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(54) Title: BIOFILM MODULATORS

(57) Abstract: Compounds described herein are useful in modulating bacterial biofilms.



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BIOFILM MODULATORS

This Application claims priority to the provisional application serial number 60/702,898 filed July 27, 2005, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD OF THE INVENTION

[001] The present invention relates to compounds useful as modulators of bacterial biofilms.

BACKGROUND OF THE INVENTION

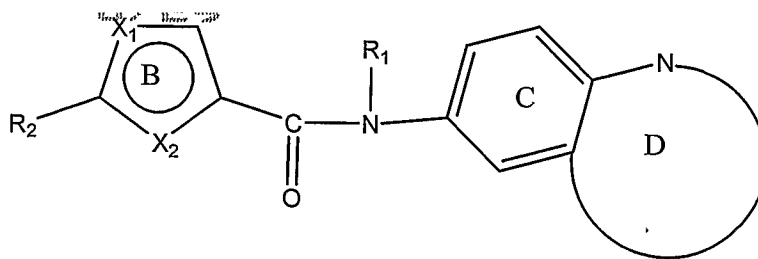
[002] Biofilms are sessile microbial communities embedded in a self-produced extracellular polymeric matrix. Biofilm formation occurs via two stages. The first stage involves attachment of cells to a surface, which may be mediated by cell wall-associated adhesions including microbial surface recognition of adhesive matrix molecules (MSCRAMMs). The second stage of biofilm development includes cell multiplication and formation of a mature, multi-layered, structured community. The second stage of biofilm formation is associated with production of extracellular factors such as the polysaccharide intercellular adhesion (PIA) produced by the IcaADBC glycosyltransferase.

[003] There is increasing awareness that biofilms have a special clinical relevance, as biofilm-associated bacteria show an innate resistance to antibiotics, disinfectants and clearance by host defenses. These properties likely contribute to the persistence and recalcitrance to treatment of biofilm infections. Biofilm formation adversely affects public health and has important implications in medicine, drinking water systems, water cooling systems, industrial fluid processing systems and food processing systems. There is a need to identify and develop compounds that are useful as modulators of biofilms.

SUMMARY

[004] The present invention addresses this need by identifying compounds that are useful as modulators of biofilms to affect the growth of biofilms and sensitivity of established biofilms to antibacterial agents or a host's immune system.

[005] In one aspect, the invention features a method of modulating a biofilm by contacting bacteria with a compound of formula I



I

or a pharmaceutically acceptable salt thereof, wherein the variables R₁, R₂, X₁, X₂, and Rings B, C, and D are defined herein.

[006] In another aspect, the invention features a pharmaceutical composition including a pharmaceutical carrier and a compound of formula I.

[007] In still another aspect, the invention features a method of treating or reducing the severity of a bacterial infection in a mammal by administering, to the mammal, a therapeutically effective amount of a compound of formula I.

[008] In yet another aspect, the invention features an implantable or indwelling device comprising a compound of formula I.

DETAILED DESCRIPTION OF THE INVENTION

I. Definitions

[009] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[010] The term "modulating" as used herein means decreasing biofilm formation and growth by a measurable amount.

[011] The phrase "treating or reducing the severity of a biofilm mediated conditions" refers both to treatments for conditions that are directly caused by biofilm sensing and/or formation, such as systemic bacterial infections, and alleviation of symptoms of conditions not directly caused by biofilms. Examples of conditions whose symptoms may be affected by biofilms include, but are not limited to, localized infections surrounding an implanted or indwelling device such as a catheter, and bloodstream infections. Symptoms may include fever, skin inflammation and septic thrombophlebitis. See C. von Eiff et al. *Drugs* 2005; 65 (2).

[012] As used herein the term aliphatic encompasses the terms alkyl, alkenyl, alkynyl.

[013] As used herein, an "alkyl" group refers to a saturated aliphatic hydrocarbon group containing 1-8 (e.g., 1-6 or 1-4) carbon atoms. An alkyl group can be straight or branched. Examples of an alkyl group include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-heptyl and 2-ethylhexyl. An alkyl group can be optionally substituted with one or more substituents such as cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy (two alkoxy groups on the same atom or adjacent atoms may form a ring together with the atom(s) to which they are bound), aroyl, heteroaroyl, alkoxycarbonyl, alkylcarbonyloxy, acyl, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, amino, nitro, carboxy, cyano, oxo, halo, hydroxy, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkyl-alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, heterocycloalkyl-carbonylamino, heterocycloalkyl-alkylcarbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino.

[014] As used herein, an "alkenyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and at least one double bond. Like an alkyl group, an alkenyl group can be straight or branched. Examples of an alkenyl group include, but are not limited to, allyl, isoprenyl, 2-butenyl and 2-hexenyl. An alkenyl group can be optionally substituted with one or more substituents such as cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy (two alkoxy groups on the same atom or adjacent atoms may form a ring together with the atom(s) to which they are bound), aroyl, heteroaroyl, alkoxycarbonyl, alkylcarbonyloxy, acyl, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, amino, nitro, carboxy, cyano, oxo, halo, hydroxy, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkyl-alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, heterocycloalkyl-carbonylamino, heterocycloalkyl-alkylcarbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino.

[015] As used herein, an "alkynyl" group refers to an aliphatic carbon group that contains 2-8 (e.g., 2-6 or 2-4) carbon atoms and has at least one triple bond. An alkynyl group can be straight or branched. Examples of an alkynyl group include, but are not limited to, propargyl and butynyl. An alkynyl group can be optionally substituted with one or more substituents

such as cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy (two alkoxy groups on the same atom or adjacent atoms may form a ring together with the atom(s) to which they are bound), aroyl, heteroaroyl, alkoxycarbonyl, alkylcarbonyloxy, acyl, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, carbamoyl, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroarylalkoxy, amino, nitro, carboxy, cyano, oxo, halo, hydroxy, sulfo, mercapto, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, cycloalkyl-alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, heterocycloalkyl-carbonylamino, heterocycloalkyl-alkylcarbonylamino, heteroarylcarbonylamino, or heteroaralkylcarbonylamino.

[016] As used herein, an "amino" group refers to $-NR^X R^Y$ wherein each of R^X and R^Y is independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, aryl, aralkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, heteroaryl, or heteroaralkyl each of which are defined herein and are optionally substituted. When the term "amino" is not the terminal group (e.g., alkylcarbonylamino), it is represented by $-NR^X-$. R^X has the same meaning as defined above.

[017] As used herein, an "aryl" group used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl" refers to phenyl, naphthyl, or a benzofused group having 2 to 3 rings. For example, a benzofused group includes phenyl fused with one or two C_{4-8} carbocyclic moieties, e.g., 1, 2, 3, 4-tetrahydronaphthyl, indanyl, or fluorenyl. An aryl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, amino, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, sulfonyl (such as alkylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[018] As used herein, an "aralkyl" group refers to an alkyl group (e.g., a C_{1-4} alkyl group) that is substituted with an aryl group. Both "alkyl" and "aryl" are defined herein. An

example of an aralkyl group is benzyl. A "heteroaralkyl" group refers to an alkyl group that is substituted with a heteroaryl. Both "alkyl" and "heteroaryl" are defined herein.

