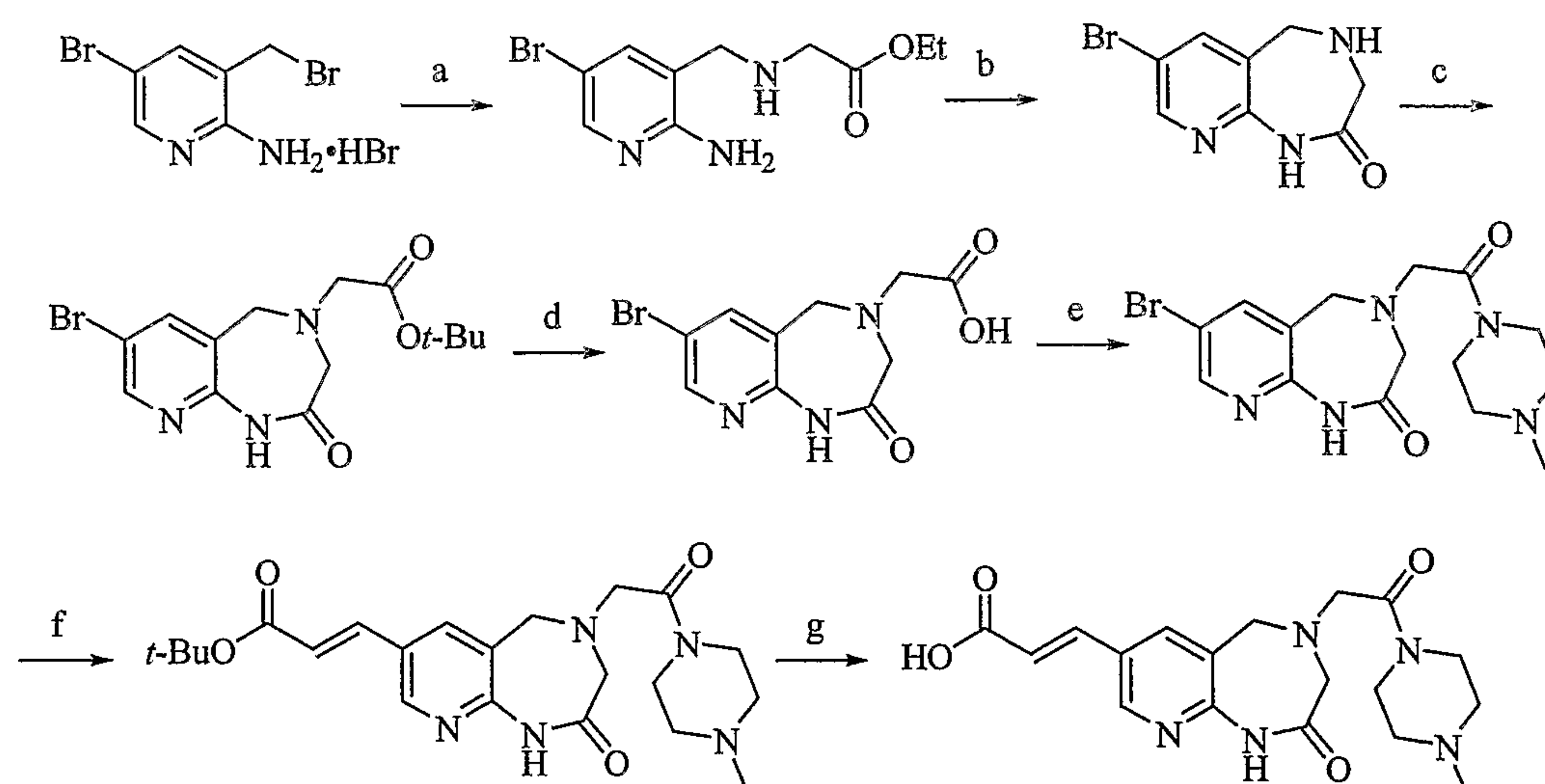
In an analogous way to the chemistry described above, 5-bromo-3-bromomethylpyridin-2-ylamine hydrobromide, may be reacted with primary amines (Scheme XVI, XVII, XVIII); subsequent cyclization with sodium hydride yields a pyridodiazepinone in which the nitrogen at the four position is unsubstituted. In Scheme XVI the final product represents a right hand side moiety of formula I wherein the requisite RHS coupling partners is an aryl bromide and the late stage chemistry involves formation of a carbon-carbon bond via Heck chemistry. One skilled in the art will recognize that the intermediate aryl bromides described in Schemes X-XX may also be used in late stage carbon-carbon bond forming chemistry.

Alternatively, the nitrogen at position four may be derivatized by reaction with alkylating (Scheme XVIIc) or acylating agents (Scheme XVIIIc). In the former case, further elaboration (Scheme XVIIId,e) yields a derivatized bromopyridodiazepinone which is subjected to standard Heck coupling/deprotection sequence to give the desired acid. In the latter case, the CBz-protected pyridodiazepinone is similarly treated (Scheme XVIII).

Scheme XVI



Scheme XVII

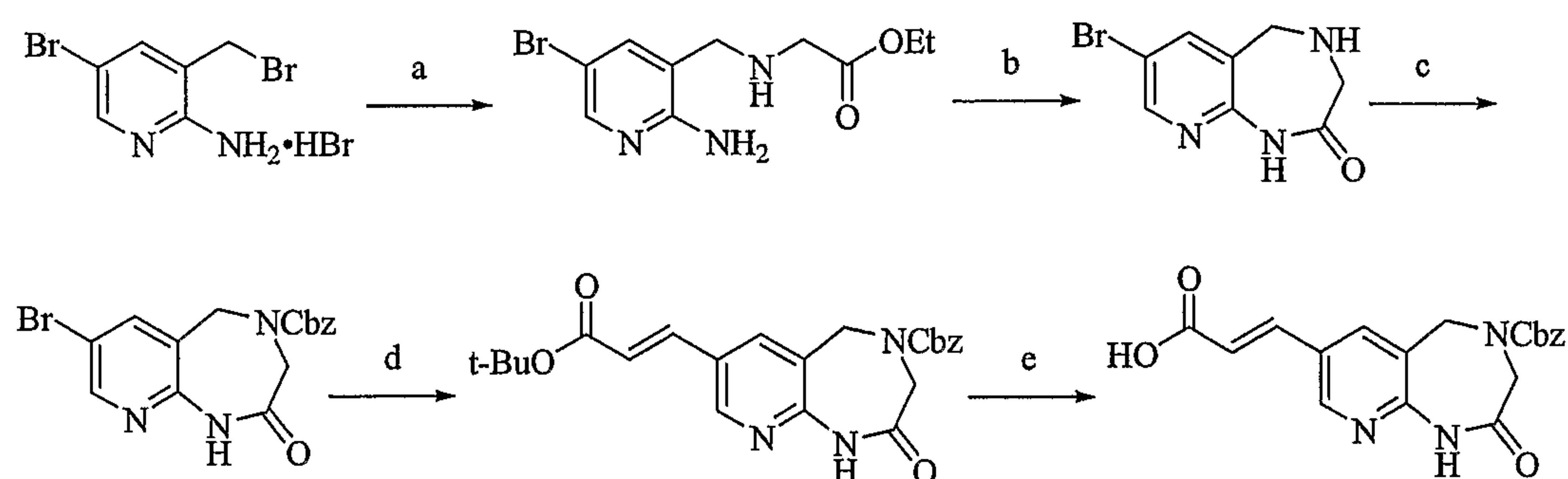


5

(a) glycine ethyl ester hydrochloride, Et_3N , DMF; (b) NaH, DMSO; (c) *tert*-butyl bromoacetate, Et_3N , DMF; (d) i. TFA, CH_2Cl_2 ; ii. 4 N HCl/dioxane; (e) 1-methylpiperazine, $(i\text{-Pr})_2\text{EtN}$, EDC, HOBT, CH_2Cl_2 ; (f) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{EtN}$, EtCN, DMF; (g) i. TFA, CH_2Cl_2 ; ii. 4 N HCl/dioxane

10

Scheme XVIII

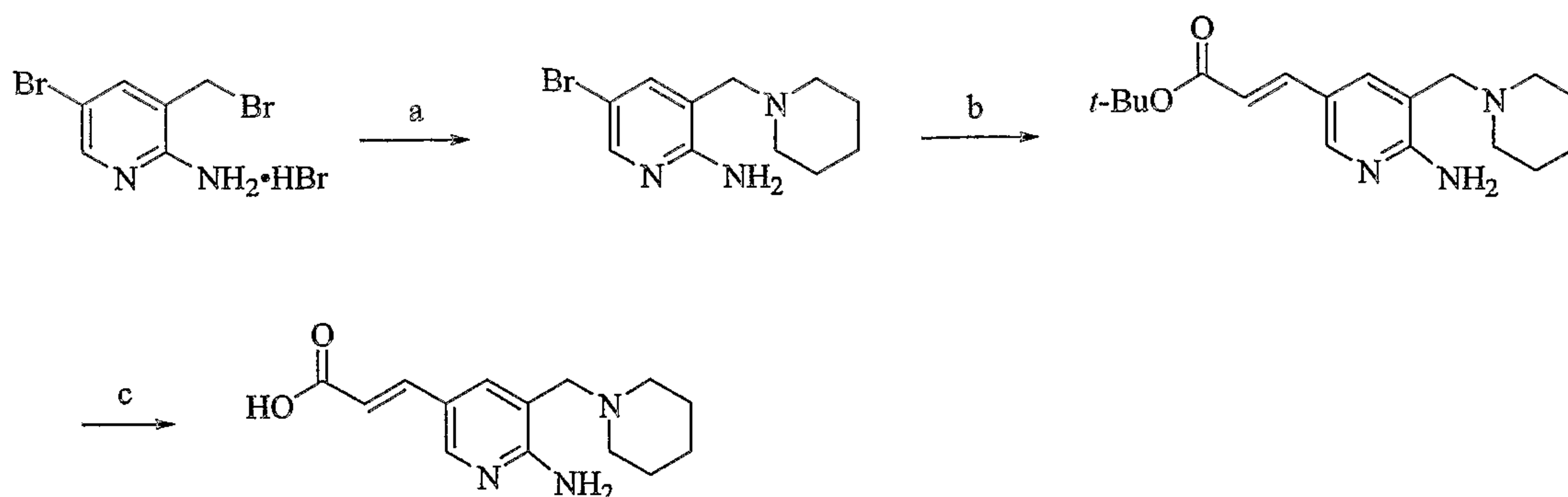


(a) glycine ethyl ester hydrochloride, Et_3N , DMF; (b) NaH, DMSO; (c) CbzCl, Et_3N , CH_2Cl_2 ; (d) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{EtN}$, EtCN, DMF; (e) i. TFA, CH_2Cl_2 ; ii. 4 N HCl/dioxane

15

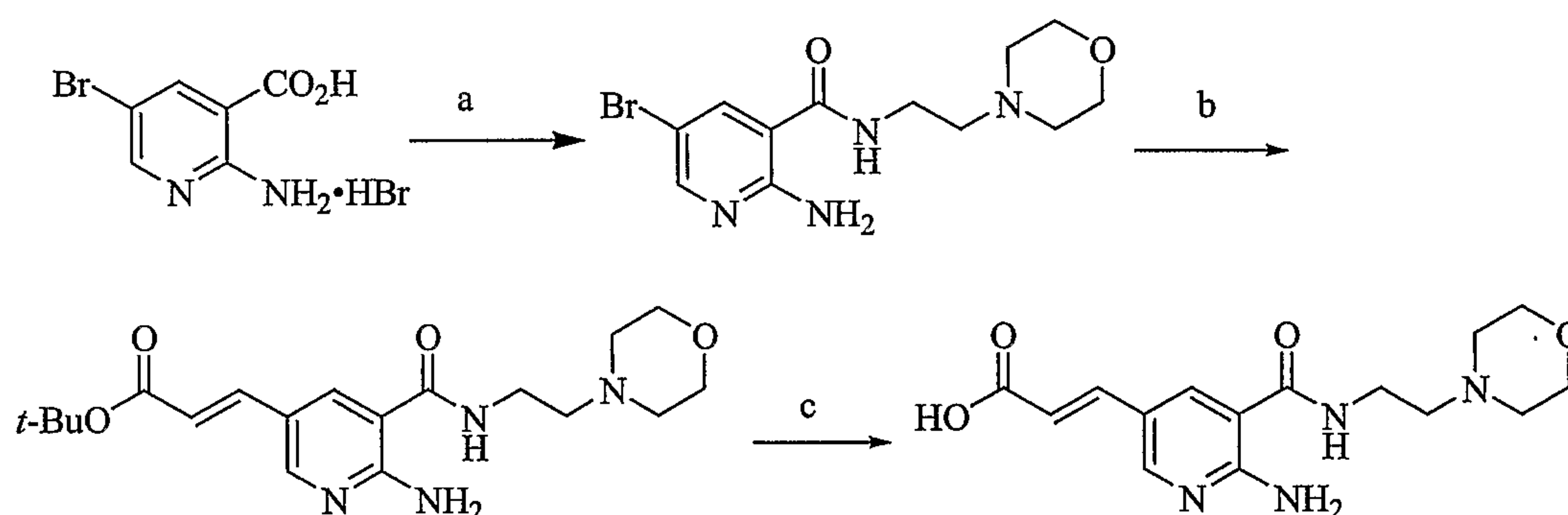
5-Bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide, may also be reacted with cyclic secondary amines (Scheme XIX); the desired acid is obtained in the usual way.

Scheme XIX



Right hand sides in which an aminopyridine ring is derivatized via an amide linkage may be realized by reaction of 2-amino-5-bromonicotinic acid hydrobromide with primary amines. Heck coupling and hydrolysis gives the desired acid (Scheme XX)

10 Scheme XX



(a) 4-(2-aminoethyl)morpholine, EDC, HOBt, Et₃N, CH₂Cl₂; (b) *tert*-butylacrylate, DIEA, Pd(OAc)₂, P(*o*-tol)₃, EtCN, DMF; (c) i. TFA, CH₂Cl₂; ii. 4 N HCl/1,4-dioxane

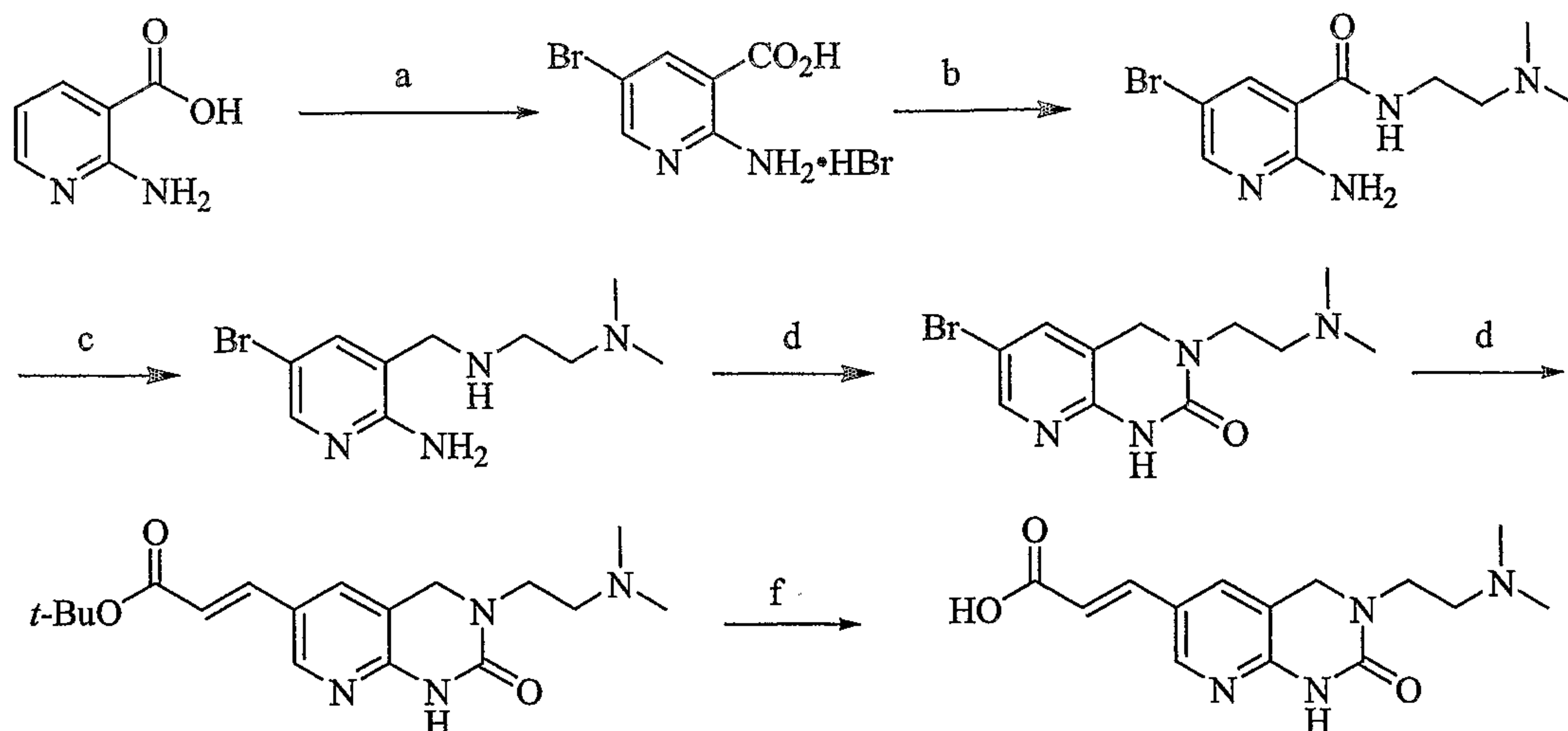
15 Schemes XXI-XXIV are illustrative of methods use for preparing RHS moieties wherein 3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-ones are incorporated as RHS moieties. Schemes XXI-XXIII show preparations wherein carboxylic acids are prepared and end stage chemistry involves amide bond formation, scheme XXIV shows preparation of an aryl bromide employed in carbon-carbon bond forming end stage chemistry.

20 In each case an intermediate aminomethyl aminopyridine is prepared by amide bond reduction (Scheme XXI), reductive amination of aldehydes (Scheme XXII and Scheme XXIV) or, as described above in Scheme XVII, by displacement of an benzylic bromide with the desired primary amine. The latter method yields the starting material for Scheme

XXIII. The subsequent step, common to all cases, is cyclization using carbonyl diimidazole to form the 3,4-dihydro-1*H*-pyrimidin-2-one ring. Other activated carbonyl equivalents are expected to affect a similar cyclization. In Schemes XXI-XXIII further elaboration using Heck coupling and hydrolysis gives the desired carboxylic acid RHS moieties.

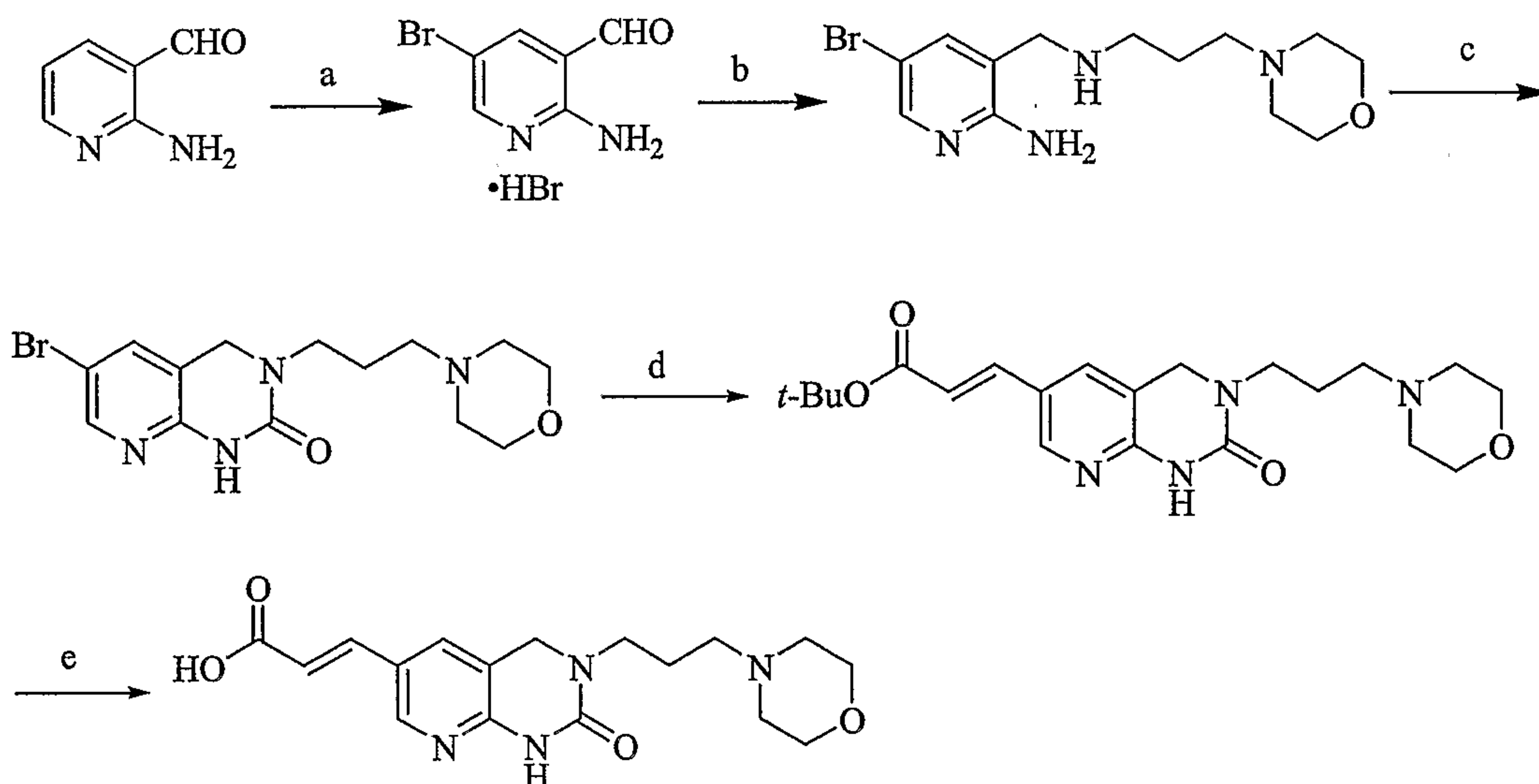
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Scheme XXI



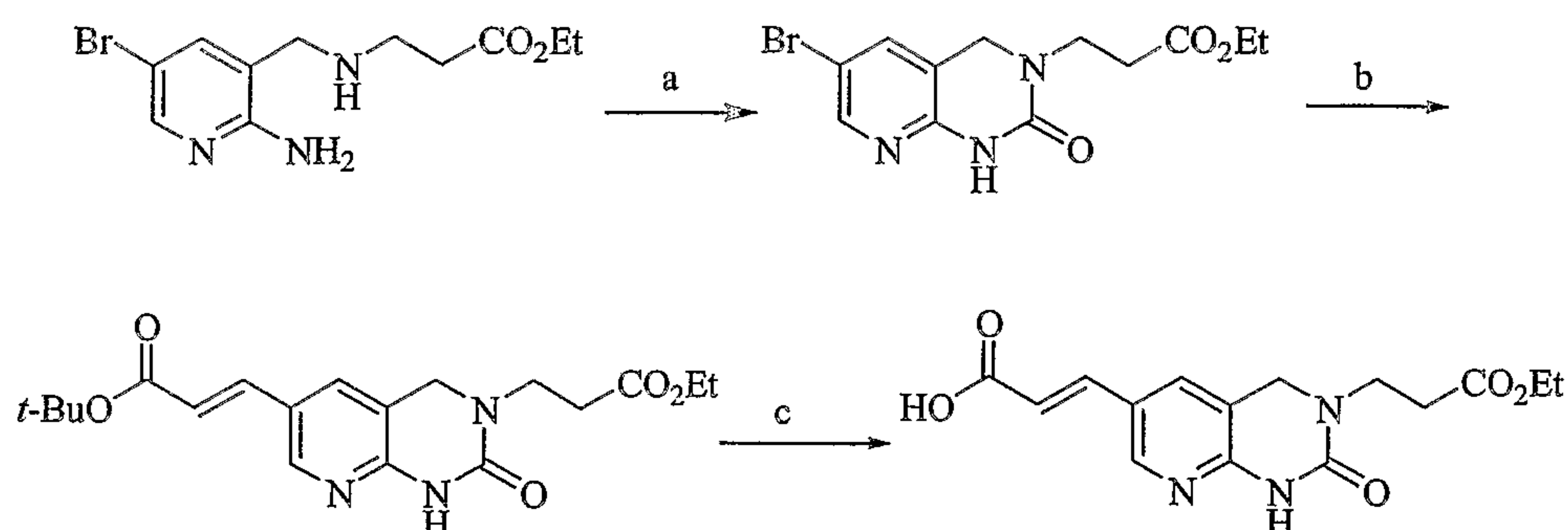
(a) Br₂, HOAc; (b) *N,N*-dimethylethylenediamine, EDC, HOBT, Et₃N, CH₂Cl₂; (c) i. BH₃; ii. HCl, MeOH; (d) CDI, 1, 4-dioxane; (e) *tert*-butylacrylate, DIEA, Pd(OAc)₂, P(*o*-tol)₃, EtCN, DMF; (f) i. TFA, CH₂Cl₂; ii. 4 N HCl/dioxane

Scheme XXII



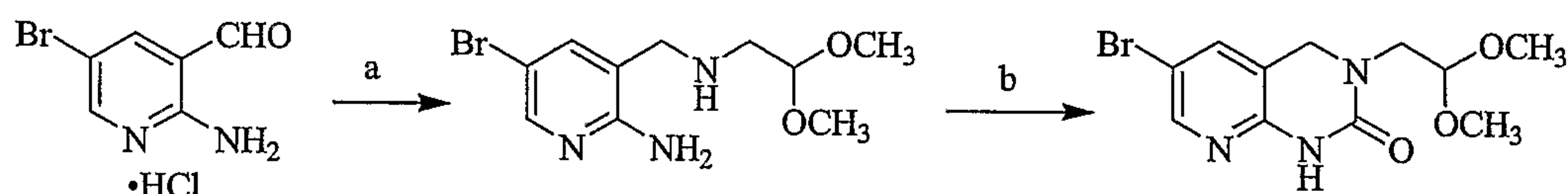
(a) Br₂, HOAc; (b) i. 4-(3-aminopropyl)morpholine, Et₃N, MeOH; ii NaBH₄; (c) CDI, 1, 4-dioxane; (d) *tert*-butylacrylate, DIEA, Pd(OAc)₂, P(*o*-tol)₃, EtCN, DMF; (e) i. TFA, CH₂Cl₂; ii. 4 N HCl/dioxane

5 Scheme XXIII



(a) CDI, 1,4-dioxane; (b) *tert*-butylacrylate, DIEA, Pd(OAc)₂, P(*o*-tol)₃, EtCN, DMF; (c) i. TFA, CH₂Cl₂; ii. 4 N HCl/dioxane.

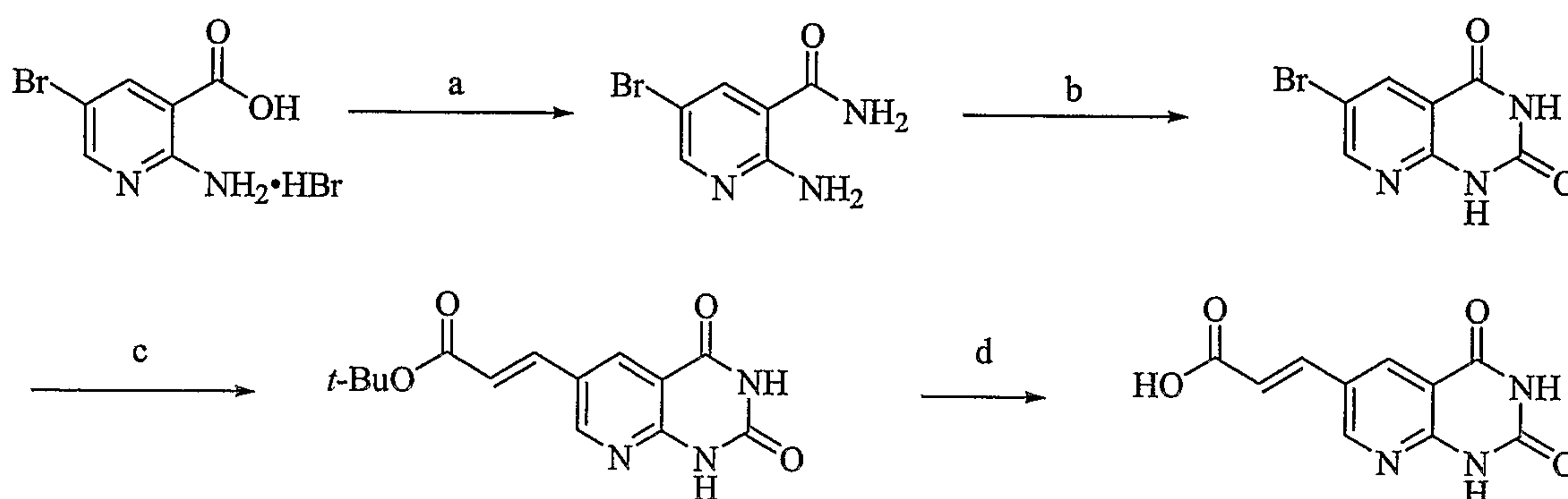
10 Scheme XXIV



(a) i. Aminoacetaldehyde diethyl acetal, Et₃N, MgSO₄, MeOH; ii NaBH₄; (b) CDI, 1,4-dioxane

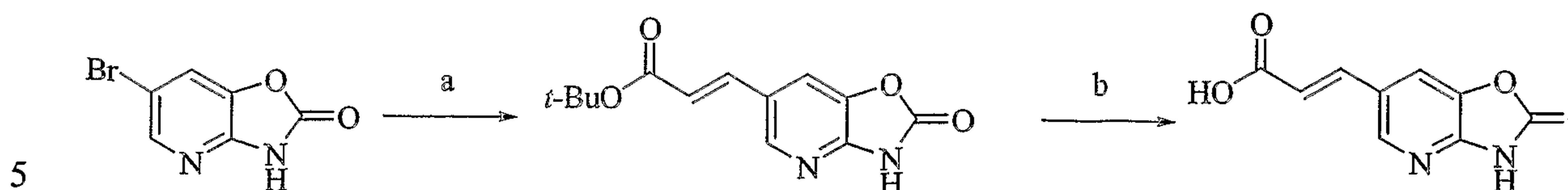
15 Schemes XXV and XXVI are illustrative of the methods used for preparing (*E*)-3-(2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-6-yl)-acrylic acid and (*E*)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-b]pyridin-6-yl)-acrylic acid right hand sides respectively.

Scheme XXV



(a) $(\text{EtO})_2\text{P}(\text{O})\text{CN}$, NH_4Cl , Et_3N , DME; (b) oxalyl chloride, xylene; (c) $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, *t*-butyl acrylate, EtCN, DMF; (d) TFA, CH_2Cl_2

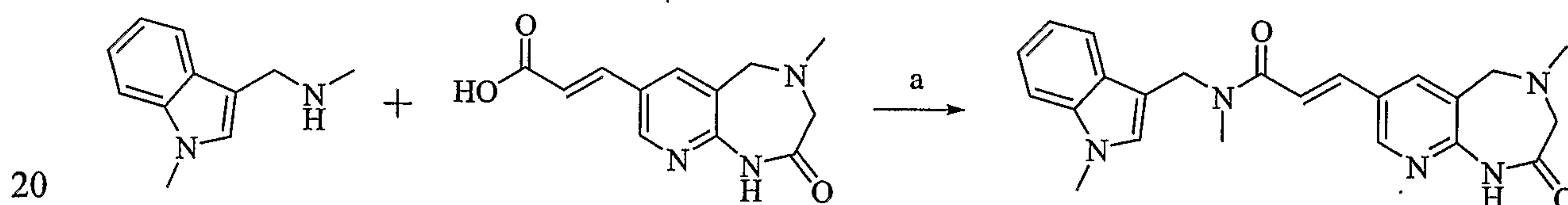
Scheme XXVI



(a) *tert*-butyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{EtN}$, EtCN, DMF; (b) i. TFA, CH_2Cl_2 ; ii. 4 N HCl/dioxane

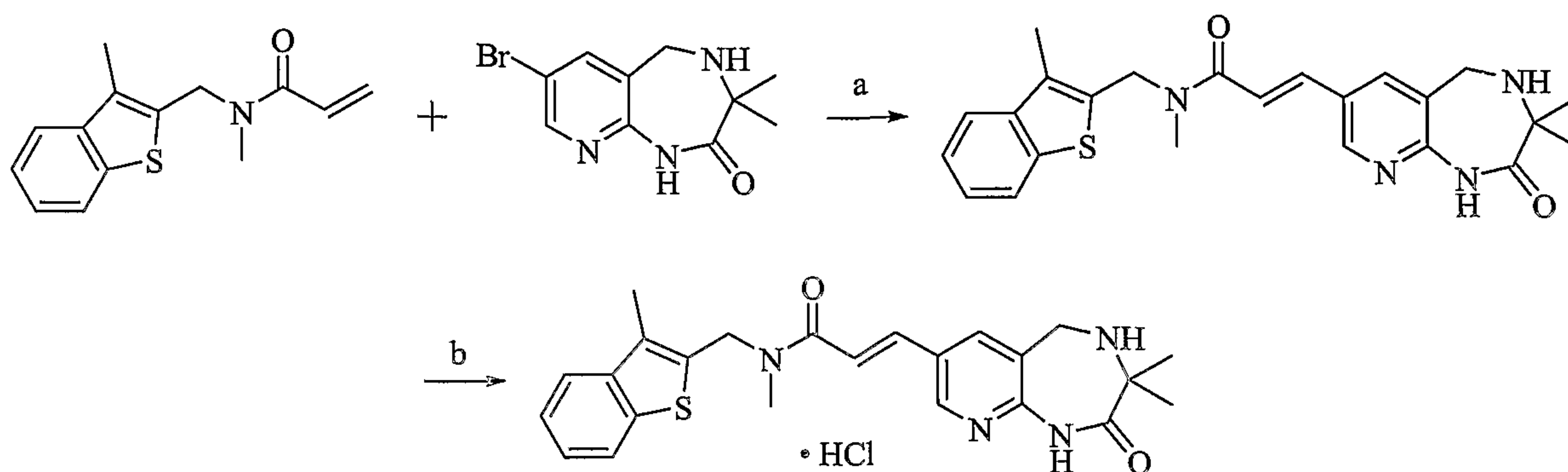
Schemes XXVII describes a specific example of a general method for assembly of compounds of formula I wherein the LHS coupling partners are amines, the RHS coupling partners are acids and the late stage chemistry involves formation of the amide linkage. There are many common methods for formation of amide linkages. In the example depicted in Scheme XXVII an acid ((*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-*e*][1,4]diazepin-7-yl)-acrylic acid) is activated by treatment with a carbodiimide (EDC) and hydroxybenzotriazole (HOBt) in the presence of a polar aprotic solvent (DMF) and reacted with a suitable amine (*N*-methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)amine) in the presence of a tertiary amine base like diisopropylethylamine.

Scheme XXVII



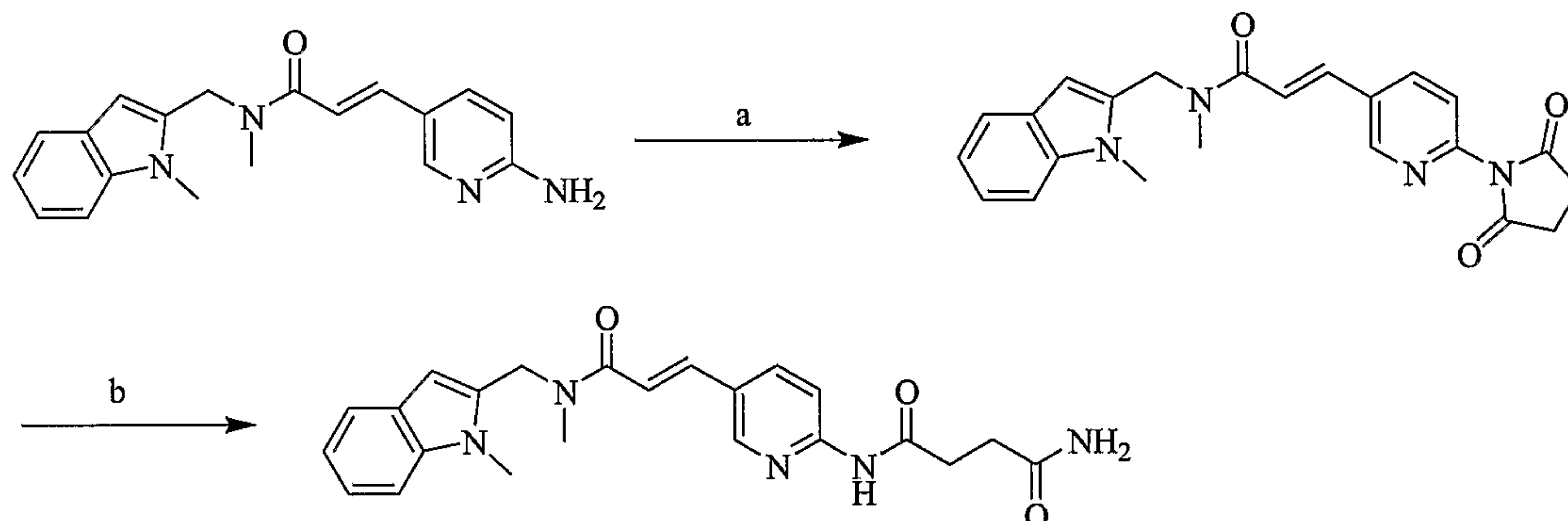
(a) *N*-methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)amine, $(i\text{-Pr})_2\text{EtN}$, EDC, HOBt, DMF

An alternative method for assembling compounds of formula 1, generally referred to as Heck coupling, is depicted in Scheme XVIII. An acrylic amide such as *N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-acrylamide is treated with an aryl bromide such as 7-bromo-3,3-dimethyl-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one in the presence of a palladium catalyst ($\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$), a tertiary amine ($(i\text{-Pr})_2\text{EtN}$) and an aprotic solvent or solvents (EtCN, DMF).

Scheme XXVIII

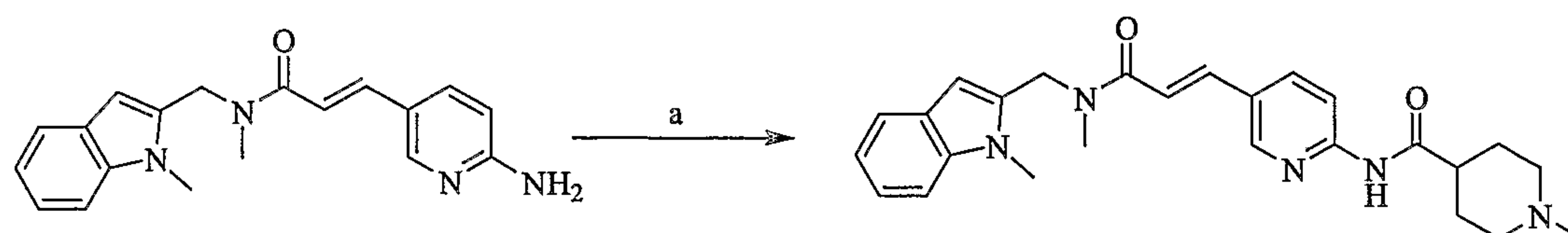
- (a) α, α -dimethylglycine methyl ester hydrochloride, Et_3N , DMF; (b) NaH, DMSO; (c) *N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{EtN}$, EtCN, DMF; (d) 1 N HCl/Et₂O, CH₂Cl₂

To access certain compounds of the invention it may be necessary to perform synthetic manipulations after the right hand side and left hand side units have been assembled. Scheme XXIX for example outlines the conversion of an aminopyridine moiety to a cyclic imide followed by ring opening with ammonia.

Scheme XXIX

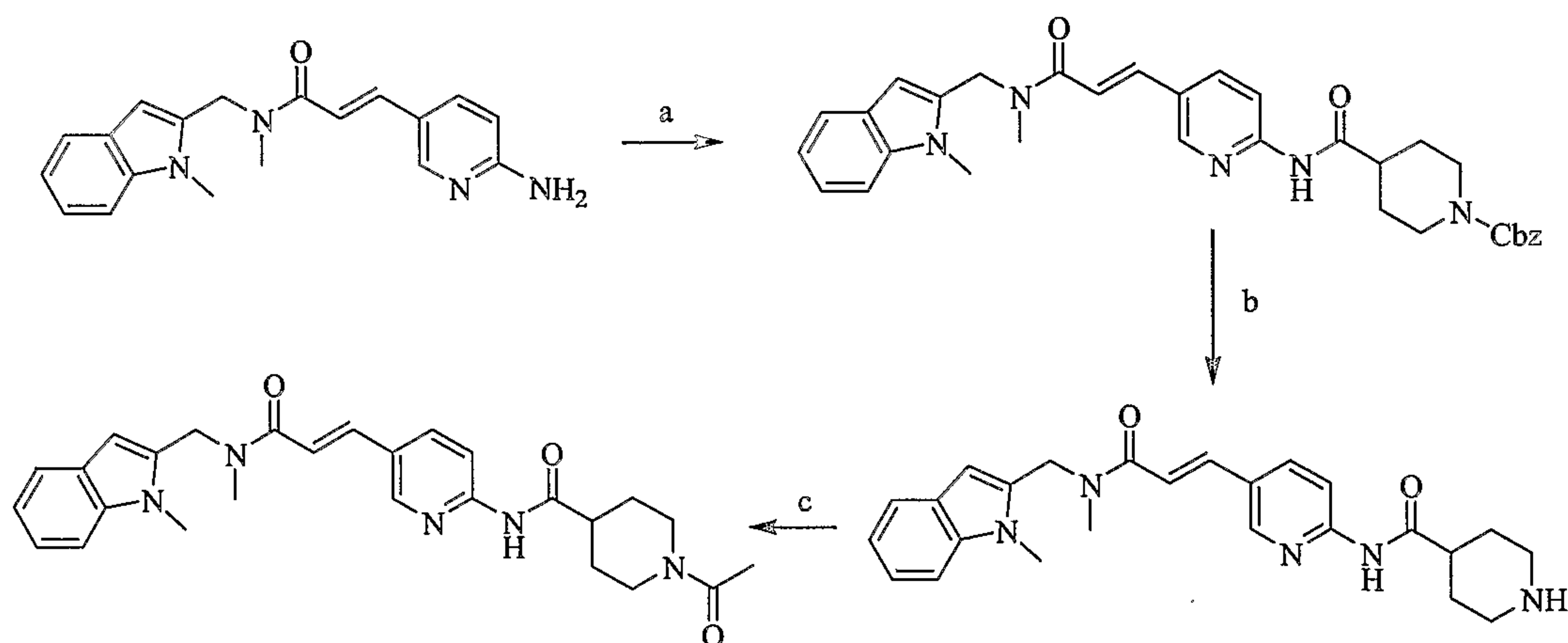
- (a) succinic anhydride, 1,4-dioxane; (b) NH_3 , 1,4-dioxane.

Additional examples of aminopyridine derivatization are given in Schemes XXX and XXXI which describe the acylation of the amine moiety to form amide linkages.

Scheme XXX

(a) 1-methyl-piperidine-4-carboxylic acid hydrochloride, CDI, 1,4-dioxane.

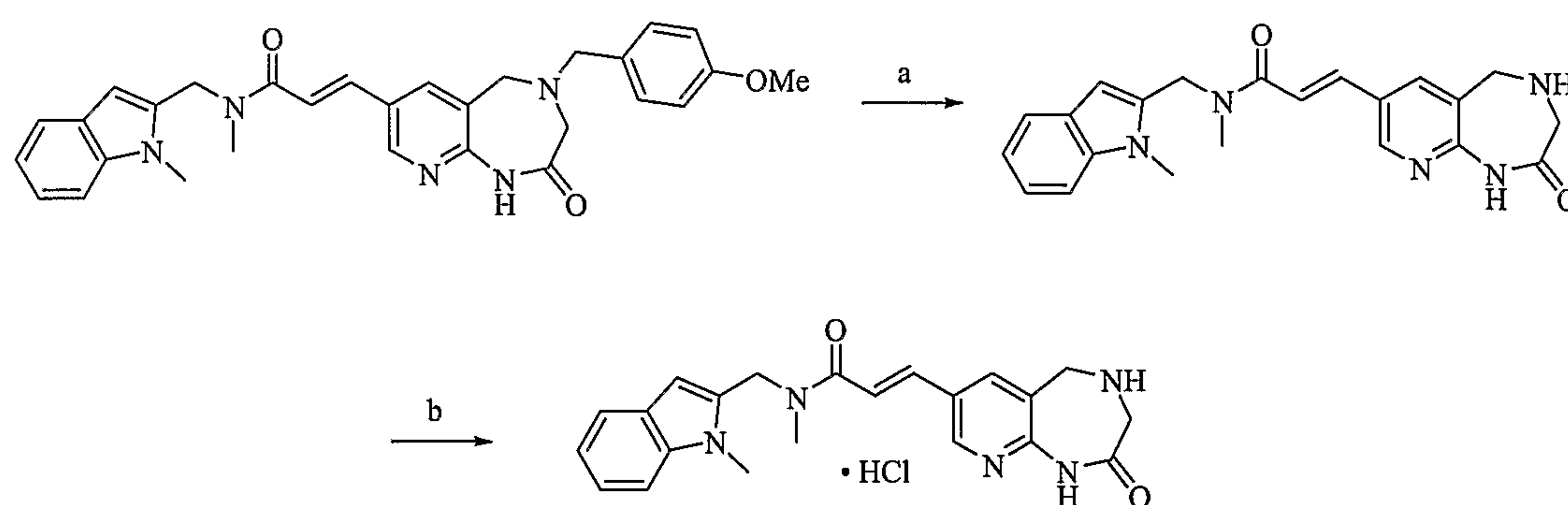
Scheme XXXI



5 (a) [1-(carbobenzoxy)-4-piperidine]carboxylic acid, CDI, 1,4-dioxane; (b) TMSI, CH_2Cl_2 ; (c) Ac_2O , Et_3N , CH_2Cl_2 .

In certain aspects of the invention it is desirable to have pyridodiazepinones in place on the right hand side with unsubstituted 4-position nitrogen. In these instances a suitable protecting group such as methoxybenzyl can temporarily mask the nitrogen. This protecting group may be removed in a two-step procedure by treatment with 1-chloroethyl chloroformate followed by hydrolysis of the intermediate carbamate. The hydrochloride salt may be prepared, if desired, through treatment with dilute acid (HCl) in an aprotic solvent such as ether (Scheme XXXII).

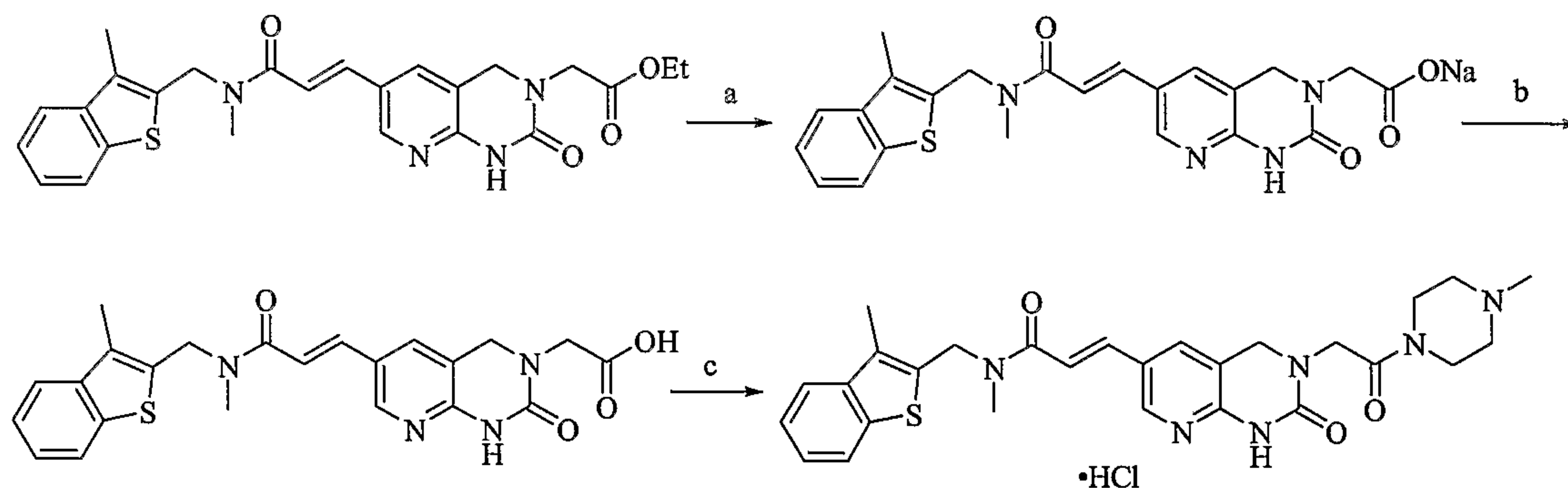
15 Scheme XXXII



(a) i. ACE-Cl, dichloroethane; ii. MeOH; (b) 2 N HCl/ Et_2O , CH_2Cl_2 .

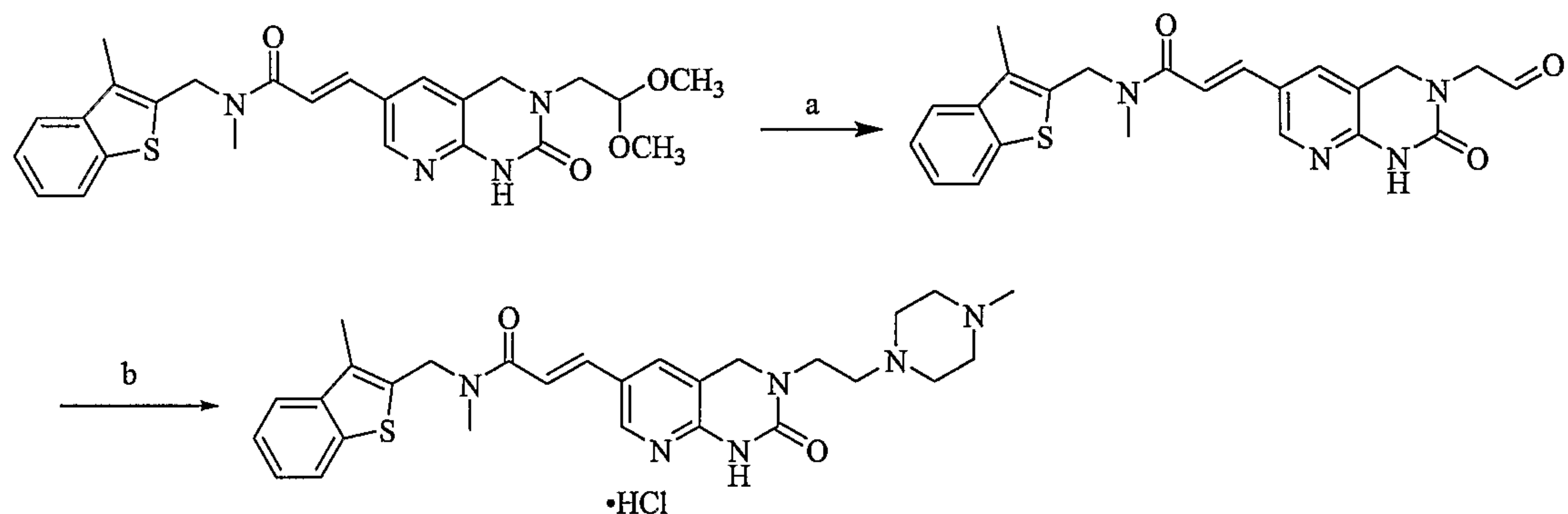
Schemes XXXIII and XXXIV respectively show methods for conversion of ester and dimethylether ether groups pendent on a 3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one right hand side to piperidine-containing tethers. These chemical manipulations are carried out after the standard coupling reactions described above are applied (e.g. Scheme XXVII or XXVIII).

Scheme XXXIII



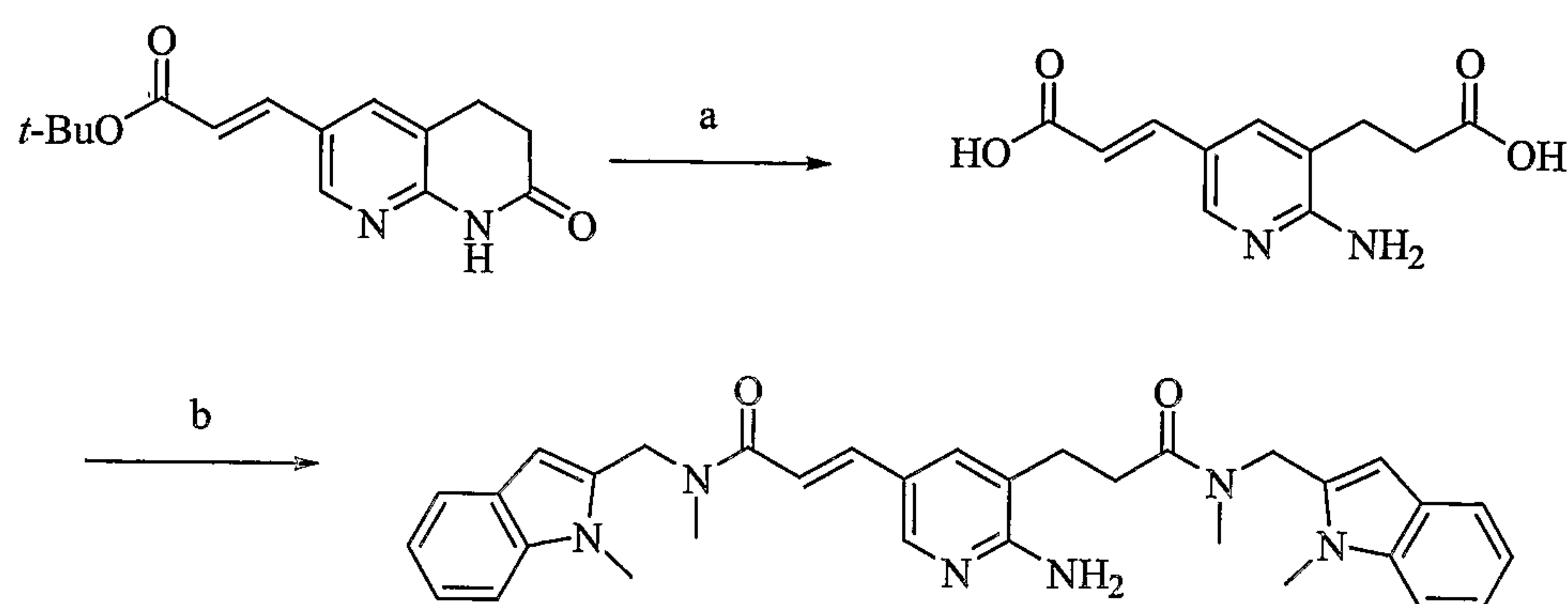
(a) 1N NaOH, MeOH; b) HCl; c) i. 1-methylpiperazine, EDC, HOBt, DIEA, DMF; ii. 2 N HCl/Et₂O

Scheme XXXIV



(a) TFA, H₂O, CH₂Cl₂; (b) i. 1-methylpiperazine, NaBH(OAc)₃, HOAc, ClCH₂CH₂Cl; ii. 1N HCl/ Et₂O, MeOH, CH₂Cl₂.

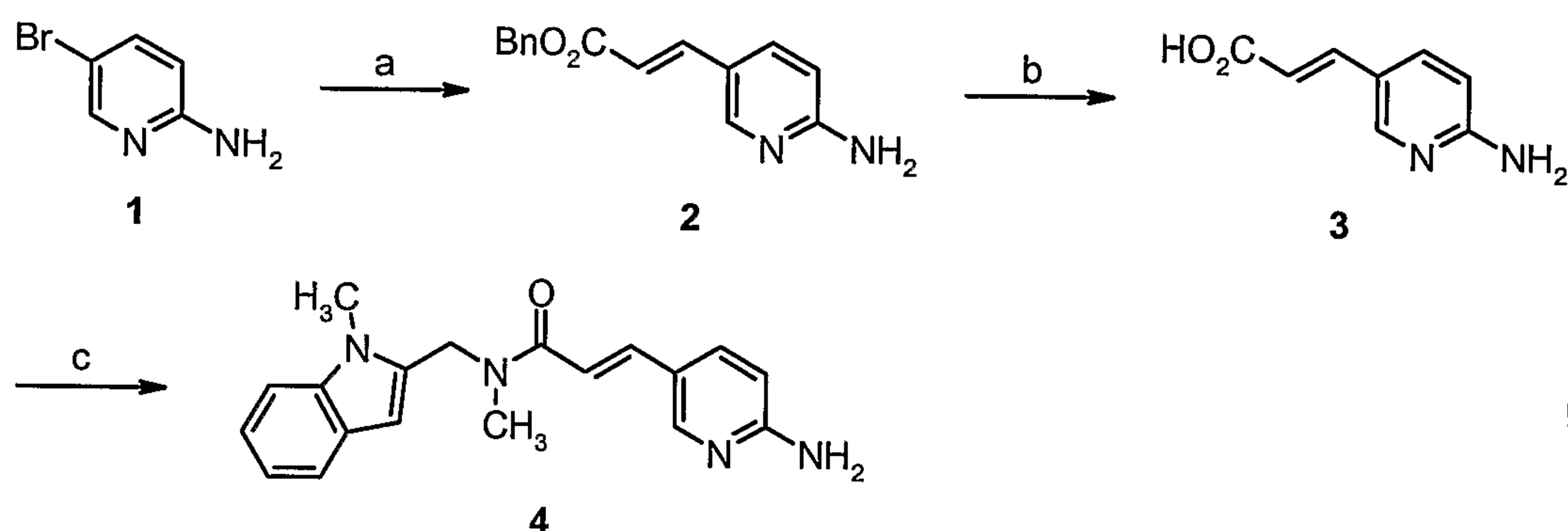
Scheme XXXV illustrates a method of compound construction falling outside the general methods described above in that a dicarboxylic acid, prepared as in Scheme XXXIVa, is reacted with two equivalents of arylmethylaniline using the standard amide coupling conditions.

Scheme XXXV

(a) i. Aq. NaOH, methanol, dioxane; (b) EDC, HOBT, DIEA, DMF, methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine.

Synthetic Routes to Compounds of Formulas II and III

Examples of the compounds of formulas II and III in the antibacterial compositions of the present invention may be prepared by the general methods described in the Schemes hereinafter.

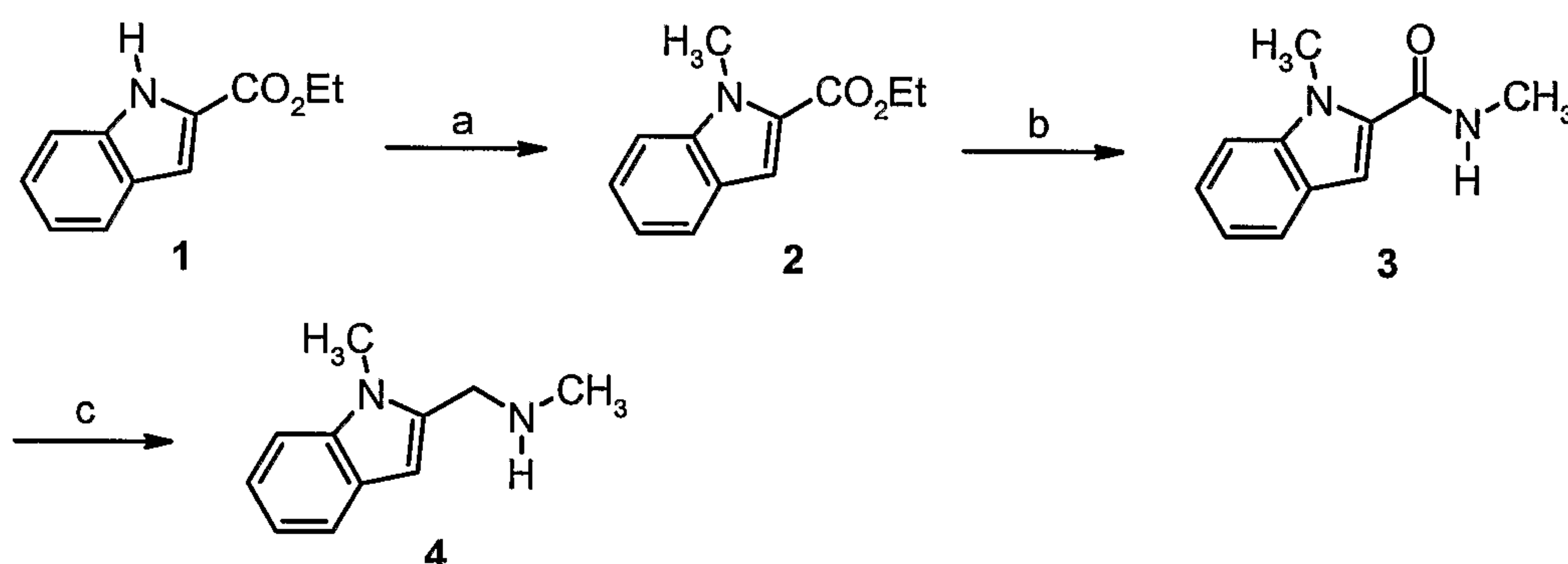
10 Scheme XXXVI

(a) benzyl acrylate, Pd(OAc)₂, P(o-tol)₃, (i-Pr)₂NEt, propionitrile; (b) 1.0 N NaOH, MeOH; (c) 1-methyl-2-(methylaminomethyl)indole, EDC, HOBT · H₂O, Et₃N, DMF.

A suitable haloaromatic derivative, for instance 2-amino-5-bromopyridine (XXXVI-1), reacts with an appropriate α,β -unsaturated ester, for example benzyl acrylate, in a Heck-type reaction to afford XXXVI-2. The reaction is mediated by a palladium(0) species, and generally is conducted in an inert solvent, such as CH₃CN, propionitrile, or toluene, in the presence of an appropriate acid scavenger, such as triethylamine (Et₃N) or diisopropylethylamine ((i-Pr)₂NEt). Typical sources of the palladium(0) species include palladium (II) acetate (Pd(OAc)₂) and palladium(II) chloride (PdCl₂), and oftentimes

phosphine ligands, for instance triphenylphosphine (PPh₃) or tri-ortho-tolylphosphine (P(tol)₃), are included. The ethyl ester of XXXVI-2 is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid XXXVI-3. The carboxylic acid of XXXVI-3 is converted to an activated form using, for example, EDC and HOBT, or SOCl₂, and the activated form is subsequently reacted with an appropriate amine, for instance 1-methyl-2-(methylaminomethyl)indole, in a suitable solvent such as DMF, CH₂Cl₂, or CH₃CN, to afford XXXVI-4. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et₃N), diisopropylethylamine ((i-Pr)₂NEt), or pyridine, may be used. Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience), or Bodansky, "The Practice of Peptide Synthesis" (published by Springer-Verlag).

