SOLID FORMS OF GYRASE INHIBITOR (R)-1-ETHYL-3-[5-[2-(1-HYDROXY-1-METHYL-ETHYL)PYRIMIDIN-5-YL]-7-(TETRAHYDROFURAN-2-YL)-1H-BENZIMIDAZOL-2-YL]UREA

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119 of United States Provisional Patent Application serial number 61/433,161 filed January 14, 2011, the entire contents of which is incorporated herein by reference.

BACKGROUND OF THE APPLICATION

[0002] Bacterial resistance to antibiotics has long been recognized, and it is today considered to be a serious worldwide health problem. As a result of resistance, some bacterial infections are either difficult to treat with antibiotics or even untreatable. This problem has become especially serious with the recent development of multiple drug resistance in certain strains of bacteria, such as *Streptococcus pneumoniae* (SP), *Mycobacterium tuberculosis*, and *Enterococcus*. The appearance of vancomycin resistant *enterococcus* was particularly alarming because vancomycin was formerly the only effective antibiotic for treating this infection, and had been considered for many infections to be the drug of "last resort". While many other drug-resistant bacteria do not cause life-threatening disease, such as enterococci, there is the fear that the genes which induce resistance might spread to more deadly organisms such as *Staphylococcus aureus*, where methicillin resistance is already prevalent (De Clerq, et al., Current Opinion in Anti-infective Investigational Drugs, 1999, 1, 1; Levy, "The Challenge of Antibiotic Resistance", Scientific American, March, 1998).

[0003] Another concern is how quickly antibiotic resistance can spread. For example, until the 1960's SP was universally sensitive to penicillin, and in 1987 only 0.02% of the SP strains in the U.S. were resistant. However, by 1995 it was reported that SP resistance to penicillin was about seven percent and as high as 30% in some parts of the U.S. (Lewis, FDA Consumer magazine (September, 1995); Gershman in The Medical Reporter, 1997).

[0004] Hospitals, in particular, serve as centers for the formation and transmission of drug-resistant organisms. Infections occurring in hospitals, known as nosocomial infections, are becoming an increasingly serious problem. Of the two million Americans infected in

hospitals each year, more than half of these infections resist at least one antibiotic. The Center for Disease Control reported that in 1992, over 13,000 hospital patients died of bacterial infections that were resistant to antibiotic treatment (Lewis, "The Rise of Antibiotic-Resistant Infections", FDA Consumer magazine, September 1995).

[0005] As a result of the need to combat drug-resistant bacteria and the increasing failure of the available drugs, there has been a resurgent interest in discovering new antibiotics. One attractive strategy for developing new antibiotics is to inhibit DNA gyrase and/or topoisomerase IV, bacterial enzymes necessary for DNA replication, and therefore, necessary for bacterial cell growth and division. Gyrase and/or topoisomerase IV activity are also associated with events in DNA transcription, repair and recombination.

[0006] Gyrase is one of the topoisomerases, a group of enzymes which catalyze the interconversion of topological isomers of DNA (see generally, Kornberg and Baker, DNA Replication, 2d Ed., Chapter 12, 1992, W. H. Freeman and Co.; Drlica, Molecular Microbiology, 1992, 6, 425; Drlica and Zhao, Microbiology and Molecular Biology Reviews, 1997, 61, pp. 377-392). Gyrase itself controls DNA supercoiling and relieves topological stress that occurs when the DNA strands of a parental duplex are untwisted during the replication process. Gyrase also catalyzes the conversion of relaxed, closed circular duplex DNA to a negatively superhelical form which is more favorable for recombination. The mechanism of the supercoiling reaction involves the wrapping of gyrase around a region of the DNA, double strand breaking in that region, passing a second region of the DNA through the break, and rejoining the broken strands. Such a cleavage mechanism is characteristic of a type II topoisomerase. The supercoiling reaction is driven by the binding of ATP to gyrase. The ATP is then hydrolyzed during the reaction. This ATP binding and subsequent hydrolysis cause conformational changes in the DNA-bound gyrase that are necessary for its activity. It has also been found that the level of DNA supercoiling (or relaxation) is dependent on the ATP/ADP ratio. In the absence of ATP, gyrase is only capable of relaxing supercoiled DNA.

[0007] Bacterial DNA gyrase is a 400 kilodalton protein tetramer consisting of two A (GyrA) and two B subunits (GyrB). Binding and cleavage of the DNA is associated with GyrA, whereas ATP is bound and hydrolyzed by the GyrB protein. GyrB consists of an amino-terminal domain which has the ATPase activity, and a carboxy-terminal domain which interacts with GyrA and DNA. By contrast, eukaryotic type II topoisomerases are homodimers that can relax negative and positive supercoils, but cannot introduce negative

supercoils. Ideally, an antibiotic based on the inhibition of bacterial DNA gyrase and/or topoisomerase IV would be selective for these enzymes and be relatively inactive against the eukaryotic type II topoisomerases.

[0008] Topoisomerase IV primarily resolves linked chromosome dimers at the conclusion of DNA replication.

[0009] The widely-used quinolone antibiotics inhibit bacterial DNA gyrase(GyrA) and/or Topoisomerase IV (ParC). Examples of the quinolones include the early compounds such as nalidixic acid and oxolinic acid, as well as the later, more potent fluoroquinolones such as norfloxacin, ciprofloxacin, and trovafloxacin. These compounds bind to GyrA and/or ParC and stabilize the cleaved complex, thus inhibiting overall gyrase function, leading to cell death. The fluoroquinolones inhibit the catalytic subunits of gyrase (GyrA) and/or Topoisomerase IV (Par C) (see Drlica and Zhao, Microbiology and Molecular Biology Reviews, 1997, 61, 377-392). However, drug resistance has also been recognized as a problem for this class of compounds (WHO Report, "Use of Quinolones in Food Animals and Potential Impact on Human Health", 1998). With the quinolones, as with other classes of antibiotics, bacteria exposed to earlier compounds often quickly develop cross-resistance to more potent compounds in the same class.

[0010] The associated subunits responsible for supplying the energy necessary for catalytic turnover/resetting of the enzymes via ATP hydrolysis are GyrB (gyrase) and ParE (topoisomerase IV), respectively (see, Champoux, J.J., Annu. Rev. Biochem., 2001, 70, pp. 369-413). Compounds that target these same ATP binding sites in the GyrB and ParE subunits would be useful for treating various bacterial infections (see, Charifson et al., J. Med. Chem., 2008, 51, pp. 5243-5263).

[0011] There are fewer known inhibitors that bind to GyrB. Examples include the coumarins, novobiocin and coumermycin A1, cyclothialidine, cinodine, and clerocidin. The coumarins have been shown to bind to GyrB very tightly. For example, novobiocin makes a network of hydrogen bonds with the protein and several hydrophobic contacts. While novobiocin and ATP do appear to bind within the ATP binding site, there is minimal overlap in the bound orientation of the two compounds. The overlapping portions are the sugar unit of novobiocin and the ATP adenine (Maxwell, Trends in Microbiology, 1997, 5, 102).

[0012] For coumarin-resistant bacteria, the most prevalent point mutation is at a surface arginine residue that binds to the carbonyl of the coumarin ring (Arg136 in E. coli GyrB).

While enzymes with this mutation show lower supercoiling and ATPase activity, they are also less sensitive to inhibition by coumarin drugs (Maxwell, Mol. Microbiol., 1993, 9, 681).

[0013] Despite being potent inhibitors of gyrase supercoiling, the coumarins have not been widely used as antibiotics. They are generally not suitable due to their low permeability in bacteria, eukaryotic toxicity, and poor water solubility (Maxwell, Trends in Microbiology, 1997, 5, 102). It would be desirable to have a new, effective GyrB and ParE inhibitor that overcomes these drawbacks and, preferably does not rely on binding to Arg136 for activity. Such an inhibitor would be an attractive antibiotic candidate, without a history of resistance problems that plague other classes of antibiotics.

[0014] As bacterial resistance to antibiotics has become an important public health problem, there is a continuing need to develop newer and more potent antibiotics. More particularly, there is a need for antibiotics that represent a new class of compounds not previously used to treat bacterial infection. Compounds that target the ATP binding sites in both the GyrB (gyrase) and ParE (topoisomerase IV) subunits would be useful for treating various bacterial infections. Such compounds would be particularly useful in treating nosocomial infections in hospitals where the formation and transmission of resistant bacteria are becoming increasingly prevalent.

SUMMARY OF THE APPLICATION

[0015] The present application is directed to solid and amorphous forms of (R)- 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[(2R)-tetrahydrofuran-2-yl]-1H-benzimidazol-2-yl]urea ("the benzimidazolyl urea compound") and methods for preparing same. In one embodiment, the present application provides for a solid form of the benzimidazolyl urea compound. In one embodiment, the solid form is Form I solid form characterized by an by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 $\theta \pm 0.2$) when measured using Cu K_α radiation, selected from the group consisting of 9.3, 11.7, 12.4, 13.8, 14.6, 16.0, 16.2, 16.7, 18.6, 18.9, 19.6, 20.2, 20.5, 21.3, 1.7, 22.7, 23.9, 24.5, 24.9, 25.8, 26.7, 27.9, 28.1, 28.4, 30.4, 33.5, and 37.4, when the XPRD is collected from about 5 to about 38 degrees two theta (2 θ). In certain embodiments, solid Form I may be characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 $\theta \pm 0.2$) when measured using Cu K_α radiation, selected from the group consisting of 9.3, 16.7, 18.6, 19.6, 21.7, and 25.8, when the XPRD is collected from about 5 to about 38 degrees 2 θ. In

further embodiments, Form I is characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 1. In yet another embodiment, Form I is characterized by an endothermic peak having an onset temperature of about 243°C as measured by differential scanning calorimetry in which the temperature is scanned at about 10°C per minute. The present application also provides for a method for preparing crystal Form I of the benzimidazolyl urea compound comprising crystallizing or precipitating the compound of formula (I) from a solvent system comprising methylene chloride, methanol, or a combination thereof.

[0016] The present application also provides for solid hydrochloride salts of the benzimidazolyl urea compound. In one embodiment, the solid hydrochloride salt is Form II solid. In one embodiment, Form II hydrochloride salt of the present application may be characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 $\theta \pm 0.2$) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 12.3, 12.4, 13.5, 16.4, 17.2, 17.9, 18.2, 19.0, 19.5, 20.6, 20.9, 22.4, 23.0, 23.5, 24.0, 24.5, 26.0, 26.5, 27.1, 27.4, 28.5, 29.4, 30.8, 33.0, when the XPRD is collected from about 5 to about 38 degrees 2 θ. In a further embodiment, Form II hydrochloride salt of the present application may be characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 $\theta \pm 0.2$) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 12.3, 12.4, 16.4, 17.9, 19.5, 24.0, and 29.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ. In certain embodiments, Form II hydrochloride salt of the present application may be characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 $\theta \pm 0.2$) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 19.5, and 24.0, when the XPRD is collected from about 5 to about 38 degrees 2 θ. In further embodiments, Form II hydrochloride salt of the present application may be characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 4. The present application also provides for a method for preparing solid hydrochloride salt of the benzimidazolyl urea compound comprising suspending a solid free base of the benzimidazolyl urea in an acidic solvent system comprising acetonitrile or water.

[0017] In another embodiment, the solid hydrochloride salt is Form III solid. In one embodiment, Form III hydrochloride salt of the present application may be characterized by

an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 6.9, 9.1, 11.0, 11.7, 12.3, 15.8, 16.9, 18.1, 18.9, 19.8, 20.9, 22.7, 23.4, 24.1, 24.8, 25.3, 27.7, 28.5, 29.5, and 31.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ. In certain embodiments, Form III hydrochloride salt of the present application may be characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 6.9, 9.1, 11.7, 18.1, 18.9, 19.8, 23.4, and 24.8, when the XPRD is collected from about 5 to about 38 degrees 2 θ. In further embodiments, Form III hydrochloride salt of the present application may be characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 7. The present application also provides a method for preparing solid Form III of the benzimidazolyl urea compound comprising suspending a solid free base of the benzimidazolyl urea in an acidic solvent system comprising one or more ethereal solvents and water.

[0018] The present application also provides an amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound. In one embodiment, Form IV may be characterized by an X-ray powder diffraction pattern (XPRD) using Cu K_α radiation characterized by a broad halo with no discernable diffraction peak.

DESCRIPTION OF FIGURES

[0019] Figure 1 shows an X-ray powder diffraction pattern of solid Form I of the benzimidazolyl urea compound (free base).

[0020] Figure 2 shows a DSC thermogram of solid Form I of the benzimidazolyl urea compound.

[0021] Figure 3 shows a TGA thermogram of solid Form I of the benzimidazolyl urea compound.

[0022] Figure 4 shows an X-ray powder diffraction pattern of solid Form II of the hydrochloride salt of the benzimidazolyl urea compound.

[0023] Figure 5 shows a DSC thermogram of solid Form II of the benzimidazolyl urea compound.

[0024] Figure 6 shows a TGA thermogram of solid Form II of the benzimidazolyl urea compound

[0025] Figure 7 is an X-ray powder diffraction pattern of solid Form III of the hydrochloride salt of the benzimidazolyl urea compound.

[0026] Figure 8 shows a DSC thermogram of solid Form III of the hydrochloride salt of the benzimidazolyl urea compound.

[0027] Figure 9 is a TGA (thermal gravimetric analysis) thermogram of solid Form III of the benzimidazolyl urea compound.

[0028] Figure 10 is an X-ray powder diffraction pattern of amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound.

[0029] Figure 11 shows a DSC thermogram of amorphous Form IV of mesylate salt of the benzimidazolyl urea compound.

[0030] Figure 12 is a ^{1}H-NMR of the mesylate salt of the benzimidazolyl urea compound.

DETAILED DESCRIPTION

[0031] The present application is directed to novel substantially pure solid forms of (R)-1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[(2R)-tetrahydrofuran-2-yl]-1H-benzimidazol-2-yl]urea ("the benzimidazolyl urea compound").

[0032] One aspect of the present application is a novel solid Form I of the benzimidazolyl urea compound (free base). In one aspect, the present application provides a process for preparing solid Form I of the benzimidazolyl urea compound.

[0033] A substantially pure Form I (free base) crystalline solid form of the benzimidazolyl urea compound may be prepared from amorphous or crystalline compound by contacting the compound with a polar solvent such as acetonitrile, methylene chloride, methanol, ethanol, or water, or combinations thereof. The benzimidazolyl urea compound may be contacted with the solvent either by saturating a solution of the benzimidazolyl urea compound in the solvent at ambient temperature and allowing the mixture to stand for an extended period of time (for example, overnight). Alternatively, the benzimidazolyl urea compound may be dissolved in the solvent at elevated temperature, for example, at reflux, followed by cooling the solution to room temperature or below and isolating solid Form I.

[0034] In one embodiment of the process, a substantially pure crystalline solid Form I of the benzimidazolyl urea compound may be prepared from amorphous or crystalline of the compound by preparing a saturated solution of the compound in a polar solvent at room temperature and isolating Form I which results. In practice this can be accomplished by dissolving a sufficient amount of the benzimidazolyl urea compound in the solvent at

elevated temperature (up to reflux) such that when the solution is allowed to cool to room temperature a saturated solution is obtained, from which Form I precipitates and can be isolated. In one embodiment, a solvent for the preparation of Form I is CH_2Cl_2 or MeOH or mixtures thereof. Isolation of the resulting solid provides Form I.

[0035] The solid Form I of the benzimidazolyl urea compound (free base) may be identified by the following characteristics: a melt endotherm with an extrapolated onset of about 243°C as determined by differential scanning calorimetry using 10°C per minute scan rate; and an X-ray powder diffraction pattern essentially as shown in Table 1 and Figure 1 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Cu X-ray tube source. The sample was illuminated with Cu $K\alpha_1$ radiation and XRPD data were collected from about 0 to about 40° 2θ. A person skilled in the art would recognize that relative intensities of the XPRD peaks may significantly vary depending on the orientation of the sample under test and on the type and setting of the instrument used, so that the intensities in the XPRD traces included herein are to such extent illustrative and are not intended to be used for absolute comparisons.

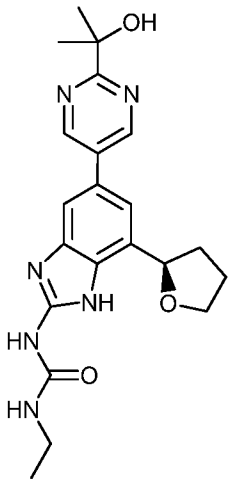
[0036] Figure 1 is an X-ray powder diffraction pattern of solid Form I of the benzimidazolyl urea compound collected from about 5 to about 38 degrees 2 θ. The peaks corresponding to X-ray powder diffraction pattern having a relative intensity greater than or equal to 5% are listed in Table 1.

[0037] Figure 2 shows a DSC thermogram of solid Form I of the benzimidazolyl urea compound exhibiting an endotherm with an onset transition at about 243°C. A person skilled in the art would recognize that the peak and onset temperatures of the endotherms may vary depending on the experimental conditions. Data in Figure 2 were collected equilibrating a 1.8 mg sample of the solid Form I at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute.

[0038] Figure 3 is a TGA (thermal gravimetric analysis) thermogram of solid Form I of the benzimidazolyl urea compound exhibiting an initial weight loss of about 35% percent in the 50 to 260°C temperature range. Data in Figure 3 were collected equilibrating a 0.87 mg sample of solid Form I at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute. While applicants do not wish to be held to a particular explanation of the endotherm in the DSC and weight loss in the TGA, it appears that the transition with large peak in the DSC is due to a melting

transition coupled with degradation of the material as suggested by the weight loss in the TGA.

[0039] In one embodiment, the present invention provides a solid compound of formula (I):



or salts thereof.

[0040] In another embodiment, the solid is a solid Form I free base.

[0041] In another embodiment, the solid Form I is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 9.3, 11.7, 12.4, 13.8, 14.6, 16.0, 16.2, 16.7, 18.6, 18.9, 19.6, 20.2, 20.5, 21.3, 21.7, 22.7, 23.9, 24.5, 24.9, 25.8, 26.7, 27.9, 28.1, 28.4, 30.4, 33.5, and 37.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0042] In another embodiment, the solid Form I is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 9.3, 16.7, 18.6, 19.6, 21.7, and 25.8, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0043] In another embodiment, the solid Form I is characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 1.

[0044] In another embodiment, the solid Form I is further characterized by an endothermic peak having an onset temperature of about 243°C as measured by differential scanning calorimetry in which the temperature is scanned at about 10°C per minute.

[0045] In another embodiment, the present invention provides a method for preparing crystal Form I of the compound of formula (I) comprising precipitating the compound of

formula (I) from a solvent system comprising methylene chloride, methanol, ethanol, or combinations thereof.

Table 1. XRPD pattern peaks for solid Form I of the benzimidazolyl urea compound

Peak No.	Position [°2θ]	Relative Intensity [%]
1	9.31	91
2	11.72	28
3	12.37	10
4	13.84	5
5	14.61	16
6	15.98	21
7	16.23	23
8	16.65	81
9	18.56	100
10	18.86	12
11	19.55	50
12	20.18	12
13	20.48	11
14	21.30	11
15	21.65	76
16	22.74	22
18	23.94	20
19	24.50	16
20	24.88	6
21	25.81	63
22	26.70	6
23	27.85	8
24	28.13	12
25	28.43	11
26	30.38	10
28	33.50	10
29	37.35	6

[0046] In one aspect, the present application provides crystal Form II of the hydrochloric acid addition salt of the benzimidazolyl urea compound. In one embodiment, the present application provides a process for preparing solid Form II of the benzimidazolyl urea compound. The pharmaceutically acceptable hydrochloric acid addition salt of the benzimidazolyl urea compound may be prepared by any method known to those skilled in the art. For example, gaseous hydrochloric acid may be bubbled through a solution of the benzimidazolyl urea compound until a mono acid addition salt of the compound is prepared. In one embodiment, the hydrochloric acid addition salt of the benzimidazolyl urea compound

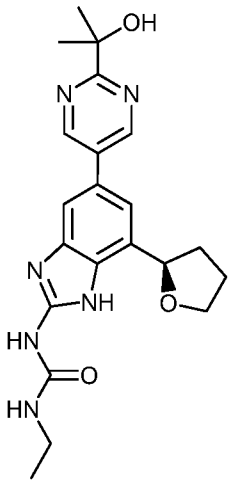
may precipitate out. In other embodiments, the acid addition salt may be isolated from the reaction mixture by modifying the solubility of the salt in the solvent. For example, removing some or all of the solvent or lowering the mixture temperature may reduce the solubility of the hydrochloride salt of the benzimidazolyl urea compound and the salt precipitate. Alternatively, adding a second solvent to the mixture may precipitate the salt.

[0047] In one embodiment, the benzimidazolyl urea compound of the present application is suspended in a polar solvent. In a further embodiment, the polar solvent is acetonitrile. In this embodiment, the benzimidazolyl urea compound of the present application is suspended in acetonitrile at room temperature and a stoichoimetric amount of an aqueous HCl solution is added. The suspension is kept in a closed container while stirring gently until it equilibrates and the benzimidazolyl urea compound is converted to the corresponding acid addition salt. In some embodiments, it may take anywhere from a few minutes to a few days for the free base suspension to be converted to the acid addition salt. The salt may be recovered by filtering the suspension to obtain a white solid, which may be dried at room temperature under vacuum for several hours.

[0048] Solid Form II of the hydrochloride salt of the benzimidazolyl urea compound may be identified by an X-ray powder diffraction pattern essentially as shown in Table 2 and Figure 4 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Cu X-ray tube source. The sample was illuminated with Cu $K\alpha_1$ radiation and XRPD data were collected from about 5 to about 40° 2θ. A person skilled in the art would recognize that relative intensities of the XPRD peaks may significantly vary depending on sample orientation.

[0049] Figure 4 is an X-ray powder diffraction pattern of solid Form II of the hydrochloride salt of the benzimidazolyl urea compound collected from about 0 to about 40 degrees 2 θ. The peaks corresponding to X-ray powder diffraction pattern having a relative intensity greater than or equal to 5% are listed in Table 2.

[0050] In one embodiment, the present invention provides a hydrochloric acid salt of the compound of formula (I):



(I).

[0051] In another embodiment, the hydrochloride salt is in a solid form.

[0052] In another embodiment, the hydrochloride salt is a solid Form II.