[019] As used herein, a "cycloaliphatic" group encompasses a "cycloalkyl" group and a "cycloalkenyl" group.

[020] As used herein, a "cycloalkyl" group refers to a saturated carbocyclic mono- or bicyclic (fused or bridged) ring of 3-10 (e.g., 5-10) carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, norbornyl, cubyl, octahydro-indenyl, decahydro-naphthyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.3.1]nonyl, and bicyclo[3.3.2.]decyl and adamantyl. A "cycloalkenyl" group, as used herein, refers to a non-aromatic carbocyclic ring of 3-10 (e.g., 4-8) carbon atoms having one or more double bond. Examples of cycloalkenyl groups include cyclopentenyl, 1,4-cyclohexa-di-enyl, cycloheptenyl, cyclooctenyl, hexahydro-indenyl, octahydro-naphthyl, bicyclo[2.2.2]octenyl, and bicyclo[3.3.1]nonenyl. A cycloalkyl or cycloalkenyl group can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, amino, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[021] As used herein, the term heterocycloaliphatic encompasses a heterocycloalkyl group and a heterocycloalkenyl group.

[022] As used herein, a "heterocycloalkyl" group refers to a 3- to 10-membered mono- or bicyclic (fused or bridged) (e.g., 5- to 10-membered mono- or bicyclic) saturated ring structure, in which one or more of the ring atoms is a heteroatom, e.g., N, O, or S. Examples of a heterocycloalkyl group include piperidiny, piperaziny, tetrahydropyrany, tetrahydrofurany, dioxolany, oxazolidiny, isooxazolidiny, morpholiny, octahydro-benzofurany, octahydro-chromenyl, octahydro-thiochromenyl, octahydro-indolyl, octahydro-pyrindiny, decahydro-quinoliny, octahydro-benzo[b]thiophenyl, 2-oxa-bicyclo[2.2.2]octyl, 1-aza-bicyclo[2.2.2]octyl, 3-aza-bicyclo[3.2.1]octyl, and 2,6-dioxa-tricyclo[3.3.1.0^{3,7}]nonyl.

A monocyclic heterocycloalkyl group may be fused with a phenyl moiety such as tetrahydroisoquinoline. A "heterocycloalkenyl" group, as used herein, refers to a mono- or bicyclic (e.g., 5- to 10-membered mono- or bicyclic) non-aromatic ring structure having one or more double bonds, and wherein one or more of the ring atoms is a heteroatom, e.g., N, O, or S. A heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl (such as a benzimidazolidinyl), (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy (two alkoxy groups on the same atom or adjacent atoms may form a ring together with the atom(s) to which they are bound), cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, amino, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino, heteroaralkylcarbonylamino, cyano, halo, hydroxy, acyl, mercapto, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl.

[023] A "heteroaryl" group, as used herein, refers to a monocyclic, bicyclic, or tricyclic ring structure having 4 to 15 ring atoms wherein one or more of the ring atoms is a heteroatom, e.g., N, O, or S and wherein one or more rings of the bicyclic or tricyclic ring structure is aromatic. A heteroaryl group includes a benzofused ring system having 2 to 3 rings. For example, a benzofused group includes phenyl fused with one or two C₄₋₈ heterocyclic moieties, e.g., indolyl and tetrahydroquinolyl. Some examples of heteroaryl are azetidyl, pyridyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, tetrazolyl, benzofuryl, isoquinolyl, benzthiazolyl, xanthene, thioxanthene, phenothiazine, dihydroindole, and benzo[1,3]dioxole. A heteroaryl is optionally substituted with one or more substituents such as alkyl (including carboxyalkyl, hydroxyalkyl, and haloalkyl such as trifluoromethyl), alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aryl, heteroaryl, alkoxy, cycloalkyloxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, aroyl, heteroaroyl, amino, nitro, carboxy, alkoxycarbonyl, alkylcarbonyloxy, aminocarbonyl, alkylcarbonylamino, cycloalkylcarbonylamino, (cycloalkyl)alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, (heterocycloalkyl)carbonylamino, (heterocycloalkyl)alkylcarbonylamino, heteroarylcarbonylamino,

heteroaralkyl, carbonylamino, cyano, halo, hydroxy, acyl, mercapto, sulfonyl (such as alkylsulfonyl or arylsulfonyl), sulfinyl (such as alkylsulfinyl), sulfanyl (such as alkylsulfanyl), sulfoxy, urea, thiourea, sulfamoyl, sulfamide, oxo, or carbamoyl. A

“heteroaralkyl” group, as used herein, refers to an alkyl group (e.g., a C₁₋₄ alkyl group) that is substituted with a heteroaryl group. Both “alkyl” and “heteroaryl” have been defined above.

[024] As used herein, “cyclic moiety” includes cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl or heteroaryl, each of which has been defined previously.

[025] As used herein, an “acyl” group refers to a formyl group or alkyl-C(=O)- where “alkyl” has been defined previously. Acetyl and pivaloyl are examples of acyl groups.

[026] As used herein, a “carbamoyl” group refers to a group having the structure -O-CO-NR^xR^y or -NR^x-CO-O-R^z wherein R^x and R^y have been defined above and R^z can be alkyl, aryl, aralkyl, heterocycloalkyl, heteroaryl or heteroaralkyl.

[027] As used herein, a “carboxy” and a “sulfo” group refer to -COOH or -COOR^x and -SO₃H or -SO₃R^x, respectively.

[028] As used herein, an “alkoxy” group refers to an alkyl-O- group where “alkyl” has been defined previously.

[029] As used herein, a “sulfoxy” group refers to -O-SO-R^x or -SO-O-R^x, where R^x has been defined above.

[030] As used herein, a “sulfonyl” group refers to -S(O)₂-R^x, wherein R^x has been defined above.

[031] As used herein a “sulfinyl” group refers to -S(O)-R^x, wherein R^x has been defined above.

[032] As used herein a “sulfanyl” group refers to -S-R^x, wherein R^x has been defined above.

[033] As used herein, a “halogen” or “halo” group refers to fluorine, chlorine, bromine or iodine.

[034] As used herein, a “haloaliphatic” group refers to an aliphatic group substituted with 1-3 halogen. For instance, the term haloalkyl includes the group -CF₃.

[035] As used herein, a “sulfamoyl” group refers to the structure -S(O)₂-NR^xR^y or -NR^x-S(O)₂-R^z wherein R^x, R^y, and R^z have been defined above.

[036] As used herein, a “sulfamide” group refers to the structure -NR^x-S(O)₂-NR^yR^z, wherein R^x, R^y, and R^z have been defined above.

[037] As used herein, a "carbonylamino" group used alone or in connection with another group refers to an amido group such as $-C(O)-NR^X$ -, $-NR^X-C(O)-$, and $-C(O)-N(R^X)_2$. For instance an alkylcarbonylamino includes alkyl- $C(O)-NR^X$ - and alkyl- $NR^X-C(O)-$.

[038] As used herein, a "urea" group refers to the structure $-NR^X-CO-NR^YR^Z$ and a "thiourea" group refers to the structure $-NR^X-CS-NR^YR^Z$. R^X , R^Y and R^Z have been defined above.