15 Scheme XXXVII

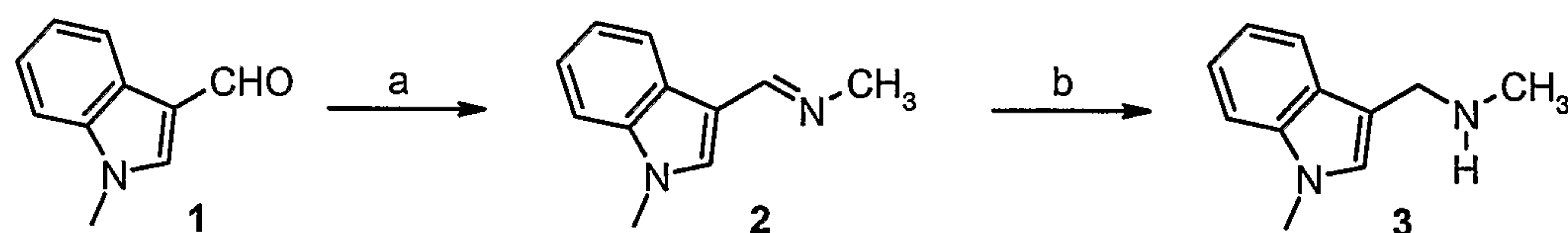


(a) NaH, MeI, DMF; (b) CH₃NH₂, H₂O, MeOH; (c) LiAlH₄, THF.

The amine coupling partners used in the present invention were prepared by established methods well-known to those of skill in the art. For example, amine XXXVII-4 is prepared by the straightforward procedure outlined in Scheme II. Commercially available ethyl indole-2-carboxylate (XXXVII-1) is deprotonated with a suitable base, generally sodium hydride (NaH), and the intermediate sodium salt is reacted with an appropriate alkylating agent, for instance methyl iodide, to afford XXXVII-2. Polar solvents such as DMF, THF, or mixtures thereof are generally preferred for this reaction. Compound XXXVII-2 can be conveniently converted to XXXVII-3 by reaction with an

excess of an amine, such as methylamine, in a polar solvent, generally H₂O or a mixture of H₂O and methanol. Alternatively, the ester of **XXXVII-2** can be saponified under standard conditions, typically with an alkali metal hydroxide such as LiOH, NaOH, or KOH, in an aqueous solvent, such as THF, ethanol, or methanol, and the resulting carboxylic acid can be converted to the desired amide. Typical methods for forming amides are described in Scheme I. Reduction of the amide **XXXVII-3** to the amine **XXXVII-4** is typically accomplished with lithium aluminum hydride (LiAlH₄) in refluxing THF, although many other methods can be used to reduce amides to amines. Such methods are well-known to those of skill in the art, and can be found in standard reference volumes, such as "Compendium of Organic Synthetic Methods" (published by Wiley-Interscience).

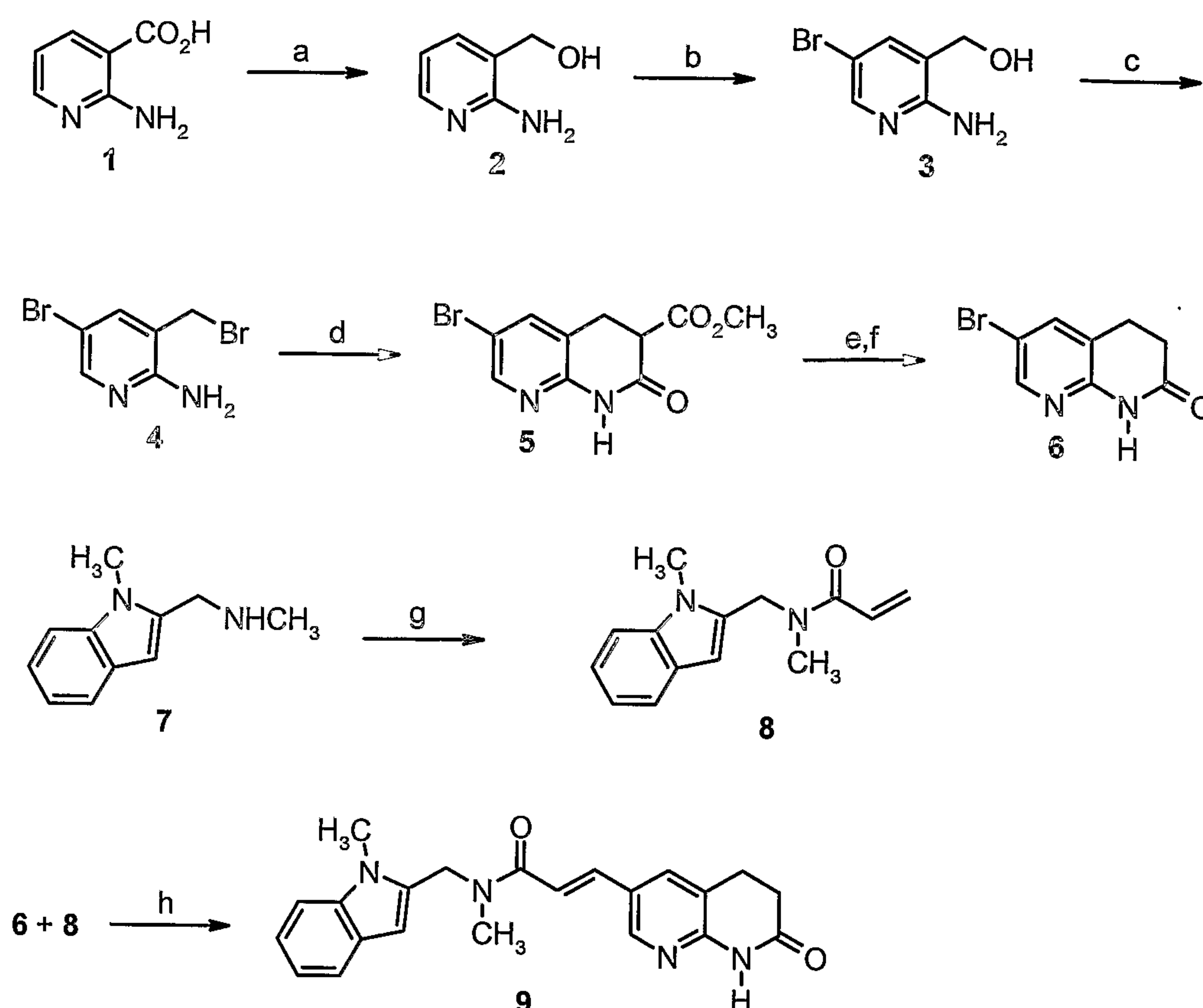
Scheme XXXVIII



(a) CH₃NH₂, MeOH; (b) NaBH₄, EtOH.

The amine coupling partners used in the present invention can also be prepared by the reductive amination of an appropriate aldehyde (Scheme III). This method, which is well-known to those of skill in the art, involves the initial conversion of an aldehyde to an intermediate imine, which is subsequently reduced, oftentimes in situ, to afford the amine. For example, the commercially-available aldehyde **XXXVIII-1** reacts with an appropriate amine, for instance methylamine, in a suitable solvent, typically methanol, to afford the imine **XXXVIII-2**. Reaction of **XXXVIII-2** with a suitable reducing agent, for example sodium borohydride, sodium cyanoborohydride or sodium (triacetoxy)borohydride, gives the amine **XXXVIII-3**.

Scheme XXXIX



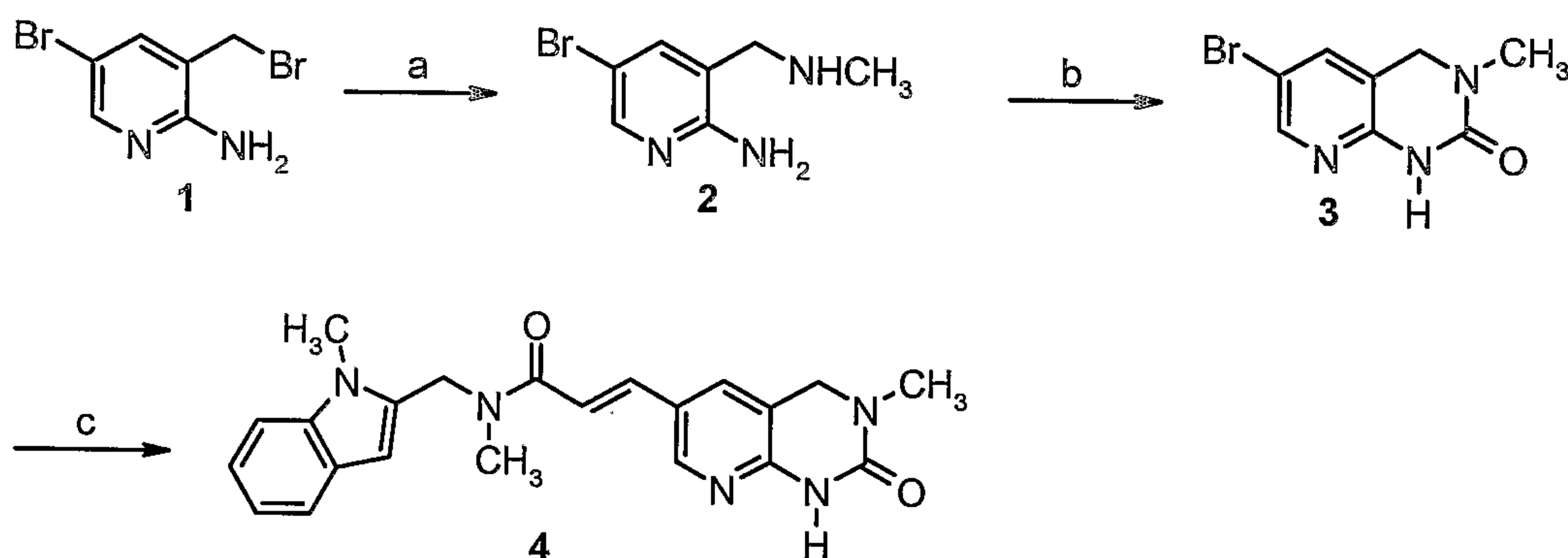
- (a) LiAlH₄, THF; (b) Br₂, AcOH; (c) 48% HBr; (d) (MeO₂C)₂CH₂, NaH, DMF, THF; (e) NaOH, H₂O, MeOH, (f) HCl, H₂O, MeOH; (g) acryloyl chloride, Et₃N, CH₂Cl₂; (h) Pd(OAc)₂, P(*o*-tol)₃, (i-Pr)₂NEt, propionitrile.

Commercially available 2-aminonicotinic acid (XXXIX-1) is reduced to alcohol XXXIX-2 under standard conditions (LiAlH₄, THF), and the aromatic ring of XXXIX-2 is brominated using, for example, bromine or N-bromosuccinimide (NBS), in a suitable solvent such as CH₂Cl₂, acetic acid (AcOH), or mixtures thereof, to afford XXXIX-3. On reaction with 48% aqueous HBr, XXXIX-3 is converted to bromide XXXIX-4, which reacts with a diester of malonic acid, for instance dimethyl malonate, under basic conditions, to afford the naphthyridone derivative XXXIX-5. Typical basic conditions include an alkali metal hydride, for instance sodium hydride, in a neutral solvent such as DMF, THF, or mixtures thereof, or an alkali metal alkoxide, such as sodium methoxide or sodium ethoxide, in an alcoholic solvent such as with methanol or ethanol. Saponification and neutralization under standard conditions affords an intermediate carboxylic acid (not shown), which is typically not isolated, but is subject to decarboxylation on gentle warming

to afford the naphthyridone **XXXIX-6**. This compound reacts with acrylamide **XXXIX-8** in a Heck-type reaction as described in Scheme I to afford **XXXIX-9**. Alternatively, **XXXIX-6** might be converted to **XXXIX-9** according to the general procedure described in Scheme I for the conversion of **XXXVI-1** to **XXXVI-4**. The acrylamide **XXXIX-8** is

5 conveniently prepared by reaction of amine **XXXIX-7** (see Scheme I) with an activated form of acrylic acid in an amide bond-forming reaction. Typical conditions for the formation of amides are described in Scheme I, and are well-known to those of skill in the art.

Scheme XL

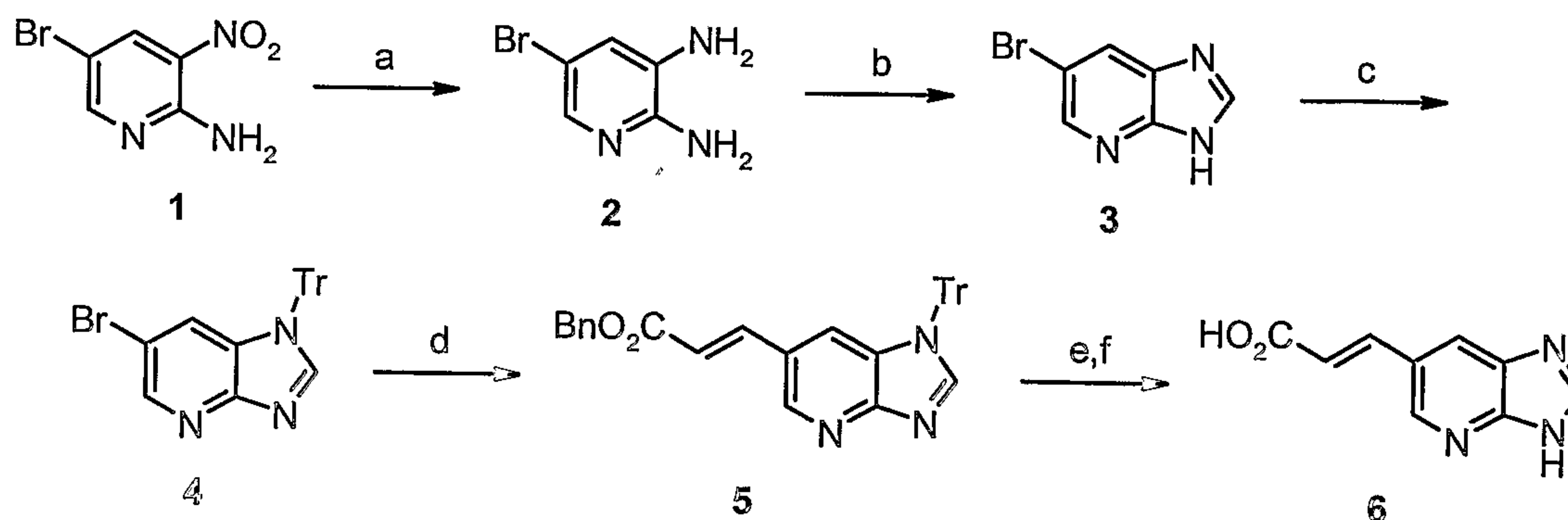


(a) CH_3NH_2 , H_2O , THF; (b) $(\text{MeO})_2\text{C}=\text{O}$, NaOMe, MeOH; (c) compound **XXXIX-8**, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile.

Benzylic bromide **XL-1**, prepared as described in Scheme XXXIX, reacts with an amine, for example aqueous methylamine, to afford benzylic amine **XL-2**. Polar solvents

15 such as THF, DMF, DMSO, or mixture thereof, are generally preferred for this reaction. **XL-2** reacts with a dialkyl carbonate, preferably dimethyl carbonate, in the presence of a suitable base, typically sodium methoxide, in an alcoholic solvent, generally methanol, to afford the cyclic urea derivative **XL-3**. This compound is converted to **XL-4** by reaction with compound **XXXIX-8** as described in Scheme XXXIX.

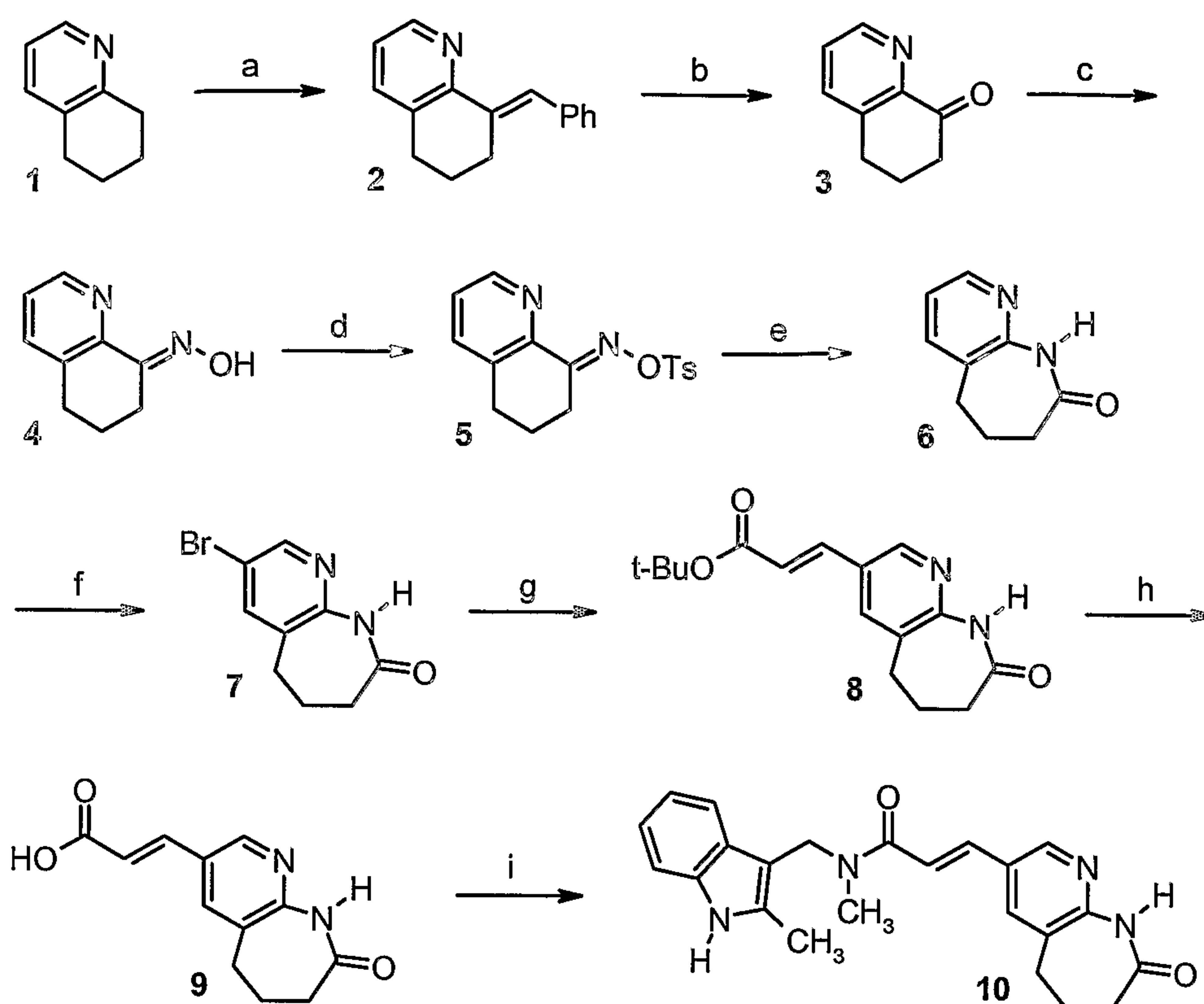
20 Scheme XLI



(a) $\text{SnCl}_2 \cdot \text{H}_2\text{O}$, EtOH; (b) 96% HCO_2H ; (c) TrCl , Et_3N , CH_2Cl_2 ; (d) benzyl acrylate, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile; (e) 4 N HCl /dioxane; (f) NaOH , H_2O , MeOH .

5 The nitro group of commercially available 2-amino-5-bromo-3-nitropyridine (**XLI-1**) is reduced under standard conditions using, for example, tin (II) chloride in EtOH. The resulting diamine, **XLI-2**, reacts with formic acid, or an appropriate equivalent, to afford the imidazopyridine derivative **XLI-3**. This compound is converted to a suitably protected derivative, for instance the N-trityl protected derivative **XLI-4**, by reaction with trityl chloride in the presence of an appropriate base, typically triethylamine or
10 diisopropylethylamine. Typical solvents for this reaction include CH_2Cl_2 , DMF, or mixtures thereof. The protecting group for the amine must be compatible with subsequent chemistry, and must be readily removable when desired. Methods for the protection of amines are well-known to those of skill in the art, and are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-
15 Interscience). **XLI-4** is converted to **XLI-5** according to the general procedure described in Scheme I. The trityl protecting group is removed under standard acidic conditions (see Greene above), and the ester is saponified as in Scheme I to afford **XLI-6**.

Scheme XLII

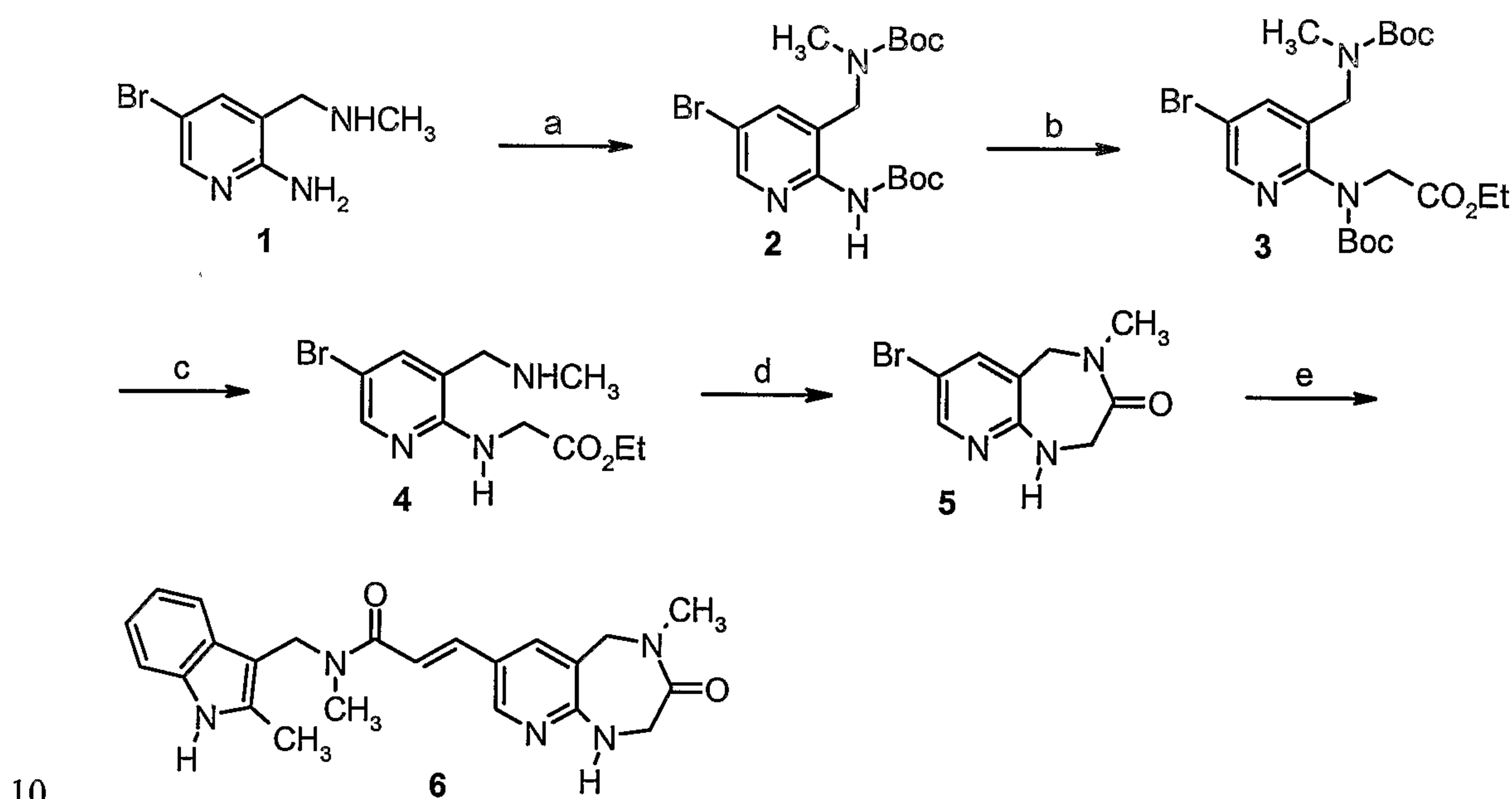


- (a) PhCHO, Ac₂O; (b) O₃, CH₂Cl₂, then DMS; (c) H₂NOH · HCl, (i-Pr)₂NEt, EtOH; (d) *p*-TsCl, KOH, acetone, H₂O; (e) KOAc, EtOH, H₂O; (f) Br₂, CH₂Cl₂; (g) *tert*-butyl acrylate, Pd(OAc)₂, P(*o*-tol)₃, (i-Pr)₂NEt, propionitrile; (h) 4.0 N HCl/dioxane; (i) 2-methyl-3-(methylaminomethyl)indole, EDC, HOBT · H₂O, (i-Pr)₂NEt, DMF.

Commercially-available tetrahydroquinoline (**XLII-1**) is condensed with an appropriate aldehyde, typically benzaldehyde (PhCHO), under standard conditions to afford the olefinic derivative **XLII-2**. Oxidative cleavage of the exocyclic olefin affords ketone **XLII-3**. Generally, ozonolysis in a neutral solvent, such as methylene chloride (CH₂Cl₂), methanol (MeOH), or mixtures thereof, followed by *in situ* reduction of the intermediate ozonide with an appropriate reducing agent, usually dimethylsulfide, is the method of choice for this transformation. Compound **XLII-3** is converted to the 7-membered lactam derivative **XLII-6** as described by Jössang-Yanagida and Gansser. This procedure involves conversion of the ketone of **XLII-3** to the corresponding oxime **XLII-4**, which is subsequently converted to the O-tosyl derivative **XLII-5**. A Beckmann-type rearrangement of **XLII-5** affords the lactam **XLII-6**. Bromination of **XLII-6** with a suitable brominating agent, such as bromine (Br₂) or N-bromosuccinimide (NBS), affords the bromo derivative

XLII-7. Typical solvents for a bromination reaction include CH_2Cl_2 , CCl_4 , MeOH, AcOH, or mixtures thereof. Bromide **VII-7** reacts with an appropriate α,β -unsaturated ester, for example *tert*-butyl acrylate, in a Heck-type reaction as described in Scheme I to afford **XLII-8**. The *tert*-butyl ester of **XLII-8** is cleaved to the corresponding carboxylic acid **XLII-9** under standard acidic conditions. Typical conditions for this transformation are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). **XLII-9** is converted to **XLII-10** by the general method described in Scheme I.

Scheme XLIII



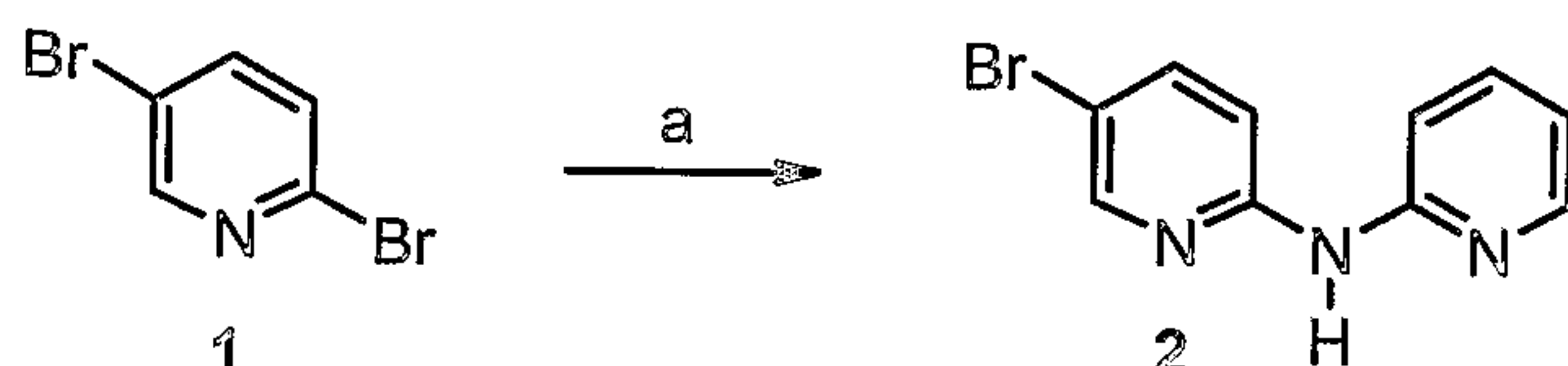
(a) $(\text{Boc})_2\text{O}$, THF; (b) NaH, ethyl bromoacetate, THF; (c) TFA, CH_2Cl_2 ; (d) Et_3N , toluene; (e) N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile.

15 Compound **XLIII-1**, prepared as described in Scheme XL, reacts with two equivalents of an appropriate acylating agent, preferably di-*tert*-butyl dicarbonate, to afford **XLIII-2**. As discussed in Scheme XLI, the protecting group for the amines must be compatible with subsequent chemistry, and must be readily removable when desired. **XLIII-2** is deprotonated with a suitable base, generally sodium hydride (NaH), and the
20 intermediate sodium salt is reacted with an appropriate alkylating agent, for instance ethyl bromoacetate, to afford **XLIII-3**. Polar solvents such as DMF, THF, or mixtures thereof are generally preferred for this reaction. The Boc protecting groups are removed under

standard acidic conditions (see Greene above) to afford **XLIII-4**, which undergoes cyclization to compound **XLIII-5** on exposure to a suitable base, typically triethylamine (Et_3N) or diisopropylethylamine ($(i\text{-Pr})_2\text{NEt}$). An inert solvent, such as toluene, is preferred. **XLIII-5** is converted to **XLIII-6** by the general method described in Scheme

5 XXXIX.

Scheme XLIV

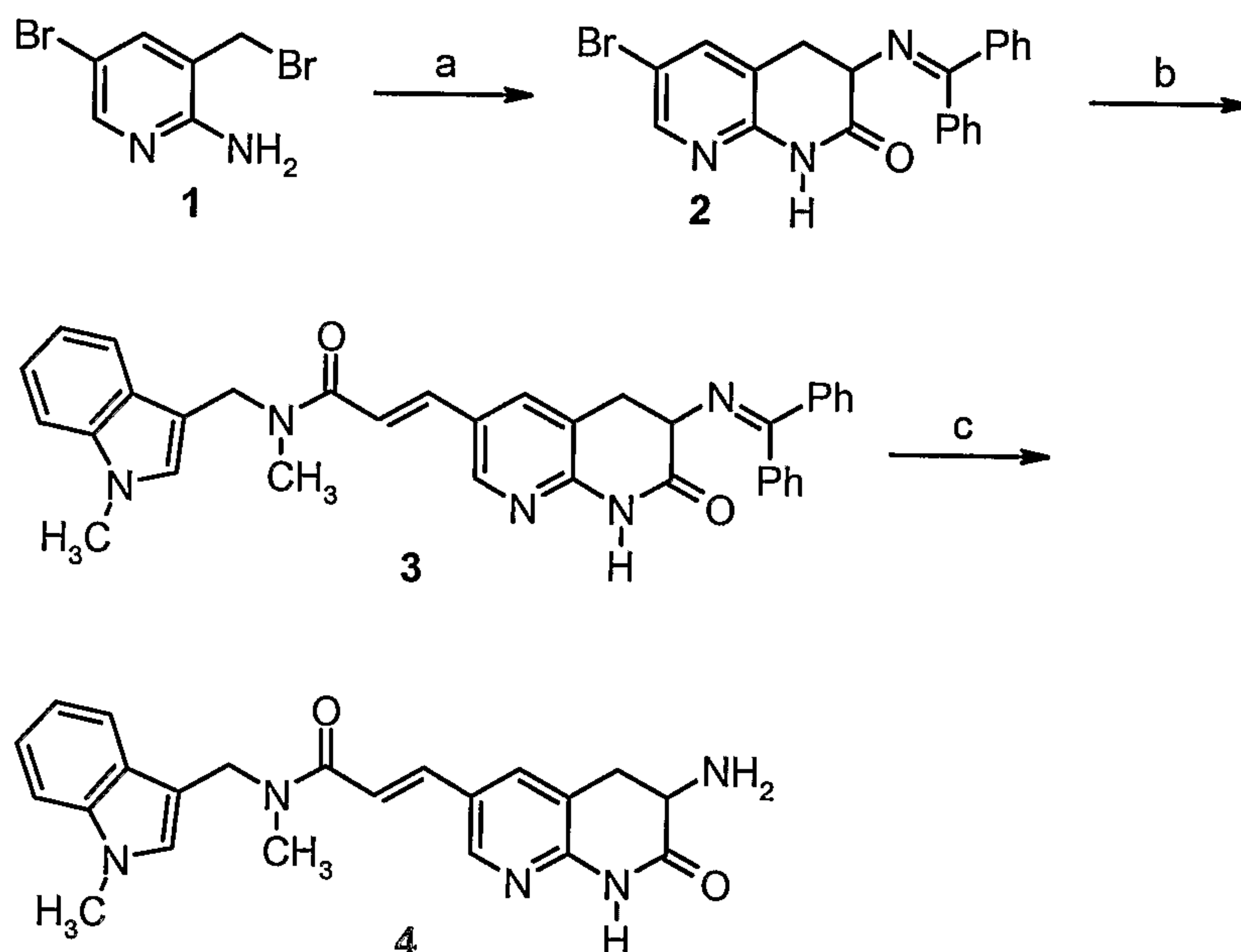


(a) 2-aminopyridine, sodium *tert*-butoxide, tris(dibenzylideneacetone)dipalladium(0), 1,3-bis(diphenylphosphino)propane, toluene.

10 Commercially available 2,5-dibromopyridine (**XLIV-1**) reacts with 2-aminopyridine in the presence of a suitable base, typically sodium *tert*-butoxide, to afford the dipyridylamine derivative **XLIV-2**. The reaction is mediated by a suitable palladium (0) catalyst, such as tris(dibenzylideneacetone)dipalladium(0), in the presence of an appropriate ligand, for example 1,3-bis(diphenylphosphino)propane. A neutral solvent such

15 as toluene is preferred.

Scheme XLV



(a) N-(Diphenylmethylene)glycine ethyl ester, NaH, DMF; (b) N-methyl-N-(1-methyl-1H-indol-3-ylmethyl)acrylamide, $\text{Pd}(\text{OAc})_2$, $\text{P}(o\text{-tol})_3$, $(i\text{-Pr})_2\text{NEt}$, propionitrile; (c) HCl, dioxane, H_2O .

20

Benzylic bromide **XLV-1**, prepared as described in Scheme XXXIX, reacts with an appropriate α -aminoester equivalent, for example N-(diphenylmethylene)glycine ethyl ester, under basic conditions, to provide **XLV-2**. A polar, aprotic solvent, such as DMF, THF, DME, or mixtures thereof, is generally preferred, and sodium hydride is typically the
5 base of choice, although LDA or $\text{LiN}(\text{TMS})_2$ might also be used. Alternatively, the reaction might be conducted in an alcoholic solvent, such as methanol or ethanol, with an alkali metal alkoxide, for example sodium methoxide or sodium ethoxide, as the base. The diphenylmethylene group is conveniently removed under acidic conditions, such as HCl in aqueous dioxane. Other conditions for the removal of a diphenylmethylene group are
10 known to those of skill in the art, and can be found in the chemical literature or in standard reference volumes, such as Greene (see above).

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
15 compounds of the invention. 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 formulas **I-III**. These possibilities are further detailed in the preparations and examples section to follow.

Acid addition salts of the compounds of formulas **I-III** can be prepared in a
20 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. 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
25 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.

Antibiotic Agents

The second component in the antibacterial compositions of the present invention is
30 usually an antibiotic agent other than a FabI inhibitor. Additional components may also be present, including other FabI inhibitors or antibiotic agents.

Non-limiting examples of antibiotic agents that may be used in the antibacterial compositions of the present invention include cephalosporins, quinolones and

fluoroquinolones, penicillins, penicillins and beta lactamase inhibitors, carbapenems, monobactams, macrolides and lincosamines, glycopeptides, rifampin, oxazolidinones, tetracyclines, aminoglycosides, streptogramins, sulfonamides, and others. Each family comprises many members.

5 *Cephalosporins*

Cephalosporins are further categorized by generation. Non-limiting examples of cephalosporins by generation include the following. Examples of cephalosporins I generation include Cefadroxil, Cefazolin, Cephalexin, Cephalothin, Cephapirin, and Cephadrine. Examples of cephalosporins II generation include Cefaclor, Cefamandol, Cefonicid, 10 Cefotetan, Cefoxitin, Cefprozil, Ceftmetazole, Cefuroxime, Cefuroxime axetil, and Loracarbef. Examples of cephalosporins III generation include Cefdinir, Ceftibuten, Cefditoren, Cefetamet, Cefpodoxime, Cefprozil, Cefuroxime (axetil), Cefuroxime (sodium), Cefoperazone, Cefixime, Cefotaxime, Cefpodoxime proxetil, Ceftazidime, Ceftizoxime, and Ceftriaxone. Examples of cephalosporins IV generation include Cefepime.

15 *Quinolones and Fluoroquinolones*

Non-limiting examples of quinolones and fluoroquinolones include Cinoxacin, Ciprofloxacin, Enoxacin, Gatifloxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin, Oxolinic acid, Gemifloxacin, and Perfloxacin.

20 *Penicillins*

Non-limiting examples of penicillins include Amoxicillin, Ampicillin, Bacampicillin, Carbenicillin Indanyl, Mezlocillin, Piperacillin, and Ticarcillin.

Penicillins and Beta Lactamase Inhibitors

Non-limiting examples of penicillins and beta lactamase inhibitors include 25 Amoxicillin-Clavulanic Acid, Ampicillin-Sulbactam, Benzylpenicillin, Cloxacillin, Dicloxacillin, Methicillin, Oxacillin, Penicillin G (Benzathine, Potassium, Procaine), Penicillin V, Piperacillin+Tazobactam, Ticarcillin+Clavulanic Acid, and Nafcillin.

Carbapenems

Non-limiting examples of carbapenems include Imipenem-Cilastatin and 30 Meropenem.

Monobactams

A non-limiting example of a monobactam includes Aztreonam.

Macrolides and Lincosamines

Non-limiting examples of macrolides and lincosamines include Azithromycin, Clarithromycin, Clindamycin, Dirithromycin, Erythromycin, Lincomycin, and Troleandomycin.

5 *Glycopeptides*

Non-limiting examples of glycopeptides include Teicoplanin and Vancomycin.

Rifampin

Non-limiting examples of rifampins include Rifabutin, Rifampin, and Rifapentine.

Oxazolidonones

10 A non-limiting example of oxazolidonones includes Linezolid.

Tetracyclines

Non-limiting examples of tetracyclines include Demeclocycline, Doxycycline, Methacycline, Minocycline, Oxytetracycline, Tetracycline, and Chlortetracycline.

Aminoglycosides

15 Non-limiting examples of aminoglycosides include Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin, Tobramycin, and Paromomycin.

Streptogramins

A non-limiting example of streptogramins includes Quinopristin+Dalfopristin.

Sulfonamides

20 Non-limiting examples of sulfonamides include Mafenide, Silver Sulfadiazine, Sulfacetamide, Sulfadiazine, Sulfamethoxazole, Sulfasalazine, Sulfisoxazole, Trimethoprim-Sulfamethoxazole, and Sulfamethizole.

Others

Non-limiting examples of other antibiotic agents include Bacitracin,
25 Chloramphenicol, Colistemetate, Fosfomycin, Isoniazid, Methenamine, Metronidazol, Mupirocin, Nitrofurantoin, Nitrofurazone, Novobiocin, Polymyxin B, Spectinomycin, Trimethoprim, Colistin, Cycloserine, Capreomycin, Pyrazinamide, Para-aminosalicylic acid, and Erythromycin ethylsuccinate + sulfisoxazole.

Toxicology of Compounds

30 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 organ(s) 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.

Cloning of *S. aureus* FabI

The *fabI* gene was cloned from the chromosomal DNA of *S. aureus* strain WCUH29 using the polymerase chain reaction. Amplification was performed using *Taq* DNA

polymerase (BRL) and the following primers: 5'-
 CGCCTCGAGATGTTAAATCTTGAAAACAAAACATATGTC-3' and 5'-
 CGCGGATCCAATCAAGTCAGGTTGAAATATCCA-3' (*Xho*I and *Bam*HI sites
 underlined). The resulting fragment was then digested with *Xho*I and *Bam*HI and ligated
 5 into *Xho*I- and *Bam*HI-digested expression vector pET-16b (Novagen), producing pET-
 His₁₀-*fabI*. The gene sequence of *fabI* was confirmed by automated cycle sequencing
 using an Applied Biosystems model 377 machine. The untagged version of pET-*fabI* was
 constructed by digesting pET-His₁₀-*fabI* with *Nco*I and *Nde*I to remove a 97 bp fragment
 encoding the His 10 tag, the factor Xa cleavage site and the first 8 amino acids of FabI, and
 10 replacing it with a linker encoding the first 8 amino acids of FabI plus a glycine residue
 between the initiator methionine and the lysine at position 2. This plasmid was called pET-
fabI. The linker was made by annealing the following two oligonucleotides: 5'-
 CATGGGCTTAAATCTTGAAAACAAAACA-3' and 5'-
 TATGTTTTGTTTTCAAGATTTAAGCC-3'. The linker sequence in pET-*fabI* was
 15 confirmed by dideoxy sequencing. Only native FabI was used for compound evaluation.
 For overproduction of native FabI, plasmid pET-*fabI* was transformed into BL21(DE3)
 (Novagen) cells, to form strain BL21(DE3):pET-*fabI*.

Purification of *S. aureus* FabI

S. aureus FabI was expressed as soluble protein to 10% of total cell protein, 400g
 20 cells being recovered from 15L fermentation in tryptone phosphate medium. The cells
 were lysed and the sample centrifuged. The resulting supernatant was filtered and purified
 using three consecutive chromatography columns: ion-exchange (Source 15Q), dye-affinity
 (Blue sepharose), and size exclusion chromatography columns (Superose 12). After each
 column the FabI containing fractions were pooled, concentrated, and checked for purity and
 25 biological activity.

Cloning/Expression *Haemophilus influenzae* FabI

The FabI gene was PCR amplified from *Haemophilus influenzae* (Q1) genomic
 DNA. Oligonucleotide primers were designed with unique restriction sites at both the N'
 and C' terminal ends of the gene to allow efficient sub-cloning into the expression vector
 30 pPROLar.

FORWARD PRIMER

*Kpn*I

5' GCGGTACCCATGCGCTTGGTTTTCTTAGAAATATTG '3

REVERSE PRIMER*NotI*

5' GCGGCCGCTTATTCTTCGCCTAATTCGCCCCATTGC '3

PCR amplification was performed using *Pfu* Turbo DNA polymerase as per the instructions of the manufacturer (Stratagene). The following cycling conditions were used: 95 °C for 3 minutes followed by 30 cycles of 94 °C 1 minute, 55 °C 1 minute and 72 °C 3 minutes. A final extension at 72 °C for 5 minutes was carried out. PCR products of expected size for *Haemophilus influenzae* FabI were cloned into the PCR cloning vector TOPO TA 2.1 as per instructions of the manufacturer (Invitrogen). The fidelity of the presumptive PCR amplified *Haemophilus influenzae* FabI gene was confirmed by DNA sequencing on both strands using an ABI 377 Automative DNA Sequencer (Applied Biosystems). pPROLar was digested with *KpnI* and *NotI* restriction endonucleases using conditions as recommended by the supplier (New England Biolabs). Purification of the linear plasmid, was achieved using agarose gel purification and the Qia-quick gel purification kit as per the protocol supplied by the manufacturer (Qiagen). The *Haemophilus influenzae* FabI gene was excised from TOPO TA 2.1 by *KpnI* and *NotI* restriction endonuclease digestion and purified as above. Subsequent fragment/vector ligations were carried out using T4 DNA ligase, using conditions supplied by the manufacturer (Promega).

Transformations into *E. coli* TOP 10 competent cells were performed using the protocol as supplied by the manufacturer (Invitrogen). Verification of the resultant clones was carried out using colony PCR and restriction endonuclease digestion. Positive clones were then transformed into the expression strain *E. coli* DH5 α PRO, which expresses *AraC* in addition to the *lac* repressor.

Subsequent clones were then evaluated for expression at small-scale using the conditions as recommended by the manufacturer (Clontech). Expression analysis showed over-expressed protein bands of correct size for *Haemophilus influenzae* FabI clearly visible by SDS PAGE. Protein identity was further confirmed by peptide mass fingerprinting. Further analysis by N-terminal Amino Acid sequencing of the purified protein showed that the N-terminus starts 35 residues downstream of the presumptive initiation codon. DNA sequence analysis also highlighted the presence of a ribosome binding site upstream and correctly spaced from the new initiation codon. These findings match perfectly with *E. coli* FabI and the protein is also now a similar size to other FabIs.

The over-expression construct has managed to use the correct ribosome binding site and start at the correct ATG to give the correct protein.

Purification of *H. influenzae* FabI

One liter of cells containing the *H. influenzae* FabI expression construct were grown to an OD600 of 0.6. Expression was induced as described above and the cells were grown for a further 3 h and then harvested. The cell pellet was re-suspended in 10 ml 50 mM Tris pH 7.5, 1 mM PMSF, 1 mM benzamidine, 1 mM DTT (buffer A) and lysed by sonication. Cell debris was removed by centrifugation. The supernatant was loaded onto a Hi-load Q (16/10) column (Pharmacia) equilibrated in buffer A. Protein was eluted over a 200 mL gradient of 0-100% buffer B, where buffer B is buffer A + 1 M KCl. Fractions containing FabI were identified by SDS PAGE and by their FabI activity and pooled.

1.5 M ammonium sulfate was added to the pooled fractions and these were then loaded onto a Hi-load phenyl sepharose (16/10) column (Pharmacia) equilibrated in 50 mM Tris pH 7.5, 1 mM PMSF, 1 mM benzamidine, 1 mM DTT, 1.5 M ammonium sulfate. Proteins were eluted with a gradient of ammonium sulfate (1.5 to 0 M) over 200 mL. Fractions containing FabI were identified as above and pooled. The pooled fractions were buffer exchanged into 100 mM Tris, pH 7.5, 2 mM DTT and glycerol was then added to 50%. The protein was stored at -20 °C. The identity of the protein was confirmed by N-terminal sequencing and MALDI mass spectrometry.

Cloning of *E. coli* FabI

A PCR fragment of correct size for *E. coli* FabI was PCR amplified from *E. coli* chromosomal DNA, subcloned into the TOPO TA cloning vector, and verified by colony PCR + restriction endonuclease analysis. The presumptive *E. coli* FabI PCR fragment was subcloned into the expression vector pBluePet. The FabI clone was transformed into *E. coli* strain BL21(DE3). Small Scale expression studies show an over-expressed protein band of correct molecular weight (~28 Kda) for *E. coli* FabI clearly visible following Coomassie staining of SDS PAGE gels. DNA sequencing of the *E. coli* FabI expression constructs illustrated that no errors were apparent. N' terminal amino acid sequencing has confirmed the over-expressed protein band to be *E. coli* FabI.

Purification of *E. coli* FabI

E. coli FabI was expressed as soluble protein to 15% of total cell protein, 120g cells being recovered from 3L fermentation in shake flasks in modified terrific broth. The cells were lysed and the sample centrifuged. The resulting supernatant was filtered and purified

using three consecutive chromatography columns: ion-exchange (Source 15Q), dye-affinity (blue sepharose), and size exclusion (superose 12). After each column the FabI containing fractions were pooled, concentrated and checked for purity and biological activity.

S. aureus FabI Enzyme Inhibition Assay (NADH)

5 Assays were carried out in half-area, 96-well microtitre plates. Compounds were 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 were typically varied over the range of 0.01-10 uM. The consumption of NADH was monitored for 20 minutes at 30 °C
10 by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC₅₀'s were 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
15 a positive control. Compounds of this invention have IC₅₀'s from about 5.0 micromolar to about 0.05 micromolar.

S. aureus FabI Enzyme Inhibition Assay (NADPH)

 Assays were carried out in half-area, 96-well microtitre plates. Compounds were 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,
20 and an appropriate dilution of *S. aureus* FabI. Inhibitors were typically varied over the range of 0.01-10 uM. The consumption of NADPH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t
25 = 0 min. IC₅₀'s were 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

30 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. IC₅₀'s are estimated from a fit of the initial velocities to a standard, 4-parameter model, and are typically reported as the mean $\pm$ S.D. of duplicate determinations. The apparent K_i 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 were carried out in half-area, 96-well microtitre plates. Compounds were 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 were typically varied over the range of 0.01-10 uM. The consumption of NADH was monitored for 20 minutes at 30 °C by following the change in absorbance at 340 nm. Initial velocities were estimated from an exponential fit of the non-linear progress curves represented by the slope of the tangent at t = 0 min. IC₅₀'s were estimated from a fit of the initial velocities to a standard, 4-parameter model and are typically reported as the mean $\pm$ 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 IC₅₀'s from about 100.0 micromolar to about 0.05 micromolar.

Preparation and purification of crotonoyl-ACP

Reactions contained 5 mg/mL *E. coli* apo-ACP, 0.8 mM crotonoyl-CoA (Fluka), 10 mM MgCl₂, and 30 uM *S. pneumoniae* ACP synthase in 50 mM NaHEPES, pH 7.5. The mixture was gently mixed on a magnetic stirrer at 23 °C for 2 hr, and the reaction was terminated by the addition of 15 mM EDTA. The reaction mixture was 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 was washed with buffer until all non-adherent material was removed (as observed by UV detection), and the crotonoyl-ACP was 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 150 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 0.01-10 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 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 IC₅₀'s from about 100.0 micromolar to about 0.04 micromolar. The apparent K_i is calculated from Equation 2 assuming the inhibition is competitive with crotonoyl-ACP.

Equation 1: $v = \text{Range}/(1+[I]/\text{IC}_{50}) + \text{Background}$

Equation 2: $K_i(\text{app}) = \text{IC}_{50}/(1+[S]/K_s)$

Antimicrobial Activity Assay

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compound was tested in serial two-fold dilutions ranging from 0.06 to 64 mcg/mL. A panel of 12 strains were evaluated in the assay. This panel consisted of the following laboratory strains: *Staphylococcus aureus* Oxford, *Streptococcus pneumoniae* R6, *Streptococcus pyogenes* CN10, *Enterococcus faecalis* I, *Haemophilus influenzae* Q1, *Escherichia coli* DC0, *E. coli* ESS, *E. coli* 7623 (*AcrAB*⁺) *E. coli* 120 (*AcrAB*⁻) *Klebsiella pneumoniae* E70, *Pseudomonas aeruginosa* K799wt and *Candida albicans* GRI 681. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

One skilled in the art would consider any antibacterial compositions of the present invention with a MIC of less than 256 µg/mL to be a potential lead composition. The antibacterial compositions used in the antimicrobial assays may have a MIC value of less than 128 µg/mL. Said compositions may have a MIC value of less than 64 µg/mL.

Method for Checkerboard Combination Studies

The combination experiments were performed and the results were interpreted using the checkerboard method as described in Eliopoulous, G. M., and R. C. Moellering, 1996, Antimicrobial combinations, p. 330-396, *In* V. Lorian (ed.), Antibiotics in laboratory medicine, 4th ed., The Williams & Wilkins Co., Baltimore, Md., in 96-well microtiter

plates. Compound A was serially diluted along the x-axis of the test plate to a final volume of 50 μ l, and compound B was serially diluted in a separate transfer plate. Dilutions in both plates were made in CAMHB (cation-adjusted Mueller Hinton broth) for *Staphylococci* and in CAMHB + 5% sheep blood for *Streptococci*. Aliquots (50 μ l) of Compound B were transferred to the test plate along the y-axis thereby achieving a checkerboard matrix of antimicrobial combinations (100 μ l total volume) as in Figure 4. The first column and last row (shaded in Figure 4) contained only compound B or compound A, respectively. Plates were then inoculated with 10 μ l of the test microorganism and MICs were determined according to NCCLS guidelines (see National Committee for Clinical Laboratory Standards, 2000, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fifth Edition, Approved Standard M7-A5, NCCLS, Wayne, PA, USA.)

Data analysis was performed as follows and according to Eliopoulous, G. M., and R. C. Moellering, 1996, Antimicrobial combinations, p. 330–396, *In* V. Lorian (ed.), Antibiotics in laboratory medicine, 4th ed., The Williams & Wilkins Co., Baltimore, Md.

First individual FIC values for each combination in a plate were calculated:

$$\text{FIC (Fractional Inhibitory Concentration)} = \text{FICA} + \text{FICB}$$

$\text{FICA} = \text{MICA+B} / \text{MICA}$ i.e. the MIC of combination of compound A + compound B divided by the MIC of compound A alone.

$\text{FICB} = \text{MICB+A} / \text{MICB}$ i.e. the MIC of combination of compound B + compound A divided by the MIC of compound B alone.

FIC values were calculated only for combinations that enabled determination of a true MIC (e.g. not $>$ or $\leq$ values). FIC indexes were then calculated as the average of individual FIC values for each combination plate. FIC index interpretation is:

<0.5 = synergy;
 $\geq 0.5 \leq 2$ = additivity or indifference; and
 >2 = antagonism.

A summary of the FIC index values is presented below in Table 1. Please see Figure 5 for the identity of compounds A, B, C, D, E, and F.

Table 1. Summary of combination MICs with compounds of formulas I-III and other antibiotics using the checkerboard method.

	FIC Index					
Antibiotic <i>Strains</i> ^a	A	B	C	D	E	F

Vancomycin						
<i>S. aureus</i> 29213	$\geq 0.5 \leq$	ND	$\geq 0.5 \leq$	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND
<i>S. aureus</i> 43300	$\geq 0.5 \leq$	ND	$\geq 0.5 \leq$	$\geq 0.5 \leq$	$\geq 0.5 \leq$	$\geq 0.5 \leq$
<i>S. epidermidis</i> 39	<0.5	ND	ND	<0.5	$\geq 0.5 \leq$	ND
Rifampicin						
<i>S. aureus</i> 29213	$\geq 0.5 \leq$	ND	ND	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND
<i>S. aureus</i> 43300	$\geq 0.5 \leq$	ND	ND	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND
<i>S. epidermidis</i> 39	<0.5	ND	ND	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND
Gentamicin						
<i>S. aureus</i> 43300	$\geq 0.5 \leq$	ND	ND	<0.5	ND	ND
Tetracycline						
<i>S. aureus</i> 29213	$\geq 0.5 \leq$	ND	ND	$\geq 0.5 \leq$	ND	ND
Ceftriaxone						
<i>S. aureus</i> 29213	$\geq 0.5 \leq$	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND	ND	ND
<i>S. aureus</i> 43300	ND	ND	$\geq 0.5 \leq$	ND	ND	ND
<i>S. pneumoniae</i> 49619	ND	ND	$\geq 0.5 \leq$	ND	ND	ND
Cefuroxime						
<i>S. aureus</i> 29213	$\geq 0.5 \leq$	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND	ND	ND
<i>S. aureus</i> 43300	ND	ND	$\geq 0.5 \leq$	ND	ND	ND
<i>S. pneumoniae</i> 49619	ND	ND	$\geq 0.5 \leq$	ND	ND	ND
Cefotaxime						
<i>S. aureus</i> 29213	$\geq 0.5 \leq$	$\geq 0.5 \leq$	$\geq 0.5 \leq$	ND	ND	ND
<i>S. aureus</i> 43300	ND	ND	$\geq 0.5 \leq$	ND	ND	ND
<i>S. pneumoniae</i> 49619	ND	ND	$\geq 0.5 \leq$	ND	ND	ND

^a Bacterial species are *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pneumoniae*.

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.

5 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
10 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
15 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.,
20 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
25 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.

30 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.

5 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 LD₅₀ and the ED₅₀.

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 ED₅₀ 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

15 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, 20 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 25 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.

30 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
5 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
10 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
15 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,
20 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)
25 wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as 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
30 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, 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 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, Pluronic, 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. 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
5 surfactants.

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
10 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 antibiotic agent contained in the subject composition, 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,
15 400% less or 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 or antibiotic agent 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
20 composition. The comparison may be made against the same or a different effective dosage of the various agents. The different regimens compared may use bacterial levels.

Alternatively, a comparison of the different treatment regimens described above may be based on the effectiveness of the treatment, using standard indices for bacterial infections known to those of skill in the art. One method of treatment may be 10%, 20%,
25 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
30 method using the same or different FabI inhibitor, antibiotic agent or combinations thereof.

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.

5 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.

10

Exemplification

General

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at either 300 or 400 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s =
15 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, $\text{DMSO}-d_6$ is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES) ionization techniques. Elemental analyses were
20 performed by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius. Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.
25 Analytical HPLC was performed on Beckman chromatography systems. Preparative HPLC was performed using Gilson chromatography systems. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a
30 registered trademark of Hamilton Co., Reno, Nevada. 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, $(I\text{-Pr})_2\text{EtN} = N$,

N-diisopropylethylamine, DMF = *N,N*-dimethylformamide, MeOH = methanol, EtOH = ethanol, THF = tetrahydrofuran, DMSO = dimethylsulfoxide, Et₂O = diethyl ether, Ar = argon, Pd(OAc)₂ = palladium(II)acetate, P(*o*-tol)₃ = tri-*ortho*-tolylphosphine, EtOAc = ethyl acetate, ACE-Cl = 1-chloroethyl chloroformate, satd = saturated, Et₃N = triethylamine,
5 TFA = trifluoroacetic acid, NaBH(OAc)₃ = sodium triacetoxyborohydride, HOAc = acetic acid, EtCN = propionitrile, CBzCl = benzyl chloroformate, MeCN = acetonitrile.

10

Preparation 1

Preparation of (E)-3-(6-aminopyridin-3-yl)acrylic acid (Method A)

a) Benzyl (E)-3-(6-aminopyridin-3-yl)acrylate

A solution of 2-amino-5-bromopyridine (2.25 g, 13.0 mmole), benzyl acrylate (3.2
15 g, 19.7 mmole), Pd(OAc)₂ (0.31 g, 1.4 mmole), tri-*ortho*-tolylphosphine (0.73 g, 2.4 mmole), and diisopropylethylamine (3.5 mL, 20.0 mmole) in propionitrile (50 mL) was heated at reflux overnight. The dark mixture was filtered through celite®, and the filtrate was concentrated. Flash chromatography on silica gel (3% MeOH/CH₂Cl₂) gave the title compound (1.3 g, 39%): MS (ES) *m/e* 255 (M + H)⁺.

20 b) (E)-3-(6-Aminopyridin-3-yl)acrylic acid

A solution of benzyl (E)-3-(6-aminopyridin-3-yl)acrylate (1.3 g, 5.1 mmole) and 1.0 N NaOH (10 mL, 10 mmole) in MeOH was heated at reflux overnight. The solution was concentrated in vacuo, and the residue was dissolved in H₂O. The pH was adjusted to 6 with dilute HCl, and the solid precipitate was collected by suction filtration and dried to
25 give the title compound (0.6 g, 72%) as a white solid: MS (ES) *m/e* 165 (M + H)⁺.

Preparation 2

Preparation of (E)-3-(6-aminopyridin-3-yl)acrylic acid (Method B)

a) (E)-3-(6-Aminopyridin-3-yl)acrylic acid

Acrylic acid (23 mL, 0.33 mole) was added carefully to a solution of 2-amino-5-
30 bromopyridine (25.92 g, 0.15 mole) and Na₂CO₃ (55.64 g, 0.53 mole) in H₂O (600 mL). PdCl₂ (0.53 g, 0.003 mole) was then added, and the mixture was heated at reflux. After 24 hr, the reaction was cooled to RT and filtered, and the filtrate was adjusted to pH 6 with

aqueous HCl. Additional H₂O (0.5 L) was added to improve mixing, and the mixture was stirred for 1 hr. The pH was readjusted to 6, then the solid was collected by suction filtration. The filter pad was washed sequentially with H₂O (2 x 0.5 L), cold absolute EtOH (100 mL), and Et₂O (2 x 250 mL). Drying in high vacuum at elevated temperature
5 gave the title compound (15.38 g, 62%) as a tan solid: ¹H NMR (300 MHz, DMSO-d₆) δ 8.11 (d, J = 2.0 Hz, 1 H), 7.75 (dd, J = 8.7, 2.0 Hz, 1 H), 7.43 (d, J = 15.8 Hz, 1 H), 6.53 (s, 2 H), 6.45 (d, J = 8.7 Hz, 1 H), 6.22 (d, J = 15.8 Hz, 1 H); MS (ES) *m/e* 165 (M + H)⁺.

Preparation 3

Preparation of (E)-3-(2-aminopyrimidin-5-yl)acrylic acid

10 a) Benzyl (E)-3-(2-aminopyrimidin-5-yl)acrylate

According to the procedure of Preparation 1 (a), except substituting 5-bromo-2-aminopyrimidine (1.95 g, 11.2 mmole) for 2-amino-5-bromopyridine, the title compound (2.25 g, 79%) was prepared as a light orange solid: MS (ES) *m/e* 256 (M + H)⁺.

b) (E)-3-(2-Aminopyrimidin-5-yl)acrylic acid

15 According to the procedure of Preparation 1 (b), except substituting benzyl (E)-3-(2-aminopyrimidin-5-yl)acrylate (2.93 g, 11.5 mmole) for benzyl (E)-3-(6-aminopyridin-3-yl)acrylate, the title compound (1.71 g, 90%) was prepared as an off-white solid: MS (ES) *m/e* 166 (M + H)⁺.

Preparation 4Preparation of 6-bromo-3,4-dihydro-1H-1,8-naphthyridin-2-one

a) 2-Amino-3-(hydroxymethyl)pyridine

Solid 2-aminonicotinic acid (199 g, 1.44 mole) was added in portions over 4 hr to
5 1.0 M LiAlH₄ in THF (3 L, 3 mole) with stirring under Argon. An ice-bath was applied to
control the temperature below 30 °C. After the addition was complete, the reaction was
heated at reflux for 16 hr, then was cooled to 0 °C and carefully quenched by sequential
addition of H₂O (120 mL), 15% NaOH in H₂O (120 mL), and H₂O (350 mL). The
resulting thick suspension was stirred for 1 hr, then was filtered through a pad of celite®.
10 The filter pad was rinsed with THF (1 L), and the filtrate was concentrated to dryness to
give the title compound (156 g, 87%) as a pale yellow waxy solid: MS (ES) *m/e* 125.1 (M
+ H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.84 (dd, 1 H), 7.37 (m, 1 H), 6.53 (dd, 1 H),
5.65 (br s, 2 H), 5.16 (t, 1 H), 4.34 (d, J = 4.6 Hz, 2 H).

b) 2-Amino-5-bromo-3-(hydroxymethyl)pyridine hydrobromide

15 To a stirred solution of 2-amino-3-(hydroxymethyl)pyridine (156 g, 1.257 mole) in
HOAc (2.5 L) at ambient temperature was added bromine (64.1 mL, 1.257 mole) dropwise
over 1 hr. A suspension began to form during the addition. An exotherm to 36 °C was
controlled with an ice bath. After the addition, the reaction mixture was stirred at ambient
temperature overnight. The yellow precipitate was filtered, washed with ether and air-dried
20 to give the title compound (289 g, 81%): MS (ES) *m/e* 203.2 (M + H)⁺; ¹H NMR (400
MHz, DMSO-d₆, free base) δ 7.89 (d, J = 2.3 Hz, 1 H), 7.52 (s, 1 H), 5.92 (br s, 2 H), 5.29
(br s, 1 H), 4.30 (s, 2 H).

c) 2-Amino-5-bromo-3-(bromomethyl)pyridine hydrobromide

A suspension of 2-amino-5-bromo-3-(hydroxymethyl)pyridine hydrobromide (289
25 g, 1.02 mole) in 48% aqueous HBr (2.9 L) was heated at reflux for 12 hrs. Complete
solution occurred during heating. The reaction mixture was cooled and a crystalline
precipitate formed. This was filtered and washed with ethyl acetate and air dried to give the
title compound (305 g, 86 %).

d) Methyl (±)-6-bromo-2-oxo-1,2,3,4-tetrahydro-1H-1,8-naphthyridine-3-carboxylate

30 To a solution of dimethyl malonate (224 g, 1.7 mole) in DMF (2 L) and THF (2 L)
stirred under argon and chilled to 3 °C with an ice-acetone bath was added NaH (60% Nujol
dispersion, 69.2 g, 1.7 mole) in portions over 1.5 hr. The anion solution was stirred for 15

min at ca. 5 °C, then 2-amino-5-bromo-3-(bromomethyl)pyridine hydrobromide (200 g, 0.56 mole) was added in portions over 15 min. The reaction mixture was allowed to warm to ambient temperature during overnight stirring and then was heated to 80 °C for 2 hr. The reaction was then cooled and filtered and the precipitate was washed with ethyl acetate.