[0053] In another embodiment, the solid Form II is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 12.3, 12.4, 13.5, 16.4, 17.2, 17.9, 18.2, 19.0, 19.5, 20.6, 20.9, 22.4, 23.0, 23.5, 24.0, 24.5, 26.0, 26.5, 27.1, 27.4, 28.5, 29.4, 30.8, 33.0, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0054] In another embodiment, the solid Form II is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 12.3, 12.4, 16.4, 17.9, 19.5, 24.0, and 29.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0055] In another embodiment, the solid Form II is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 19.5, and 24.0, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0056] In another embodiment, the solid Form II is characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 4.

[0057] In another embodiment, the present invention provides a method for preparing the solid Form II comprising suspending a solid free base of the benzimidazolyl urea in an acidic solvent system comprising acetonitrile or water.

Table 2. XRPD pattern peaks for solid Form II of the benzimidazolyl urea compound

Peak No.	Position [°2 θ]	Relative Intensity [%]
1	6.9708	25
2	9.1428	42
3	11.5027	44
4	12.3483	18
5	12.4346	22
6	13.4801	7
8	16.3614	20
9	17.1885	12
10	17.9001	18
11	18.1737	14
12	19.0475	16
13	19.5145	59
14	20.6258	15
15	20.8832	16
16	22.3823	6
17	22.9956	14
18	23.4554	7
19	23.9821	100
20	24.5317	9
22	26.0542	7
23	26.5376	9
24	27.1366	5
25	27.4365	9
26	28.4887	14
27	29.3904	18
28	30.8478	6
29	32.9868	5

[0058] Solid Form III of the hydrochloride salt of the benzimidazolyl urea compound may be identified by an X-ray powder diffraction pattern essentially as shown in Table 3 and Figure 7 wherein the XRPD patterns were measured using a powder diffractometer equipped with a Cu X-ray tube source. The sample was illuminated with Cu $K\alpha_1$ radiation and XRPD data were collected from about 5 to about 40° 2θ. A person skilled in the art would recognize that relative intensities of the XPRD peaks may significantly vary depending on sample orientation.

[0059] Figure 5 shows a DSC thermogram of solid Form II of the hydrochloride salt of the benzimidazolyl urea compound exhibiting an endotherm with an onset transition at

about 216°C. A person skilled in the art would recognize that the peak and onset temperatures of the endotherms may vary depending on the experimental conditions. Data in Figure 5 were collected equilibrating a 1.26 mg sample of the solid Form II at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute.

[0060] Figure 6 is a TGA (thermal gravimetric analysis) thermogram of solid Form II of the benzimidazolyl urea compound exhibiting an initial weight loss of about 22% percent in the 50 to 230°C temperature range. Data in Figure 6 were collected equilibrating a 1.82 mg sample of solid Form II at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute. While applicants do not wish to be held to a particular explanation of the endotherm in the DSC and weight loss in the TGA, it appears that the transition with large peak in the DSC is due to a melting transition coupled with degradation of the material as suggested by the weight loss in the TGA.

[0061] Figure 7 is an X-ray powder diffraction pattern of solid Form III of the hydrochloride salt of the benzimidazolyl urea compound collected from about 5 to about 40 degrees 2 θ. The peaks corresponding to X-ray powder diffraction pattern having a relative intensity greater than or equal to 5% are listed in Table 3.

[0062] In one embodiment, the present invention provides a solid compound, wherein said hydrochloric salt of compound of formula (I) is a solid Form III.

[0063] In another embodiment, the solid Form III is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 6.9, 9.1, 11.0, 11.7, 12.3, 15.8, 16.9, 18.1, 18.9, 19.8, 20.9, 22.7, 23.4, 24.1, 24.8, 25.3, 27.7, 28.5, 29.5, and 31.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0064] In another embodiment, the solid Form III is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 6.9, 9.1, 11.7, 18.1, 18.9, 19.8, 23.4, and 24.8, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

[0065] In another embodiment, the solid Form III is characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 7.

[0066] In another embodiment, the present invention provides a method for preparing solid Form III comprising suspending a solid free base of the benzimidazolyl urea in an acidic solvent system comprising one or more ethereal solvents and water.

Table 3. XRPD pattern peaks for solid Form III of the benzimidazolyl urea compound

Peak No.	Position [°2 θ]	Relative Intensity [%]
2	6.8885	17.17
3	9.117	100
4	10.9885	10.17
5	11.7157	44.44
6	12.3217	6.19
9	15.7808	8.76
11	16.8739	5.45
12	18.1446	15.24
13	18.936	15.13
14	19.7837	36.72
15	20.8775	9.43
16	22.7073	5.83
17	23.4025	15.86
18	24.1018	9.69
19	24.795	16.19
20	25.2909	7.51
23	27.6802	5.81
24	28.4615	6.56
25	29.5173	5.52
26	31.4273	6.34

[0067] Figure 8 shows a DSC thermogram of solid Form III of the hydrochloride salt of the benzimidazolyl urea compound exhibiting a melting endotherm with an onset transition at about 214°C. A person skilled in the art would recognize that the peak and onset temperatures of the endotherms may vary depending on the experimental conditions. Data in Figure 8 were collected equilibrating a 1.03 mg sample of the solid form at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute.

[0068] Figure 9 is a TGA (thermal gravimetric analysis) thermogram of solid Form III of the benzimidazolyl urea compound exhibiting an initial weight loss of about 28% percent in the 50 to 260°C temperature range. Data in Figure 9 were collected equilibrating a 3.71 mg sample of the solid form at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute. While

applicants do not wish to be held to a particular explanation of the endotherm in the DSC and weight loss in the TGA, it appears that the transition with large peak in the DSC is due to a melting transition coupled with degradation of the material as suggested by the weight loss in the TGA.

[0069] In one embodiment, solid Form III of the hydrochloride salt of the benzimidazolyl urea compound may be prepared from a mixture of an ethereal solvent and aqueous HCl. In one embodiment, the ethereal solvent is THF, methyl-*tert*-butyl ether (MTBE), or mixtures thereof. In a particular embodiment, the benzimidazolyl urea compound may be suspended in an ethereal solvent followed by addition of a stoichiometric amount of HCl. Additional ethereal solvent may be added and the suspension may be allowed to equilibrate for a certain period of time enough to convert the free base to the corresponding HCl addition salt. It may take less than an hour to several hours for the equilibration to be completed. In certain embodiments, the suspension may be allowed to equilibrate for up to 24 hours before collecting the white solid. The solid may be collected using any method known to those skilled in the art. The solid may be dried under vacuum for several hours.

[0070] In another aspect, the present application provides an amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound. In one embodiment, the present application provides a process for preparing amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound. A pharmaceutically acceptable methanesulphonic acid salt of the benzimidazolyl urea compound may be prepared by any method known to those skilled in the art. For example, a solution of methanesulphonic acid may be added to a solution of the benzimidazolyl urea compound until a mono acid addition salt of the compound is prepared.

[0071] The mesylate salt of the benzimidazolyl urea compound may be converted to an amorphous solid Form IV using any method known to those skilled in the art. The amorphous benzimidazolyl urea compound mesylate salt may be characterized by the absence of a diffraction pattern characteristic of a crystalline form. The X-ray powder diffraction of a partially amorphous benzimidazolyl urea compound mesylate salt may still lack features characteristic of a crystal form because the diffraction peaks from the crystalline portion of the sample may be too weak to be observable over the noise. Figure 10 is an X-ray powder diffraction pattern of an amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound.

[0072] In one embodiment, the amorphous mesylate salt of the benzimidazolyl urea compound may be prepared by spray drying a solution of the salt in appropriate solvent. Spray drying is well known in the art and is often used to dry thermally-sensitive materials such as pharmaceutical drugs. Spray drying also provides consistent particle distribution that can be reproduced fairly well. Any gas may be used to dry the powder although air is commonly used. If the material is sensitive to air, an inert gas, such nitrogen or argon, may be used. Any method that converts a solution, slurry, suspension or an emulsion of the salt to produce a solid powder may be suitable for preparing the amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound. For example, freeze drying, drum drying, or pulse conversion drying may be used to produce an amorphous mesylate salt of the benzimidazolyl urea compound.

[0073] In one embodiment, the present invention provides a solid compound of formula (I), wherein said solid is an amorphous mesylate salt of Form IV.

[0074] In another embodiment, the solid amorphous mesylate salt Form IV is characterized by an X-ray powder diffraction pattern (XPRD) using Cu K_α radiation, characterized by a broad halo with no discernable diffraction peak.

[0075] In one embodiment, a solution of the benzimidazolyl urea compound in a polar solvent may be spray dried using a nanospray dryer equipped a condenser.

[0076] Figure 11 shows a DSC thermogram of amorphous Form IV of the mesylate salt of the benzimidazolyl urea compound. Data in Figure 11 were collected equilibrating a 1.6 mg sample of the amorphous material at about 35°C for about 10 minutes. During the data collection period, the temperature was increased at a rate of about 10°C per minute.

[0077] It is to be understood that solid Forms I, II and III and amorphous solid Form IV of the benzimidazolyl urea compound or its salts, in addition to having the XRPD, DSC, TGA and other characteristics described herein, may also possess other characteristics not described, such as but not limited to the presence of water or one or more solvent molecules.

[0078] **X-Ray Powder Diffraction (XRPD)**: The XRPD pattern of the crystalline forms were recorded at room temperature in reflection mode using a Bruker D8 Discover system equipped with a sealed tube source and a Hi-Star area detector (Bruker AXS, Madison, WI). The X-Ray generator was operating at a tension of 40 kV and a current of 35 mA. The powder sample was placed on a Si zero-background wafer. Two frames were registered with an exposure time of 120 s each. The data were subsequently integrated over the range of 3°-41° 2 with a step size of 0.02° and merged into one continuous pattern.

[0079] **X-Ray Powder Diffraction (XRPD) for amorphous forms**: The XRPD pattern of the amorphous solid form was recorded at room temperature in reflection mode using a Bruker D8 Advance system equipped with a Vantec-1 position sensitive detector (Bruker AXS, Madison, WI). The X-Ray generator was operating at a tension of 40 kV and a current of 45 mA. The powder sample was placed on a Si zero-background holder, spinning at 15 rpm during the experiment in a continuous mode using variable slit at the detector. Data was collected from 3 to 40 degrees with 0.0144653 degree increments (0.25s/step).

[0080] **Differential Scanning Calorimetry (DSC)**: DSC was performed on a sample of the material using a DSC Q2000 differential scanning calorimeter (TA Instruments, New Castle, DE). The instrument was calibrated with indium. A sample of approximately 1-2 mg was weighed into an aluminum pan that was crimped using lids with either no pin-hole or pin-hole lids. The DSC samples were scanned from 30°C to temperatures indicated in the plots at a heating rate of 10°C/min with 50 mL/min nitrogen flow. The samples run under modulated DSC (MDSC) were modulated + and – 1°C every 60s with ramp rates of 2 or 3 C/min.

[0081] Data was collected by Thermal Advantage Q SeriesTM software and analyzed by Universal Analysis 2000 software (TA Instruments, New Castle, DE).

Thermogravimetric analysis (TGA): A Model Q5000 Thermogravimetric Analyzer (TA Instruments, New Castle, DE) was used for TGA measurement. Typically, approximately 3-5 mg of the sampleswere scanned from 30°C to temperatures indicated on the plots at a heating rate of 10°C/min. Data was collected by Thermal Advantage Q SeriesTM software and analyzed by Universal Analysis 2000 software (TA Instruments, New Castle, DE).

[0082] The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0083] The present invention also provides a method of controlling, treating or reducing the advancement, severity or effects of a nosocomial or a non-nosocomial bacterial infection in a patient, comprising administering to said patient a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof.

[0084] In another embodiment, the present invention provides a a method of controlling, treating or reducing the advancement, severity or effects of a nosocomial or a non-nosocomial bacterial infection in a patient, comprising administering to said patient a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically

acceptable salt thereof, wherein the bacterial infection is characterized by the presence of one or more of *Streptococcus pneumoniae*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Clostridium difficile*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Mycobacterium avium* complex, *Mycobacterium abscessus*, *Mycobacterium kansasii*, *Mycobacterium ulcerans*, *Chlamydophila pneumoniae*, *Chlamydia trachomatis*, *Haemophilus influenzae*, *Streptococcus pyogenes* or β-haemolytic streptococci.

[0085] In another embodiment, the present invention provides a method of controlling, treating or reducing the advancement, severity or effects of a nosocomial or a non-nosocomial bacterial infection in a patient, comprising administering to said patient a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein the bacterial infection is selected from one or more of the following: upper respiratory infections, lower respiratory infections, ear infections, pleuropulmonary and bronchial infections, complicated urinary tract infections, uncomplicated urinary tract infections, intra-abdominal infections, cardiovascular infections, a blood stream infection, sepsis, bacteremia, CNS infections, skin and soft tissue infections, GI infections, bone and joint infections, genital infections, eye infections, or granulomatous infections, uncomplicated skin and skin structure infections (uSSSI), complicated skin and skin structure infections (cSSSI), catheter infections, pharyngitis, sinusitis, otitis externa, otitis media, bronchitis, empyema, pneumonia, community-acquired bacterial pneumoniae (CABP), hospital-acquired pneumonia (HAP), hospital-acquired bacterial pneumonia, ventilator-associated pneumonia (VAP), diabetic foot infections, vancomycin resistant enterococci infections, cystitis and pyelonephritis, renal calculi, prostatitis, peritonitis, complicated intra-abdominal infections (cIAI) and other inter-abdominal infections, dialysis-associated peritonitis, visceral abscesses, endocarditis, myocarditis, pericarditis, transfusion-associated sepsis, meningitis, encephalitis, brain abscess, osteomyelitis, arthritis, genital ulcers, urethritis, vaginitis, cervicitis, gingivitis, conjunctivitis, keratitis, endophthalmitisa, an infection in cystic fibrosis patients or an infection of febrile neutropenic patients.

[0086] In another embodiment, the bacterial infection is selected from one or more of the following: community-acquired bacterial pneumoniae (CABP), hospital-acquired pneumonia (HAP), hospital-acquired bacterial pneumonia, ventilator-associated pneumonia (VAP), bacteremia, diabetic foot infections, catheter infections, uncomplicated skin and skin structure infections (uSSSI), complicated skin and skin structure infections (cSSSI), vancomycin resistant enterococci infections or osteomyelitis.

[0087] According to another embodiment, the invention provides a method of decreasing or inhibiting bacterial quantity in a biological sample. This method comprises contacting said biological sample with a compound of formula (I) or a pharmaceutically acceptable salt thereof.

[0088] The term "biological sample", as used herein, includes cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. The term "biological sample" also includes living organisms, in which case "contacting a compound of this invention with a biological sample" is synonymous with the term "administering said compound or composition comprising said compound) to a mammal".

[0089] The gyrase and/or topoisomerase IV inhibitors of this invention, or pharmaceutical salts thereof, may be formulated into pharmaceutical compositions for administration to animals or humans. These pharmaceutical compositions effective to treat or prevent a bacterial infection which comprise the gyrase and/or topoisomerase IV inhibitor in an amount sufficient to measurably decrease bacterial quantity and a pharmaceutically acceptable carrier, are another embodiment of the present invention. The term "measurably decrease bacterial quantity", as used herein means a measurable change in the number of bacteria between a sample containing said inhibitor and a sample containing only bacteria.

[0090] According to another embodiment, the methods of the present invention are useful to treat patients in the veterinarian field including, but not limited to, zoo, laboratory, human companion, and farm animals including primates, rodents, reptiles and birds. Examples of said animals include, but are not limited to, guinea pigs, hamsters, gerbils, rat, mice, rabbits, dogs, cats, horses, pigs, sheep, cows, goats, deer, rhesus monkeys, monkeys, tamarinds, apes, baboons, gorillas, chimpanzees, orangutans, gibbons, ostriches, chickens, turkeys, ducks, and geese.

[0091] The term "non-nosocomial infections" is also referred to as community acquired infections.

[0092] In another embodiment, the bacterial infection is characterized by the presence of one or more of *Streptococcus pneumoniae*, *Enterococcus faecalis*, or *Staphylococcus aureus*.

[0093] In another embodiment, the bacterial infection is characterized by the presence of one or more of *E. coli*, *Moraxella catarrhalis*, or *Haemophilus influenzae.*

[0094] In another embodiment, the bacterial infection is characterized by the presence of one or more of *Clostridium difficile*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*,

Mycobacterium avium complex, *Mycobacterium abscessus*, *Mycobacterium kansasii*, *Mycobacterium ulcerans*, *Chlamydophila pneumoniae* and *Chlamydia tracomatis*.

[0095] In another embodiment, the bacterial infection is characterized by the presence of one or more of *Streptococcus pneumoniae, Staphylococcus epidermidis, Enterococcus faecalis, Staphylococcus aureus, Clostridium difficile, Moraxella catarrhalis, Neisseria gonorrhoeae, Neisseria meningitidis, Mycobacterium avium complex, Mycobacterium abscessus, Mycobacterium kansasii, Mycobacterium ulcerans, Chlamydophila pneumoniae, Chlamydia trachomatis, Haemophilus influenzae, Streptococcus pyogenes* or *β-haemolytic streptococci*.

[0096] In some embodiments, the bacterial infection is characterized by the presence of one or more of Methicillin resistant *Staphylococcus aureus*, Fluoroquinolone resistant *Staphylococcus aureus*, Vancomycin intermediate resistant *Staphylococcus aureus*, Linezolid resistant *Staphylococcus aureus*, Penicillin resistant *Streptococcus pneumoniae*, Macrolide resistant *Streptococcus pneumoniae*, Fluoroquinolone resistant *Streptococcus pneumoniae*, Vancomycin resistant *Enterococcus faecalis*, Linezolid resistant *Enterococcus faecalis*, Fluoroquinolone resistant *Enterococcus faecalis*, Vancomycin resistant *Enterococcus faecium*, Linezolid resistant *Enterococcus faecium*, Fluoroquinolone resistant *Enterococcus faecium*, Ampicillin resistant *Enterococcus faecium*, Macrolide resistant *Haemophilus influenzae*, β-lactam resistant *Haemophilus influenzae*, Fluoroquinolone resistant *Haemophilus influenzae*, β-lactam resistant *Moraxella catarrhalis*, Methicillin resistant *Staphylococcus epidermidis*, Methicillin resistant *Staphylococcus epidermidis*, Vancomycin resistant *Staphylococcus epidermidis*, Fluoroquinolone resistant *Staphylococcus epidermidis*, Macrolide resistant *Mycoplasma pneumoniae*, Isoniazid resistant *Mycobacterium tuberculosis*, Rifampin resistant *Mycobacterium tuberculosis*, Methicillin resistant *Coagulase negative staphylococcus,* Fluoroquinolone resistant *Coagulase negative staphylococcus*, Glycopeptide intermediate resistant *Staphylococcus aureus*, Vancomycin resistant *Staphylococcus aureus*, Hetero vancomycin intermediate resistant *Staphylococcus aureus*, Hetero vancomycin resistant *Staphylococcus aureus*, Macrolide-Lincosamide-Streptogramin resistant *Staphylococcus*, β-lactam resistant *Enterococcus faecalis*, β-lactam resistant *Enterococcus faecium*, Ketolide resistant *Streptococcus pneumoniae*, Ketolide resistant *Streptococcus pyogenes*, Macrolide resistant *Streptococcus pyogenes,* Vancomycin resistant *staphylococcus epidermidis*, Fluoroquinolone resistant *Neisseria gonorrhoeae*, Multidrug Resistant *Pseudomonas aeruginosa* or Cephalosporin resistant *Neisseria gonorrhoeae.*

[0097] According to another embodiment, the Methicillin resistant Staphylococci are selected from Methicillin resistant *Staphylococcus aureus*, Methicillin resistant *Staphylococcus epidermidis*, or Methicillin resistant *Coagulase negative staphylococcus*.

[0098] In some embodiments, a form of a compound of formula (I), or a pharmaceutically acceptable salt thereof, is used to treat community acquired MRSA (i.e., cMRSA).

[0099] In other embodiments, a form of a compound of formula (I), or a pharmaceutically acceptable salt thereof, is used to treat daptomycin resistant organism including, but not limited to, Daptomycin resistant *Enterococcus faecium* and Daptomycin resistant *Staphylococcus aureus*.

[00100] According to another embodiment, the Fluoroquinolone resistant Staphylococci are selected from Fluoroquinolone resistant *Staphylococcus aureus*, Fluoroquinolone resistant *Staphylococcus epidermidis*, or Fluoroquinolone resistant *Coagulase negative staphylococcus*.

[00101] According to another embodiment, the Glycopeptide resistant Staphylococci are selected from Glycopeptide intermediate resistant *Staphylococcus aureus*, Vancomycin resistant *Staphylococcus aureus*, Vancomycin intermediate resistant *Staphylococcus aureus*, Hetero vancomycin intermediate resistant *Staphylococcus aureus*, or Hetero vancomycin resistant *Staphylococcus aureus*.

[00102] According to another embodiment, the Macrolide-Lincosamide-Streptogramin resistant Staphylococci is Macrolide-Lincosamide-Streptogramin *resistant Staphylococcus aureus*.

[00103] According to another embodiment, the Linezolid resistant Enterococci are selected from Linezolid resistant *Enterococcus faecalis*, or Linezolid resistant *Enterococcus faecium*.

[00104] According to another embodiment, the Glycopeptide resistant Enterococci are selected from Vancomycin resistant *Enterococcus faecium* or Vancomycin resistant *Enterococcus faecalis*.

[00105] According to another embodiment, the β-lactam resistant Enterococcus faecalis is β-lactam resistant *Enterococcus faecium*.

[00106] According to another embodiment, the Penicillin resistant Streptococci is Penicillin resistant *Streptococcus pneumoniae*.

[00107] According to another embodiment, the Macrolide resistant Streptococci is Macrolide resistant *Streptococcus pneumonia.*

[00108] According to another embodiment, the Ketolide resistant Streptococci are selected from Macrolide resistant *Streptococcus pneumoniae* and Ketolide resistant *Streptococcus pyogenes*.

[00109] According to another embodiment, the Fluoroquinolone resistant Streptococci is Fluoroquinolone resistant *Streptococcus pneumoniae.*

[00110] According to another embodiment, the β-lactam resistant Haemophilus is β-lactam resistant *Haemophilus influenzae.*

[00111] According to another embodiment, the Fluoroquinolone resistant Haemophilus is Fluoroquinolone resistant *Haemophilus influenzae.*

[00112] According to another embodiment, the Macrolide resistant Haemophilus is Macrolide resistant *Haemophilus influenzae.*

[00113] According to another embodiment, the Macrolide resistant Mycoplasma is Macrolide resistant *Mycoplasma pneumoniae*.