[039] The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. As described herein, the variables R_1 , R_2 , X_1 , X_2 , and Rings B, C, and D are defined herein encompass specific groups, such as alkyl or aryl. Unless the variables R_1 , R_2 , X_1 , X_2 , and Rings B, C, and D are otherwise noted as including specific substituents, each of the specific moieties for the variables R_1 , R_2 , X_1 , X_2 , and Rings B, C, and D may be optionally substituted with one or more substituents described herein. Each substituent of a specific group is further optionally substituted with one to three of halo, cyano, alkoxy, hydroxyl, nitro, haloalkyl and alkyl. For instance, an alkyl group may be substituted with alkylsulfanyl and the alkylsulfanyl may be optionally substituted with one to three of halo, cyano, alkoxy, hydroxyl, nitro, haloalkyl and alkyl. As an additional example, the cycloalkyl portion of a (cycloalkyl)carbonylamino may be optionally substituted with one to three of halo, cyano, alkoxy, hydroxyl, nitro, haloalkyl and alkyl.

[040] In general, the term "substituted," whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Specific substituents are described above in the definitions and below in the description of compounds and examples thereof. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. A ring substituent, such as a heterocycloalkyl, may be bound to another ring, such as a cycloalkyl, to form a spiro-bicyclic ring system, e.g., both rings share one common atom. As one of ordinary skill in the art will recognize, combinations of substituents envisioned by this invention are those combinations that result in the formation of stable or chemically feasible compounds.

[041] The phrase "stable or chemically feasible," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and preferably their recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[042] As used herein, an effective amount is defined as the amount required to confer a therapeutic effect on the treated patient, and is typically determined based on age, surface area, weight and condition of the patient. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich et al., *Cancer Chemother. Rep.*, 50: 219 (1966). Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, New York, 537 (1970). As used herein, "patient" refers to a mammal, including a human.

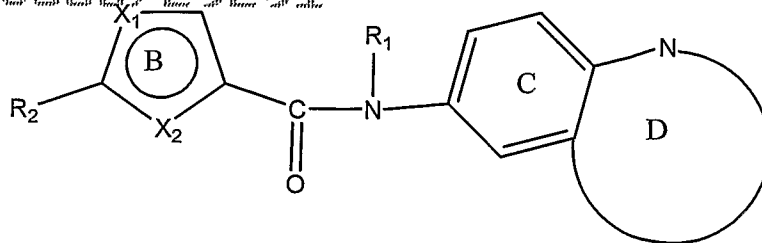
[043] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention.

[044] Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

II. Description of Compounds:

A. Generic Compound Description

[045] In one aspect, the invention features a method of modulating a biofilm by contacting bacteria with a compound of formula I



I

or a pharmaceutically acceptable salt thereof, wherein

X_1 is O, S, $=CH-$, or $=N-$, $-NH-$;

X_2 is O, S, $=N-$, $-NH-$, or $=CH-$, provided that at least one of X_1 and X_2 is a heteroatom;

Ring B is optionally substituted with (C_1-C_4) alkyl;

Ring C is optionally substituted with 1-2 of $-COOR_6$, $-CN$, $-N(R_6)_2$, $-OR_6$, halo, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)O-R_6$, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, $N(R_7)_2$ and nitro;

Ring D is a 5 or 6 membered heterocycloaliphatic optionally including an additional hetero atom, or a 5 or 6 membered heteroaryl optionally including an additional hetero atom, each of the 5 or 6 membered heterocycle and the 5 or 6 membered heteroaryl is optionally substituted with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, $-OR_6$, halo, $-COOR_6$, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)O-R_6$ and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R_1 is independently H or C_1-C_4 aliphatic optionally substituted with 1-3 halo, hydroxyl, cyano, alkoxy and nitro;

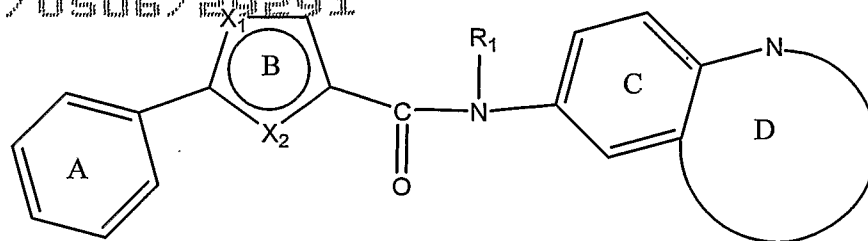
Each R_2 is independently aryl or heteroaryl each optionally substituted with 1-4 of $-COOR_6$, $-CN$, $-N(R_6)_2$, $-OR_6$, halo, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)OR_6$, $-S(O)_2R_6$, $-S(O)R_6$, $-SR_6$, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R_6 is independently H, $-(C_1-C_6)$ alkyl, cycloaliphatic, aryl, heterocycloalkyl, or heteroaryl ring, wherein each of the $-(C_1-C_6)$ alkyl, cycloaliphatic, aryl, heterocyclic, and heteroaryl are optionally substituted with 1-3 substituents selected from halo, hydroxyl, cyano, nitro, OH, and $-N(R_7)_2$; and

Each R_7 is independently H or an unsubstituted $-(C_1-C_6)$ alkyl.

[046] In another aspect, the invention features a method of modulating a biofilm by contacting bacteria with a compound of formula II

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II

wherein

or a pharmaceutically acceptable salt thereof, wherein

X_1 is O, S, =CH-, =N-, or -NH-;

X_2 is O, S, =N-, -NH-, or =CH-, provided that at least one of X_1 and X_2 is a heteroatom;

Ring A is optionally substituted with 1-4 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)OR₆, -S(O)₂R₆, -S(O)R₆, -SR₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Ring B is optionally substituted with (C₁-C₄)alkyl;

Ring C is optionally substituted with 1-2 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro;

Ring D is a 5 or 6 membered heterocycloaliphatic optionally including an additional hetero atom, or a 5 or 6 membered heteroaryl optionally including an additional hetero atom, each of the 5 or 6 membered heterocycle and the 5 or 6 membered heteroaryl is optionally substituted with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, -OR₆, halo, -COOR₆, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆ and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R₁ is independently H or C₁-C₄ aliphatic optionally substituted with 1-3 halo, hydroxyl, cyano, alkoxy and nitro;

Each R₆ is independently H, -(C₁-C₆)alkyl, cycloaliphatic, aryl, heterocycloalkyl, or heteroaryl ring, wherein each of the -(C₁-C₆)alkyl, cycloaliphatic, aryl, heterocyclic, and heteroaryl are optionally substituted with 1-3 substituents selected from halo, hydroxyl, cyano, nitro, OH, and -N(R₇)₂; and

Each R₇ is independently H or an unsubstituted -(C₁-C₆)alkyl.

B. Specific Embodiments

i. R₂ Substituents

[047] As defined in the following paragraphs, the R₂ moieties can be optionally substituted with 1-4 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)OR₆, -S(O)₂R₆, -S(O)R₆, -SR₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro.

[048] Each R₂ is an optionally substituted aryl, such as mono- or bi-carbocyclic aromatic group. Each R₂ is an optionally substituted mono-carbocyclic aromatic ("monocyclic aryl") group, e.g., an optionally substituted phenyl. Each R₂ is a mono-carbocyclic aromatic group, e.g., phenyl. Each R₂ is an optionally substituted bi-carbocyclic aromatic group, e.g., naphthyl, indenyl or azulenyl. Each R₂ is a bi-carbocyclic aromatic ("bicyclic aryl") group, e.g., naphthyl, indenyl or azulenyl.