- 5 This solid was then vigorously stirred in 2 L water for 15 min and again filtered and air-dried to give the title compound (113 g, 71 %): MS (ES) *m/e* 286 (M + H)⁺.

e) 6-Bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one

- To a suspension of methyl (±)-6-bromo-2-oxo-1,2,3,4-tetrahydro-1*H*-1,8-naphthyridine-3-carboxylate (170 g, 0.596 mole) in CH₃OH (10 L) was added 1.0 M NaOH
10 (2.5 L). The reaction mixture was stirred and heated at reflux for 5 hrs and then cooled to ambient temperature. The suspension was acidified with 1.0 M HCl (3.0 L) and then was stirred and heated at reflux overnight. The reaction slurry was cooled and filtered and the solid was washed with water and vacuum dried to give the title compound (122 g of the hydrate, 90 %) as an off-white solid, HPLC purity, 94 %: MS (ES) *m/e* 228 (M + H)⁺.

15 Preparation 5

Preparation of 6-bromo-3-methyl-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

a) 2-Amino-5-bromo-3-(methylaminomethyl)pyridine

- A solution of 2-amino-5-bromo-3-(hydroxymethyl)pyridine (5.00 g, 24.6 mmole), from Preparation 4 (b), in 48% aqueous HBr (50 mL) was heated at reflux for 12 hrs. The
20 reaction was concentrated and toluene was used to azeotrope the residual H₂O. The resulting light brown solid was placed under high vacuum overnight and used directly.

- A solution of the 2-amino-3-(bromomethyl)-5-bromopyridine hydrobromide salt (prepared above) in 40% aqueous methylamine (50 mL) and THF (50 mL) was stirred at RT overnight in a pressure bottle. The reaction solution was concentrated and extracted
25 with EtOAc (2 x 100 mL). The combined organic phases were washed with H₂O, dried over Na₂SO₄ and concentrated. Purification on silica gel afforded the title compound (4.25 g, 80 %) as a yellow oil: MS (ES) *m/e* 217 (M + H)⁺.

b) 6-Bromo-3-methyl-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

- To a solution of 2-amino-5-bromo-3-(methylaminomethyl)pyridine (2.0 g, 9.3
30 mmole) in dichloroethane (50 mL) was added 1,1'-carbonyldiimidazole (1.9 g, 11.5 mmole). The reaction was heated at 50 °C overnight and concentrated. The residue was

purified on silica gel (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) to give the title compound (1.72 g, 77 %) as an off-white solid: MS (ES) *m/e* 243 (M + H)⁺.

Preparation 6

Preparation of (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylic acid

5 a) 5-Bromo-2,3-diaminopyridine

To a suspension of 2-amino-5-bromo-3-nitropyridine (2.0 g, 9.17 mmole) in absolute EtOH (50 mL) was added SnCl₂ hydrate (9.3 g, 41.3 mmole), then the mixture was heated to reflux. After 3 hr the mixture was cooled to RT and concentrated. The residue was taken up in 2.0 M NaOH and extracted with EtOAc (3x). The combined
10 organic layers were dried (MgSO₄), filtered, and concentrated to give the title compound (1.69 g, 98%) which was sufficiently pure for use in the next step: MS (ES) *m/e* 188/190 (M + H)⁺.

b) 6-Bromo-3*H*-imidazo[4,5-*b*]pyridine

5-Bromo-2,3-diaminopyridine (1.69 g, 8.99 mmole) was taken up in 96% formic
15 acid (50 mL) and heated to reflux. After 18 hr the mixture was cooled to RT and concentrated. The residue was taken up in H₂O and the pH was adjusted to 7 with 2.0 M NaOH. The title compound (1.54 g, 87%) was collected as a solid by filtration, washed with H₂O, and dried *in vacuo*: MS (ES) *m/e* 198/200 (M + H)⁺.

c) 6-Bromo-4-trityl-3*H*-imidazo[4,5-*b*]pyridine

20 To a suspension of 6-bromo-3*H*-imidazo[4,5-*b*]pyridine (1.2 g, 6.06 mmole) in CH₂Cl₂ (30 mL) was added Et₃N (1.3 mL, 9.09 mmole) then trityl chloride (2.03 g, 7.27 mmole) at RT. After 72 hr the mixture was washed with H₂O (2x) and brine, then was dried (MgSO₄), filtered, and concentrated under reduced pressure to afford the title compound. This was used directly in the next step.

25 d) Benzyl (E)-3-(4-trityl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylate

A solution of 6-bromo-4-trityl-3*H*-imidazo[4,5-*b*]pyridine (from step a) (6.06 mmole), benzyl acrylate (1.18 g, 7.27 mmole), Pd(OAc)₂ (67 mg, 0.30 mmole), P(o-tolyl)₃ (183 mg, 0.6 mmole), and (i-Pr)₂NEt (2.64 mL, 15.15 mmole) in propionitrile (30 mL) was degassed (3 x N₂/vacuum) then heated to reflux. After 4 hr the mixture was cooled to RT
30 and concentrated. Flash chromatography on silica gel (30% EtOAc/hexanes) gave the title compound (1.75 g, 55% over 2 steps) as an off-white foam: ¹H NMR (400 MHz, CDCl₃) δ

8.24 (d, $J = 2.0$ Hz, 1 H), 8.19 (d, $J = 2.0$ Hz, 1 H), 8.06 (s, 1 H), 7.77 (d, $J = 16.0$ Hz, 1 H), 7.42-7.11 (m, 20 H), 6.48 (d, $J = 16.0$ Hz, 1 H), 5.25 (s, 2 H).

d) (E)-3-(3*H*-Imidazo[4,5-*b*]pyridin-6-yl)acrylic acid

Benzyl (E)-3-(4-trityl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)acrylate (1.75 g, 3.35 mmole) was dissolved in 4 N HCl in dioxane (20 mL). After 1 hr the mixture was concentrated. The residue was taken up in 1:1 MeOH/H₂O (15 mL). 2.0 N NaOH (15 mL, 15 mmole) was added and the mixture was heated to reflux. After 18 hr the mixture was cooled to RT and concentrated to approximately 1/3 volume. The mixture was adjusted to pH 4 using 10% HCl. The solid was collected by filtration, washed with H₂O, and dried *in vacuo* to give the title compound (329 mg, 52% over 2 steps) as a white solid: ¹H NMR (400 MHz, d⁶-DMSO) δ 9.10 (s, 1 H), 8.94 (s, 1 H), 8.84 (s, 1 H), 8.20 (d, $J = 16.0$ Hz, 1 H), 7.10 (d, $J = 16.0$ Hz, 1 H).

Preparation 7

Preparation of (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl)acrylic acid

a) 3,4-Dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine

To a suspension of 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (2.0 g, 13.3 mmole) in dry THF (40 mL) was added a solution of LiAlH₄ in THF (1.0 M, 26.6 mL, 26.6 mmole) slowly at 0°C. After 1 hr the mixture was quenched with 2.0 M NaOH until a solid formed. The mixture was dried (MgSO₄), filtered, and concentrated under reduced pressure to give the title compound (1.44 g, 79%) as a white solid which was sufficiently pure for use in the next step: MS (ES) m/e 137 ($M + H$)⁺.

b) 4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine

To a solution of 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (1.44 g, 10.6 mmole) and di-*tert*-butyl dicarbonate (2.78 g, 12.7 mmole) in dry THF (50 mL) was added a solution of LiHMDS in THF (1.0 M, 12.7 mL, 12.7 mmole) dropwise at 0°C. After 30 min the mixture was quenched with saturated NH₄Cl and extracted with EtOAc (3x). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Flash chromatography on silica gel (40% EtOAc/hexanes) gave the title compound (2.0 g, 80%) as a clear oil: MS (ES) m/e 237 ($M + H$)⁺.

c) 4-(*tert*-Butoxycarbonyl)-7-bromo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine

To a solution of 4-(*tert*-butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (2.0 g, 8.46 mmole) in MeOH (40 mL) was added Br₂ (0.53 mL, 10.2 mmole) dropwise at

0°C. After 1 hr the mixture was concentrated. The residue was taken up in 1:1 Et₂O/hexanes and filtered. The filtrate was concentrated under reduced pressure to give the title compound (1.27 g, 48%) as an oil which solidified under vacuum: ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1 H), 7.33 (s, 1 H), 4.25 (m, 2 H), 3.92 (m, 2 H), 1.54 (s, 9 H).

- 5 d) (E)-3-[4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl]acrylic acid

A solution of 4-(*tert*-butoxycarbonyl)-7-bromo-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazine (1.27 g, 4.03 mmole), benzyl acrylate (785 mg, 4.84 mmole), Pd(OAc)₂ (45 mg, 0.20 mmole), P(*o*-tolyl)₃ (122 mg, 0.4 mmole), and (*i*-Pr)₂NEt (1.76 mL, 10.1 mmole) in propionitrile (20 mL) was degassed (3 x N₂/vacuum) then heated to reflux. After 18 hr the mixture was cooled to RT and concentrated. Flash chromatography on silica gel (25% EtOAc/hexanes) gave the title compound (1.17 g, 73%) as a yellow oil: MS (ES) *m/e* 397 (M + H)⁺.

- e) (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)acrylic acid

15 (E)-3-[4-(*tert*-Butoxycarbonyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazin-7-yl]acrylic acid (1.17 g, 2.95 mmole) was dissolved in 4 N HCl in dioxane (15 mL). After 72 hr the mixture was concentrated. The residue was taken up in 1:1 MeOH/H₂O (20 mL). 1.0 N LiOH (15 mL, 15 mmole) was added and the mixture was heated to reflux. After 18 hr the mixture was cooled to RT and concentrated to approximately 1/3 volume. The mixture was adjusted to pH 6 using 10% HCl. The solid was collected by filtration, washed with H₂O and dried *in vacuo* to give the title compound (315 mg, 52% over 2 steps): MS (ES) *m/e* 207 (M + H)⁺.

Preparation 8

Preparation of 5-bromo-2,2'-dipyridylamine

25 To a stirred solution of 2,5-dibromopyridine (2.4 g, 10.1 mmole) in dry toluene (75 mL) were added 2-aminopyridine (1.0 g, 10.6 mmole), tris(dibenzylideneacetone)dipalladium(0) (183 mg, 0.2 mmole), 1,3-bis(diphenylphosphino)propane (165 mg, 0.4 mmole) and sodium *tert*-butoxide (1.35 g, 14 mmole). The reaction was purged with Ar then heated with stirring at 70 °C. After 4 h the reaction was cooled to RT, taken up in Et₂O (200 mL), washed with brine, dried (MgSO₄) and concentrated to dryness. The remaining residue was purified by flash chromatography on silica gel (0.5% (5% NH₄OH/MeOH)/CHCl₃), triturated with hexane and dried under

vacuum to give the title product (1.31 g, 52%) as a pale yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 9.88 (s, 1 H), 8.31 (s, 1 H), 8.23 (d, $J = 4.8$ Hz, 1 H), 7.83 (m, 2 H), 7.67 (t, 1 H), 7.62 (d, $J = 8.4$ Hz, 1 H), 6.90 (t, 1 H); MS (ES) m/e 250.0 ($\text{M} + \text{H}$) $^+$.

Preparation 9

5 Preparation of 1-methyl-2-(methylaminomethyl)-1H-indole

a) Ethyl 1-methyl-1H-indole-2-carboxylate

NaH (60% dispersion in mineral oil, 8.02 g, 200.49 mmole) was washed with hexanes, then was suspended in dry DMF (530 mL). Solid ethyl indole-2-carboxylate (25.29 g, 133.66 mmole) was added portionwise over 5 - 10 min, allowing gas evolution to
10 subside between additions. When the addition was complete, the yellow mixture was stirred for 15 min, then methyl iodide (42 mL, 668.3 mmole) was added all at once. The reaction was exothermic, and the internal temperature rose to 40 - 45°C. After 1 hr, the reaction was quenched with 10% NH_4Cl (100 mL) and concentrated on the rotavap (high vacuum). The residue was partitioned between Et_2O (500 mL) and H_2O (100 mL), and the
15 layers were separated. The Et_2O layer was washed with H_2O (100 mL), dried (MgSO_4), and concentrated to leave the title compound (27.10 g, quantitative) as a light yellow solid. This was used without further purification: TLC (10% EtOAc /hexanes) $R_f = 0.39$.

b) N,1-Dimethyl-1H-indole-2-carboxamide

A suspension of ethyl 1-methyl-1H-indole-2-carboxylate (27.10 g, 133.34 mmole)
20 in 40% aqueous CH_3NH_2 (300 mL) and MeOH (30 mL) was stirred at RT. A solid tended to gradually creep up the walls of the flask, and was washed down periodically with MeOH. The flask was tightly stoppered to keep the material inside the flask. As the reaction proceeded, the solid dissolved, but eventually the product began to precipitate. The reaction was stirred at RT for 5 days, then was concentrated to remove approximately 200
25 mL of the solvent. The remaining residue was diluted with H_2O (300 mL), and the solid was collected by suction filtration and washed with H_2O . Drying at 50 - 60°C in high vacuum left the title compound (23.45 g, 93%) as a faintly yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 7.63 (d, $J = 8.0$ Hz, 1 H), 7.27 - 7.43 (m, 2 H), 7.10 - 7.20 (m, 1 H), 6.80 (s, 1 H), 6.10 - 6.30 (m, 1 H), 4.06 (s, 3 H), 3.01 (d, $J = 4.9$ Hz, 3 H).

30 c) 1-Methyl-2-(methylaminomethyl)-1H-indole

A 3-liter 3-necked roundbottom flask equipped with overhead stirring was charged with N,1-dimethyl-1H-indole-2-carboxamide (23.45 g, 124.58 mmole) and anhydrous THF

(170 mL). The solution was stirred while a solution of LiAlH_4 in THF (1.0 M, 250 mL, 250 mmole) was added via syringe. Gas was evolved during the addition of the first 50 mL of LiAlH_4 solution. When the addition was complete, the resulting light yellow solution was heated at gentle reflux. After 23 hr, the reaction was cooled in ice and quenched by the sequential dropwise addition of H_2O (9.5 mL), 15% NaOH (9.5 mL), and H_2O (28.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad was washed thoroughly with THF. The filtrate was concentrated and the residue was flash chromatographed on silica gel (10% $\text{MeOH}/\text{CHCl}_3$ containing 0.5% conc. NH_4OH). The title compound (20.17 g, 93%) was obtained as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 7.56 (d, $J = 7.8$ Hz, 1 H), 7.02 - 7.35 (m, 3 H), 6.38 (s, 1 H), 3.88 (s, 2 H), 3.75 (s, 3 H), 2.49 (s, 3 H).

Preparation 10

Preparation of 1-methyl-3-(methylaminomethyl)-1H-indole (Method A)

a) Methyl 1-methyl-1H-indole-3-carboxylate

NaH (60% dispersion in mineral oil, 8.56 g, 214.0 mmole) was added portionwise, allowing for gas evolution, to a solution of methyl 1H-indole-3-carboxylate (25.00 g, 142.7 mmole) in DMF (350 mL) at 0 °C. When the NaH addition was complete, methyl iodide (44.4 mL, 713.5 mmole) was added at 0 °C. The reaction was stirred at 0 °C for 15 minutes then at RT overnight. The reaction was diluted with water and extracted with ethyl acetate. The combined extracts were dried over K_2CO_3 and concentrated to afford the title compound (26.00 g, 96%) as an orange solid: MS (ES) m/e 190 ($\text{M} + \text{H}$)⁺.

b) N,1-Dimethyl-1H-indole-3-carboxamide

A suspension of methyl 1-methyl-1H-indole-3-carboxylate (4.30 g, 22.74 mmole) in 40% aqueous CH_3NH_2 (400 mL) was stirred at RT. The flask was tightly stoppered to keep the material inside the flask. As the reaction proceeded the product began to precipitate. The reaction was stirred at RT for 3 days, then was concentrated to remove approximately 200 mL of the solvent. The remaining residue was diluted with H_2O (500 mL), and the solid was collected by suction filtration and washed with H_2O . Flash chromatography on silica gel (ethyl acetate) gave the title compound (2.4 g, 56%) as a white solid: MS (ES) m/e 189 ($\text{M} + \text{H}$)⁺.

c) 1-Methyl-3-(methylaminomethyl)-1H-indole

A solution of LiAlH_4 in THF (1.0 M, 5.20 mL, 5.2 mmole) was slowly added via syringe to a solution of N,1-dimethyl-1*H*-indole-3-carboxamide (0.50 g, 2.6 mmole) in anhydrous THF (15 mL). Gas was evolved during the addition of the first 2 mL of LiAlH_4 solution. When the addition was complete, the resulting light yellow solution was heated at gentle reflux. After 23 hr, the reaction was cooled in ice and quenched by the sequential dropwise addition of H_2O (0.5 mL), 1.0 N NaOH (0.5 mL), and H_2O (0.5 mL). The mixture was stirred for 15 min, then was filtered through celite®, and the filter pad was washed thoroughly with THF. The filtrate was concentrated and the residue was flash chromatographed on silica gel (10% MeOH/ CHCl_3 containing 0.5% conc. NH_4OH) to afford the title compound (0.30 g, 67%) as a light yellow oil: MS (ES) m/e 175 ($\text{M} + \text{H}$)⁺.

Preparation 11

Preparation of 1-methyl-3-(methylaminomethyl)-1*H*-indole (Method B)

To a solution of 1-methylindole-3-carboxaldehyde (10.0 g, 62.8 mmole) in MeOH (100 mL) was added a solution of 2.0 M CH_3NH_2 in MeOH (126 mL, 252.0 mmole). The reaction was stirred at RT for 2 hrs, then was concentrated to a light yellow oil. This oil was dissolved in EtOH (300 mL), and NaBH_4 (2.38 g, 62.8 mmole) was added. After 2 hrs the reaction was concentrated to a slurry and dissolved in 1.0 N NaOH (75 mL). The aqueous solution was extracted with Et_2O (2 x 200 mL) and the combined organic fractions were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (9:1 $\text{CHCl}_3/\text{MeOH}$ containing 5% NH_4OH) and drying in high vacuum left the title compound (10.1 g, 92%) as a faintly yellow oil: MS (ES) m/e 175 ($\text{M} + \text{H}$)⁺.

Preparation 12

Preparation of 2-methyl-3-(methylaminomethyl)indole

To a solution of 2-methylindole-3-carboxaldehyde (10.00 g, 62.84 mmole) in MeOH (100 mL) was added 2 M CH_3NH_2 in MeOH (200 mL). After stirring for 3 hours at RT, the reaction solution was concentrated to a yellow oil which solidified under vacuum. This solid was dissolved in ethanol (350 mL) and NaBH_4 (2.38 g, 62.8 mmole) was added. The reaction was stirred at RT for 6 hours, then was concentrated under vacuum. The remaining residue was diluted with saturated aqueous Na_2CO_3 (50 mL) and extracted with EtOAc (2 x 200 mL). The organic phase was separated, washed with brine, and dried over Na_2SO_4 . Flash chromatography on silica gel (9:1 $\text{CHCl}_3/\text{MeOH}$ containing

5% NH₄OH) and drying under high vacuum gave the title compound (6.88 g, 63%) as a faintly yellow viscous solid: MS (ES) *m/e* 175 (M + H)⁺.

Preparation 13

Preparation of 1,3-dimethyl-2-(methylaminomethyl)-1*H*-indole

5 a) 1,3-Dimethyl-1*H*-indole

To a stirred solution of 3-methylindole (15.0 g, 114 mmole) in dry DMF (200 mL) was added NaH (60% dispersion in oil, 5.0 g, 125 mmole) in portions. Gas evolution was observed. The mixture was stirred for 30 min, then iodomethane (8 mL, 129 mmole) was added in one portion. The reaction became exothermic and was cooled in an ice bath.

10 After 16 hr at RT, the reaction was concentrated under vacuum and the residue was taken up in ethyl acetate. The solution was washed with H₂O then with brine, dried (MgSO₄), and concentrated to dryness. Purification by short path distillation under vacuum (bp 88-92°C, 0.5 mmHg) gave the title compound (16.10 g, 97%) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 7.9 Hz, 1 H), 7.35 (d, J = 8.2 Hz, 1 H), 7.13 (t, 1 H), 7.06 (s, 1 H), 7.00 (t, 1 H), 3.71 (s, 3 H), 2.24 (s, 3 H).

15 b) 1,3-Dimethyl-1*H*-indole-2-carboxaldehyde

To a stirred solution of phosphorus oxychloride (7.0 mL, 75 mmole) in DMF (25 mL) was added dropwise a solution of 1,3-dimethylindole (12.0 g, 83 mmole) in dry DMF (6.0 mL). The reaction was stirred at RT for 2 hr then was poured onto ice. The mixture was basified with a solution of NaOH (13.2 g, 330 mmole) in H₂O (44 mL), then was extracted with Et₂O (2x 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), and concentrated under vacuum. Flash chromatography on silica gel (10% ethyl acetate/hexanes) gave the title compound (13.03 g, 91%) as an off-white solid:

20 LCMS (ES) *m/e* 174.2 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃) δ 10.16 (s, 1 H), 7.68 (d, J = 8.1 Hz, 1 H), 7.42 (t, 1 H), 7.32 (d, J = 8.5 Hz, 1 H), 7.15 (t, 1 H), 4.04 (s, 3 H), 2.63 (s, 3 H).

c) 1,3-Dimethyl-2-(methylaminomethyl)-1*H*-indole

To 1,3-dimethyl-1*H*-indole-2-carboxaldehyde (13.0 g, 75 mmole) was added a solution of 2.0 M methylamine in methanol (150 mL, 300 mmole) and HOAc (4.3 mL, 75 mmole). The solution was stirred at RT for 4 hr, then was cooled to 0 °C, and sodium cyanoborohydride (5.0 g, 80 mmole) was added portionwise over 5 min. The reaction was then allowed to warm to RT. After 16 hr, the reaction was concentrated under vacuum and

the residue was taken up in Et₂O. The solution was washed with 1.0 N NaOH then with brine, dried (Na₂SO₄), and concentrated to dryness. Flash chromatography on silica gel (95:5 CHCl₃/methanol containing 5% NH₄OH) gave the title compound (7.34 g, 52%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 7.8 Hz, 1 H), 7.26 (d, J = 7.8 Hz, 1 H), 7.20 (t, 1 H), 7.09 (t, 1 H), 3.88 (s, 2 H), 3.76 (s, 3 H), 2.46 (s, 3 H), 2.32 (s, 3 H), 1.36 (br s, 1 H).

Preparation 14

Preparation of 1-methyl-3-(methylaminomethyl)-1H-pyrrolo[2,3-b]pyridine

a) 1-Methyl-1H-pyrrolo[2,3-b]pyridine

According to the procedure of Preparation 13 (a), except substituting 7-azaindole (2.28 g, 1.83 mmole) for the 3-methylindole, the title compound (1.4 g, 58%) was prepared as a yellow oil: MS (ES) *m/e* 133 (M + H)⁺.

b) 1-Methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 1-methyl-1H-pyrrolo[2,3-b]pyridine (0.7 g, 5.3 mmole) for the 1,3-dimethylindole, the title compound (0.4 g, 47%) was prepared as a white solid: MS (ES) *m/e* 161 (M + H)⁺.

c) 1-Methyl-3-(methylaminomethyl)-1H-pyrrolo[2,3-b]pyridine

According to the procedure of Preparation 13 (c), except substituting 1-methyl-1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde (0.4 g, 2.5 mmole) for the 1,3-dimethyl-1H-indole-2-carboxaldehyde, the title compound (0.2 g, 45%) was prepared as a yellow oil: MS (ES) *m/e* 176 (M + H)⁺.

Preparation 15

Preparation of 2-methyl-3-(methylaminomethyl)benzo[*b*]thiophene

a) 2-Methylbenzo[*b*]thiophene-3-carboxaldehyde

SnCl₄ (20 mL, 67 mmole) was added over 5 min to a stirred solution of 2-methylbenzo[*b*]thiophene (5.0 g, 33.7 mmole) in CH₂Cl₂ (75 mL) at 0 °C under argon. After 15 minutes, dichloromethyl methyl ether (3.7 mL, 41 mmole) was added. The reaction became a yellowish colored suspension. The reaction was allowed to warm to RT and stirred for 16 h, then was poured onto ice water (200 mL). The aqueous mixture was acidified with 1.0 N HCl (100 mL) and stirred until the suspension dissolved. The organic phase was separated, dried (MgSO₄), and concentrated under vacuum. Purification by flash chromatography on silica gel (10% ethyl acetate/hexane) gave the title compound

(5.83 g, 98%) as a white crystalline solid: ^1H NMR (400 MHz, CDCl_3) δ 10.38 (s, 1 H), 8.61 (d, $J = 8.1$ Hz, 1 H), 7.77 (d, $J = 8.0$ Hz, 1 H), 7.48 (t, 1 H), 7.39 (t, 1 H), 2.93 (s, 3 H)
 b) 2-Methyl-3-(methylaminomethyl)benzo[*b*]thiophene

According to the procedures of Preparation 1, except substituting 2-methylbenzo[*b*]thiophene-3-carboxaldehyde (5.0 g, 28.4 mmole) for 1-methylindole-3-carboxaldehyde, the title compound (4.89 g, 90%) was prepared as an oil which solidified in the freezer: ^1H NMR (400 MHz, CDCl_3) δ 7.78 (d, $J = 7.9$ Hz, 1 H), 7.75 (d, $J = 7.9$ Hz, 1 H), 7.37 (t, 1 H), 7.29 (t, 1 H), 3.95 (s, 2 H), 2.60 (s, 3 H), 2.50 (s, 3 H)

Preparation 16

10 Preparation of 3-(methylaminomethyl)-1*H*-indole

a) 3-(Methylaminomethyl)-1*H*-indole

To a solution of indole-3-carboxaldehyde (5.4 g, 34.1 mmole) in MeOH (30 mL) was added a solution of 2.0 M CH_3NH_2 in MeOH (51.3 mL, 102.6 mmole). The reaction was stirred at RT overnight, then was concentrated to a light yellow oil. This oil was
 15 dissolved in EtOH (40 mL), and NaBH_4 (1.3 g, 34.1 mmole) was added. After 16 hrs the reaction was concentrated to a slurry and dissolved in 10% Na_2CO_3 (100 mL). The aqueous solution was extracted with EtOAc (2 x 200 mL) and the combined organic fractions were dried over Na_2SO_4 and concentrated. Drying in high vacuum left the title compound (5.2 g, 94%) as a faintly yellow oil: MS (ES) m/e 161 ($\text{M} + \text{H}$) $^+$.

20 Preparation 17

Preparation of 1-benzyl-3-(methylaminomethyl)-1*H*-indole

a) 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1*H*-indole

N-(Benzyloxycarbonyloxy)succinimide (8.9 g, 35.7 mmole) was added to a solution of 3-(methylaminomethyl)-1*H*-indole (5.2 g, 32.5 mmole), from Preparation 16, and
 25 triethylamine (5.0 mL, 65.7 mmole) in DMF (100 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and the mixture was extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography on silica gel (33% ethyl acetate/hexanes) gave the title compound (7.0 g, 74%) as an off-white solid: MS (ES) m/e 295 ($\text{M} + \text{H}$) $^+$.

30 b) 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-benzyl-1*H*-indole

NaH (60% dispersion in mineral oil, 0.15 g, 3.8 mmole) was added portionwise, allowing for gas evolution, to a solution of 3-[N-(benzyloxycarbonyl)-N-

methyaminomethyl]-1*H*-indole (0.7 g, 2.5 mmole) in DMF (25 mL) at 0 °C. When the NaH addition was complete, benzyl bromide (1.2 mL, 10.0 mmole) was added at 0 °C. The reaction was stirred at 0 °C for 15 minutes then at RT overnight. The reaction was diluted with water and extracted with ethyl acetate. The combined extracts were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (33% ethyl acetate/hexanes) gave the title compound (0.9 g, 93%) as an off white solid: MS (ES) *m/e* 385 (M + H)⁺.

c) 1-Benzyl-3-(methyaminomethyl)-1*H*-indole

3-[N-(Benzyloxycarbonyl)-N-methyaminomethyl]-1-benzyl-1*H*-indole (0.9 g, 2.3 mmole) was added to a suspension of Pearlman's catalyst (about 0.30 g) in MeOH at RT in a Parr flask. The reaction was placed under 50 p.s.i. of H₂ and shaken for 5 hr. The mixture was filtered through celite® and the filter pad was washed with MeOH. The filtrate was concentrated to afford the title compound (0.5 g, 86%) as a light yellow solid: MS (ES) *m/e* 251 (M + H)⁺.

Preparation 18

15 Preparation of 2,3-dihydro-8-(methyaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene

a) 2,3-Dihydro-1*H*-3a-azacyclopenta[*a*]indene-8-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 2,3-dihydro-1*H*-3a-azacyclopenta[*a*]indene (*J. Med. Chem.* **1965**, 8, 700; 0.24 g, 1.53 mmole) for the 1,3-dimethylindole, the title compound (0.17 g, 60%) was prepared as a yellow solid: MS (ES) *m/e* 186 (M + H)⁺.

b) 2,3-Dihydro-8-(methyaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene

According to the procedure of Preparation 13 (c), except substituting 2,3-dihydro-1*H*-3a-azacyclopenta[*a*]indene-8-carboxaldehyde (0.17 g, 0.92 mmole) for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.1 g, 54%) was prepared as a yellow oil: MS (ES) *m/e* 201 (M + H)⁺.

Preparation 19

Preparation of 1,4-dimethyl-3-(methyaminomethyl)-1*H*-indole

a) 1,4-Dimethyl-1*H*-indole

According to the procedure of Preparation 9 (a), except substituting 4-methylindole for ethyl indole-2-carboxylate, the title compound (1.5 g, 94%) was prepared as an amber oil: MS (ES) *m/e* 146.2 (M + H)⁺.

b) 1,4-Dimethyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 9 (b), except substituting 1,4-dimethyl-1*H*-indole for 1,3-dimethylindole, the title compound (1.8 g, 95%) was prepared as an amber oil: MS (ES) *m/e* 174.2 (M + H)⁺.

c) 1,4-Dimethyl-3-(methylaminomethyl)-1*H*-indole

- 5 According to the procedure of Preparation 11, except substituting 1,4-dimethyl-1*H*-indole-3-carboxaldehyde for 1,3-dimethyl-1*H*-indole-1-carboxaldehyde, the title compound (1.9 g, 99%) was prepared as an oil: MS (ES) *m/e* 189.0 (M + H)⁺.

Preparation 20

Preparation of (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt

- 10 a) 3,3,5-Tribromo-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one

To a solution of 7-azaindole (5.0 g, 42.3 mmole) in H₂O (210 mL) and *tert*-butanol (210 mL) at RT was added Br₂ (27 mL, 529.0 mmole) over 20 minutes. The reaction was stirred for 12 hr at RT and concentrated to an aqueous slurry. The reaction contents were made basic with solid NaHCO₃ and the remaining solid was filtered and washed with H₂O.

- 15 The filtered mass was dried under high vacuum to give the title compound (14.0 g, 89 %) as a brown solid: MS (ES) *m/e* 370 (M + H)⁺.

b) 5-Bromo-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one

- To a stirred solution of 3,3,5-tribromo-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one (2.0 g, 5.4 mmole) in acetic acid (50 mL) at RT was added Zn metal. The reaction became
20 exothermic and was cooled by the use of an ice bath during the initial 30 minutes. After 5 hr the reaction was filtered through celite®, and the filter pad was washed with EtOAc. The filtrate was concentrated under vacuum and neutralized with saturated aqueous NaHCO₃ solution. The neutralized aqueous filtrate was then extracted with EtOAc (2 x 200 mL), and the combined organic extracts were dried over Na₂SO₄ and concentrated to a
25 solid. The solid was washed with hexanes and dried under high vacuum to give the title compound (0.36 g, 32%): MS (ES) *m/e* 215 (M + H)⁺. This was used without further purification.

c) *tert*-Butyl (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylate

- A solution of 5-bromo-1,3-dihydropyrrolo[2,3-*b*]pyridin-2-one (2.0 g, 9.49 mmole),
30 *tert*-butyl acrylate (1.8 g, 14.1 mmole), Pd(OAc)₂ (0.32 g, 1.4 mmole), tri-*ortho*-tolylphosphine (0.57 g, 1.9 mmole), and diisopropylethylamine (4.9 mL, 28.2 mmole) in propionitrile (100 mL) and DMF (10 mL) was heated at reflux overnight. The dark mixture

was filtered through celite®, and the filtrate was concentrated. Flash chromatography on silica (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) gave the title compound (0.80 g, 33%) as a light yellow solid. MS (ES) *m/e* 261 (M + H)⁺.

d) (E)-3-(2-Oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt

- 5 To a stirred solution of *tert*-butyl (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylate (0.80 g, 3.1 mmole) in CH₂Cl₂ (50 mL) at RT was added trifluoroacetic acid (20 mL). After 1 hr the reaction solution was concentrated and the residue was dried under vacuum. An HCl solution (20 mL, 4 M in dioxane) was added and the mixture was concentrated under vacuum. The remaining solid was triturated with diethyl ether and filtered giving the
10 title compound (0.74 g, 33%) as a white solid: MS (ES) *m/e* 205 (M + H - HCl)⁺.

Preparation 21

Preparation of 1-ethyl-3-(methylaminomethyl)-1*H*-indole

a) 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-ethyl-1*H*-indole

- According to the procedure of Preparation 17 (b), except substituting ethyl iodide
15 (0.92 mL, 11.44 mmole) for the benzyl bromide, the title compound (0.90 g, 98%) was prepared as a white solid: MS (ES) *m/e* 323 (M + H)⁺.

b) 1-Ethyl-3-(methylaminomethyl)-1*H*-indole

- According to the procedure of Preparation 17 (c), except substituting 3-[N-(benzyloxycarbonyl)-N-methylaminomethyl]-1-ethyl-1*H*-indole (0.90 g, 2.80 mmole) for
20 the 3-[N-(benzyloxycarbonyl)-N-methylaminomethyl]-1-benzyl-1*H*-indole, the title compound (0.50 g, 94%) was prepared as a white solid: MS (ES) *m/e* 189 (M + H)⁺.

Preparation 22

Preparation of 1-isopropyl-3-(methylaminomethyl)-1*H*-indole

a) 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-isopropyl-1*H*-indole

- 25 According to the procedure of Preparation 17 (b), except substituting isopropyl iodide (1.34 mL, 11.84 mmole) for the benzyl bromide, the title compound (0.99 g, 99%) was prepared as a white solid: MS (ES) *m/e* 337 (M + H)⁺.

b) 1-ethyl-3-(methylaminomethyl)-1*H*-indole

- According to the procedure of Preparation 17 (c), except substituting 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-isopropyl-1*H*-indole (0.99 g, 2.98 mmole)
30 for the 3-[N-(Benzyloxycarbonyl)-N-methylaminomethyl]-1-benzyl-1*H*-indole, the title compound (0.49 g, 82%) was prepared as a white solid: MS (ES) *m/e* 405 (2M + H)⁺.

Preparation 23Preparation of 1-acetyl-3-(methylaminomethyl)-1H-indole

a) 1-Acetyl-3-(methylaminomethyl)indole

According to the procedure of Preparation 16 (a), except substituting N-acetyl-3-indole carboxaldehyde (1.33 g, 7.10 mmole), the title compound (1.40 g, 99%) was prepared as a light yellow oil: MS (ES) m/e 203 ($M + H$)⁺.

Preparation 24Preparation of N-(1H-indol-3-ylmethyl)-N-methylacrylamide

a) N-(1H-Indol-3-ylmethyl)-N-methylacrylamide

Acryloyl chloride (0.33 mL, 4.10 mmole) was added to a solution of 3-(methylaminomethyl)-1H-indole (0.60 g, 3.70 mmole) and Et₃N (1.03 mL, 7.40 mmole) in CH₂Cl₂ (30 mL) at 0 °C. The reaction was held at 0 °C for ten minutes, then was stirred overnight at RT. The solution was concentrated in vacuo and the residue was diluted with water. The solution was extracted with ethyl acetate, and the combined organic extracts were washed with brine and dried over Na₂SO₄. The title compound (0.64 g, 80%) was obtained as a light yellow solid: MS (ES) m/e 215 ($M + H$)⁺.

Preparation 25Preparation of N-(1-benzyl-1H-indol-3-ylmethyl)-N-methylacrylamide

a) N-(1-Benzyl-1H-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Preparation 24 (a), except substituting 1-benzyl-3-(methylaminomethyl)-1H-indole (1.30 g, 5.20 mmole) for of 3-(methylaminomethyl)-1H-indole, the title compound (1.40 g, 89%) was a brown solid: MS (ES) m/e 305 ($M + H$)⁺.

Preparation 26Preparation of N-[1-(2-dimethylamino)-1H-indol-3-ylmethyl]-N-methylacrylamide

a) N-[1-(2-dimethylamino)-1H-indol-3-ylmethyl]-N-methylacrylamide

According to the procedure of Preparation 25 (a), except substituting [1-(2-dimethylamino)]-3-(methylaminomethyl)-1H-indole (1.00 g, 2.74 mmole) for of 3-(methylaminomethyl)-1H-indole, the title compound (0.50 g, 79%) was a yellow solid: MS (ES) m/e 463 ($2M + H$)⁺.

30 Preparation 27Preparation of 3-bromo-5,6,7,9-tetrahydro-pyrido[2,3-b]azepin-8-one

a) 8-Benzylidene-5,6,7,8-tetrahydro-quinoline

Benzaldehyde (3.59 mL, 35.30 mmole) was added to a solution of 5,6,7,8-tetrahydro-quinoline (4.70 g, 35.30 mmole) in acetic anhydride (25 mL), and the solution was heated to reflux under a nitrogen atmosphere. After overnight at reflux, the reaction was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on silica gel (33% EtOAc/hexanes) to give the title compound (4.50 g, 58%) as a waxy yellow solid after drying in vacuo: MS (ES) *m/e* 222 (M + H)⁺.

b) 6,7-Dihydro-5*H*-quinolin-8-one

A solution of 8-benzylidene-5,6,7,8-tetrahydro-quinoline (4.30 g, 19.4 mmole) in CH₂Cl₂ (150 mL) was reacted with ozone at -78 °C for 30 minutes. Dimethyl sulfide (5 mL) was added, and the reaction was warmed to RT and stirred overnight. The mixture was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (EtOAc). The title compound (2.20 g, 79%) was obtained as an off-white solid after drying in vacuo: MS (ES) *m/e* 148 (M + H)⁺.

c) 6,7-Dihydro-5*H*-quinolin-8-one oxime

According to the reported procedure (*J. Het. Chem.* **1978**, *15*, 249-251), 6,7-dihydro-5*H*-quinolin-8-one was reacted with hydroxylamine hydrochloride to afford the title compound (2.40 g, 96%) as a white solid after drying in vacuo: MS (ES) *m/e* 163 (M + H)⁺.

d) 6,7-Dihydro-5*H*-quinolin-8-one, O-toluenesulfonyloxime

According to the reported procedure (*J. Het. Chem.* **1978**, *15*, 249-251), 6,7-dihydro-5*H*-quinolin-8-one oxime was reacted with *p*-toluenesulfonyl chloride to afford the title compound (4.00 g, 85%) as a white solid after drying in vacuo: MS (ES) *m/e* 317 (M + H)⁺.

e) 5,6,7,9-Tetrahydro-pyrido[2,3-*b*]azepin-8-one

According to the reported procedure (*J. Het. Chem.* **1978**, *15*, 249-251), 6,7-dihydro-5*H*-quinolin-8-one, O-toluenesulfonyloxime was reacted to afford the title compound (1.00 g, 50%) as a white solid after drying in vacuo: MS (ES) *m/e* 163 (M + H)⁺.

f) 3-Bromo-5,6,7,9-tetrahydro-pyrido[2,3-*b*]azepin-8-one

A 10 % solution of bromine (0.57 mL, 11.1 mmole) in CH₂Cl₂ was added dropwise

over 1 hr to a solution of 5,6,7,9-tetrahydro-pyrido[2,3-*b*]azepin-8-one (1.20 g, 7.4 mmole) in CH₂Cl₂ at RT. The mixture was stirred at RT overnight, then was concentrated in vacuo. The residue was diluted with 10% Na₂CO₃ and extracted with EtOAc. The combined organics were dried over Na₂SO₄ and concentrated. Flash chromatography on silica gel (EtOAc) gave the title compound (1.00 g, 56%) as a light yellow solid after drying in vacuo: MS (ES) *m/e* 241/243.

Preparation 28

Preparation of 5-bromo-2-(methylaminocarbonylmethyl)aminopyridine

a) 5-Bromo-2-(*tert*-butoxycarbonyl)aminopyridine

To a solution of 2-amino-5-bromopyridine (27.56 g, 159 mmole) in THF (150 mL) was added di-*tert*-butyl dicarbonate (38 g, 174 mmole). The reaction was gradually heated to reflux. Vigorous gas evolution was observed initially, which subsided after approximately 10 min. After 18 hr at reflux, the reaction was concentrated to dryness. The residue was triturated with 1:1 Et₂O/petroleum ether, filtered and dried under vacuum to give the title compound (34.79 g, 80%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1 H), 8.37 (dd, 1 H), 7.94 (d, *J* = 9.0 Hz, 1 H), 7.77 (dd, 1 H), 1.57 (s, 9 H).

b) 5-Bromo-2-[N-(*tert*-butoxycarbonyl)-N-(methoxycarbonylmethyl)amino]pyridine

To a solution of 5-bromo-2-(*tert*-butoxycarbonyl)aminopyridine (25.0 g, 91.5 mmole) in DMF (400 mL) was added portionwise with stirring a 60% dispersion of NaH in mineral oil (4.0 g, 100 mmole). The reaction was stirred for 15 min, then methyl bromoacetate (15 mL, 158.5 mmole) was added dropwise over 15 min. After stirring for 18 h at room temperature the reaction was concentrated to dryness. The remaining residue was taken up in EtOAc (200 mL) and H₂O (200 mL) and filtered to remove insoluble material. The EtOAc phase was separated, washed with brine, dried (Na₂SO₄) and concentrated to dryness. Purification by flash chromatography on silica gel (10% EtOAc/Hexane) gave the title compound (16.56 g, 50%): ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1 H), 7.73 (d, *J* = 2.5 Hz, 1 H), 7.71 (d, *J* = 2.5 Hz, 1 H), 4.69 (s, 2 H), 3.75 (s, 3 H), 1.51 (s, 9 H).

c) 5-Bromo-2-(methoxycarbonylmethyl)aminopyridine

A 50% solution of TFA in CH₂Cl₂ (200 mL) was added to 5-bromo-2-[N-(*tert*-butoxycarbonyl)-N-(methoxycarbonylmethyl)amino]pyridine (16.5 g, 46 mmole). After stirring for 45 min the reaction was concentrated to dryness, and the residue was diluted with 1.0 N Na₂CO₃ (300 mL). The mixture was extracted with EtOAc (300 mL), and the

organic layer was washed with brine, dried (Na_2SO_4), and concentrated to dryness under vacuum. The title compound (11.32 g, 100%) was obtained as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 2.3$ Hz, 1 H), 7.48 (dd, 1 H), 6.40 (d, $J = 8.8$ Hz, 1 H), 4.95 (br s, 1H), 4.12 (d, $J = 5.5$ Hz, 2 H), 3.78 (s, 3H).

5 d) 5-Bromo-2-(methylaminocarbonylmethyl)aminopyridine

A solution of 2.0 M methylamine in MeOH (75 mL) was added to 5-bromo-2-(methoxycarbonylmethyl)aminopyridine (2.9 g, 12 mmole). The reaction was stirred for 24 h then was concentrated to dryness. The residue was triturated with 10% petroleum ether/ Et_2O (100 mL), then was collected and dried under vacuum to give the title

10 compound (2.96 g, 100%) as an off-white solid: MS (ES) m/e 244.2 ($\text{M} + \text{H}$) $^+$.

Preparation 29

Preparation of methyl 2-amino-5-bromonicotinate

a) Methyl 2-aminonicotinate

Concentrated H_2SO_4 (20 mL, 360 mmole) was added dropwise over 5 minutes to a
15 suspension of 2-aminonicotinic acid (25 g, 181 mmole) in MeOH (400 mL), and the mixture was heated at reflux; a homogeneous solution formed within 5 min. After 72 h, the reaction was cooled to room temperature and concentrated under vacuum. The residue was basified with 1.0 N Na_2CO_3 (500 mL) (Gas evolution!) and extracted with EtOAc (500 mL). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to
20 dryness to give the title compound (19.6 g, 71%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.22 (dd, 1 H), 8.13 (dd, 1 H), 6.63 (dd, 1 H), 6.30 (br s, 2 H), 3.89 (s, 3 H).

b) Methyl 2-amino-5-bromonicotinate

Bromine (0.7 mL, 14 mmole) was added dropwise to a stirred solution of methyl 2-aminonicotinate (2.0 g, 13 mmole) in HOAc (50 mL). A suspension formed within 30 min.
25 The reaction was allowed to stir at room temperature for 2 h, then was concentrated under vacuum. The residue was triturated with 1.0 N Na_2CO_3 (50 mL) and the solid was collected by suction filtration. The solid was washed with H_2O (50 mL) and dried under vacuum to give the title compound (2.95 g, 98%) as a pale yellow solid: ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 2.5$ Hz, 1 H), 8.23 (d, $J = 2.5$ Hz, 1 H), 6.40 (br s, 2 H), 3.90
30 (s, 3 H).

Preparation 30

Preparation of (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]acrylic acid hydrochloride salt

a) *tert*-Butyl (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]acrylate

A solution of 5-bromo-2-(methoxycarbonylmethyl)aminopyridine (4.69 g, 19.1 mmole, from Preparation 28 (c)), *tert*-butyl acrylate (11.2 mL, 76.5 mmole), DIEA (6.7 mL, 38.5 mmole), Pd(OAc)₂ (215 mg, 1 mmole), and P(o-tol)₃ (583 mg, 2 mmole) in propionitrile (100 mL) was purged with Ar, then was heated at reflux. After 18 h, the reaction was allowed to cool to room temperature then was concentrated to dryness. The residue was purified by flash chromatography on silica gel (40% EtOAc/hexane) to give the title compound (5.21 g, 93%) as a white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.19 (s, 1 H), 7.62 (dd, 1 H), 7.47 (d, J = 16.0 Hz, 1 H), 6.48 (d, J = 8.7 Hz, 1 H), 6.17 (d, J = 15.9 Hz, 1 H), 5.21 (br s, 1 H), 4.20 (d, J = 5.4 Hz, 2 H), 3.79 (s, 3 H), 1.52 (s, 1 H).

b) (E)-3-[6-[N-(Methoxycarbonylmethyl)amino]pyridin-3-yl]acrylic acid hydrochloride salt

A solution of 50% TFA in CH₂Cl₂ (75 mL) was added to *tert*-butyl (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]acrylate (5.20 g, 17.8 mmole). The reaction was stirred at room temperature for 45 min then was concentrated under vacuum. The residue was taken up in 4.0 N HCl in dioxane (75 mL), stirred for 5 min, then concentrated to dryness under vacuum. The remaining solid was triturated with 1:1 Et₂O/petroleum ether, filtered and dried under vacuum to give the title compound (4.87 g, 100%) as a white solid: MS (ES) *m/e* 237.2 (M + H)⁺.

Preparation 31

Preparation of (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt

a) *tert*-Butyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate

A solution of 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (12.99 g, 57 mmole), *tert*-butyl acrylate (34 mL, 232 mmole), DIEA (21.2 mL, 122 mmole), Pd(OAc)₂ (1.3 g, 5.8 mmole) and P(o-tol)₃ (3.5 g, 11.5 mmole) in propionitrile (200 mL) and DMF (50 mL) was purged with Ar, then was heated at reflux. After 18 h the reaction was allowed to cool to room temperature and was concentrated to dryness. The residue was purified by flash chromatography on silica gel (2-4% MeOH/CHCl₃). The resulting residue was triturated with 1:1 Et₂O/petroleum ether, collected, and dried, and the resulting material was

trituated with 1:1 MeOH/H₂O, collected, and dried, to give the title compound (7.09 g, 45%) as an off-white solid: ¹H NMR (400 MHz, d₆-DMSO) δ 10.70 (s, 1 H), 8.35 (d, J = 2.0 Hz, 1H), 8.04 (s, 1 H), 7.50 (d, J = 16.0 Hz, 1 H), 6.51 (d, J = 16.0 Hz, 1 H), 2.89 (t, 2 H), 2.53 (t, 2 H), 1.48 (s, 9H); MS (ES) *m/e* 275.2 (M + H)⁺.

5 b) (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt

To *tert*-butyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate (7.0 g, 25.5 mmole) was added 1:1 TFA/CH₂Cl₂ (100 mL). The reaction was stirred for 30 min, then was concentrated under vacuum. The residue was suspended in 4 N HCl/dioxane (100 mL), trituated, and concentrated to dryness. The resulting solid was trituated with Et₂O,
10 collected, and dried under vacuum to give the title compound (6.55 g, 100%) as a off-white solid: ¹H NMR (400 MHz, d₆-DMSO) □ 10.72 (s, 1 H), 8.35 (d, J = 2.0 Hz, 1 H), 8.04 (s, 1 H), 7.54 (d, J = 16.0 Hz, 1 H), 6.51 (d, J = 16.0 Hz, 1 H), 2.91 (t, 2 H), 2.53 (t, 2 H); MS (ES) *m/e* 219.0 (M + H)⁺.

Preparation 32

15 Preparation of N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-ylmethyl)acrylamide

A solution of acryloyl chloride (0.43 g, 5.58 mmole) in CH₂Cl₂ (10 mL) was added dropwise with stirring to a solution of 1-methyl-3-(methylaminomethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (0.93 g, 5.28 mmole) and triethylamine (0.8 mL, 5.8 mmole) in CH₂Cl₂ (40 mL) at 0 °C under N₂. The reaction was allowed to warm to RT and stir for 1 hr, then was
20 concentrated in vacuo. The residue was dissolved in 10% NaOH and extracted with CH₂Cl₂ (3 x 20 mL). The extracts were dried (MgSO₄), filtered, and concentrated. The residual oil was flash chromatographed on silica gel (5% MeOH/CH₂Cl₂) to give the title compound (1.0 g, 80%) as a colorless oil: MS (ES) *m/e* 216 (M + H)⁺.

Preparation 33

25 Preparation of 7-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole

a) 7-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 11 (b), except substituting 7-fluoroindole (0.5 g, 3.7 mmole) for the 1,3 dimethylindole, the title compound (0.5 g, 83%) was prepared as a waxy solid: MS (ES) *m/e* 164 (M + H)⁺.

b) 7-Fluoro-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 9 (a), except substituting 7-fluoro-1*H*-indole-3-carboxaldehyde (0.5 g, 3.1 mmole) for the ethyl indole-2-carboxylate, the title compound (0.23 g, 43%) was prepared as a viscous oil: MS (ES) *m/e* 178 (M + H)⁺.

5 c) 7-Fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 11 (c), except substituting 7-fluoro-1-methyl-1*H*-indole-3-carboxaldehyde (0.23 g, 1.3 mmole) for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.18 g, 72%) was prepared as a viscous oil: MS (ES) *m/e* 193 (M + H)⁺.

10 Preparation 34Preparation of 6-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indolea) 6-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 11 (b), except substituting 6-fluoroindole (0.5 g, 3.7 mmole) for the 1,3-dimethylindole, the title compound (0.3 g, 50%) was
15 prepared as a waxy solid: MS (ES) *m/e* 164 (M + H)⁺.

b) 6-Fluoro-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 9 (a), except substituting 6-fluoro-1*H*-indole-3-carboxaldehyde (0.3 g, 1.8 mmole) for the ethyl indole-2-carboxylate, the title compound (0.3 g, 94%) was prepared as a viscous oil: MS (ES) *m/e* 178 (M + H)⁺.

20 c) 6-Fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 11 (c), except substituting 6-fluoro-1-methyl-1*H*-indole-3-carboxaldehyde (0.3 g, 1.69 mmole) for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.11 g, 35%) was prepared as a viscous oil: MS (ES) *m/e* 193 (M + H)⁺.

25 Preparation 35Preparation of 5-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indolea) 5-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 11 (b), except substituting 5-fluoroindole (0.5 g, 3.7 mmole) for the 1,3-dimethylindole, the title compound (0.3 g, 50%) was
30 prepared as a waxy solid: MS (ES) *m/e* 164 (M + H)⁺.

b) 5-Fluoro-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 9 (a), except substituting 5-fluoro-1*H*-indole-3-carboxaldehyde (0.3 g, 1.8 mmole) for the ethyl indole-2-carboxylate, the title compound (0.16 g, 50%) was prepared as a viscous oil: MS (ES) *m/e* 178 (M + H)⁺.

c) 5-Fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole

- 5 According to the procedure of Preparation 11 (c), except substituting 5-fluoro-1-methyl-1*H*-indole-3-carboxaldehyde (0.3 g, 1.69 mmole) for the 1,3 dimethyl-1*H*-2-carboxaldehyde, the title compound (0.11 g, 35%) was prepared as a viscous oil: MS (ES) *m/e* 193 (M + H)⁺.

Preparation 36

- 10 Preparation of 4-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole

a) 4-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 11 (b), except substituting 4-fluoroindole (0.5 g, 3.7 mmole) for the 1,3-dimethylindole, the title compound (0.41 g, 68%) was prepared as a waxy solid: MS (ES) *m/e* 164(M + H)⁺.

- 15 b) 4-Fluoro-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 9 (a), except substituting 4-fluoro-1*H*-indole-3-carboxaldehyde (0.41 g, 2.5 mmole) for the ethyl-indole-2-carboxylate, the title compound (0.24 g, 54%) was prepared as a viscous oil: MS (ES) *m/e* 178 (M + H)⁺.

c) 4-Fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole

- 20 According to the procedure of Preparation 11 (c), except substituting 4-fluoro-1-methyl-1*H*-indole-3-carboxaldehyde (0.3 g, 1.69 mmole) for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.2 g, 77%) was prepared as a viscous oil: MS (ES) *m/e* 193 (M + H)⁺.

Preparation 37

- 25 Preparation of (1-ethyl-5-fluoro-3-(methylaminomethyl)-1*H*-indole

a) 5-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 11 (b), except substituting 5-fluoroindole (0.5 g, 3.7 mmole) for the 1,3-dimethylindole, the title compound (0.3 g, 50%) was prepared as a waxy solid: MS (ES) *m/e* 164(M + H)⁺.

- 30 b) 1-Ethyl-5-fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 9 (a), except substituting 5-fluoro-1*H*-indole-3-carboxaldehyde (0.41 g, 2.5 mmole) for the ethylindole-2-carboxylate, the title compound (0.20 g, 57%) was prepared as a viscous oil: MS (ES) *m/e* 191 ($M + H$)⁺.

c) 1-Ethyl-5-fluoro-3-(methylaminomethyl)-1*H*-indole

- 5 According to the procedure of Preparation 11 (c), except substituting 1-ethyl-5-fluoro-1*H*-indole-3-carboxaldehyde (0.2 g, 1.9 mmole) for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.1 g, 50%) was prepared as a viscous oil: MS (ES) *m/e* 207 ($M + H$)⁺.

Preparation 38

10 Preparation of 4,6-dichloro-1-methyl-2-(methylaminomethyl)-1*H*-indole

a) Ethyl 4,6-dichloro-1-methyl-1*H*-indole-2-carboxylate

- NaH (60% dispersion in mineral oil, 0.24 g, 6 mmole) was washed with hexanes, then was suspended in anhydrous DMF (16 mL). The mixture was cooled to 0 °C, and ethyl 4,6-dichloroindole-2-carboxylate (1.03 g, 4 mmole) was added. After 2-3 min, 15 iodomethane (1.3 mL, 20 mmole) was added, and the mixture was warmed to RT. The mixture became thick, and stirring became difficult for several minutes. After 0.5 hr, the reaction was cooled to 0 °C and quenched with 10% NH₄Cl (2 mL). The mixture was concentrated to dryness, and the residue was partitioned between Et₂O (50 mL) and H₂O (10 mL). The layers were separated and the organic layer was washed with H₂O (5 mL), 20 dried (MgSO₄), and filtered, and the filter pad was washed with a little CH₂Cl₂.

Concentration afforded the title compound (1.06 g, 97%) as an off-white solid: ¹H NMR (400 MHz, CDCl₃) δ 7.34 (s, 1 H), 7.30 (s, 1 H), 7.17 (d, *J* = 1.5 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.05 (s, 3 H), 1.42 (t, *J* = 7.1 Hz, 3 H); MS (ES) *m/e* 272 and 274 ($M + H$)⁺.

b) N,1-Dimethyl-1*H*-indole-2-carboxamide

- 25 A suspension of ethyl 4,6-dichloro-1-methyl-1*H*-indole-2-carboxylate (1.06 g, 3.90 mmole) in 2.0 M CH₃NH₂/CH₃OH (40 mL) in a sealed pressure bottle was heated in an oil bath preset at 50 °C. A homogeneous solution formed within 2.5 hr. The reaction was kept at 50 °C for 17.5 hr, during which time a solid precipitated. The mixture was cooled to RT and poured into H₂O (40 mL). The resulting mixture was concentrated on the rotavap to 30 remove the methanol, and the solid was collected by suction filtration. This was washed with plenty of H₂O and dried in high vacuum at 45-50 °C to afford the title compound

(0.99 g, 99%) as an off-white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.29 (s, 1 H), 7.16 (d, J = 1.5 Hz, 1 H), 6.86 (s, 1 H), 6.21 (br s, 1 H), 4.02 (s, 3 H), 3.02 (d, J = 4.9 Hz, 3 H); MS (ES) m/e 257 and 259 ($\text{M} + \text{H}$) $^+$.

c) 4,6-Dichloro-1-methyl-2-(methylaminomethyl)-1*H*-indole

- 5 A solution of 2.0 M $\text{BH}_3 \cdot \text{DMS}$ in THF (3.6 mL, 7.2 mmole) was added to a solution of N,1-dimethyl-1*H*-indole-2-carboxamide (0.74 g, 2.88 mmole) in anhydrous THF (25 mL), and the reaction was heated at reflux. After 18 hr, the reaction was cooled to 0 °C and quenched with MeOH (5 mL). The solution was warmed to RT, stirred for 0.5 hr, then concentrated on the rotavap. The residue was re-concentrated from MeOH, then was
- 10 purified by flash chromatography on silica gel (5% MeOH/ CHCl_3 containing 0.5 % conc. NH_4OH). The title compound (197.5 mg, 28%) was obtained as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 7.19 (dd, J = 1.5, 0.8 Hz, 1 H), 7.09 (d, J = 1.5 Hz, 1 H), 6.45 (s, 1 H), 3.88 (s, 2 H), 3.74 (s, 3 H), 2.50 (s, 3 H); MS (ES) m/e 212 and 214 ($\text{M} + \text{H} - \text{CH}_3\text{NH}_2$) $^+$.

Preparation 39

15 Preparation of 1,7-dimethyl-3-(methylaminomethyl)-1*H*-indole

a) 1,7-Dimethyl-1*H*-indole

According to the procedure of Preparation 13 (a), except substituting 7-methylindole for the 3-methylindole, the title compound (1.95 g, 90%) was obtained as a light-colored oil: MS (ES) m/e 146.2 ($\text{M} + \text{H}$) $^+$.

20 b) 1,7-Dimethyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 1,7-dimethylindole for the 1,2-dimethylindole, the title compound (1.85 g, 82%) was obtained as an off white solid: MS (ES) m/e 174.2 ($\text{M} + \text{H}$) $^+$.

c) 1,7-Dimethyl-3-(methylaminomethyl)-1*H*-indole

- 25 According to the procedure of Preparation 13 (c), except substituting 1,7-dimethyl-1*H*-indole-3-carboxylate for the 1,3-dimethyl-1*H*-indole-2-carboxylate, the title compound (0.74 g, 98%) was obtained as an amber oil: MS (ES) m/e 189.2 ($\text{M} + \text{H}$) $^+$.

Preparation 40

Preparation of 4-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

- 30 a) 4-Methoxy-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 1-methyl-4-methoxyindole for the 1,2-dimethylindole, the title compound (2.17 g, 93%) was obtained as an off white solid: MS (ES) m/e 190.2 ($M + H$)⁺.

b) 4-Methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

5 According to the procedure of Preparation 13 (c), except substituting 1-methyl-4-methoxy-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (2.0 g, 95%) was obtained as a white solid: MS (ES) m/e 205.2 ($M + H$)⁺.

Preparation 41

10 Preparation of 5-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

a) 5-Methoxy-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (a), except substituting 5-methoxy-1*H*-indole-3-carboxaldehyde for the 3-methyl-1*H*-indole-3-carboxaldehyde, the title compound (0.86 g, 92%) was obtained as a light tan solid: MS (ES) m/e 190.2 ($M + H$)⁺.

15 b) 5-Methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 13 (c), except substituting 5-methoxy-1-methyl-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.85 g, 98%) was obtained as a light yellow oil: MS (ES) m/e 205.2 ($M + H$)⁺.

20 Preparation 42

Preparation of 7-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

a) 7-Methoxy-1-methyl-1*H*-indole

According to the procedure of Preparation 13 (a), except substituting 7-methoxyindole for 3-methylindole, the title compound (1.55 g, 96%) was obtained as a tan solid: MS (ES) m/e 162.2 ($M + H$)⁺.

b) 7-Methoxy-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13(b), except substituting 7-methoxy-1-methyl-1*H*-indole for the 1,2-dimethylindole, the title compound (1.6 g, 91%) was obtained as an off white solid: MS (ES) m/e 190.2 ($M + H$)⁺.

30 c) 7-Methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 13(c), except substituting 7-methoxy-1-methyl-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (1.6 g, 94%) was obtained as an amber oil: MS (ES) *m/e* 205.2 (M + H)⁺.

Preparation 43

5 Preparation of 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole

a) 7-Chloro-1-methyl-1*H*-indole

According to the procedure of Preparation 13 (a), except substituting 7-chloroindole for the 3-methylindole, the title compound (2.2 g, 100%) was obtained as a white solid: MS (ES) *m/e* 166.2 (M + H)⁺.

10 b) 7-Chloro-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 7-chloro-1-methyl-1*H*-indole for the 1,2-dimethylindole, title compound (2.1 g, 84%) was obtained as a white solid: MS (ES) *m/e* 194.0 (M + H)⁺.

c) 7-Chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole

15 According to the procedure of Preparation 13 (c), except substituting 7-chloro-1-methyl-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (2.0 g, 93%) was obtained as an amber oil: MS (ES) *m/e* 209.2 (M + H)⁺.