[00114] According to another embodiment, the Isoniazid resistant Mycobacterium is Isoniazid resistant *Mycobacterium tuberculosis.*

[00115] According to another embodiment, the Rifampin resistant Mycobacterium is Rifampin resistant *Mycobacterium tuberculosis*.

[00116] According to another embodiment, the β-lactam resistant Moraxella is β-lactam resistant *Moraxella catarrhalis*.

[00117] According to another embodiment, the bacterial infection is characterized by the presence of one or more of the following: Methicillin resistant *Staphylococcus aureus*, Fluoroquinolone resistant *Staphylococcus aureus*, Vancomycin intermediate resistant *Staphylococcus aureus,* Linezolid resistant *Staphylococcus aureus*, Penicillin resistant *Streptococcus pneumoniae,* Macrolide resistant *Streptococcus pneumoniae*, Fluoroquinolone resistant *Streptococcus pneumoniae*, Vancomycin resistant *Enterococcus faecalis*, Linezolid resistant *Enterococcus faecalis,* Fluoroquinolone resistant *Enterococcus faecalis*, Vancomycin resistant *Enterococcus faecium,* Linezolid resistant *Enterococcus faecium,* Fluoroquinolone resistant *Enterococcus faecium*, Ampicillin resistant *Enterococcus faecium*, Macrolide resistant *Haemophilus influenzae*, β-lactam resistant *Haemophilus influenzae*, Fluoroquinolone resistant *Haemophilus influenzae*, β-lactam resistant *Moraxella catarrhalis*, Methicillin resistant *Staphylococcus epidermidis*, Methicillin resistant *Staphylococcus*

epidermidis, Vancomycin resistant *Staphylococcus epidermidis*, Fluoroquinolone resistant *Staphylococcus epidermidis,* Macrolide resistant *Mycoplasma pneumoniae*, Isoniazid resistant *Mycobacterium tuberculosis*, Rifampin resistant *Mycobacterium tuberculosis*, Fluoroquinolone resistant *Neisseria gonorrhoeae* or Cephalosporin resistant *Neisseria gonorrhoeae*.

[00118] According to another embodiment, the bacterial infection is characterized by the presence of one or more of the following: Methicillin resistant *Staphylococcus aureus*, Methicillin resistant *Staphylococcus epidermidis*, Methicillin resistant *Coagulase negative staphylococcus*, Fluoroquinolone resistant *Staphylococcus aureus,* Fluoroquinolone resistant *Staphylococcus epidermidis*, Fluoroquinolone resistant *Coagulase negative staphylococcus*, Vancomycin resistant *Staphylococcus aureus*, Glycopeptide intermediate resistant *Staphylococcus aureus*, Vancomycin resistant *Staphylococcus aureus*, Vancomycin intermediate resistant *Staphylococcus aureus*, Hetero vancomycin intermediate resistant *Staphylococcus aureus*, Hetero vancomycin resistant *Staphylococcus aureus*, Vancomycin resistant *Enterococcus faecium*, Vancomycin resistant *Enterococcus faecalis*, Penicillin resistant *Streptococcus pneumoniae*, Macrolide resistant *Streptococcus pneumoniae*, Fluoroquinolone resistant *Streptococcus pneumoniae*, Macrolide resistant *Streptococcus pyogenes*, or β-lactam resistant *Haemophilus influenzae*.

[00119] According to another embodiment, the bacterial infection is characterized by the presence of one or more of the following: Methicillin resistant *Staphylococcus aureus*, Vancomycin resistant *Enterococcus faecium*, Vancomycin resistant *Enterococcus faecalis*, Vancomycin resistant *Staphylococcus aureus*, Vancomycin intermediate resistant *Staphylococcus aureus*, Hetero vancomycin intermediate resistant *Staphylococcus aureus*, Hetero vancomycin resistant *Staphylococcus aureus*, Multidrug Resistant *Pseudomonas aeruginosa*, Isoniazid resistant *Mycobacterium tuberculosis,* and Rifampin resistant *Mycobacterium tuberculosis*.

[00120] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,

malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[00121] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4}$ alkyl$)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[00122] Pharmaceutical compositions of this invention comprise a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Such compositions may optionally comprise an additional therapeutic agent. Such agents include, but are not limited to, an antibiotic, an anti-inflammatory agent, a matrix metalloprotease inhibitor, a lipoxygenase inhibitor, a cytokine antagonist, an immunosuppressant, an anti-cancer agent, an anti-viral agent, a cytokine, a growth factor, an immunomodulator, a prostaglandin or an anti-vascular hyperproliferation compound.

[00123] The term "pharmaceutically acceptable carrier" refers to a non-toxic carrier that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

[00124] Pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat and self-emulsifying drug delivery systems (SEDDS) such as alpha-tocopherol, polyethyleneglycol 1000 succinate, or other similar polymeric delivery matrices.

[00125] The term "pharmaceutically effective amount" refers to an amount effective in treating or ameliorating a bacterial infection in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening a bacterial infection in a patient.

[00126] Depending upon the particular condition, or disease state, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may be administered together with the inhibitors of this invention. Such therapeutic agents include, but are not limited to, an antibiotic, an anti-inflammatory agent, a matrix metalloprotease inhibitor, a lipoxygenase inhibitor, a cytokine antagonist, an immunosuppressant, an anti-cancer agent, an anti-viral agent, a cytokine, a growth factor, an immunomodulator, a prostaglandin or an anti-vascular hyperproliferation compound.

[00127] The compounds of this invention may be employed in a conventional manner for controlling bacterial infections levels *in vivo* and for treating diseases or reducing the advancement or severity of effects which are mediated by bacteria. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques.

[00128] For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration to a patient suffering from a bacterial infection or disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that infection or disease.

[00129] Alternatively, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against bacterial infections or diseases over extended periods of time. In one embodiment, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against bacterial infections or diseases over a 1-2 week period. In another embodiment, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against bacterial infections or diseases over a 4-8 week period (for example, in the treatment of patients with or at risk for developing endocarditis or osteomyelitis). In another embodiment, the compounds of this invention may be used in compositions and methods for treating or protecting individuals against bacterial infections or diseases over an 8-12 week period. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional utilization of enzyme inhibitors in pharmaceutical compositions. For example, a compound of this

invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against bacterial infections or diseases.

[00130] In some embodiments, compounds of formula (I), or a pharmaceutically acceptable salt thereof, may be used prophylactically to prevent a bacterial infection. In some embodiments, compounds of formula (I), or a pharmaceutically acceptable salt thereof, may be used before, during or after a dental or surgical procedure to prevent opportunistic infections such as those encountered in bacterial endocarditis. In other embodiments, compounds of formula (I), or a pharmaceutically acceptable salt thereof, may be used prophylactically in dental procedures, including but not limited to extractions, periodontal procedures, dental implant placements and endodontic surgery. In other embodiments, compounds of formula (I), or a pharmaceutically acceptable salt thereof, may be used prophylactically in surgical procedures including but not limited to general surgery, respiratory surgery (tonsillectomy/adenoidectomy), gastrointestinal surgery (upper GI and elective small bowel surgery, esophageal sclerotherapy and dilation, large bowel resections, acute appendectomy), trauma surgery (penetrating abdominal surgery), genito-urinary tract surgery (prostatectomy, urethral dilation, cystoscopy, vaginal or abdominal hysterectomy, cesarean section), transplant surgery (kidney, liver, pancreas or kidney transplantation), head and neck surgery (skin excisions, neck dissections, laryngectomy, head and neck cancer surgeries, mandibular fractures), orthopaedic surgery (total joint replacement, traumatic open fractures), vascular surgery (peripheral vascular procedures), cardiothoracic surgery, coronary bypass surgery, pulmonary resection and neurosurgery.

[00131] The term "prevent a bacterial infection" as used herein, unless otherwise indicated, means the prophylactic use of an antibiotic, such as a gyrase and/or topoisomerase IV inhibitor of the present invention, to prevent a bacterial infection. Treatment with a gyrase and/or topoisomerase IV inhibitor could be done prophylactically to prevent an infection caused by an organism that is susceptible to the gyrase and/or topoisomerase IV inhibitor. One general set of conditions where prophylactic treatment could be considered is when an individual is more vulnerable to infection due to, for example, weakened immunity, surgery, trauma, presence of an artificial device in the body (temporary or permanent), an anatomical defect, exposure to high levels of bacteria or possible exposure to a disease-causing pathogen. Examples of factors that could lead to weakened immunity include chemotherapy, radiation therapy, diabetes, advanced age, HIV infection, and transplantation.

An example of an anatomical defect would be a defect in the heart valve that increases the risk of bacterial endocarditis. Examples of artificial devices include artificial joints, surgical pins, catheters, etc. Another set of situations where prophylactic use of a gyrase and/or topoisomerase IV inhibitor might be appropriate would be to prevent the spread of a pathogen between individuals (direct or indirect). A specific example of prophylactic use to prevent the spread of a pathogen is the use of a gyrase and/or topoisomerase IV inhibitor by individuals in a healthcare institution (for example a hospital or nursing home).

[00132] The compounds of formula (I), or a pharmaceutically acceptable salt thereof, may also be co-administered with other antibiotics to increase the effect of therapy or prophylaxis against various bacterial infections. When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention comprise a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another therapeutic or prophylactic agent.

[00133] In some embodiments, the additional therapeutic agent or agents is an antibiotic selected from a natural penicillin, a penicillinase-resistant penicillin, an antipseudomonal penicillin, an aminopenicillin, a first generation cephalosporin, a second generation cephalosporin, a third generation cephalosporin, a fourth generation cephalosporin, a carbapenem, a cephamycin, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide, a ketolide, a polymyxin, a tetracycline, a glycopeptide, a streptogramin, an oxazolidinone, a rifamycin, or a sulfonamide.

[00134] In some embodiments, the additional therapeutic agent or agents is an antibiotic selected from a penicillin, a cephalosporin, a quinolone, an aminoglycoside or an oxazolidinone.

[00135] In other embodiments, the additional therapeutic agents are selected from a natural penicillin including Benzathine penicillin G, Penicillin G and Penicillin V, from a penicillinase-resistant penicillin including Cloxacillin, Dicloxacillin, Nafcillin and Oxacillin, from a antipseudomonal penicillin including Carbenicillin, Mezlocillin, Pipercillin, Pipercillin/tazobactam, Ticaricillin and Ticaricillin/Clavulanate, from an aminopenicillin including Amoxicillin, Ampicillin and Ampicillin/Sulbactam, from a first generation cephalosporin including Cefazolin, Cefadroxil, Cephalexin and Cephadrine, from a second generation cephalosporin including Cefaclor, Cefaclor-CD, Cefamandole, Cefonacid,

Cefprozil, Loracarbef and Cefuroxime, from a third generation cephalosporin including Cefdinir, Cefixime, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxme and Ceftriaxone, from a fourth generation cephalosporin including Cefepime, Ceftaroline and Ceftobiprole, from a Cephamycin including Cefotetan and Cefoxitin, from a carbapenem including Doripenem, Imipenem and Meropenem, from a monobactam including Aztreonam, from a quinolone including Cinoxacin, Nalidixic acid, Oxolininc acid and Pipemidic acid, from a fluoroquinolone including Besifloxacin, Ciprofloxacin, Enoxacin, Gatifloxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Moxifloxacin, Norfloxacin, Ofloxacin and Sparfloxacin, from an aminoglycoside including Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Spectinomycin, Streptomycin and Tobramycin, from a macrolide including Azithromycin, Clarithromycin and Erythromycin, from a ketolide including Telithromycin, from a Tetracycline including Chlortetracycline, Demeclocycline, Doxycycline, Minocycline and Tetracycline, from a glycopeptide including Oritavancin, Dalbavancin, Telavancin, Teicoplanin and Vancomycin, from a streptogramin including Dalfopristin/quinupristin, from an oxazolidone including Linezolid, from a Rifamycin including Rifabutin and Rifampin and from other antibiotics including bactitracin, colistin, Tygacil, Daptomycin, chloramphenicol, clindamycin, isoniazid, metronidazole, mupirocin, polymyxin B, pyrazinamide, trimethoprim/sulfamethoxazole and sulfisoxazole.

[00136] In other embodiments, the additional therapeutic agents are selected from a natural penicillin including Penicillin G, from a penicillinase-resistant penicillin including Nafcillin and Oxacillin, from an antipseudomonal penicillin including Pipercillin/tazobactam, from an aminopenicillin including Amoxicillin, from a first generation cephalosporin including Cephalexin, from a second generation cephalosporin including Cefaclor, Cefaclor-CD and Cefuroxime, from a third generation cephalosporin including Ceftazidime and Ceftriaxone, from a fourth generation cephalosporin including Cefepime, from a carbapenem including Imepenem, Meropenem, Ertapenem, Doripenem, Panipenem and Biapenem,a fluoroquinolone including Ciprofloxacin, Gatifloxacin, Levofloxacin and Moxifloxacin, from an aminoglycoside including Tobramycin, from a macrolide including Azithromycin and Clarithromycin, from a Tetracycline including Doxycycline, from a glycopeptide including Vancomycin, from a Rifamycin including Rifampin and from other antibiotics including isoniazid, pyrazinamide, Tygacil, Daptomycin or trimethoprim/sulfamethoxazole.

[00137] In some embodiments, a solid form of a compound of formula (I), or a pharmaceutically acceptable salt thereof, can be administered for the treatment of a gram

positive infection. In some embodiments, the composition is a solid, liquid (e.g., a suspension), or an iv (e.g., a form of the formula (I) compound, or a pharmaceutically acceptable salt thereof, is dissolved into a liquid and administered iv) composition. In some embodiments, the composition including a formula (I) compound, or a pharmaceutically acceptable salt thereof, is administered in combination with an additional antibiotic agent, for example, a natural penicillin, a penicillinase-resistant penicillin, an antipseudomonal penicillin, an aminopenicillin, a first generation cephalosporin, a second generation cephalosporin, a third generation cephalosporin, a fourth generation cephalosporin, a carbapenem, a cephamycin, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide, a ketolide, a polymyxin, a tetracycline, a glycopeptide, a streptogramin, an oxazolidinone, a rifamycin, or a sulfonamide. In some embodiments, the composition including a solid form of a formula (I) compound, or a pharmaceutically acceptable salt thereof, is administered orally, and the additional antibiotic agent, for example, a natural penicillin, a penicillinase-resistant penicillin, an antipseudomonal penicillin, an aminopenicillin, a first generation cephalosporin, a second generation cephalosporin, a third generation cephalosporin, a fourth generation cephalosporin, a carbapenem, a cephamycin, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide, a ketolide, a polymyxin, a tetracycline, a glycopeptide, a streptogramin, an oxazolidinone, a rifamycin, or a sulfonamide is administered iv.

[00138] In some embodiments, a solid form of a formula (I) compound, or a pharmaceutically acceptable salt thereof, can be administered for the treatment of a gram negative infection. In some embodiments, the composition is a solid, liquid (e.g., a suspension), or an iv (e.g., a form of a formula (I) compound, or a pharmaceutically acceptable salt thereof, is dissolved into a liquid and administered iv) composition. In some embodiments the composition including a formula (I) compound, or a pharmaceutically acceptable salt thereof, is administered in combination with an additional antibiotic agent, selected from a: natural penicillin, a penicillinase-resistant penicillin, an antipseudomonal penicillin, an aminopenicillin, a first generation cephalosporin, a second generation cephalosporin, a third generation cephalosporin, a fourth generation cephalosporin, a carbapenem, a cephamycin, a monobactam, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide, a ketolide, a polymyxin, tetracycline or a sulfonamide. In some embodiments, the composition including a solid form of a formula (I) compound, or a pharmaceutically acceptable salt thereof, is administered orally, and the additional antibiotic agent, for example, a natural penicillin, a penicillinase-resistant penicillin, an

antipseudomonal penicillin, an aminopenicillin, a first generation cephalosporin, a second generation cephalosporin, a third generation cephalosporin, a fourth generation cephalosporin, a carbapenem, a cephamycin, a monobactam, a quinolone, a fluoroquinolone, an aminoglycoside, a macrolide, a ketolide, a polymyxin, tetracycline or a sulfonamide is administered orally. In some embodiments, the additional therapeutic agent is administered iv.

[00139] The additional therapeutic agents described above may be administered separately, as part of a multiple dosage regimen, from the inhibitor-containing composition. Alternatively, these agents may be part of a single dosage form, mixed together with the inhibitor in a single composition.

[00140] The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[00141] The pharmaceutical, compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain

alcohol diluent or dispersant, such as those described in Pharmacopeia Helvetica, or a similar alcohol.

[00142] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and solutions and propylene glycol are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

[00143] The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00144] Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches are also included in this invention.

[00145] The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-

known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

[00146] According to another embodiment, compounds of formula (I), or a pharmaceutically acceptable salt thereof, may also be delivered by implantation (e.g., surgically), such as with an implantable or indwelling device. An implantable or indwelling device may be designed to reside either permanently or temporarily in a subject. Examples of implantable and indwelling devices include, but are not limited to, contact lenses, central venous catheters and needleless connectors, endotracheal tubes, intrauterine devices, mechanical heart valves, pacemakers, peritoneal dialysis catheters, prosthetic joints, such as hip and knee replacements, tympanostomy tubes, urinary catheters, voice prostheses, stents, delivery pumps, vascular filters and implantable control release compositions. Biofilms can be detrimental to the health of patients with an implantable or indwelling medical device because they introduce an artificial substratum into the body and can cause persistent infections. Thus, providing compounds of formula (I), or a pharmaceutically acceptable salt thereof, in or on the implantable or indwelling device can prevent or reduce the production of a biofilm. In addition, implantable or indwelling devices may be used as a depot or reservoir of compounds of formula (I), or a pharmaceutically acceptable salt thereof. Any implantable or indwelling device can be used to deliver a compound of formula (I), or a pharmaceutically acceptable salt thereof, provided that a) the device, a compound of formula (I), or a pharmaceutically acceptable salt thereof, and any pharmaceutical composition including a compound of formula (I), or a pharmaceutically acceptable salt thereof, are biocompatible, and b) that the device can deliver or release an effective amount of compounds of formula (I), or a pharmaceutically acceptable salt thereof, to confer a therapeutic effect on the treated patient.

[00147] Delivery of therapeutic agents via implantable or indwelling devices is known in the art. See for example, "Recent Developments in Coated Stents" by Hofma et al. published in *Current Interventional Cardiology Reports* 2001, **3:**28-36, the entire contents of which, including references cited therein, incorporated herein by reference. Other descriptions of implantable devices can be found in U.S. Patent Nos. 6,569,195 and 6,322,847; and U.S. Patent Application Numbers 2004/0044405, 2004/0018228, 2003/0229390, 2003/0225450, 2003/0216699 and 2003/0204168, each of which is incorporated herein by reference in its entirety.

[00148] In some embodiments, the implantable device is a stent. In one specific embodiment, a stent can include interlocked meshed cables. Each cable can include metal wires for structural support and polymeric wires for delivering the therapeutic agent. The polymeric wire can be dosed by immersing the polymer in a solution of the therapeutic agent. Alternatively, the therapeutic agent can be embedded in the polymeric wire during the formation of the wire from polymeric precursor solutions.

[00149] In other embodiments, implantable or indwelling devices can be coated with polymeric coatings that include the therapeutic agent. The polymeric coating can be designed to control the release rate of the therapeutic agent. Controlled release of therapeutic agents can utilize various technologies. Devices are known that have a monolithic layer or coating incorporating a heterogeneous solution and/or dispersion of an active agent in a polymeric substance, where the diffusion of the agent is rate limiting, as the agent diffuses through the polymer to the polymer-fluid interface and is released into the surrounding fluid. In some devices, a soluble substance is also dissolved or dispersed in the polymeric material, such that additional pores or channels are left after the material dissolves. A matrix device is generally diffusion limited as well, but with the channels or other internal geometry of the device also playing a role in releasing the agent to the fluid. The channels can be pre-existing channels or channels left behind by released agent or other soluble substances.

[00150] Erodible or degradable devices typically have the active agent physically immobilized in the polymer. The active agent can be dissolved and/or dispersed throughout the polymeric material. The polymeric material is often hydrolytically degraded over time through hydrolysis of labile bonds, allowing the polymer to erode into the fluid, releasing the active agent into the fluid. Hydrophilic polymers have a generally faster rate of erosion relative to hydrophobic polymers. Hydrophobic polymers are believed to have almost purely surface diffusion of active agent, having erosion from the surface inwards. Hydrophilic polymers are believed to allow water to penetrate the surface of the polymer, allowing hydrolysis of labile bonds beneath the surface, which can lead to homogeneous or bulk erosion of polymer.

[00151] The implantable or indwelling device coating can include a blend of polymers each having a different release rate of the therapeutic agent. For instance, the coating can include a polylactic acid/polyethylene oxide (PLA-PEO) copolymer and a polylactic acid/polycaprolactone (PLA-PCL) copolymer. The polylactic acid/polyethylene oxide (PLA-PEO) copolymer can exhibit a higher release rate of therapeutic agent relative to the

polylactic acid/polycaprolactone (PLA-PCL) copolymer. The relative amounts and dosage rates of therapeutic agent delivered over time can be controlled by controlling the relative amounts of the faster releasing polymers relative to the slower releasing polymers. For higher initial release rates the proportion of faster releasing polymer can be increased relative to the slower releasing polymer. If most of the dosage is desired to be released over a long time period, most of the polymer can be the slower releasing polymer. The device can be coated by spraying the device with a solution or dispersion of polymer, active agent, and solvent. The solvent can be evaporated, leaving a coating of polymer and active agent. The active agent can be dissolved and/or dispersed in the polymer. In some embodiments, the co-polymers can be extruded over the device.

[00152] Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between 0.5 and about 75 mg/kg body weight per day and most preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in a monotherapy for the prevention and treatment of bacterial infections.

[00153] Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Alternatively, the compositions of the present invention may be administered in a pulsatile formulation. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

[00154] When the compositions of this invention comprise a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 10% to 80% of the dosage normally administered in a monotherapy regime.

[00155] Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may,

however, require intermittent treatment on a long-term basis upon any recurrence or disease symptoms.

[00156] As the skilled artisan will appreciate, lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician.

[00157] According to another embodiment, the invention provides methods for treating or preventing a bacterial infection, or disease state, comprising the step of administering to a patient any compound, pharmaceutical composition, or combination described herein. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00158] The compounds of this invention are also useful as commercial reagents which effectively bind to the gyrase B and/or topoisomerase IV enzymes. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block gyrase B and/or topoisomerase IV activity in biochemical or cellular assays for bacterial gyrase B and/or topoisomerase IV or their homologs or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial gyrase B and/or topoisomerase IVinhibitors will be evident to those of ordinary skill in the art.