[049] Each R₂ is an optionally substituted heteroaryl, such as a mono- or bi-heterocyclic aromatic group. Each R₂ is an optionally substituted mono-heterocyclic aromatic ("monocyclic heteroaryl") group, e.g., furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, triazolyl, pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, each of which are optionally substituted. Each R₂ is an optionally substituted 5-membered mono-heterocyclic aromatic group, e.g., furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, and triazolyl, each of which is optionally substituted. Each R₂ is an optionally substituted 6-membered mono-heterocyclic aromatic group, e.g., pyridinyl, pyridazinyl, pyrimidinyl, and pyrazinyl, each of which is optionally substituted.

[050] Each R₂ is an optionally substituted bi-heterocyclic aromatic ("bicyclic heteroaryl") group, e.g., indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothiopenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and pteridinyl, each of which is optionally substituted. Each R₂ is an optionally substituted 9-membered bi-heterocyclic aromatic group, e.g., indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothiopenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, and purinyl, each of which is optionally substituted. Each R₂ is an optionally substituted 10-membered bi-heterocyclic aromatic group, e.g., 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and pteridinyl, each of which are optionally substituted.

[051] R₂ is an optionally substituted benzofused bicyclic aryl moiety covered under the term aryl, e.g., tetrahydronaphthalyl. R₂ is an optionally substituted benzofused bicyclic heteroaryl moiety covered under the term heteroaryl, e.g., indolinyl and tetrahydroquinolinyl.

[052] R_2 in formula I and Ring A in formula II is substituted with at least one of $-COOR_6$, $-CN$, $-N(R_6)_2$, $-OR_6$, halo, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)OR_6$, $-S(O)_2R_6$, $-S(O)R_6$, $-SR_6$, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro. R_2 in formula I and Ring A in formula II is substituted with at least one of $-COOH$, $-CN$, $-NH_2$, $-OH$, halo, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro. R_2 in formula I and Ring A in formula II is substituted with at least one of $-COOR_6$, $-N(R_6)_2$, $-OR_6$, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)OR_6$, $-S(O)_2R_6$, $-S(O)R_6$, $-SR_6$. R_2 in formula I and Ring A in formula II is substituted with at least one of halo and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, and cyano. R_2 in formula I and Ring A in formula II is substituted with at least one of halo, $-CF_3$ and unsubstituted $-(C_1-C_6)$ alkyl.

[053] Ring A in formula II is substituted ortho or para relative to the attachment between the phenyl and Ring B. R_2 is a 6 membered ring and is substituted ortho or para relative to the attachment between R_2 and Ring B. Ring A in formula II is substituted para relative to the attachment between the phenyl and Ring B. R_2 is a 6 membered ring and is substituted para relative to the attachment between R_2 and Ring B.

ii. Ring C and Ring D

[054] As defined in the following paragraphs, Ring C can be optionally substituted with 1-2 of $-COOR_6$, $-CN$, $-N(R_6)_2$, $-OR_6$, halo, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)O-R_6$, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, $N(R_7)_2$ and nitro.

[055] As defined in the following paragraphs, Ring D can be optionally substituted with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, $-OR_6$, halo, $-COOR_6$, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro.

[056] Ring D is a 5 or 6 membered heterocycloaliphatic or a 5 or 6 membered heteroaryl optionally including an additional hetero atom. Ring D is a 5 membered heterocycloaliphatic, e.g., 2H-pyrrole, 2-pyrroline, pyrrolidine, 2-imidazoline, 2-pyrazoline. Ring D is a 6 membered heterocycloaliphatic. Ring D is a 5 membered heteroaryl, e.g., pyrrole, oxazole, thiazole, pyrazole, isoxazole, isothiazole, oxodiazole, and triazole. Ring D is a 6 membered heteroaryl, e.g., pyridine, pyrimidine, pyridiazine, and pyrazine.

[057] Ring D is a 6 membered heteroaryl, e.g., pyridine, pyrimidine, pyridiazine, and pyrazine, substituted with at least one of with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, $-OR_6$, halo, $-COOR_6$, $-C(O)N(R_6)_2$, $-N(R_6)_2C(O)-R_6$, $-N(R_6)_2C(O)O-R_6$, and $-(C_1-C_6)$ alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro. Ring D is a 6 membered heteroaryl, e.g., pyridine, pyrimidine, pyridiazine, and pyrazine, substituted with

at least one of -COOR₆, -OR₆, halo, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro. Ring D is a 5 membered heteroaryl, e.g., pyrrole, oxazole, thiazole, pyrazole, isoxazole, isothiazole, oxodiazole, and triazole, substituted with at least one of with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, -OR₆, halo, -COOR₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro. Ring D is a 5 membered heteroaryl, e.g., pyrrole, oxazole, thiazole, pyrazole, isoxazole, isothiazole, oxodiazole, and triazole, substituted with at least one of -COOR₆, -OR₆, halo, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro. Ring D is a 5 membered heteroaryl, e.g., pyrrole, oxazole, thiazole, pyrazole, isoxazole, isothiazole, oxodiazole, and triazole, substituted with at least one of cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, cyano, N(R₇)₂, -OR₆, halo, -COOR₆, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro.

[058] Ring C is optionally substituted with 1-2 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro. Ring C is substituted with 1-2 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro. Ring C is substituted with 1-2 of -COOR₆, -N(R₆)₂, -OR₆, halo, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro. Ring C is substituted with 1-2 of -COOH, -NH₂, -OH, halo, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro. Ring C is substituted with 1-2 of -COOH, -NH₂, -OH, halo, and unsubstituted -(C₁-C₆)alkyl.

iii. X₁ and X₂ Substituents and Ring B

[059] X₂ is =N- or =CH-. X₁ is O, S, or =N-. X₁ is =N- and X₂ is =N-. X₁ is O and X₂ is =N-. X₁ is S and X₂ is =N-. X₁ is =N- and X₂ is =CH-. X₁ is O and X₂ is =CH-. X₁ is S and X₂ is =CH-. X₁ is =N- or =CH-. X₂ is O, S, or =N-. X₂ is =N- and X₁ is =N-. X₂ is O and X₁ is =N-. X₂ is S and X₁ is =N-. X₂ is =N- and X₁ is =CH-. X₂ is O and X₁ is =CH-. X₂ is S and X₁ is =CH-.