Preparation 44

Preparation of 6-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole

20 a) 6-Chloro-1-methyl-1*H*-indole

According to the procedure of Preparation 13 (a), except substituting 6-chloroindole for the 3-methylindole, the title compound (2.2 g, 100%) was obtained as a white solid: MS (ES) *m/e* 166.2.0 (M + H)⁺.

b) 6-Chloro-1-methyl-1*H*-indole-3-carboxaldehyde

25 According to the procedure of Preparation 13 (b), except substituting 6-chloro-1-methyl-1*H*-indole for the 1,2-dimethylindole, title compound (2.2 g, 88%) was obtained as an amber oil: MS (ES) *m/e* 194.2 (M + H)⁺.

c) 6-Chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole

30 According to the procedure of Preparation 13 (c), except substituting 6-chloro-1-methyl-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (2.1 g, 93%) was obtained as an amber oil: MS (ES) *m/e* 209.2 (M + H)⁺.

Preparation 45Preparation of 5-chloro-1-methyl-3-(methylaminomethyl)-1H-indole

a) 5-Chloro-1-methyl-1H-indole

According to the procedure of Preparation 13 (a), except substituting 5-chloroindole
5 for the 3-methylindole, the title compound (2.0 g, 91%) was obtained as an amber oil: MS
(ES) m/e 166.0 (M + H)⁺.

b) 5-Chloro-1-methyl-1H-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 5-chloro-1-
methyl-1H-indole for the 1,2-dimethylindole, title compound (2.0 g, 83%) was obtained as
10 an white solid: MS (ES) m/e 194.0 (M + H)⁺.

c) 5-Chloro-1-methyl-3-(methylaminomethyl)-1H-indole

According to the procedure of Preparation 13 (c), except substituting 5-chloro-1-
methyl-1H-indole-3-carboxaldehyde for the 1,3-dimethyl-1H-indole-2-carboxaldehyde, the
title compound (2.1 g, 93%) was obtained as an amber oil: MS (ES) m/e 209.0 (M + H)⁺.

15 Preparation 46Preparation of 4-chloro-1-methyl-3-(methylaminomethyl)-1H-indole

a) 4-Chloro-1-methyl-1H-indole

According to the procedure of Preparation 13 (a), except substituting 4-chloroindole
for the 3-methylindole, the title compound (2.2 g, 100%) was obtained as an amber oil: MS
20 (ES) m/e 166.0 (M + H)⁺.

b) 4-Chloro-1-methyl-1H-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 4-chloro-1-
methyl-1H-indole for the 1,2-dimethylindole, title compound (1.9 g, 76%) was obtained as
an off-white solid: MS (ES) m/e 194.0 (M + H)⁺.

25 c) 4-Chloro-1-methyl-3-(methylaminomethyl)-1H-indole

According to the procedure of Preparation 13 (c), except substituting 4-chloro-1-
methyl-1H-indole-3-carboxaldehyde for the 1,3-dimethyl-1H-indole-2-carboxaldehyde, the
title compound (1.75 g, 78%) was obtained as a yellow solid: MS (ES) m/e 209.0 (M +
H)⁺.

30 Preparation 47Preparation of 1,1-dimethyl-3-(methylaminomethyl)-3H-indene

a) 1,1-Dimethyl-3H-indene-3-carboxaldehyde

The title compound was obtained in quantitative yield according to established literature procedures (*Chem. Pharm. Bull.* **1986**, *34*, 390-395; *Tet. Lett.* **1993**, *34*, 2979): ¹H NMR (400 MHz, CDCl₃) δ10.05 (s, 1 H), 8.05 (d, 2 H), 7.35 (m, 4 H), 1.40 (s, 6 H).

b) 1,1-Dimethyl-3-(methylaminomethyl)-3*H*-indene

5 According to the procedure of Preparation 12, except substituting 1,1-dimethyl-3*H*-indene-3-carboxaldehyde for the 2-methylindole-3-carboxaldehyde, the title compound (3 g, 81%) was obtained as a reddish oil: MS (ES) *m/e* 188.2 (M + H)⁺.

Preparation 48

Preparation of 7-hydroxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

10 a) 7-Benzyloxy-1-methyl-1*H*-indole

According to the procedure of Preparation 13 (a), except substituting 7-benzyloxyindole for the 3-methylindole, the title compound (4.8 g, 100%) was obtained as an amber oil: MS (ES) *m/e* 238.0 (M + H)⁺.

b) 7-Benzyloxy-1-methyl-1*H*-indole-3-carboxaldehyde

15 According to the procedure of Preparation 13 (b), except substituting 7-benzyloxy-1-methyl-1*H*-indole for the 1,2-dimethylindole, title compound (4.5 g, 85%) was obtained as an oil: MS (ES) *m/e* 266.0 (M + H)⁺.

c) 7-Benzyloxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

20 According to the procedure of Preparation 13 (c), except substituting 7-benzyloxy-1-methyl-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (3.7 g, 88%) was obtained as an oil: MS (ES) *m/e* 281.2 (M + H)⁺.

d) 7-Hydroxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

25 According to the literature procedure (*J. Org. Chem.* **1978**, *43*, 4195-96), 7-benzyloxy-1-methyl-3-(methylaminomethyl)-1*H*-indole was hydrogenated to afford the title compound (300 mg, 79%) as a brown solid: MS (ES) *m/e* 191.2 (M + H)⁺.

Preparation 49

Preparation of 3-(methylaminomethyl)-1,2,7-trimethyl-1*H*-indole

a) 1,2,7-Trimethyl-1*H*-indole

30 According to the procedure of Preparation 13 (a), except substituting 2,7-dimethylindole for the 3-methylindole, the title compound (960 mg, 87%) was obtained as an oil: MS (ES) *m/e* 160.2 (M + H)⁺.

b) 1,2,7-Trimethylindole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 1,2,7-trimethyl-1*H*-indole for the 1,4-dimethylindole, the title compound (800 mg, 62%) was obtained as a light tan solid: MS (ES) *m/e* 188.2 (M + H)⁺.

c) 3-(Methylaminomethyl)-1,2,7-trimethyl-1*H*-indole

- 5 According to the procedure of Preparation 13 (c) except substituting 1,2,7-trimethyl-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (570 mg, 71%) was obtained as an oil which slowly crystallized: MS (ES) *m/e* 405.4 (2M + H)⁺.

Preparation 50

10 Preparation of 7-chloro-3-(methylaminomethyl)-1*H*-indole

a) 7-Chloro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 7-chloroindole for the 1,2-dimethylindole, the title compound (0.48 g, 44%) was obtained as a white solid after recrystallization from hot EtOAc: MS (ES) *m/e* 180.0 (M + H)⁺.

15 b) 7-Chloro-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 13 (c), except substituting 7-chloro-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (440 mg, 92%) was obtained as an off white solid: MS (ES) *m/e* 195.2 (M + H)⁺.

20 Preparation 51

Preparation of 2-(methylaminomethyl)naphthalene

- To a stirred solution of 40 wt% methylamine in H₂O (50 mL, 581 mmole) in THF (50 mL) at 0 °C was added 2-(bromomethyl)naphthalene (10 g, 43 mmole) in one portion. The reaction was allowed to warm to RT and stirred for 16 hr, then was then concentrated under vacuum. The residue was taken up in Et₂O and washed with 1.0 N NaOH then with brine, dried (Na₂SO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (98:2 to 9:1 CHCl₃/methanol containing 5% NH₄OH) gave the title compound (3.95 g, 54%) as a clear oil: ¹H NMR (400 MHz, CDCl₃) δ 7.85 (m, 3 H), 7.79 (s, 1 H), 7.49 (m, 3 H), 3.94 (s, 2 H), 2.53 (s, 3 H).

30 Preparation 52

Preparation of 3-(methylaminomethyl)quinoline

A solution of 3-quinolinecarboxaldehyde (1.5 g, 10 mmole), 2.0 M CH₃NH₂/MeOH (10 mL, 20 mmole), glacial AcOH (0.6 mL, 10 mmole), and NaBH₃CN (0.35 g, 11 mmole) in MeOH (20 mL) was stirred at RT overnight, then was concentrated in vacuo. The residue was diluted with 5% NaOH and extracted with CH₂Cl₂. The combined organic
 5 extracts were washed with brine, dried over MgSO₄, and concentrated. Flash chromatography on silica gel (10% MeOH/CH₂Cl₂) gave the title compound (0.83 g, 24%) as a slightly yellow viscous oil: MS (ES) *m/e* 173 (M + H)⁺.

Preparation 53

Preparation of (E)-2-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid
 10 hydrochloride salt

a) *tert*-Butyl (E)-2-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate

According to the procedure of Preparation 31 (a), except substituting *tert*-butyl methacrylate (4.7 g, 33.2 mmole) for the *tert*-butyl acrylate, the title compound (2.7 g, 42 %)
 was prepared as a yellow solid: MS (ES) *m/e* 289 (M + H)⁺.

15 b) (E)-2-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt

According to the procedure of Preparation 31 (b), except substituting *tert*-butyl (E)-2-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate (2.7 g, 9.3 mmole) for the *tert*-butyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate, the title
 20 compound (2.5 g, 99 %) was prepared as a white solid: MS (ES) *m/e* 232 (M + H)⁺.

Preparation 54

Preparation of (E)-3-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid
hydrochloride salt

a) *tert*-Butyl (E)-3-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate

25 According to the procedure of Preparation 31 (a), except substituting *tert*-butyl crotonate (4.7 g, 33.2 mmole) for the *tert*-butyl acrylate, the title compound (3.7 g, 58 %) was prepared as a yellow solid: MS (ES) *m/e* 289 (M + H)⁺.

b) (E)-3-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt

30 According to the procedure of Preparation 31 (b), except substituting *tert*-butyl (E)-3-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate (3.7 g, 12.8 mmole)

for the *tert*-butyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate, the title compound (3.4 g, 99 %) was prepared as a white solid: MS (ES) *m/e* 232 (M + H)⁺.

Preparation 55

Preparation of 7-bromo-4-methyl-1,2,4,5-tetrahydropyrido[2,3-*e*]-1,4-diazepin-3-one

- 5 a) 5-Bromo-3-[N-(*tert*-butoxycarbonyl)-N-methylaminomethyl]-2-[N-(*tert*-butoxycarbonyl)amino]pyridine

To a solution of 2-amino-5-bromo-3-(methylaminomethyl)pyridine (3.8 g, 17.6 mmole), from Preparation 5 (a), in THF was added di-*tert*-butyl dicarbonate (8.8 g, 40.5 mmole). The reaction was heated to reflux for 12 hr then was concentrated under vacuum.

- 10 Flash chromatography on silica gel (1:1 hexanes/EtOAc) gave the title compound (6.2 g, 85 %) as a white waxy solid: MS (ES) *m/e* 416 (M + H)⁺.

- b) 5-Bromo-2-[(ethoxycarbonyl)methylamino]-3-(methylaminomethyl)-2-[N-(*tert*-butoxycarbonyl)amino]pyridine bis-trifluoroacetic acid salt

- To a suspension of 60% NaH (0.46 g, 11.5 mmole) in THF (100 mL) at RT was
15 added 5-bromo-3-[N-(*tert*-butoxycarbonyl)-N-methylaminomethyl]-2-[N-(*tert*-butoxycarbonyl)amino]pyridine (4.0 g, 9.61 mmole). After 30 min, ethyl bromoacetate (1.8 g, 10.6 mmole) was added. The reaction was stirred at RT for 12 hr, then was quenched with H₂O (5 mL) and concentrated. The residue was dissolved in EtOAc (200 mL), and the solution was washed with H₂O (100 mL), dried over Na₂SO₄, and concentrated under high
20 vacuum to a light yellow solid. This was dissolved in CH₂Cl₂ (50 mL) and trifluoroacetic acid (20 mL). After 2 hr, the reaction was concentrated under vacuum and the residue was purified flash chromatography on silica gel (95:5 CHCl₃/CH₃OH). The title compound (4.1 g, 80%) was obtained as a yellow solid: MS (ES) *m/e* 302 (M + H)⁺.

- c) 7-Bromo-4-methyl-1,2,4,5-tetrahydropyrido[2,3-*e*]-1,4-diazepin-3-one

- 25 To a solution of 5-bromo-2-[(ethoxycarbonyl)methylamino]-3-(methylaminomethyl)-2-[N-(*tert*-butoxycarbonyl)amino]pyridine bis-trifluoroacetic acid salt (4.1 g, 7.7 mmole) in toluene was added triethylamine (3.3 mL, 23.7 mmole). The reaction was heated at reflux for 72 hr then concentrated under vacuum. Flash chromatography on silica gel (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) gave the title
30 compound (1.4 g, 72 %) as a tan solid: MS (ES) *m/e* 256 (M + H)⁺.

Preparation 56

Preparation of (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)-acrylic acid hydrochloride salt

a) *tert*-butyl (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylate

A solution of 3-bromo-5,6,7,9-tetrahydro-pyrido[2,3-b]azepin-8-one (1.00 g, 4.15 mmole), *tert*-butyl acrylate (0.67 mL, 4.60 mmole), DIEA (1.45 mL, 8.30 mmole), Pd(OAc)₂ (0.09 g, 0.42 mmole) and P(*o*-tol)₃ (0.25 g, 0.85 mmole) in propionitrile (25 mL) was purged with N₂ and then heated at reflux overnight. The dark mixture was filtered through a pad of celite®, and the filter pad was rinsed with acetonitrile (250 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (ethyl acetate). The title compound (0.70 g, 58%) was obtained as a light yellow solid after drying in vacuo: MS (ES) *m/e* 289 (M + H)⁺.

b) (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)-acrylic acid hydrochloride salt

According to the procedure of Preparation 31 (b), except substituting *tert*-butyl (E)-3-(8-oxo-6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepin-3-yl)acrylate (0.70 g, 2.40 mmole) for the *tert*-butyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylate, the title compound (0.49 g, 77%) was obtained as an off-white solid after drying in vacuo: MS (ES) *m/e* 233 (M + H)⁺.

Preparation 57

20 Preparation of 1-(2-hydroxyethyl)-3-(methylaminomethyl)-1H-indole

According to the reported literature procedure (*J. Org. Chem.* **1998**, *63*, 6721-6726) except substituting 3-[N-(benzyloxycarbonyl)-N-methylaminomethyl]-1H-indole (3.70 g, 12.60 mmole) for the 5-bromoindole, the title compound (4.00 g, 93%) was obtained as a yellow solid after drying in vacuo: MS (ES) *m/e* 338 (M + H)⁺.

25 Preparation 58

Preparation of 2-chloro-1-methyl-2-(methylaminomethyl)-1H-indole

a) 2-Chloro-1H-indole-3-carboxaldehyde

To DMF (30 mL) with stirring at 0 °C was added dropwise phosphorus oxychloride (10 mL, 107 mmole) over 5 minutes. The reaction was stirred for an additional 15 minutes, then oxindole (6.0 g, 45 mmole) was added portionwise over 5 min. The reaction was allowed to warm to RT and stirred for 18 h then was carefully poured into ice water (350 mL). The solution was stirred for 6 h after which time a suspension formed. The solids were filtered off, washed with cold water, pressed dry and dried under vacuum to give the

title compound (6.83 g, 84%) as a yellowish solid: ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 10.0 (s, 1 H), 8.05 (dd, 1 H), 7.43 (dd, 1 H), 7.23-7.31 (m, 2 H); MS (ES) m/e 179.0 ($\text{M} + \text{H}$) $^+$.

b) 2-Chloro-1-methyl-1*H*-indole-3-carboxaldehyde

NaH (60% dispersion in mineral oil) (0.9 g, 22.5 mmole) was added portionwise over 5 min to a solution of 2-chloro-1*H*-indole-3-carboxaldehyde (3.8 g, 21.2 mmole) and iodomethane (1.5 mL, 24 mmole) in DMF (50 mL) with stirring at 0 °C. The reaction was allowed to warm to RT and stir for 4 h, then was concentrated under vacuum. The remaining residue was taken up in EtOAc, and the solution was washed with water then brine, dried (MgSO_4), and concentrated to dryness. Trituration with 1:1 Et_2O /petroleum ether, filtration, and drying under vacuum gave the title compound (3.10 g, 76%) as an off-white solid: ^1H NMR (400 MHz, CDCl_3) δ 10.12 (s, 1 H), 8.29 (m, 1 H), 7.33 (m, 3 H), 3.81 (s, 3 H); MS (ES) m/e 194.0 ($\text{M} + \text{H}$) $^+$.

c) 2-Chloro-1-methyl-2-(methyaminomethyl)-1*H*-indole

According to the procedure of Preparation 12, except substituting 2-chloro-1-methyl-1*H*-indole-3-carboxaldehyde (3.0 g, 15.5 mmole) for the 1-methylindole-3-carboxaldehyde, the title compound (2.91 g, 90%) was prepared as an oil: ^1H NMR (400 MHz, CDCl_3) δ 7.60 (d, $J = 7.9$ Hz, 1 H), 7.22 (m, 2 H), 7.13 (m, 1 H), 3.92 (s, 2 H), 3.71 (s, 3 H), 2.44 (s, 3 H).

Preparation 59

20 Preparation of 3-(benzhydrylideneamino)-6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one

NaH (60% dispersion in mineral oil, 1.2 g, 30 mmole) was added portionwise over 10 min to a solution of N-(diphenylmethylene)glycine ethyl ester (8.0 g, 30 mmole) in DMF (150 mL) with stirring under Ar at 0 °C. The reaction was stirred for 15 min, then 2-amino-5-bromo-3-(bromomethyl)pyridine hydrobromide (5.0 g, 14.4 mmole) was added in one portion. The reaction was allowed to warm to RT and stir for 18 h, then was concentrated under vacuum. The remaining residue was taken up in EtOAc (150 mL), hexane (150 mL), and H_2O (150 mL). The resulting suspension was triturated and filtered, and the solid was dried under vacuum to give the title compound (3.27 g, 56%) as an off-white solid: ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 10.92 (s, 1 H), 8.23 (s, 1 H), 7.86 (s, 1 H), 7.26-7.55 (m, 10 H), 4.05 (dd, 1 H), 3.10 (t, 2 H); MS (ES) m/e 406.0 ($\text{M} + \text{H}$) $^+$.

Preparation 60

Preparation of 2-(methylaminomethyl)benzofuran

To a stirred solution of 2-benzofurancarboxaldehyde (2.22 g, 15.2 mmole) in MeOH (5 mL) was added 2 M methylamine in MeOH (15 mL), HOAc (0.86 mL, 15 mmole), and NaBH₃CN (1.0 g, 15.9 mmole). The reaction was stirred for 18 h at RT then concentrated under vacuum. The remaining residue was taken up in Et₂O, and the solution was washed with 1 N NaOH then brine, dried (Na₂SO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (5% (5% NH₄OH in MeOH)/CHCl₃) gave the title compound (1.23 g, 50%) as a pale yellow oil: MS (ES) *m/e* 162.4 (M + H)⁺.

Preparation 6110 Preparation of methyl 1-methyl-3-(methylaminomethyl)-1*H*-indole-7-carboxylatea) Methyl 1-methyl-1*H*-indole-7-carboxylate

According to the procedure of Preparation 9 (a), except substituting methyl indole-7-carboxylate for the ethyl indole-2-carboxylate, the title compound (2.4 g, 90%) was obtained as an oil: MS (ES) *m/e* 190.2 (M + H)⁺.

15 b) N-Methyl-7-methoxycarbonyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting methyl 1-methyl-1*H*-indole-7-carboxylate for the 1,3-dimethylindole, the title compound (1.8 g, 70%) was obtained as a white solid: MS (ES) *m/e* 218.2 (M + H)⁺.

c) Methyl 1-methyl-3-(methylaminomethyl)-1*H*-indole-7-carboxylate

20 According to the procedure of Preparation 12, except substituting 1-methyl-7-methoxycarbonyl-1*H*-indole 3-carboxaldehyde for the 2-methylindole-3-carboxaldehyde, the title compound (1.7 g, 92%) was obtained as an oil: MS (ES) *m/e* 233.2 (M + H)⁺.

Preparation 62Preparation of methyl 1-methyl-3-(methylaminomethyl)-1*H*-indole-6-carboxylate25 a) Methyl 1-methyl-1*H*-indole-6-carboxylate

According to the procedure of Preparation 9 (a), except substituting methyl indole-6-carboxylate for the ethyl indole-2-carboxylate, the title compound (2.5 g, 95%) was obtained as white solid: MS (ES) *m/e* 190.2 (M + H)⁺.

b) N-Methyl-7-methoxycarbonyl-1*H*-indole-3-carboxaldehyde

30 According to the procedure of Preparation 13 (b), except substituting methyl 1-methyl-1*H*-indole-6-carboxylate for the 1,3-dimethylindole, the title compound (2.6 g, 98%) was obtained as a white solid: MS (ES) *m/e* 218.2 (M + H)⁺.

c) Methyl 1-methyl-3-(methylaminomethyl)-1*H*-indole-6-carboxylate

According to the procedure of Preparation 12, except substituting 1-methyl-7-methoxycarbonyl-1*H*-indole 3-carboxaldehyde for the 2-methylindole-3-carboxaldehyde, the title compound (1.9 g, 63%) was obtained as an oil: MS (ES) *m/e* 233.2 (M + H)⁺.

5 Preparation 63Preparation of 6-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indolea) 6-Methoxy-1-methyl-1*H*-indole

According to the procedure of Preparation 9 (a), except substituting 6-methoxy-1*H*-indole for the ethyl indole-2-carboxylate, the title compound (2.3 g, 95%) was obtained as
10 an oil: MS (ES) *m/e* 162.2 (M + H)⁺.

b) 6-Methoxy-1-methyl-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 6-methoxy-1-methyl-1*H*-indole for the 1,3-dimethylindole, the title compound (2.3 g, 82%) was obtained as a tan solid: MS (ES) *m/e* 190.2 (M + H)⁺.

15 c) 6-Methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 12, except substituting 6-methoxy-1-methyl-1*H*-indole-3-carboxaldehyde for the 2-methylindole-3-carboxaldehyde, the title compound (2.1 g, 87%) was obtained as an oil: MS (ES) *m/e* 205.2 (M + H)⁺.

Preparation 6420 Preparation of 7-fluoro-3-(methylaminomethyl)-1*H*-indolea) 7-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 7-fluoroindole (0.5 g, 3.7 mmole) for the 1,3-dimethylindole, the title compound (0.3 g, 55%) was prepared as a waxy solid: MS (ES) *m/e* 164 (M + H)⁺.

25 b) 7-Fluoro-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 13 (c), except substituting 7-fluoro-1*H*-indole-3-carboxaldehyde (0.5 g, 3.1 mmole) for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound (0.5 g, 90%) was prepared as a viscous oil: MS (ES) *m/e* 179 (M + H)⁺.

30 Preparation 65Preparation of 4-fluoro-3-(methylaminomethyl)-1*H*-indolea) 4-Fluoro-1*H*-indole-3-carboxaldehyde

According to the procedure of Preparation 13 (b), except substituting 4-fluoroindole

(0.4 g, 2.45 mmole) for the 1,3-dimethylindole, the title compound (0.31 g, 72%) was prepared as a viscous oil: MS (ES) m/e 164 ($M + H$)⁺.

b) 4-Fluoro-3-(methylaminomethyl)-1*H*-indole

According to the procedure of Preparation 13 (c), except substituting 4-fluoro-1*H*-indole-3-carboxaldehyde for the 1,3-dimethyl-1*H*-indole-2-carboxaldehyde, the title compound was prepared as a viscous oil: MS (ES) m/e 179 ($M + H$)⁺.

Preparation 66

Preparation of 6-bromo-3-(2-methoxyethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

a) 2-Amino-5-bromo-3-[(2-methoxyethyl)aminomethyl]pyridine

2-Methoxyethylamine (1.49 mL, 17.16 mmole) was added to a solution of 2-amino-5-bromo-3-(bromomethyl)pyridine hydrobromide (1.49 g, 4.29 mmole) and DIEA (2.24 mL, 12.87 mmole) in CH₂Cl₂ (10 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and the solution was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated to afford the title compound (1.00 g, 90%) as a light brown liquid after drying in vacuo: MS (ES) m/e 260/262 ($M + H$)⁺.

b) 6-Bromo-3-(2-methoxyethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

1,1'-Carbonyldiimidazole (0.74 g, 4.60 mmole) was added to a solution of 2-amino-5-bromo-3-[(2-methoxyethyl)aminomethyl]pyridine (1.00 g, 3.80 mmole) in 1,2-dichloroethane (35 mL) at RT. The reaction was heated at 65 °C with stirring overnight, then was concentrated in vacuo. Flash chromatography on silica gel (5% MeOH/CHCl₃) gave title compound (0.90 g, 83%) as a yellow solid after drying in vacuo: MS (ES) m/e 286/288 ($M + H$)⁺.

Preparation 67

Preparation of Methyl-(1-propyl-naphthalen-2-yl)methylamine

A solution of 2.0 M methylamine in methanol (20 mL) was added to 1-propyl-naphthalene-2-carbaldehyde (0.983 g, 4.95 mmol) under N₂ and allowed to stir for 18 h. The solution was concentrated under reduced pressure. Then the resulting dark yellow oil was solvated in EtOH (20 mL) under N₂. To the solution was added NaBH₄ (0.187 g, 4.95 mmol) and the mixture allowed to stir for 6.5 h. The reaction was concentrated under reduced pressure, then solvated in 1 N NaOH (20 mL) and extracted with Et₂O (3 x 50 mL). The organics were combined, washed with brine (2 x 100 mL), dried over Na₂SO₄, filtered

and concentrated to yield the title compound (0.94 g, 89%) as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.87–7.73 (m, 4H), 7.51–7.43 (m, 3H), 3.53 (m, 1H), 2.09 (s, 3H), 1.70–1.52 (m, 2H), 1.26–1.12 (m, 2H), 0.87–0.79 (m, 3H).

Preparation 68

5 Preparation of (4-Fluoro-naphthalen-1-ylmethyl)methylamine

a) 4-Fluoro-naphthalene-1-carbaldehyde

A solution of α,α -dichloromethyl methyl ether (5.9 mL, 65 mmol) in CH_2Cl_2 (30 mL) was cooled in an ice bath and then treated dropwise over 15 min with SnCl_4 (7.6 mL, 65 mmol). After stirring for 45 min, a solution of 1-fluoronaphthalene (5.5 mL, 50 mmol) 10 in CH_2Cl_2 (30 mL) was added. The mixture was allowed to slowly warm to room temperature while stirring overnight. The mixture was poured in ice water (100 mL) and diluted with CH_2Cl_2 (50 mL). The layers were separated. The organic layer was diluted with CH_2Cl_2 (100 mL), washed with H_2O (3 x 50 mL), dried over Na_2SO_4 , filtered, and the solvent was removed in vacuo to give the title compound (7.62 g, 87%) as a pale yellow 15 solid: MS (ESI) m/e 175 ($\text{M} + \text{H}$) $^+$.

b) (4-Fluoro-naphthalen-1-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 4-fluoro-naphthalene-1-carbaldehyde for the 1-propyl-naphthalene-2-carbaldehyde, the title 20 compound (3.18 g, 98%) was prepared as a golden oil: MS (ESI) m/e 190 ($\text{M} + \text{H}$) $^+$.

Preparation 69

Preparation of (4-Chloro-naphthalen-1-ylmethyl)methylamine

a) 4-Chloro-naphthalene-1-carbaldehyde

According to the procedure of Preparation 2(a), except substituting 1- 25 chloronaphthalene for 1-fluoronaphthalene, the title compound (5.36 g, 55%) was prepared as a pale yellow oil: MS (ESI) m/e 191 ($\text{M} + \text{H}$) $^+$.

b) (4-Chloro-naphthalen-1-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 4-chloro-naphthalene-1-carbaldehyde for the 1-propyl-naphthalene-2-carbaldehyde, the title 30 compound (1.06 g, 60%) was prepared as a pale yellow oil: MS (ESI) m/e 206 ($\text{M} + \text{H}$) $^+$.

Preparation 70

Preparation of (3-chlorobenzo[*b*]thiophen-2-ylmethyl)methylamine

a) 3-chloro-benzo[*b*]thiophene-2-carbaldehyde

Vilsmeier reagent was prepared via the dropwise addition of POCl₃ (7.9 mL, 84 mmol) into ice-cold DMF (14 mL). A solution of 2-carboxymethylsulfanyl-benzoic acid (3.0 g, 14 mmol) in DMF (15 mL) was added dropwise to the Vilsmeier reagent. The resulting mixture was warmed to room temperature and then heated to 80 °C for 3.5 h. The reaction mixture was cooled to ambient temperature. Crushed ice was added until a bright yellow precipitate appeared. The solid was isolated by filtration. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate 3:2) gave the title compound (1.87 g, 68%) as a yellow powder: ¹H NMR (300 MHz, CDCl₃) δ 10.36 (s, 1H), 8.03 (m, 1H), 7.86 (m, 1H), 7.59–7.53 (m, 2H).

b) (3-chlorobenzo[*b*]thiophen-2-ylmethyl)methylamine

To 3-chloro-benzo[*b*]thiophene-2-carbaldehyde (1.9 g, 9.5 mmol) was added a solution of 2 M methylamine in methanol (32 mL) and the resulting mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure and the residue taken up in ethanol (32 mL). The solution was cooled to 0 °C, NaBH₄ (0.54 g, 14 mmol) was added in one portion and stirring continued overnight. The mixture was concentrated under reduced pressure and the residue solvated in 1 M NaOH (200 mL). The mixture was extracted with diethyl ether (3 x 150 mL) and the combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a yellow oil. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate 1:1) gave the title compound (1.62 g, 80%) as a pale yellow oil which crystallized under vacuum: ¹H NMR (300 MHz, CDCl₃) δ 7.70 (m, 2H), 7.45 (m, 2H), 4.08 (s, 2H), 2.51 (s, 3H).

Preparation 71

Preparation of (5-Chloro-1-methyl-1*H*-indol-2-ylmethyl)methylamine

a) 5-Chloro-1-methyl-1*H*-indole-2-carboxylic acid methylamide

To a solution of 5-chloro-1-methyl-1*H*-indole-2-carboxylic acid ethyl ester (1.27 g, 5.3 mmol) in toluene (10 mL) was added *O,N*-dimethyl-hydroxylamine (9.6 mL of a 1 M solution in toluene, 9.6 mmol). The resulting mixture was heated to reflux overnight after which the reaction was cooled to room temperature and quenched by the addition of 10% aqueous K₂CO₃ (50 mL). The mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to give the title compound (2.12 g, 96%) as a yellow solid: ¹H NMR (300

MHz, CDCl₃) δ 7.59 (s, 1H), 7.27 (m, 2H), 6.73 (s, 1H), 6.13 (s, 1H), 4.03 (s, 3H), 3.01 (d, $J = 4.9$ Hz, 3H); MS (ESI) m/e 222 ($M + H$)⁺.

b) (5-Chloro-1-methyl-1*H*-indol-2-ylmethyl)methylamine

To an ice-cold solution of 5-chloro-1-methyl-1*H*-indole-2-carboxylic acid
 5 methylamide (2.12 g, 9.5 mmol) in THF (15 mL) was added lithium aluminum hydride (19 mL of a 1 M solution in THF, 19.0 mmol). Once the addition was complete, the resulting slurry was heated to reflux overnight. The mixture was cooled in an ice bath and carefully quenched by the consecutive addition of water (0.90 mL), 15% aqueous NaOH (0.90 mL) and water (2.5 mL). The resulting mixture was filtered through diatomaceous earth and the
 10 filtrate concentrated to give the title (2.00 g, quantitative) compound as an orange oil: ¹H NMR (300 MHz, CDCl₃) δ 7.51 (d, $J = 1.8$ Hz, 1H), 7.25–1.14 (m, 2H), 6.32 (s, 1H), 3.86 (s, 2H), 3.73 (d, $J = 4.8$ Hz, 3H), 2.49 (s, 3H).

Preparation 72

Preparation of (1,7-dimethyl-1*H*-indol-2-ylmethyl)methylamine

15 a) 1,7-Dimethyl-1*H*-indole

Sodium hydride (1.15 g, 28.7 mmol, 60% in mineral oil) was rinsed with hexanes and then suspended in DMF (20 mL). To this suspension was added 7-methylindole (2.5 g, 19 mmol) portionwise. Gas evolution was allowed to subside between additions. The resulting brown mixture was stirred at room temperature for 15 min and then CH₃I (2.71 g, 95.5 mmol) was added in one portion. The exothermic reaction was cooled to 30 °C and
 20 stirred for 1 h. Saturated aqueous NH₄Cl (10 mL) was added and the mixture was concentrated under reduced pressure. The residue was combined with water (100 mL) and the mixture was then extracted with diethyl ether (3 x 100 mL). The combined organics were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced
 25 pressure to give the title compound (2.85 g, quantitative) as a red-pink oil which crystallized upon vacuum drying: ¹H NMR (300 MHz, CDCl₃) δ 7.43 (d, $J = 7.6$ Hz, 1H), 6.97–6.87 (m, 3H), 6.41 (d, $J = 3.1$ Hz, 1H), 4.04 (s, 3H), 2.7 (s, 3H).

b) 1,7-Dimethyl-1*H*-indole-2-carbaldehyde

To a solution of 1,7-dimethylindole (2.85 g, 19.6 mmol) and TMEDA (3.3 mL, 21.6
 30 mmol) in diethyl ether (30 mL) at –30 °C under N₂ was added *n*-butyllithium (13.5 mL of a 1.6 M solution in hexanes, 21.6 mmol) dropwise. The resulting orange solution was heated to reflux for 1 h and then DMF (4.6 mL, 58.8 mmol) was added in one portion. The solution was stirred at room temperature overnight. Saturated aqueous NH₄Cl solution was

added and the mixture was then extracted with ethyl acetate (3 x 150 mL). The combined organics were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to provide an orange oil. Purification by flash column chromatography (silica gel, hexanes/ethyl acetate, 95:5) gave the title compound
 5 (1.57 g, 46%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 9.83 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 7.09–7.02 (m, 2H), 4.39 (s, 3H), 2.79 (s, 3H).

c) (1,7-Dimethyl-1*H*-indol-2-ylmethyl)methylamine

To 1,7-dimethyl-1*H*-indole-2-carbaldehyde (1.57 g, 9.06 mmol) was added a solution of 2 M solution of methylamine in methanol (30 mL) and the resulting mixture
 10 stirred overnight at room temperature. The mixture was concentrated under reduced pressure and the residue taken up in ethanol (30 mL). The solution was cooled to 0 °C and then NaBH₄ (0.34 g, 9.1 mmol) was added in one portion. The mixture was stirred overnight. Additional NaBH₄ (0.18 g, 4.5 mmol) was added and the mixture was again stirred overnight. The mixture was concentrated under reduced pressure and the residue
 15 combined with 1 M NaOH (200 mL). The mixture was extracted with diethyl ether (3 x 150 mL). The combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound as a pale yellow oil (1.60 g, 94%): ¹H NMR (300 MHz, CDCl₃) δ 7.37 (d, *J* = 7.8 Hz, 1H), 6.93–6.87 (m, 2H), 6.34 (s, 1H), 4.02 (s, 3H), 3.84 (s, 2H), 2.77 (s, 3H), 2.50 (s, 3H).

20 Preparation 73

Preparation of (5-Fluoro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)methylamine

a) 5-Fluoro-3-methyl-benzo[*b*]thiophene-2-carbaldehyde

To a solution of 5-fluoro-3-methyl-benzo[*b*]thiophene (4.83 g, 29.1 mmol) in THF (50 mL) at –30 °C under N₂ was added *n*-butyllithium (20.0 mL of a 1.6 M solution in
 25 hexanes, 32.0 mmol) dropwise. The resulting orange solution was stirred for 1 h and then DMF (3.4 mL, 43.7 mmol) was added in one portion. The solution was warmed slowly to room temperature and stirred overnight. Saturated aqueous NH₄Cl was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organics were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and
 30 concentrated under reduced pressure to give the title compound (5.55 g, 97%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 10.32 (s, 1H), 7.80 (dd, *J* = 9.0, 4.8 Hz, 1H), 7.53 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.31–7.24 (m, 1H), 2.76 (s, 3H).

b) (5-Fluoro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)methylamine

To 5-fluoro-3-methyl-benzo[*b*]thiophene-2-carbaldehyde (5.43 g, 28.0 mmol) was added a solution of 2 M methylamine in methanol (94 mL) and the resulting mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure and the residue taken up in ethanol (90 mL). The solution was cooled to 0 °C and then NaBH₄ (1.06 g, 28.0 mmol) was added in one portion. The mixture was stirred 4 hr, after which time NaBH₄ (0.54 g, 14.0 mmol) was added and the mixture was stirred overnight. The mixture was concentrated under reduced pressure and the residue combined with 1 M NaOH (200 mL). The mixture was extracted with diethyl ether (3 x 150 mL) and the combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to the title compound (5.26 g, 90%) as a pale yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 7.71 (dd, *J* = 9.0, 4.8 Hz, 1H), 7.27 (dd, *J* = 9.3, 2.6 Hz, 1H), 7.09–7.04 (m, 1H), 4.00 (s, 2H), 2.51 (s, 3H), 2.31 (s, 3H).

Preparation 74

Preparation of (5-Chloro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)methylamine

15 a) 5-Chloro-3-methyl-benzo[*b*]thiophene-2-carbaldehyde

To a solution of 5-chloro-3-methyl-benzo[*b*]thiophene (4.98 g, 27.3 mmol) in THF (50 mL) at –40 °C was added *n*-butyllithium (18.7 mL of a 1.6 M solution in hexanes, 30.0 mmol) dropwise. The resulting yellow solution was stirred for 1 h and then DMF (6.3 mL, 81.9 mmol) was added in one portion. The solution was warmed slowly to room temperature and stirred overnight. Saturated aqueous NH₄Cl was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organics were washed with water (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (6.62 g, 89%) as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 10.32 (s, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.46 (dd, *J* = 8.7, 2.0 Hz, 1H), 2.74 (s, 3H).

b) (5-Chloro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)methylamine

To 5-chloro-3-methyl-benzo[*b*]thiophene-2-carbaldehyde (5.10 g, 24.2 mmol) was added a solution of 2 M methylamine in methanol (81 mL) and the resulting mixture was stirred overnight at room temperature. The mixture was concentrated under reduced pressure and the residue taken up in ethanol (81 mL). The solution was cooled to 0 °C, NaBH₄ (1.37 g, 36.3 mmol) was added in one portion, and stirring was continued overnight. The mixture was concentrated under reduced pressure and the residue was combined with 1 M NaOH (200 mL). The mixture was extracted with diethyl ether (3 x 150 mL). The

combined organics were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to the title compound (4.83 g, 88%) as a pale yellow oil which crystallized under vacuum: ¹H NMR (300 MHz, CDCl₃) δ 7.69-7.59 (m, 2H), 7.25 (m, 1H), 3.96 (s, 2H), 2.50 (s, 3H), 2.31 (s, 3H).

5 Preparation 75

Preparation of (3-Methoxy-2-propoxy-benzyl)methylamine

a) 3-Methoxy-2-propoxy-benzaldehyde

A suspension of 2-hydroxy-3-methoxy-benzaldehyde (10.0 g, 65.6 mmol), 1-bromopropane (60 mL, 657 mmol) and K₂CO₃ (11.3 g, 82.1 mmol) in MeCN (250 mL) was
10 heated to reflux for 12 h. The mixture was cooled to ambient temperature and the solution filtered. The filtrate was concentrated to give the title compound (12.9 g, quantitative) as light yellow oil: MS (ESI) *m/e* 195 (M + H)⁺.

b) (3-Methoxy-2-propoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 3-methoxy-2-propoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (13.2
15 g, 96%) was prepared as a light yellow oil: MS (ESI) *m/e* 210 (M + H)⁺.

Preparation 76

Preparation of (2-Isopropoxy-3-methoxy-benzyl)methylamine

20 a) 2-Isopropoxy-3-methoxy-benzaldehyde

According to the procedure of Preparation 75(a), except substituting 2-iodopropane for 1-bromopropane, the title compound (6.35 g, quantitative) was prepared as light yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 10.5 (s, 1H), 7.42 (dd, *J* = 6.6, 2.9 Hz, 1H), 7.16–7.08 (m, 2H), 4.63 (app septet, *J* = 6.2 Hz, 1H), 3.89 (s, 3H), 1.33 (d, *J* = 6.2 Hz, 6H).

25 b) (2-Isopropoxy-3-methoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 2-isopropoxy-3-methoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (6.39 g, 93%) was prepared as a yellow oil: MS (ESI) *m/e* 210 (M + H)⁺.

Preparation 77

30 Preparation of (2-Ethoxy-3-methyl-benzyl)methylamine

a) 2-Ethoxy-3-methyl-benzaldehyde

According to the procedure of Preparation 75(a), except substituting 2-hydroxy-3-methyl-benzaldehyde for 2-hydroxy-3-methoxy-benzaldehyde, and substituting iodoethane

for 1-bromopropane, the title compound (10.8 g, 99%) was prepared as a brown oil: ^1H NMR (300 MHz, CDCl_3) δ 10.4 (s, 1H), 7.69 (dd, $J = 7.6, 1.4$ Hz, 1H), 7.46–7.43 (m, 1H), 7.13 (dd, $J = 7.6, 7.6$ Hz, 1H), 4.01 (q, $J = 7.0$ Hz, 2H), 2.34 (s, 3H), 1.46 (t, $J = 7.0$ Hz, 3H).

5 b) (2-Ethoxy-3-methyl-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 2-ethoxy-3-methyl-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (11.2 g, 95%) was prepared as a yellow oil: MS (ESI) m/e 180 ($\text{M} + \text{H}$) $^+$.

Preparation 78

10 Preparation of Methyl-naphthalen-2-yl-methylamine

According to the procedure of Preparation 67, except substituting naphthalene-2-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.00 g, 91%) was prepared as a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 7.84–7.80 (m, 3H), 7.75 (s, 1H), 7.47–7.44 (m, 3H), 3.92 (s, 2H), 2.50 (s, 3H), 1.52 (br s, 1H).

15 Preparation 79

Preparation of Methyl-naphthalen-1-yl-methylamine

According to the procedure of Preparation 67, except substituting naphthalene-1-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.44 g, 91%) was prepared as an orange oil: ^1H NMR (300 MHz, CDCl_3) δ 8.12 (d, $J = 8.1$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 7.77 (d, $J = 8.4$ Hz, 1H), 7.54–7.40 (m, 4H), 4.20 (s, 2H), 2.55 (s, 3H), 1.50 (br s, 1H).

Preparation 80

Preparation of (4-Methanesulfonyl-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 4-methanesulfonyl-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.35 g, 63%) was prepared as an off-white solid: MS (ESI) m/e 200 ($\text{M} + \text{H}$) $^+$.

Preparation 81

Preparation of Methyl-quinolin-5-yl-methylamine

According to the procedure of Preparation 67, except substituting quinoline-5-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.21 g, 84%) was prepared as an orange solid: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.90 (d, $J = 6.0$ Hz, 1H), 8.61 (d, $J = 9.3$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.68 (t, $J = 10.2$ Hz, 1H), 7.57–7.51 (m, 2H), 4.08 (s, 2H), 2.34 (s, 3H), 2.13 (br s, 1H).

Preparation 82Preparation of (2,3-Dimethylbenzyl)methylamine

According to the procedure of Preparation 67, except substituting 2,3-dimethylbenzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.69 g, 72%) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.09–7.08 (m, 1H), 7.01–6.99 (m, 2H), 3.59 (s, 2H), 3.45 (br s, 1H), 2.29 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H).

Preparation 83Preparation of (2,4,5-Trimethoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 2,4,5-trimethoxybenzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.90 g, 88%) was prepared as a light yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 7.11 (s, 1H), 6.84 (s, 1H), 3.94 (s, 6H), 3.86 (s, 3H), 3.71 (s, 2H), 3.53 (br s, 1H), 2.44 (s, 3H).

Preparation 84Preparation of Benzo[1,3]dioxol-5-ylmethyl-methylamine

According to the procedure of Preparation 67, except substituting benzo[1,3]dioxole-5-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (3.23 g, 97%) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 6.88–6.75 (m, 3H), 5.96 (s, 2H), 3.52 (s, 2H), 2.20 (s, 3H), 1.95 (br s, 1H).

Preparation 85Preparation of Benzo[1,3]dioxol-4-ylmethyl-methylamine

According to the procedure of Preparation 67, except substituting benzo[1,3]dioxole-4-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.79 g, 81%) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 6.84–6.82 (m, 1H), 6.79–6.77 (m, 2H), 5.97 (s, 2H), 3.58 (s, 2H), 2.24 (s, 3H), 1.96 (br s, 1H).

Preparation 86Preparation of (4-Ethoxy-3-methoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 4-ethoxy-3-methoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.93 g, 89%) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 6.90–6.76 (m, 3H),

3.97 (q, $J = 6.9$ Hz, 2H), 3.71 (s, 3H), 3.53 (s, 2H), 2.22 (s, 3H), 2.12 (br s, 1H), 1.33–1.29 (t, $J = 6.9$ Hz, 3H).

Preparation 87

Preparation of (2-Ethoxy-3-methoxy-benzyl)methylamine

5 According to the procedure of Preparation 67, except substituting 2-ethoxy-3-methoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.03 g, 93%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 6.99–6.88 (m, 3H), 3.92 (q, $J = 6.9$ Hz, 2H), 3.77 (s, 3H), 3.61 (s, 2H), 2.25 (s, 3H), 1.87 (br s, 1H), 1.26 (t, $J = 6.3$ Hz, 3H).

10 Preparation 88

Preparation of (3,4-Dimethyl-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 3,4-dimethyl-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.96 g, 89%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 6.92–6.80 (m, 3H), 3.71 (s, 15 6H), 3.55 (s, 2H), 2.23 (s, 3H), 1.94 (br s, 1H).

Preparation 89

Preparation of (2,4,5-Trimethyl-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 2,4,5-trimethyl-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.48 g, 67%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 7.00 (s, 1H), 6.87 (s, 1H), 20 3.51 (s, 2H), 2.27 (s, 3H), 2.19 (s, 3H), 2.14 (s, 6H), 1.76 (br s, 1H).

Preparation 90

Preparation of Methyl-quinolin-3-yl-methylamine

According to the procedure of Preparation 67, except substituting quinoline-3-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.73 g, 73%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 9.29 (s, 1H), 8.60–8.58 (s, 25 2H), 8.09–8.04 (m, 2H), 7.85–7.79 (m, 1H), 7.69–7.64 (m, 1H), 3.52 (s, 3H), 3.33 (s, 2H).

Preparation 91

Preparation of (3,4-Dimethoxy-benzyl)methylamine

30 According to the procedure of Preparation 67, except substituting 3,4-dimethoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.10 g, 96%) was prepared as a light yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 6.92–6.80 (m, 3H), 3.72 (d, $J = 4.5$ Hz, 6H), 3.54 (s, 2H), 2.71 (br s, 1H), 2.23 (s, 3H).

Preparation 92Preparation of (3,4-Dimethyl-thieno[2,3-*b*]thiophen-2-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 3,4-dimethyl-thieno[2,3-*b*]thiophene-2-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (3.13 g, 97%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO-*d*₆) δ 7.07 (s, 1H), 3.78 (s, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 2.30 (s, 3H), 2.19 (br s, 1H).

Preparation 93Preparation of Benzofuran-2-ylmethyl-methylamine

According to the procedure of Preparation 67, except substituting benzofuran-2-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (4.98 g, 92%) was prepared as an orange oil: ^1H NMR (300 MHz, DMSO-*d*₆) δ 7.58–7.49 (m, 2H), 7.24–7.19 (m, 2H), 6.70 (s, 1H), 3.77 (s, 2H), 2.17 (s, 3H).

Preparation 94Preparation of Methyl-(2-methyl-naphthalen-1-ylmethyl)amine

According to the procedure of Preparation 67, except substituting 2-methyl-naphthalene-1-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.72 g, 79%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO-*d*₆) δ 8.14 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.1 Hz, 1H), 7.50–7.39 (m, 2H), 7.33 (d, J = 8.3 Hz, 1H), 4.02 (s, 2H), 2.51 (s, 3H), 2.41 (s, 3H), 1.74 (br s, 1H).

Preparation 95Preparation of Biphenyl-3-ylmethyl-methylamine

According to the procedure of Preparation 67, except substituting biphenyl-3-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (0.78 g, 76%) was prepared as a white solid: ^1H NMR (300 MHz, DMSO-*d*₆) δ 7.66–7.52 (m, 2H), 7.48–7.28 (m, 7H), 3.69 (s, 2H), 2.28 (s, 3H), 2.15 (br s, 1H).

Preparation 96Preparation of (2-Ethoxy-naphthalen-1-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 2-ethoxy-naphthalene-1-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.02 g, 94%) was prepared as a yellow-orange oil: ^1H NMR (300 MHz, DMSO-*d*₆) δ 8.08 (d, J = 8.4 Hz, 1H), 7.85–7.82 (d, J = 8.8 Hz, 2H), 7.74–7.33 (m, 3H), 4.18 (q, J = 6.9 Hz, 2H), 4.06 (s, 2H), 2.31 (s, 3H), 1.62 (br s, 1H), 1.37 (t, J = 6.9 Hz, 3H).

Preparation 97

Preparation of (2,3,4-Trimethoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 2,3,4-trimethoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.17 g, quantitative) was prepared as light yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 7.99 (d, J = 8.5 Hz 1H), 6.74 (d, J = 8.5 Hz, 1H), 3.76 (s, 6H), 3.72 (s, 3H), 2.53 (s, 2H), 2.25 (s, 3H), 1.92 (br s, 1H).

Preparation 98Preparation of (2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.28 g, 59%) was prepared as a pale yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 6.78–6.73 (m, 3H), 4.20 (s, 4H), 3.48 (s, 2H), 2.20 (s, 3H), 1.96 (br s, 1H).

Preparation 99Preparation of (2,3-Dihydro-benzo[1,4]dioxin-5-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 2,3-dihydro-benzo[1,4]dioxine-5-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.97 g, 91%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 6.85–6.82 (m, 1H), 6.77–6.70 (m, 2H), 4.25–4.20 (m, 4H), 3.56 (s, 2H), 2.25 (s, 3H), 1.76 (br s, 1H).

Preparation 100Preparation (4,5-Dimethyl-naphthalen-1-ylmethyl)methylamine

According to the procedure of Preparation 67, except substituting 4,5-dimethyl-naphthalene-1-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (0.88 g, 88%) was prepared as an off-white solid: ^1H NMR (500 MHz, DMSO- d_6) δ 8.00 (d, J = 8 Hz, 1H), 7.33–7.28 (m, 3H), 7.21 (s, 1H), 3.98 (s, 2H), 2.87 (two s, 6H), 2.33 (s, 3H), 1.96 (br s, 1H).

Preparation 101Preparation of (2,3-Diethoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 2,3-diethoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.81 g, 84%) was prepared as a yellow oil: ^1H NMR (300 MHz, DMSO- d_6) δ 6.96–6.83 (m, 3H), 4.01 (q, J = 6.9 Hz, 2H), 3.95 (q, J = 6.9 Hz, 2H), 3.61 (s, 2H), 2.25 (s, 3H), 1.81 (br s, 1H), 1.33 (t, J = 6.9 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H).

Preparation 102Preparation of (3-Ethoxy-2-methoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 3-ethoxy-2-methoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.60 g, 74%) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 6.95–6.88 (m, 3H), 4.04 (q, $J = 6.9$ Hz, 2H), 3.72 (s, 3H), 3.60 (s, 2H), 2.25 (s, 3H), 1.80 (br s, 1H), 1.34 (t, $J = 6.9$ Hz, 3H).

Preparation 103Preparation of Methyl-(3-methyl-benzofuran-2-ylmethyl)amine

According to the procedure of Preparation 67, except substituting 3-methyl-benzofuran-2-carbaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (2.05 g, quantitative) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.52 (dd, $J = 6.7, 2.1$ Hz, 1H), 7.46 (dd, $J = 6.5, 2.0$ Hz, 1H), 7.25–7.21 (m, 2H), 3.74 (s, 2H), 2.25 (s, 3H), 2.19 (s, 3H), 2.07 (br s, 1H).

Preparation 104Preparation of (3-Chloro-2-methoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 3-chloro-2-methoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.15 g, 55%) was prepared as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.37–7.33 (m, 2H), 7.11 (t, $J = 7.5$ Hz, 1H), 3.77 (s, 3H), 3.68 (s, 2H), 2.27 (s, 3H), 2.01 (br s, 1H).

Preparation 105Preparation of (3-Chloro-2-ethoxy-benzyl)methylamine

a) 3-Chloro-2-ethoxy-benzaldehyde

Iodoethane (1.54 mL, 19.2 mmol) was added to a stirring solution of 3-chloro-2-hydroxy-benzaldehyde (2.01 g, 12.8 mmol) and K_2CO_3 (3.90 g, 28.2 mmol) in DMF (25 mL). The mixture was heated to 50 °C and stirred for 2.5 h. The heat was removed and reaction stirred at room temperature for 18 h. The reaction was quenched with H_2O (70 mL). The mixture was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (2 x 50 mL), dried over Na_2SO_4 , filtered and concentrated to yield the title compound (2.16 g, 91%) as a yellow oil: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.27 (s, 1H), 7.85 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.72 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.33 (t, $J = 7.8$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 1.39 (t, $J = 6.9$ Hz, 3H).

b) (3-Chloro-2-ethoxy-benzyl)methylamine

According to the procedure of Preparation 67, except substituting 3-chloro-2-ethoxy-benzaldehyde for 1-propyl-naphthalene-2-carbaldehyde, the title compound (1.36 g, 58%) was prepared as a yellow oil: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.36–7.33 (m, 2H), 7.14–7.08 (m, 1H), 3.93 (q, $J = 7.0$ Hz, 2H), 3.67 (s, 2H), 2.24 (s, 3H), 2.07 (br s, 1H), 1.32 (t, $J = 6.9$ Hz, 3H).

Preparation 106

Preparation of Methyl-thieno[3,2-*c*]pyridin-2-ylmethyl-amine

a) Thieno[3,2-*c*]pyridine-2-carbaldehyde

A solution of thieno[3,2-*c*]pyridine (500 mg, 3.70 mmol) in anhydrous THF (10 mL) was stirred under argon and maintained at -78°C while a solution of 1.6 M *n*-butyllithium in hexane (2.5 mL, 4.07 mmol) was added dropwise. The resulting wine red solution was stirred for 5 min. then DMF (573 μL , 7.4 mmol) was added. The cooling bath was removed and the reaction mixture was stirred at room temperature for 16 hr. The reaction mixture was treated with 10% aqueous HCl, made alkaline with saturated aqueous NaHCO_3 and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic fractions were concentrated in vacuo to give an oily residue which was subjected to flash chromatography on silica gel (70% ethyl acetate:hexanes) to give the title compound as a white solid (41.5%): ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.20 (s, 1H), 9.39 (s, 1H), 8.60 (s, 1H), 8.59 (d, $J = 5.5$ Hz, 1H), 8.19 (d, $J = 5.6$ Hz, 1H); MS (ES) m/e 164 ($\text{M}+\text{H}$) $^+$.

b) Methylthieno[3,2-*c*]pyridine-2-methylamine

A solution of thieno[3,2-*c*]pyridine-2-carbaldehyde (720 mg, 4.41 mmol) in a 2.0 M solution of methylamine in methanol (25 mL) was stirred at room temperature for 5 hours. After this time, the mixture was concentrated to dryness, dissolved in anhydrous methanol (10 mL) then cooled to 0°C . To this solution was added NaBH_4 (167 mg, 4.41 mmol) in one portion. The mixture was allowed to warm to room temperature and stirred at this temperature overnight. The mixture was concentrated, dissolved in CH_2Cl_2 (100 mL) and treated with 1.0 N NaOH (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic fractions were washed with brine, dried over Na_2SO_4 then concentrated to give a yellow residue which was subjected to flash chromatography on silica gel (10% 2M NH_3 in $\text{MeOH}:\text{CH}_2\text{Cl}_2$). The title compound was obtained as a white solid in 63.6% yield: ^1H -NMR (300 MHz, CDCl_3) δ 9.01 (s, 1H), 8.45 (d, $J = 5.5$ Hz, 1H), 7.76 (d, $J = 5.5$ Hz, 1H), 7.29 (s, 1H), 4.10 (s, 2H), 2.54 (s, 3H); MS (ES) m/e 179 ($\text{M}+\text{H}$) $^+$.

Preparation 107Preparation of (1*H*-Indol-5-ylmethyl)methylamine

Indole-5-carbaldehyde (1.0 g, 6.9 mmol) was dissolved in anhydrous methanol (15 mL). Methylamine (9.9 mL of 2M solution in methanol, 19.8 mmol) was added and the reaction was stirred for 3 hr. The solution was concentrated to a yellow oil and then dissolved into anhydrous methanol (20 mL). Sodium borohydride (262 mg, 6.9 mmol) was added and the mixture was stirred overnight. Water (1 mL) was added and the solution was concentrated. Sodium hydroxide (5 mL, 1N) was added and the product was extracted with ethyl acetate (3 x 20 mL), dried over MgSO₄ and concentrated to afford the title compound as a brown oil (980 mg, 91%). ¹H NMR (200 MHz, CDCl₃) δ 8.60 (s, 1H), 7.56 (s, 1H), 7.35-7.15 (m, 3H), 6.55 (m, 1H), 3.85 (s, 2H), 2.49 (s, 3H).

Preparation 108Preparation of Methyl-(1-methylindol-5-ylmethyl)amine

a) 1-Methylindole-5-carbaldehyde

To a solution of indole-5-carbaldehyde (1.0 g, 6.9 mmol) in DMF (15 mL) was added sodium hydride (303 mg of 60% dispersion in oil, 7.59 mmol) in 3 portions. The mixture was stirred for 30 mins. Methyl iodide (1.96 g, 13.8 mmol) was then added and the mixture was stirred overnight. Ethyl acetate (200 mL) was added and solution was washed with H₂O (3 x 20 mL) and brine (25 mL) dried over MgSO₄ and concentrated to afford *N*-methylindole-5-carboxaldehyde as an orange oil (1.0 g, 91 %). ¹H NMR (200 MHz, CDCl₃) δ 10.05 (s, 1H), 8.09 (s, 1H), 7.90-7.80 (m, 1H), 7.35-7.15 (m, 2H), 6.85-6.80 (m, 1H), 3.95 (s, 3H).

b) Methyl-(1-methylindol-5-ylmethyl)amine

N-Methylindole-5-carbaldehyde (800 mg, 5.1 mmol) was dissolved in anhydrous methanol (15 mL). Methylamine (7.15 mL of 2M solution in methanol, 15.3 mmol) was added and the reaction was stirred for 3 hr. The solution was concentrated to a yellow oil and then dissolved into anhydrous methanol (15 mL). Sodium borohydride (194 mg, 5.1 mmol) was added and the mixture was stirred overnight. Water (1 mL) was added and the solution was concentrated to an orange oil. Sodium hydroxide (5 mL, 1N) was added and the product was extracted with ethyl acetate (3 x 20 mL), dried over MgSO₄ and concentrated to afford the title compound as an orange oil (885 mg, 100%). ¹H NMR (200 MHz, CDCl₃) δ 7.57(s, 1H), 7.35-7.11(m, 3H), 6.51 (d, *J* = 2.9 Hz, 1H), 3.85 (s, 2H), 3.79 (s, 3H), 2.48 (s, 3H).

Preparation 109Preparation of (1*H*-Indol-7-ylmethyl)methylamine

Indole-7-carbaldehyde (500 mg, 3.4 mmol) was dissolved in anhydrous methanol (10 mL). Methylamine (5.1 mL of 2M solution in methanol, 9.55 mmol) was added and the
5 reaction was stirred for 3 hr. The solution was concentrated to a yellow oil and then dissolved into anhydrous methanol (10 mL). Sodium borohydride (131 mg, 3.45 mmol) was added and the mixture was stirred overnight. Water (1 mL) was added and the solution was concentrated. Sodium hydroxide (5 mL, 1N) was added and the indole was extracted with ethyl acetate (3 x 20 mL), dried over MgSO₄ and concentrated to afford the title
10 compound as a yellow oil (484 mg, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.54 (s, 1H), 7.29-7.17 (m, 2H), 7.04 (d, *J* = 3.1 Hz, 1H), 6.44 (d, *J* = 3.1 Hz, 1H), 3.84 (s, 2H), 2.46 (s, 3H).

Preparation 110Preparation of Methyl-(1-methylindol-7-ylmethyl)amine

To a solution of indole-7-carboxaldehyde (500 mg, 3.45 mmol) in DMF (8 mL) was
15 added sodium hydride (152 mg of 60% dispersion in oil, 3.8 mmol). The mixture was stirred for 30 mins. Methyl iodide (0.98 g, 6.9 mmol) was then added and the mixture was stirred for 2 hrs. Ethyl acetate (200 mL) was added and solution was washed with H₂O (3 x 20 mL) and brine (25 mL) dried over MgSO₄ and concentrated to afford N-methylindole-7-carboxaldehyde as a brown oil which was used without further purification.

20 The crude oil was dissolved in anhydrous methanol (10 mL). Methylamine (5.1 mL of 2M solution in methanol, 9.55 mmol) was added and the mixture was stirred for 3 hours. The solution was concentrated to a yellow oil and then dissolved into anhydrous methanol (10 mL). Sodium borohydride (131 mg, 3.45 mmol) was added and the mixture was stirred overnight. Water (1 mL) was added and the solution was concentrated to an orange oil.
25 Sodium hydroxide (5 mL, 1N) was added and the product was extracted with ethyl acetate (3 x 20 mL), dried over MgSO₄ and concentrated to afford the title compound as a brown oil (400 mg, 68%). ¹H NMR (200 MHz, CDCl₃) δ 7.52 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.23-6.94 (m, 3H), 6.44 (d, *J* = 3.1 Hz, 1H), 4.10 (s, 3H), 4.04 (s, 2H), 2.51 (s, 3H).

Preparation 11130 Preparation of (1*H*-Indol-6-ylmethyl)methylaminea) (1*H*-Indol-6-yl) methanol

Indole-6-carboxylic acid (1.0 g, 6.2 mmol) was dissolved into anhydrous THF (20 mL) under argon. Lithium aluminum hydride (494 mg, 13 mmol) was added portionwise and

the mixture was stirred overnight. The mixture was cooled to 0°C and ethyl acetate (10 mL) was carefully added, followed by methanol (5 mL) and water (5 mL). The mixture was stirred for 30 min. and filtered through celite. The solution was concentrated and dissolved into ethyl acetate (200 mL) and washed with brine (2 x 20 mL), dried over
5 MgSO₄ and concentrated to afford the title compound as a brown oil (880 mg, 96%). ¹H NMR (300 MHz, CDCl₃) δ 8.30 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.23 (d, *J* = 1.1 Hz, 1H), 7.13-7.05 (m, 2H), 6.51-6.49 (m, 1H), 4.70 (s, 2H).

b) 1*H*-Indole-6-carbaldehyde

Dess-Martin periodinane (1.53 g, 2.6 mmol) was dissolved into methylene chloride (15
10 mL). Indol-6-yl-methanol (500 mg, 3.4 mmol) in methylene chloride (12 mL) was added and the mixture was stirred for 1 hr. Sodium hydroxide (5 mL of 1 N solution) was added and the reaction was stirred for 15 min. The organic layer was separated and washed with H₂O (5 mL), brine (5 mL), dried over MgSO₄ and concentrated to afford the title compound as a brown solid (275 mg, 56%). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.7 (s, 1H), 9.98 (s,
15 1H), 7.97 (s, 1H), 7.70-7.65 (m, 2H), 7.52 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.57-6.5 (m, 1H).

c) (1*H*-Indol-6-ylmethyl)methylamine

Indole-6-carboxaldehyde (90 mg, 0.62 mmol) was dissolved in anhydrous methanol (3 mL). Methylamine (0.95 mL of 2M solution in methanol, 1.86 mmol) was added and the reaction was stirred for 3 hr. The solution was concentrated to a yellow oil and then dissolved into
20 anhydrous methanol (3 mL). Sodium borohydride (24 mg, 0.62 mmol) was added and the mixture was stirred overnight. Water (1 mL) was added and the solution was concentrated. Sodium hydroxide (2 mL, 1N) was added and the indole was extracted with ethyl acetate (3 x 10 mL), dried over MgSO₄ and concentrated to afford the title compound as a yellow oil (98 mg, 100%). ¹H NMR (300 MHz, CDCl₃) δ 9.02 (s, 1H), 7.57(d, *J* = 8.1 Hz, 1H), 7.29 (s,
25 1H), 7.12 (d, *J* = 3.1 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 3.81 (s, 2H), 2.50 (s, 3H).