[00159] In order that this invention be more fully understood, the following schemes and examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

[00160] The following definitions describe terms and abbreviations used herein:

Ac	acetyl
Bu	butyl
Et	ethyl
Ph	phenyl
Me	methyl
THF	tetrahydrofuran
DCM	dichloromethane
CH_2Cl_2	dichloromethane
EtOAc	ethyl acetate
CH_3CN	acetonitrile
EtOH	ethanol
Et_2O	diethyl ether

MeOH	methanol
MTBE	methyl *tert*-butyl ether
DMF	*N,N*-dimethylformamide
DMA	*N,N*-dimethylacetamide
DMSO	dimethyl sulfoxide
HOAc	acetic acid
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Et_3N	triethylamine
DIPEA	diisopropylethylamine
DIEA	diisopropylethylamine
K_2CO_3	potassium carbonate
Na_2CO_3	sodium carbonate
$Na_2S_2O_3$	sodium thiosulfate
Cs_2CO_3	cesium carbonate
$NaHCO_3$	sodium bicarbonate
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
$MgSO_4$,	magnesium sulfate
K_3PO_4	potassium phosphate
NH_4Cl	ammonium chloride
LC/MS	liquid chromatography/mass spectra
GCMS	gas chromatography mass spectra
HPLC	high performance liquid chromatography
GC	gas chromatography
LC	liquid chromatography
IC	ion chromatography
IM	intramuscular
CFU/cfu	colony forming units
MIC	minimum inhibitory concentration
Hr or h	hours
atm	atmospheres
rt or RT	room temperature
TLC	thin layer chromatography
HCl	hydrochloric acid
H_2O	water
EtNCO	ethyl isocyanate
Pd/C	palladium on carbon
NaOAc	sodium acetate
H_2SO_4	sulfuric acid
N_2	nitrogen gas
H_2	hydrogen gas
n-BuLi	*n*-butyl lithium
DI	de-ionized
$Pd(OAc)_2$	palladium(II)acetate
PPh_3	triphenylphosphine
i-PrOH	isopropyl alcohol
NBS	*N*-bromosuccinimide
$Pd[(Ph_3)P]_4$	tetrakis(triphenylphosphine)palladium(0)

PTFE	polytetrafluoroethylene
rpm	revolutions per minute
SM	starting material
Equiv.	equivalents
^{1}H-NMR	proton nuclear magnetic resonance

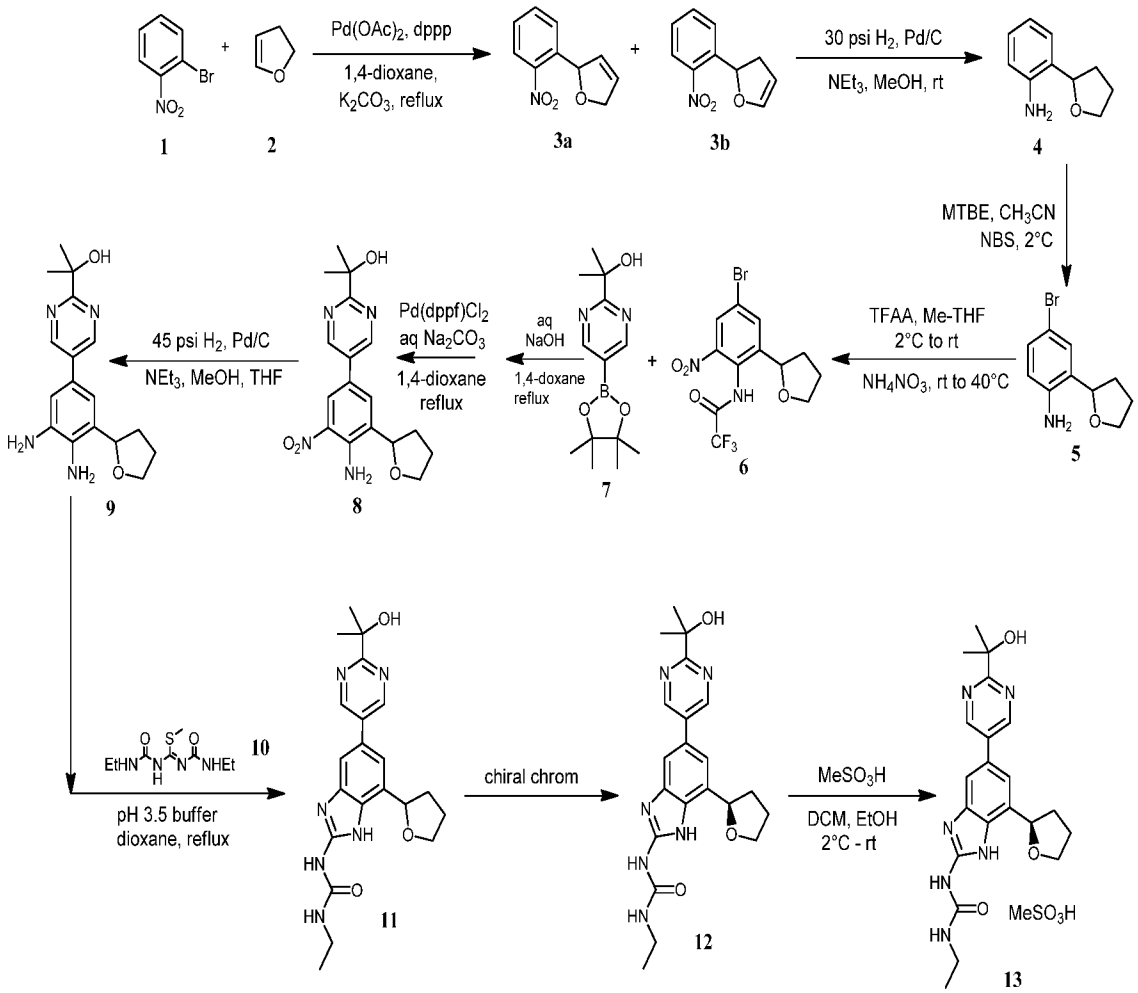
Synthesis of the Compounds

EXAMPLES

THE BENZIMIDAZOLYL UREA COMPOUND

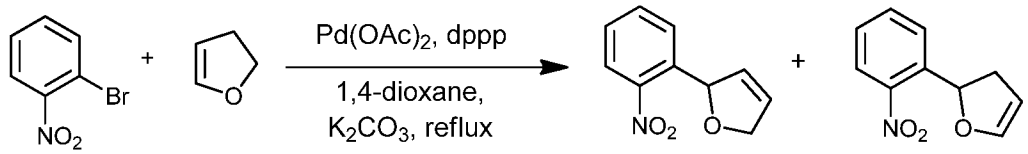
Scheme 2 provides a method for preparing the benzimidazolyl urea compound.

Scheme 2



Example 1.a

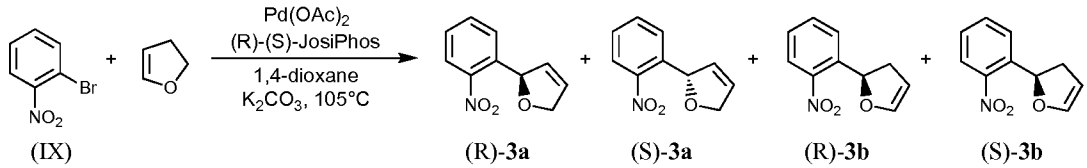
Preparation of 2-(2-nitrophenyl)-2,5-dihydrofuran (**3a**) and 2-(2-nitrophenyl)-2,3-dihydrofuran (**3b**)



[00161] 1-Bromo-2-nitro-benzene (**1**) (600 g, 99%, 2.941 mol, Alfa Aesar A11686), 1,3-bis(diphenylphosphino)propane (62.50 g, 97%, 147.0 mmol, Alfa Aesar A12931), 1,4-dioxane (2.970 L, Sigma-Aldrich 360481), potassium carbonate (812.9 g, 5.882 mol, JT-Baker 301201), and 2,3-dihydrofuran (**2**) (1.041 kg, 99%, 1.124 L, 14.70 mol, Aldrich 200018) were mixed in a reaction vessel. A stream of nitrogen was bubbled through the stirring mixture for 4 hrs, followed by addition of palladium (II) acetate (16.51 g, 73.52 mmol, Strem 461780) and continuation of deoxygenation for another 10 minutes. The reaction mixture was stirred at reflux under nitrogen overnight (NMR of a worked-up aliquot showed complete consumption of arylbromide). The reaction mixture was allowed to cool, diluted with hexane (1 L), filtered through a short plug of Florisil® (500 g, -200 mesh), and eluted with EtOAc. The filtrate was concentrated under reduced pressure (2-(2-nitrophenyl)-2,3-dihydrofuran (**3b**) is volatile under high vacuum and may be somewhat unstable at room temperature) giving a mixture of (**3a**) and (**3b**) as a dark brown oil (654.0 g). The crude material was stored in the refrigerator and carried forward without further purification.

Example 1.a.1

Asymmetric Preparation of 2-(2-nitrophenyl)-2,5-dihydrofuran (3a) and 2-(2-nitrophenyl)-2,3-dihydrofuran (3b)



[00162] 1-bromo-2-nitrobenzene (50.0 mg, 98%, 0.2426 mmol, Aldrich 365424), potassium carbonate (67.1 mg, 0.4852 mmol, JT-Baker 301201), (R)-(-)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine ethanol adduct ((R)-(S)-JosiPhos, 7.8 mg, 0.01213 mmol, Strem 261210), 2,3-dihydrofuran (1.0 mL, 99%, 13.08 mmol, Aldrich 200018), and 1,4-dioxane (0.98 mL) were mixed in a reaction tube. A stream of nitrogen was bubbled through the stirring mixture for 20 minutes, and then palladium (II) acetate (1.36 mg, 0.006065 mmol, Strem 461780) was added. The tube was sealed and the

reaction mixture stirred at 105°C overnight. HPLC of the crude reaction mixture showed nearly complete consumption of aryl bromide and formation of a 1:1 mixture of the 2-(2-nitrophenyl)-2,5-dihydrofuran (**3a**) and 2-(2-nitrophenyl)-2,3-dihydrofuran (**3b**). The reaction mixture was allowed to cool, diluted with hexane (2 mL), filtered, and rinsed with ethyl acetate. The filtrate was concentrated on a rotary evaporator to afford a brown oil (51 mg). The material was not placed under high vacuum due to volatility and stability concerns. The crude reaction mixture was determined to be a 1:1 mixture of (**3a**) and (**3b**) by ^{1}H NMR analysis. The oil was purified by silica gel chromatography eluting with 0 to 38% EtOAc in hexane (or 0 to 100% CH_2Cl_2 in hexane) to afford pure samples of (**3a**) and (**3b**). Analytical data for these samples was as follows:

[00163] 2-(2-nitrophenyl)-2,5-dihydrofuran (**3a**) was obtained as a yellow solid (97% HPLC purity, 97.0% ee): LCMS (C18 column eluting with 10-90% MeOH / water gradient from 3-5 minutes with formic acid modifier) M+1: 192.05 (3.40 min); HPLC retention time of 4.2 min (YMC ODS-AQ 150 x 3.0 mm column eluting with 10-90% CH_3CN / water gradient over 8 minutes with 0.1% TFA modifier and 1 mL/min flow rate); analytical chiral HPLC retention time of 7.4 min (major enantiomer) and 8.1 min (minor enantiomer) eluting with 10% iPrOH / hexane on a CHIRALCEL® OJ® 4.6 x 250 mm column with 1 mL/min flow rate at 30°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.45 – 7.38 (m, 1H), 6.37 – 6.30 (m, 1H), 6.11 – 6.06 (m, 1H), 6.04 – 5.98 (m, 1H), 5.02 – 4.83 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.97, 139.11, 133.95, 129.58, 128.10, 128.09, 126.78, 124.38, 84.28, 76.42 ppm; ^{13}C DEPT NMR (75 MHz, $CDCl_3$) δ 133.95 (CH), 129.58 (CH), 128.10 (CH), 128.09 (CH), 126.78 (CH), 124.38 (CH), 84.28 (CH), 76.42 (CH_2) ppm.

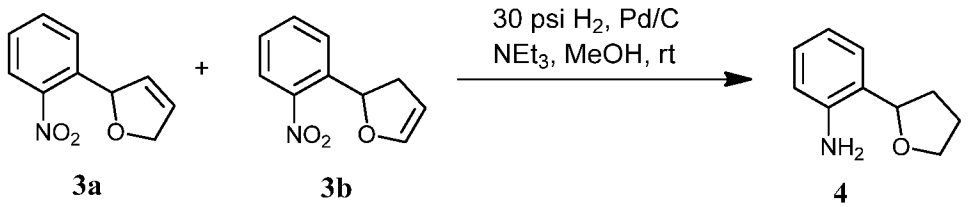
[00164] 2-(2-nitrophenyl)-2,3-dihydrofuran (**3b**) was obtained as a yellow oil (79-90% HPLC purity, 44.0% ee): LCMS (C18 column eluting with 10-90% MeOH / water gradient from 3-5 minutes with formic acid modifier) M+1: 192.05 (3.72 min); HPLC retention time of 4.8 min (YMC ODS-AQ 150 x 3.0 mm column eluting with 10-90% CH_3CN / water gradient over 8 minutes with 0.1% TFA modifier and 1 mL/min flow rate); analytical chiral HPLC retention time of 5.96 min (major enantiomer) and 6.35 min (minor enantiomer) eluting with 10% iPrOH / hexane on a CHIRALCEL® OJ® 4.6 x 250 mm column with 1 mL/min flow rate at 30°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.48 – 7.39 (m, 1H), 6.50 (q, J = 2.4 Hz, 1H), 6.10 (dd, J = 10.9, 7.4 Hz, 1H), 4.95 (q, J = 2.5 Hz, 1H), 3.46 – 3.35 (m, 1H), 2.50 – 2.39 (m, 1H)

ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.60, 144.98, 139.73, 133.93, 128.07, 127.11, 124.85, 99.29, 78.45, 38.29 ppm; ^{13}C DEPT NMR (75 MHz, $CDCl_3$) δ 144.98 (CH), 133.93 (CH), 128.07 (CH), 127.11 (CH), 124.85 (CH), 99.29 (CH), 78.45 (CH), 38.29 (CH_2) ppm.

[00165] **3a** and **3b** were carried through the reduction step to afford 2-tetrahydrofuran-2-yl-aniline (**4**) as set forth in Example 1.b (below). Analysis of this material revealed that both **3a** and **3b** were formed with the same major enantiomer, with an overall 70% ee. It is unknown whether the absolute stereochemistry of the major enantiomer was (R) or (S).

Example 1.b

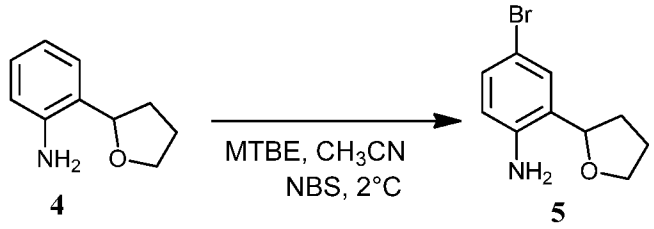
Preparation of 2-tetrahydrofuran-2-yl-aniline (**4**)



[00166] 5% Palladium on carbon (16.3 g, 50% wet, 3.83 mmol, Aldrich 330116) was placed in a Parr bottle under nitrogen, followed by MeOH (100 mL, JT-Baker 909333). The crude mixture of 2-(2-nitrophenyl)-2,5-dihydrofuran and 2-(2-nitrophenyl)-2,3-dihydrofuran (**3a** & **3b**) (163 g) dissolved in MeOH (389 mL) was added to the Parr bottle, followed by NEt_3 (237.6 mL, 1.705 mol, Sigma-Aldrich 471283). The bottle was placed on a Parr shaker and saturated with H_2. 30 psi H_2 was added and the bottle was shaken until starting material was completely consumed (LCMS and NMR showed complete reaction). The reaction mixture was purged with nitrogen, filtered through Celite™ and rinsed with EtOAc. The filtrate was concentrated on a rotary evaporator giving a brown oil. The reaction was repeated three more times on the same scale and the batches were combined for purification. The crude product was vacuum distilled (ca. 15 torr) collecting the distillate at 108 - 129°C to give (**4**) as a clear faint yellow oil (427.9 g, average yield was 84%; 98% GCMS purity). LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 163.95 (1.46 min). ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 – 7.04 (m, 2H), 6.77 – 6.62 (m, 2H), 4.85 – 4.77 (m, 1H), 4.18 (s, 2H), 4.12 – 4.02 (m, 1H), 3.94 – 3.85 (m, 1H), 2.25 – 1.95 (m, 4H) ppm.

Example 1.c

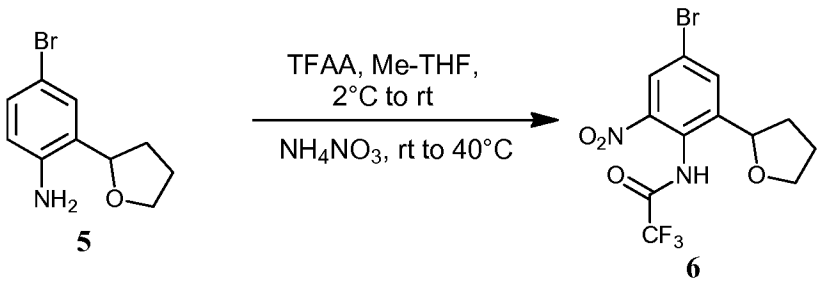
Preparation of 4-bromo-2-tetrahydrofuran-2-yl-aniline (**5**).



[00167] To a stirring solution of 2-tetrahydrofuran-2-yl-aniline (**4**) (53.45 g, 327.5 mmol) in methyl tert-butyl ether (MTBE, 641.4 mL) and acetonitrile (213.8 mL) cooled to 2°C was added N-bromosuccinimide (NBS, 58.88 g, 99%, 327.5 mmol, Aldrich B81255) in 4 portions maintaining internal temperature below about 8°C. The reaction mixture was stirred while cooling with an ice-water bath for 30 minutes (NMR of a worked-up aliquot showed complete consumption of starting material). Aqueous 1 N $Na_2S_2O_3$ (330 mL) was added to the reaction mixture, removed the cold bath and stirred for 20 minutes. The mixture was diluted with EtOAc and the layers were separated. The organic phase was washed with saturated aqueous $NaHCO_3$ (2x), water, brine, dried over $MgSO_4$, filtered through a short plug of silica, eluted with EtOAc, and concentrated under reduced pressure to give (**5**) as a very dark amber oil (82.25 g, 77-94% HPLC purity). Carried forward without further purification. LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 242.10 (2.89 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J = 2.3 Hz, 1H), 7.16 (dd, J = 8.4, 2.3 Hz, 1H), 6.54 (d, J = 8.4 Hz, 1H), 4.79 – 4.73 (m, 1H), 4.15 (s, 2H), 4.10 – 4.01 (m, 1H), 3.93 – 3.85 (m, 1H), 2.26 – 2.13 (m, 1H), 2.12 – 1.97 (m, 3H) ppm.

Example 1.d

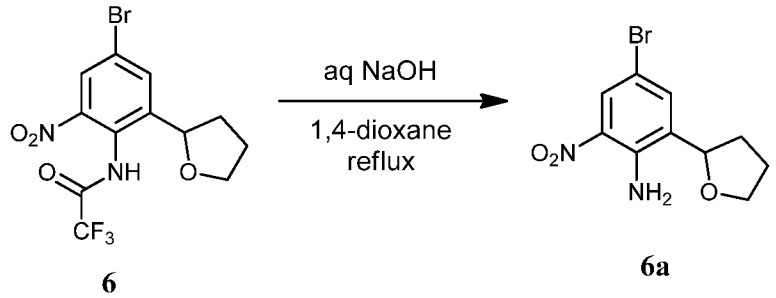
Preparation of N-(4-bromo-2-nitro-6-tetrahydrofuran-2-yl-phenyl)-2,2,2-trifluoro-acetamide (**6**).



[00168] To trifluoroacetic anhydride (455.3 mL, 3.275 mol, Sigma-Aldrich 106232) stirring at 2°C was slowly added 4-bromo-2-tetrahydrofuran-2-yl-aniline (**5**) (79.29 g, 327.5 mmol) as a thick oil via addition funnel over 15 minutes (reaction temperature rose to 14°C). The remaining oil was rinsed into the reaction mixture with anhydrous 2-methyltetrahydrofuran (39.6 mL, Sigma-Aldrich 414247). The cold bath was removed and ammonium nitrate (34.08 g, 425.8 mmol, Aldrich 467758) was added. The reaction temperature rose to 40°C over about 30 minutes at which time a cold water bath was used to control the exotherm and bring the reaction to room temperature. The cold bath was then removed and stirring continued for another 40 minutes (HPLC showed very little remaining un-nitrated material). The reaction mixture was slowly poured into a stirring mixture of crushed ice (800 g). The solid precipitate was collected by filtration, washed with water, saturated aqueous $NaHCO_3$ (to pH 8), water again, and hexane. The wet solid was dried first in a convection oven at 50°C for several hours and then under reduced pressure in an oven at 40°C overnight giving (**6**) as a light brown solid (77.86 g, 62% yield; 98% HPLC purity). LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 383.19 (3.27 min). ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.08 (d, J = 2.2 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 4.88 (dd, J = 9.0, 6.5 Hz, 1H), 4.17 – 4.08 (m, 1H), 4.03 – 3.95 (m, 1H), 2.45 – 2.34 (m, 1H), 2.17 – 2.06 (m, 2H), 1.96 – 1.83 (m, 1H) ppm.

Example 1.e

Preparation of 4-bromo-2-nitro-6-tetrahydrofuran-2-yl-aniline (**6a**).