[060] Ring B is substituted with a -(C₁-C₆)alkyl. Ring B is substituted with an unsubstituted -(C₁-C₆)alkyl.

iv. R₁ Substituents

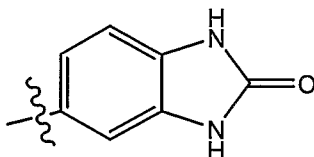
[061] R₁ is H. R₁ is C₁-C₄ aliphatic optionally substituted with 1-3 halo, hydroxyl, cyano, alkoxy, and nitro. R₁ is unsubstituted C₁-C₄ aliphatic. R₁ is C₁-C₄ alkyl optionally

substituted with 1-3 halo, hydroxyl, cyano, and nitro. R₁ is unsubstituted C₁-C₄ alkyl. R₁ is C₁-C₄ alkenyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro. R₁ is unsubstituted C₁-C₄ alkenyl.

v. Excluded Compounds

[062] In certain embodiments, the following compounds are excluded from formula I and II:

1. N-[4-amino-3-butyl-quinolin-7-yl]-5-[4-chlorophenyl]-2-furamide; and
2. Compounds in which Rings C and D together form



; and

3. N-[2-oxo-benzothiazol-6-yl]-5-[4-chlorophenyl]-3-[2-methylfuramide].

C. Specific Compounds

[063] Specific compounds useful for modulating biofilms may include any combination of the specific embodiments described herein. Specific compounds include

- 5-(4-chlorophenyl)-N-(quinolin-6-yl)furan-2-carboxamide;
- 5-(4-chlorophenyl)-N-(1H-indazol-5-yl)furan-2-carboxamide;
- 2-(4-chlorophenyl)-4-methyl-N-(2-methyl-1H-indol-5-yl)thiazole-5-carboxamide;
- 5-(pyridin-2-yl)-N-(quinolin-6-yl)thiophene-2-carboxamide;
- 5-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)furan-2-carboxamide;
- 2-(4-chlorophenyl)-N-(1H-indol-5-yl)thiazole-4-carboxamide;
- 2-(4-chlorophenyl)-4-methyl-N-(quinolin-6-yl)thiazole-5-carboxamide;
- N-(2-methyl-1H-indol-5-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide;
- N-(1H-benzo[d]imidazol-5-yl)-2-(4-chlorophenyl)thiazole-4-carboxamide;
- 2-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)thiazole-4-carboxamide;
- N-(1H-indazol-5-yl)-2-p-tolylthiazole-4-carboxamide;
- 2-(4-chlorophenyl)-N-(quinolin-6-yl)thiazole-4-carboxamide;
- 2-(4-chlorophenyl)-N-(1H-indazol-5-yl)thiazole-4-carboxamide;
- N-(1H-indazol-5-yl)-2-phenylthiazole-4-carboxamide; and
- N-(quinolin-6-yl)-2-p-tolylthiazole-4-carboxamide.

III. General Synthetic Methodology

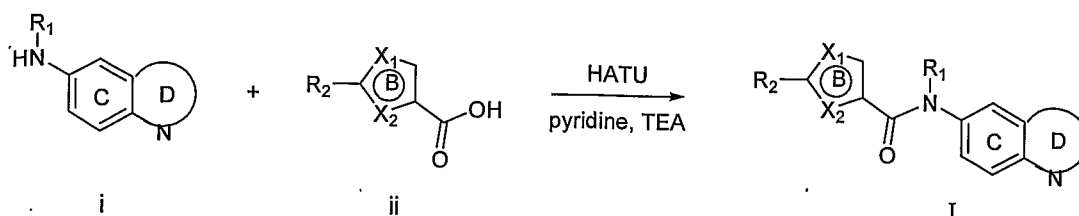
[064] The compounds useful for modulating biofilms may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the

general scheme below and the examples that follow. The compounds of formula I and starting materials useful for producing the compounds of formula I are commercially available from chemical reagent supply companies, such as, Aldrich Chemicals Co., Sigma Chemical Company, and the like. Compounds that are not commercially available can be prepared by those of ordinary skill in art following procedures set forth in references such as, "Fieser and Fieser's Reagents for Organic Synthesis", Volumes 1-15, John Wiley and Sons, 1991; "Rodd's Chemistry of Carbon Compounds", Volumes 1-5 and Supplementals, Elsevier Science Publishers, 1989; and "Organic Reactions", Volumes 1-40, John Wiley and Sons, 1991.

[065] Reaction Scheme A, below, illustrates a step in the synthesis of compounds formulae I and II. As shown in Scheme A, the reaction of a fused bicyclic aniline derivative of type *i* with a carboxylic acid derivative of type *ii* affords a compound of formulae I and II. The amide bond formation is conducted in an appropriate solvent such as DMF, DCM, pyridine, CH₃CN or the like and may be performed with a variety of coupling reagents suitable for amide forming reactions such as HATU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), BOP (Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), or DPPA (diphenylphosphoryl azide). Modifications to the procedure may include, but are not limited to, the use of an appropriate base such as triethylamine (TEA), diisopropylethylamine (DIEA), *N*-methylmorpholine, or NaHCO₃. Modifiers such as DMAP (4-dimethylaminopyridine), HOBt (1-hydroxybenzotriazole), or HOAt (1-hydroxy-7-azabenzotriazole) may also be used.

[066] Alternatively, the amide bond in Formulae I and II may be formed by the treatment of amine *i* with either with a pentafluorophenyl ester or other activated ester derived from carboxylic acid *ii*, or with an acid chloride or acid fluoride derived from carboxylic acid *ii*. The amide bond formation illustrated in Scheme A is typically performed from 0 °C to room temperature, but may be performed alternatively at elevated temperature or under microwave conditions.

Scheme A:



[067] Although, Scheme A illustrates Ring A as phenyl, Ring A may be a bicyclic aryl or heteroaryl. Variables R_A, R_B, and R_C represent the chemical moieties that can be substituted on Rings A, B, and C, respectively.

IV. Uses, Formulations, Compositions, and Administration

[068] The present invention includes within its scope pharmaceutically acceptable prodrugs of the compounds of the present invention. A "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester, or other derivative of a compound of the present invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. Preferred prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal or which enhance delivery of the parent compound to a biological compartment relative to the parent species.

[069] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the 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, polyethylene glycol and wool fat.

[070] 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, oxalate, 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.

[071] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., calcium or magnesium), ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts or salts of lysine and arginine. 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. Other salts can be found in "Practical Process, Research, & Development," Anderson, Neal G., Academic Press, 2000, the contents of which are incorporated herein by reference.

[072] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, intermuscularly, subcutaneously, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents 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 water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[073] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. 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 carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[074] The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers 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 cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[075] Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[076] The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[077] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[078] For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water.

Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. 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.

[079] For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as

benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[080] The pharmaceutically acceptable compositions of this invention may also 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 conventional solubilizing or dispersing agents.

[081] In certain embodiments, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[082] The compounds of formula I may also be delivered by implantation (e.g., surgically) such as with an implantable device. Examples of implantable devices include, but are not limited to, catheters, sutures, contact lenses, stents, delivery pumps, vascular filters, implantable control release compositions, and joint replacements, such as hip and knee replacements. Any implantable device can be used to deliver the compound provided that 1) the device, compound and any pharmaceutical composition including the compound are biocompatible, and 2) that the device can deliver or release an effective amount of the compound to confer a therapeutic effect on the treated patient.

[083] The compounds of formula I 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, dental implants, dental aspirators, 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 a compound of formula I 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 a compound of formula I. Any implantable or indwelling device can be used to deliver the compound provided that 1) the device, compound and any pharmaceutical composition

including the compound are biocompatible, and 2) that the device can deliver or release an effective amount of the compound to confer a therapeutic effect on the treated patient.