Preparation 112

Preparation of *N*-Methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide

According to the procedure of Example 1 (a), except substituting acrylic acid for the
30 (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(1-methyl-1*H*-indol-3-ylmethyl)amine for the methyl-(1-propyl-napthalen-2-ylmethyl)amine, the title compound (1.51 g, 58%) was prepared as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.71-7.50 (s, 1H), 7.34-7.21

(m, 2H), 7.15–6.90 (m, 2H), 6.80–6.53 (m, 1H), 6.45–6.35 (s, 1H), 5.72–5.67 (m, 1H), 4.80–4.75 (m, 2H), 3.77 (s, 3H), 3.05–2.99 (m, 3H).

Preparation 113

Preparation of *N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide

- 5 A solution of methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine (1.95 g, 11.4 mmol) in CH₂Cl₂ (40 mL) was treated with acryloyl chloride (1.2 mL, 14 mmol) and triethylamine (3.2 mL, 22 mmol). The mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL). The solution was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure.
- 10 Purification by column chromatography (silica gel, EtOAc/hexanes, 40/60) gave the title compound (2.10 g, 75%) as a pale yellow solid: MS (ESI) *m/e* 246 (M + H)⁺.

Preparation 114

Preparation of (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid

- 15 a) [2-Amino-5-bromo-pyridin-3-ylmethyl)methylamino]acetic acid ethyl ester
- A solution of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (1.98 g, 5.71 mmol) and sarcosine ethyl ester hydrochloride (0.90 g, 5.86 mmol) in DMF (60 mL) was treated with triethylamine (2.6 mL, 18.5 mmol). After stirring at room temperature under N₂ for 2 h, the cloudy mixture was diluted with H₂O (100 mL) and extracted with
- 20 EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (3 x 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2) gave the title compound (1.37 g, 79%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.03 (d, *J* = 2.3 Hz, 1H), 7.32 (d, *J* = 2.3 Hz, 1H), 5.76 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H),
- 25 3.24 (s, 2H), 2.28 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/e* 302 (M + H)⁺.
- b) 7-Bromo-4-methyl-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one
- A solution of [2-amino-5-bromo-pyridin-3-ylmethyl)methylamino]acetic acid ethyl ester (1.37 g, 4.53 mmol) in DMSO (50 mL) was treated with NaH (0.18 g, 4.5 mmol). After stirring at room temperature under N₂ for 2 h, the mixture was stored in the freezer
- 30 overnight. The mixture was allowed to warm to room temperature, diluted with H₂O (200 mL), and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H₂O (2 x 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered, and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel,

CH₂Cl₂/MeOH, 98:2) gave the title compound (0.88 g, 76%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.57 (s, 1H), 8.35 (d, *J* = 2.2 Hz, 1H), 7.61 (d, *J* = 2.1 Hz, 1H), 3.91 (s, 2H), 3.74 (s, 2H), 2.49 (s, 3H); MS (ESI) *m/e* 256 (M + H)⁺.

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

A suspension of 7-bromo-4-methyl-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (0.63 g, 2.5 mmol) in propionitrile (10 mL) and DMF (3 mL) was de-oxygenated with Ar for 25 min. The mixture was treated with *tert*-butyl acrylate (1.5 mL, 10 mmol) and (*i*-Pr)₂EtN (0.9 mL, 5 mmol) and was de-oxygenated with Ar for 10 min. Pd(OAc)₂ (56 mg, 0.25 mmol) and P(*o*-tol)₃ (150 mg, 0.49 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 5 min. The mixture was heated to reflux for 18 h, then allowed to cool. The resulting precipitate was isolated by filtration, dissolved in CH₂Cl₂, filtered through Celite, and the solvent was removed in vacuo to give the title compound (0.60 g, 80%) as an off-white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.63 (s, 1H), 8.41 (d, *J* = 2.0 Hz, 1H), 7.62 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 16.0 Hz, 1H), 6.37 (d, *J* = 16.0 Hz, 1H), 3.96 (s, 2H), 3.77 (s, 2H), 2.49 (s, 3H), 1.53 (s, 9H); MS (ESI) *m/e* 304 (M + H)⁺.

d) (E)-3-(4-Methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid

A suspension of (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid *tert*-butyl ester (0.59 g, 1.9 mmol) in CH₂Cl₂ (7 mL) was treated with TFA (7 mL). After stirring at room temperature under N₂ for 45 min, the clear tan solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl in dioxane (10 mL, 4.0 M) and sonicated until the oil was converted to a fine off-white solid. After stirring under N₂ for 20 min, the solid was isolated by filtration, washed with Et₂O, and dried under vacuum for several hours to give the title compound (0.77 g, quantitative) as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.27 (bs, 1H), 11.28 (s, 1H), 8.78 (d, *J* = 1.9 Hz, 1H), 8.32 (d, *J* = 1.9 Hz, 1H), 7.65 (d, *J* = 16.1 Hz, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 4.32 (s, 2H), 3.82 (s, 2H), 2.89 (s, 3H); MS (ESI) *m/e* 248 (M + H)⁺.

Preparation 115

Preparation of (E)-3-(4-Ethoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride

a) [(2-Amino-5-bromo-pyridin-3-ylmethyl)ethoxycarbonylmethyl-amino]acetic acid ethyl ester

A suspension of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (12.0 g, 34.6 mmol) and diethyl iminodiacetate (7.0 mL, 39.1 mmol) in CH₃CN (350 mL) was treated with triethylamine (10.7 mL, 76.1 mmol). After stirring at room temperature under N₂ for 4 h, the solvent was removed in vacuo. The resulting yellow slurry was partitioned
 5 between H₂O (400 mL) and EtOAc (400 mL), and the aqueous layer was extracted with EtOAc (200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1) gave the title compound (6.55 g, 51%) as a light tan oil: MS (ESI) *m/e* 374 (M + H)⁺.

10 b) (7-Bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid ethyl ester

A solution of [(2-amino-5-bromo-pyridin-3-ylmethyl)ethoxycarbonylmethyl-amino]-acetic acid ethyl ester (6.52 g, 17.4 mmol) in DMSO (170 mL) was treated with NaH (0.70 g, 17.5 mmol). After stirring at room temperature overnight, the mixture was
 15 diluted with H₂O (300 mL) and extracted with EtOAc (4 x 200 mL). The combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo to give the title compound (6.18 g, quantitative) as an off-white solid: MS (ESI) *m/e* 328 (M + H)⁺.

c) (*E*)-3-(4-Ethoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-
 20 7-yl)acrylic acid *tert*-butyl ester

A suspension of (7-Bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid ethyl ester (6.18 g, 17.4 mmol) in propionitrile (70 mL) and DMF (17 mL) was de-oxygenated with Ar for 30 min. The mixture was treated with *tert*-butyl acrylate (10.2 mL, 69.6 mmol) and (*i*-Pr)₂EtN (6.4 mL, 37 mmol) and was then de-oxygenated with
 25 Ar for 10 min. Pd(OAc)₂ (0.39 g, 1.7 mmol) and P(*o*-tol)₃ (1.06 mg, 3.48 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 5 min. After heating to reflux for 14 h, the mixture was allowed to cool and then concentrated in vacuo. The resulting residue was diluted with CH₂Cl₂ and filtered through Celite. The orange filtrate was concentrated in vacuo. The resulting residue was diluted with EtOAc (200 mL)
 30 and washed with H₂O (100 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with H₂O (2 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3) and again by flash column

chromatography (silica gel, CH₂Cl₂/MeOH, 99:1) gave the title compound (2.55 g, 39%) as an off-white solid: MS (ESI) *m/e* 376 (M + H)⁺.

d) (*E*)-3-(4-Ethoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride

- 5 A solution of (*E*)-3-(4-ethoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid *tert*-butyl ester (1.14 g, 3.04 mmol) in CH₂Cl₂ (8 mL) was treated with TFA (8 mL). After stirring at room temperature under N₂ for 45 min, the clear tan solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl in dioxane (10 mL, 4.0 M) and sonicated until the oil was converted to a fine off-white solid. The resulting mixture was diluted with Et₂O (100 mL) and stirred under N₂ for 20 min. The solid was isolated by filtration, washed with Et₂O, and dried under vacuum at 50 °C overnight to give the title compound (1.05 g, 88%) as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 8.56–8.55 (m, 1H), 8.10 (s, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 4.14–4.05 (m, 3H), 3.62–3.56 (m, 6H), 1.18 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/e* 320 (M + H)⁺.

Preparation 116

Preparation of (*R*)-(*E*)-3-(10-Oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid hydrochloride

- a) (*R*)-1-(2-Amino-5-bromo-pyridin-3-ylmethyl)pyrrolidine-2-carboxylic acid methyl ester
- 20 A suspension of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (8.00 g, 23.1 mmol) and D-proline methyl ester hydrochloride (4.53 g, 27.4 mmol) in CH₃CN (100 mL) was treated with a solution of triethylamine (10.4 mL, 74.0 mmol) in CH₃CN (100 mL). After stirring at room temperature for 5 h, the cloudy mixture was diluted with H₂O (300 mL) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1 to 98:2) gave the title compound (6.55 g, 90%) as a colorless oil: MS (ESI) *m/e* 314 (M + H)⁺
- b) (*R*)-6-Bromo-1,2,3,4,9,10a-hexahydro-3a,8,9-triaza-benzo[*f*]azulen-10-one

- 30 A solution of (*R*)-1-(2-amino-5-bromo-pyridin-3-ylmethyl)pyrrolidine-2-carboxylic acid methyl ester (6.52 g, 20.8 mmol) in DMSO (200 mL) was treated with NaH (60% dispersion in mineral oil, 0.83 g, 20.7 mmol). After stirring at room temperature for 3 h, the mixture was stored in the freezer for 3 d. The mixture was allowed to warm to room temperature, diluted with H₂O (400 mL), and extracted with EtOAc (4 x 200 mL). The

combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1) gave the title compound (3.94 g, 67%) as an off-white solid: MS (ESI) *m/e* 282 (M + H)⁺.

- 5 c) (R)-(E)-3-(10-Oxo-2,3,4,9,10,10a-hexahydro-1H-3a,8,9-triaza-benzo[f]azulen-6-yl)acrylic acid *tert*-butyl ester

A suspension of (R)-6-bromo-1,2,3,4,9,10a-hexahydro-3a,8,9-triaza-benzo[f]azulen-10-one (3.91 g, 13.8 mmol) in propionitrile (80 mL) and DMF (20 mL) was de-oxygenated with Ar for 25 min. The mixture was treated with *tert*-butyl acrylate (8.1 mL, 55 mmol) and (*i*-Pr)₂EtN (5.1 mL, 29 mmol) and was de-oxygenated with Ar for 15 min. Pd(OAc)₂ (0.31 g, 1.4 mmol) and P(*o*-tol)₃ (0.84 mg, 2.8 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 10 min. The mixture was heated to reflux overnight then allowed to cool. The resulting precipitate was isolated by filtration, dissolved in CH₂Cl₂, filtered through Celite, and the solvent was removed in vacuo to give the title compound (2.53 g, 56%) as an off-white solid: MS (ESI) *m/e* 330 (M + H)⁺.

- d) (R)-(E)-3-(10-Oxo-2,3,4,9,10,10a-hexahydro-1H-3a,8,9-triaza-benzo[f]azulen-6-yl)acrylic acid hydrochloride

A solution of (R)-(E)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1H-3a,8,9-triaza-benzo[f]azulen-6-yl)acrylic acid *tert*-butyl ester (2.53 g, 7.68 mmol) in CH₂Cl₂ (15 mL) was treated with TFA (15 mL). After stirring at room temperature under N₂ for 45 min, the clear tan solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl (30 mL of a 4.0 M solution in dioxane, 120 mmol). The resulting mixture was sonicated for 10 min, stirred under N₂ for 20 min, diluted with Et₂O (100 mL), sonicated for 20 min and stirred for 20 min. The solid was isolated by filtration, washed with Et₂O, and dried under vacuum at 50 °C overnight to give the title compound (2.66 g, quantitative) as an off-white solid: MS (ESI) *m/e* 274 (M + H)⁺.

Preparation 117

Preparation of (S)-(E)-3-(10-Oxo-2,3,4,9,10,10a-hexahydro-1H-3a,8,9-triaza-benzo[f]azulen-6-yl)acrylic acid hydrochloride

- 30 a) (S)-1-(2-Amino-5-bromo-pyridin-3-ylmethyl)pyrrolidine-2-carboxylic acid methyl ester

A solution of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (6.00 g, 17.3 mmol) and L-proline methyl ester hydrochloride (2.88 g, 17.4 mmol) in DMF (125 mL) was treated with a solution of triethylamine (7.8 mL, 55.5 mmol) in DMF (75 mL).

After stirring at room temperature under N₂ for 3 h, the cloudy mixture was diluted with H₂O (300 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with H₂O (2 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1 to 98:2) gave the title compound (3.66 g, 67%) as a pale yellow oil:
 5 MS (ESI) *m/e* 314 (M + H)⁺.

b) (*S*)-6-Bromo-1,2,3,4,9,10a-hexahydro-3a,8,9-triaza-benzo[*f*]azulen-10-one

A solution of (*S*)-1-(2-amino-5-bromo-pyridin-3-ylmethyl)pyrrolidine-2-carboxylic acid methyl ester (3.66 g, 11.6 mmol) in DMSO (120 mL) was treated with NaH (60% dispersion in mineral oil, 0.47 g, 11.7 mmol). After stirring at room temperature for 4 h,
 10 the mixture was diluted with H₂O (2500 mL) and extracted with EtOAc (5 x 150 mL). The combined organic layers were washed with H₂O (4 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1) gave the title compound (2.75 g, 84%) as
 15 an off-white solid: MS (ESI) *m/e* 282 (M + H)⁺.

c) (*S*)-(E)-3-(10-Oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid *tert*-butyl ester

A suspension of (*S*)-6-bromo-1,2,3,4,9,10a-hexahydro-3a,8,9-triaza-benzo[*f*]azulen-10-one (1.46 g, 5.17 mmol) in propionitrile (40 mL) and DMF (10 mL) was de-oxygenated
 20 with Ar for 30 min. The mixture was treated with *tert*-butyl acrylate (3.0 mL, 20 mmol) and (*i*-Pr)₂EtN (1.9 mL, 11 mmol) and was de-oxygenated with Ar for 10 min. Pd(OAc)₂ (0.12 g, 0.53 mmol) and P(*o*-tol)₃ (0.34 mg, 1.12 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 resulting precipitate was isolated by filtration,
 25 dissolved in CH₂Cl₂, filtered through Celite and the solvent was removed in vacuo to give the title compound (0.68 g, 40%) as an off-white solid: MS (ESI) *m/e* 330 (M + H)⁺.

d) (*S*)-(E)-3-(10-Oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid hydrochloride

A solution of (*S*)-(E)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid *tert*-butyl ester (0.65 g, 1.97 mmol) in CH₂Cl₂ (7 mL) was
 30 treated with TFA (7 mL). After stirring at room temperature for 30 min, the clear tan solution was concentrated in vacuo. The resulting oil was treated with anhydrous dioxane (20 mL of a 4.0 M solution in dioxane, 80 mmol). The resulting mixture was sonicated for

5 min, stirred under N₂ for 5 min and diluted with Et₂O. The solid was isolated by filtration, suspended in Et₂O, concentrated to dryness, and dried under vacuum overnight to give the title compound (0.60 g, 88%) as an off-white solid: MS (ESI) *m/e* 274 (M + H)⁺.

Preparation 118

5 Preparation of (*E*)-3-[4-(4-Methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride

a) (4-Methoxy-benzylamino)acetic acid ethyl ester

A suspension of glycine ethyl ester hydrochloride (10.0 g, 71.6 mmol) and NaBH₃CN (5.00 g, 79.6 mmol) in MeOH (60 mL) was treated dropwise over 15 min with
 10 *p*-anisaldehyde (11.0 mL, 90.4 mmol). After stirring at room temperature overnight, the solvent was removed in vacuo. The residue was partitioned between CH₂Cl₂ (200 mL) and saturated aqueous NaHCO₃ (300 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 200 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column
 15 chromatography (silica gel, hexanes/EtOAc, 90:10 to 50:50) gave the title compound (7.77 g, 49%) as a colorless liquid: MS (ESI) *m/e* 224 (M + H)⁺.

b) [(2-Amino-5-bromo-pyridin-3-ylmethyl)-(4-methoxy-benzyl)amino]acetic acid ethyl ester

A solution of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (11.9 g, 34.3 mmol) and (4-methoxy-benzylamino)acetic acid ethyl ester (7.70 g, 34.5 mmol) in
 20 DMF (200 mL) was treated with triethylamine (10.0 mL, 71.2 mmol). After stirring at room temperature overnight, the cloudy mixture was diluted with H₂O (400 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed
 25 in vacuo to give the title compound (13.0 g, 93%) as a yellow syrup: MS (ESI) *m/e* 408 (M + H)⁺.

c) 7-Bromo-4-(4-methoxy-benzyl)-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one

A solution of [(2-amino-5-bromo-pyridin-3-ylmethyl)-(4-methoxy-benzyl)amino]acetic acid ethyl ester (13.0 g, 31.9 mmol) in DMSO (200 mL) was treated
 30 with NaH (60% dispersion in mineral oil, 1.30 g, 32.5 mmol). After stirring at room temperature overnight, the mixture was diluted with H₂O (500 mL) and a precipitate formed. The solid was isolated by filtration, washed with H₂O, and dried under vacuum at

50 °C for 6.5 h to give the title compound (7.16 g, 62%) as a tan powder: MS (ESI) m/e 362 ($M + H$)⁺.

d) (*E*)-3-[4-(4-Methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid *tert*-butyl ester

5 A suspension of 7-bromo-4-(4-methoxy-benzyl)-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (5.00 g, 13.8 mmol) in propionitrile (80 mL) and DMF (20 mL) was de-oxygenated with Ar for 25 min. The mixture was treated with *tert*-butyl acrylate (8.1 mL, 55 mmol) and (*i*-Pr)₂EtN (5.1 mL, 29 mmol) and was de-oxygenated with Ar for 15 min. Pd(OAc)₂ (0.32 g, 1.43 mmol) and P(*o*-tol)₃ (0.85 g, 2.79 mmol) were added
10 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 resulting precipitate was isolated by filtration. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1) gave the title compound (3.54 g, 63%) as a white solid: MS (ESI) m/e 410 ($M + H$)⁺.
e) (*E*)-3-[4-(4-Methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride
15

A suspension of (*E*)-3-[4-(4-methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid *tert*-butyl ester (3.54 g, 8.65 mmol) in CH₂Cl₂ (20 mL) was treated with TFA (20 mL). After stirring at room temperature under N₂ for 25 min, the clear tan solution was concentrated in vacuo. The resulting residue was treated
20 with anhydrous HCl (40 mL of a 4.0 M solution in dioxane, 160 mmol) and sonicated for 15 min. The solid was isolated by filtration, washed with Et₂O and dried under vacuum at 50 °C for 3 d to give the title compound (3.40 g, 92%) as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.38 (br s, 1H), 11.32 (s, 1H), 8.77 (s, 1H), 8.28 (s, 1H), 7.66–7.58 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 16.1 Hz, 1H), 4.41–4.27 (m, 5H), 3.79 (s, 3H),
25 3.68 (s, 2H); MS (ESI) m/e 354 ($M + H$)⁺.

Preparation 119

Preparation of (*E*)-3-[4-(2-Morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride

a) [*tert*-Butoxycarbonyl-(2-morpholin-4-yl-ethyl)amino]acetic acid methyl ester

30 A solution of *N*-*tert*-butoxycarbonyl glycine methyl ester (9.4 mL, 63.6 mmol) in DMF (250 mL) was cooled in an ice bath and treated with NaH (60% dispersion in mineral oil, 2.85 g, 71.2 mmol). After stirring at 0 °C under N₂ for 30 min and then at room temperature for 30 min, the mixture was cooled in an ice bath and treated with a solution of

4-(2-chloroethyl)morpholine (10.5 g, 70 mmol) in DMF (50 mL). After stirring at 0 °C for 30 min, the mixture was stirred at room temperature overnight. The mixture was diluted with H₂O (600 mL) and then extracted with EtOAc (5 x 300 mL). The combined organic layers were washed with H₂O (4 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2) gave the title compound (0.79 g, 4%) as a colorless oil: MS (ESI) *m/e* 303 (M + H)⁺.

b) (2-Morpholin-4-yl-ethylamino)acetic acid methyl ester

A solution of [*tert*-butoxycarbonyl-(2-morpholin-4-yl-ethyl)amino]acetic acid methyl ester (0.79 g, 2.61 mmol) in CH₂Cl₂ (10 mL) was treated with TFA (10 mL). After stirring at room temperature for 1 h, the solution was concentrated in vacuo. The oil was dissolved in CH₂Cl₂ (50 mL) and the resulting solution was washed with saturated aqueous NaHCO₃ (50 mL). The aqueous layer was extracted with CH₂Cl₂ (10 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed in vacuo to give the title compound (0.40 g, 76%) as a yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 3.69–3.74 (m, 7H), 3.45 (s, 2H), 2.69–2.73 (m, 2H), 2.45–2.52 (m, 6H), 1.84 (s, 1H).

c) [(2-Amino-5-bromo-pyridin-3-ylmethyl)-(2-morpholin-4-yl-ethyl)amino]acetic acid methyl ester

A solution of (2-Morpholin-4-yl-ethylamino)acetic acid methyl ester (0.40 g, 2.0 mmol) and triethylamine (1.0 mL, 7.11 mmol) in DMF (20 mL) was treated with 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (0.70 g, 2.0 mmol). After stirring at room temperature under for 7 h, the cloudy mixture was diluted with H₂O (50 mL) and then extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with H₂O (3 x 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2 to 96:4) gave the title compound (0.46 g, 60%) as a colorless oil: MS (ESI) *m/e* 387 (M + H)⁺.

d) 7-Bromo-4-(2-morpholin-4-yl-ethyl)-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one

A solution of [(2-amino-5-bromo-pyridin-3-ylmethyl)-(2-morpholin-4-yl-ethyl)amino]acetic acid methyl ester (0.34 g, 0.88 mmol) in DMSO (10 mL) was treated with NaH (60% dispersion in mineral oil, 35 mg, 0.88 mmol). After stirring at room temperature overnight, the mixture was diluted with H₂O (20 mL), and then extracted with

EtOAc (4 x 50 mL). The combined organic layers were washed with H₂O (3 x 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. The resulting pale yellow oil was purified by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3 to 90:10) to give the title compound (0.24 g, 57%) as an off-white solid: MS (ESI) *m/e* 355 (M + H)⁺.

e) (E)-3-[4-(2-Morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl]acrylic acid *tert*-butyl ester

A suspension of 7-bromo-4-(2-morpholin-4-yl-ethyl)-1,3,4,5-tetrahydro-pyrido[2,3-e][1,4]diazepin-2-one (0.18 g, 0.52 mmol) in propionitrile (4 mL) and DMF (1 mL) was de-oxygenated with Ar for 15 min. The mixture was treated with *tert*-butyl acrylate (0.3 mL, 2 mmol) and (*i*-Pr)₂EtN (0.2 mL, 1 mmol) and was de-oxygenated with Ar for 10 min. Pd(OAc)₂ (12 mg, 0.053 mmol) and P(*o*-tol)₃ (32 mg, 0.10 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 Et₂O (50 mL) and the resulting solution washed with H₂O (20 mL). The organic layer was dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3) gave the title compound (92 mg, 44%) as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.51 (s, 1H), 8.52 (s, 1H), 7.61–7.49 (m, 2H), 6.36 (d, *J* = 16.0 Hz, 1H), 4.07 (s, 2H), 3.90 (s, 2H), 3.70–3.67 (m, 4H), 2.78–2.74 (m, 2H), 2.52–2.49 (m, 6H), 1.53 (s, 9H); MS (ESI) *m/e* 403 (M + H)⁺.

f) (E)-3-[4-(2-Morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl]acrylic acid hydrochloride

A solution of (E)-3-[4-(2-morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl]acrylic acid *tert*-butyl ester (92 mg, 0.23 mmol) in CH₂Cl₂ (2 mL) was treated with TFA (2 mL). After stirring at room temperature for 30 min, the clear tan solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl (4 mL of a 4.0 M solution in dioxane, 16 mmol) and then sonicated for 15 min. The mixture was diluted with Et₂O and sonicated for 10 min. The solid was isolated by filtration, washed with Et₂O and dried under vacuum at 50 °C for 4.5 hr to give the title compound (0.10 g, 96%) as an off-white solid: MS (ESI) *m/e* 347 (M + H)⁺.

Preparation 120

Preparation of (E)-3-{4-[2-(4-Methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl}acrylic acid hydrochloride

a) [(2-Amino-5-bromo-pyridin-3-ylmethyl)amino]acetic acid ethyl ester

A solution of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (6.00 g, 17.3 mmol) and glycine ethyl ester hydrochloride (2.41 g, 17.3 mmol) in DMF (200 mL) was treated with triethylamine (7.8 mL, 56 mmol). After stirring at room temperature for 3.5 h, the cloudy mixture was diluted with H₂O (300 mL) and then extracted with EtOAc (2 x 300 mL). The combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2) gave the title compound (2.83g, 57%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, *J* = 2.3 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 5.56 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.71 (s, 2H), 3.38 (s, 2H), 1.73 (s, 1H), 1.30 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/e* 288 (M + H)⁺.

b) 7-Bromo-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one

A solution of [(2-amino-5-bromo-pyridin-3-ylmethyl)amino]acetic acid ethyl ester (1.79 g, 6.21 mmol) in DMSO (70 mL) was treated with NaH (60% dispersion in mineral oil, 0.25 g, 6.2 mmol). After stirring at room temperature for 27 h, the mixture was diluted with H₂O (300 mL), and extracted then with EtOAc (4 x 150 mL). The combined organic layers were washed with H₂O (3 x 50 mL) and brine (50 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo to give the title compound (1.09 g, 72%) as an off-white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.26 (d, *J* = 2.1 Hz, 1H), 8.17 (s, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 4.03 (s, 2H), 3.93 (s, 2H), 1.85 (br s, 1H); MS (ESI) *m/e* 242 (M + H)⁺.

c) (7-Bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid *tert*-butyl ester

A solution of 7-bromo-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (2.29 g, 9.46 mmol) in DMF (100 mL) was treated with *tert*-butylbromoacetate (1.7 mL, 12 mmol) and triethylamine (1.5 mL, 11 mmol). After stirring at room temperature overnight, the mixture was diluted with H₂O (300 mL) and then extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, hexanes/EtOAc, 2:1) gave the title compound (1.61 g, 48%) as a white powder: MS (ESI) *m/e* 356 (M + H)⁺.

d) (7-Bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid hydrochloride

A solution of (7-bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid *tert*-butyl ester (1.61 g, 4.52 mmol) in CH₂Cl₂ (20 mL) was treated with TFA (15 mL). After stirring at room temperature for 1 h, the solution was concentrated in vacuo. The resulting slurry was treated with anhydrous HCl (40 mL of a 4.0 M) and sonicated for 1.5 h, diluted with Et₂O and stirred for 1 h. The solid was isolated by filtration, washed with Et₂O, and dried under vacuum at 50 °C overnight to give the title compound (1.66 g, 98%) as a white solid: MS (ESI) *m/e* 300 (M + H)⁺.

e) 7-Bromo-4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one

10 A suspension of (7-bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid hydrochloride (1.66 g, 4.45 mmol) in CH₂Cl₂ (50 mL) was treated sequentially with (*i*-Pr)₂EtN (3.1 mL, 18 mmol), *N*-methyl piperazine (0.54 mL, 4.87 mmol), HOBt (0.66 g, 4.88 mmol), and EDC (0.95 g, 4.96 mmol). After stirring overnight, the mixture was diluted with CH₂Cl₂ (100 mL) and then washed with H₂O (100 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3 to 95:5) gave the title compound (1.42 g, 83%) as an off-white solid: MS (ESI) *m/e* 382 (M + H)⁺.

15 f) (*E*)-3-{4-[2-(4-Methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylic acid *tert*-butyl ester

20 A suspension of 7-Bromo-4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (1.39 g, 3.64 mmol) in propionitrile (32 mL) and DMF (8 mL) was de-oxygenated with Ar for 15 min. The mixture was treated with *tert*-butyl acrylate (2.1 mL, 14 mmol) and (*i*-Pr)₂EtN (1.3 mL, 7.4 mmol) and then was de-oxygenated with Ar for 10 min. Pd(OAc)₂ (83 mg, 0.37 mmol) and P(*o*-tol)₃ (0.22 g, 0.73 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 10 min. The mixture was heated to reflux overnight, then allowed to cool. The resulting precipitate was isolated by filtration and dissolved in CH₂Cl₂. The solution was filtered through Celite and the solvent was removed in vacuo to give the title compound (1.13 g, 72%) as an off-white solid: MS (ESI) *m/e* 430 (M + H)⁺.

30 g) (*E*)-3-{4-[2-(4-Methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylic acid hydrochloride

A suspension of (*E*)-3-{4-[2-(4-Methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl} acrylic acid *tert*-butyl ester (1.12 g, 2.61 mmol) in CH₂Cl₂ (10 mL) was treated with TFA (10 mL). After stirring at room temperature for 35 min, the solution was concentrated in vacuo. The resulting oil was
 5 treated with anhydrous HCl (20 mL of a 4.0 M solution in dioxane, 80 mmol) and the resulting mixture was sonicated for 1 h. The mixture was diluted with Et₂O (50 mL) and sonicated for 10 min. The solid was isolated by filtration, washed with Et₂O and dried under vacuum at 50 °C for 4 h to give the title compound (1.72 g, quantitative) as an off-white solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 11.60 (br s, 1H), 11.09 (br s, 1H), 8.82 (s, 1H), 8.47 (s, 1H), 7.66 (d, *J* = 19.9 Hz, 1H), 6.65 (d, *J* = 16.1 Hz, 1H), 4.43–4.40 (m, 2H),
 10 4.31 (br s, 2H), 3.95–3.91 (m, 1H), 3.84 (br s, 2H), 3.56 (s, 4H), 3.42 (br s, 2H), 3.23–2.97 (m, 2H), 2.76 (d, *J* = 4.1 Hz, 3H); MS (ESI) *m/e* 374 (M + H)⁺.

Preparation 121

Preparation of (*E*)-3-[4-(3-Morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride
 15

a) (3-Morpholin-4-yl-propylamino)acetic acid ethyl ester

A solution of 4-(3-aminopropyl)morpholine (10.0 mL, 68.4 mmol) in MeOH (180 mL) was cooled in an ice bath and treated with ethyl glyoxylate (~50% solution in toluene, 20.0 mL, 98.0 mmol) and HOAc (12 mL). After stirring for 15 min, NaBH₃CN (4.81 g, 76.5 mmol) was added and the mixture was allowed to stir at 0 °C for 2 h. The mixture was
 20 diluted with saturated aqueous NaHCO₃ (500 mL) and then extracted with EtOAc (5 x 300 mL) followed by CH₂Cl₂ (9 x 200 mL). The combined CH₂Cl₂ layers were dried over Na₂SO₄, filtered and the solvent was removed in vacuo to give the title compound (7.44 g, 47%) as a colorless oil: MS (ESI) *m/e* 231 (M + H)⁺.

25 b) [(2-Amino-5-bromo-pyridin-3-ylmethyl)-(3-morpholin-4-yl-propyl)amino]acetic acid ethyl ester

A solution of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (11.2 g, 32.3 mmol) and (3-morpholin-4-yl-propylamino)acetic acid ethyl ester (7.44 g, 32.3 mmol) in DMF (200 mL) was treated with triethylamine (9.5 mL, 68 mmol). After stirring at room
 30 temperature overnight, the mixture was diluted with H₂O (400 mL) and then extracted with EtOAc (5 x 250 mL). The combined organic layers were washed with H₂O (2 x 200 mL) and brine (200 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo to give the title compound (11.8 g, 87%) as a yellow oil: MS (ESI) *m/e* 415 (M + H)⁺.

c) 7-Bromo-4-(3-morpholin-4-yl-propyl)-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one

A solution of [(2-amino-5-bromo-pyridin-3-ylmethyl)-(3-morpholin-4-yl-propyl)amino]acetic acid ethyl ester (11.8 g, 28.3 mmol) in DMSO (200 mL) was treated with NaH (60% dispersion in mineral oil, 1.13 g, 28.3 mmol). After stirring at room temperature overnight, the mixture was diluted with H₂O (400 mL) and then extracted with EtOAc (7 x 250 mL). The combined organic layers were washed with H₂O (2 x 200 mL) and brine (200 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3 to 96:4) gave the title compound (5.76 g, 55%) as an off-white powder: MS (ESI) *m/e* 369 (M + H)⁺.

d) (*E*)-3-[4-(3-Morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid *tert*-butyl ester

A suspension of 7-bromo-4-(3-morpholin-4-yl-propyl)-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (5.70 g, 15.4 mmol) in propionitrile (120 mL) and DMF (30 mL) was de-oxygenated with Ar for 15 min. The mixture was treated with *tert*-butyl acrylate (9.0 mL, 61 mmol) and (*i*-Pr)₂EtN (5.7 mL, 33 mmol) and was de-oxygenated with Ar for 10 min. Pd(OAc)₂ (0.35 g, 1.6 mmol) and P(*o*-tol)₃ (0.94 g, 3.1 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 Et₂O (200 mL). The organic solution was filtered through Celite, washed with H₂O (200 mL), dried over Na₂SO₄, filtered and then concentrated in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3 to 96:4) gave the title compound (3.49 g, 55%) as a tan solid: MS (ESI) *m/e* 417 (M + H)⁺.

e) (*E*)-3-[4-(3-Morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride

A solution of (*E*)-3-[4-(3-Morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid *tert*-butyl ester (2.21 g, 5.30 mmol) in CH₂Cl₂ (20 mL) was treated with TFA (20 mL). After stirring at room temperature for 30 min, the solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl (50 mL of a 4.0 M solution in dioxane, 200 mmol) and the mixture was sonicated for 1.5 h. The mixture was diluted with Et₂O (200 mL) and sonicated for 15 min. The solid was isolated by filtration, washed with Et₂O, and dried under vacuum at 50 °C for 5 h to give the title compound (3.08 g, quantitative) as an off-white solid: ¹H NMR (500 MHz,

DMSO- d_6) δ 11.23 (br s, 2H), 8.74 (s, 1H), 8.36 (s, 1H), 7.63 (d, $J = 15.9$, 1H), 6.63 (d, $J = 16.0$ Hz, 1H), 4.33 (br s, 2H), 3.90 (br s, 6H), 3.24 (m, 8H), 2.22 (br s, 2H); MS (ESI) m/e 361 ($M + H$)⁺.

Preparation 122

5 Preparation of (*E*)-7-(2-carboxy-vinyl)-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3- e][1,4]diazepine-4-carboxylic acid benzyl ester hydrochloride

a) 7-Bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester

10 A suspension of 7-bromo-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (1.08 g, 4.46 mmol) in CH_2Cl_2 (60 mL) was treated with Et_3N (0.80 mL, 5.7 mmol) and then cooled in an ice bath. The chilled suspension was treated dropwise with CbzCl (4.5 mmol) to give a clear solution. The ice bath was removed and the solution was allowed to stir overnight. The mixture was diluted with CH_2Cl_2 (90 mL), washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4 , filtered and the solvent was removed in vacuo.

15 Purification by flash column chromatography (silica gel, $CH_2Cl_2/MeOH$, 99.5:0.5 to 99:1) gave the title compound (0.52 g, 31%) as a white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.31–8.36 (m, 2H), 7.49–7.71 (m, 1H), 7.34–7.40 (m, 4H), 7.19–7.21 (m, 1H), 5.08–5.12 (m, 2H), 4.43–4.65 (m, 4H); MS (ESI) m/e 376 ($M + H$)⁺.

20 b) (*E*)-7-(2-*tert*-Butoxycarbonyl-vinyl)-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-
e][1,4]diazepine-4-carboxylic acid benzyl ester

A suspension of 7-bromo-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester (0.52 g, 1.4 mmol) in propionitrile (10 mL) and DMF (3 mL) was de-oxygenated with Ar for 20 min. The mixture was treated with *tert*-butyl acrylate (0.83 mL, 10 mmol) and (*i*-Pr) $_2$ EtN (0.50 mL, 2.9 mmol) and was de-oxygenated with Ar for 10 min. Pd(OAc) $_2$ (34 mg, 0.15 mmol) and P(*o*-tol) $_3$ (84 mg, 0.27 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 resulting precipitate was isolated by filtration, washed with EtOAc and dissolved in CH_2Cl_2 . The solution was filtered through Celite and the solvent was removed in vacuo to give the title compound (0.31 g, 53%) as an off-white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.49–8.57 (m, 1H), 8.30 (s, 1H), 7.43–7.73 (m, 2H), 7.33 (s, 4H), 7.17–7.18 (m, 1H), 6.21–6.40 (m, 1H), 5.05–5.11 (m, 2H), 4.46–4.68 (m, 4H), 1.54–1.57 (m, 9H); MS (ESI) m/e 424 ($M + H$)⁺.

30

c) (*E*)-7-(2-Carboxy-vinyl)-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester hydrochloride

A solution of (*E*)-7-(2-*tert*-butoxycarbonyl-vinyl)-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester (0.31 g, 0.73 mmol) in CH₂Cl₂ (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 treated with anhydrous HCl (10 mL of a 4.0 M solution in dioxane, 40 mmol) to give a cloudy mixture. The mixture was diluted with Et₂O (200 mL) to give an off-white precipitate. After stirring for 15 min, the solid was isolated by filtration, washed with Et₂O, and dried under vacuum for 1.5 h to give the title compound (0.27 g, 91%) as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.50–10.47 (m, 1H), 8.49 (s, 1H), 8.09–8.15 (m, 1H), 7.53–7.59 (m, 1H), 7.15–7.33 (m, 5H), 6.51–6.65 (m, 1H), 5.42 (bs, 2H), 5.05–5.08 (m, 2H), 4.63 (s, 2H), 4.43 (s, 2H); MS (ESI) *m/e* 368 (M + H)⁺.

Preparation 123

15 Preparation of (*E*)-3-(2-Oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridine-6-yl)acrylic acid hydrochloride

a) (*E*)-3-(2-Oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridin-6-yl)acrylic acid *tert*-butyl ester

A stirred solution of 6-bromo-3*H*-oxazolo[4,5-*b*]pyridin-2-one (1.00 g, 4.65 mmol), *tert*-butyl acrylate (2.7 mL, 18 mmol), palladium(II) acetate (104 mg, 0.465 mmol), tri-*o*-tolylphosphine (283 mg, 0.930 mmol), and *N,N*-diisopropylethylamine (1.7 mL, 9.7 mmol) in *N,N*-dimethylformamide (4 mL) and propionitrile (16 mL) was deoxygenated by bubbling argon through the solution for 20 min. The mixture was heated to reflux for 21 h, then allowed to cool. The mixture was concentrated in vacuo. The residue was dissolved in dichloromethane (100 mL). The solution was washed with water (2 × 200 mL), dried over sodium sulfate, filtered, and the solvent removed in vacuo to give a dark brown oil. Purification by flash column chromatography (silica gel, gradient from 98:2 to 94:6 CHCl₃/MeOH) gave the title compound (283 mg, 23%) as a brown solid: ¹H NMR (300 MHz, CDCl₃) δ 8.24 (d, *J* = 1.4 Hz, 1H), 7.64–7.55 (m, 2H), 6.37 (d, *J* = 16.0 Hz, 1H), 1.55 (s, 9H).

30 b) (*E*)-3-(2-Oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridin-6-yl)acrylic acid hydrochloride

A solution of (*E*)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridine-6-yl)acrylic acid *tert*-butyl ester (274 mg, 1.04 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was stirred for 30 min, then the solvents were removed in vacuo. The residue was

suspended in anhydrous HCl (5 mL of a 4 M solution in 1,4-dioxane, 20 mmol) and the mixture was sonicated for 1 min. The resulting solid was collected by filtration, washed with diethyl ether and then dried in vacuo to give the title compound (194 mg, 77%) as a light brown solid: ^1H NMR (300 MHz, DMSO- d_6) δ 8.31 (s, 1H), 8.13 (s, 1H), 7.63 (d, J = 16.0 Hz, 1H), 6.60 (d, J = 16.0 Hz, 1H).

Preparation 124

Preparation of (*E*)-3-[6-Amino-5-(2-carboxy-ethyl)pyridin-3-yl]acrylic acid

A solution of (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylic acid *tert*-butyl ester (0.86 g, 3.0 mmol) was stirred in methanol (10 mL), dioxane (10 mL) and aq. NaOH (15 mL of a 1 N solution, 15 mmol) for 4 days. The clear solution was neutralized with aq. HCl (15 mL of a 1 N solution, 15 mmol) and stirred for 20 min. The white precipitate was collected by filtration to give (*E*)-3-[6-amino-5-(2-carboxy-ethyl)pyridin-3-yl]acrylic acid (0.57 g, 78%): MS (ESI) m/e 237 ($M + H$) $^+$.

Preparation 125

Preparation of (*E*)-3-(6-Amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride

a) 5-Bromo-3-piperidin-1-ylmethyl-pyridin-2-ylamine

An ice-cold suspension of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (10.0 g, 28.8 mmol) in MeCN (100 mL) was treated with piperidine (6.4 mL, 64.8 mmol). After stirring at room temperature for 3.5 h, the mixture was diluted with Et₂O (500 mL). The solution was filtered and then concentrated to give the title compound (4.16 g, 53%) as a pale, yellow solid: MS (ESI) m/e 270 ($M + H$) $^+$.

b) (*E*)-3-(6-Amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester

A solution of 5-bromo-3-piperidin-1-ylmethyl-pyridin-2-ylamine (500 mg, 1.85 mmol), *tert*-butyl acrylate (0.3 mL, 2.0 mmol), (*i*-Pr)₂EtN (0.5 mL, 2.8 mmol) and P(*o*-tol)₃ (114 mg, 0.37 mmol) in EtCN (10 mL) was de-oxygenated with argon for 30 min. Pd(OAc)₂ (43 mg, 0.19 mmol) was added, and the mixture was de-oxygenated for 15 min. The mixture was heated to reflux for 18 h and then allowed to cool. The solvent was removed in vacuo. The residue was partitioned between EtOAc and H₂O. The organic layer was washed with H₂O and satd NaCl, dried over Na₂SO₄ and concentrated. Purification by column chromatography (silica gel, CH₂Cl₂ to 96:4 CH₂Cl₂/CH₃OH) gave the title compound (350 mg, 60%) as a yellow solid: MS (ESI) m/e 318 ($M + H$) $^+$.

c) (*E*)-3-(6-Amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride

A suspension of 3-(6-amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester (250 mg, 0.79 mmol) in CH₂Cl₂ (3 mL) was treated with TFA (2 mL). After stirring at room temperature under N₂ for 45 min, the solution was concentrated. The resulting oil was treated with anhydrous HCl in dioxane (10 mL, 4.0 M) and then sonicated until the oil was converted to a fine off-white solid. After stirring under N₂ for 20 min, the solid was isolated by filtration, washed with Et₂O, and dried under vacuum for several hours to give the title compound (282 mg, quantitative) as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.6 (br s, 1H), 8.53 (d, *J* = 2.1 Hz, 1H), 8.39–8.28 (m, 3H), 7.53 (d, *J* = 15.0 Hz, 1H), 6.46 (d, *J* = 15.0 Hz, 1H), 4.33 (s, 2H), 3.43–3.35 (m, 2H), 2.97 (s, 2H), 1.79–1.69 (m, 5H), 1.35 (s, 1H).

Preparation 126

Preparation of (*E*)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride

a) 5-Bromo-3-pyrrolidin-1-ylmethyl-pyridin-2-ylamine

According to the procedure of Preparation 125(a), except substituting pyrrolidine for piperidine, the title compound (2.40 g, 34%) was prepared as an off-white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.01 (d, *J* = 2.3 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 5.67 (s, 2H), 3.51 (s, 2H), 2.48–2.44 (m, 4H), 1.80–1.60 (m, 4H).

b) (*E*)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester

According to the procedure of Preparation 125(b), except substituting 5-bromo-3-pyrrolidin-1-ylmethyl-pyridin-2-ylamine for 5-bromo-3-piperidin-1-ylmethyl-pyridin-2-ylamine, the title compound (1.60 g, 61%) was prepared as a light yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, *J* = 2.1 Hz, 1H), 7.50–7.44 (m, 2H), 6.17 (d, *J* = 15.9 Hz, 1H), 6.00 (s, 2H), 3.56 (s, 2H), 2.49–2.45 (m, 4H), 1.81–1.76 (m, 4H), 1.52 (s, 9H).

c) (*E*)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride

According to the procedure of Preparation 125(c), except substituting (*E*)-3-(6-amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester for (*E*)-3-(6-amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester, the title compound (1.68 g, quantitative) was prepared as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.9 (br s, 1H), 8.66–8.38 (m, 4H), 7.56 (d, *J* = 15.9 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 4.46 (s, 2H), 3.57–3.50 (m, 2H), 3.19–3.01 (m, 2H), 1.91–1.88 (m, 4H).

Preparation 127Preparation of (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]acrylic acid hydrochloride

a) 5-Bromo-3-(4-methyl-piperazin-1-ylmethyl)pyridin-2-ylamine

5 According to the procedure of Preparation 125(a), except substituting 1-methylpiperazine for piperidine, the title compound (2.32 g, 30%) was prepared as a light, yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 8.03 (d, $J = 2.3$ Hz, 1H), 7.32 (d, $J = 2.3$ Hz, 1H), 5.63 (s, 2H), 3.42 (s, 2H), 2.46–2.36 (m, 8H), 2.30 (s, 3H).

10 b) (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]acrylic acid *tert*-butyl ester

According to the procedure of Preparation 125(b), except substituting 5-bromo-3-(4-methyl-piperazin-1-ylmethyl)pyridin-2-ylamine for 5-bromo-3-piperidin-1-ylmethyl-pyridin-2-ylamine, the title compound (1.18 g, 45%) was prepared as a yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 8.09 (d, $J = 2.2$ Hz, 1H), 7.49–7.44 (m, 2H), 6.18 (d, $J = 15.9$ Hz, 1H), 5.95 (br s, 2H), 3.47 (s, 2H), 2.38–2.59 (m, 7H), 2.96 (s, 4H), 1.52 (s, 9H).

15 c) (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]acrylic acid hydrochloride

According to the procedure of Preparation 125(c), except substituting (*E*)-3-[6-amino-5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]acrylic acid *tert*-butyl ester (1.18 g, 3.55 mmol) for (*E*)-3-(6-amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester, the title compound (1.72 g, quantitative) was prepared as an off-white solid: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.98 (br s, 1H), 8.61–8.34 (m, 4H), 7.53 (d, $J = 16.0$ Hz, 1H), 6.53 (d, $J = 15.9$ Hz, 1H), 3.81 (br s, 2H), 3.56 (s, 3H), 3.45–3.37 (m, 2H), 3.20–3.08 (m, 2H), 2.76 (s, 4H); MS (ESI) m/e 277 ($\text{M} + \text{H}$) $^+$.

25 Preparation 128

Preparation of (*E*)-3-[6-Amino-5-(4-benzyl-piperidin-1-ylmethyl)pyridin-3-yl]acrylic acid hydrochloride

a) 3-(4-Benzyl-piperidin-1-ylmethyl)-5-bromo-pyridin-2-ylamine

30 According to the procedure of Preparation 125(a), except substituting 4-benzylpiperidine (5.6 mL, 31.7 mmol) for piperidine and adding K_2CO_3 (19.9 g, 144 mmol) as base, the title compound (9.81 g, 95%) was prepared as a light, yellow solid: MS (ESI) m/e 36 ($\text{M} + \text{H}$) $^+$.

b) (*E*)-3-[6-Amino-5-(4-benzyl-piperidin-1-ylmethyl)pyridin-3-yl]acrylic acid *tert*-butyl ester

According to the procedure of Preparation 125(b), except substituting 3-(4-Benzyl-piperidin-1-ylmethyl)-5-bromo-pyridin-2-ylamine for 5-bromo-3-piperidin-1-ylmethyl-pyridin-2-ylamine, the title compound (4.48 g, 80%) was prepared as a yellow solid: MS (ESI) *m/e* 408 (*M* + *H*)⁺.

c) (*E*)-3-[6-Amino-5-(4-benzyl-piperidin-1-ylmethyl)pyridin-3-yl]acrylic acid hydrochloride

According to the procedure of Preparation 125(c), except substituting (*E*)-3-[6-amino-5-(4-benzyl-piperidin-1-ylmethyl)pyridin-3-yl]acrylic acid *tert*-butyl ester for 3-(6-amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester, the title compound (5.24 g, quantitative) was prepared as an off-white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.56 (br s, 1H), 8.61–8.37 (m, 3H), 7.51 (d, *J* = 15.9, 1H), 7.32–7.17 (m, 6H), 6.50–6.42 (m, 1H), 4.35 (br s, 2H), 3.45–3.37 (m, 2H), 3.11–2.92 (m, 2H), 1.75–1.51 (m, 6H); MS (ESI) *m/e* 352 (*M* + *H*)⁺.

Preparation 129

Preparation of (*E*)-3-(2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid

a) 2-Amino-5-bromo-nicotinic acid hydrobromide

Bromine (7.5 mL, 146 mmol) was added dropwise over 10 min to a suspension of 2-amino-nicotinic acid (20.0 g, 145 mmol) in glacial acetic acid (250 mL) cooled in an ice bath. After the bromine addition was complete, the mixture was stirred at ambient temperature for 2 d. The resulting light yellow solid was isolated by filtration, washed with Et₂O, and dried under high vacuum (40 °C) for several hours to give the title compound (40.0 g, 93%): ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 2.5 Hz, 1H), 8.20 (d, *J* = 2.5 Hz, 1H), 8.02 (bs, 3H); ESI MS *m/e* 217 (*M* + *H*)⁺.

b) 2-Amino-5-bromo-nicotinamide

To an ice-cold suspension of 2-amino-5-bromo-nicotinic acid hydrobromide (5.11 g, 17.1 mmol) and ammonium chloride (9.15 g, 171 mmol) in dimethoxyethane (170 mL) was added Et₃N (4.8 mL, 34.2 mmol). After 10 min, diethylphosphoryl cyanide was added dropwise and the cold bath removed. After 4 h, the solution was filtered and the filtrate concentrated. The resulting residue was partitioned between EtOAc and water. The organic layer was washed with satd NaHCO₃ (2 x) and satd NaCl, dried (Na₂SO₄) and concentrated under reduced pressure. The yellow solid was dissolved in EtOAc and then hexanes were

added until precipitation occurred. The solid was collected by filtration and then triturated with EtOAc to give the title compound (1.62 g, 44%) as a yellow solid: ^1H NMR (300 MHz, DMSO- d_6) δ 8.13 (s, 2H), 8.04 (bs, 1H), 7.46 (bs, 1H), 7.37 (bs, 2H).

c) 6-Bromo-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione

5 Oxalyl chloride (100 mL, 1.16 mmol) was added dropwise to a suspension of 2-amino-5-bromo-nicotinamide (500 mg, 2.31 mmol) in toluene (5 mL) and the resulting mixture was heated to reflux for 4 h. The reaction mixture was cooled and the mustard-colored solid which had formed was collected by filtration. The solid was washed with a small amount of water, MeOH, and then dried under high vacuum (40 °C) overnight to give
10 the title compound (435 mg, 77%): ^1H NMR (300 MHz, DMSO- d_6) δ 11.86 (s, 1H), 11.60 (s, 1H), 8.72 (d, $J = 2.5$ Hz, 1H), 8.35 (d, $J = 2.5$ Hz, 1H); ^{13}C NMR (126 MHz, DMSO- d_6) δ 161.4, 154.8, 151.2, 150.17, 137.8, 112.6, 111.6.

d) (*E*)-3-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid *tert*-butyl ester

15 A suspension of 6-bromo-1*H*-pyrido[2,3-*d*]pyrimidine-2,4-dione (430 mg, 1.59 mmol) in propionitrile (8 mL) and DMF (2 mL) was treated with *tert*-butyl acrylate (0.93 mL, 6.4 mmol), (*i*-Pr) $_2$ EtN (0.6 mL, 3.3 mmol) and P(*o*-tol) $_3$ (100 mg, 0.32 mmol). The solution was deoxygenated with Ar for 20 min. Pd(OAc) $_2$ (36 mg, 0.16 mmol) was added and the mixture was deoxygenated with a stream of Ar for 10 min. The mixture was heated
20 to reflux for 17 h, then allowed to cool. The resulting precipitate was isolated by filtration to give the title compound (384 mg, 83%) as a gray solid: ^1H NMR (300 MHz, DMSO- d_6) δ 11.88 (s, 1H), 11.54 (s, 1H), 8.96 (d, $J = 2.2$ Hz, 1H), 8.53 (d, $J = 2.2$ Hz, 1H), 7.65 (d, $J = 16.1$ Hz, 1H), 6.72 (d, $J = 16.1$ Hz, 1H), 1.49 (s, 9H); ESI MS m/e 290 ($\text{M} + \text{H}$) $^+$.

e) (*E*)-3-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid

25 To a suspension of (*E*)-3-(2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid *tert*-butyl ester (379 mg, 1.19 mmol) in CH $_2$ Cl $_2$ (10 mL) was added trifluoroacetic acid (2 mL). After 6 h, the solvent was concentrated, the resulting solid was treated with anhydrous HCl (10 mL of a 4 M solution in dioxane, 40 mmol) and the mixture was sonicated for 10 min. The mixture was diluted with Et $_2$ O and the solution was filtered.
30 The olive solid was dried under high vacuum at 45 °C overnight to give the title compound (323 mg, 91%) as the TFA salt: ^1H NMR (300 MHz, DMSO- d_6) δ 11.89 (s, 1H), 11.56 (s, 1H), 8.94 (d, $J = 1.8$ Hz, 1H), 8.53 (d, $J = 1.8$ Hz, 1H), 7.69 (d, $J = 16.1$ Hz, 1H), 6.72 (d, $J = 16.1$ Hz, 1H), 4.40 (bs, 1H); ESI MS m/e 234 (C $_{10}$ H $_7$ N $_3$ O $_4$ + H) $^+$.

Preparation 130Preparation of (E)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-d]-pyrimidin-6-yl]acrylic acid hydrochloride

a) 2-Amino-5-bromo-N-(2-dimethylamino-ethyl)nicotinamide

5 To a suspension of 2-amino-5-bromo-nicotinic acid hydrobromide (4.00 g, 13.4 mmol) in CH₂Cl₂ (150 mL) was added Et₃N (2.79 mL, 20.1 mmol), EDC (2.70 g, 14.1 mmol), and HOBt (1.91 g, 14.1 mmol) at 0 °C, and the mixture was stirred for 10 min. *N,N*-dimethylethylenediamine was then added, and the mixture was allowed to stir overnight at room temperature. The organic solution was washed with 2 N NaOH (2 x 20 mL), H₂O (2
10 x 20 mL) and brine, dried over Na₂SO₄ and filtered. The solvent was concentrated to give the title compound (2.70 g, 70%) as a yellow solid: MS (ESI) *m/e* 287 (M + H)⁺.

b) 5-Bromo-3-[(2-dimethylamino-ethylamino)methyl]pyridin-2-ylamine

2-Amino-5-bromo-N-(2-dimethylamino-ethyl)nicotinamide (2.15 g, 7.48 mmol) was added to a BH₃ solution (37.5 mL of a 1 M solution in THF, 37.5 mmol), and the mixture
15 was heated to reflux for 6 h. After cooling, the solvent was removed in vacuo. The residue was dissolved in MeOH (20 mL). Concentrated HCl (3 mL) and H₂O (3 mL) were added and the mixture was heated to reflux for 2 h. The solvent was then concentrated and the aqueous residue was basified to pH 12 with aqueous NaOH (6 N). The resulting aqueous suspension was extracted with CH₂Cl₂ (3 x 60 mL). The combined organics were washed
20 with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound (0.50 g, 25%) as a colorless oil: MS (ESI) *m/e* 273 (M + H)⁺.

c) 6-Bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

A solution of 5-bromo-3-[(2-dimethylamino-ethyl)methyl]pyridin-2-ylamine (490 mg, 1.79 mmol) and 1,1'-carbonyldiimidazole (349 mg, 2.15 mmol) in 1,4-dioxane (15 mL)
25 was heated to 80 °C for 14 h. TLC analysis indicated remaining starting material. After cooling, additional 1,1'-carbonyldiimidazole (349 mg, 2.15 mmol) and 1,4-dioxane (10 mL) were added, and the solution was heated to reflux overnight. The solvent was removed in vacuo. The residue was dissolved in CH₂Cl₂ (80 mL). The solution was washed with satd NaHCO₃, water and brine, dried over Na₂SO₄ and concentrated. Purification by
30 column chromatography (silica gel, CH₂Cl₂/MeOH/Et₃N, 92:7:1) gave the title compound (270 mg, 50%) as a tan solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.83 (s, 1H), 8.16 (d, *J* = 2.1 Hz, 1H), 7.76 (s, 1H), 4.48 (s, 2H), 3.37 (t, *J* = 6.5 Hz, 2H), 2.40 (t, *J* = 6.5 Hz, 2H), 2.16 (s, 6H).

d) (*E*)-3-[3-(2-Dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester

To a solution of 6-bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one (240 mg, 0.802 mmol) in propionitrile (16 mL) and DMF (4 mL) was added *tert*-butyl acrylate (0.46 mL, 3.2 mmol) and (*i*-Pr)₂EtN (0.28 mL, 1.6 mmol), Pd(OAc)₂ (18 mg, 0.080 mmol) and P(*o*-tol)₃ (49 mg, 0.16 mmol). The mixture was degassed with Ar for 15 min. The mixture was heated to reflux overnight, and then allowed to cool. The dark solution was filtered through a pad of Celite. The filtrate was concentrated. Purification by column chromatography (silica gel, CH₂Cl₂/MeOH/Et₃N, 94/5.5/0.5) gave the title compound (150 mg, 54%) as a pale-yellow solid: MS (ESI) *m/e* 347 (M + H)⁺.

e) (*E*)-3-[3-(2-Dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid hydrochloride

A solution of (*E*)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester (145 mg, 0.419 mmol) in CH₂Cl₂ (4 mL) was treated with TFA (2 mL). After stirring at room temperature for 30 min, the clear tan solution was concentrated in vacuo. The resulting oil was treated with anhydrous HCl (4.0 mL of 4 M solution in dioxane, 16 mmol) and stirred until the oil was converted to a solid. The solid was isolated by filtration, washed with Et₂O and dried under vacuum over night to give the title compound (155 mg, quantitative) as a pale yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.18 (s, 1H), 9.70 (br s, 1H), 8.36 (d, *J* = 1.4 Hz, 1H), 7.92 (s, 1H), 7.55 (d, *J* = 16.0 Hz, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 4.53 (s, 2H), 4.50 (br s, 2H), 3.71 (t, *J* = 5.6 Hz, 2H), 3.31 (t, *J* = 5.6 Hz, 2H), 2.84 (s, 3H), 2.82 (s, 3H).

Preparation 131

25 Preparation of (*E*)-3-[3-(2-Morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid hydrochloride

a) 2-Amino-5-bromo-*N*-(2-morpholin-4-yl-ethyl)nicotinamide

According to the procedure of Preparation 130(a), except substituting 4-(2-aminoethyl)morpholine for the *N,N*-dimethylethylenediamine, the title compound (18 g, 82%) was prepared as a pale yellow solid: MS (ESI) *m/e* 329 (M + H)⁺.

b) 5-Bromo-3-[(2-morpholin-4-yl-ethylamino)methyl]pyridin-2-ylamine

According to the procedure of Preparation 130(b), except substituting 2-amino-5-bromo-*N*-(2-morpholin-4-yl-ethyl)nicotinamide for 2-amino-5-bromo-*N*-(2-dimethylamino-

ethyl)nicotinamide, the title compound (5.0 g, 35%) was prepared as a colorless oil: MS (ESI) m/e 315 ($M + H$)⁺.

c) 6-Bromo-3-(2-morpholin-4-yl-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

According to the procedure of Preparation 130(c), except substituting 5-bromo-3-
5 [(2-morpholin-4-yl-ethylamino)methyl]pyridin-2-ylamine for 5-bromo-3-[(2-dimethylamino-ethyl)methyl]pyridin-2-ylamine, the title compound (1.1 g, 20%) was prepared as pale yellow solid: MS (ESI) m/e 341 ($M + H$)⁺.

d) (*E*)-3-[3-(2-Morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester

10 According to the procedure of Preparation 130(d), except substituting 6-bromo-3-(2-morpholin-4-yl-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one for 6-bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one, the title compound (0.67 g, 54%) was prepared as a white solid: MS (ES) m/e 389 ($M + H$)⁺.

e) (*E*)-3-[3-(2-Morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid hydrochloride
15

According to the procedure of Preparation 130(e), except substituting (*E*)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester for the (*E*)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester, the title compound (0.71 g,
20 quantitative) was prepared as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.64 (br s, 1H), 10.17 (br s, 1H), 8.36 (s, 1H), 7.93 (s, 1H), 7.54 (d, $J = 15.9$ Hz, 1H), 6.49 (d, $J = 16.0$ Hz, 1H), 5.95 (br s, 2H), 4.56 (s, 2H), 3.98–3.94 (m, 2H), 3.79–3.72 (m, 4H), 3.56–3.53 (m, 2H), 3.37–3.35 (m, 2H), 3.15–3.05 (m, 2H); MS (ESI) m/e 333 ($M + H$)⁺.

Preparation 132

25 Preparation of (*E*)-3-[3-(3-Morpholin-4-yl-propyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid hydrochloride

a) 2-Amino-5-bromo-pyridine-3-carbaldehyde hydrobromide

Bromine (1.1 mL, 20 mmol) in HOAc (20 mL) was added dropwise to a solution of 2-amino-pyridine-3-carbaldehyde (2.5 g, 20 mmol) in HOAc (50 mL) while stirring. After
30 the addition, the mixture was allowed to stir for 2 h at room temperature. The precipitate was collected by filtration and washed with diethyl ether to afford the title compound (4.4 g, 77%) as a pale yellow solid: MS (ESI) m/e 201 ($M + H$)⁺.

b) 5-Bromo-3-[(3-morpholin-4-yl-propylamino)methyl]pyridin-2-ylamine

To a solution of 2-amino-5-bromo-pyridine-3-carbaldehyde hydrobromide (4.30 g, 15.3 mmol) in MeOH (100 mL) was added triethylamine (4.3 mL, 31 mmol) and the mixture was stirred at room temperature for 10 min. The resulting suspension was treated with 4-(3-aminopropyl)morpholine (2.5 mL, 17 mmol) and the mixture was stirred for 7 h.