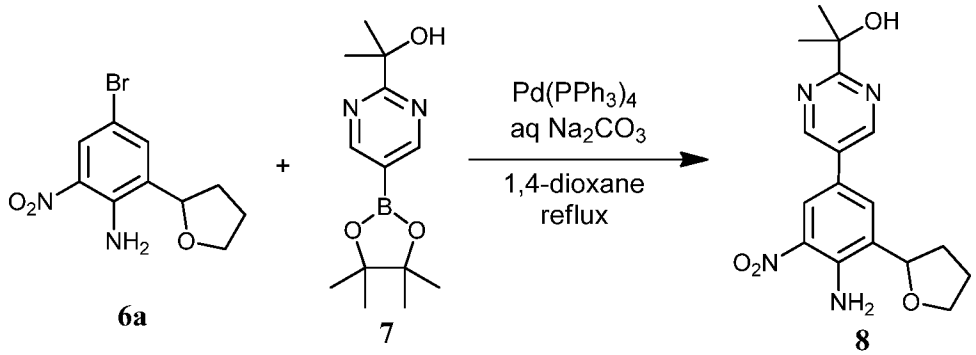


[00169] N-(4-bromo-2-nitro-6-tetrahydrofuran-2-yl-phenyl)-2,2,2-trifluoro-acetamide (**6**) (54.00 g, 140.9 mmol) was dissolved in 1,4-dioxane (162 mL) and added aqueous 6 M NaOH (70.45 mL, 422.7 mmol, JT-Baker 567202). The reaction mixture was stirred at reflux for 2 days (HPLC showed complete conversion). The mixture was allowed to cool, diluted with MTBE (800 mL), and washed with water (2 x 200 mL), saturated aqueous NH_4Cl,

water, and brine. The mixture was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give (**6a**) as a dark amber oil (40.96 g, 93% yield; overall 92% HPLC plus NMR purity). LCMS (C18 column eluting with 10-90% MeOH / water gradient from 3-5 minutes with formic acid modifier) M+1: 287.28 (3.44 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 2.3 Hz, 1H), 6.91 (s, 2H), 4.80 (t, J = 7.2 Hz, 1H), 4.14 – 4.05 (m, 1H), 3.98 – 3.90 (m, 1H), 2.36 – 2.19 (m, 1H), 2.15 – 2.01 (m, 3H) ppm.

Example 1.f

Preparation of 2-[5-(4-amino-3-nitro-5-tetrahydrofuran-2-yl-phenyl)pyrimidin-2-yl]propan-2-ol (**8**).

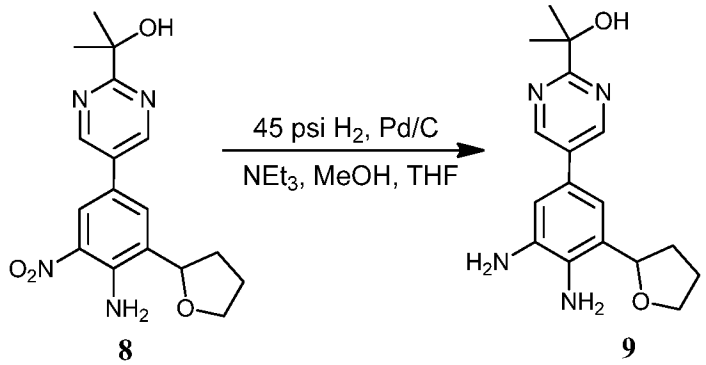


[00170] 4-Bromo-2-nitro-6-tetrahydrofuran-2-yl-aniline (**6a**) (40.40 g, 92%, 129.5 mmol), 1,4-dioxane (260 mL, Sigma-Aldrich 360481), 2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]propan-2-ol (**7**) (41.05 g, 155.4 mmol), and aqueous 2.7 M Na_2CO_3 (143.9 mL, 388.5 mmol) were mixed. A stream of nitrogen was bubbled through the stirring mixture for 1 hr, followed by addition of tetrakis(triphenylphosphine)palladium (0) (7.48 g, 6.47 mmol, Strem 462150). The reaction mixture was stirred at reflux for 2 hrs (HPLC showed complete reaction), allowed to cool, and diluted with EtOAc. The mixture was washed with water, saturated aqueous NH_4Cl, and brine, dried over $MgSO_4$, and filtered through a short plug of Florisil® eluting with EtOAc. The filtrate was concentrated under reduced pressure giving dark brown oil. The oil was dissolved in CH_2Cl_2 and eluted through a short plug of silica gel with CH_2Cl_2 and then EtOAc. The desired fraction was concentrated on a rotary evaporator until a precipitate formed giving a thick brown slurry, which was triturated with MTBE. The solid was collected by filtration, washed with MTBE, and dried under high vacuum giving (**8**) as a yellow solid (35.14 g, 99+% HPLC purity). LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 345.00 (2.69 min). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 2H), 8.36 (d, J =

2.2 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.09 (s, 2H), 4.92 (t, J = 7.2 Hz, 1H), 4.62 (s, 1H), 4.20 – 4.11 (m, 1H), 4.03 – 3.94 (m, 1H), 2.39 – 2.26 (m, 1H), 2.23 – 2.08 (m, 3H), 1.64 (s, 6H) ppm. The filtrate was concentrated and purified by ISCO silica gel chromatography eluting with 0 to 80% EtOAc / hexane giving a second crop of product (**8**) as an amber solid (4.46 g, 88% overall yield ; 88% HPLC purity).

Example 1.g

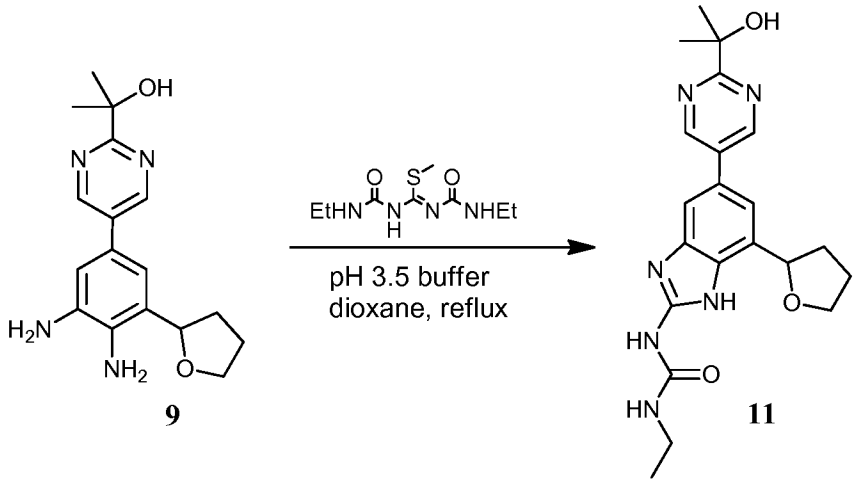
Preparation of 2-[5-(3,4-diamino-5-tetrahydrofuran-2-yl-phenyl)pyrimidin-2-yl]propan-2-ol (9).



[00171] To a suspension of 2-[5-(4-amino-3-nitro-5-tetrahydrofuran-2-yl-phenyl)pyrimidin-2-yl]propan-2-ol (**8**) (30.10 g, 87.41 mmol) and THF (90 mL) in a Parr bottle under nitrogen was added a slurry of 5% palladium on carbon (3.01 g, 50% wet, 0.707 mmol, Aldrich 330116) in MeOH (90 mL, JT-Baker 909333), followed by NEt_3 (24.37 mL, 174.8 mmol, Sigma-Aldrich 471283). The vessel was placed on a Parr shaker and saturated with H_2. After adding 45 psi H_2, the vessel was shaken until consumption was complete (HPLC showed complete conversion). The reaction mixture was purged with nitrogen, filtered through Celite™ and rinsed with EtOAc. The filtrate was re-filtered through a 0.5 micron glass fiber filter paper sandwiched between two P5 papers, and concentrated under reduced pressure giving (**9**) as a light brown foam (28.96 g, 98% yield; 93% NMR purity). LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 315.32 (1.54 min). ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 2H), 6.92 (d, J = 1.8 Hz, 1H), 6.88 (d, J = 1.8 Hz, 1H), 4.90 (dd, J = 7.9, 6.2 Hz, 1H), 4.72 (s, 1H), 4.18 (s, 2H), 4.17 – 4.08 (m, 1H), 3.99 – 3.89 (m, 1H), 3.46 (s, 2H), 2.34 – 2.19 (m, 1H), 2.17 – 2.05 (m, 3H), 1.63 (s, 6H) ppm.

Example 1.h

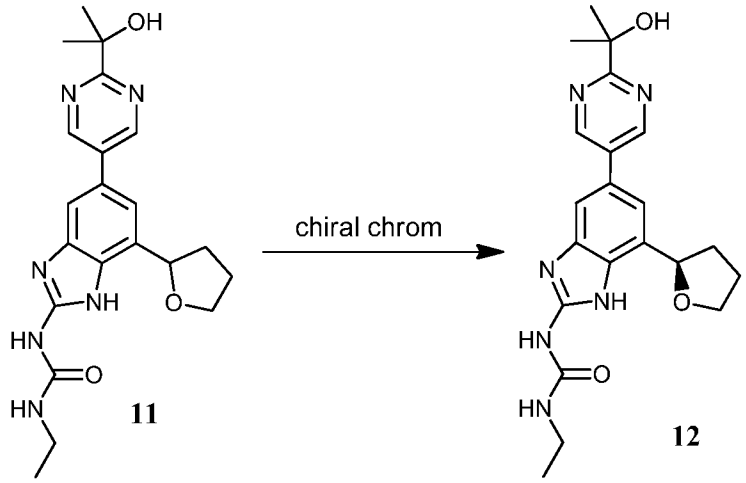
Preparation of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-tetrahydrofuran-2-yl-*1H*-benzimidazol-2-yl]urea (11).



[00172] To a stirring solution of 2-[5-(3,4-diamino-5-tetrahydrofuran-2-yl-phenyl)pyrimidin-2-yl]propan-2-ol (**9**) (32.10 g, 102.1 mmol) in 1,4-dioxane (160.5 mL, Sigma-Aldrich 360481) was added pH 3.5 buffer (240.8 mL), prepared by dissolving NaOAc trihydrate (34.5 g) in 1N aqueous H_2SO_4 (240 mL). 1-Ethyl-3-(N-(ethylcarbamoyl)-C-methylsulfanyl-carbonimidoyl)urea (**10**) (28.46 g, 122.5 mmol, CB Research and Development) was added to the reaction mixture and stirred at reflux overnight (HPLC showed 99% consumption of starting diamine). The reaction mixture was cooled to room temperature and poured portion-wise (frothing) into a stirring solution of aqueous saturated $NaHCO_3$ (480 mL) and water (120 mL) giving pH 8-9. This was stirred for 30 minutes, the solid was collected by filtration, washed copiously with water to neutral pH, and then more sparingly with EtOH. The solid was dried under reduced pressure giving (**11**) as an off-white solid (34.48 g, 82% yield; 99.4% HPLC purity). LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 411.41 (1.73 min). ^{1}H NMR (300 MHz, MeOD) δ 9.02 (s, 2H), 7.62 (s, 1H), 7.37 (s, 1H), 5.31 (s, 1H), 4.23 (dd, J = 14.5, 7.3 Hz, 1H), 4.01 (dd, J = 15.0, 7.1 Hz, 1H), 3.38 – 3.28 (m, 2H), 2.58 – 2.46 (m, 1H), 2.16 – 2.05 (m, 2H), 2.02 – 1.88 (m, 1H), 1.63 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H) ppm.

Example 1.i

Chiral chromatographic isolation of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[(2R)-tetrahydrofuran-2-yl]-1H-benzimidazol-2-yl]urea (**12**)



[00173] A racemic sample of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-tetrahydrofuran-2-yl-1H-benzimidazol-2-yl]urea (**11**) (24.60 g) was resolved on a CHIRALPAK® IC® column (by Chiral Technologies) eluting with CH_2Cl_2 / MeOH / TEA (60 / 40 / 0.1) at 35°C giving the desired enantiomer (**12**) as a white solid (11.35 g, 45% yield; 99+% HPLC purity, 99+% ee). Analytical chiral HPLC retention time was 6.2 min (CHIRALPAK® IC® 4.6 x 250 mm column, 1 mL/min flow rate, 30°C).

[00174] The structure and absolute stereochemistry of **12** were confirmed by single-crystal x-ray diffraction analysis. Single crystal diffraction data was acquired on a Bruker Apex II diffractometer equipped with sealed tube Cu K-alpha source (Cu $K\alpha$ radiation, γ = 1.54178 Å) and an Apex II CCD detector. A crystal with dimensions of 1/2x 0.05 x 0.05 mm was selected, cleaned using mineral oil, mounted on a MicroMount and centered on a Bruker *APEX*II system. Three batches of 40 frames separated in reciprocal space were obtained to provide an orientation matrix and initial cell parameters. Final cell parameters were obtained and refined after data collection was completed based on the full data set. Based on systematic absences and intensities statistics the structure was solved and refined in acentric $P2_1$ space group.

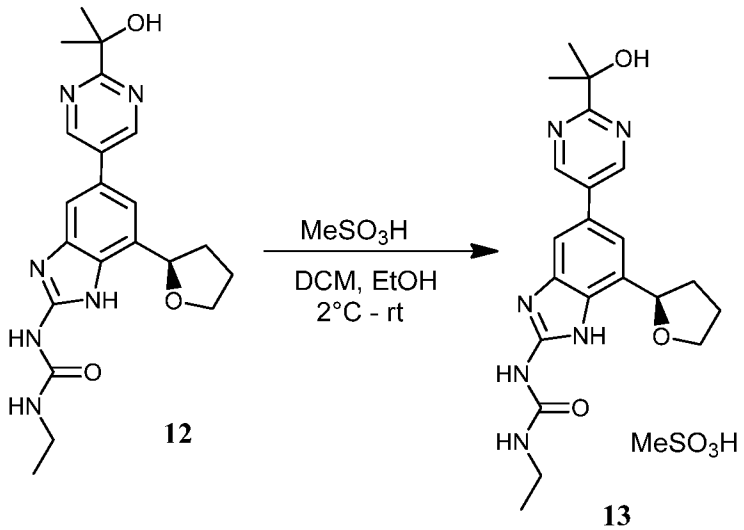
[00175] A diffraction data set of reciprocal space was obtained to a resolution of 0.9 Å using 0.5° steps using 60 s exposure for each frame. Data were collected at 100 (2) K. Integration of intensities and refinement of cell parameters were accomplished using APEXII

software. Observation of the crystal after data collection showed no signs of decomposition. As shown in Fig. 1, there are two symmetry independent molecules in the structure and both symmetry independent molecules are *R* isomers.

[00176] The data was collected, refined and reduced using the Apex II software. The structure was solved using the *SHELXS97* (Sheldrick, 1990); program(s) and the structure refined using the *SHELXL97* (Sheldrick, 1997) program. The crystal shows monoclinic cell with $P2_1$ space group. The lattice parameters are a = 9.8423(4) Å, b = 10.8426(3) Å, c = 19.4441 (7) Å, β = 102.966(3)°. Volume = 2022.09(12) $Å^3$.

Example 1.j

Preparation of the methanesulfonic acid salt of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[(2R)-tetrahydrofuran-2-yl]-1H-benzimidazol-2-yl]urea (**13**)



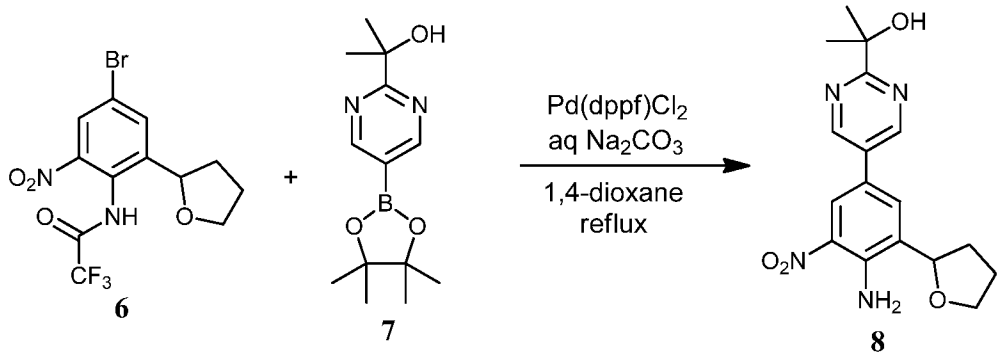
[00177] A stirring suspension of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[(2R)-tetrahydrofuran-2-yl]-1H-benzimidazol-2-yl]urea (**12**) (9.32 g, 22.71 mmol) in absolute ethanol (93.2 mL) was cooled with an ice-water bath. Methanesulfonic acid (1.548 mL, 23.85 mmol, Sigma-Aldrich 471356) was added, removed cold bath and stirred at room temperature for 20 minutes. It was concentrated on a rotary evaporator at 35°C to a thick slurry, diluted with EtOAc, collected the solid by filtration, washed with EtOAc, and dried under reduced pressure giving an initial crop of (**13**) as a white solid (8.10 g). The filtrate was concentrated on a rotary evaporator giving a yellowish glassy foam, which was dissolved in EtOH, concentrated to a solid slurry, triturated with EtOAc / Et_2O, and collected by filtration. The solid was washed with EtOAc / Et_2O, combined with the first crop, and dried under reduced pressure giving (**13**) as a white solid (9.89 g, 86% yield; 99+% HPLC purity,

99+% ee). Analytical chiral HPLC shows one enantiomer with retention time of 6.3 min eluting with CH_2Cl_2 / MeOH / TEA (60 / 40 / 0.1) on a CHIRALPAK® IC® 4.6 x 250 mm column with 1 mL/min flow rate at 30°C. LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 411.53 (1.74 min). ^{1}H NMR (300 MHz, MeOD) δ 9.07 (s, 2H), 7.79 (s, 1H), 7.62 (s, 1H), 5.30 (t, J = 7.3 Hz, 1H), 4.24 (dd, J = 14.6, 7.3 Hz, 1H), 4.04 (dd, J = 15.0, 7.6 Hz, 1H), 3.40 – 3.30 (m, 2H), 2.72 (s, 3H), 2.65 – 2.54 (m, 1H), 2.20 – 2.07 (m, 2H), 2.04 – 1.90 (m, 1H), 1.64 (s, 6H), 1.23 (t, J = 7.2 Hz, 3H) ppm.

Example 1.k

1-pot deprotection / Suzuki procedure

Preparation of 2-[5-(4-amino-3-nitro-5-tetrahydrofuran-2-yl-phenyl)pyrimidin-2-yl]propan-2-ol (**8**).



[00178] N-(4-Bromo-2-nitro-6-tetrahydrofuran-2-yl-phenyl)-2,2,2-trifluoro-acetamide (**6**) (19.00 g, 49.59 mmol), 2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidin-2-yl]propan-2-ol (**7**) (14.41 g, 54.55 mmol), aqueous 2.7 M sodium carbonate (73.48 mL, 198.4 mmol), and 1,4-dioxane (190 mL, Sigma-Aldrich 360481) were mixed. A stream of nitrogen was bubbled through the stirring mixture for 40 minutes, followed by addition of 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium dichloromethane adduct (2.025 g, 2.480 mmol, Strem 460450). The reaction mixture was stirred at reflux under N_2 for 7 hrs, added another 50 mL of saturated aqueous sodium carbonate, and refluxed for another 16 hrs. The reaction mixture was allowed to cool, then diluted with EtOAc (500 mL) and water (200 mL). The layers were separated and the aqueous phase extracted with EtOAc (200 mL). The combined organic phase was washed with water (500 mL), brine (500 mL), dried over Na_2SO_4, filtered through a Florisil® plug, and concentrated on a rotary evaporator to give crude (**8**) as an orange oil. Purified by ISCO silica gel chromatography eluting with 20-90%

EtOAc / hexane to give (**8**) as an orange solid (15.00 g, 81-88% purity). LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 345.35 (2.68 min). ^1H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 2H), 8.36 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 2.1 Hz, 1H), 7.09 (s, 2H), 4.92 (t, J = 7.2 Hz, 1H), 4.62 (s, 1H), 4.20 – 4.11 (m, 1H), 4.03 – 3.94 (m, 1H), 2.39 – 2.26 (m, 1H), 2.23 – 2.08 (m, 3H), 1.64 (s, 6H) ppm.

Example 1.k

Preparation of Form I: Chiral chromatographic isolation of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-[(2R)-tetrahydrofuran-2-yl]-1H-benzimidazol-2-yl]urea

[00179] A racemic sample of 1-ethyl-3-[5-[2-(1-hydroxy-1-methyl-ethyl)pyrimidin-5-yl]-7-tetrahydrofuran-2-yl-1H-benzimidazol-2-yl]urea (24.60 g) was resolved on a CHIRALPAK® IC® column (by Chiral Technologies) eluting with DCM / MeOH / TEA (60 / 40 / 0.1) at 35°C. The desired fractions were collected, concentrated to dryness on a rotary evaporator, then dried overnight in a vacuum oven at about 40°C giving the desired enantiomer as a white solid (11.35 g, 99+% HPLC purity, 99+% ee) which was used for physical form characterization. LCMS (C18 column eluting with 10-90% CH_3CN / water gradient over 5 minutes with formic acid modifier) M+1: 411.66 (1.74 min). HPLC retention time was 3.61 min (YMC ODS-AQ 150 x 3.0 mm column eluting with 10-90% CH_3CN / water gradient over 8 minutes with 0.1% TFA modifier and 1 mL/min flow rate). Analytical chiral HPLC shows one enantiomer with retention time of 6.2 min (CHIRALPAK® IC® 4.6 x 250 mm column, 1 mL/min flow rate, 30°C). ^1H NMR (300 MHz, MeOD) δ 9.02 (s, 2H), 7.62 (d, J = 1.6 Hz, 1H), 7.37 (s, 1H), 5.32 (br.s, 1H), 4.23 (dd, J = 14.8, 6.7 Hz, 1H), 4.01 (dd, J = 15.1, 7.0 Hz, 1H), 3.37 – 3.29 (m, 2H), 2.58 – 2.46 (m, 1H), 2.17 – 2.06 (m, 2H), 2.03 – 1.90 (m, 1H), 1.63 (s, 6H), 1.22 (t, J = 7.2 Hz, 3H) ppm.

Example 1.l

Preparation of Form II

[00180] To 20 mg of the benzimidazolyl urea compound was added to an HPLC vial and 1 mL acetonitrile (CH_3CN) was added to the vial with stirring at room temperature. To the resulting suspension a stoichiometric amount of 1 Molar HCl solution (0.049 mL) in water was added. The vial was crimp-capped and the mixture (suspension) was allowed to equilibrate for 6 days under gentle stirring before it was filtered and the white solid, dried under vacuum for several hours and recovered for physical form characterization.

Example 1.m

Preparation of Form III

[00181] To 20 mg of the benzimidazolyl urea compound in an HPLC vial 0.5 ml of THF was added under stirring at room temperature. Stoichiometric amount of HCl was added as 1M aqueous solution (0.049 mL). 2 mL of methyl *tert*-butyl ether was added and the suspension was allowed to equilibrate overnight with stirring. It was then filtered, and the white solid was dried under vacuum for several hours before subjecting the compound to physical form characterization.