[084] 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, are incorporated herein. Other descriptions of implantable devices can be found in U.S. Patent Nos. 6,569,195 and 6,322,847; and PCT International Publication Numbers WO04/0044405; WO04/0018228; WO03/0229390; WO03/0228346; WO03/0225450; WO03/0216699; WO03/0204168; WO 03/011821; and WO 01/16624, each of which is incorporated herein in its entirety.

[085] 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.

[086] 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.

[087] 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 copolymers can be extruded over the device.

[088] The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01-100 mg/kg body weight/day of the modulator can be administered to a patient receiving these compositions.

[089] It should also be understood that a specific dosage and treatment regimen 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, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

[090] Depending upon the particular condition, or disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention. For instance, compounds of formula I may be administered in combination with other antibacterial agents. The compounds of formula I may be administered with other antibacterial or antimicrobial agents in any order such as sequentially or simultaneously. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[091] In other embodiments, the compounds of formula I are useful at modulating biofilms in drinking water systems, water cooling systems, industrial fluid processing systems, food processing systems, and any surface-fluid interface.

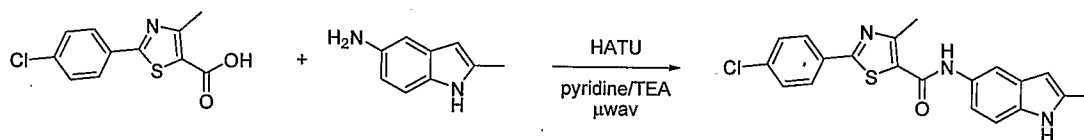
[092] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

[093] All references cited above are incorporated herein by reference.

[094] Other embodiments of the compounds of formula I are shown below. The following examples are illustrative of the compounds of formula I and are not meant to be limiting.

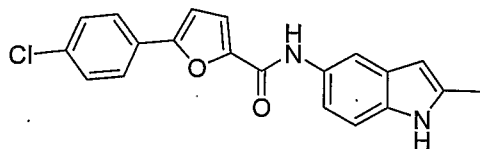
EXAMPLES

Example 1: 2-(4-chlorophenyl)-4-methyl-N-(2-methyl-1H-indol-5-yl)thiazole-5-carboxamide:



[095] 2-(4-chlorophenyl)-4-methylthiazole-5-carboxylic acid (51 mg, 0.2 mmol), 2-methyl-1H-indol-5-amine (29 mg, 0.2 mmol), and O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (76 mg, 0.2 mmol) were dissolved in 0.8 mL anhydrous pyridine followed by the addition of 0.8 mL TEA. The mixture was microwaved at 200° C for 420 s. The crude mixture was dried down, redissolved in 2 mL 1:1 DMSO/MeOH, and purified by reverse phase HPLC (C-18, 10-99% acetonitrile/0.05% TFA gradient over 10 min). Pure fractions were pooled and concentrated to yield the product as a beige powder. ¹H NMR (400 MHz, DMSO-d₆) δ 10.89 (s, 1H), 10.05 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.75 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.23 (s, 2H), 6.11 (s, 1H), 2.66 (s, 3H), 2.38 (s, 3H). LC/MS (RP-C₁₈, 10-99% CH₃CN/0.05% TFA gradient over 5 min): *m/z* 382.0, retention time 3.57 minutes.

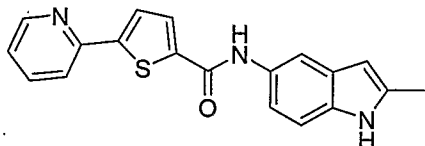
Example 2: 5-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)furan-2-carboxamide



5-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)furan-2-carboxamide was prepared following the procedure in example 1.

¹H NMR (400 MHz, DMSO-d₆) δ 10.90 (s, 1H), 10.04 (s, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.77 (d, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 3.6 Hz, 1H), 7.29 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.12 (s, 1H), 2.38 (d, *J* = 0.5 Hz, 3H). LC/MS (RP-C₁₈, 10-99% CH₃CN/0.05% TFA gradient over 5 min): *M/Z* 351.2, retention time 3.48 minutes.

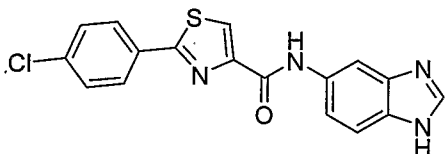
Example 3: N-(2-methyl-1H-indol-5-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide



N-(2-methyl-1H-indol-5-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide was prepared following the procedure in example 1.

¹H NMR (400 MHz, DMSO-d₆) δ 10.89 (s, 1H), 10.08 (s, 1H), 8.60 (dq, *J* = 4.8 Hz, *J* = 0.9 Hz, 1H), 8.02-8.00 (m, 2H), 7.91 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.88 (d, *J* = 4.0 Hz, 1H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.37-7.34 (m, 1H), 7.28 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 1H), 6.11 (s, 1H), 2.38 (s, 3H). LC/MS (RP-C₁₈, 10-99% CH₃CN/0.05% TFA gradient over 5 min): *M/Z* 334.2, retention time 3.09 minutes.

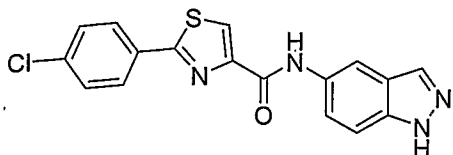
Example 4: N-(1H-benzo[d]imidazol-5-yl)-2-(4-chlorophenyl)thiazole-4-carboxamide



N-(1H-benzo[d]imidazol-5-yl)-2-(4-chlorophenyl)thiazole-4-carboxamide was prepared following the procedure in example 1.

¹H NMR (400 MHz, DMSO-d₆) δ 10.59 (s, 1H), 9.29 (s, 1H), 8.56 (s, 1H), 8.51 (d, *J* = 1.6 Hz, 1H), 8.22 (d, *J* = 8.7 Hz, 2H), 7.91 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 2H). LC/MS (10-99%); LC/MS (RP-C₁₈, 10-99% CH₃CN/0.05% TFA gradient over 5 min): *M/Z* 355.0, retention time 2.75 minutes.

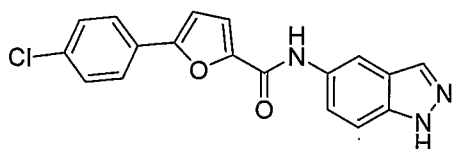
Example 5: 2-(4-chlorophenyl)-N-(1H-indazol-5-yl)thiazole-4-carboxamide



2-(4-chlorophenyl)-N-(1H-indazol-5-yl)thiazole-4-carboxamide was prepared following the procedure in example 1.

^1H NMR (400 MHz, DMSO- d_6) δ 13.06 (s, 1H), 10.32 (s, 1H), 8.50 (s, 1H), 8.30 (d, J = 1.4 Hz, 1H), 8.21 (d, J = 8.7 Hz, 2H), 8.09 (s, 1H), 7.73 (dd, J = 8.9, 1.9 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.56 (d, J = 8.9 Hz, 1H). LC/MS (RP- C_{18} , 10-99% CH_3CN /0.05% TFA gradient over 5 min): M/Z 355.0, retention time 3.74 minutes.