- 5 TLC analysis indicated remaining starting material. Additional 4-(3-aminopropyl)morpholine (1.0 mL, 6.8 mmol) was added, and the mixture was allowed to stir overnight at room temperature. The mixture was cooled and then NaBH₄ (0.87 g, 23.0 mmol) was added in two portions. The mixture was stirred at room temperature for 4h. The solvent was removed in vacuo. Purification by column chromatography (silica gel, CH₂Cl₂/MeOH/Et₃N, 97/2.5/0.5 to 85/14.5/0.5) gave the title compound (2.70 g, 54%) as a brown oil: MS (ESI) *m/e* 329 (M + H)⁺.

c) 6-Bromo-3-(3-morpholin-4-yl-propyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

- According to the procedure of Preparation 130(c), except substituting 5-bromo-3-[(3-morpholin-4-yl-propylamino)methyl]pyridin-2-ylamine for 5-bromo-3-[(2-dimethylamino-ethyl)methyl]pyridin-2-ylamine, the title compound (2.00 g, 69%) was prepared as pale yellow solid: MS (ESI) *m/e* 355 (M + H)⁺.

d) (*E*)-3-[3-(2-Morpholin-4-yl-propyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester

- According to the procedure of Preparation 130(d), except substituting 6-bromo-3-(3-morpholin-4-yl-propyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one for 6-bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one, the title compound (1.5 g, 66%) was prepared as a pale yellow solid: MS (ESI) *m/e* 403 (M + H)⁺.

e) (*E*)-3-[3-(3-Morpholin-4-yl-propyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid hydrochloride

- 25 According to the procedure of Preparation 130(e), except substituting (*E*)-3-[3-(2-morpholin-4-yl-propyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester for (*E*)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester, the title compound (1.5 g, 99%) was prepared as a yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.08 (s, 1H), 8.36 (d, *J* = 1.5 Hz, 1H), 7.96 (s, 1H), 7.59–7.49 (m, 1H), 6.53–6.45 (m, 1H), 4.55–4.48 (m, 2H), 4.00–3.75 (m, 4H), 3.48–3.36 (m, 4H), 3.20–2.95 (m, 4H), 2.10–1.96 (m, 2H); MS (ESI) *m/e* 347 (M + H)⁺.

Preparation 133

Preparation of (*E*)-3-(3-Ethoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid hydrochloride

a) (6-Bromo-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)acetic acid ethyl ester

According to the procedure of Preparation 130(c), except substituting [(2-amino-5-bromo-pyridin-3-ylmethyl)amino]acetic acid ethyl ester for 5-bromo-3-[(2-dimethylamino-ethyl)methyl]pyridin-2-ylamine, the title compound (6.70 g, 67%) was prepared as a white solid: MS (ESI) *m/e* 314 (*M* + *H*)⁺.

b) (*E*)-3-(3-Ethoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid *tert*-butyl ester

According to the procedure of Preparation 130(d), except substituting (6-bromo-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)acetic acid ethyl ester for 6-bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one, the title compound (2.10 g, 76%) was prepared as a white solid: MS (ESI) *m/e* 362 (*M* + *H*)⁺.

c) (*E*)-3-(3-Ethoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid hydrochloride

According to the procedure of Preparation 130(e), except substituting (*E*)-3-(3-ethoxycarbonylmethyl-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid *tert*-butyl ester for the (*E*)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester, the title compound (1.80 g, 96%) was prepared as a white solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.90–9.51 (m, 2H), 8.37 (s, 1H), 7.95 (s, 1H), 7.57–7.51 (m, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 4.53 (s, 2H), 4.18–4.11 (m, 4H), 1.21 (t, *J* = 7.0 Hz, 3H); MS (ESI) *m/e* 306 (*M* + *H*)⁺.

Preparation 134

Preparation of (*E*)-3-[3-(2-Ethoxycarbonyl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid hydrochloride

a) 3-[(2-Amino-5-bromo-pyridin-3-ylmethyl)amino]propionic acid ethyl ester

A mixture of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (9.41 g, 27.1 mmol) and β-alanine ethyl ester hydrochloride (5.00 g, 32.5 mmol) in DMF (75 mL) was treated with *N,N*-diisopropylethylamine (16.5 mL, 94.9 mmol). After stirring at room temperature for 4 h, the cloudy mixture was diluted with CH₂Cl₂ (100 mL) and H₂O. The aqueous layer was extracted with CH₂Cl₂ (2 x 150 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the solvent removed in vacuo. Purification by column chromatography (silica gel, CH₂Cl₂/MeOH/Et₃N, 95/4.5/0.5 to

80/19.5/0.5) gave the title compound (1.90 g, 23%) as a tan oil: MS (ESI) m/e 302 ($M + H$)⁺.

b) 3-(6-Bromo-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)propionic acid ethyl ester

5 According to the procedure of Preparation 130(c), except substituting 3-[(2-amino-5-bromo-pyridin-3-ylmethyl)amino]propionic acid ethyl ester for 5-bromo-3-[(2-dimethylamino-ethyl)methyl]pyridin-2-ylamine, the title compound (1.7 g, 83%) was prepared as a white solid: MS (ESI) m/e 328 ($M + H$)⁺.

10 c) (*E*)-3-[3-(2-Ethoxycarbonyl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester

According to the procedure of Preparation 130(d), except substituting 3-(6-bromo-2-oxo-1,4-dihydro-2*H*-pyrido[2,3-*d*]pyrimidin-3-yl)propionic acid ethyl ester for the 6-bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one, the title compound (0.39 g, 21 %) was prepared as a white solid: MS (ESI) m/e 376 ($M + H$)⁺.

15 d) (*E*)-3-[3-(2-Ethoxycarbonyl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid

According to the procedure of Preparation 130(e), except substituting (*E*)-3-[3-(2-ethoxycarbonyl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester for the (*E*)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-
20 pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester, the title compound (0.16 g, 44 %) was prepared as a yellow solid: ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.30 (d, $J = 1.5$ Hz, 1H), 8.16 (s, 1H), 7.70–7.60 (m, 1H), 6.60–6.50 (m, 1H), 4.70 (s, 2H), 4.13 (q, $J = 7.0$ Hz, 2H), 3.74–3.68 (t, $J = 6.5$ Hz, 2H), 2.74–2.66 (t, $J = 6.5$ Hz, 2H), 1.25 (t, $J = 5.5$ Hz, 3H); MS (ESI) m/e 320 ($M + H$)⁺.

25 Preparation 135

Preparation of 6-Bromo-3-(2,2-dimethoxy-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

a) 5-Bromo-3-[(2,2-dimethoxy-ethylamino)methyl]pyridin-2-ylamine

According to the procedure of Preparation 132(b), except substituting
30 aminoacetaldehyde diethyl acetal for the 4-(3-aminopropyl)morpholine, the title compound (1.30 g, 45%) was prepared as a yellow solid: MS (ESI) m/e 290 ($M + H$)⁺.

b) 6-Bromo-3-(2,2-dimethoxy-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one

According to the procedure of Preparation 130(c), except substituting 5-bromo-3-[(2,2-dimethoxy-ethylamino)methyl]pyridin-2-ylamine for 5-bromo-3-[(2-dimethylamino-ethyl)methyl]pyridin-2-ylamine, the title compound (6.40 g, 73%) was prepared as a white solid: MS (ESI) *m/e* 316 (*M* + *H*)⁺.

Preparation 136Preparation of (*E*)-3-{6-Amino-5-[(2-morpholin-4-yl-ethylamino)methyl]pyridin-3-yl}acrylic acid hydrochloride

a) (*E*)-3-[6-Amino-5-(2-morpholin-4-yl-ethylcarbamoyl)pyridin-3-yl]acrylic acid *tert*-butyl ester

According to the procedure of Preparation 130(d), except substituting 2-amino-5-bromo-*N*-(2-morpholin-4-yl-ethyl)nicotinamide for 6-bromo-3-(2-dimethylamino-ethyl)-3,4-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-2-one, the title compound (2.48 g, 99%) was prepared as a yellow solid: ¹H NMR (300 MHz, CDCl₃) δ 8.30 (d, *J* = 2.4 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 15.9 Hz, 1H), 7.02–6.83 (m, 1H), 6.65 (br s, 2H), 6.22 (d, *J* = 15.9, 1H), 3.77–3.69 (m, 4H), 3.56–3.50 (m, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 2.53 (t, *J* = 4.5 Hz, 4H), 1.53 (s, 9H); MS (ESI) *m/e* 377 (*M* + *H*)⁺.

b) (*E*)-3-[6-Amino-5-(2-morpholin-4-yl-ethylcarbamoyl)-pyridin-3-yl]acrylic acid hydrochloride

According to the procedure of Preparation 130(e), except substituting (*E*)-3-[6-amino-5-(2-morpholin-4-yl-ethylcarbamoyl)pyridin-3-yl]acrylic acid *tert*-butyl ester for (*E*)-3-[3-(2-dimethylamino-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl]acrylic acid *tert*-butyl ester, the title compound (2.34 g, 91%) was prepared as a white solid: MS (ESI) *m/e* 321 (*M* + *H*)⁺.

Preparation 137Preparation of (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride

a) 5-Bromo-3-morpholin-4-ylmethyl-pyridin-2-ylamine

According to the procedure of Preparation 125(a), except substituting morpholine for piperidine, the title compound (11.5 g, 97%) was prepared as yellow foam: ¹H NMR (300 MHz, CDCl₃) δ 8.04 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 2.3 Hz, 1H), 5.61 (s, 2H), 3.72–3.69 (m, 4H), 3.42 (s, 2H), 2.44–2.41 (m, 4H).

b) (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester

According to the procedure of Preparation 125(b), except substituting 5-bromo-3-morpholin-4-ylmethyl-pyridin-2-ylamine for 5-bromo-3-piperidin-1-ylmethyl-pyridin-2-ylamine, the title compound (11.3 g, 84%) was prepared as a yellow solid: ^1H NMR (300 MHz, CDCl_3) δ 8.11 (d, $J = 2.2$ Hz, 1H), 7.49–7.44 (m, 2H), 6.19 (d, $J = 15.9$ Hz, 1H),

5 5.89 (s, 2H), 3.72–3.69 (m, 4H), 3.47 (s, 2H), 2.45–2.42 (m, 4H), 1.53 (s, 9H).

c) (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride

According to the procedure of Preparation 125(c), except substituting (*E*)-3-(6-amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester for (*E*)-3-(6-amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid *tert*-butyl ester, the title compound

10 (12.9 g, quantitative) was prepared as an off-white solid: MS (ESI) m/z 264 $[\text{M} + \text{H}]^+$.

Preparation 138

Preparation of 7-Bromo-4-[3-(4-methyl-piperazin-1-yl)-propyl]-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one

a) [3-(4-Methyl-piperazin-1-yl)propylamino]acetic acid ethyl ester

15 A solution of 4-(3-aminopropyl)-1-methylpiperazine (3.1 mL, 20 mmol) in MeOH (50 mL) was cooled in an ice bath and treated with ethyl glyoxylate (~50% solution in toluene, 5.6 mL, 27 mmol) and AcOH (3 mL). After stirring for 15 min, NaBH_3CN (1.37 g, 21.8 mmol) was added and the mixture was allowed to stir for 7 h while slowly warming to room temperature. The mixture was diluted with saturated aqueous NaHCO_3 (150 mL)

20 and then extracted with EtOAc (3 x 100 mL) followed by CH_2Cl_2 (3 x 100 mL). The combined CH_2Cl_2 layers were dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to give the title compound (1.81 g, 38%) as a colorless oil: MS (ESI) m/e 244 ($\text{M} + \text{H}$) $^+$.

b) {(2-Amino-5-bromo-pyridin-3-ylmethyl)-[3-(4-methyl-piperazin-1-yl)propyl]amino}acetic acid ethyl ester

25

A solution of [3-(4-methyl-piperazin-1-yl)propylamino]acetic acid ethyl ester (1.80 g, 7.41 mmol) and triethylamine (2.3 mL, 16.4 mmol) in DMF (50 mL) was treated with 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (2.57 g, 7.41 mmol). After stirring at room temperature for 3 d, the mixture was diluted with H_2O (100 mL) and then

30 extracted with EtOAc (4 x 100 mL). The combined organic layers were dried over Na_2SO_4 , filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, $\text{CH}_2\text{Cl}_2/\text{MeOH}$, 97:3 to 90:10) gave the title compound (0.50 g, 16%) as a colorless oil: MS (ESI) m/e 428 ($\text{M} + \text{H}$) $^+$.

c) 7-Bromo-4-[3-(4-methyl-piperazin-1-yl)propyl]-1,3,4,5-tetrahydro-pyrido[2,3-
e][1,4]diazepin-2-one

A solution of {(2-amino-5-bromo-pyridin-3-ylmethyl)-[3-(4-methyl-piperazin-1-yl)propyl]amino}acetic acid ethyl ester (0.50 g, 1.17 mmol) in DMSO (10 mL) was treated
5 with NaH (60% dispersion in mineral oil, 47 mg, 1.17 mmol). After stirring at room temperature for 3 d, the mixture was diluted with H₂O (30 mL) and then extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 92:8 to 87:13) gave the title compound (0.23 g, 51%) as a white solid: MS
10 (ESI) *m/e* 382 (M + H)⁺.

Preparation 139

Preparation of 7-Bromo-3,3-dimethyl-1,3,4,5-tetrahydro-pyrido[2,3-e][1,4]diazepin-2-one

a) 2-[(2-Amino-5-bromo-pyridin-3-ylmethyl)amino]-2-methylpropionic acid methyl ester

A solution of 5-bromo-3-bromomethyl-pyridin-2-ylamine hydrobromide (11.0 g, 31.7 mmol) and 2-amino-2-methyl-propionic acid methyl ester (5.80 g, 49.5 mmol) in DMF
15 (220 mL) was treated with triethylamine (9.0 mL, 18.5 mmol). After stirring at room temperature for 3 d, the mixture was diluted with H₂O (400 mL) and then extracted with EtOAc (4 x 200 mL). The combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo.
20 Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1) gave the title compound (3.87 g, 40%) as a light yellow solid: MS (ESI) *m/e* 302 (M + H)⁺.

b) 7-Bromo-3,3-dimethyl-1,3,4,5-tetrahydro-pyrido[2,3-e][1,4]diazepin-2-one

A solution of 2-[(2-amino-5-bromo-pyridin-3-ylmethyl)amino]-2-methylpropionic acid methyl ester (2.63 g, 8.71 mmol) in DMSO (100 mL) was treated with NaH (60%
25 dispersion in mineral oil, 0.35 g, 8.7 mmol). After stirring at room temperature overnight, the mixture was diluted with H₂O (200 mL) and then extracted with EtOAc (5 x 150 mL). The combined organic layers were washed with H₂O (3 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 99:1 to 98:2) gave (0.79 g, 33%) as an
30 off-white solid: MS (ESI) *m/e* 270 (M + H)⁺.

The following examples illustrate methods for preparing compounds of the antibacterial compositions of the present invention from intermediate compounds such as those described in the foregoing Preparations.

Example 1Preparation of (E)-3-(2-aminopyrimidin-5-yl)-N-(2-methyl-1H-indol-3-ylmethyl)-N-methylacrylamide

a) N-Methyl-N-(2-methyl-1H-indol-3-ylmethyl)acrylamide

5 To a solution of 2-methyl-3-(methylaminomethyl)indole (1.5 g, 8.6 mmole) and triethylamine (1.7 g, 17.3 mmole) in CH₂Cl₂ at 5 °C under a nitrogen atmosphere was added acryloyl chloride (0.86 g, 9.48 mmole). After 1 hr the reaction solution was poured into H₂O (100 mL) and the layers were separated. The organic fraction was washed with H₂O (100 mL) followed by brine and then dried over Na₂SO₄. Concentration under

10 vacuum gave the title compound as an orange oil which solidified under high vacuum: MS (ES) *m/e* 457 (2M + H)⁺. This material was used without further purification.

b) (E)-3-(2-Aminopyrimidin-5-yl)-N-(2-methyl-1H-indol-3-ylmethyl)-N-methylacrylamide

A solution of N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)acrylamide (1.18 g, 6.5 mmole), 2-amino-5-bromopyrimidine (0.5 g, 2.9 mmole), Pd(OAc)₂ (0.11 g, 0.49 mmole),

15 tri-*ortho*-tolylphosphine (0.17 g, 0.55 mmole), and diisopropylethylamine (1.5 mL, 8.6 mmole) in propionitrile (100 mL) and DMF (10 mL) was heated at reflux overnight. The dark mixture was filtered through celite®, and the filtrate was concentrated. Flash chromatography on silica gel (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) gave the title compound (1.2 g, 65%): MS (ES) *m/e* 372 (M + H)⁺.

20 Example 2Preparation of (E)-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide

According to the procedure of Example 1 (b), except substituting 6-bromo-3-methyl-3,4-dihydro-1H-pyrido[2,3-*d*]pyrimidin-2-one (1.2 g, 5.0 mmole) for the 2-amino-

25 5-bromopyrimidine, the title compound (73 %) was prepared as a light yellow solid: MS (ES) *m/e* 390 (M + H)⁺.

Example 3Preparation of (E)-N-methyl-N-(1-methyl-1H-indol-3-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide

30 a) N-Methyl-N-(1-methyl-indol-3-ylmethyl)acrylamide

According to the procedure of Example 1 (a), except substituting 1-methyl-3-(methylaminomethyl)indole for the 2-methyl-3-(methylaminomethyl)indole, the title

compound (1.7 g, 99%) was prepared as an orange oil that solidified under vacuum: MS (ES) m/e 229 ($M + H$)⁺. This material was used without further purification.

b) (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl)acrylamide

- 5 According to the procedure of Preparation 1 (b), except substituting N-methyl-N-(1-methyl-indol-3-ylmethyl)acrylamide (1.7 g, 7.5 mmole) for N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide, the title compound (70 %) was prepared as a light yellow solid: MS (ES) m/e 390 ($M + H$)⁺.

Example 4

- 10 Preparation of (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(2-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)acrylamide

To a solution of (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt (0.50 g, 2.1 mmole), hydroxybenzotriazole monohydrate (0.31 g, 2.3 mmole), diisopropylethylamine (0.80 mL, 4.6 mmole), and 2-methyl-3-(methylaminomethyl)indole
15 (0.40 g, 2.3 mmole) in DMF (50 mL) at RT was added EDC (0.46, 2.3 mmole). After 12 hr the reaction solution was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) to give the title compound (0.66 g, 88 %) as a light yellow solid: MS (ES) m/e 361 ($M + H$)⁺.

Example 5

- 20 Preparation of (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide

According to the procedure of Example 4, except substituting (E)-3-(3*H*-imidazo[4,5-*b*]pyridin-6-yl) acrylate (0.14 g, 0.74 mmole), from Preparation 6, for the (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt, and substituting 1-
25 methyl-3-(methylaminomethyl)indole (0.14 g, 0.81 mmole) for the 2-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (0.23 g, 89 %) was prepared as a light yellow solid: MS (ES) m/e 346 ($M + H$)⁺.

Example 6

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

According to the procedure of Example 4, except substituting (E)-3-(3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-7-yl)acrylic acid (0.11 g, 0.53 mmole), from Preparation 7, for the (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt, and substituting

1-methyl-3-(methylaminomethyl) indole (0.10 g, 0.59 mmole) for the 2-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (0.16 g, 82 %) was prepared as a light yellow solid: MS (ES) *m/e* 363 (M + H)⁺.

Example 7

5 Preparation of (E)-3-[6-amino-5-[[N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)amino]carbonylethyl]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide

a) Ethyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl) acrylate

A solution of 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (5.0 g, 21.9 mmole),
10 from Preparation 4, ethyl acrylate (3.3 g, 32.9 mmole), Pd(OAc)₂ (1.1 g, 0.74 mmole), tri-*ortho*-tolylphosphine (1.3 g, 4.4 mmole), and diisopropylethylamine (11.4 mL, 65.7 mmole) in propionitrile (200 mL) and DMF (25 mL) was heated at reflux overnight. The dark mixture was filtered through celite®, and the filtrate was concentrated. Flash chromatography on silica gel (9:1 CHCl₃/CH₃OH containing 5% NH₄OH) gave the title
15 compound (3.0 g, 59 %) as a light yellow solid: MS (ES) *m/e* 233 (M + H)⁺.

b) (E)-3-[6-Amino-5-(2-carboxyethyl)pyridin-3-yl]acrylic acid hydrochloride salt

Ethyl (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl) acrylate (1.54 g, 6.6 mmole) was dissolved in acetic acid (25 mL) and concentrated hydrochloric acid (25 mL) and the solution was heated to 100 °C. After 6 hr the solution was concentrated and the
20 residue was dried under high vacuum. The resulting solid was triturated with diethyl ether and filtered to give a 1.46 g of a mixture of (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl) acrylic acid hydrochloride salt (82%) and the title compound (18%), both as white solids: MS (ES) *m/e* 218 (M + H)⁺ (major) and MS (ES) *m/e* 236 (M + H)⁺ (minor). This mixture was used without further purification.

25 c) (E)-3-[6-Amino-5-[[N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)amino]carbonylethyl]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide

According to the procedure of Example 4, except substituting a mixture (1.46 g) of
(E)-3-[6-amino-5-(2-carboxyethyl)pyridin-3-yl]acrylic acid hydrochloride salt and (E)-3-(7-
30 oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl) acrylic acid hydrochloride salt for the (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt, the title compound (0.47 g) was prepared as a light yellow solid: MS (ES) *m/e* 549 (M + H)⁺. (E)-N-Methyl-N-(2-

methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide (1.56 g) was also obtained as a light yellow solid: MS (ES) *m/e* 375 (M + H)⁺.

Example 8

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1-ethyl-1*H*-indol-3-ylmethyl)-N-

5 methylacrylamide

EDC (0.56 g, 2.93 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.48 g, 2.93 mmole), 1-ethyl-3-(methylaminomethyl)-1*H*-indole (0.50 g, 2.66 mmole), HOBt · H₂O (0.40 g, 2.93 mmole) and diisopropylethylamine (0.93 mL, 5.32 mmole) in DMF (30 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (10% MeOH/CHCl₃) gave title compound (0.46 g, 52%) as a yellow solid after drying in vacuo: MS (ES) *m/e* 335 (M + H)⁺.

Example 9

15 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1-isopropyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

EDC (0.51 g, 2.64 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.43 g, 2.64 mmole), 1-isopropyl-3-(methylaminomethyl)indole (0.49 g, 2.40 mmole), HOBt · H₂O (0.36 g, 2.64 mmole) and diisopropylethylamine (0.84 mL 4.80 mmole) in DMF (40 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (10% MeOH/CHCl₃) gave the title compound (0.49 g, 58%) as a yellow solid after drying in vacuo: MS (ES) *m/e* 349 (M + H)⁺.

25 Example 10

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1*H*-indol-3-ylmethyl)-N-methylacrylamide

EDC (1.03 g, 5.40 mmole) was added to a solution of (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.89 g, 5.40 mmole), 1-acetyl-3-(methylaminomethyl)indole (1.00 g, 4.95 mmole), HOBt · H₂O (0.73 g, 5.40 mmole) and diisopropylethylamine (1.72 mL, 9.90 mmole) in DMF (50 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash

chromatography on silica gel (5% MeOH/CHCl₃) gave the title compound (0.90 g, 52%) as a light yellow solid after drying in vacuo: MS (ES) *m/e* 307 (M + H)⁺.

Example 11

Preparation of (E)-N-(1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

A solution of 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (0.64 g, 2.80 mmole), N-(1*H*-indol-3-ylmethyl)-N-methylacrylamide (0.60 g, 2.80 mmole), Pd(OAc)₂ (0.06 g, 0.28 mmole), tri-*ortho*-tolylphosphine (0.17 g, 0.56 mmole) and diisopropylethylamine (0.73 mL, 4.2 mmole) in propionitrile (50 mL) was deoxygenated, then was heated to reflux under N₂ overnight. The dark mixture was filtered through a pad of celite®, and the filter pad was rinsed with acetonitrile (250 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (10% MeOH/CHCl₃). The title compound (0.37 g, 37%) was obtained as a light yellow solid after drying in vacuo: MS (ES) *m/e* 361 (M + H)⁺.

Example 12

Preparation of (E)-N-(1-benzyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

A solution of 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (1.05 g, 4.60 mmole), N-(1-benzyl-1*H*-indol-3-ylmethyl)-N-methyl-acrylamide (1.40 g, 4.60 mmole), Pd(OAc)₂ (0.10 g, 0.46 mmole), tri-*ortho*-tolylphosphine (0.28 g, 0.92 mmole) and diisopropylethylamine (1.20 mL 6.90 mmole) in propionitrile (75 mL) was deoxygenated, then was and heated to reflux under a N₂ overnight. The dark mixture was filtered through a pad of celite®, and the filter pad was rinsed with acetonitrile (300 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (5% MeOH/CHCl₃). The title compound (0.70 g, 35%) was obtained as a light yellow solid after drying in vacuo: MS (ES) *m/e* 451 (M + H)⁺.

Example 13

Preparation of (E)-N-[1-(2-dimethylaminoethyl)-1*H*-indol-3-ylmethyl]-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

A solution of 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (0.61 g, 2.70 mmole), N-[1-(2-dimethylaminoethyl)-1*H*-indol-3-ylmethyl]-N-methyl-acrylamide (1.00 g, 3.50 mmole), Pd(OAc)₂ (0.08 g, 0.35 mmole), tri-*ortho*-tolylphosphine (0.21 g, 0.70

mmole), and diisopropylethylamine (0.91 mL, 5.25 mmole) in propionitrile (70 mL) was deoxygenated, then was and heated to reflux under a N₂ overnight. The dark mixture was filtered through a pad of celite®, and the filter pad was rinsed with acetonitrile (250 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (10% MeOH/CHCl₃ containing 5% NH₄OH in the MeOH).
 5 The title compound (0.20 g, 13%) was obtained as a light yellow solid after drying in vacuo: MS (ES) *m/e* 432 (M + H)⁺.

Example 14

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

A solution of 3-bromo-5,6,7,9-tetrahydro-pyrido[2,3-*b*]azepin-8-one (0.60 g, 2.50 mmole), N-(2-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide (0.85 g, 3.75 mmole), Pd(OAc)₂ (0.06 g, 0.25 mmole), tri-*ortho*-tolylphosphine (0.15 g, 0.50 mmole) and diisopropylethylamine (0.87 mL, 5.00 mmole) in propionitrile (50 mL) was deoxygenated,
 15 then was and heated to reflux under a N₂ overnight. The dark mixture was filtered through a pad of celite®, and the filter pad was rinsed with acetonitrile (200 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (10% MeOH/CHCl₃). The title compound (0.35 g, 35%) was obtained as a light tan solid after drying in vacuo: MS (ES) *m/e* 246 (M + H)⁺.

Example 15

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-[6-(pyridin-2-ylamino)pyridin-3-yl]acrylamide

a) N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

To a stirred solution of 1-methyl-3-(methylaminomethyl)-1*H*-indole (1.0 g, 5.7 mmole) and Et₃N (0.8 mL, 5.7 mmole) in CH₂Cl₂ (50 mL) at 0 °C was added acryloyl chloride (0.47 mL, 5.8 mmole) in one portion. After stirring for 1 h the reaction was washed with cold H₂O and brine, then was dried (MgSO₄) and concentrated under vacuum. This material was used without further purification.

b) (E)-N-Methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-[6-(pyridin-2-ylamino)pyridin-3-yl]acrylamide

To a solution of N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide, from Example 1 (a), in propionitrile (50 mL) was added 5-bromo-2,2'-dipyridylamine (1.2 g, 4.8

mmole), DIEA (1.8 mL, 10.3 mmole), Pd(OAc)₂ (112 mg, 0.5 mmole), and P(o-tol)₃ (304 mg, 1 mmole). The reaction was purged with Ar then stirred at reflux for 16 h. After cooling to room temperature the reaction was concentrated to dryness under vacuum. Flash chromatography on silica gel (3% (5% NH₄OH/MeOH)/CHCl₃), trituration with 1:1

- 5 Et₂O/petroleum ether, filtration, and drying under vacuum gave the title compound (1.24 g, 65%) as an off-white solid: MS (ES) *m/e* 398.2 (M + H)⁺.

Example 16

Preparation of (E)-N-methyl-N-(2-methylbenzo[*b*]thiophen-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

- 10 a) N-(Benzo[*b*]thiophen-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 15 (a), except substituting 2-methyl-3-(methylaminomethyl)benzo[*b*]thiophene (1.0 g, 5.2 mmole) for 1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound was prepared. This was used without further purification.

- 15 b) (E)-N-Methyl-N-(2-methylbenzo[*b*]thiophen-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 15 (b), except substituting 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (1.3 g, 5.7 mmole) for the 5-bromo-2,2'-dipyridylamine, the title compound (0.849 g, 42%) was prepared as a white solid: MS (ES)

- 20 *m/e* 392.2 (M + H)⁺.

Example 17

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-[N-(methylaminocarbonylmethyl)amino]pyridin-3-yl]acrylamide

- a) N-(1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

- 25 According to the procedure of Example 15 (a), except substituting 1-methyl-2-(methylaminomethyl)-1*H*-indole (1.2 g, 6.9 mmole) for the 1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound was prepared. This was used without further purification.

- b) (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-[6-[N-(methylaminocarbonylmethyl)amino]pyridin-3-yl]acrylamide
- 30

According to the procedure of Example 15 (b), except substituting 5-bromo-2-(methylaminocarbonylmethyl)aminopyridine (1.5 g, 6.2 mmole) for the 5-bromo-2,2'-

dipyridylamine, the title compound (1.7 g, 72%) was prepared as a white solid: MS (ES) m/e 392.2 (M + H)⁺.

Example 18

Preparation of (E)-3-(6-amino-5-(methoxycarbonyl)pyridin-3-yl)-N-(1-methyl-1H-indol-3-ylmethyl)-N-methylacrylamide

a) N-(1-methyl-1H-indol-2-ylmethyl)-N-methylacrylamide

According to the procedure of Example 15 (a), except substituting 1-methyl-2-(methylaminomethyl)-1H-indole (1.2 g, 6.9 mmole) for the 1-methyl-3-(methylaminomethyl)-1H-indole, the title compound was prepared. This was used without further purification.

b) (E)-3-(6-Amino-5-(methoxycarbonyl)pyridin-3-yl)-N-(1-methyl-1H-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 15 (b), except substituting methyl 2-amino-5-bromonicotinate (1.4 g, 6.1 mmole) for the 5-bromo-2,2'-dipyridylamine, the title compound (1.78 g, 77%) was prepared as a white solid: MS (ES) m/e 379.2 (M + H)⁺.

Example 19

Preparation of (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)acrylamide

To a stirred solution of (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]acrylic acid hydrochloride salt (2.0 g, 7.3 mmole) in 1:1 DMF/CH₂Cl₂ (100 mL) was added 2-methyl-3-(methylaminomethyl)indole (1.3 g, 7.5 mmole), Et₃N (2.1 mL, 15 mmole), and HOBt · H₂O (1.0 g, 7.4 mmole), followed by EDC (1.4 g, 7.3 mmole). After stirring at room temperature for 18 h the reaction was concentrated to dryness. The residue was taken up in EtOAc, and the solution was washed with H₂O then brine, dried (Na₂SO₄), and concentrated under vacuum. The remaining residue was purified by flash chromatography on silica gel (4% MeOH/CHCl₃) to give the title compound (2.08 g, 73%) as an off-white solid: MS (ES) m/e 393.2 (M + H)⁺.

Example 20

Preparation of (E)-3-[6-[N-(carboxymethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)acrylamide

To a stirred solution of (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)acrylamide (0.5 g, 1.3 mmole) in dioxane (30

mL) was added 1 N NaOH (2 mL, 2 mmole). After stirring for 18 h the reaction was neutralized with 1 N HCl (2 mL, 2 mmole) and concentrated to near dryness. The resulting suspension was diluted with H₂O and filtered. The solid was washed with H₂O and dried under vacuum to give the title compound (505 mg, 100%) as a off-white solid: MS (ES)

5 *m/e* 379.2 (M + H)⁺.

Example 21

Preparation of (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]acrylamide

To (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide (0.7 g, 1.8 mmole) was added a solution of 2.0 M methylamine in MeOH (50 mL). After stirring for 72 h the reaction was concentrated to dryness. The residue was triturated with Et₂O, filtered, and dried under vacuum to give the title compound (0.703 g, 100%) as an off-white solid: MS (ES) *m/e* 392.2 (M + H)⁺.

Example 22

15 Preparation of (E)-3-(2-aminopyrimidin-5-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)acrylamide

A solution of 2-amino-5-bromopyrimidine (0.27 g, 1.55 mmole), N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)acrylamide (0.5 g, 2.33 mmole), Pd(OAc)₂ (0.037 g, 0.163 mmole), P(*o*-tolyl)₃ (0.085 g, 0.28 mmole), and (i-Pr)₂NEt (0.42 mL, 2.33 mmole) in propionitrile (20 mL) was degassed then heated to reflux. After 18 hr the mixture was cooled to RT and concentrated. Flash chromatography on silica gel (10% MeOH/CH₂Cl₂) gave the title compound (0.100 g, 18%): MS (ES) *m/e* 363 (M + H)⁺.

Example 23

25 Preparation of (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 22, except substituting 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (0.352 g, 1.55 mmole) for the 2-amino-5-bromopyrimidine, the title compound (0.14 g, 16%) was prepared as a white powder: MS (ES) *m/e* 376 (M + H)⁺.

30 Example 24

Preparation of (E)-N-(2,3-dihydro-1*H*-3a-azacyclopenta[*a*]indene-8-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

EDC (0.192 g, 1.0 mmole) was added to a solution of (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt (0.254 g, 1.0 mmole), 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene (0.2 g, 1.0 mmole), HOBt · H₂O (0.135 g, 1.0 mmole), and Et₃N (0.15 mL, 1.1 mmole) in DMF (20 mL) at RT. The
5 reaction was stirred overnight, then was poured into H₂O (50 mL) and extracted with CH₂Cl₂ (2 x 30 mL). The combined extracts were washed with brine and dried (MgSO₄). Flash chromatography on silica gel (5% MeOH/CH₂Cl₂) gave the title compound (0.1 g, 25%) a yellow solid: MS (ES) *m/e* 401 (M + H)⁺.

Example 25

10 Preparation of (E)-N-(1-ethyl-5-fluoro-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting (1-ethyl-5-fluoro-3-(methylaminomethyl)-1*H*-indole (0.1 g, 0.49 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, the title compound (0.028 g, 15%)
15 was prepared as a white powder: MS (ES) *m/e* 407 (M + H)⁺.

Example 26

Preparation of (E)-N-(5-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 5-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.13 g, 0.67 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, the title compound (0.1 g, 37%) was
20 prepared as a slightly yellow crystalline solid: MS (ES) *m/e* 393 (M + H)⁺.

Example 27

Preparation of (E)-N-(5-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 6-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.12 g, 0.59 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, the title compound (0.1 g, 43%) was
25 prepared as a white crystalline solid: MS (ES) *m/e* 393 (M + H)⁺.

Example 28

Preparation of (E)-N-(7-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 7-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.18 g, 0.93 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, the title compound (0.1 g, 27%) was prepared as a white powder: MS (ES) *m/e* 393 (M + H)⁺.

5 Example 29

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(6-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 24, except substituting 6-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.11 g, 0.59 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, and substituting (E)-3-(6-amino-
10 pyridin-3-yl)acrylic acid (0.098 g, 0.59 mmole) for the (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt, the title compound (0.1 g, 27%) was prepared as a white powder: MS (ES) *m/e* 339 (M + H)⁺.

Example 30

15 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(4,6-dichloro-1-methyl-1*H*-indol-2-ylmethyl)-N-methylacrylamide

EDC (84.4 mg, 0.44 mmole) was added all at once to a solution of (E)-3-(6-amino-pyridin-3-yl)acrylic acid (65.7 mg, 0.40 mmole), 4,6-dichloro-1-methyl-2-(methylaminomethyl)-1*H*-indole (107.0 mg, 0.44 mmole), HOBT · H₂O (59.5 mg, 0.44
20 mmole), and Et₃N (0.14 mL, 1.0 mmole) in anhydrous DMF (4 mL) at RT. After 17 hr, the reaction was concentrated to dryness and the residue was re-concentrated from CHCl₃/xylenes (2 x). Flash chromatography on silica gel (7% MeOH in 1:1 EtOAc/CHCl₃) gave the R_f 0.44 component (10% MeOH in 1:1 EtOAc/CHCl₃) as a foam. This was solidified by re-concentration from MeOH/EtOAc/CHCl₃ several times. This
25 material was triturated with hot EtOAc/MeOH, and the mixture was cooled to 0 °C. The title compound was collected by suction filtration. The filtrate was concentrated and the residue was triturated with EtOAc to afford additional title compound. The combined desired solids were dried in high vacuum at 50-60 °C to afford the title compound (108.9 mg, 70%) as a light yellow solid: ¹H NMR (400 MHz, CDCl₃) 1.8:1 mixture of amide
30 rotamers; δ 8.08 - 8.20 (2 x s, 1 H), 7.70 - 7.90 (2 x d, 1 H), 7.57 - 7.70 (2 x s, 1 H), 7.46 (d, J = 15.2 Hz, 1 H), 7.18 (s, 1 H), 6.97 (d, J = 15.2 Hz, 1 H), 6.45 and 6.15 (2 x m, 4 H), 5.02 and 4.82 (2 x s, 2 H), 3.60 - 3.80 (2 x s, 3 H), 2.99 and 3.11 (2 x s, 3 H); MS (ES) *m/e* 239

and 391 (M + H)⁺.

Example 31

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,4-dimethyl-1*H*-indole-3-ylmethyl)-N-methylacrylamide

5 To a stirred solution of 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole (188.2 mg, 1 mmole) and (E)-3-(6-aminopyridin-3-yl)acrylic acid (164 mg, 1 mmole) in dry DMF (12 mL) containing dry Et₃N (4 mL) was added HOBt · H₂O (153 mg, 1 mmole) and EDC (191.8 mg, 1 mmole). The reaction was stirred overnight under argon at ambient temperature, then was concentrated in vacuo. The residue was partitioned between EtOAc and 5% NaHCO₃ solution, and the layers were separated. The organic layer was washed with brine, dried (MgSO₄), filtered, and concentrated. Flash chromatography on silica gel afforded the title compound (120 mg, 36%) as a white solid: MS (ES) *m/e* 335.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O · 0.25 H₂O: C, 70.88; H, 6.69; N, 16.53. Found: C, 71.11; H, 6.72; N, 16.36.

15 Example 32

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(4-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 4-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-indole, the title compound (100 mg, 29%) was obtained as a light yellow solid: MS (ES) *m/e* 351.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · 0.25 H₂O: C, 67.68; H, 6.39; N, 15.79. Found: C, 67.31; H, 6.21; N, 15.97.

Example 33

25 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(5-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 5-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (110 mg, 31%) was obtained as a light tan solid: MS (ES) *m/e* 351.2 (M + H)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · 0.75 H₂O: C, 66.01; H, 6.51; N, 15.39. Found: C, 65.83; H, 6.29; N, 15.60.

Example 34

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-chloro-1*H*-indol-3-ylmethyl)-N-

methylacrylamide

According to the procedure of Example 31, except substituting 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole for the dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (180 mg, 52%) as obtained as a yellow solid: MS (ES) *m/e* 355.2 (*M* + *H*)⁺. Anal. Calcd for C₁₉H₁₉ClN₄O · 0.25 H₂O: C, 63.51; H, 5.47; N, 15.59. Found: C, 63.55; H, 5.32; N, 15.68.

Example 35Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 7-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (140 mg, 40%) was obtained as a tan solid: MS (ES) *m/e* 351.2 (*M* + *H*)⁺. Anal. Calcd for C₂₀H₂₂N₄O₂ · 0.5 H₂O: C, 66.83; H, 6.45; N, 15.58. Found: C, 66.81; H, 6.41; N, 15.19.

Example 36Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(6-chloro-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 6-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (176 mg, 50%) was obtained as a yellow solid: MS (ES) *m/e* 355.2 (*M* + *H*)⁺. Anal. Calcd for C₁₉H₁₉ClN₄O · 0.5 H₂O: C, 62.72; H, 5.54; N, 15.40. Found: C, 62.79; H, 5.20; N, 15.85.

Example 37Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(5-chloro-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 5-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole the title compound was obtained as a tan solid (176 mg, 54%): MS (ES) *m/e* 355.2 (*M* + *H*)⁺. Anal. Calcd for C₁₉H₁₉ClN₄O · 0.25 H₂O: C, 63.51; H, 5.47; N, 15.59. Found: C, 63.63; H, 5.84; N, 15.83.

Example 38

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(4-chloro-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 4-Chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-indole the
5 title compound was obtained as a tan solid (150 mg, 42%): MS (ES) *m/e* 355.2 (M + H)⁺.
Anal. Calcd for C₁₉H₁₉ClN₄O · 0.25 H₂O: C, 63.51; H, 5.47; N, 15.59. Found: C, 63.33;
H, 5.38; N, 15.34.

Example 39

10 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(3,3-dimethyl-3*H*-indene-1-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 1,1-dimethyl-3-(methylaminomethyl)-3*H*-indene for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (43 mg, 13%) was obtained as a white solid: MS (ES) *m/e* 334.2 (M + H)⁺. Anal. Calcd for C₂₁H₂₃N₃O · 0.75 H₂O: C, 72.70; H, 7.12; N, 12.11. Found: C,
15 72.38; H, 6.80; N, 11.69.

Example 40

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-hydroxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 7-hydroxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound was obtained as a tan solid (60 mg, 17.9 %): MS (ES) *m/e* 337.2 (M + H)⁺. Anal. Calcd for C₁₉H₂₀N₄O₂ · 1.0 H₂O: C, 64.39; H, 6.26; N, 15.81. Found: C, 63.99; H, 5.78; N, 15.54.

Example 41

25 Preparation of (E)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)-acrylamide

a) N-Methyl-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)acrylamide

To a cold solution (ice bath) of 3-(methylaminomethyl)-1,2,7-trimethyl-1*H*-indole (570 mg, 2.8 mmole) in dry CH₂Cl₂ (24 mL) was added dry Et₃N (0.25 mL, 2.9 mmole).
30 The reaction was stirred in the cold under argon for 2 h then was poured into H₂O (40 mL). The layers were separated, and the organic layer was washed with brine, dried (MgSO₄),

filtered, and concentrated. The title compound (0.7 g, 97%) was obtained as a light orange solid: MS (ES) m/e 257.2 ($M + H$)⁺.

b) (E)-N-Methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)-acrylamide

- 5 A mixture of N-methyl-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)acrylamide (256 mg, 1 mmole) and 6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (227 mg, 1 mmole) in propionitrile (20 mL) was treated with DIEA (0.3 mL), Pd(OAc)₂ (29 mg, 0.13 mmole), and tri-*o*-tolylphosphine (50 mg, 0.16 mmole). The reaction was heated at reflux under argon for 10 h, then was cooled to RT and filtered through supercel. The filtrate was
- 10 concentrated and the residue was purified by flash chromatography on silica gel to afford the title compound (100 mg, 25%) as an off-white solid: MS (ES) m/e 403.2 ($M + H$)⁺. Anal. Calcd for C₂₄H₂₆N₄O₂ · 2.75 H₂O: C, 63.77; H, 7.02; N, 12.39. Found: C, 63.81; H, 7.25; N, 11.90.

Example 42

- 15 Preparation of (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-acrylamide

- A solution of 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole (104.3 mg, 0.5 mmole) and (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-acrylic acid (109.1 mg, 0.5 mmole) in dry DMF (8 mL) was treated with dry Et₃N (0.2 mL), HOBt · H₂O (76.5
- 20 mg, 0.5 mmole) and EDC (96 mg, 0.5 mmole). The solution was stirred at RT under argon for 20 h, then was concentrated. The oily residue was dissolved in MeOH and the solution was cooled. The precipitated solid was collected, washed with cold MeOH, and dried to give the title compound (95 mg, 47%): MS (ES) m/e 409.2 ($M + H$)⁺. Anal. Calcd for C₂₂H₂₁ClN₄O₂ · 0.25 H₂O: C, 63.92; H, 5.24; N, 13.55. Found: C, 63.56; H, 5.14; N,
- 25 13.73.

Example 43

Preparation of (E)-N-(7-chloro-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-acrylamide

- According to the procedure of Example 42, except substituting 7-chloro-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-
- 30 indole, the title compound (25 mg, 13%) was obtained as an off white solid after chromatography on silica gel: MS (ES) m/e 395.0 ($M + H$)⁺

Example 44Preparation of (E)-2,N-dimethyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 4, except substituting (E)-2-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt (0.50 g, 1.8 mmole) for the (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt, the title compound (0.64 g, 89 %) was prepared as a light yellow solid: MS (ES) *m/e* 389 (M + H)⁺.

Example 45

10 Preparation of (E)-3,N-dimethyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 1, except substituting (E)-3-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt (0.50 g, 1.8 mmole) for the (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt, the title compound (0.67 g, 92 %) was prepared as a light yellow solid: MS (ES) *m/e* 389 (M + H)⁺.

Example 46

20 Preparation of (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(4-methyl-3-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*]-1,4-diazepin-7-yl)acrylamide

According to the procedure of Example 162, except substituting 7-bromo-4-methyl-1,2,4,5-tetrahydropyrido[2,3-*e*]-1,4-diazepin-3-one (0.50 g, 1.9 mmole) for the 2-amino-5-bromopyrimidine, the title compound (0.30 g, 62 %) was prepared as a light yellow solid: MS (ES) *m/e* 404 (M + H)⁺.

Example 47

25 Preparation of (E)-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylamide

EDC (0.18 g, 0.96 mmole) was added to a solution of (E)-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylic acid hydrochloride salt (0.24 g, 0.87 mmole), 2-methyl-3-(methylaminomethyl)indole (0.15 g, 0.87 mmole), HOBt · H₂O (0.13 g, 0.96 mmole) and diisopropylethylamine (0.45 mL, 2.61 mmole) in DMF (15 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Preparative HPLC on a Waters C-18 ODSA column

(gradient: 20-100% H₂O/CH₃CN) gave the title compound (0.13 g, 38%) as a light yellow solid after drying in vacuo: MS (ES) *m/e* 389 (M + H)⁺.

Example 48

Preparation of (E)-N-[1-(2-hydroxyethyl)-1*H*-indol-3-ylmethyl]-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

- EDC (0.54 g, 2.80 mmole) was added to a solution of (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt (0.71 g, 2.80 mmole), 1-(2-hydroxyethyl)-3-(methylaminomethyl)-1*H*-indole (0.52 g, 2.55 mmole), HOBt · H₂O (0.38 g, 2.80 mmole) and diisopropylethylamine (1.11 mL, 6.40 mmole) in DMF (25 mL) at RT.
- The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (20% EtOH/EtOAc) gave title compound (0.28 g, 27%) as an off-white solid after drying in vacuo: MS (ES) *m/e* 405 (M + H)⁺.

Example 49

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-indol-3-ylmethyl)-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylamide

- EDC (0.06 g, 0.30 mmole) was added to a solution of (E)-3-(8-oxo-6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepin-3-yl)acrylic acid hydrochloride salt (0.07 g, 0.27 mmole), 1-methyl-3-(methylaminomethyl)-1*H*-indole (0.05 g, 0.27 mmole), HOBt · H₂O (0.04 g, 0.30 mmole) and diisopropylethylamine (0.14 mL, 0.81 mmole) in DMF (15 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (20% EtOH/EtOAc) gave title compound (0.05 g, 48%) as an off-white solid after drying in vacuo: MS (ES) *m/e* 389 (M + H)⁺.

Example 50

Preparation of (E)-N-[1-(2-hydroxyethyl)-1*H*-indol-3-ylmethyl]-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

- EDC (0.35 g, 1.81 mmole) was added to a solution of (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt (0.42 g, 1.65 mmole), 1-ethyl-3-(methylaminomethyl)-1*H*-indole (0.31 g, 1.65 mmole), HOBt · H₂O (0.24 g, 1.81

mmole) and diisopropylethylamine (0.86 mL, 4.95 mmole) in DMF (15 mL) at RT. The reaction was stirred overnight then was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over Na₂SO₄. Flash chromatography on silica gel (10%

- 5 EtOH/EtOAc) gave title compound (0.39 g, 61%) as a light yellow solid after drying in vacuo: MS (ES) *m/e* 389 (M + H)⁺.

Example 51

Preparation of (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methylacrylamide

- 10 According to the procedure of Example 19, except substituting 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole (1.4 g, 6.7 mmole) for the 2-methyl-3-(methylaminomethyl)indole, the title compound (2.38 g, 84%) was prepared as a pale yellow solid: MS (ES) *m/e* 427.0 (M + H)⁺.

Example 52

- 15 Preparation of (E)-3-[6-[N-(carboxymethyl)amino]pyridin-3-yl]-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 20, except substituting (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methylacrylamide (0.75 g, 1.8 mmole) for the (E)-3-[6-[N-

- 20 (methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide, the title compound (0.746 g, 100%) was prepared as a white solid: MS (ES) *m/e* 413.2 (M + H)⁺.

Example 53

Preparation of (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-[6-[N-(methylaminocarbonylmethyl)amino]pyridin-3-yl]acrylamide

- 25 According to the procedure of Example 21, except substituting (E)-N-(7-chloro-1-methyl-1*H*-indol-3-ylmethyl)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methylacrylamide (0.75 g, 1.8 mmole) for the (E)-3-[6-[N-(methoxycarbonylmethyl)amino]pyridin-3-yl]-N-methyl-N-(2-methyl-1*H*-indol-3-ylmethyl)acrylamide, the title compound (0.721 g, 94%) was prepared as a white solid: MS
- 30 (ES) *m/e* 426.0 (M + H)⁺.

Example 54Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(2-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 2-chloro-1-methyl-2-(methylaminomethyl)-1*H*-indole (0.7 g, 3.0 mmole) for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (0.935 g, 88%) was obtained as an off-white solid: MS (ES) *m/e* 355.2 (M + H)⁺.

Example 55

10 Preparation of (E)-N-(2-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 2-chloro-1-methyl-2-(methylaminomethyl)-1*H*-indole (0.7 g, 3.0 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, the title compound (1.03 g, 84%) was obtained as a white solid: MS (ES) *m/e* 409.0 (M + H)⁺.

15 Example 56

Preparation of (E)-N-(naphthalen-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 2-(methylaminomethyl)naphthalene (0.55 g, 3.2 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, the title compound (0.871 g, 73%) was obtained as a white solid: MS (ES) *m/e* 372.2 (M + H)⁺.

Example 57

Preparation of (E)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(6-amino-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

25 a) (E)-N-(1-Methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-[6-(benzhydrylideneamino)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]acrylamide

According to the procedure of Example 15, except substituting 3-(benzhydrylideneamino)-6-bromo-3,4-dihydro-1*H*-1,8-naphthyridin-2-one (3.5 g, 8.6 mmole) for the 5-bromo-2,2'-dipyridylamine, the title compound (3.72 g, 78%) was obtained as a pale yellow solid: MS (ES) *m/e* 554.4 (M + H)⁺.

b) (E)-N-(1-Methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(6-amino-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

To a suspension of (E)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-[6-(benzhydrylideneamino)-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl]acrylamide (0.5 g, 0.9 mmole) in dioxane (15 mL) was added 1 N HCl (10 mL) with stirring at RT. After approximately 5 min the suspension cleared up then gradually reformed. After stirring for 1 h the reaction was neutralized with 1 N NaOH (10 mL) and concentrated to near dryness under vacuum. The resulting suspension was diluted with H₂O (20 mL) and filtered, and the solid was rinsed with cold H₂O and dried under vacuum. The slightly pinkish solid was triturated with Et₂O, filtered, and dried under vacuum to give the title compound (248 mg, 71%) as an off-white solid: MS (ES) *m/e* 390.4 (M + H)⁺.

10 Example 58

Preparation of (E)-N-(benzofuran-2-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 4, except substituting (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt (1.60 g, 6.3 mmole) for the (E)-3-(2-oxo-2,3-dihydro-1*H*-indol-5-yl)acrylic acid hydrochloride salt, and substituting 2-(methylaminomethyl)benzofuran (1.20 g, 6.9 mmole) for the 2-methyl-3-(methylaminomethyl)indole, the title compound (2.0 g, 90%) was prepared as a tan solid: MS (ES) *m/e* 363 (M + H)⁺.

Example 59

20 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-methoxycarbonyl-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting methyl 1-methyl-3-(methylaminomethyl)-1*H*-indole-7-carboxylate for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (150 mg, 34%) was obtained, after trituration with diethyl ether, as an off-white solid: MS (ES) *m/e* 379.2 (M + H)⁺. Anal. Calcd for C₂₁H₂₂N₄O₃ · 0.25 H₂O: C, 65.87; H, 5.92; N, 14.63. Found: C, 66.02; H, 5.71; N, 14.29.

Example 60

30 Preparation of (E)-3-(aminopyridin-3-yl)-N-methyl-N-(1,2,7-trimethyl-1*H*-indol-3-ylmethyl)acrylamide

According to the procedure of Example 31, except substituting 3-(methylaminomethyl)-1,2,7-trimethyl-1*H*-indole for the 1,4-dimethyl-3-

(methylaminomethyl)-1*H*-indole, the title compound (120 mg, 29%) was obtained, after trituration with ethyl acetate, as a light yellow solid: MS (ES) *m/e* 349.0 (*M* + *H*)⁺. Anal. Calcd for C₂₁H₂₄N₄O · H₂O: C, 68.82; H, 7.69; N, 15.29. Found: C, 68.42; H, 6.86; N, 15.61.

5 Example 61

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-chloro-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting 7-chloro-3-(methylaminomethyl)-1*H*-indole for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole,
10 the title compound (150 mg, 25%) was obtained, after trituration with ethyl acetate, as a light yellow solid: MS (ES) *m/e* 341.0 (*M* + *H*)⁺. Anal. Calcd for C₁₈H₁₇N₄O · 0.25 H₂O: C, 62.60; H, 5.10; N, 16.22. Found: C, 62.29; H, 5.01; N, 16.32.

Example 62

15 Preparation of (E)-N-(5-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 5-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (100 mg, 49%) was obtained as a light tan solid: MS (ES) *m/e* 409.0 (*M* + *H*)⁺. Anal. Calcd for C₂₂H₂₁ClN₄O₂ · 0.5 H₂O: C, 63.23; H, 5.32; N, 13.40.
20 Found: C, 63.19; H, 5.23; N, 13.45.

Example 63

Preparation of (E)-N-(6-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 6-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (125 mg, 61%) was obtained as a light tan solid: MS (ES) *m/e* 409.0 (*M* + *H*)⁺. Anal. Calcd for C₂₂H₂₁ClN₄O₂ · 0.25 H₂O: C, 63.92; H, 5.24; N, 13.55.
25 Found: C, 63.96; H, 4.98; N, 13.66.

Example 64

30 Preparation of (E)-N-(1,7-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 1,7-dimethyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (100 mg, 51%) was obtained as a white solid: MS (ES) *m/e* 389.2 (*M* + *H*)⁺. Anal. Calcd for C₂₃H₂₄N₄O₂ · 0.25 H₂O: C, 70.29; H, 6.28; N, 14.25.

5 Found: C, 70.06; H, 6.23; N, 14.29

Example 65

Preparation of (E)-N-(1,6-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

10 According to the procedure of Example 42, except substituting 1,6-dimethyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (95 mg, 49%) was obtained as a white solid: MS (ES) *m/e* 389.2 (*M* + *H*)⁺. Anal. Calcd for C₂₃H₂₄N₄O₂ · 0.75 H₂O: C, 68.72; H, 6.39; N, 13.93. Found: C, 68.98; H, 6.07; N, 13.81.

Example 66

15 Preparation of (E)-N-(1,4-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (90 mg, 46%) was obtained as a white solid: MS (ES) *m/e* 389.0 (*M* + *H*)⁺. Anal. Calcd for C₂₃H₂₄N₄O₂ · 0.5 H₂O: C, 69.50; H, 6.33; N, 14.10. Found: C, 69.40; H, 6.24; N, 14.20.

Example 67

Preparation of (E)-N-(1,5-dimethyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

25 According to the procedure of Example 42, except substituting 1,5-dimethyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (100 mg, 51%) was obtained as a white solid: MS (ES) *m/e* 389.2 (*M* + *H*)⁺. Anal. Calcd for C₂₃H₂₄N₄O₂ · 0.125 H₂O: C, 70.70; H, 6.25; N, 14.34. Found: C, 70.75; H, 6.15; N, 14.38.

Example 68Preparation of (E)-N-(7-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 7-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (85 mg, 42%) was obtained as an off-white solid: MS (ES) *m/e* 405.2 (M + H)⁺. Anal. Calcd for C₂₃H₂₄N₄O₃: C, 68.30; H, 5.95; N, 13.85. Found: C, 67.95; H, 5.94; N, 13.94.

Example 69

10 Preparation of (E)-N-(7-hydroxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 7-hydroxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (200 mg, 51%) was obtained as a tan solid: MS (ES) *m/e* 391.2 (M + H)⁺. Anal. Calcd for C₂₂H₂₂N₄O₃ · 0.75 H₂O: C, 65.41; H, 5.85; N, 13.86. Found: C, 65.25; H, 5.95; N, 13.79.

Example 70

20 Preparation of (E)-N-(4-chloro-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 4-chloro-1-methyl-3-(methylaminomethyl) for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (100 mg, 49%) was obtained as a white solid: MS (ES) *m/e* 409.0 (M + H)⁺. Anal. Calcd for C₂₂H₂₁ClN₄O₂ · 0.75 H₂O: C, 62.55; H, 5.36; N, 13.26. Found: C, 62.71; H, 5.24; N, 13.15.

Example 71Preparation of (E)-N-(4-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 4-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (65 mg, 32%) was obtained as an off-white solid: MS (ES) *m/e* 405.2 (*M* + *H*)⁺. Anal. Calcd for C₂₃H₂₄N₄O₃ · 1.25 H₂O: C, 64.69; H, 6.19; N, 13.33. Found: C, 64.49; H, 5.94; N, 13.76

Example 72

10 Preparation of (E)-N-(5-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 402, except substituting 5-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (90 mg, 44%) was obtained as an off-white solid: MS (ES) *m/e* 405.2 (*M* + *H*)⁺. Anal. Calcd for C₂₃H₂₄N₄O₃ · 0.5 H₂O: C, 66.81; H, 6.09; N, 13.55. Found: C, 66.67; H, 5.96; N, 13.87.

Example 73

20 Preparation of (E) 3-(6-aminopyridin-3-yl)-N-(7-methoxycarbonyl-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

A solution of (E)-3-(6-aminopyridin-3-yl)-N-(7-methoxycarbonyl-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide (76 mg, 0.2 mmole) in methanol (4 mL), water (2 mL), and tetrahydrofuran (2 mL) was treated with LiOH (39 mg, 1.6 mmole), and the reaction was stirred at ambient temperature for 48 h. The mixture was filtered, and the filtrate was acidified to pH 4.0-4.5 with 1.0 N HCl. The precipitate was collected, washed with water and dried giving the title compound (25 mg, 35%) as a white solid: MS (ES) *m/e* 365.2 (*M* + *H*)⁺. Anal. Calcd for C₂₀H₂₀N₄O₃ · 0.25 H₂O: C, 65.11; H, 5.60; N, 15.18. Found: C, 64.83; H, 5.52; N, 15.07.

Example 74

30 Preparation of (E)-N-(6-methoxy-1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 6-methoxy-1-methyl-3-(methylaminomethyl)-1*H*-indole for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (65 mg, 32%) was obtained as a

yellow solid: MS (ES) m/e 405.2 ($M + H$)⁺. Anal. Calcd for C₂₃H₂₄N₄O₃ · H₂O: C, 65.38; H, 6.20; N, 13.26. Found: C, 65.36; H, 5.98; N, 13.16.

Example 75

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(6-methoxycarbonyl-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 31, except substituting methyl 1-methyl-3-(methylaminomethyl)-1*H*-indole-6-carboxylate for the 1,4-dimethyl-3-(methylaminomethyl)-1*H*-indole, the title compound (168 mg, 39%) was obtained, after silica gel chromatography, as a white solid: MS (ES) m/e 379.2 ($M + H$)⁺. Anal. Calcd for C₂₁H₂₂N₄O₃ · 0.125 H₂O: C, 66.25; H, 5.93; N, 14.71. Found: C, 66.60; H, 6.13; N, 14.18.

Example 76

Preparation of (E)-N-(3,3-dimethyl-3*H*-indene-1-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 42, except substituting 3,3-dimethyl-1-(methylaminomethyl)-3*H*-indene for the 7-chloro-1-methyl-3-(methylaminomethyl)-1*H*-indole, the title compound (48 mg, 12%) was obtained, after silica gel chromatography, as a tan solid: MS (ES) m/e 388.2 ($M + H$)⁺. Anal. Calcd for C₂₃H₂₄N₄O₃ · 0.375 H₂O: C, 73.31; H, 6.51; N, 10.66. Found: C, 72.91; H, 6.37; N, 11.16.

Example 77

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(4-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 24, except substituting 4-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.2 g, 1.04 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, and substituting (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.17 g, 1.04 mmole) for the (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt, the title compound (0.11 g, 37%) was prepared as an off-white powder: MS (ES) m/e 339 ($M + H$)⁺.

Example 78

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(5-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 24, except substituting 5-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.2 g, 1.04 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, and substituting (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.17 g, 1.04 mmole) for the (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt, the title compound (0.14 g, 41%) was prepared as an off-white powder: MS (ES) *m/e* 339 (M + H)⁺.

Example 79

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-fluoro-1-methyl-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 24, except substituting 7-fluoro-1-methyl-3-(methylaminomethyl)-1*H*-indole (0.2 g, 1.04 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, and substituting (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.17 g, 1.04 mmole) for the (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt, the title compound (0.1 g, 27%) was prepared as an off-white powder: MS (ES) *m/e* 339 (M + H)⁺.

Example 80

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(4-fluoro-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 24, except substituting 4-fluoro-3-(methylaminomethyl)-1*H*-indole (0.31 g, 1.74 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, and substituting (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.285 g, 1.74 mmole) for the (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt, the title compound (0.2 g, 36%) was prepared as a white powder: MS (ES) *m/e* 325 (M + H)⁺.

Example 81

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(7-fluoro-1*H*-indol-3-ylmethyl)-N-methylacrylamide

According to the procedure of Example 24, except substituting 7-fluoro-3-(methylaminomethyl)-1*H*-indole (0.31 g, 1.74 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1*H*-3a-azacyclopenta[*a*]indene, and substituting (E)-3-(6-aminopyridin-3-yl)acrylic acid (0.285 g, 1.74 mmole) for the (E)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylic acid hydrochloride salt, the title compound (0.1 g, 18%) was prepared as a white powder: MS (ES) *m/e* 325 (M + H)⁺.

Example 82Preparation of (E)-N-(4-fluoro-1-methyl-1H-indol-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 4-fluoro-1-methyl-3-(methylaminomethyl)-1H-indole (0.13 g, 0.68 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1H-3a-azacyclopenta[*a*]indene), the title compound (0.15 g, 56%) was prepared as an off-white powder: MS (ES) *m/e* 393 (M + H)⁺.

Example 83

10 Preparation of (E)-N-(quinolin-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting 3-(methylaminomethyl)quinoline (0.12 g, 0.67 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1H-3a-azacyclopenta[*a*]indene), the title compound (0.1 g, 40%) was prepared as an off-white powder: MS (ES) *m/e* 373 (M + H)⁺.

15 Example 84

Preparation of (E)-N-(naphthalen-1-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

According to the procedure of Example 24, except substituting N-methyl-1-naphthalenemethylamine hydrochloride (0.162 g, 0.95 mmole) for the 2,3-dihydro-8-(methylaminomethyl)-1H-3a-azacyclopenta[*a*]indene), the title compound (0.15 g, 43%) was prepared as a white powder: MS (ES) *m/e* 372 (M + H)⁺.