Example 1.n

Preparation of Form IV

[00182] A suspension of 2-[5-[3,4-diamino-5-[(2R)-tetrahydrofuran-2-yl]phenyl]pyrimidin-2-yl]propan-2-ol (2 g, 6.362 mmol) and (3Z)-1-ethyl-3-[(ethylcarbamoylamino)-methylsulfanyl-methylene]urea (1.478 g, 6.362 mmol) in dioxane (26.00 mL) and buffer pH 3.5 (100 mL, stock solution made from 1N H_2SO_4 and NaOAc) was stirred for 3 h under reflux (~95 °C). Then the reaction mixture was quenched with approximately 50 mL water. The crude reaction mixture was transferred to a larger roundbottom flask, neutralized with $NaHCO_3$, then filtered to give a beige solid which was washed with hot water (~200 mL). The solid (1.84 g) was dried and was salted as $MeSO_3H$ salts. 2.25 g (81%ee; 98% pure; 69.8 % yield) of pure product was obtained which was submitted for supercritical fluid chromatography (SFC) chiral separation to give peak one (S-enantiomer) and peak two (R-enantiomer).

[00183] The material (the R-enantiomer) from SFC (peak 2) was suspended in MeOH (~20 mL) and basified with sat $NaHCO_3$ (200 mL). The mixture was stirred for 1h, then filtered. After filtration, the solids were collected, washed with warm water (~500 mL) and dried. 1.22 g of parent molecule (free base; peak 2) was obtained which was then salted as the mesylate. 1.43 g of pure mesylate was obtained (R; 99 % ee; 99% pure).

[00184] The mesylate salt of the compound of the present application may be prepared using methods known to those skilled in the art. For example, the free base of the benzimidazolyl urea compound may be mixed with a stoichiometric amount of a methanesulfonic acid and the mixture concentrated until a solid is obtained. Alternatively, the free base of the benzimidazolyl urea compound may be suspended in an appropriate solvent containing the acid and allowing the mixture to equilibrate until the free base if

converted to the corresponding acid addition salt. Figure 12 shows a ^{1}H NMR spectrum of the mesylate salt of the benzimidazolyl urea compound.

[00185] Example 2

[00186] ENZYMOLOGY STUDIES

[00187] The enzyme inhibition activities of compounds of this invention may be determined in the experiments described below:

[00188] DNA Gyrase ATPase Assay

[00189] The ATP hydrolysis activity of *S. aureus* DNA gyrase is measured by coupling the production of ADP through pyruvate kinase/lactate dehydrogenase to the oxidation of NADH. This method has been described previously (Tamura and Gellert, 1990, *J. Biol. Chem.*, 265, 21342).

[00190] ATPase assays are carried out at 30°C in buffered solutions containing 100 mM TRIS pH 7.6, 1.5 mM $MgCl_2$, 150 mM KCl. The coupling system contains final concentrations of 2.5 mM phosphoenol pyruvate, 200 μM nicotinamide adenine dinucleotide (NADH), 1 mM DTT, 30 ug/ml pyruvate kinase, and 10 ug/ml lactate dehydrogenase. The enzyme (90 nM final concentration) and a DMSO solution (3 % final concentration) of a compound is added. The reaction mixture is allowed to incubate for 10 minutes at 30°C. The reaction is initiated by the addition of ATP to a final concentration of 0.9 mM, and the rate of NADH disappearance is monitored at 340 nanometers over the course of 10 minutes. The K_i and IC_{50} values are determined from rate versus concentration profiles.

[00191] DNA Topo IV ATPase Assay

[00192] The conversion of ATP to ADP by *S. aureus* TopoIV enzyme is coupled to the conversion of NADH to NAD+, and the progress of the reaction is measured by the change in absorbance at 340 nm. TopoIV (64 nM) is incubated with the selected compound (3% DMSO final) in buffer for 10 minutes at 30 °C. The buffer consists of 100 mM Tris 7.5, 1.5 mM MgCl2, 200 mM K•Glutamate, 2.5 mM phosphoenol pyruvate, 0.2 mM NADH, 1 mM DTT, 5 μg/mL linearized DNA, 50 μg/mL BSA, 30 μg/mL pyruvate kinase, and 10 μg/mL lactate dehyrodgenase (LDH). The reaction is initiated with ATP, and rates are monitored continuously for 20 minutes at 30°C on a Molecular Devices SpectraMAX plate reader. The inhibition constant, Ki, and the IC_{50} are determined from plots of rate vs. concentration of selected compound fit to the Morrison Equation for tight binding inhibitors.

[00193] Example 3

[00194] **Susceptibility Testing in Liquid Media**

[00195] Compounds of this invention were tested for antimicrobial activity by susceptibility testing in liquid media. Such assays can be performed within the guidelines of the latest CLSI document governing such practices: "M07-A8 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard--Eighth Edition (2009)". Other publications such as "Antibiotics in Laboratory Medicine" (Edited by V. Lorian, Publishers Williams and Wilkins, 1996) provide essential practical techniques in laboratory antibiotic testing. The specific protocols used were as follows:

[00196] Protocol #1: Gyrase MIC determination of compounds using microdilution broth method

[00197] Materials:

[00198] Round bottom 96-well microtiter plates (Costar 3788)

[00199] Mueller Hinton II agar plates (MHII; BBL premix)

[00200] Mueller Hinton II liquid broth (MHII; BBL premix)

[00201] BBL Prompt Inoculation System (Fisher B26306)

[00202] Test Reading Mirror (Fisher)

[00203] Agar plates with bacteria streaked to single colonies, freshly prepared

[00204] Sterile DMSO

[00205] Human serum (U.S. Biologicals S1010-51)

[00206] Laked horse blood (Quad Five 270-100)

[00207] Resazurin 0.01%

[00208] Sprague Dawley Rat serum (U.S. Biologicals 1011-90B or Valley BioMedical AS3061SD)

[00209] Pooled Mouse serum (Valley BioMedical AS3054)

[00210] Strains (media, broth and agar):

1. *Staphylococcus aureus* ATCC #29213
    a. MHII
    b. MHII + 50% human serum
    c. MHII + 50% rat serum
    d. MHII + 50% mouse serum
2. *Staphylococcus aureus* ATCC #29213 GyrB T173I (MHII)
3. *Staphylococcus aureus,* JMI collection strains; see table 5 (MHII)
4. *Staphylococcus epidermidis,* JMI collection strains; see table 5 (MHII)
5. *Enterococcus faecalis* ATCC #29212 (MHII + 3% laked horse blood)

6. *Enterococcus faecium* ATCC #49624 (MHII + 3% laked horse blood)
7. *Enterococus faecalis,* JMI collection strains; see table 5 (MHII + 3% laked horse blood)
8. *Enterococus faecium,* JMI collection strains; see table 5 (MHII + 3% laked horse blood)
9. *Streptococcus pneumoniae* ATCC #10015 (MHII + 3% laked horse blood)
10. *Streptococcus pneumoniae,*JMI collection strains; see table 5 (MHII + 3% laked horse blood)
11. *β-haemolytic streptococci,Groups A, B, C, G)* JMI collection strains; see table 5 (MHII + 3% laked horse blood)
12. *Bacillus cereus* ATCC 10987 (MHII)
13. *Bacillus cereus* ATCC 14579(MHII)
14. *Bacillus subtilis* ATCC 6638 (MHII)
15. *Bacillus subtilis* (168) ATCC 6051 (MHII)

[00211] Inoculum prep (for all strains other than *S. aureus* + 50% sera):

1. Using the BBL Prompt kit, picked 5 big or 10 small, well separated colonies from culture grown on the appropriate agar medium as indicated above and inoculated 1 mL of sterile saline provided in the kit.
2. Vortexed the wells for ~ 30 s to provide a suspension of ~10^8 cells/mL. Actual density could be confirmed by plating out dilutions of this suspension.
3. Diluted the suspension 1/100 by transferring 0.15 mL of cells into 15 mL (~10^6 cells/mL) sterile broth (or see below) for each plate of compounds tested, then swirled to mix. If more than 1 plate of compounds (> 8 compounds), including compound 12 or 13, which may be prepared by following Examples 1.i and 1.j, respectively (above), were tested, volumes were increased accordingly.
    a. For *E. faecalis*, *E. faecium* and *S. pneumoniae*: 14.1 mL MHII + 0.9 mL laked horse blood was used.
4. Used 50 µl cells (~5 x 10^4 cells) to inoculate each microtiter well containing 50 µl of the drug diluted in broth (see below).

[00212] Drug dilutions, inoculation, MIC determination:

1. All drug/compound stocks were prepared at 12.8 mg/mL concentration, usually in 100% DMSO.

2. Diluted drug/compound stocks to 200x desired final concentration in 50 µL DMSO. If starting concentration of MICs was 8 µg/mL final concentration, then required 6.25 µL of stock + 43.75 µL DMSO. Each 200x stock was placed in a separate row of column 1 of a new 96 well microtiter plate.
3. Added 25 µL of DMSO to columns 2 -12 of all rows of the microtiter plate containing 200x compound stocks and serially diluted 25 µL from column 1 through column 11, changed tips after each column. i.e. 25 µL compound + 25 µL DMSO = 2x dilution. Left "no compound" DMSO well at the end of the series for control.
4. For each strain tested (except *S. aureus* + 50% human serum), prepared two microtiter plates with 50 µL of MHII broth using a Matrix pipettor.
5. Transferred 0.5 µL of each dilution (w/Matrix auto-pipettor) to 50 µL of medium/microtiter well prior to the addition of 50 µl of cells. The usual starting concentration of compound was 8 µg/mL after the 1/200 dilution into medium + cells – compound concentrations decreased in 2x steps across the rows of the microtiter plate. All MICs were done in duplicate.
6. All wells were inoculated with 50 µl of diluted cell suspension (see above) to a final volume of 100 µl.
7. After inoculum was added, mixed each well thoroughly with a manual multichannel pipettor; same tips were used going from low to high concentration of drug in the same microtiter plate.
8. Plates were incubated at 37°C for at least 18 hours.
9. Plates were viewed with a test reading mirror after 18 hours and the MIC was recorded as the lowest concentration of drug where no growth was observed (optical clarity in the well).

[00213] Preparation of *S. aureus* + 50% human serum, *S. aureus* + 50% rat serum or *S. aureus* + 50% mouse serum.

1. Prepared 50% serum media by combining 15 mL of MHII + 15 mL human serum – total 30 mL. Increased volume in 30 mL increments when more than 1 compound plate was tested.
2. Used the same BBL Prompt inoculum of *S. aureus* ATCC #29213 as described above, diluted 1/200 by transferring 0.15 mL of cells into 30 mL (~$5x10^5$ cells/mL) of the 50% human serum media prepared above and swirled to mix.

3. Filled all test wells of the desired number of microtiter plates with 100 μL cells in 50% serum media.
4. Transferred 0.5 μL of each compound dilution (w/Matrix auto-pipettor) to 100 μL of cells/media. The usual starting concentration of compound was 8 μg/mL after the 1/200 dilution into medium + cells – compound concentrations decreased in 2x steps across the rows of a microtiter plate. All MICs were done in duplicate.
5. Mixed each well thoroughly with a manual multichannel pipettor; same tips were used going from low to high concentration of drug in the same microtiter plate.
6. Plates were incubated at 37°C for at least 18 hours. After incubation, added 25 μL of 0.01% Resazurin to each well and continued to incubate at 37°C for at least 1 additional hour or until the Resazurin color changes.
7. Plates were viewed with a test reading mirror and the MIC was recorded. When using Resazurin, the color of the dye changed from a dark blue to a bright pink in wells with no growth. The lowest concentration of drug that turned the dye pink was the MIC.

[00214] Protocol 2: Gyrase MIC determination of compounds against Gram negatives using microdilution broth method

[00215] Materials:

[00216] Round bottom 96-well microtiter plates (Costar 3788)

[00217] Mueller Hinton II agar plates (MHII; BBL premix)

[00218] Mueller Hinton II liquid broth (MHII; BBL premix)

[00219] BBL Prompt Inoculation System (Fisher b26306)

[00220] Test Reading Mirror (Fisher)

[00221] Agar plates with bacteria streaked to single colonies, freshly prepared

[00222] Sterile DMSO

[00223] Strains (MHII media for all; broth and agar):

1. *Escherichia coli* ATCC # 25922
2. *Escherichia coli,* JMI collection strains, see table 5
3. *Escherichia coli* AG100 WT
4. Escherichia coli AG100 tolC
5. *Acinetobacter baumannii* ATCC # BAA-1710
6. *Acinetobacter baumannii* ATCC # 19606
7. *Acinetobacter baumannii,* JMI collection strains, see table 5

8. *Klebsiella pneumoniae* ATCC # BAA-1705
9. *Klebsiella pneumoniae* ATCC # 700603
10. *Klebsiella pneumoniae,* JMI collection strains, see table 5
11. *Moraxella catarrhalis* ATCC# 25238
12. *Moraxella catarrhalis* ATCC# 49143
13. *Moraxella catarrhalis,* JMI collection strains, see table 5
14. *Haemophilus influenzae* ATCC 49247
15. *Haemophilus influenzae* (Rd1 KW20) ATCC 51907
16. *Haemophilus influenzae* Rd0894 (AcrA-)
17. *Haemophilus influenzae*, JMI collection strains, see table 5
18. *Pseudomonas aeruginosa* PAO1
19. *Pseudomonas aeruginosa,* JMI collection strains, see table 5
20. *Proteus mirabilis*, JMI collection strains, see table 5
21. *Enterobacter cloacae,* JMI collection strains, see table 5
22. *Stenotrophomonas maltophilia* ATCC BAA-84
23. *Stenotrophomonas maltophilia* ATCC13637

[00224] Inoculum prep:

1. Using the BBL Prompt kit, picked 5 big or 10 small, well separated colonies from cultures grown on agar medium and inoculated 1 mL sterile saline that came with the kit.
2. Vortexed the wells for ~ 30 s to give a suspension of ~10^8 cells/mL. Actual density could be confirmed by plating out dilutions of this suspension.
3. Diluted the suspension 1/100 by transferring 0.15 mL of cells into 15 mL (~10^6 cells/mL) sterile broth (see below) for each plate of compounds tested, swirled to mix. If more than 1 plate of compounds (> 8 compounds), including compound 12 or 13, was to be tested, increased volumes accordingly.
4. Used 50 µl cells (~5 x 10^4 cells) to inoculate each microtiter well containing 50 µl of the drug diluted in broth (see below).

[00225] Drug dilutions, inoculation, MIC determination:

1. All drug/compound stocks were prepared at 12.8 mg/mL concentration, usually in 100% DMSO.

2. Diluted drug/compound stocks to 200x desired final concentration in 50 µL DMSO. If starting concentration of MICs was 8 µg/mL final concentration, then required 6.25 µL of stock + 43.75 µL DMSO. Each 200x stock was placed in a separate row of column 1 of a new 96 well microtiter plate.
3. Added 25 µL of DMSO to columns 2 -12 of all rows of the microtiter plate containing 200x compound stocks and serially diluted 25 µL from column 1 through column 11, changed tips after each column. i.e. 25 µL compound + 25 µL DMSO = 2x dilution. Left "no compound" DMSO well at the end of the series for control.
4. For each strain tested, prepared two microtiter plates with 50 µL of MHII broth using a Matrix pipettor.
5. Transferred 0.5 µL of each dilution (w/Matrix auto-pipettor) to 50 µL of medium/microtiter well prior to the addition of 50 µl of cells. The usual starting concentration of compound was 8 µg/mL after the 1/200 dilution into medium + cells – compound concentrations decreased in 2x steps across the rows of a microtiter plate. All MICs were done in duplicate.
6. All wells were inoculated with 50 µl of diluted cell suspension (see above) to a final volume of 100 µl.
7. After inoculum was added, each well was mixed thoroughly with a manual multichannel pipettor; same tips were used going from low to high concentration of drug in the same microtiter plate.
8. Plates were incubated at 37°C for at least 18 hours.
9. Plates were viewed with a test reading mirror after 18 hours and the MIC was recorded as the lowest concentration of drug where no growth was observed (optical clarity in the well).

[00226] Protocol #3: Gyrase MIC determination of compounds using Agar dilution method

[00227] Materials:

[00228] Petri plates 60 x 15 mm (Thermo Scientific Cat. # 12567100)

[00229] Centrifuge tubes, 15 mL (Costar)

[00230] BBL Prompt Inoculation System (Fisher b26306)

[00231] Agar plates with bacteria streaked to single colonies, freshly prepared

[00232] Sterile DMSO

[00233] GasPak™ incubation containers (BD Cat. #260672)

[00234] GasPak ™ EZ Anaerobe container system sachets (BD Cat. #260678)

[00235] GasPak ™ EZ C02 container system sachets (BD Cat. #260679)

[00236] GasPak ™ EZ Campy container system sachets (BD Cat. #260680)

[00237] **Strains:**

1. *Clostridium difficile* ATCC BAA-1382;
2. *Clostridium difficile,* CMI collection strains, see table 4
3. *Clostriudium perfringens,* CMI collection strains, see table 4
4. *Bacteroides fragilis and Bacteroides spp.,* CMI collection strains, see table 4
5. *Fusobacterium spp.,* CMI collection strains, see table 4
6. *Peptostreptococcus, spp.,* CMI collections strains, see table 4
7. *Prevotella spp.,* CMI collection strains, see table 4
8. *N. gonorrhoeae* ATCC 35541
9. *N. gonorrhoeae* ATCC 49226
10. *Neisseria gonorrhoeae,* JMI collection strains, see table 4
11. *Neisseria meningitidis,* JMI collection strains, see table 4

[00238] **Media preparation and growth conditions:**

Growth medium recommended for each microbial species was prepared according tothe CLSI publication 'M11-A7 Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Seventh Edition (2007)' with the exception of *N. gonorrhoeae* and *N. meningitidis*for which media was prepared according to"M07-A8 Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard--Eighth Edition (2009)".

[00239] **Plate pouring:**

1. Prepared 100x drug stocks of each test compound as described in **Table 1A**. Used a 15 mL centrifuge tube, added 100 uL of each drug stock to 10 mL of molten agar (cooled to ~ 55°C in water bath). Mixed by inverting tube 2 -3x then pour into individually labeled 60X15 mm Petri dish.
2. Routine test concentrations were: 0.002 ug/mL – 16 ug/mL (14 plates).
3. Poured 4 drug free plates: 2 as positive control, 2 as aerobic control.
4. Allowed plates to dry. Used same day or stored overnight at RT or stored up to 3daysat 4°C.

5. Plates were labeled accordingly for drug concentration and strain placement.

[00240] Growth of cells requiring the maintenance of an anaerobic environment:

1. All work performed with anaerobic bacteria was done as rapidly as possible; work performed in biosafety cabinets (i.e., aerobic environment) was completed in less then 30 minutes before cells were returned to anaerobic chambers.
2. Incubation of anaerobic bacteria was achieved using GasPak™ chambers. The large box style chambers (VWR 90003-636) required 2 anaerobic sachets (VWR 90003-642), while the tall cylinder style chambers (VWR 90003-602) only required 1 sachet.

[00241] Plate inoculation (performed in biosafety cabinet):

1. Streaked each strain onto individual agar plates as described above. Incubated for required time and environmental condition (i.e. anaerobic, microaerophilic, etc).
2. Used direct colony suspension method to suspend loopfuls of freshly streaked cells into ~ 4 mL 0.9% $NaCl_2$ and vortexed.
3. Adjusted suspension to $O.D._{600}$ 0.05 (5x10e7 cfu/mL). Vortexed to mix.
4. Transferred ~0.2 mL of adjusted, mixed cultures to a 96 well plate. When ≤ 5 strains were tested, all strains were lined together in a single row. When testing > 5 strains, transfered strains into plate with no more that 5 strains in a single row. This was necessary to fit on the small plates.
5. Used multi-channel pipettor, spotted 0.002 mL of each strain from prepared 96 well plates onto each MIC test plate. This resulted in ~ 1x10e5 cfu/spot. When testing *C. difficile*, strains swarmed when grown, however distance between multi-channel pipettor spots was far enough such that swarming cells did not impair assay results.
    a. Inoculated2 drug free plates first, while the other 2 drug free plates were inoculated last after the MIC test plates. The former and latter served as growth and inoculation controls. Incubated one plate from each set of drug-free controls under required atmospheric conditions with MIC plates and one set aerobically to test for contamination with aerobic bacteria. Aerobic culture was negative for growth when working with strict anaerobe or microaerophilic strain. Some growth was visible with *N. gonorrhoeae*.
6. Allowed inoculum to dry (for as short a time as necessary), then placed upside down in GasPak with appropriate number of sachets and incubate.
7. *Neisseria*spp.were incubated at 37°C in a5% CO_2environment for 24h.

[00242] **MIC determination:**

[00243] Examined the test plates after the correct incubation time and read the MIC endpoint at the concentration where a marked reduction occurred in the appearance of growth on the test plate as compared to that of growth on the positive control plates.

Table 1A: Compound dilutions for MIC determination using the agar dilution method.

Step	Stock (ug/ml)	Source	Volume from stock (uL)	Diluent, DMSO (uL)**	Intermediate Conc. (ug/mL)	Final Conc. At 1:100 (ug/mL)	Volume (uL) added to 10 mL agar
1	1,600*	Stock			1,600	16	100
2	1,600	Stock	75	75	800	8	100
3	1,600	Stock	75	225	400	4	100
4	1,600	Stock	75	525	200	2	100
5	200	Step 4	75	75	100	1	100
6	200	Step 4	75	225	50	0.5	100
7	200	Step 4	75	525	25	0.25	100
8	25	Step 7	75	75	12.5	0.125	100
9	25	Step 7	75	225	6.25	0.06	100
10	25	Step 7	75	525	3.1	0.03	100
11	3	Step 10	75	75	1.6	0.016	100
12	3	Step 10	75	225	0.8	0.008	100
13	3	Step 10	75	525	0.4	0.004	100
14	0.4	Step 13	75	75	0.2	0.002	100

*1,600 ug/ml = 64 ul (10mg/ml stock) + 336 ul DMSO; 400 ul total volume to start
**compound dissolved and diluted in 100%
DMSO

[00244] **Protocol #4. MIC Determination Procedure for *Mycobacterium* species**

[00245] **Materials**

[00246] Round bottom 96-well microtiter plates (Costar 3788) or similar

[00247] Film plate seals (PerkinElmer, TopSeal-A #6005250 or similar)

[00248] Middlebrook 7H10 broth with 0.2% glycerol

[00249] Middlebrook 7H10 agar with 0.2% glycerol

[00250] Middlebrook OADC Enrichment

[00251] **Inoculum Preparation for *M. tuberculosis*:**

1. Used prepared frozen *M. tuberculosis* stock stored at -70^{0}C. *M. tuberculosis* was grown in 7H10 broth + 10% OADC, then frozen at a concentration of 100 Klett or 5 x 10^7cfu/ml,
2. Prepared a 1:20 dilution by removal of 1 ml of the frozen stock and added it to 19 ml of 7H10 broth + 10% OADC (final concentration 2.5 x 10^6cfu/ml).
3. From this dilution prepared a second 1:20 dilution, removed 1 ml and added it to 19 ml of fresh broth. This was the final inoculum to add to the 96-well plates.