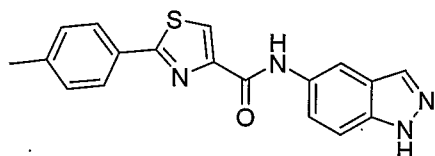
Example 6: 5-(4-chlorophenyl)-N-(1H-indazol-5-yl)furan-2-carboxamide



5-(4-chlorophenyl)-N-(1H-indazol-5-yl)furan-2-carboxamide was prepared following the procedure in example 1.

^1H NMR (400 MHz, DMSO- d_6) δ 13.06 (s, 1H), 10.26 (s, 1H), 8.18 (d, J = 1.2 Hz, 1H), 8.09 (s, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.64 (dd, J = 8.9, 1.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 10.2 Hz, 1H), 7.40 (d, J = 3.6 Hz, 1H), 7.24 (d, J = 3.6 Hz, 1H). LC/MS (RP- C_{18} , 10-99% CH_3CN /0.05% TFA gradient over 5 min): M/Z 338.2, retention time 3.08 minutes.

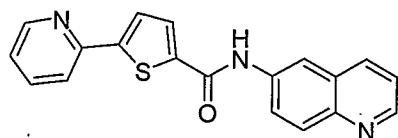
Example 7: N-(1H-indazol-5-yl)-2-p-tolylthiazole-4-carboxamide



N-(1H-indazol-5-yl)-2-p-tolylthiazole-4-carboxamide was prepared following the procedure in example 1.

^1H NMR (400 MHz, DMSO- d_6) δ 13.06 (s, 1H), 10.27 (s, 1H), 8.43 (s, 1H), 8.31 (d, J = 1.3 Hz, 1H), 8.09 (s, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.75 (dd, J = 8.9, 1.9 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 2.40 (s, 3H). LC/MS (RP- C_{18} , 10-99% CH_3CN /0.05% TFA gradient over 5 min): M/Z 335.2, retention time 3.65 minutes.

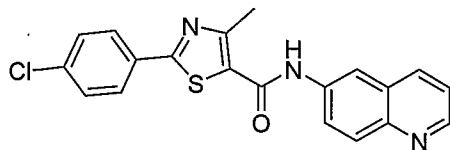
Example 8: 5-(pyridin-2-yl)-N-(quinolin-6-yl)thiophene-2-carboxamide



5-(pyridin-2-yl)-N-(quinolin-6-yl)thiophene-2-carboxamide was prepared following the procedure in example 1.

^1H NMR (400 MHz, DMSO- d_6) δ 10.75 (s, 1H), 8.99 (dd, J = 4.6, 1.5 Hz, 1H), 8.69-8.67 (m, 2H), 8.62-8.60 (m, 1H), 8.19 (dd, J = 9.2, 2.2 Hz, 1H), 8.15-8.13 (m, 2H), 8.05 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 4.0 Hz, 1H), 7.91 (dd, J = 7.9, 1.8 Hz, 1H), 7.74 (q, J = 4.3 Hz, 1H), 7.39 (ddd, J = 3.7, 1.0 Hz, 1H), 7.40-7.37 (m, 1H). LC/MS (RP- C_{18} , 10-99% CH_3CN /0.05% TFA gradient over 5 min): M/Z 332.0, retention time 1.93 minutes.

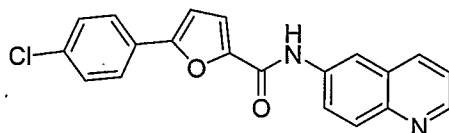
Example 9: 2-(4-chlorophenyl)-4-methyl-N-(quinolin-6-yl)thiazole-5-carboxamide



2-(4-chlorophenyl)-4-methyl-N-(quinolin-6-yl)thiazole-5-carboxamide was prepared following the procedure in example 1.

^1H NMR (400 MHz, DMSO- d_6) δ 10.74 (s, 1H), 8.96 (dd, J = 4.5, 1.6 Hz, 1H), 8.61 (d, J = 7.9 Hz, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 9.1 Hz, 1H), 8.07 (dd, J = 9.2, 2.2 Hz, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.69 (q, J = 4.3 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 2.71 (s, 3H). LC/MS (RP- C_{18} , 10-99% CH_3CN /0.05% TFA gradient over 5 min): M/Z 380.0, retention time 2.53 minutes.

Example 10: 5-(4-chlorophenyl)-N-(quinolin-6-yl)furan-2-carboxamide



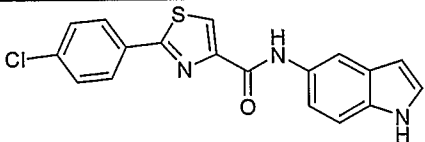
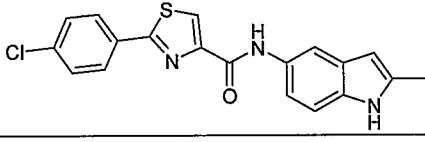
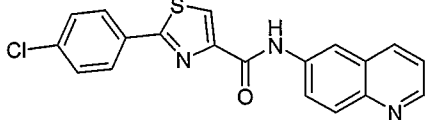
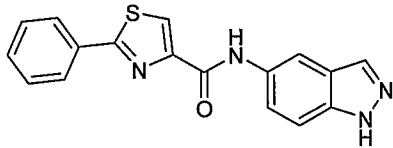
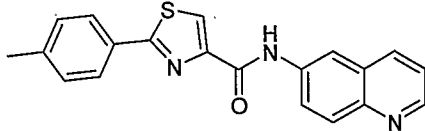
5-(4-chlorophenyl)-N-(quinolin-6-yl)furan-2-carboxamide was prepared following the procedure in example 1.

^1H NMR (400 MHz, DMSO- d_6) δ 10.90 (s, 1H), 9.13 (dd, J = 5.0, 1.4 Hz, 1H), 9.01 (d, J = 8.3 Hz, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.42 (dd, J = 9.3, 2.2 Hz, 1H), 8.35 (d, J = 9.2 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.95 (q, J = 4.5 Hz, 1H), 7.61 (s, 1H), 7.60 (d, J = 6.1 Hz, 2H), 7.30 (d, J = 3.7 Hz, 1H). LC/MS (RP- C_{18} , 10-99% CH_3CN /0.05% TFA gradient over 5 min): M/Z 349.0, retention time 2.52 minutes.

Examples 11 through 15: Additional Compounds

The compounds in Table 1 were produced using known methods and those described herein.

Table 1:

Example	Structure	Name	Mass (MH ⁺)	LC RT (min)
11		2-(4-chlorophenyl)-N-(1H-indol-5-yl)thiazole-4-carboxamide	354.2	4.05
12		2-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)thiazole-4-carboxamide	368.0	3.65
13		2-(4-chlorophenyl)-N-(quinolin-6-yl)thiazole-4-carboxamide	366.0	3.34
14		N-(1H-indazol-5-yl)-2-phenylthiazole-4-carboxamide	321.2	3.40
15		N-(quinolin-6-yl)-2-p-tolylthiazole-4-carboxamide	345.8	3.33

LC/MS Conditions: 10-99% CH₃CN/0.05% TFA gradient over 5 minutes, RP-C₁₈. LC RT = compound retention time.

Example 16: Assay for Determining Activation or Inhibition of Bacterial Biofilms

[096] An assay was developed to characterize the efficacy of compounds of formula I at modulating, e.g., disrupting or retarding, bacterial biofilms.