Example 85

Preparation of (E)-N-methyl-N-(2-methyl-1H-indol-3-ylmethyl)-3-[3-(2-methoxyethyl)-2-oxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidin-6-yl]acrylamide

25 A solution of 6-bromo-3-(2-methoxyethyl)-3,4-dihydro-1H-pyrido[2,3-*d*]pyrimidin-2-one (0.86 g, 3.00 mmole), N-(2-methyl-1H-indol-3-ylmethyl)-N-methylacrylamide (see Example 1 (a), 0.68 g, 3.00 mmole), Pd(OAc)₂ (0.07 g, 0.30 mmole), tri-*ortho*-tolylphosphine (0.18 g, 0.60 mmole) and diisopropylethylamine (1.31 mL, 7.50 mmole) in propionitrile (50 mL) was deoxygenated, then was heated at reflux under N₂ overnight.

30 The dark mixture was filtered through a pad of celite®, and the filter pad was rinsed with acetonitrile (250 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (10% EtOAc/EtOH). The title compound (0.46 g, 36%) was obtained as a light yellow solid after drying in vacuo: MS (ES) *m/e* 434 (M +

H)⁺.

Example 86

Preparation of (E)-N-(1-methyl-1*H*-indol-3-ylmethyl)-N-methyl-3-(6-methoxycarbonyl-7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

- 5 According to the procedure of Example 15 (b), except substituting methyl (±)-6-bromo-2-oxo-1,2,3,4-tetrahydro-1*H*-1,8-naphthyridine-3-carboxylate (2.5 g, 8.8 mmole), from Preparation 4 (d), for the 5-bromo-2,2'-dipyridylamine, the title compound (1.82 g, 48%) was prepared as an off-white solid: MS (ES) *m/e* 433.4 (M + H)⁺.

Example 87

- 10 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-N-methylacrylamide

The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 88

- 15 Preparation of (E)-N-(1,3-dimethyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 89

- 20 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-3-ylmethyl)acrylamide

The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 90

- 25 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-3-ylmethyl)acrylamide

The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 91

- 30 Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-ylmethyl)acrylamide

The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 92

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[2,3-*c*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

5 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 93

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*c*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

10 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 94

Preparation of (E)-N-methyl-N-(1-methyl-1*H*-pyrrolo[3,2-*b*]pyridin-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

15 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 95

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-(benzofuran-3-ylmethyl)-N-methylacrylamide

20 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 96

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(3-methylbenzofuran-2-ylmethyl)acrylamide

25 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 97

Preparation of (E)-3-(6-aminopyridin-3-yl)-N-methyl-N-(2-methylbenzofuran-3-ylmethyl)acrylamide

30 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 98Preparation of (E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

5 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 99Preparation of (E)-N-methyl-N-(3-methylbenzofuran-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

10 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 100Preparation of (E)-N-methyl-N-(2-methylbenzofuran-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

15 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 101Preparation of (E)-(6-aminopyridin-3-yl)-N-methyl-N-[1-(1-methyl-1H-indol-2-yl)ethyl]acrylamide

20 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 102Preparation of (E)-(6-aminopyridin-3-yl)-N-methyl-N-[1-(1-methyl-1H-indol-3-yl)ethyl]acrylamide

25 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 103Preparation of (E)-N-methyl-N-[1-(1-methyl-1H-indol-2-yl)ethyl]-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

30 The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 104Preparation of (E)-N-methyl-N-[1-(1-methyl-1H-indol-3-yl)ethyl]-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide

The title compound is prepared following methods analogous to those described in the previous preparations and examples.

Example 105

Preparation of (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-

5 *e*][1,4]diazepin-7-yl)-*N*-(1-propyl-naphthalen-2-ylmethyl)acrylamide hydrochloride

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

(*E*)-3-(4-Methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride (1.40 g, 1.25 mmol) was added to a solution of methyl-(1-propyl-naphthalen-2-ylmethyl)amine (0.292 g, 1.37 mmol) and diisopropylethylamine (0.65 mL, 3.75 mmol) in DMF (25 mL) followed by the addition of 1-hydroxybenzotriazole hydrate (0.185 g, 1.37 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.263 g, 1.37 mmol). The reaction was allowed to stir at room temperature for 18 h. The reaction was quenched with H₂O (70 mL) then concentrated to a yellow oil.

15 Purification by column chromatography (silica gel, CH₂Cl₂/ MeOH, 99:1 to 95:5) gave the title compound (0.229 g, 41%) as a glassy orange solid and as a mixture of amide rotamers: ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.35 (s, 1H), 8.55–8.54 (m, 1H), 8.24–8.14 (m, 1H), 7.98–7.86 (m, 5H), 7.72–7.24 (m, 3H), 3.75 (s, 2H), 3.42 (s, 2H), 3.86 (s, 2H), 2.54–2.36 (m, 6H), 2.11–2.02 (m, 2H), 1.40–1.34 (m, 2H), 1.01–0.98 (m, 3H).

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

A 2 M solution of hydrogen chloride in Et₂O (0.25 mL, 0.518 mmol) was added to (*E*)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(1-propyl-naphthalen-2-ylmethyl)acrylamide (0.229 g, 0.518 mmol) in CH₂Cl₂ (5 mL) via

25 syringe. The solution was allowed to stir for 18 h during time which a precipitate fell out of the solution. The product was collected by filtration and was washed with Et₂O (100 mL). The product was dried to give the title compound (0.182 g, 73%) as an orange solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 11.22 (s, 1H), 8.86–8.82 (m, 1H), 8.38–8.32 (m, 1H), 7.94–7.87 (m, 4H), 7.74–7.29 (m, 5H), 6.06–

30 5.64 (m, 1H), 4.40–4.30 (m, 2H), 3.94–3.91 (br s, 2H), 2.93–2.57 (m, 6H), 2.10–2.05 (m, 2H), 1.37–1.32 (m, 2H), 1.02–0.97 (m, 3H); MS (ESI) *m/e* 443 (M + H)⁺.

Example 106

Preparation of (*E*)-3-(3,3-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride

5 a) (*E*)-3-(3,3-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide

A suspension of 7-bromo-3,3-dimethyl-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one (0.17 g, 0.63 mmol) in propionitrile (4 mL) and DMF (1 mL) was de-oxygenated with Ar for 10 min. The mixture was treated with *N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide (0.20 g, 0.81 mmol) and (*i*-Pr)₂EtN (0.24 mL, 1.3 mmol) and was de-oxygenated with Ar for 5 min. Pd(OAc)₂ (14 mg, 0.062 mmol) and P(*o*-tol)₃ (38 mg, 0.12 mmol) were added simultaneously, and the mixture was de-oxygenated a third time for 5 min. The mixture was heated to reflux for 4 h, then allowed to cool. The resulting precipitate was isolated by filtration, washed with EtOAc, dissolved in CH₂Cl₂, and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 98:2) gave the title compound (0.15 g, 56%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.97 (s, 1H), 8.45 (s, 1H), 7.77–7.65 (m, 3H), 7.53 (s, 1H), 7.40–7.29 (m, 2H), 6.98–6.84 (m, 1H), 4.94–4.89 (m, 2H), 4.02 (s, 2H), 3.15–3.10 (m, 3H), 2.43 (s, 3H), 1.70 (s, 1H), 1.49 (s, 6H); MS (ESI) *m/e* 435 (M + H)⁺.

20 b) (*E*)-3-(3,3-Dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride

A suspension of (*E*)-3-(3,3-dimethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide (0.15 g, 0.35 mmol) in CH₂Cl₂ (10 mL) was treated with anhydrous HCl in Et₂O (0.35 mL, 1.0 M). After stirring for 5 min, the mixture was diluted with Et₂O (50 mL) and allowed to stir for 1 h. The solid was isolated by filtration, washed with Et₂O, and dried under vacuum at 60 °C for 4 d to give the title compound (0.16 g, 96%) as a light yellow powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.92 (s, 1H), 10.56 (br s, 2H), 8.66–8.67 (m, 1H), 8.40 (s, 1H), 7.86–7.89 (m, 1H), 7.73–7.75 (m, 1H), 7.58–7.63 (m, 1H), 7.30–7.40 (m, 3H), 4.90–5.13 (m, 2H), 4.39–4.41 (m, 2H), 2.94–3.17 (m, 3H), 2.43 (s, 3H), 1.63 (s, 6H); MS (ESI) *m/e* 435 (M + H)⁺.

Example 107

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

According to the procedure of Example 1, except substituting methyl-naphthalen-2-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.397 g, quantitative) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, DMSO- d_6) δ 11.00–10.86 (br s, 1H), 11.28–11.24 (m, 1H), 8.85–8.81 (m, 1H), 8.35–8.29 (m, 1H), 7.95–7.75 (m, 4H), 7.67–7.62 (m, 1H), 7.54–7.38 (m, 4H), 5.01–4.81 (m, 2H), 4.31 (br s, 2H), 3.73 (br s, 2H), 3.17–2.97 (m, 3H), 2.91–2.87 (m, 3H); MS (ESI) m/e 401 ($M + H$) $^+$.

Example 108

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

According to the procedure of Example 1, except substituting methyl-naphthalen-1-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.382 g, quantitative) was prepared as an off white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, DMSO- d_6) δ 12.24–12.15 (br s, 1H), 11.27–11.21 (m, 1H), 8.85–8.76 (m, 1H), 8.36–8.30 (m, 1H), 8.20–7.02 (m, 9H), 5.36–5.12 (m 2H), 4.29 (br s, 2H), 3.86–3.77 (br s, 2H), 3.17–3.10 (m, 3H), 2.90–2.84 (m, 3H); MS (ESI) m/e 401 ($M + H$) $^+$.

Example 109

Preparation of (*E*)-*N*-(4-Acetylamino-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting 4-acetamidobenzyl methyl amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3yl)acrylic acid hydrochloride for (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.283 g, 53%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, DMSO- d_6) δ 10.66–10.64 (m, 1H), 9.94–9.92 (m, 1H), 8.36–8.33 (m, 1H), 8.07–8.06 (m, 1H), 7.56–7.48 (m, 3H), 7.33–7.13 (m, 3H), 4.74–4.54 (m, 2H), 3.07–2.86 (m, 5H), 2.53–2.49 (m 2H), 2.01 (s, 3H); MS (ESI) m/e 379 ($M + H$) $^+$.

Example 110Preparation of (E)-N-(4-Methanesulfonyl-benzyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting (4-methanesulfonyl-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (E)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.400 g, 71%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.6–10.65 (m, 1H), 8.38–8.34 (m, 1H), 8.10–8.04 (m, 1H), 7.95–7.89 (m, 2H), 7.57–7.46 (m, 3H), 7.28–7.23 (m, 1H), 4.96–4.72 (m, 2H), 3.20–3.16 (m, 5H), 2.94–2.84 (m, 3H) 2.56–2.49 (m, 2H); MS (APCI) *m/e* 400 (M + H)⁺.

Example 111Preparation of (E)-N-(2-Methoxy-naphthalen-1-ylmethyl)-N-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting (2-methoxy-naphthalen-1-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (E)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.403 g, 71%) was prepared as an orange-brown solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.66 (s, 1H), 8.37 (s, 1H), 8.08–7.81 (m, 4H), 7.70–7.11 (m, 5H), 5.22–5.09 (m, 2H), 3.98–3.90 (m, 3H), 2.91–2.87 (m, 5H), 2.63–2.49 (m, 2H); MS (ESI) *m/e* 402 (M + H)⁺.

Example 112Preparation of (E)-N-Methyl-N-(4-methyl-naphthalen-1-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting methyl-(4-methyl-naphthalen-1-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (E)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.410 g, 76%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz,

DMSO-*d*₆) δ 10.67-10.62 (m, 1H), 8.38-8.29 (m, 1H), 8.15-7.94 (m, 3H), 7.60-7.55 (m, 3H), 7.36-7.02 (m, 3H), 5.30-5.06 (m, 2H), 3.04-2.73 (m, 5H), 2.65-2.45 (m, 5H); MS (ESI) *m/e* 386 (M + H)⁺.

Example 113

5 Preparation of (*E*)-*N*-(2,3-Dimethyl-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting 2,3-dimethylbenzylmethyl amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-
10 *e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.368 g, 75%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.68-10.64 (m, 1H), 8.38-8.32 (m, 1H), 8.10-7.99 (m, 1H), 7.57-7.50 (m, 1H), 7.29-7.04 (m, 3H), 6.94-6.77 (m, 1H), 4.82-4.65 (m, 2H), 3.06-2.85 (m, 5H), 2.57-
15 2.48 (m 2H), 2.28-2.14 (m, 6H); MS (APCI) *m/e* 350 (M + H)⁺.

Example 114

Preparation of (*E*)-*N*-(4-Isopropyl-benzyl)-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting (4-isopropyl-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-
20 *e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.223 g, 61%) was prepared as a light orange solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.66-10.64 (m, 1H), 8.36-8.33 (m, 1H), 8.07 (s, 1H), 7.55-7.48 (m, 1H), 7.33-7.11 (m, 5H), 4.77-4.56 (m, 2H), 3.09-2.81 (m, 6H), 2.56-2.49 (m 2H), 1.19-1.16 (m, 6H); MS (APCI) *m/e* 364 (M + H)⁺.

Example 115

30 Preparation of (*E*)-*N*-Indan-5-ylmethyl-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting indan-5-ylmethylmethylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-

(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.232 g, 45%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.66-10.64 (m, 1H), 8.36–8.33 (m, 1H), 8.07–8.06 (m, 1H), 7.54–7.49 (m, 1H), 7.33–6.89 (m, 4H), 4.75–4.56 (m, 2H), 3.07–2.72 (m, 9H), 2.53–2.49 (m, 2H), 2.04–1.94 (m, 2H); MS (APCI) *m/e* 362 (M + H)⁺.

Example 116

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

According to the procedure of Example 1, except substituting indan-5-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.060 g, 88%) was prepared as a white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.02 (br s, 1H), 11.20 (s, 1H), 8.82–8.79 (m, 1H), 8.32–8.29 (m, 1H), 7.64–7.57 (m, 1H), 7.45–7.32 (m, 1H), 7.22–6.85 (m, 3H), 4.77–4.58 (m, 2H), 4.42 (br s, 2H), 3.80 (br s, 2H), 3.09–2.73 (m, 10H), 2.04–1.94 (m, 2H); MS (ESI) *m/e* 391 (M + H)⁺.

Example 117

Preparation of (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.295 g, 98%) was prepared as a white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.20 (br s, 1H), 11.22 (s, 1H), 8.83 (s, 1H), 8.34–8.31 (m, 1H), 7.89–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.65–7.31 (m, 4H), 5.13–4.90 (m, 2H), 4.29 (br s, 2H), 3.80 (br s, 2H), 3.17–2.95 (m, 3H), 2.87 (s, 3H), 2.42 (s, 3H); MS (APCI) *m/e* 421 (M + H)⁺.

Example 118

Preparation of (*E*)-*N*-(3,5-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3,5-dimethoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.307 g, quantitative) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.7 (br s, 1H), 10.88 (s, 1H), 8.71–8.68

(m, 1H), 8.25–8.22 (m, 1H), 7.61–7.56 (m, 1H), 7.39–7.31 (m, 1H), 6.42–6.35 (m, 3H), 4.75–4.55 (m, 2H), 4.09 (br s, 2H), 3.72–3.71 (m, 6H), 3.37 (br s, 2H), 3.11–2.89 (m, 3H), 2.73 (br s, 3H); MS (ESI) m/e 411 ($M + H$)⁺.

Example 119

5 Preparation of (*E*)-*N*-[2-(1*H*-Indol-3-yl)-ethyl]-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting [2-(1*H*-indole-3-yl)-ethyl]methylaniline for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.027 g, 72%) was prepared as a yellow solid and as a mixture of amide
10 rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 11.26–11.22 (m, 1H), 10.85 (s, 1H), 8.82–8.41 (m, 1H), 8.33–7.82 (m, 1H), 7.64–6.73 (m, 7H), 4.59–4.31 (m, 4H), 3.78–3.64 (m, 3H), 3.17–2.91 (m, 7H); MS (APCI) m/e 404 ($M + H$)⁺.

Example 120

15 Preparation of (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(2,4,5-trimethoxy-benzyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(2,4,5-trimethoxy-benzyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.220 g, 78%) was prepared as a light orange solid and as a mixture of amide
20 rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.75 (br s, 1H), 11.19 (s, 1H), 8.81–8.78 (m, 1H), 8.30–8.26 (m, 1H), 7.60–7.31 (m, 2H), 6.73–6.72 (m, 2H), 4.66–4.52 (m, 2H), 4.27 (br s, 2H), 3.79–3.64 (m, 11H), 3.09–2.86 (m, 6H); MS (ESI) m/e 441 ($M + H$)⁺.

Example 121

25 Preparation of (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-phenanthren-9-ylmethyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-phenanthren-9-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.511 g, 95%) was prepared as an off-white solid and as a mixture of amide
30 rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.99 (br s, 1H), 11.23–11.14 (m, 1H), 8.92–8.74 (m, 3H), 8.36–8.04 (m, 2H), 7.99–7.95 (m, 1H), 7.74–7.28 (m, 7H), 5.39–5.17 (m, 2H), 4.30–4.19 (m, 2H), 3.95–3.39 (m, 2H), 3.16–3.01 (m, 3H), 2.89–2.73 (m, 3H); MS (ESI) m/e 451 ($M + H$)⁺.

Example 122

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

According to the procedure of Example 1, except substituting acenaphthen-5-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.395 g, 91%) was prepared as a off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.01 (br s, 1H), 11.19 (s, 1H), 8.82–8.76 (m, 1H), 8.32–8.22 (m, 1H), 7.81–7.63 (m, 2H), 7.55–7.14 (m, 5H), 5.25–5.03 (m, 2H), 4.28 (br s, 2H), 3.79 (m, 2H), 3.36 (br s, 4H), 3.04–2.73 (m, 6H); MS (ESI) *m/e* 427 (M + H)⁺.

Example 123

10 Preparation of (*E*)-*N*-(4-Methoxy-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (4-methoxy-naphthalen-1-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.369 g, 87%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.95 (br s, 1H), 11.22 (s, 1H), 8.83–8.76 (m, 1H), 8.32–8.02 (m, 2H), 8.10–8.00 (m, 1H), 7.69–7.32 (m, 5H), 7.11–6.95 (m, 1H), 5.25–5.03 (m, 2H), 4.29 (br s, 2H), 3.98–3.95 (m, 3H), 3.79 (m, 2H), 3.02–2.69 (m, 3H), 2.87–2.72 (m, 3H); MS (ESI) *m/e* 431 (M + H)⁺.

Example 124

20 Preparation of (*E*)-*N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting benzo[1,3]dioxol-5-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.374 g, 91%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 11.23 (s, 1H), 8.81 (s, 1H), 8.32 (s, 1H), 7.62–6.57 (m, 1H), 7.46–7.31 (m, 1H), 6.93–6.71 (m, 3H), 5.99 (s, 2H), 4.72–4.52 (m, 2H), 4.29 (br s, 2H), 3.81 (br s, 2H), 3.10–2.88 (m, 6H); MS (APCI) *m/e* 395 (M + H)⁺.

Example 125

30 Preparation of (*E*)-*N*-(2,5-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,5-dimethoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title

compound (0.396 g, 93%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.05 (br s, 1H), 11.20 (m, 1H), 8.82–8.77 (m, 1H), 8.33–8.27 (m, 1H), 7.61–7.56 (m, 1H), 7.41–7.34 (m, 1H), 6.98–6.93 (m, 1H), 6.86–6.82 (m, 1H), 6.60–6.59 (m, 1H), 4.73–4.55 (m, 2H), 4.28 (br s, 2H), 3.79–3.74 (m, 5H),
 5 3.66–3.65 (m, 3H), 3.16–2.86 (m, 6H); MS (ESI) m/e 411 ($\text{M} + \text{H}$) $^+$.

Example 126

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

According to the procedure of Example 1, except substituting methyl-quinolin-4-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound
 10 (0.259 g, 92%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.22–11.14 (m, 1H), 8.98–8.94 (m, 1H), 8.84–8.74 (m, 1H), 8.37–8.16 (m, 3H), 7.93–7.88 (m, 1H), 7.78–7.73 (m, 1H), 7.69–7.63 (m, 1H), 7.48–7.21 (m, 2H), 5.50–5.24 (m, 2H), 4.30–4.19 (m, 2H), 3.81–3.74 (m, 2H), 3.27 (s, 2H), 3.06
 15 (s, 1H), 2.87–2.80 (m, 3H); MS (ESI) m/e 402 ($\text{M} + \text{H}$) $^+$.

Example 127

Preparation of (*E*)-*N*-(4-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (4-ethoxy-3-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title
 20 compound (0.310 g, 95%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.18 (m, 1H), 8.80–8.79 (m, 1H), 8.30–8.28 (m, 1H), 7.61–7.57 (m, 1H), 7.44–7.30 (m, 1H), 6.95–6.71 (m, 3H), 4.72–4.53 (m, 2H), 4.27 (br s, 2H), 3.99–3.92 (m, 2H), 3.79–3.72 (m, 5H), 3.08–2.72 (m, 6H), 1.33–1.26 (m,
 25 3H); MS (ESI) m/e 425 ($\text{M} + \text{H}$) $^+$.

Example 128

Preparation of (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-ethoxy-3-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title
 30 compound (0.381 g, 89%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.01 (br s, 1 H), 11.21 (s, 1H), 8.82–8.78 (m, 1H), 8.33–8.25 (m, 1H), 7.61–7.56 (m, 1H), 7.40–7.34 (m, 1H), 7.05–6.97 (m, 2H), 6.71–

6.61 (m, 1H), 4.80–4.52 (m, 2H), 4.29 (br s, 2H), 4.0–3.94 (m, 2H), 3.79 (m, 5H), 3.11–2.87 (m, 6H), 1.31–1.25 (m, 3H); MS (ESI) m/e 425 ($M + H$)⁺.

Example 129

Preparation of (*E*)-*N*-(3,4-Dimethyl-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-
5 tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3,4-dimethyl-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.346 g, 91%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.35 (br s, 1H), 11.23 (s, 1H), 8.82–8.79 (m, 10 1H), 8.34–8.30 (m, 1H), 7.62–7.57 (m, 1H), 7.44–7.32 (m, 1H), 7.14–7.08 (m, 1H), 7.02–6.92 (m, 2H), 4.74–4.55 (m, 2H), 4.28 (br s, 2H), 3.80 (m, 2H), 3.08–2.86 (m, 6H), 2.20–2.19 (m, 6H); MS (ESI) m/e 379 ($M + H$)⁺.

Example 130

Preparation of (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-
15 *e*][1,4]diazepin-7-yl)-*N*-(2,4,6-trimethyl-benzyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,4,6-trimethyl-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.410 g, 94%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.80 (br s, 1H), 11.20 (m, 1H), 8.84–8.80 (m, 20 1H), 8.37–8.31 (m, 1H), 7.61–7.56 (m, 1H), 7.32–7.27 (m, 1H), 6.87 (m, 2H), 4.83–4.68 (m, 2H), 4.28 (br s, 2H), 3.80 (m, 2H), 2.87–2.55 (m, 6H), 2.21–2.16 (m, 9H); MS (ESI) m/e 393 ($M + H$)⁺.

Example 131

Preparation of (*E*)-*N*-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-
25 *e*][1,4]diazepin-7-yl)-*N*-(2,4,5-trimethyl-benzyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,4,5-trimethyl-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.344 g, 95%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.91 (br s, 1H), 11.25–11.22 (m, 1H), 8.83–30 8.78 (m, 1H), 8.34–8.24 (m, 1H), 7.63–7.57 (m, 1H), 7.40–7.32 (m, 1H), 6.97–6.95 (m, 1H), 6.85–6.73 (m, 1H), 4.73–4.57 (m, 2H), 4.30 (br s, 2H), 3.96–3.82 (m, 2H), 3.04–2.87 (m, 6H), 2.21–2.15 (m, 9H); MS (ESI) m/e 393 ($M + H$)⁺.

Example 132

Preparation of (E)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-quinolin-3-ylmethyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-quinolin-3-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound
 5 (0.360 g, 92%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.00 (br s, 1H), 11.23–11.20 (m, 1H), 8.92–8.89 (m, 1H), 8.83–8.80 (m, 1H), 8.34–8.24 (m, 2H), 8.08–8.03 (m, 2H), 7.80–7.78 (m, 1H), 7.69–6.61 (m, 2H), 7.52–7.36 (m, 1H), 5.09–4.86 (m, 2H), 4.30–4.25 (m, 2H), 3.81 (br s, 2H), 3.25 (s, 2H), 3.01 (s, 1H), 2.88–2.85 (m, 3H); MS (ESI) *m/e* 402 (M + H)⁺.

10 Example 133

Preparation of (E)-N-(3,4-Dimethoxy-benzyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3,4-dimethoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title
 15 compound (0.330 g, 92%) was prepared as a pale yellow solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.95 (br s, 1H), 11.23 (s, 1H), 8.82–8.81 (m, 1H), 8.32–8.30 (m, 1H), 7.63–7.57 (m, 1H), 7.45–7.32 (m, 1H), 6.95–6.86 (m, 2H), 6.81–6.71 (m, 1H), 4.74–4.55 (m, 2H), 4.28 (br s, 2H), 3.95–3.72 (m, 8H), 3.10–2.88 (m, 6H); MS (ESI) *m/e* 411 (M + H)⁺.

20 Example 134

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

According to the procedure of Example 1, except substituting benzofuran-2-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title
 25 compound (0.399 g, 93%) was prepared as an off white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.86 (br s, 1H), 11.22 (s, 1H), 8.83 (s, 1H), 8.32 (s, 1H), 7.63–7.20 (m, 6H), 6.86–6.82 (m, 1H), 5.02–4.81 (m, 2H), 4.28 (s, 2H), 3.80 (s, 2H), 3.24–3.02 (m, 3H), 2.87 (s, 3H); MS (ESI) *m/e* 391 (M + H)⁺.

Example 135

30 Preparation of (E)-N-Methyl-N-(2-methyl-naphthalen-1-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(2-methyl-naphthalen-1-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the

title compound (0.431 g, 95%) was prepared as a white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.01 (br s, 1H), 11.24 (s, 1H), 8.93–8.83 (m, 1H), 8.44–8.32 (m, 1H), 8.10–8.07 (m, 1H), 7.92–7.82 (m, 2H), 7.71–7.66 (m, 1H), 7.49–7.28 (m, 4H), 5.30–5.18 (m, 2H), 4.29 (br s, 2H), 3.79 (br s, 2H), 2.87–2.81 (m, 6H), 2.55–2.51 (s, 3H); MS (ESI) m/e 415 ($\text{M} + \text{H}$) $^+$.

Example 136

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

According to the procedure of Example 1, except substituting biphenyl-2-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.255 g, 88%) was prepared as a white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.95 (br s, 1H), 11.22 (s, 1H), 8.80–8.76 (m, 1H), 8.31–8.19 (m, 1H), 7.57–7.17 (m, 11H), 4.76–4.59 (m, 2H), 4.29 (br s, 2H), 3.81 (br s, 2H), 2.99–2.73 (m, 6H); MS (ESI) m/e 427 ($\text{M} + \text{H}$) $^+$.

Example 137

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

According to the procedure of Example 1, except substituting biphenyl-3-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.404 g, 85%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.95 (br s, 1H), 11.22–11.21 (m, 1H), 8.82–8.81 (m, 1H), 8.32–8.30 (m, 1H), 7.65–7.21 (m, 11H), 7.92–7.82 (m, 2H), 4.92–4.71 (m, 2H), 4.28 (br s, 2H), 3.79 (br s, 2H), 2.17–2.96 (m, 3H), 2.88–2.84 (m, 3H); MS (ESI) m/e 427 ($\text{M} + \text{H}$) $^+$.

Example 138

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

According to the procedure of Example 1, except substituting methyl-(2-ethoxy-naphthalen-1-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.405 g, 90%) was prepared as a white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.35 (br s, 1H), 11.25 (s, 1H), 8.84–8.82 (m, 1H), 8.40–8.31 (m, 1H), 8.07–8.05 (m, 1H), 7.96–7.87 (m, 2H), 7.68–7.63 (m, 1H), 7.52–7.25 (m, 4H), 5.26–5.16 (m, 2H), 4.29–4.20 (m, 4H), 4.09 (br s, 2H), 2.91–2.63 (m, 6H), 1.43–1.29 (s, 3H); MS (ESI) m/e 445 ($\text{M} + \text{H}$) $^+$.

Example 139Preparation of (E)-N-(2-Ethoxy-benzyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-ethoxy-
 5 benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.409 g, 87%) was prepared as a white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.05 (br s, 1H), 11.20 (s, 1H), 8.82–8.77 (m, 1H), 8.32–8.27 (m, 1H), 7.61–7.55 (m, 1H), 7.44–7.35 (m, 1H), 7.27–7.20 (m, 1H), 7.09–6.90 (m, 3H), 4.76–4.59 (m, 2H), 4.28 (br s, 2H), 4.09–4.01 (m, 2H), 3.80 (br s, 2H), 3.16–
 10 2.85 (m, 6H), 1.37–1.27 (m, 3H); MS (ESI) *m/e* 395 (M + H)⁺.

Example 140Preparation of (E)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-(2,3,4-trimethoxy-benzyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,3,4-trimethoxy-
 15 benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.440 g, 92%) was prepared as a white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 11.23 (s, 1H), 8.82–8.79 (m, 1H), 8.34–8.29 (m, 1H), 7.61–7.55 (m, 1H), 7.46–7.33 (m, 1H), 6.81–6.75 (m, 2H), 4.71–4.56 (m, 2H), 4.30 (br s, 2H), 3.81–3.74 (m, 11H), 3.11–2.85 (m, 6H); MS (ESI) *m/e* 441
 20 (M + H)⁺.

Example 141Preparation of (E)-N-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,3-dihydro-
 25 benzo[1,4]dioxin-6-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.196 g, 93%) was prepared as a white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 11.25 (s, 1H), 8.82 (s, 1H), 8.32 (s, 1H), 7.63–7.56 (m, 1H), 7.45–7.31 (m, 1H), 6.86–6.68 (m, 3H), 4.70–4.49 (m, 2H), 4.30 (br s, 2H), 4.21 (m, 4H), 3.82 (br s, 2H), 3.09–2.87 (m, 6H); MS
 30 (APCI) *m/e* 409 (M + H)⁺.

Example 142Preparation of (E)-N-(2,3-Diethoxy-benzyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,3-diethoxy-
 5 benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.331 g, 87%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.49 (br s, 1H), 11.24–11.22 (m, 1H), 8.83–8.78 (m, 1H), 8.36–8.28 (m, 1H), 7.62–7.56 (m, 1H), 7.42–7.35 (m, 1H), 7.05–6.92 (m, 2H), 6.69–6.63 (m, 1H), 4.80–4.65 (m, 2H), 4.30 (br s, 2H), 4.07–3.93 (m, 4H), 3.81 (br s,
 10 2H), 3.12–2.80 (m, 6H), 1.37–1.25 (m, 6H); MS (APCI) *m/e* 439 (M + H)⁺.

Example 143Preparation of (E)-N-(3-Ethoxy-2-methoxy-benzyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3-ethoxy-2-methoxy-
 15 benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.397 g, quantitative) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.25 (br s, 1H), 11.23–11.21 (m, 1H), 8.82–8.78 (m, 1H), 8.34–8.27 (m, 1H), 7.62–7.56 (m, 1H), 7.44–7.34 (m, 1H), 7.04–6.96 (m, 2H), 6.69–6.66 (m, 1H), 4.78–4.63 (m, 2H), 4.30 (br s, 2H), 4.09–4.02 (m, 2H),
 20 3.82–3.76 (m, 5H), 3.12–2.86 (m, 6H), 1.38–1.32 (m, 3H); MS (ESI) *m/e* 425 (M + H)⁺.

Example 144Preparation of (E)-N-(2-Ethoxy-3-methyl-benzyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-ethoxy-3-methyl-
 25 benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.358 g, 84%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.21 (br s, 1H), 11.23–11.21 (m, 1H), 8.82–8.78 (m, 1H), 8.34–8.25 (m, 1H), 7.63–7.56 (m, 1H), 7.41–7.35 (m, 1H), 7.16–7.11 (m, 1H), 7.05–6.87 (m, 2H), 4.82–4.67 (m, 2H), 4.30 (br s, 2H), 3.90–3.80 (m, 4H), 3.18–2.86
 30 (m, 6H), 2.24 (s, 3H), 1.42–1.28 (m, 3H); MS (ESI) *m/e* 409 (M + H)⁺.

Example 145Preparation of (E)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-quinolin-5ylmethyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-quinolin-5-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.399 g, quantitative) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.30 (br s, 1H), 11.19–11.13 (m, 1H), 8.90–8.98 (m, 1H), 8.82–8.62 (m, 2H), 8.34–8.18 (m, 1H), 8.06–7.99 (m, 1H), 7.83–7.87 (m, 1H), 7.72–7.27 (m, 4H), 5.41–5.15 (m, 2H), 4.28–4.19 (m, 2H), 3.79–3.74 (m, 2H), 3.12–3.01 (m, 3H), 2.85–2.79 (m, 3H); MS (ESI) *m/e* 402 (M + H)⁺.

Example 146

Preparation of (*E*)-*N*-(3-Methoxy-2-propoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3-methoxy-2-propoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.275 g, 87%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.21 (m, 1H), 11.23–11.21 (m, 1H), 8.83–8.78 (m, 1H), 8.34–8.25 (m, 1H), 7.63–7.56 (m, 1H), 7.40–7.34 (m, 1H), 7.05–6.97 (m, 2H), 6.69–6.64 (m, 1H), 4.80–4.65 (m, 2H), 4.30 (m, 2H), 3.92–3.85 (m, 2H), 3.79 (s, 3H), 3.49 (br s, 2H), 3.12–2.86 (m, 6H), 1.75–1.68 (m, 2H), 1.01–0.94 (m, 3H); MS (ESI) *m/e* 439 (M + H)⁺.

Example 147

Preparation of (*E*)-*N*-(3-Methoxy-2-isopropoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3-methoxy-2-isopropoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.304 g, 85%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.20 (br s, 1H), 11.24–11.21 (m, 1H), 8.82–8.77 (m, 1H), 8.35–8.23 (m, 1H), 7.61–7.56 (m, 1H), 7.40–7.30 (m, 1H), 7.04–6.93 (m, 2H), 6.67–6.61 (m, 1H), 4.79–4.65 (m, 2H), 4.59–4.48 (m, 1H), 4.30–4.28 (br s, 2H), 3.79 (s, 3H), 3.58–3.55 (m, 2H), 3.10–2.86 (m, 6H), 1.24–1.21 (m, 6H); MS (ESI) *m/e* 439 (M + H)⁺.

Example 148

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

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzofuran-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.376 g, 87%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.16 (br s, 1H), 11.23 (s, 1H), 8.85–8.82 (m, 1H), 8.33 (s, 1H), 7.63–7.22 (m, 6H), 5.01–4.81 (m, 2H), 4.30 (m, 2H), 3.58 (br s, 2H), 3.20–2.88 (m, 6H), 2.27 (m, 3H); MS (ESI) m/e 405 ($\text{M} + \text{H}$) $^+$.

Example 149

Preparation of (*E*)-*N*-(3-Chloro-2-methoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3-chloro-2-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.312 g, 92%) was prepared as an off-white solid and as a mixture of amide rotamers: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.55 (br s, 1H), 11.21–11.19 (m, 1H), 8.82–8.79 (m, 1H), 8.35–8.28 (m, 1H), 7.61–7.57 (m, 1H), 7.45–7.31 (m, 2H), 7.19–7.11 (m, 2H), 4.87–4.70 (m, 2H), 4.30 (m, 2H), 3.82–3.77 (m, 5H), 3.17–2.86 (m, 6H); MS (ESI) m/e 415 ($\text{M} + \text{H}$) $^+$.

Example 150

Preparation of (*E*)-*N*-(3-Chloro-2-ethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3-chloro-2-ethoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.169 g, 91%) was prepared as a white solid and as a mixture of amide rotamers: ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.44 (br s, 1H), 11.20–11.18 (m, 1H), 8.82–8.78 (m, 1H), 8.34–8.25 (m, 1H), 7.62–7.57 (m, 1H), 7.44–7.36 (m, 2H), 7.18–7.10 (m, 2H), 4.87–4.70 (m, 2H), 4.30 (m, 2H), 4.05–3.98 (m, 2H), 3.79–3.61 (m, 2H), 3.16–2.85 (m, 6H), 1.39–1.35 (m, 3H); MS (ESI) m/e 429 ($\text{M} + \text{H}$) $^+$.

Example 151

Preparation of (*E*)-*N*-(2,3-Dihydro-benzo[1,4]dioxin-5-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,3-dihydro-benzo[1,4]dioxin-5-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.058 g, quantitative) was prepared as a white solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.15 (br s, 1H),

11.22–11.20 (m, 1H), 8.82–8.76 (m, 1H), 8.34–8.27 (m, 1H), 7.60–7.55 (m, 1H), 7.40–7.33 (m, 1H), 6.84–6.76 (m, 2H), 6.62–6.57 (m, 1H), 4.74–4.57 (m, 2H), 4.30–4.24 (m, 6H), 3.80 (br s, 2H), 3.16–2.87 (m, 6H); MS (ESI) m/e 409 ($M+H$)⁺.

Example 152

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

According to the procedure of Example 1, except substituting (4,5-dimethyl-naphthalen-1-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.244 g, 66%) was prepared as a white solid and as a
 10 mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.08 (br s, 1H), 11.22–11.17 (m, 1H), 8.83–8.73 (m, 1H), 8.33–8.17 (m, 1H), 7.94–7.87 (m, 1H), 7.68–7.62 (m, 1H), 7.45–7.22 (m, 5H), 5.25–5.03 (m, 2H), 4.29–4.21 (m, 2H), 3.80 (br s, 2H), 3.11–3.04 (m, 3H), 2.97–2.81 (m, 9H); MS (ESI) m/e 429 ($M+H$)⁺.

Example 153

15 Preparation of (*E*)-*N*-Methyl-*N*-(2-methyl-benzofuran-3-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(2-methyl-benzofuran-3-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.213 g, 53%) was prepared as a white solid and as a mixture of amide
 20 rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.24 (br s, 1H), 11.22 (s, 1H), 8.88–8.82 (m, 1H), 8.38–8.33 (m, 1H), 7.79–7.15 (m, 6H), 4.95–4.75 (m, 2H), 4.29 (br s, 2H), 3.80 (br s, 2H), 3.13–2.83 (m, 6H), 2.59–2.44 (m, 3H); MS (ESI) m/e 405 ($M+H$)⁺.

Example 154

25 Preparation of (*E*)-*N*-Methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-*N*-quinolin-5-ylmethyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-quinolin-5-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid
 30 hydrochloride, the title compound (0.387 g, quantitative) was prepared as a tan solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.69–10.63 (m, 1H), 9.26–9.13 (m, 2H), 8.39–8.25 (m, 2H), 8.11–7.93 (m, 3H), 7.77–7.45 (m, 2H), 7.30–7.17 (m,

1H), 5.50–5.22 (m, 2H), 3.15–3.01 (m, 3H), 2.94–2.78 (m, 2H), 2.56–2.44 (m, 2H); MS (ESI) m/e 373 ($M + H$)⁺.

Example 155

5 Preparation of (*E*)-*N*-benzyl-*N*-methyl-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylamide

According to the procedure of Example 1 (a), except substituting benzyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.462 g, 93%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 8.37–8.33 (m, 1H), 8.08–8.06 (m, 1H), 7.54–7.49 (m, 1H), 7.37–7.21 (m, 6H), 4.82–4.61 (m, 2H), 3.10–2.85 (m, 5H), 2.56–2.49 (m, 2H); MS (APCI) m/e 322 ($M + H$)⁺.

Example 156

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

According to the procedure of Example 1, except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.27 g, 86%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.96 (br s, 1H), 11.06–11.22 (m, 1H), 8.80–8.83 (m, 1H), 8.25–8.34 (m, 1H), 7.61–7.66 (m, 1H), 7.33–7.52 (m, 3H), 7.11–7.15 (m, 1H), 6.97–7.04 (m, 1H), 6.18–6.43 (m, 1H), 4.87–5.08 (m, 2H), 4.26–4.29 (m, 2H), 3.69–3.80 (m, 5H), 3.02–3.14 (m, 3H), 2.85–2.88 (m, 3H); MS (ESI) m/e 404 ($M + H$)⁺.

Example 157

25 Preparation of (*E*)-(7-{2-[Methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]vinyl}-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-4-yl)acetic acid ethyl ester hydrochloride

According to the procedure of Example 1, except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(4-ethoxycarbonylmethyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.22 g, 56%) was prepared as a yellow powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.53–10.54 (m, 1H), 8.56–8.59 (m, 1H),

8.09–8.16 (m, 1H), 7.28–7.61 (m, 4H), 7.10–7.15 (m, 1H), 6.99–7.04 (m, 1H), 6.19–6.42 (m, 1H), 4.86–5.06 (m, 2H), 4.00–4.14 (m, 5H), 3.62–3.72 (m, 7H), 2.99–3.12 (m, 3H), 1.12–1.20 (m, 3H); MS (ESI) m/e 476 ($M + H$)⁺.

Example 158

- 5 Preparation of (*E*)-*N*-(2,3-Dimethoxy-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2,3-dimethoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.25 g, 58%) was prepared as an off-white powder and as a mixture of amide
10 rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.89 (br s, 1H), 11.21 (s, 1H), 8.78–8.82 (m, 1H), 8.26–8.33 (m, 1H), 7.56–7.61 (m, 1H), 7.34–7.44 (m, 1H), 6.96–7.07 (m, 2H), 6.67–6.71 (m, 1H), 4.64–4.79 (m, 2H), 4.28 (s, 2H), 3.74–3.81 (m, 8H), 2.87–3.13 (m, 6H); MS (ESI) m/e 411 ($M + H$)⁺.

Example 159

- 15 Preparation of (*E*)-*N*-Methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(4-methyl-naphthalen-1-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.41 g, 74%) was prepared as a tan powder and as a mixture of amide
20 rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.82 (br s, 1H), 11.16–11.20 (m, 1H), 8.74–8.83 (m, 1H), 8.06–8.33 (m, 3H), 7.56–7.69 (m, 3H), 7.33–7.39 (m, 3H), 5.09–5.32 (m, 2H), 4.20–4.28 (m, 2H), 3.80 (s, 2H), 2.99–3.06 (m, 3H), 2.81–2.86 (m, 3H), 2.64–2.66 (m, 3H); MS (ESI) m/e 415 ($M + H$)⁺.

Example 160

- 25 Preparation of (*E*)-*N*-(2-Methoxy-naphthalen-1-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-methoxy-naphthalen-1-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.41 g, 71%) was prepared as an off-white powder and
30 as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.88 (br s, 1H), 11.20 (s, 1H), 8.81–8.85 (m, 1H), 8.30–8.36 (m, 1H), 7.88–8.08 (m, 3H), 7.24–7.69 (m, 5H), 5.15–5.24 (m, 2H), 4.28 (s, 2H), 3.80–3.99 (m, 5H), 2.64–2.90 (m, 6H); MS (ESI) m/e 431 ($M + H$)⁺.

Example 161Preparation of (R)-(+)-(E)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-(1-naphthalen-1-yl-ethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (R)-(+)-N-methyl-1-(1-naphthyl)ethylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.26 g, 48%) was prepared as an off-white powder and as a mixture of amide rotamers: $[\alpha]^{25}_D +92.6^\circ$ (*c* 1.00, methanol); ^1H NMR (300 MHz, DMSO-*d*₆) δ 12.11 (br s, 1H), 11.22 (s, 1H), 8.81–8.89 (m, 1H), 8.30–8.42 (m, 1H), 7.92–7.98 (m, 3H), 7.67–7.79 (m, 2H), 7.50–7.60 (m, 3H), 7.20–7.25 (m, 1H), 6.53–6.57 (m, 1H), 4.28 (s, 2H), 3.80 (s, 2H), 2.86–2.89 (m, 3H), 2.45–2.73 (m, 3H), 1.60–1.75 (m, 3H); MS (ESI) *m/e* 415 (*M* + *H*)⁺.

Example 162Preparation of (S)-(-)-(E)-N-Methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-(1-naphthalen-1-yl-ethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (S)-(-)-N-methyl-1-(1-naphthyl)ethylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.34 g, 63%) was prepared as an off-white powder: $[\alpha]^{25}_D -89.1^\circ$ (*c* 1.00, methanol); ^1H NMR (300 MHz, DMSO-*d*₆) δ 12.20 (br s, 1H), 11.21 (s, 1H), 8.88–8.81 (m, 1H), 8.41–8.30 (m, 1H), 7.98–7.92 (m, 3H), 7.72–7.67 (m, 2H), 7.59–7.50 (m, 3H), 7.25–7.19 (m, 1H), 6.57–6.51 (m, 1H), 4.28 (br s, 2H), 3.79 (br s, 2H), 2.89–2.85 (m, 3H), 2.73–2.67 (m, 3H), 1.75–1.59 (m, 3H); MS (ESI) *m/e* 415 (*M* + *H*)⁺.

Example 163Preparation of (E)-N-Benzo[*b*]thiophen-2-ylmethyl-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting benzo[*b*]thiophen-2-ylmethyl-methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.40 g, 74%) was prepared as a tan powder: ^1H NMR (300 MHz, DMSO-*d*₆) δ 11.94 (br s, 1H), 11.14 (s, 1H), 8.89–8.84 (m, 1H), 8.33–8.31 (m, 1H), 7.90–7.87 (m, 1H), 7.81–7.79 (m, 1H), 7.66–7.52 (m, 1H), 7.39–7.31 (m, 4H), 5.13–4.87 (m, 2H), 4.30 (br s, 2H), 3.81 (br s, 2H), 3.20–3.00 (m, 3H), 2.89 (s, 3H); MS (ESI) *m/e* 407 (*M* + *H*)⁺.

Example 164Preparation of (E)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-N-(3-trifluoromethyl-benzyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-trifluoromethyl-benzyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.39 g, 69%) was prepared as a tan powder: ^1H NMR (300 MHz, DMSO- d_6) δ 12.08 (br s, 1H), 11.23 (s, 1H), 8.83–8.81 (m, 1H), 8.33–8.27 (m, 1H), 7.66–7.35 (m, 6H), 4.96–4.72 (m, 2H), 4.30 (br s, 2H), 3.80 (br s, 2H), 3.17–2.85 (m, 6H); MS (ESI) m/e 419 ($M + H$) $^+$.

Example 165

Preparation of (*E*)-*N*-(2-Chloro-benzyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-chlorobenzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.38 g, 72%) was prepared as an off-white powder: ^1H NMR (300 MHz, DMSO- d_6) δ 11.90 (br s, 1H), 11.23–11.91 (m, 1H), 8.83–8.78 (m, 1H), 8.34–8.24 (m, 1H), 7.63–7.32 (m, 5H), 7.20–7.16 (m, 1H), 4.92–4.71 (m, 2H), 4.30 (br s, 2H), 3.81 (br s, 2H), 3.20 (s, 2H), 2.91–2.86 (m, 4H); MS (ESI) m/e 385 ($M + H$) $^+$.

Example 166

Preparation of (*E*)-*N*-Methyl-*N*-(4-methyl-benzyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting *N*-methyl-*N*-(4-methylbenzyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.24 g, 48%) was prepared as tan powder: ^1H NMR (300 MHz, DMSO- d_6) δ 12.25 (br s, 1H), 11.23–11.22 (m, 1H), 8.82–8.79 (m, 1H), 8.33–8.30 (m, 1H), 7.62–7.58 (m, 1H), 7.57–7.32 (m, 1H), 7.19–7.10 (m, 4H), 4.78–4.58 (m, 2H), 4.29 (br s, 2H), 3.80 (br s, 2H), 3.09–2.87 (m, 6H), 2.28 (s, 3H); MS (ESI) m/e 365 ($M + H$) $^+$.

Example 167

Preparation of (*R*)-(-)-(*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*R*)-(*E*)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.19 g, 35%) was prepared as a tan powder: $[\alpha]_D^{25}$ -173.9° (c 1.00, methanol); ^1H NMR (300 MHz,

DMSO-*d*₆) δ 12.50 (br s, 1H), 11.27 (s, 1H), 8.83–8.74 (m, 1H), 8.32–8.25 (m, 1H), 7.65–7.60 (m, 1H), 7.51–7.32 (m, 3H), 7.15–6.96 (m, 2H), 6.43–6.18 (m, 1H), 5.07–4.86 (m, 2H), 4.47–4.21 (m, 3H), 3.79–2.88 (m, 9H), 2.09–1.88 (m, 3H); MS (ESI) *m/e* 430 (M + H)⁺.

5 Example 168

Preparation of (S)-(+)-(E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and
 10 substituting (S)-(E)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (91 mg, 23%) was prepared as a tan powder: $[\alpha]^{25}_{\text{D}} +197.7^{\circ}$ (*c* 1.00, methanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.51 (br s, 1H), 11.28 (s, 1H), 8.83–8.74 (m, 1H), 8.32–8.25 (m, 1H),
 15 7.65–7.60 (m, 1H), 7.51–7.32 (m, 3H), 7.15–6.98 (m, 2H), 6.43–6.18 (m, 1H), 5.07–4.86 (m, 2H), 4.46–4.21 (m, 3H), 3.73–3.62 (m, 4H), 3.18–2.87 (m, 5H), 2.08–1.88 (m, 3H); MS (ESI) *m/e* 430 (M + H)⁺.

Example 169

Preparation of (E)-3-[4-(4-Methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]-N-methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and
 substituting (E)-3-[4-(4-methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-
 25 tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.20 g, 83%) was prepared as a tan powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.07 (br s, 1H), 11.23–11.21 (m, 1H), 8.78 (s, 1H), 8.27–8.20 (m, 1H), 7.64–6.99 (m, 10H), 6.42–6.18 (m, 1H), 5.06–4.86 (m, 2H), 4.32–4.20 (m, 4H), 3.77–3.68 (m, 8H), 3.12–
 30 3.00 (m, 3H); MS (ESI) *m/e* 510 (M + H)⁺.

Example 170

Preparation of (E)-N-Methyl-N-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride [AP-501382]

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

A solution of (*E*)-3-[4-(4-methoxy-benzyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide (2.00 g, 3.92 mmol), from Example 65, in dichloroethane (80 mL) was cooled in an ice bath and treated with 1-chloroethyl chloroformate (0.47 mL, 4.31 mmol). After stirring at 0 °C under N₂ for 30 min and then at room temperature for 30 min, the mixture was heated to reflux for 1.5 h. The mixture was allowed to cool and then concentrated to dryness. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3) gave a tan solid. The solid was suspended in methanol and heated to reflux for 2 h. The mixture was allowed to cool and the solid was isolated by filtration, dissolved in CH₂Cl₂, washed with 1 N NaOH, dried over Na₂SO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (silica gel, CH₂Cl₂/MeOH, 97:3 to 95:5) gave the title compound (0.70 g, 49%) as an off-white solid: ¹H NMR (300 MHz, CDCl₃) δ 8.38–8.33 (m, 2H), 7.72–7.67 (m, 1H), 7.60–7.57 (m, 2H), 7.32–7.20 (m, 3H), 7.14–7.09 (m, 1H), 6.90–6.80 (m, 1H), 6.49–6.38 (m, 1H), 4.93–4.78 (m, 2H), 4.08 (s, 2H), 3.95 (s, 2H), 3.71 (s, 3H), 3.13–3.07 (m, 3H); MS (ESI) *m/e* 390 (M + H)⁺.

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

According to the procedure of Example 1(b), except substituting (*E*)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide for the (*E*)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)-*N*-(1-propyl-naphthalen-2-ylmethyl)acrylamide, the title compound (0.14 g, 89%) was prepared as a tan solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.09–11.06 (m, 1H), 9.90–9.89 (s, 2H), 8.76–8.73 (m, 1H), 8.31–8.23 (m, 1H), 7.64–7.59 (m, 1H), 7.51–7.31 (m, 3H), 7.15–7.10 (m, 1H), 7.03–6.96 (m, 1H), 6.43–6.16 (m, 1H), 5.07–4.86 (m, 2H), 4.26–4.20 (m, 2H), 3.85–3.80 (m, 2H), 3.73–3.69 (m, 3H), 3.13–3.01 (m, 3H); MS (ESI) *m/e* 390 (M + H)⁺.

Example 171

30 Preparation of (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[4-(2-morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-[4-(2-morpholin-4-yl-ethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (90 mg, 74%) was prepared as a tan solid: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.58 (br s, 2H), 8.62 (s, 1H), 8.27–8.25 (m, 1H), 7.88–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.61–7.53 (m, 1H), 7.42–7.29 (m, 3H), 5.15–4.89 (m, 2H), 4.03–3.65 (m, 12H), 3.28–3.17 (m, 4H), 3.01–2.64 (m, 3H), 2.42 (s, 3H); MS (ESI) *m/e* 520 (M + H)⁺.

10 Example 172

Preparation of (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl} acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl} acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.18 g, 53%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.91 (br s, 1H), 10.55 (br s, 1H), 8.61 (s, 1H), 8.18 (s, 1H), 7.88–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.61–7.52 (m, 1H), 7.42–7.28 (m, 3H), 5.14–4.89 (m, 2H), 4.42–4.38 (m, 1H), 4.01 (br s, 3H), 3.65 (s, 4H), 3.39 (br s, 4H), 3.16 (s, 2H), 3.04–2.94 (m, 3H), 2.74 (br s, 3H), 2.42 (s, 3H); MS (ESI) *m/e* 547 (M + H)⁺.

Example 173

25 Preparation of (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.20 g, 56%) was prepared as an off-white powder: ¹H

NMR (300 MHz, DMSO-*d*₆) δ 10.88 (br s, 1H), 10.48 (br s, 1H), 8.58 (s, 1H), 8.31 (s, 1H), 7.88–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.60–7.55 (m, 1H), 7.42–7.30 (m, 3H), 5.16–4.89 (m, 2H), 3.98 (br s, 2H), 3.92–3.79 (m, 4H), 3.63 (br s, 2H), 3.37–3.33 (m, 6H), 3.18–3.10 (m, 2H), 2.94 (s, 1H), 2.63 (br s, 2H), 2.42 (s, 3H), 1.92 (br s, 2H); MS (ESI) *m/e* 534 (M + H)⁺.

Example 174

Preparation of (*E*)-*N*-(2-Ethoxy-3-methoxy-benzyl)-*N*-methyl-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-ethoxy-3-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-{4-[2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (82 mg, 47%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.97 (br s, 1H), 10.67 (br s, 1H), 8.64–8.60 (m, 1H), 8.23–8.14 (m, 1H), 7.58–7.52 (m, 1H), 7.39–7.33 (m, 1H), 7.07–6.94 (m, 2H), 6.69–6.63 (m, 1H), 4.80–4.64 (m, 2H), 4.42–4.38 (m, 1H), 4.09–3.93 (m, 3H), 3.79 (s, 3H), 3.68 (br s, 2H), 3.47–3.37 (m, 8H), 3.11–2.97 (m, 5H), 2.75 (br s, 3H), 1.31–1.24 (m, 3H); MS (ESI) *m/e* 551 (M + H)⁺.

Example 175

Preparation of (*S*)-(+)-(*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*S*)-(*E*)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1*H*-3a,8,9-triaza-benzo[*f*]azulen-6-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.15 g, 62%) was prepared as a tan powder: $[\alpha]^{25}_{\text{D}} +167.8^{\circ}$ (*c* 1.05, methanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.33 (br s, 1H), 11.30 (br s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 7.89–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.65–7.55 (m, 1H), 7.42–7.31 (m, 3H), 5.13–4.90 (m, 2H), 4.47–4.22 (m, 2H), 3.61 (br s, 1H), 3.42–3.39 (br s, 4H), 3.17–2.95 (m, 3H), 2.42 (s, 3H), 2.10–1.88 (2H); MS (ESI) *m/e* 447 (M + H)⁺.

Example 176Preparation of (R)-(-)-(E)-N-Methyl-N-(3-methyl-benzo[b]thiophen-2-ylmethyl)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1H-3a,8,9-triaza-benzo[f]azulen-6-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzo[b]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (R)-(E)-3-(10-oxo-2,3,4,9,10,10a-hexahydro-1H-3a,8,9-triaza-benzo[f]azulen-6-yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (96 mg, 57%) was prepared as a tan powder: $[\alpha]_D^{25} -154.3^\circ$ (c 1.01, methanol); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.47 (br s, 1H), 11.29 (br s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 7.89–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.65–7.60 (m, 1H), 7.42–7.31 (m, 3H), 5.13–4.90 (m, 2H), 4.48–4.25 (m, 2H), 3.59–3.47 (m, 5H), 3.17–2.95 (m, 3H), 2.42 (s, 3H), 2.10–1.89 (m, 2H); MS (ESI) *m/e* 447 (M + H)⁺.

Example 177

15 Preparation of (E)-N-(4-Fluoro-naphthalen-1-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (4-fluoro-naphthalen-1-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.20 g, 72%) was prepared as a white powder: ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.22 (br s, 1H), 11.26–11.17 (m, 1H), 8.83–8.76 (m, 1H), 8.34–8.10 (m, 3H), 7.72–7.64 (m, 3H), 7.44–7.32 (m, 3H), 5.32–5.09 (m, 2H), 4.30 (br s, 2H), 3.85 (br s, 2H), 3.12–2.98 (m, 3H), 2.89–2.83 (m, 3H); MS (ESI) *m/e* 419 (M + H)⁺.

Example 178

25 Preparation of (E)-N-(4-Chloro-naphthalen-1-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (4-chloro-naphthalen-1-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.28 g, 48%) was prepared as a white powder: ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.29 (br s, 1H), 11.23–11.17 (m, 1H), 8.84–8.75 (m, 1H), 8.33–8.18 (m, 3H), 7.76–7.32 (m, 6H), 5.37–5.12 (m, 2H), 4.31 (br s, 2H), 3.80 (br s, 2H), 3.11–3.00 (m, 3H), 2.89–2.82 (m, 3H); MS (ESI) *m/e* 435 (M + H)⁺.

Example 179

Preparation of (*E*)-*N*-Methyl-*N*-(3-methyl-benzofuran-2-ylmethyl)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(3-methyl-benzofuran-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.28 g, 78%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.74–10.54 (m, 2H), 8.61 (s, 1H), 8.29 (s, 1H), 7.63–7.47 (m, 3H), 7.34–7.23 (m, 3H), 5.03–4.80 (m, 2H), 4.02 (br s, 2H), 3.87–3.79 (m, 4H), 3.65 (br s, 2H), 3.48–3.38 (br s, 4H), 3.20–2.93 (m, 5H), 2.72–2.57 (br s, 2H), 2.26 (s, 3H), 1.95 (s, 2H); MS (ESI) *m/e* 518 (M + H)⁺.

Example 180

Preparation of (*E*)-*N*-(2-Isopropoxy-3-methoxy-benzyl)-*N*-methyl-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-isopropoxy-3-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.17 g, 44%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.01 (br s, 1H), 10.66 (br s, 1H), 8.62 (br s, 1H), 8.35–8.22 (m, 1H), 7.57–7.52 (m, 1H), 7.40–7.32 (m, 1H), 7.05–6.93 (m, 2H), 6.66–6.62 (m, 1H), 4.80–4.64 (m, 2H), 4.60–4.45 (m, 1H), 4.08 (br s, 2H), 3.87–3.81 (m, 6H), 3.79 (s, 3H), 3.68 (br s, 2H), 3.50–3.38 (m, 4H), 3.21 (br s, 2H), 3.10–2.72 (m, 3H), 2.01 (br s, 2H), 1.27–1.15 (m, 6H); MS (ESI) *m/e* 552 (M + H)⁺.

Example 181

Preparation of (*E*)-*N*-Methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)-3-{4-[3-(4-methyl-piperazin-1-yl)propyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl}acrylamide hydrochloride

According to the procedure of Example 2, except substituting 7-bromo-4-[3-(4-methyl-piperazin-1-yl)propyl]-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one for the 7-bromo-3,3-dimethyl-1,3,4,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepin-2-one, the title compound (0.15 g, 49%) was prepared as a tan powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.06 (br s, 1H), 10.64 (br s, 1H), 8.63 (s, 1H), 8.29–8.22 (m, 1H), 7.88–7.86 (m, 1H), 7.75–7.72 (m, 1H), 7.61–7.53 (m, 1H), 7.42–7.29 (m, 3H), 5.14–4.89 (m, 2H), 4.04 (br s, 2H), 3.65 (br s, 2H), 3.48–3.31 (m, 13H), 3.24–2.29 (m, 3H), 2.76 (br s, 2H), 2.42 (s, 3H), 1.89 (br s, 2H); MS (ESI) *m/e* 547 (M + H)⁺.

Example 182

10 Preparation of (*E*)-*N*-Methyl-*N*-(2-methyl-benzofuran-3-ylmethyl)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylamide hydrochloride

According to the procedure of Example 1, except substituting methyl-(2-methyl-benzofuran-3-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-[4-(3-morpholin-4-yl-propyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.24 g, 68%) was prepared as a white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.86 (br s, 1H), 10.47 (br s, 1H), 8.54 (br s, 1H), 8.38–8.29 (m, 1H), 7.78–7.46 (m, 3H), 7.32–7.15 (m, 3H), 4.97–4.74 (m, 2H), 4.02–3.91 (m, 5H), 3.87–3.79 (m, 4H), 3.63 (br s, 2H), 3.45–3.29 (m, 4H), 3.27–3.15 (m, 4H), 3.07–2.82 (m, 3H), 1.93 (br s, 2H); MS (ESI) *m/e* 518 (M + H)⁺.

Example 183

25 Preparation of (*E*)-*N*-(3-Chloro-benzo[*b*]thiophen-2-ylmethyl)-*N*-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (3-chlorobenzo[*b*]thiophen-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.39 g, 88%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.40–11.21 (m, 2H), 8.84 (s, 1H), 8.35–8.30 (m, 1H), 8.04–8.00 (m, 1H), 7.79–7.77 (m, 1H), 7.55–7.34 (m, 4H), 5.21–4.94 (m, 2H), 4.29 (br s, 2H), 3.81 (br s, 2H), 3.24–3.00 (m, 3H), 2.88 (s, 3H); MS (ESI) *m/e* 441 (M + H)⁺.

Example 184

Preparation of (E)-N-(5-Chloro-1-methyl-1H-indol-2-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (5-chloro-1-methyl-1H-indol-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.32 g, 43%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.50–11.20 (m, 2H), 8.83–8.80 (m, 1H), 8.35–8.27 (m, 1H), 7.66–7.34 (m, 4H), 7.14–7.11 (m, 1H), 6.41–6.18 (m, 1H), 5.08–4.86 (m, 2H), 4.45–4.15 (m, 2H), 3.80–3.45 (m, 5H), 3.02–2.88 (m, 3H), 2.73 (s, 3H); MS (ESI) *m/e* 438 (M + H)⁺.

10 Example 185

Preparation of (E)-N-(1,7-Dimethyl-1H-indol-2-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (1,7-dimethyl-1H-indol-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.25 g, 43%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.85–11.12 (m, 2H), 8.78 (s, 1H), 8.31–8.21 (m, 1H), 7.65–7.60 (m, 1H), 7.38–7.27 (m, 2H), 6.88–6.82 (m, 2H), 6.39–6.11 (m, 1H), 5.03–4.83 (m, 2H), 4.24 (br s, 2H), 3.95–3.44 (m, 5H), 3.17–3.01 (m, 6H), 2.82–2.72 (m, 3H); MS (ESI) *m/e* 418 (M + H)⁺.