[00252] Inoculum Preparation for *M. kansasii, M. avium, M. abscessus* and *Nocardia* spc.:

1. Used prepared frozen stock of culture or a fresh culture grown in 7H10 broth at a concentration of 10 Klett or 5 x 10^7/ml.
2. Prepared a 1:20 dilution by removing 1.0 ml of the culture stock and added it to 19 ml of 7H10 broth (final concentration 2.5 x 10^6cfu/ml).
3. From this dilution prepared a 1:20 dilution, removed 1 ml and added it to 19 ml of fresh broth (final suspension).

[00253] Plate Preparation:

1. Labeled plates.
2. Added 50 µl of 7H10 broth + 10% OADC to all wells being utilized for MIC determination using a multichannel electronic pipettor.
3. Prepared stock solutions of drugs (e.g. 1 mg/ml concentration) to be tested.
4. Thawed and diluted frozen stock solutions using 7H10 broth + 10% OADC to obtain a working solution 4x the maximum concentration tested (e.g. final concentration 32 µg/ml, highest concentration tested was 8 µg/ml). Dilutions were made from the stock solution. To start at a concentration of 1 µg/ml , the drugs were prepared at 4 µg/ml, so the starting concentration was 1 µg/ml. Removed 25 µl of the 1mg/ml stock and added to 6.2 ml of broth. All dilutions of drugs were done in broth.
5. Added 50 µl of the 4x working solution to the first well of the designated row. Continued for all compounds to be tested. Using a multichannel electronic pipettor, mixed 4X and serial diluted compounds through the 11th well. Discarded remaining 50 µl. Used the 12th well as the positive control.
6. Incubated plates at 37° C *M. tuberculosis* for ~18 days; *M. avium* and *M. kansasii* for ~7 days; *Nocardia* and *M. abcessus* for ~4 days; with film seals.

7. Read visually and recorded the results. The MIC was recorded as the lowest concentration of drug where no growth was observed (optical clarity in the well).

[00254] **Protocol #5. Protocol for *Mycobacterium tuberculosis* Serum Shift MIC Assay**

[00255] **Materials and reagents**:

[00256] Costar #3904 Black-sided, flat-bottom 96-well microtiter plates

[00257] Middlebrook 7H9 broth (BD271310) with 0.2% glycerol

[00258] Middlebrook OADC Enrichment

[00259] Fetal Bovine Serum

[00260] Catalase (Sigma C1345)

[00261] Dextrose

[00262] $NaCl_2$

[00263] BBL Prompt Inoculation System (Fisher b26306)

[00264] Agar plates (Middlebrook 7H11 with 0.2% glycerol and OADC enrichment) with bacteria streaked to single colonies

[00265] Sterile DMSO

[00266] **Media prep**:

1. For serum shifted MICs, three different media were required which all had a base of 7H9 + 0.2% glycerol. It was important that all media and supplements were sterilized prior to MICs.
2. Prepared all media below and inoculated as described in next section. Tested all compounds against Mtb using each media.
    a. 7H9 + 0.2% glycerol + 10% OADC ("standard" MIC media).
    b. 7H9 + 0.2% glycerol + 2 g/L dextrose + 0.85 g/L NaCl + 0.003 g/L catalase (0% FBS).
    c. 2x 7H9 + 0.2% glycerol + 2 g/L dextrose + 0.85 g/L NaCl + 0.003 g/L catalase combined with equal volume Fetal Bovine Serum (50% FBS).

[00267] **Inoculum prep**:

1. Using BBL Prompt, picked5-10 well-separated colonies and inoculated 1 ml sterile saline that came in the kit. Typically plates were two to three weeks of age when used for this assay due to the slow growth of this organism in culture.

2. Vortexed well, then sonicated in water bath for 30 sec providing a suspension of ~10^8 cells/ml. Actual density could be confirmed by plating out dilutions of this suspension.
3. Prepared inoculum in each of the three media formulations by diluting the BBL Prompt suspension 1/200 (for example: transferred 0.2 ml of cells to 40 ml of medium) to obtain a starting cell density of ~10^6 cells/ml.
4. Used 100 µl cells (~5 x 10^4 cells) to inoculate each microtiter well containing 1 µl of drug in DMSO (see below).

[00268] Drug dilutions, inoculation, MIC determination:

1. Control drug stocks Isoniazid and Novobiocin were prepared at 10 mM in 100% DMSO while Ciprofloxacin and Rifampin were prepared at 1 mM in 50% DMSO and 100% DMSO, respectively. Prepared dilutions- dispensed 100 µL of the stock solution into the first column of a 96-well plate. Prepared 11-step, 2-fold serial dilutions across the row for each compound by transferring 50 µl from column 1 into 50 µl of DMSO in column 2. Continued to transfer 50 µL from column 2 through column 11 while mixing and changing tips at each column. Left column 12 with DMSO only as a control.
2. Transferred 1 µl of each dilution into an empty microtiter well prior to the addition of 100 µl of cells. The starting concentration of Isoniazid and Novobiocin was 100 µM after the dilution into medium + cells; the starting concentration of Ciprofloxacin and Rifampin was 10 µM after the dilution into medium + cells. Compound concentrations decreased in 2x steps moving across the rows of the microtiter plate. All MICs were done in duplicate at each of the three medium conditions.
3. Test sets of compounds were typically at 10 mM and 50 µL volume.
4. Used a multichannel pipettor, removed all of the volume from each column of the master plate and transferred into the first column of a new 96-well microtiter plate. Repeated for each column of compounds on master plate, transferring into column 1 of a new 96-well plate.
5. As described above for control compounds, generated 2-fold, 11-point dilutions of each compound using DMSO as diluent. In all cases, left column 12 as DMSO only for a control. Once all dilutions were complete, again transferred 1 µl of each dilution into an empty microtiter well prior to the addition of 100 µl of cells as done for the control compounds.

6. All wells were inoculated with 100 µl of diluted cell suspension (see above).
7. After inoculum addition, mixed plates by gently tapping sides of plate.
8. Plates were incubated in a humidified 37°C chamber for 9 days.
9. At 9 days added 25 µl 0.01% sterile resazurin to each well. Measured background fluorescence at Excitation 492 nm, Emission 595 nm and returned the plate to the incubator for another 24 hours.

[00269] After 24 hours the fluorescence of each well was measured at Excitation 492 nm, Emission 595 nm.

[00270] Percent inhibition by a given compound was calculated as follows: Percent inhibition=100-([well fluorescence-average background fluorescence]/[DMSO control - average background fluorescence] x100). MICs were scored for all three medium conditions as the lowest compound concentration that inhibited resazurin reduction ('%-inhibition') signal ≥70% at a given medium condition.

[00271] Table 2A shows the results of the MIC assay for the mesylate salt of the benzimidazolyl urea compound of this invention.

[00272] In Table 2A and in subsequent Tables and Examples, "Compound 13" relates to the mesylate salt of Compound 12. Compounds 12 and 13 may be prepared by following Examples 1.i and 1.j, respectively (above). These are the same numbers used to identify said compounds and salts as used in the Examples above.

[00273] **Table 2A – MIC Values of Selected Compounds**

Strain/Special Condition	Protocol	Compound 13
Staphylococcus aureus ATCC 29213	1	0.13
*Staphylococcus aureus*ATCC 29213 with Human Serum	1	0.31
Staphylococcus aureus ATCC 29213 with Rat Serum	1	0.53
Staphylococcus aureus ATCC 29213 with Mouse Serum	1	2
Staphylococcus aureus ATCC 29213 GyrB T173I	1	1.29
Enterococcus faecalis ATCC 29212, with Laked Horse Blood	1	0.081
Enterococcus faecium ATCC 49624 with Laked Horse	1	0.39

Strain/Special Condition	Protocol	Compound 13
Blood		
Enterococcus faecium ATCC 49624	1	0.25
Streptococcus pneumoniae ATCC 10015, with Laked Horse Blood	1	0.022
Bacillus cereus ATCC 10987	1	0.5
Bacillus cereus ATCC 14579	1	0.5
Bacillus subtilis ATCC 6638	1	>8
Bacillus subtilis (168) ATCC 6051	1	>8
Clostridium difficile ATCC BAA-1382	3	1
Haemophilus influenzae ATCC 49247	2	1
Haemophilus influenzae (Rd1 KW20) ATCC 51907	2	2.5
Haemophilus influenzae Rd0894 (AcrA-)	2	0.14
Moraxella catarrhalis ATCC 25238	2	0.071
Moraxella catarrhalis ATCC 49143	2	0.04
Neisseria gonorrhoeae ATCC 35541	3	1.3
Neisseria gonorrhoeae ATCC 49226	3	2.3
Escherichia coli AG100 WT	2	>16
Escherichia coli AG100 *tolC*	2	0.11
Escherichia coli ATCC 25922	2	16
Escherichia coli CHE30	2	>16
Escherichia coli CHE30 *tolC*	2	0.5
Escherichia coli MC4100	2	>16
Escherichia coli MC4100 *tolC*	2	1
Klebsiella pneumoniae ATCC 700603	2	>16
Klebsiella pneumoniae ATCC BAA-1705	2	>16
Acinetobacter baumannii ATCC 19606	2	>16
Acinetobacter baumannii ATCC BAA-1710	2	>16
Pseudomonas aeruginosa PAO1	2	>16

Strain/Special Condition	Protocol	Compound 13
Pseudomonas aeruginosa PAO750	2	0.33
Stenotrophomonas maltophilia ATCC BAA-84	2	Not done
Stenotrophomonas maltophilia ATCC13637	2	Not done
Mycobacterium avium 103	4	0.47
M. avium Far	4	0.94
M. avium 3404.4	4	0.94
Nocardia caviae 2497	4	2
N. asteroids 2039	4	8
N. nova 10	4	8
M. kansasii *303*	4	Not Done
M. kansasii 316	4	Not Done
M. kansasii 379	4	Not Done
M. tuberculosis H37Rv ATCC 25618	4	0.37
M. tuberculosis Erdman ATCC 35801	4	0.25
M. tuberculosis Erdman ATCC 35801	5	0.045
M. tuberculosis Erdman ATCC 35801 with Mouse Serum	5	2
M. abscessus BB2	4	Not Done
M. abscessus MC 6005	4	Not Done
M. abscessus MC 5931	4	Not Done
M. abscessus MC 5605	4	Not Done
M. abscessus MC 6025	4	Not Done
M. abscessus MC 5908	4	Not Done
M. abscessus BB3	4	Not Done
M. abscessus BB4	4	Not Done
M. abscessus BB5	4	Not Done
M. abscessus MC 5922	4	Not Done
M. abscessus MC 5960	4	Not Done
M. abscessus BB1	4	Not Done
M. abscessus MC 5812	4	Not Done
M. abscessus MC 5901	4	Not Done
M. abscessus BB6	4	Not Done
M. abscessus BB8	4	Not Done
M. abscessus MC 5908	4	Not Done
M. abscessus LT 949	4	Not Done
M. abscessus BB10	4	Not Done
M. abscessus MC 6142	4	Not Done
M. abscessus MC 6136	4	Not Done
M. abscessus MC 6111	4	Not Done

Strain/Special Condition	Protocol	Compound 13
M. abscessus MC 6153	4	Not Done

[00274] Table 3A shows the results of the MIC90 assay for selected compounds of this invention.

[00275] Table 3A – MIC90 Values of Selected Compounds with Panels of Gram Positive, Gram Negative and Anaerobic Pathogens

Organism	Number of Isolates Tested	Protocol	Compound 13 Range (µg/ml)	Compound 13 MIC90 (µg/ml)
Aerobic Gram-positive				
Staphylococcus aureus	67	1	0.03-0.5	0.25
Staphlococcus epidermidis	35	1	0.03-0.25	0.12
Enterococcus faecalis	34	1	0.03-0.25	0.25
Enterococcus faecium	33	1	0.12-0.5	0.5
Streptococcus pneumoniae	67	1	0.015-0.06	0.06
β-haemolytic streptococci (Groups A, B, C and G)	28	1	0.06-0.5	0.25
Aerobic Gram-negative				
Haemophilus influenzae	55	2	0.25- 8	2
Moraxella catarrhalis	26	2	0.015-0.12	0.12
Acinetobacter baumannii	12	2	>8- >8	>8
Pseudomonas aeruginosa	12	2	>8- >8	>8
Escherichia coli	12	2	>8- >8	>8
Klebsiella pneumoniae	12	2	>8- >8	>8
Proteus mirabilis	12	2	>8- >8	>8
Enterobacter cloacae	12	2	>8- >8	>8
Neisseria gonorrhoeae	13	3	0.5- 1	1
Neisseria meningitidis	12	3	0.015-0.25	0.12
Anaerobes				
Bacteroides and *Parabacter spp.*	26	3	2- >16	>16
Bacteroides fragilis	25	3	8- >16	>16
Clostridium difficile	16	3	0.5- 16	1
Clostridium perfringens	12	3	0.12-	0.5

Organism	Number of Isolates Tested	Protocol	Compound 13 Range (µg/ml)	Compound 13 MIC90 (µg/ml)
			0.5	
Fusobacterium spp.	16	3	1-4	2
Peptostreptococcus spp.	11	3	0.06- >16	>16
Prevotella spp.	13	3	0.5- >16	>16

[00276] In Table 4 below, the term "CMI" stands for The Clinical Microbiology Institute located in Wilsonville, Oregon.

[00277] **Table 4: Panels of Anaerobic Organism Used to Generate MIC90 Data**

CMI#	ORGANISM
A2380	*B. fragilis*
A2381	*B. fragilis*
A2382	*B. fragilis*
A2486	*B. fragilis*
A2487	*B. fragilis*
A2489	*B. fragilis*
A2527	*B. fragilis*
A2529	*B. fragilis*
A2562	*B. fragilis*
A2627	*B. fragilis*
A2802	*B. fragilis*
A2803	*B. fragilis*
A2804	*B. fragilis*
A2805	*B. fragilis*
A2806	*B. fragilis*
A2807	*B. fragilis*
A2808	*B. fragilis*
A2809	*B. fragilis*

CMI#	ORGANISM
A2810	*B. fragilis*
A2811	*B. fragilis*
A2812	*B. fragilis*
A2813	*B. fragilis*
A2814	*B. fragilis*
A2460	*B. thetaiotaomicron*
A2462	*B. thetaiotaomicron*
A2463	*B. thetaiotaomicron*
A2464	*B. thetaiotaomicron*
A2536	*B. thetaiotaomicron*
A2591	*B. uniformis*
A2604	*B. vulgatus*
A2606	*B. vulgatus*
A2613	*B. ovatus*
A2616	*B. ovatus*
A2815	*Bacteroides tectum*
A2816	*B. ureolyticus*
A2817	*Bacteroides capillosus*

CMI#	ORGANISM
A2818	*B. ureolyticus*
A2824	*Parabacter distasonis*
A2825	*B. ovatus*
A2826	*B. uniformis*
A2827	*B. uniformis*
A2828	*B. vulgatus*
A2829	*B. vulgatus*
A2830	*B. ovatus*
A2831	*B. thetaiotaomicron*
A2832	*Parabacter distasonis*
A2833	*B. thetaiotaomicron*
A2767	*C. difficile*
A2768	*C. difficile*
A2769	*C. difficile*
A2770	*C. difficile*
A2771	*C. difficile*
A2772	*C. difficile*
A2773	*C. difficile*

CMI#	ORGANISM
A2774	*C. difficile*
A2775	*C. difficile*
A2776	*C. difficile*
A2777	*C. difficile*
A2778	*C. difficile*
A2779	*C. difficile*
A2780	*C. difficile*
A2140	*C. perfringens*
A2203	*C. perfringens*
A2204	*C. perfringens*
A2227	*C. perfringens*
A2228	*C. perfringens*
A2229	*C. perfringens*
A2315	*C. perfringens*
A2332	*C. perfringens*
A2333	*C. perfringens*
A2334	*C. perfringens*
A2389	*C. perfringens*

CMI#	ORGANISM
A2390	*C. perfringens*
A864	*F. necrophorum*
A871	*F. nucleatum*
A1667	*F. necrophorum*
A1666	*F. necrophorum*
A2249	*F. nucleatum*
A2716	*Fusobacterium species*
A2717	*Fusobacterium species*
A2719	*Fusobacterium species*
A2721	*Fusobacterium species*
A2722	*Fusobacterium species*
A2710	*Fusobacterium species*
A2711	*Fusobacterium species*
A2712	*Fusobacterium species*
A2713	*Fusobacterium species*
A2714	*Fusobacterium species*
A2715	*Fusobacterium species*
A1594	*Peptostreptococcus anaerobius*

CMI#	ORGANISM
A2158	*Peptostreptococcus magnus*
A2168	*Peptostreptococcus anaerobius*
A2170	*Peptostreptococcus magnus*
A2171	*Peptostreptococcus magnus*
A2575	*Peptostreptococcus spp.*
A2579	*Peptostreptococcus asaccharolyticus*
A2580	*Peptostreptococcus asaccharolyticus*
A2614	*Peptostreptococcus asaccharolyticus*
A2620	*Peptostreptococcus asaccharolyticus*
A2629	*Peptostreptococcus spp.*
A2739	*Prevotella denticola*
A2752	*Prevotella bivia*
A2753	*Prevotella intermedia*
A2754	*Prevotella intermedia*
A2756	*Prevotella bivia*
A2759	*Prevotella bivia*
A2760	*Prevotella denticola*
A2761	*Prevotella intermedia*

CMI#	ORGANISM
A2762	*Prevotella melaninogenica*
A2765	*Prevotella melaninogenica*
A2766	*Prevotella melaninogenica*
A2821	*Prevotella bivia*
A2822	*Prevotella bivia*
QCBF	*B. fragilis*
QCBT	*B. thetaiotaomicron*
QCCD	*C. difficile*
QCBF	*B. fragilis*
QCBT	*B. thetaiotaomicron*
QCCD	*C. difficile*

[00278] In Table 5 below, the term "JMI" stands for The Jones Microbiology Institute located in North Liberty, Iowa.

[00279] Table 5: Panels of Gram Positive and Gram Negative Organism Used to Generate MIC90 Data

JMI Isolate #	JMI Organism Code	Organism
394	ACB	*Acinetobacter baumannii*
2166	ACB	*Acinetobacter baumannii*
3060	ACB	*Acinetobacter baumannii*
3170	ACB	*Acinetobacter baumannii*
9328	ACB	*Acinetobacter baumannii*
9922	ACB	*Acinetobacter baumannii*
13618	ACB	*Acinetobacter baumannii*
14308	ACB	*Acinetobacter baumannii*
17086	ACB	*Acinetobacter baumannii*
17176	ACB	*Acinetobacter baumannii*
30554	ACB	*Acinetobacter baumannii*
32007	ACB	*Acinetobacter baumannii*
1192	ECL	*Enterobacter cloacae*
3096	ECL	*Enterobacter cloacae*
5534	ECL	*Enterobacter cloacae*
6487	ECL	*Enterobacter cloacae*
9592	ECL	*Enterobacter cloacae*
11680	ECL	*Enterobacter cloacae*
12573	ECL	*Enterobacter cloacae*
12735	ECL	*Enterobacter cloacae*
13057	ECL	*Enterobacter cloacae*
18048	ECL	*Enterobacter cloacae*
25173	ECL	*Enterobacter cloacae*
29443	ECL	*Enterobacter cloacae*
44	EF	*Enterococcus faecalis*
355	EF	*Enterococcus faecalis*
886	EF	*Enterococcus faecalis*
955	EF	*Enterococcus faecalis*
1000	EF	*Enterococcus faecalis*
1053	EF	*Enterococcus faecalis*

JMI Isolate #	JMI Organism Code	Organism
1142	EF	*Enterococcus faecalis*
1325	EF	*Enterococcus faecalis*
1446	EF	*Enterococcus faecalis*
2014	EF	*Enterococcus faecalis*
2103	EF	*Enterococcus faecalis*
2255	EF	*Enterococcus faecalis*
2978	EF	*Enterococcus faecalis*
2986	EF	*Enterococcus faecalis*
5027	EF	*Enterococcus faecalis*
5270	EF	*Enterococcus faecalis*
5874	EF	*Enterococcus faecalis*
7430	EF	*Enterococcus faecalis*
7904	EF	*Enterococcus faecalis*
8092	EF	*Enterococcus faecalis*
8691	EF	*Enterococcus faecalis*
9090	EF	*Enterococcus faecalis*
10795	EF	*Enterococcus faecalis*
14104	EF	*Enterococcus faecalis*
16481	EF	*Enterococcus faecalis*
18217	EF	*Enterococcus faecalis*
22442	EF	*Enterococcus faecalis*
25726	EF	*Enterococcus faecalis*
26143	EF	*Enterococcus faecalis*
28131	EF	*Enterococcus faecalis*
29765	EF	*Enterococcus faecalis*
30279	EF	*Enterococcus faecalis*
31234	EF	*Enterococcus faecalis*
31673	EF	*Enterococcus faecalis*
115	EFM	*Enterococcus faecium*
227	EFM	*Enterococcus faecium*

JMI Isolate #	JMI Organism Code	Organism
414	EFM	*Enterococcus faecium*
712	EFM	*Enterococcus faecium*
870	EFM	*Enterococcus faecium*
911	EFM	*Enterococcus faecium*
2356	EFM	*Enterococcus faecium*
2364	EFM	*Enterococcus faecium*
2762	EFM	*Enterococcus faecium*
3062	EFM	*Enterococcus faecium*
4464	EFM	*Enterococcus faecium*
4473	EFM	*Enterococcus faecium*
4653	EFM	*Enterococcus faecium*
4679	EFM	*Enterococcus faecium*
6803	EFM	*Enterococcus faecium*
6836	EFM	*Enterococcus faecium*
8280	EFM	*Enterococcus faecium*
8702	EFM	*Enterococcus faecium*
9855	EFM	*Enterococcus faecium*
10766	EFM	*Enterococcus faecium*
12799	EFM	*Enterococcus faecium*
13556	EFM	*Enterococcus faecium*
13783	EFM	*Enterococcus faecium*
14687	EFM	*Enterococcus faecium*
15268	EFM	*Enterococcus faecium*
15525	EFM	*Enterococcus faecium*
15538	EFM	*Enterococcus faecium*
18102	EFM	*Enterococcus faecium*
18306	EFM	*Enterococcus faecium*
19967	EFM	*Enterococcus faecium*
22428	EFM	*Enterococcus faecium*
23482	EFM	*Enterococcus faecium*