20 Example 186

Preparation of (E)-N-(5-Fluoro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (5-fluoro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.33 g, 75%) was prepared as a white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.15–11.20 (m, 2H), 8.82 (s, 1H), 8.33–8.29 (m, 1H), 7.93–7.89 (m, 1H), 7.65–7.19 (m, 4H), 5.14–4.89 (m, 2H), 4.27 (br s, 2H), 3.80 (br s, 2H), 3.18–2.96 (m, 3H), 2.86 (s, 3H), 2.40 (s, 3H); MS (ESI) *m/e* 439 (M + H)⁺.

30 Example 187

Preparation of (E)-N-(5-Chloro-3-methyl-benzo[*b*]thiophen-2-ylmethyl)-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (5-chloro-3-methylbenzo[*b*]thiophen-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.39 g, 75%) was prepared as an off-white powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.90–11.25 (m, 2H), 8.85 (s, 1H), 8.34–8.31 (m, 1H), 7.94–7.32 (m, 5H), 5.15–4.90 (m, 2H), 4.31 (br s, 2H), 3.83 (br s, 2H), 3.18–2.89 (m, 6H), 2.38 (s, 3H); MS (ESI) *m/e* 455 (M + H)⁺.

Example 188

Preparation of (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-(1,7-dimethyl-1*H*-indol-2-ylmethyl)-*N*-methyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting (1,7-dimethyl-1*H*-indol-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(6-amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.31 g, 80%) was prepared as pale yellow powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.49 (s, 1H), 8.38–8.35 (m, 1H), 7.54–7.49 (m, 1H), 7.31–7.14 (m, 2H), 6.85–6.81 (m, 2H), 6.37–6.08 (m, 1H), 5.03–4.81 (m, 2H), 4.31 (br s, 2H), 3.96–3.72 (m, 7H), 3.42–2.99 (m, 10H), 2.72 (s, 3H); MS (ESI) *m/e* 434 (M + H)⁺.

Example 189

Preparation of (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-(2-ethoxy-3-methoxy-benzyl)-*N*-methyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting (2-ethoxy-3-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(6-amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.27 g, 70%) was prepared as pale yellow powder: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83–8.65 (m, 1H), 8.40 (s, 1H), 7.52–7.45 (m, 1H), 7.29–7.24 (m, 1H), 7.04–6.96 (m, 2H), 6.65–6.64 (m, 1H), 4.80–4.64 (m, 2H), 4.35 (br s, 2H), 4.02–3.79 (m, 10H), 3.39–2.83 (m, 8H), 1.31–1.25 (m, 3H); MS (ESI) *m/e* 441 (M + H)⁺.

Example 190

Preparation of (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylamide

According to the procedure of Example 1 (a), except substituting methyl-(1-methyl-1*H*-indol-3-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (0.70 g, 75%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, CDCl₃) δ 8.39–8.26 (m, 2H), 7.72–7.53 (m, 3H), 7.36–7.09 (m, 3H), 7.02–6.84 (m, 1H), 4.86–4.84 (m, 2H), 3.95–3.90 (m, 2H), 3.78–3.76 (m, 5H), 3.13–3.08 (m, 3H), 2.49–2.46 (m, 3H); MS (ESI) *m/e* 404 (M + H)⁺.

Example 191

Preparation of (*E*)-7-{2-[Methyl-(1-methyl-1*H*-indol-3-ylmethyl)-carbamoyl]-vinyl}-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester

According to the procedure of Example 1 (a), except substituting methyl-(1-methyl-1*H*-indol-3-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-7-(2-carboxy-vinyl)-2-oxo-1,2,3,5-tetrahydro-pyrido[2,3-*e*][1,4]diazepine-4-carboxylic acid benzyl ester hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.29 g, 73%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.43 (s, 1H), 8.51 (s, 1H), 8.11–8.25 (m, 1H), 7.53–7.64 (m, 2H), 7.30–7.42 (m, 5H), 7.12–7.20 (m, 4H), 6.98–7.03 (m, 1H), 5.03–5.08 (m, 2H), 4.75–4.93 (m, 2H), 4.62 (s, 2H), 4.41 (s, 2H), 3.73–3.77 (m, 3H), 2.91–3.06 (m, 3H); MS (ESI) *m/e* 524 (M + H)⁺.

Example 192

Preparation of (*E*)-3-(2,4-Dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)acrylamide

According to the procedure of Example 1 (a), except substituting methyl-(1-methyl-1*H*-indol-3-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidin-6-yl)acrylic acid for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.16 g, 34%) was prepared as a tan solid and as a mixture of amide rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.84 (s, 1H), 11.53 (s, 1H), 8.91 (s, 1H), 8.73–8.66 (m, 1H), 7.78–7.30 (m, 5H), 7.17–7.12 (m, 1H), 7.03–6.98 (m, 1H), 4.96–4.73 (m, 2H), 3.76 (s, 3H), 3.07–2.90 (m, 3H); MS (ESI) *m/e* 390 (M + H)⁺.

Example 193

Preparation of (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridin-6-yl)acrylamide

According to the procedure of Example 1 (a), except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridine-6-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.23 g, 34%) was prepared as an off-white solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.64 (br s, 1H), 8.37–8.12 (m, 2H), 7.64 (d, *J* = 15.3 Hz, 1H), 7.51–7.26 (m, 3H), 7.17–7.07 (m, 1H), 7.04–6.94 (m, 1H), 6.42–6.17 (m, 1H), 5.06–4.85 (m, 2 H), 3.73–3.68 (m, 3H), 3.12–2.99 (m, 3H); MS (ESI) *m/e* 363 (*M* + *H*)⁺.

10 Example 194

Preparation of (*E*)-*N*-Methyl-*N*-(1-methyl-1*H*-indol-3-ylmethyl)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridin-6-yl)acrylamide

According to the procedure of Example 1 (a), except substituting methyl-(1-methyl-1*H*-indol-3-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-(2-oxo-2,3-dihydro-oxazolo[4,5-*b*]pyridine-6-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.075 g, 23%) was prepared as a light brown solid: ¹H NMR (300 MHz, CDCl₃) δ 8.28–8.24 (m, 1H), 7.82 (d, *J* = 15.4 Hz, 1H), 7.71–7.49 (m, 2H), 7.37–6.87 (m, 5H), 4.88–4.86 (m, 2H), 3.78 (s, 3H), 3.16–3.12 (m, 3H); MS (ESI) *m/e* 363 (*M* + *H*)⁺.

20 Example 195

Preparation of (*E*)-3-(6-Amino-5-{2-[methyl-(1-methyl-1*H*-indol-2-ylmethyl)carbamoyl]ethyl}pyridin-3-yl)-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide

According to the procedure of Example 1 (a), except substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, and substituting (*E*)-3-[6-amino-5-(2-carboxy-ethyl)pyridin-3-yl]acrylic acid for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, the title compound (0.37 g, 28%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.07 (m, 1H), 7.75–7.68 (m, 1H), 7.49–7.34 (m, 5H), 7.11–6.98 (m, 5H), 6.39–6.12 (m, 4H), 4.95–4.68 (m, 4H), 3.69 (s, 3H), 3.61 (s, 3H), 3.02–2.71 (m, 10H); MS (ESI) *m/e* 549 (*M* + *H*)⁺.

Example 196Preparation of (E)-3-(6-Amino-5-piperidin-1-ylmethyl-pyridin-3-yl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide

According to the procedure of Example 1 (a), except substituting (E)-3-(6-amino-5-piperidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(1-methyl-1H-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (294 mg, 54%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.12 (s, 1H), 7.78–7.68 (m, 1H), 7.49–7.38 (m, 3H), 7.14–6.97 (m, 3H), 6.63 (s, 2H), 6.41–6.18 (m, 1H), 5.02–4.83 (m, 2H), 3.72–3.67 (m, 3H), 3.39–3.34 (m, 3H), 3.09–2.96 (m, 3H), 2.29 (br s, 3H), 1.49–1.40 (m, 6H); MS (ESI) *m/e* 418 (M + H)⁺.

Example 197Preparation of (E)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (E)-3-(6-amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(1-methyl-1H-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (223 mg, 82%) was prepared as a light, yellow powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.2 (br s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 7.52–7.39 (m, 3H), 7.24–7.01 (m, 4H), 6.41–6.16 (m, 1H), 5.05–4.85 (m, 2H), 4.29 (s, 2H), 3.74–3.68 (m, 3H), 3.10–3.00 (m, 6H), 2.10–1.82 (m, 5H); MS (ESI) *m/e* 404 (M + H)⁺.

Example 198Preparation of (E)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (E)-3-[6-amino-5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(1-methyl-1H-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (136 mg, 14%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz,

DMSO-*d*₆) δ 10.7 (br s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 8.07 (br s, 2H), 7.55–7.01 (m, 6H), 6.41–6.17 (m, 1H), 5.07–4.85 (m, 2H), 3.73–3.62 (m, 7H), 3.11–2.98 (m, 8H), 2.73 (s, 3H); MS (ESI) *m/e* 433 (M + H)⁺.

Example 199

5 Preparation of (*E*)-3-[6-Amino-5-(4-benzyl-piperidin-1-ylmethyl)pyridin-3-yl]-*N*-methyl-*N*-(1-methyl-1*H*-indol-2-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (*E*)-3-[6-amino-5-(4-benzyl-piperidin-1-ylmethyl)-pyridin-3-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(1-methyl-1*H*-indol-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (156 mg, 30%) was prepared as an off-white powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.36–8.25 (m, 2H), 7.52–6.98 (m, 14H), 6.40–6.15 (m, 1H), 5.05–4.84 (m, 2H), 4.20 (s, 2H), 3.74–3.67 (m, 3H), 3.58–5.30 (m, 8H), 3.10–2.73 (m, 6H); MS (ESI) *m/e* 508 (M + H)⁺.

Example 200

15 Preparation of (*E*)-3-(6-Amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-naphthalen-2-ylmethyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting (*E*)-3-(6-amino-5-pyrrolidin-1-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-naphthalen-2-ylmethyl-amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (51 mg, 57%) was prepared as a light, yellow solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.36–8.25 (m, 2H), 7.52–6.98 (m, 4H), 6.40–6.15 (m, 1H), 5.05–4.84 (m, 2H), 4.20 (s, 2H), 3.74–3.67 (m, 3H), 3.58–5.30 (m, 8H), 3.10–2.73 (m, 6H); MS (ESI) *m/e* 401 (M + H)⁺.

Example 201

25 Preparation of (*E*)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride

30 According to the procedure of Example 1, except substituting (*E*)-3-[6-amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for

the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (101 mg, 46%) was prepared as a light, yellow powder and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.6 (br s, 1H), 8.27 (s, 1H), 8.16 (s, 1H), 7.87 (d, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 7.1$ Hz, 1H), 7.52–7.28 (m, 5H), 7.11 (d, $J = 15.3$ Hz, 1H), 5.11–4.89 (m, 2H), 3.55 (br s, 2H), 3.37–3.23 (m, 4H), 3.14 (s, 2H), 3.10–2.92 (m, 5H), 2.72 (s, 3H), 2.42 (s, 3H); MS (ESI) m/e 450 ($\text{M} + \text{H}$) $^+$.

Example 202

Preparation of (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (*E*)-3-(6-amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-*N*-(4-methyl-naphthalen-1-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (66 mg, 62%) was prepared as a pale, yellow powder and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.61–8.35 (m, 2H), 8.14–8.05 (m, 2H), 7.61–7.52 (m, 3H), 7.36–7.03 (m, 3H), 5.30–5.07 (m, 2H), 4.45–4.23 (m, 2H), 3.94–3.65 (m, 6H), 3.45–3.17 (m, 4H), 3.04–2.94 (m, 4H), 2.65 (s, 3H); MS (ESI) m/e 431 ($\text{M} + \text{H}$) $^+$.

Example 203

Preparation of (*E*)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-*N*-methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (*E*)-3-(6-amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid for the (*E*)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-pyrido[2,3-*e*][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-*N*-(3-methyl-benzo[*b*]thiophen-2-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (111 mg, 67%) was prepared as a pale, yellow solid and as a mixture of amide rotamers: ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.60 (br s, 1H), 8.40 (s, 1H), 7.87 (d, $J = 7.4$ Hz, 1H), 7.73 (d, $J = 6.9$ Hz, 1H), 7.51 (d, $J = 15.3$ Hz, 1H), 7.42–7.15 (m, 3H), 5.12–4.88 (m, 2H), 3.91–3.35 (m, 12H), 3.15 (s, 3H), 2.93 (s, 1H), 2.41 (s, 3H); MS (ESI) m/e 437 ($\text{M} + \text{H}$) $^+$;

Example 204Preparation of (E)-3-(6-Amino-5-morpholin-4-ylmethyl-pyridin-3-yl)-N-(3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)-N-methyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting (E)-3-(6-amino-5-morpholin-4-ylmethyl-pyridin-3-yl)acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting (3,4-dimethyl-thieno[2,3-b]thiophen-2-ylmethyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound was prepared (70 mg, 13%) as a light, yellow powder and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.40 (s, 1H), 7.51 (d, *J* = 15.1 Hz, 1H), 7.20–7.12 (m, 2H), 5.00–4.77 (m, 2H), 4.40–4.32 (m, 2H), 3.95–3.15 (m, 10H), 3.13 (s, 3H), 2.90 (s, 1H), 2.46 (s, 3H), 2.45 (s, 3H); MS (ESI) *m/e* 457 (M + H)⁺.

Example 205Preparation of (E)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-N-(2-ethoxy-3-methoxy-benzyl)-N-methyl-acrylamide hydrochloride

According to the procedure of Example 1, except substituting (E)-3-[6-amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting (2-ethoxy-3-methoxy-benzyl)methylamine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (177 mg, 25%) was prepared as a pale, yellow solid and as a mixture of amide rotamers: ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.4 (s, 1H), 8.28–8.19 (m, 2H), 7.73 (s, 1H), 7.47 (d, *J* = 15.3 Hz, 1H), 7.21 (dd, *J* = 14.9, 5.4 Hz, 1H), 7.05–6.94 (m, 2H), 6.64 (dd, *J* = 7.2, 7.2 Hz, 1H), 4.78–4.63 (m, 2H), 4.03–3.93 (m, 2H), 3.79 (s, 3H), 3.55–3.33 (m, 7H), 3.09–2.85 (m, 7H), 2.74 (s, 3H), 1.31–1.25 (m, 3H); MS (ESI) *m/e* 454 (M + H)⁺.

Example 206Preparation of (E)-3-[6-Amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]-N-methyl-N-(4-methyl-naphthalen-1-ylmethyl)acrylamide hydrochloride

According to the procedure of Example 1, except substituting (E)-3-[6-amino-5-(4-methyl-piperazin-1-ylmethyl)pyridin-3-yl]acrylic acid hydrochloride for the (E)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)acrylic acid hydrochloride, and substituting methyl-(4-methyl-naphthalen-1-ylmethyl)amine for the methyl-(1-propyl-naphthalen-2-ylmethyl)amine, the title compound (143 mg, 20%) was

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CECI EST LE TOME __1__ DE __2__

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

What is claimed is:

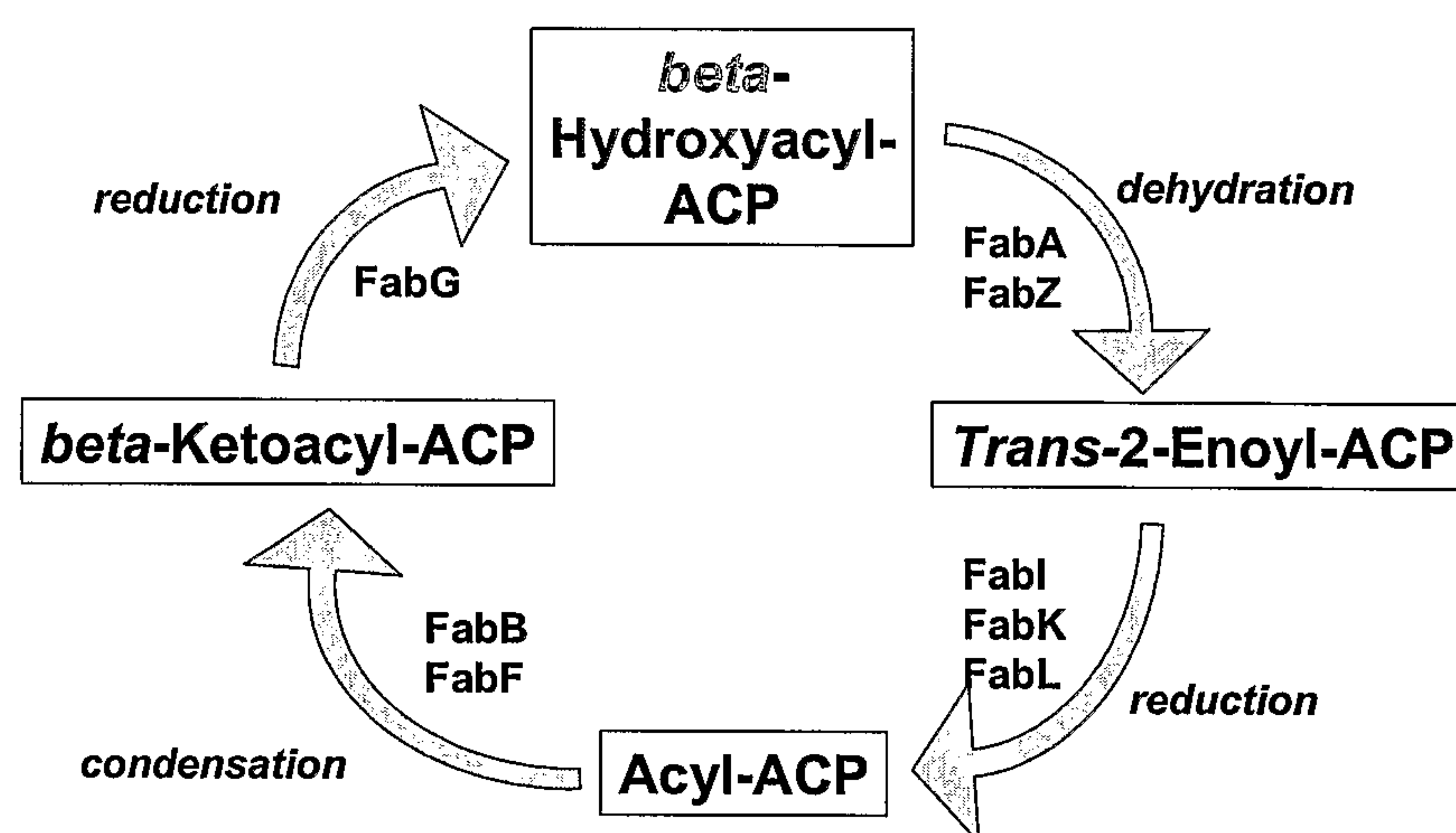
1. A composition comprising a compound and at least one other antibiotic agent,
 5 wherein the compound is selected from the group consisting of:
 (E)-N-methyl-N-(3-methylbenzofuran-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide;
 N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]-naphthyridin-3-yl)-acrylamide;
 10 N-methyl-N-(3-methyl-benzo[b]thiophen-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide; and
 pharmaceutically acceptable salts thereof; wherein the at least one other antibiotic agent is selected from the group consisting of gentamicin, linezolid, meropenem, vancomycin, and rifampicin; wherein the composition exhibits a synergistic antibacterial
 15 effect compared to its individual components.
2. The composition of claim 1, wherein the compound is (E)-N-methyl-N-(3-methylbenzofuran-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)acrylamide.
 20
3. The composition of claim 1, wherein the compound is N-methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]-naphthyridin-3-yl)-acrylamide.
4. The composition of claim 1, wherein the compound is N-methyl-N-(3-methyl-
 25 benzo[b]thiophen-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide.
5. The composition of any one of claims 1 to 4, wherein the antibiotic agent is gentamicin.
 30
6. The composition of any one of claims 1 to 4, wherein the antibiotic agent is linezolid.
7. The composition of any one of claims 1 to 4, wherein the antibiotic agent is meropenem.

8. The composition of any one of claims 1 to 4, wherein the antibiotic agent is vancomycin.
- 5 9. The composition of any one of claims 1 to 4, wherein the antibiotic agent is rifampicin.
- 10 10. A pharmaceutical composition comprising the composition of any one of claim 1 to 9, and a pharmaceutically acceptable carrier or excipient.
11. The composition of claim 10, wherein the composition is formulated for intravenous administration.
12. The composition of claim 10, wherein the composition is formulated for injectable
15 administration.
13. The composition of claim 10, wherein the composition is formulated for topical application.
- 20 14. The composition of claim 10, wherein the composition is formulated as a suppository.
15. The composition of claim 10, wherein the composition is formulated for systemic administration.
- 25 16. The composition of claim 10, wherein the composition is formulated for oral administration.
- 30 17. The composition of claim 16, 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 ED₅₀ but no more than ten times the ED₅₀.
18. The composition of claim 10, 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 ED₅₀ but no more than ten times the ED₅₀.

19. The composition of claim 10, 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 ED₅₀ but no more than ten times the ED₅₀.
- 5
20. A pill for reducing bacterial levels in a subject with a bacteria related illness, comprising a composition of any one of claims 1-9.
21. The pill of claim 20, wherein the pill provides effective bacterial treatment for at
- 10 least about 8 hours.
22. The pill of claim 20, wherein the pill provides effective bacterial treatment for at least about 12 hours.
- 15 23. The pill of claim 20, wherein the pill provides effective bacterial treatment for at least about 24 hours.
24. The pill of claim 20, wherein the pill provides effective bacterial treatment for at least about one week.
- 20
25. A pack of pills in number sufficient for treatment of a bacterial illness, comprising a plurality of pills wherein each pill comprises a composition of any one of claims 1-9.
26. The pack of pills of claim 25, wherein the pack contains at least 5 pills.
- 25
27. The pack of pills of claim 25, wherein the pack contains at least 10 pills.
28. The pack of pills of claim 25, wherein the pack contains at least 20 pills.
- 30 29. Use of a composition of any one of claims 1-9 for the manufacture of a medicament for treating a subject with a bacterial illness.
30. The use of claim 29, wherein the subject is a human.

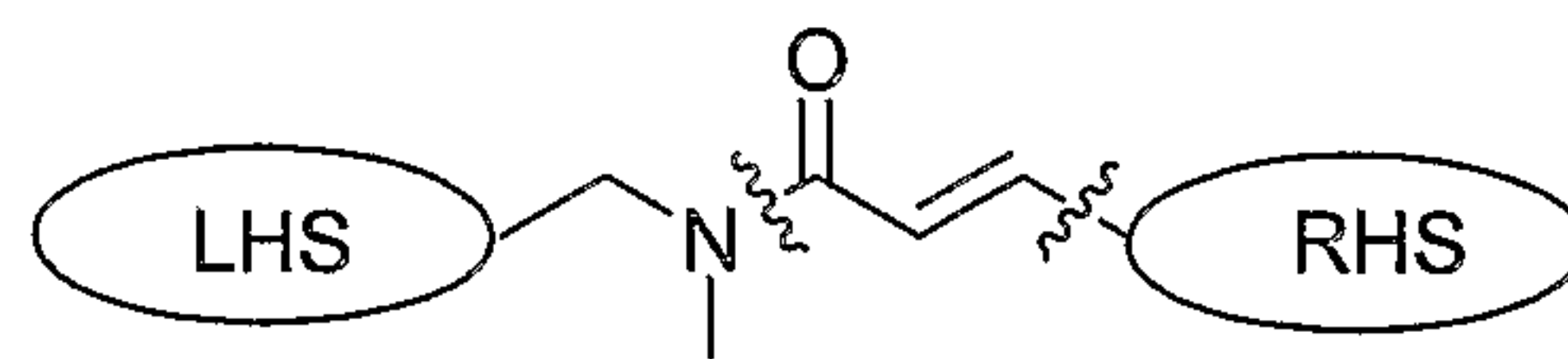
31. A method of disinfecting an inanimate surface comprising administering to the inanimate surface a composition of any one of claim 1-9.
32. A kit comprising the pharmaceutical composition of claim 10 and instructions for use
5 thereof.
33. Use of a composition of any one of claim 1-9 for treating a subject with a bacterial illness.
- 10 34. The use of claim 33, wherein the subject is a human.

Figure 1



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Figure 2



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Figure 3a

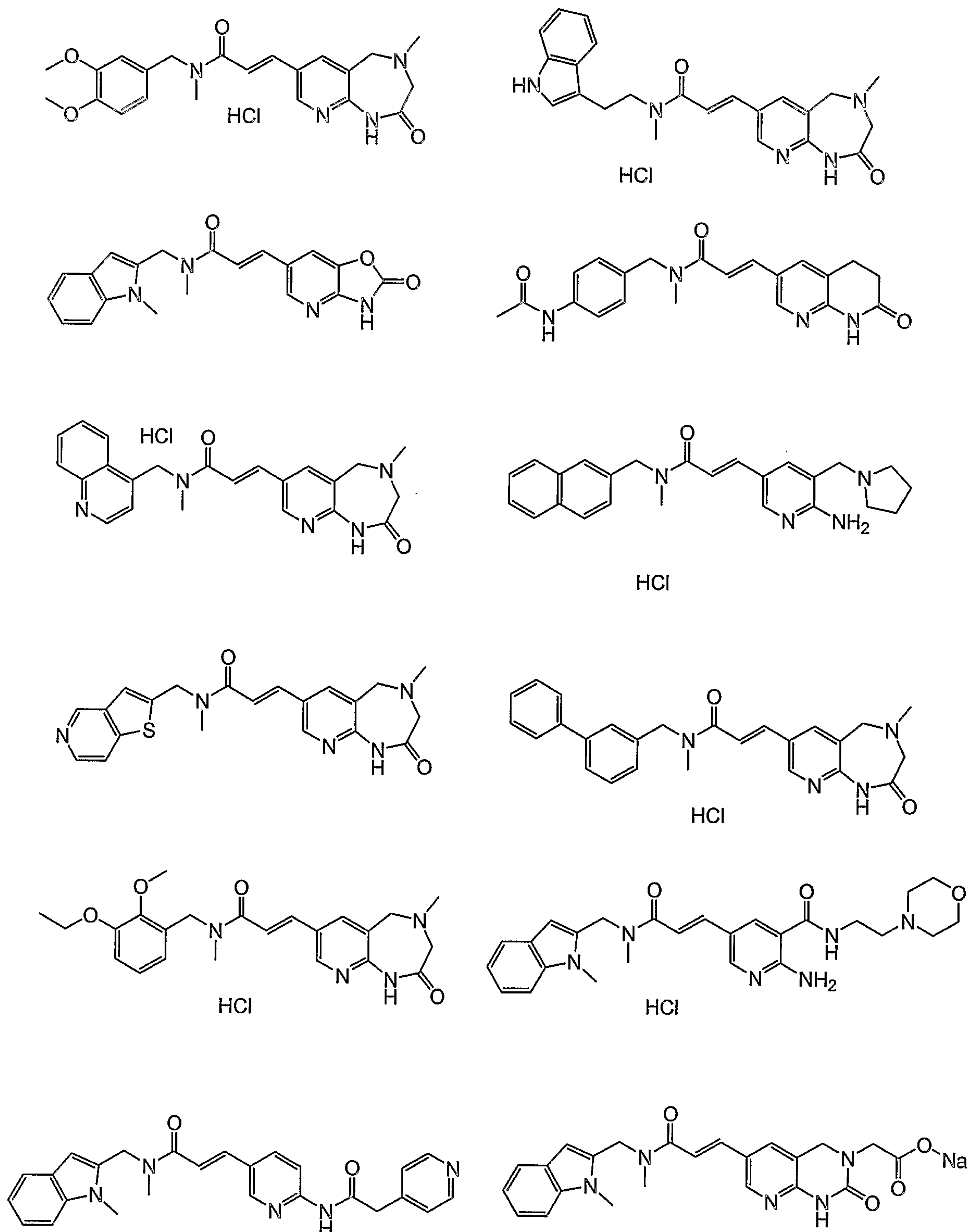
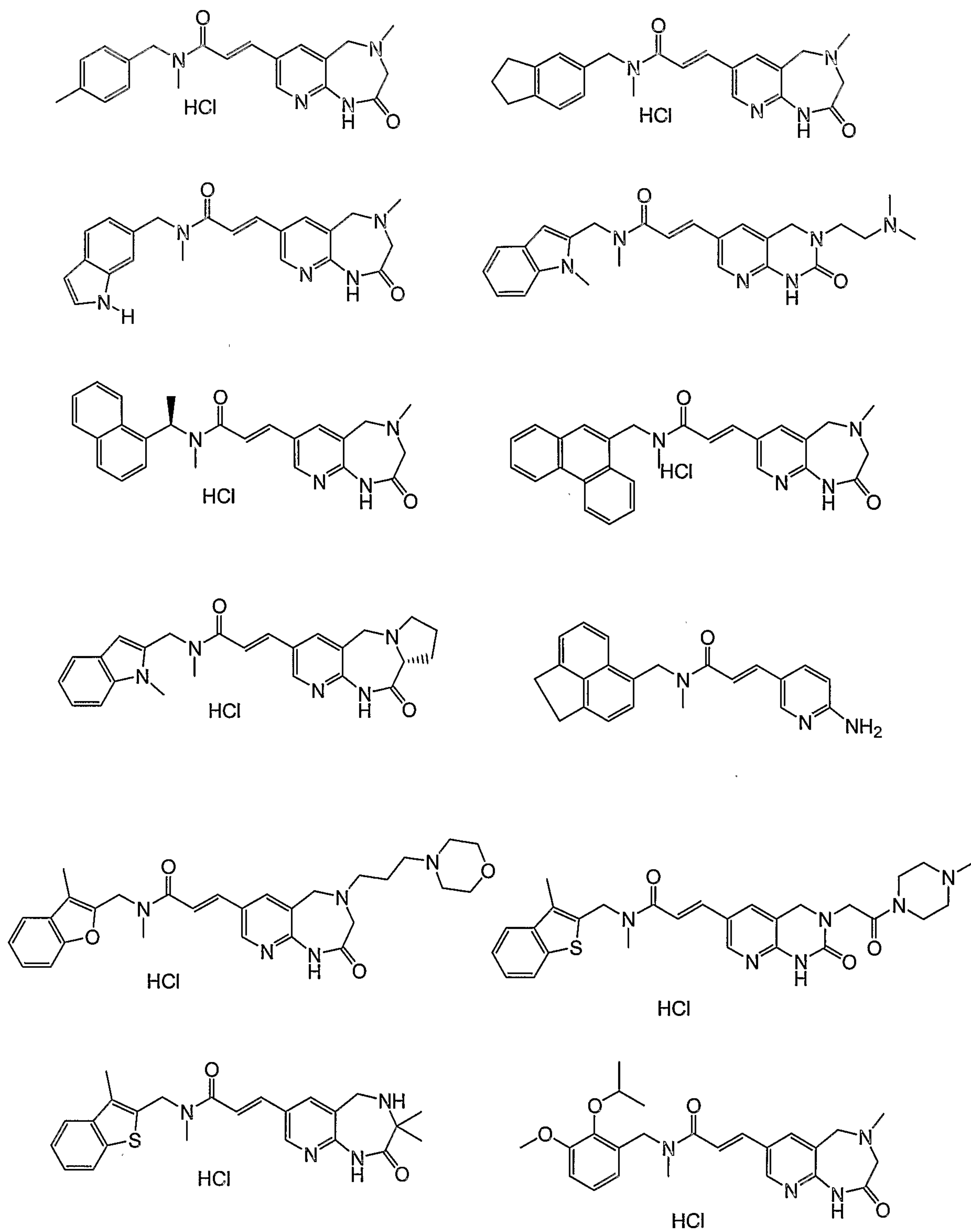


Figure 3b



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Figure 3c

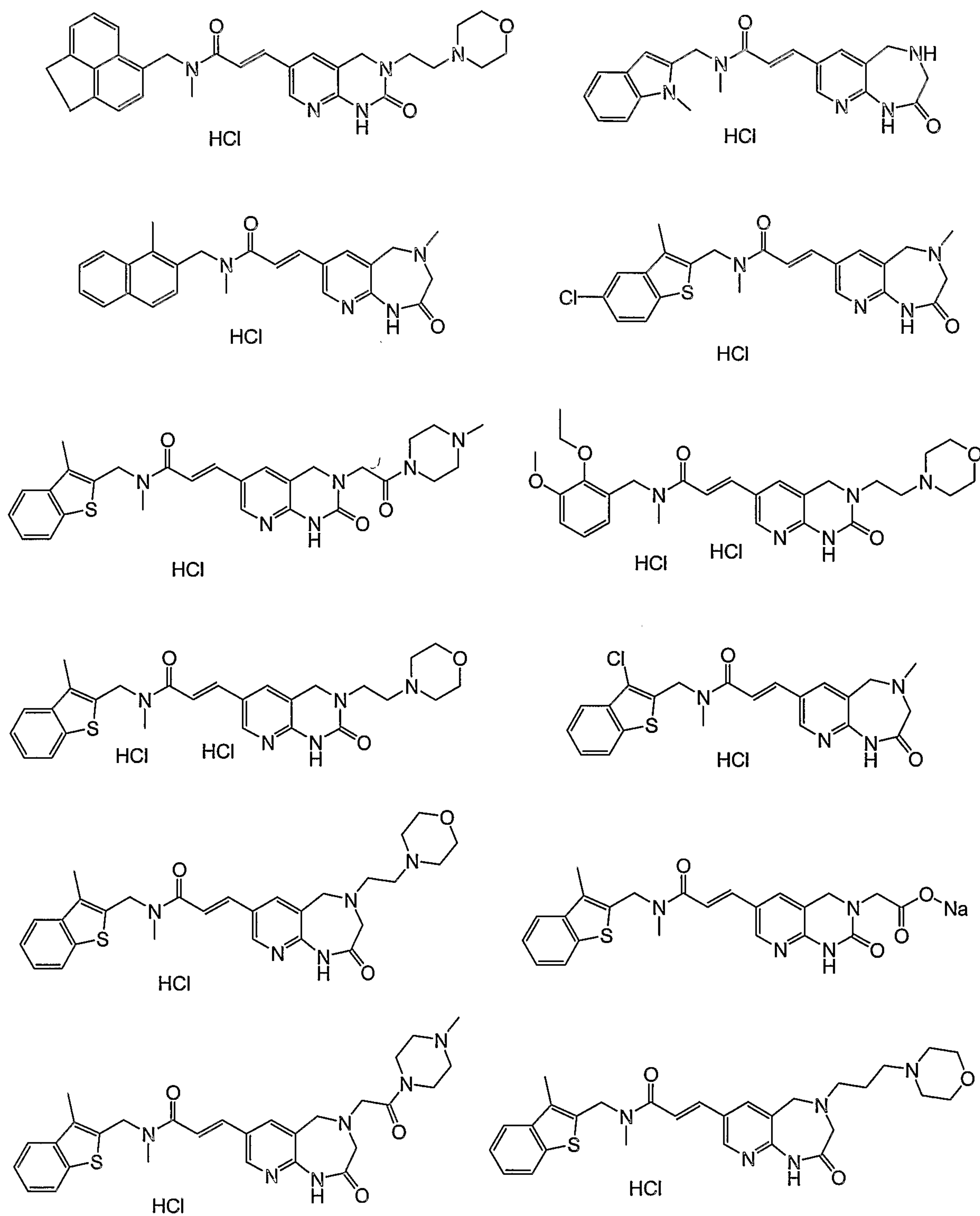
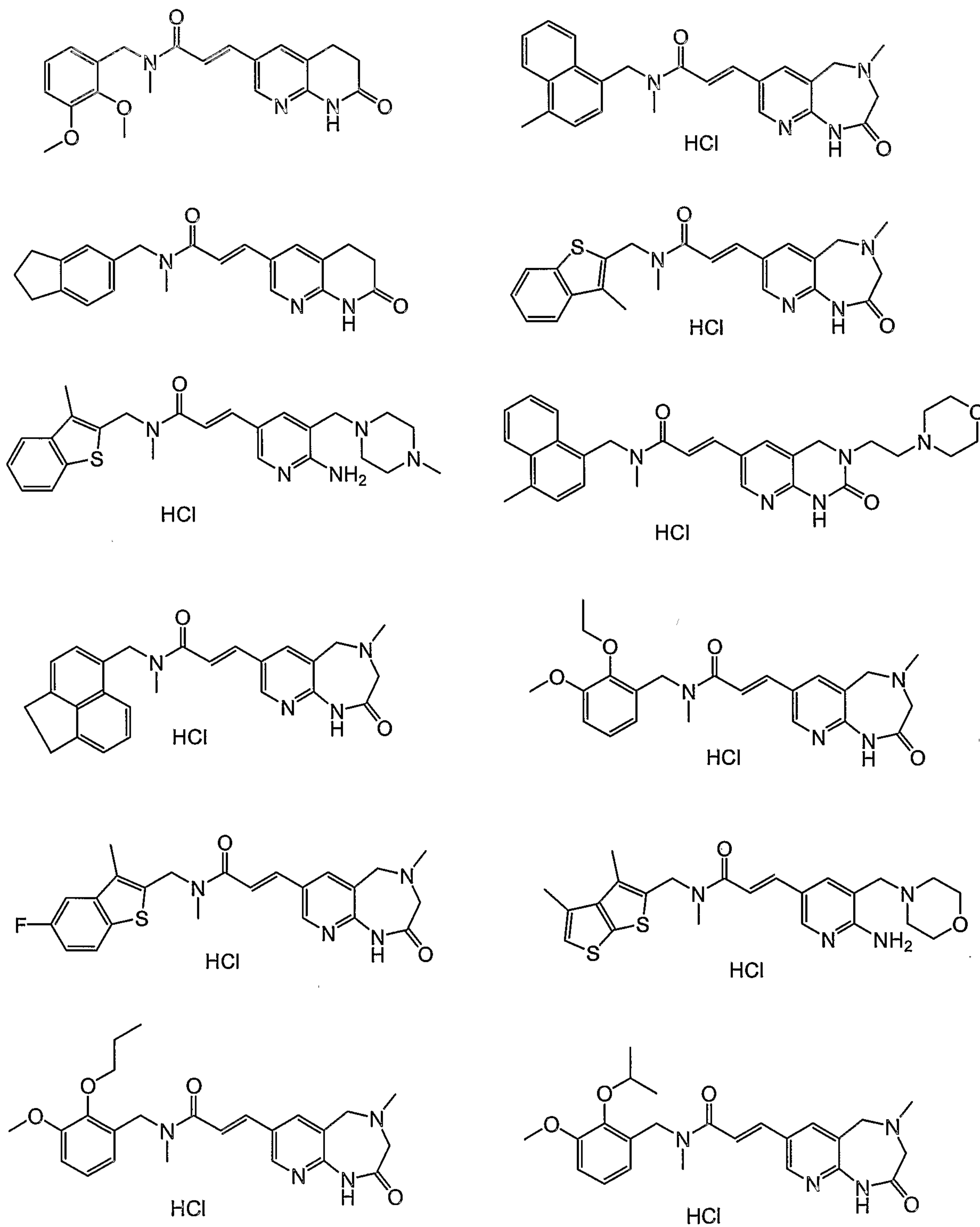


Figure 3d



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Figure 3e

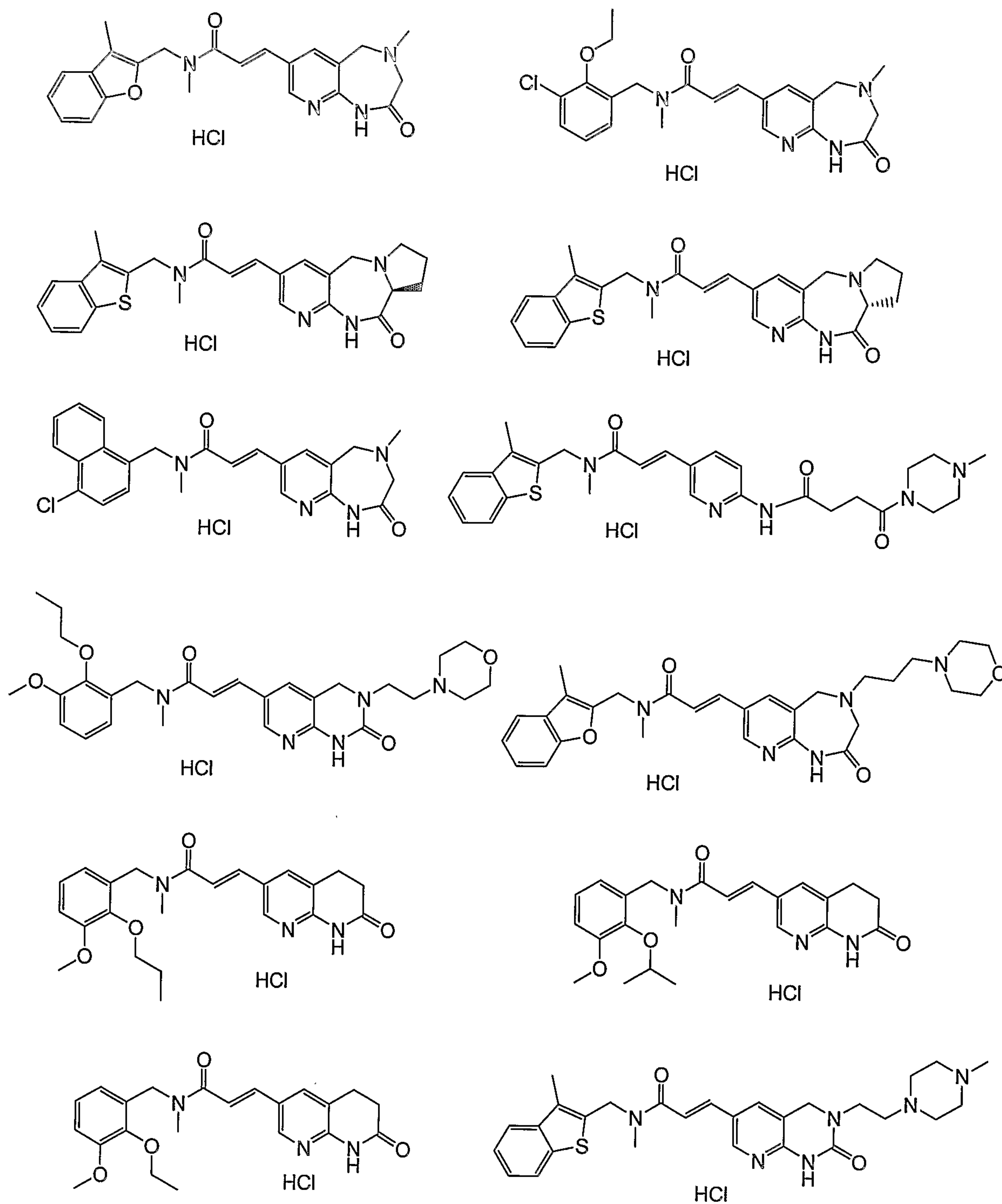
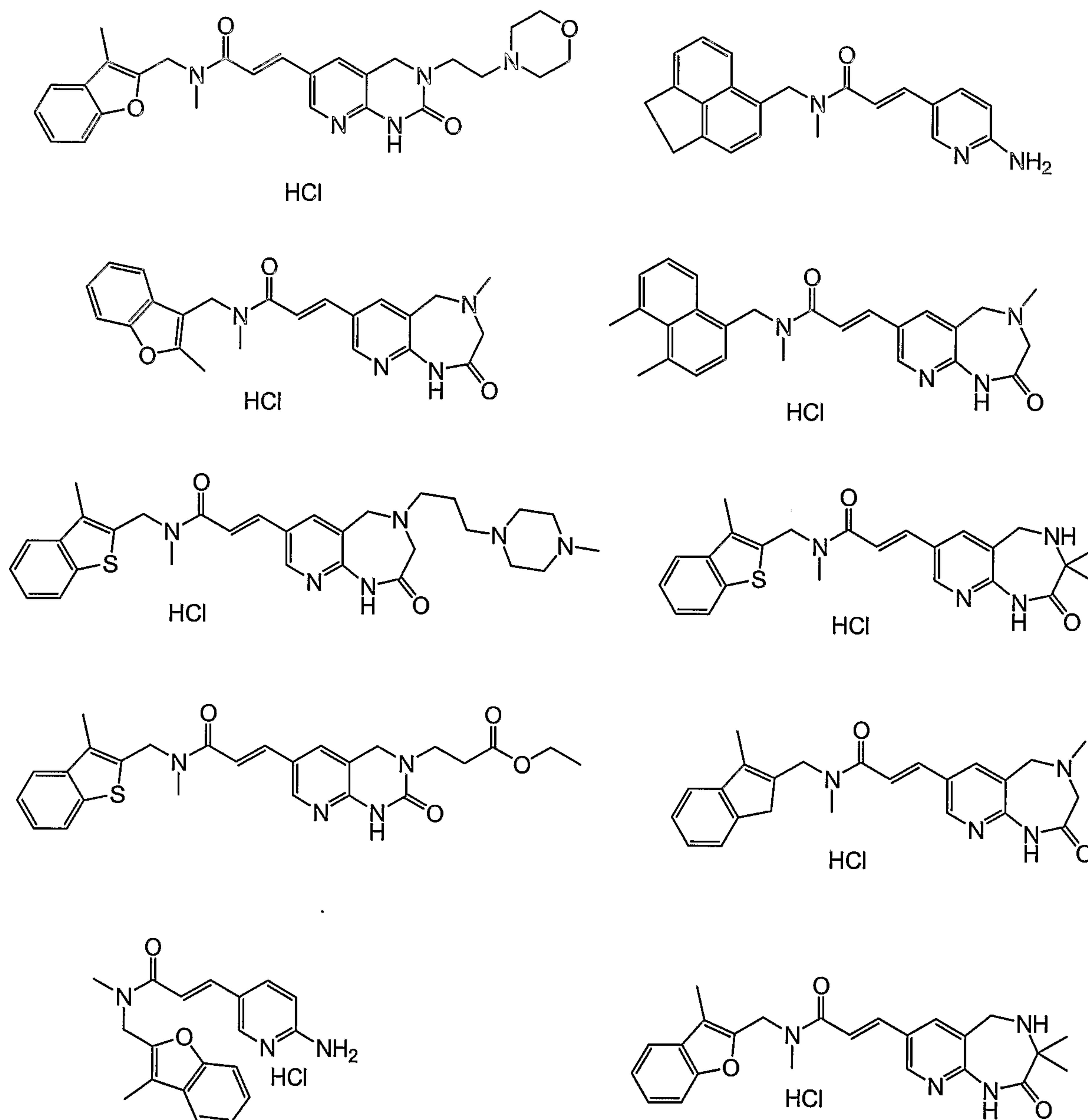


Figure 3f



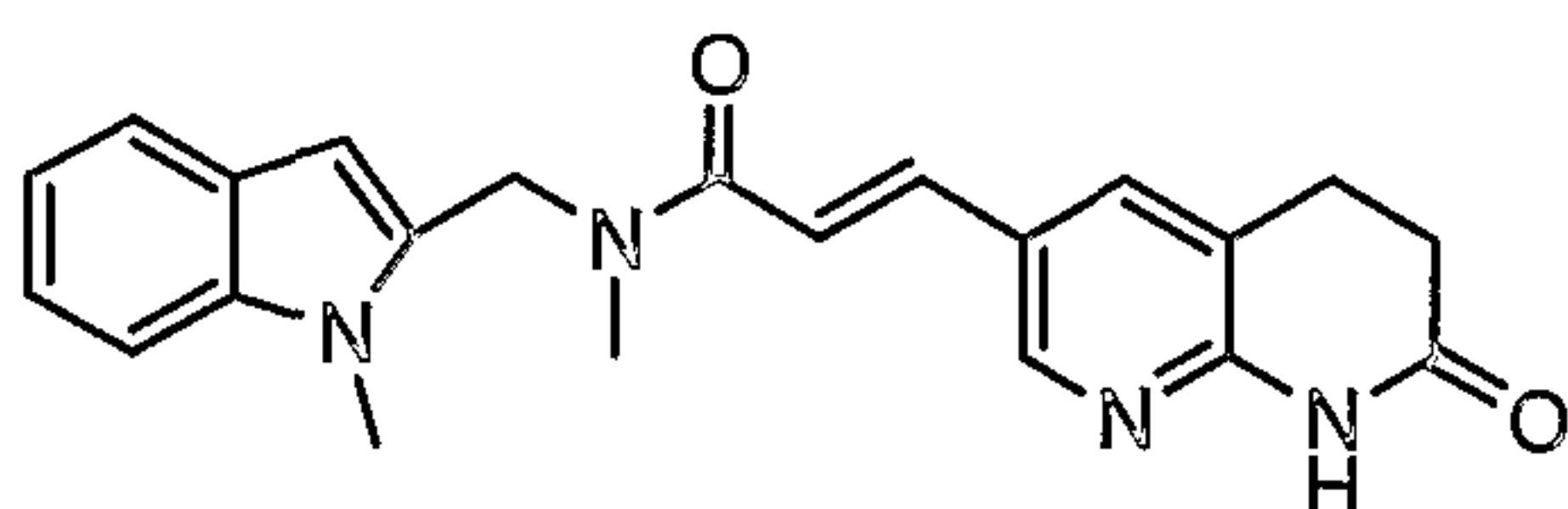
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Figure 4

Compound B (x MC)	4												
	2												
	1												
	0.5												
	0.25												
	0.125												
	0.06												
		+	0.015	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16
		Compound A (x MIC)											

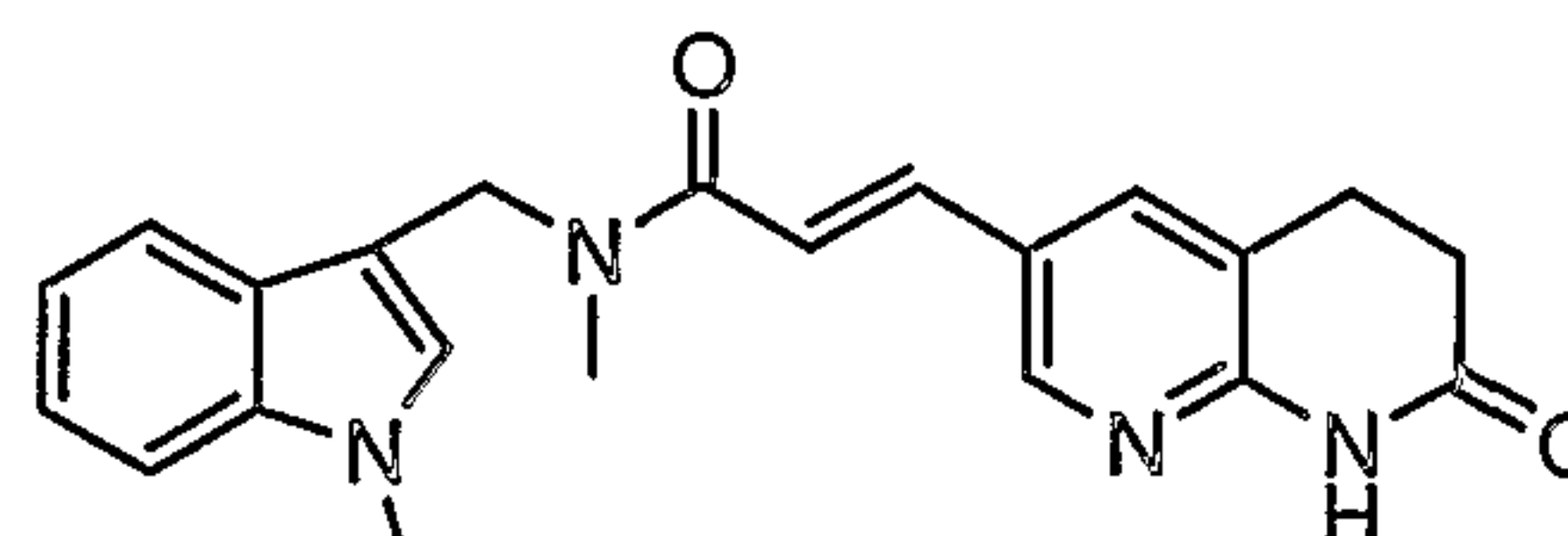
5

Figure 5



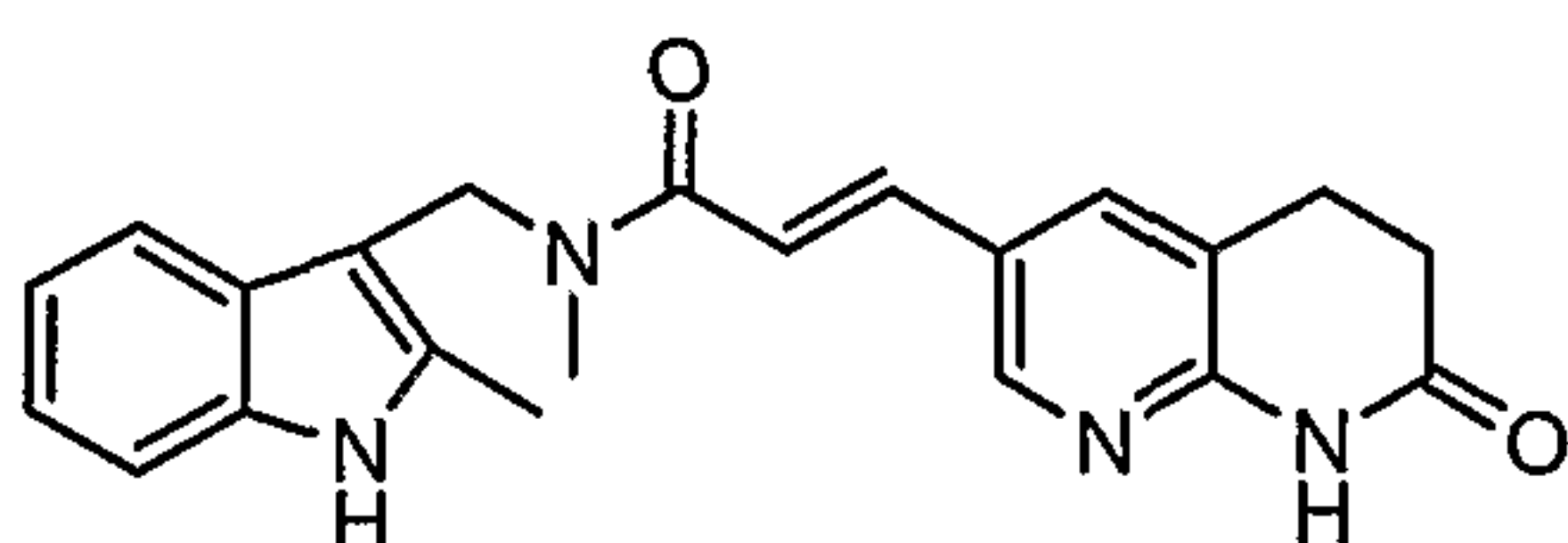
A

N-Methyl-N-(1-methyl-1H-indol-2-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-acrylamide



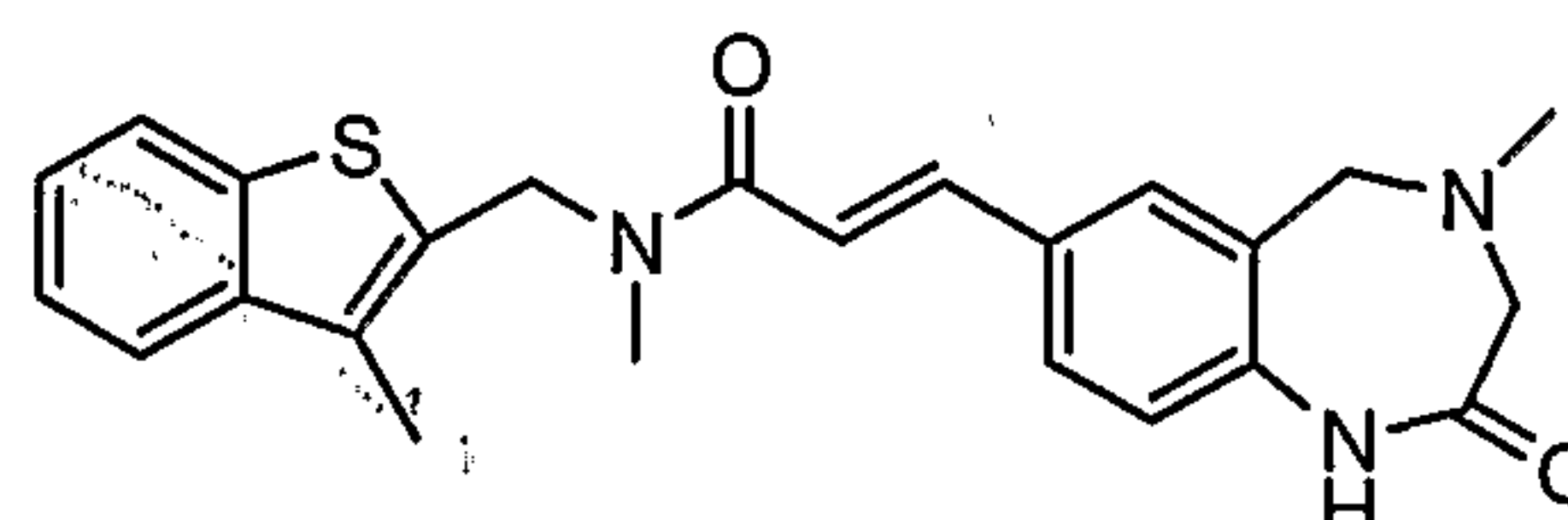
B

N-Methyl-N-(1-methyl-1H-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-acrylamide



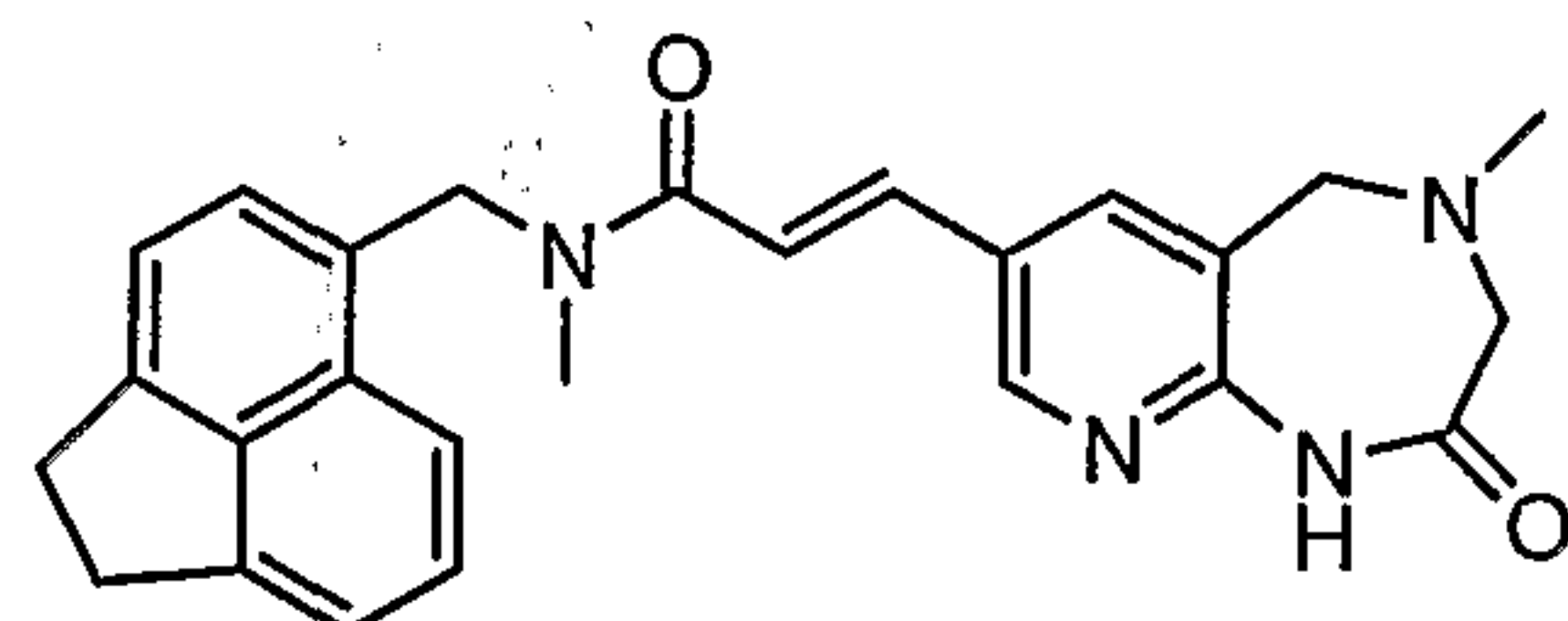
C

N-Methyl-N-(2-methyl-1H-indol-3-ylmethyl)-3-(7-oxo-5,6,7,8-tetrahydro-[1,8]naphthyridin-3-yl)-acrylamide



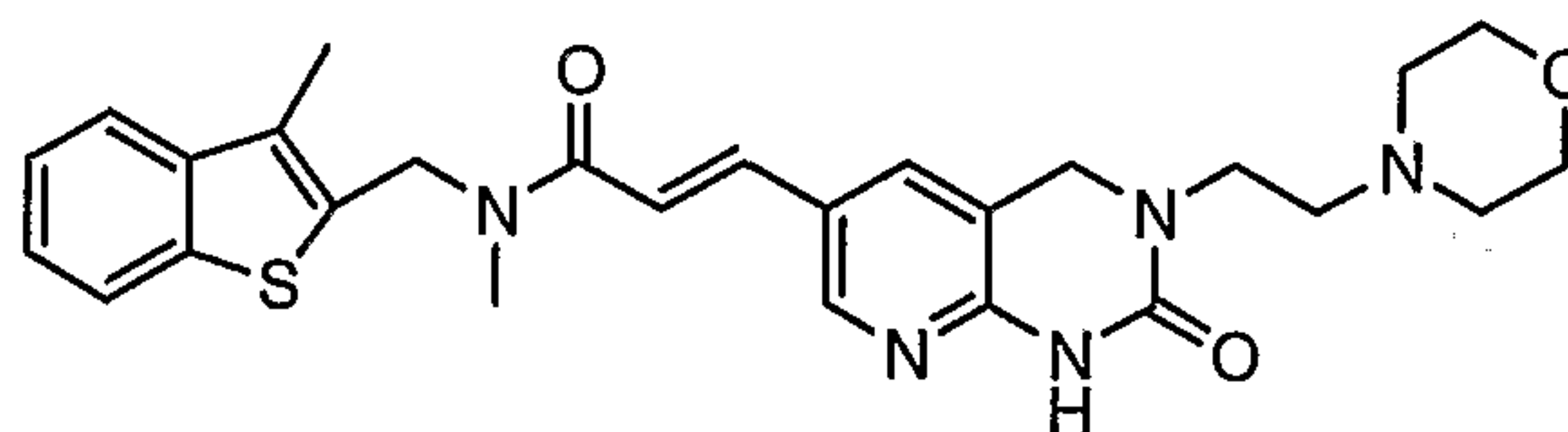
D

N-Methyl-N-(3-methyl-benzo[b]thiophen-2-ylmethyl)-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide



E

N-Acenaphthen-5-ylmethyl-N-methyl-3-(4-methyl-2-oxo-2,3,4,5-tetrahydro-1H-pyrido[2,3-e][1,4]diazepin-7-yl)-acrylamide



F

N-Methyl-N-(3-methyl-benzo[b]thiophen-2-ylmethyl)-3-[3-(2-morpholin-4-yl-ethyl)-2-oxo-1,2,3,4-tetrahydro-pyrido[2,3-d]pyrimidin-6-yl]-acrylamide