JMI Isolate #	JMI Organism Code	Organism
29658	EFM	*Enterococcus faecium*
597	EC	*Escherichia coli*
847	EC	*Escherichia coli*
1451	EC	*Escherichia coli*
8682	EC	*Escherichia coli*
11199	EC	*Escherichia coli*
12583	EC	*Escherichia coli*
12792	EC	*Escherichia coli*
13265	EC	*Escherichia coli*
14594	EC	*Escherichia coli*
22148	EC	*Escherichia coli*
29743	EC	*Escherichia coli*
30426	EC	*Escherichia coli*
470	BSA	Group A *Streptococcus*
2965	BSA	Group A *Streptococcus*
3112	BSA	Group A *Streptococcus*
3637	BSA	Group A *Streptococcus*
4393	BSA	Group A *Streptococcus*
4546	BSA	Group A *Streptococcus*
4615	BSA	Group A *Streptococcus*
5848	BSA	Group A *Streptococcus*
6194	BSA	Group A *Streptococcus*
8816	BSA	Group A *Streptococcus*
11814	BSA	Group A *Streptococcus*
16977	BSA	Group A *Streptococcus*
18083	BSA	Group A *Streptococcus*
18821	BSA	Group A *Streptococcus*
25178	BSA	Group A *Streptococcus*
30704	BSA	Group A *Streptococcus*
12	BSB	Group B *Streptococcus*

JMI Isolate #	JMI Organism Code	Organism
10366	BSB	Group B *Streptococcus*
10611	BSB	Group B *Streptococcus*
16786	BSB	Group B *Streptococcus*
18833	BSB	Group B *Streptococcus*
30225	BSB	Group B *Streptococcus*
10422	BSC	Group C *Streptococcus*
14209	BSC	Group C *Streptococcus*
29732	BSC	Group C *Streptococcus*
8544	BSG	Group G *Streptococcus*
18086	BSG	Group G *Streptococcus*
29815	BSG	Group G *Streptococcus*
147	HI	*Haemophilus influenzae*
180	HI	*Haemophilus influenzae*
934	HI	*Haemophilus influenzae*
970	HI	*Haemophilus influenzae*
1298	HI	*Haemophilus influenzae*
1819	HI	*Haemophilus influenzae*
1915	HI	*Haemophilus influenzae*
2000	HI	*Haemophilus influenzae*
2562	HI	*Haemophilus influenzae*
2821	HI	*Haemophilus influenzae*
3133	HI	*Haemophilus influenzae*
3140	HI	*Haemophilus influenzae*
3497	HI	*Haemophilus influenzae*
3508	HI	*Haemophilus influenzae*
3535	HI	*Haemophilus influenzae*
4082	HI	*Haemophilus influenzae*
4108	HI	*Haemophilus influenzae*
4422	HI	*Haemophilus influenzae*
4868	HI	*Haemophilus influenzae*

JMI Isolate #	JMI Organism Code	Organism
4872	HI	*Haemophilus influenzae*
5858	HI	*Haemophilus influenzae*
6258	HI	*Haemophilus influenzae*
6875	HI	*Haemophilus influenzae*
7063	HI	*Haemophilus influenzae*
7600	HI	*Haemophilus influenzae*
8465	HI	*Haemophilus influenzae*
10280	HI	*Haemophilus influenzae*
10732	HI	*Haemophilus influenzae*
10850	HI	*Haemophilus influenzae*
11366	HI	*Haemophilus influenzae*
11716	HI	*Haemophilus influenzae*
11724	HI	*Haemophilus influenzae*
11908	HI	*Haemophilus influenzae*
12093	HI	*Haemophilus influenzae*
12107	HI	*Haemophilus influenzae*
13424	HI	*Haemophilus influenzae*
13439	HI	*Haemophilus influenzae*
13672	HI	*Haemophilus influenzae*
13687	HI	*Haemophilus influenzae*
13792	HI	*Haemophilus influenzae*
13793	HI	*Haemophilus influenzae*
14440	HI	*Haemophilus influenzae*
15351	HI	*Haemophilus influenzae*
15356	HI	*Haemophilus influenzae*
15678	HI	*Haemophilus influenzae*
15800	HI	*Haemophilus influenzae*
17841	HI	*Haemophilus influenzae*
18614	HI	*Haemophilus influenzae*
25195	HI	*Haemophilus influenzae*

JMI Isolate #	JMI Organism Code	Organism
27021	HI	*Haemophilus influenzae*
28326	HI	*Haemophilus influenzae*
28332	HI	*Haemophilus influenzae*
29918	HI	*Haemophilus influenzae*
29923	HI	*Haemophilus influenzae*
31911	HI	*Haemophilus influenzae*
428	KPN	*Klebsiella pneumoniae*
791	KPN	*Klebsiella pneumoniae*
836	KPN	*Klebsiella pneumoniae*
1422	KPN	*Klebsiella pneumoniae*
1674	KPN	*Klebsiella pneumoniae*
1883	KPN	*Klebsiella pneumoniae*
6486	KPN	*Klebsiella pneumoniae*
8789	KPN	*Klebsiella pneumoniae*
10705	KPN	*Klebsiella pneumoniae*
11123	KPN	*Klebsiella pneumoniae*
28148	KPN	*Klebsiella pneumoniae*
29432	KPN	*Klebsiella pneumoniae*
937	MCAT	*Moraxella catarrhalis*
1290	MCAT	*Moraxella catarrhalis*
1830	MCAT	*Moraxella catarrhalis*
1903	MCAT	*Moraxella catarrhalis*
4346	MCAT	*Moraxella catarrhalis*
4880	MCAT	*Moraxella catarrhalis*
6241	MCAT	*Moraxella catarrhalis*
6551	MCAT	*Moraxella catarrhalis*
7074	MCAT	*Moraxella catarrhalis*
7259	MCAT	*Moraxella catarrhalis*
7544	MCAT	*Moraxella catarrhalis*
8142	MCAT	*Moraxella catarrhalis*

JMI Isolate #	JMI Organism Code	Organism
8451	MCAT	*Moraxella catarrhalis*
9246	MCAT	*Moraxella catarrhalis*
9996	MCAT	*Moraxella catarrhalis*
12158	MCAT	*Moraxella catarrhalis*
13443	MCAT	*Moraxella catarrhalis*
13692	MCAT	*Moraxella catarrhalis*
13817	MCAT	*Moraxella catarrhalis*
14431	MCAT	*Moraxella catarrhalis*
14762	MCAT	*Moraxella catarrhalis*
14842	MCAT	*Moraxella catarrhalis*
15361	MCAT	*Moraxella catarrhalis*
15741	MCAT	*Moraxella catarrhalis*
17843	MCAT	*Moraxella catarrhalis*
18639	MCAT	*Moraxella catarrhalis*
241	GC	*Neisseria gonorrhoeae*
291	GC	*Neisseria gonorrhoeae*
293	GC	*Neisseria gonorrhoeae*
344	GC	*Neisseria gonorrhoeae*
451	GC	*Neisseria gonorrhoeae*
474	GC	*Neisseria gonorrhoeae*
491	GC	*Neisseria gonorrhoeae*
493	GC	*Neisseria gonorrhoeae*
503	GC	*Neisseria gonorrhoeae*
521	GC	*Neisseria gonorrhoeae*
552	GC	*Neisseria gonorrhoeae*
573	GC	*Neisseria gonorrhoeae*
592	GC	*Neisseria gonorrhoeae*
25	NM	*Neisseria meningitidis*
813	NM	*Neisseria meningitidis*
1725	NM	*Neisseria meningitidis*

JMI Isolate #	JMI Organism Code	Organism
2747	NM	*Neisseria meningitidis*
3201	NM	*Neisseria meningitidis*
3335	NM	*Neisseria meningitidis*
7053	NM	*Neisseria meningitidis*
9407	NM	*Neisseria meningitidis*
10447	NM	*Neisseria meningitidis*
12685	NM	*Neisseria meningitidis*
12841	NM	*Neisseria meningitidis*
14038	NM	*Neisseria meningitidis*
1127	PM	*Proteus mirabilis*
3049	PM	*Proteus mirabilis*
4471	PM	*Proteus mirabilis*
8793	PM	*Proteus mirabilis*
10702	PM	*Proteus mirabilis*
11218	PM	*Proteus mirabilis*
14662	PM	*Proteus mirabilis*
17072	PM	*Proteus mirabilis*
19059	PM	*Proteus mirabilis*
23367	PM	*Proteus mirabilis*
29819	PM	*Proteus mirabilis*
31419	PM	*Proteus mirabilis*
1881	PSA	*Pseudomonas aeruginosa*
5061	PSA	*Pseudomonas aeruginosa*
7909	PSA	*Pseudomonas aeruginosa*
8713	PSA	*Pseudomonas aeruginosa*
14318	PSA	*Pseudomonas aeruginosa*
14772	PSA	*Pseudomonas aeruginosa*
15512	PSA	*Pseudomonas aeruginosa*
17093	PSA	*Pseudomonas aeruginosa*
17802	PSA	*Pseudomonas aeruginosa*

JMI Isolate #	JMI Organism Code	Organism
19661	PSA	*Pseudomonas aeruginosa*
29967	PSA	*Pseudomonas aeruginosa*
31539	PSA	*Pseudomonas aeruginosa*
82	SA	*Staphylococcus aureus*
99	SA	*Staphylococcus aureus*
138	SA	*Staphylococcus aureus*
139	SA	*Staphylococcus aureus*
140	SA	*Staphylococcus aureus*
141	SA	*Staphylococcus aureus*
142	SA	*Staphylococcus aureus*
272	SA	*Staphylococcus aureus*
287	SA	*Staphylococcus aureus*
354	SA	*Staphylococcus aureus*
382	SA	*Staphylococcus aureus*
1112	SA	*Staphylococcus aureus*
1687	SA	*Staphylococcus aureus*
1848	SA	*Staphylococcus aureus*
2031	SA	*Staphylococcus aureus*
2159	SA	*Staphylococcus aureus*
2645	SA	*Staphylococcus aureus*
3256	SA	*Staphylococcus aureus*
3276	SA	*Staphylococcus aureus*
4044	SA	*Staphylococcus aureus*
4214	SA	*Staphylococcus aureus*
4217	SA	*Staphylococcus aureus*
4220	SA	*Staphylococcus aureus*
4231	SA	*Staphylococcus aureus*
4240	SA	*Staphylococcus aureus*
4262	SA	*Staphylococcus aureus*
4370	SA	*Staphylococcus aureus*

JMI Isolate #	JMI Organism Code	Organism
4665	SA	*Staphylococcus aureus*
4666	SA	*Staphylococcus aureus*
4667	SA	*Staphylococcus aureus*
5026	SA	*Staphylococcus aureus*
5666	SA	*Staphylococcus aureus*
6792	SA	*Staphylococcus aureus*
7023	SA	*Staphylococcus aureus*
7461	SA	*Staphylococcus aureus*
7899	SA	*Staphylococcus aureus*
7901	SA	*Staphylococcus aureus*
8714	SA	*Staphylococcus aureus*
9374	SA	*Staphylococcus aureus*
9437	SA	*Staphylococcus aureus*
10056	SA	*Staphylococcus aureus*
10110	SA	*Staphylococcus aureus*
11379	SA	*Staphylococcus aureus*
11629	SA	*Staphylococcus aureus*
11659	SA	*Staphylococcus aureus*
12788	SA	*Staphylococcus aureus*
12789	SA	*Staphylococcus aureus*
13043	SA	*Staphylococcus aureus*
13086	SA	*Staphylococcus aureus*
13721	SA	*Staphylococcus aureus*
13742	SA	*Staphylococcus aureus*
13932	SA	*Staphylococcus aureus*
14210	SA	*Staphylococcus aureus*
14384	SA	*Staphylococcus aureus*
15428	SA	*Staphylococcus aureus*
15430	SA	*Staphylococcus aureus*
17721	SA	*Staphylococcus aureus*

JMI Isolate #	JMI Organism Code	Organism
18688	SA	*Staphylococcus aureus*
19095	SA	*Staphylococcus aureus*
20195	SA	*Staphylococcus aureus*
22141	SA	*Staphylococcus aureus*
22689	SA	*Staphylococcus aureus*
27398	SA	*Staphylococcus aureus*
29048	SA	*Staphylococcus aureus*
29051	SA	*Staphylococcus aureus*
30491	SA	*Staphylococcus aureus*
30538	SA	*Staphylococcus aureus*
25	SEPI	*Staphylococcus epidermidis*
53	SEPI	*Staphylococcus epidermidis*
385	SEPI	*Staphylococcus epidermidis*
398	SEPI	*Staphylococcus epidermidis*
701	SEPI	*Staphylococcus epidermidis*
713	SEPI	*Staphylococcus epidermidis*
1381	SEPI	*Staphylococcus epidermidis*
2174	SEPI	*Staphylococcus epidermidis*
2286	SEPI	*Staphylococcus epidermidis*
2969	SEPI	*Staphylococcus epidermidis*
3417	SEPI	*Staphylococcus epidermidis*
3447	SEPI	*Staphylococcus epidermidis*
4753	SEPI	*Staphylococcus epidermidis*
7241	SEPI	*Staphylococcus epidermidis*
9366	SEPI	*Staphylococcus epidermidis*
10665	SEPI	*Staphylococcus epidermidis*
11792	SEPI	*Staphylococcus epidermidis*
12311	SEPI	*Staphylococcus epidermidis*
13036	SEPI	*Staphylococcus epidermidis*
13227	SEPI	*Staphylococcus epidermidis*

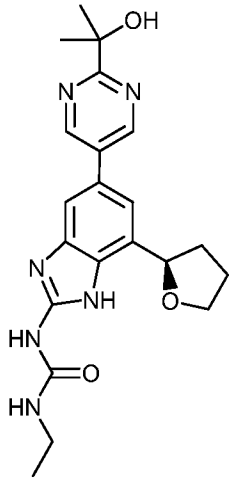
JMI Isolate #	JMI Organism Code	Organism
13243	SEPI	*Staphylococcus epidermidis*
13621	SEPI	*Staphylococcus epidermidis*
13638	SEPI	*Staphylococcus epidermidis*
13800	SEPI	*Staphylococcus epidermidis*
14078	SEPI	*Staphylococcus epidermidis*
14392	SEPI	Staphylococcus epidermidis
15007	SEPI	Staphylococcus epidermidis
16733	SEPI	*Staphylococcus epidermidis*
18871	SEPI	*Staphylococcus epidermidis*
23285	SEPI	*Staphylococcus epidermidis*
27805	SEPI	*Staphylococcus epidermidis*
29679	SEPI	*Staphylococcus epidermidis*
29985	SEPI	*Staphylococcus epidermidis*
30259	SEPI	*Staphylococcus epidermidis*
31444	SEPI	*Staphylococcus epidermidis*
268	SPN	*Streptococcus pneumoniae*
1264	SPN	*Streptococcus pneumoniae*
2482	SPN	*Streptococcus pneumoniae*
2653	SPN	*Streptococcus pneumoniae*
2994	SPN	*Streptococcus pneumoniae*
3123	SPN	*Streptococcus pneumoniae*
3124	SPN	*Streptococcus pneumoniae*
4336	SPN	*Streptococcus pneumoniae*
4858	SPN	*Streptococcus pneumoniae*
5606	SPN	*Streptococcus pneumoniae*
5881	SPN	*Streptococcus pneumoniae*
5897	SPN	*Streptococcus pneumoniae*
5900	SPN	*Streptococcus pneumoniae*
6051	SPN	*Streptococcus pneumoniae*
6216	SPN	*Streptococcus pneumoniae*

JMI Isolate #	JMI Organism Code	Organism
6556	SPN	*Streptococcus pneumoniae*
7270	SPN	*Streptococcus pneumoniae*
7584	SPN	*Streptococcus pneumoniae*
8479	SPN	*Streptococcus pneumoniae*
8501	SPN	*Streptococcus pneumoniae*
9256	SPN	*Streptococcus pneumoniae*
9257	SPN	*Streptococcus pneumoniae*
10246	SPN	*Streptococcus pneumoniae*
10467	SPN	*Streptococcus pneumoniae*
10886	SPN	*Streptococcus pneumoniae*
11217	SPN	*Streptococcus pneumoniae*
11228	SPN	*Streptococcus pneumoniae*
11238	SPN	*Streptococcus pneumoniae*
11757	SPN	*Streptococcus pneumoniae*
11768	SPN	*Streptococcus pneumoniae*
12121	SPN	*Streptococcus pneumoniae*
12124	SPN	*Streptococcus pneumoniae*
12149	SPN	*Streptococcus pneumoniae*
12767	SPN	*Streptococcus pneumoniae*
12988	SPN	*Streptococcus pneumoniae*
13321	SPN	*Streptococcus pneumoniae*
13393	SPN	*Streptococcus pneumoniae*
13521	SPN	*Streptococcus pneumoniae*
13544	SPN	*Streptococcus pneumoniae*
13700	SPN	*Streptococcus pneumoniae*
13704	SPN	*Streptococcus pneumoniae*
13822	SPN	*Streptococcus pneumoniae*
13838	SPN	*Streptococcus pneumoniae*
14131	SPN	*Streptococcus pneumoniae*
14413	SPN	*Streptococcus pneumoniae*

JMI Isolate #	JMI Organism Code	Organism
14744	SPN	*Streptococcus pneumoniae*
14808	SPN	*Streptococcus pneumoniae*
14827	SPN	*Streptococcus pneumoniae*
14835	SPN	*Streptococcus pneumoniae*
14836	SPN	*Streptococcus pneumoniae*
15832	SPN	*Streptococcus pneumoniae*
17336	SPN	*Streptococcus pneumoniae*
17343	SPN	*Streptococcus pneumoniae*
17349	SPN	*Streptococcus pneumoniae*
17735	SPN	*Streptococcus pneumoniae*
18060	SPN	*Streptococcus pneumoniae*
18567	SPN	*Streptococcus pneumoniae*
18595	SPN	*Streptococcus pneumoniae*
19082	SPN	*Streptococcus pneumoniae*
19826	SPN	*Streptococcus pneumoniae*
22174	SPN	*Streptococcus pneumoniae*
22175	SPN	*Streptococcus pneumoniae*
27003	SPN	*Streptococcus pneumoniae*
28310	SPN	*Streptococcus pneumoniae*
28312	SPN	*Streptococcus pneumoniae*
29890	SPN	*Streptococcus pneumoniae*
29910	SPN	*Streptococcus pneumoniae*

WHAT IS CLAIMED IS:

1. A solid compound of formula (I):



or salts thereof.

2. The solid compound of claim 1, wherein said solid is a solid Form I free base.

3. The solid compound of claim 2, wherein said solid Form I is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 9.3, 11.7, 12.4, 13.8, 14.6, 16.0, 16.2, 16.7, 18.6, 18.9, 19.6, 20.2, 20.5, 21.3, 21.7, 22.7, 23.9, 24.5, 24.9, 25.8, 26.7, 27.9, 28.1, 28.4, 30.4, 33.5, and 37.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

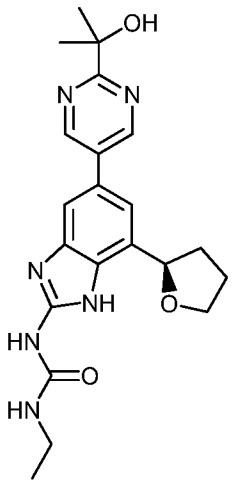
4. The solid compound of claim 2, wherein said solid Form I is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 9.3, 16.7, 18.6, 19.6, 21.7, and 25.8, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

5. The solid compound of claim 2, wherein said solid Form I is characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 1.

6. The solid compound of claim 2, wherein said solid Form I is further characterized by an endothermic peak having an onset temperature of about 243°C as measured by differential scanning calorimetry in which the temperature is scanned at about 10°C per minute.

7. A method for preparing crystal Form I of the compound of formula (I) according to claim 1 comprising precipitating the compound of formula (I) from a solvent system comprising methylene chloride, methanol, ethanol, or combinations thereof.

8. A hydrochloric acid salt of the compound of formula (I):



(I).

9. The hydrochloride salt of claim 8 in solid form.

10. The hydrochloride salt of claim 9, wherein said salt is a solid Form II.

11. The solid Form II of claim 10, wherein said solid Form II is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 12.3, 12.4, 13.5, 16.4, 17.2, 17.9, 18.2, 19.0, 19.5, 20.6, 20.9, 22.4, 23.0, 23.5, 24.0, 24.5, 26.0, 26.5, 27.1, 27.4, 28.5, 29.4, 30.8, 33.0, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

12. The solid Form II of claim 10, wherein said solid Form II is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 12.3, 12.4, 16.4, 17.9, 19.5, 24.0, and 29.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

13. The solid Form II of claim 10, which is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 7.0, 9.1, 11.5, 19.5, and 24.0, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

14. The solid Form II of claim 10, characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 4.

15. A method for preparing the solid Form II of claim 10, comprising suspending a solid free base of the benzimidazolyl urea in an acidic solvent system comprising acetonitrile or water.

16. The solid hydrochloride salt compound of claim 9, wherein said hydrochloric salt of compound of formula (I) is a solid Form III.

17. The solid Form III of claim 16, wherein said Form III is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 6.9, 9.1, 11.0, 11.7, 12.3, 15.8, 16.9, 18.1, 18.9, 19.8, 20.9, 22.7, 23.4, 24.1, 24.8, 25.3, 27.7, 28.5, 29.5, and 31.4, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

18. The solid Form III of claim 16, wherein said Form III is characterized by an X-ray powder diffraction pattern (XPRD) comprising at least three approximate peak positions (degrees 2 θ ± 0.2) when measured using Cu K_α radiation, selected from the group consisting of 6.9, 9.1, 11.7, 18.1, 18.9, 19.8, 23.4, and 24.8, when the XPRD is collected from about 5 to about 38 degrees 2 θ.

19. The solid Form III of claim 16, characterized by an X-ray powder diffraction pattern, as measured using Cu K_α radiation, substantially similar to Figure 7.

20. A method for preparing solid Form III according to claim 16 comprising suspending a solid free base of the benzimidazolyl urea in an acidic solvent system comprising one or more ethereal solvents and water.

21. The solid compound of claim 1, wherein said solid is an amorphous mesylate salt of Form IV.

22. The solid amorphous mesylate salt Form IV of claim 21, which is characterized by an X-ray powder diffraction pattern (XPRD) using Cu K_α radiation, characterized by a broad halo with no discernable diffraction peak.