Primary High Throughput Screening Methods

[097] The high throughput screening methods described are based on the ability of bacteria to adhere and accumulate on abiotic or biotic surfaces in 96 or 384-well microplates. The microplates could be made of polystyrene, polypropylene and coated with lysine or other biotic coatings such as bovine serum proteins to aid in adherence. Biofilm quantification was carried out through the use of either the previously reported absorbance dyes (crystal violet or saffranin) followed by ethanolic extraction and quantification (See O'Toole et. al. Mol Microbiol. 1998 May; 28(3):449-61 and WO 02/088298 A1) or the novel biofilm fluorescence dye via the dye thioflavin T (Sigma T-3516). Thioflavin was shown to be non-fluorescent in aqueous solution and became fluorescent in the presence of Staphylococcal biofilm (excitation 430 nM, emission 535 nM). (See provisional application serial number 60/751,790, filed December 20, 2005.)

Production of Stock Cells

[0098] Overnight cultures of *S. epidermidis* RP62A (ATCC35984) grown on TSB (30 g/L BD Bacto™ Tryptic Soy Broth) agar plates at 37° C were harvested via addition of TSB media and scraping of cells from surface of agar plate with plastic spreader. Glycerol was added to the cells to a final concentration of 20% and aliquots frozen at -80° C.

Total Biofilm Assay (*S. epidermidis*)

[0099] An aliquot of RP62A cells described above were thawed at room temperature. The cells were then diluted into TSB media to an OD₆₀₀ of 0.5 (1 cm pathlength). The cells were aliquoted into wells using the Thermo systems multidrop 384 instrument. 384 well plates (Costar TC treated plates (#3712)) received 50 µl aliquots, 96 well (Costar TC Treated (#3902)) received 200 µl aliquots. For compound testing, the compounds were added to the wells prior to addition of cells in DMSO with a final DMSO concentration no higher than 2%. The plates were incubated statically for 20 hours at 37° C in a humidified chamber. Following incubation the OD₆₂₀ of the plates were read with the Spectrafluor Plus to determine effects on growth.

[0100] Half the volume of a well of 0.1 mg/ml Thioflavin T dye ((Sigma) dissolved in water) is added to the wells and incubated at room temp for 10 minutes. The wells are decanted by inverting and gently shaking. The wells are then washed with sterile MilliQ water dispensed with the Multidrop 384 instrument. A single 70 µl wash for the 384 well plates and a 200 µl was for 96 well plates. Following the wash the plates are decanted again and dried on a paper towel. The wells are then read using Spectrafluor Plus using the following settings. (Fluorescence settings – Excitation filter 430 nm, Emission filter 535 nm, Number of flashes 5, Lag time 0 µs, Integration time 40 µs, Gain 70, Bottom read)

Example 12: Assay Results

[0101] The compounds in Examples 1-15 were tested in the assay of Example 16. The results are listed below in Table 2.

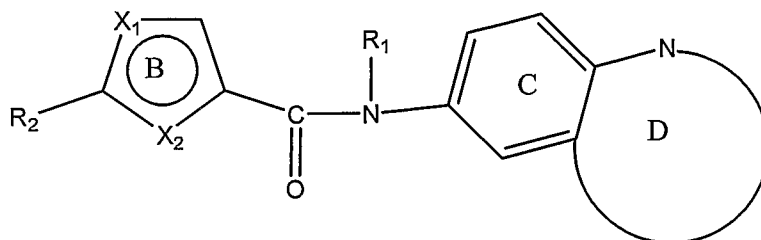
Table 2: ~~Table 2: Activity of various examples~~

Example	Activity (μ M)
1	+++
2	+++
3	++
4	++
5	+
6	+++
7	+
8	+++
9	++
10	+++
11	++
12	++
13	+
14	+
15	+

+++ represents greater activity than ++ and +. ++ represents greater activity than +.

PCT/US2006/029291 What is claimed is:

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

X_1 is O, S, =CH-, =N-, or -NH-;

X_2 is O, S, =N-, -NH-, or =CH-, provided that at least one of X_1 and X_2 is a heteroatom;

Ring B is optionally substituted with (C₁-C₄)alkyl;

Ring C is optionally substituted with 1-2 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, N(R₇)₂ and nitro;

Ring D is a 5 or 6 membered heterocycloaliphatic optionally including an additional hetero atom, or a 5 or 6 membered heteroaryl optionally including an additional hetero atom, each of the 5 or 6 membered heterocycloaliphatic and the 5 or 6 membered heteroaryl is optionally substituted with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, -OR₆, halo, -COOR₆, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)O-R₆ and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R₁ is independently H or C₁-C₄ aliphatic optionally substituted with 1-3 halo, hydroxyl, cyano, alkoxy, and nitro;

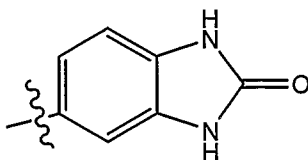
Each R₂ is independently aryl or heteroaryl each optionally substituted with 1-4 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)OR₆, -S(O)₂R₆, -S(O)R₆, -SR₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R₆ is independently H, -(C₁-C₆)alkyl, cycloaliphatic, aryl, heterocycloalkyl, or heteroaryl ring, wherein each of the -(C₁-C₆)alkyl, cycloaliphatic, aryl, heterocyclic, and heteroaryl are optionally substituted with 1-3 substituents selected from halo, hydroxyl, cyano, nitro, OH, and -N(R₇)₂; and

Each R₇ is independently H or an unsubstituted -(C₁-C₆)alkyl;

provided that the compounds do not include the following:

1. N-[4-amino-3-butylquinolin-7-yl]-5-[4-chlorophenyl]-2-furamide; and
2. Compounds in which Rings C and D together form

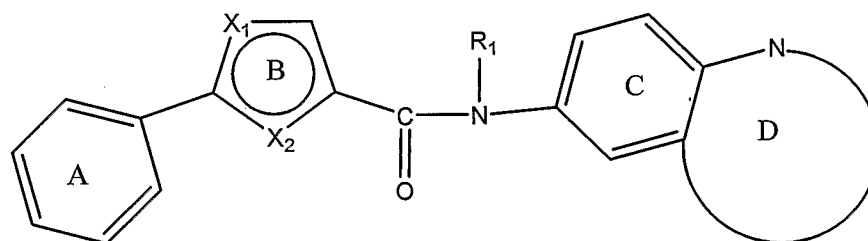


; and

3. N-[2-oxo-benzothiazol-6-yl]-5-[4-chlorophenyl]-3-[2-methylfuramide].

2. The compound of claim 1, wherein R₂ is a 6 membered aryl or heteroaryl ring.
3. The compound of claim 2, wherein R₂ is substituted on the 6 membered ring at either an ortho or para position relative to the attachment between R₂ and Ring B.
4. The compound of claim 3, wherein R₂ is substituted on the 6 membered ring para relative to the attachment between R₂ and Ring B.
5. The compound of claim 1, wherein R₂ is substituted with halogen.
6. The compound of claim 5, wherein R₂ is substituted with chloro.
7. The compound of claim 1, wherein R₂ is substituted with C₁-C₆ aliphatic.
8. The compound of claim 7, wherein Ring A is substituted with methyl.
9. The compound of claim 1, wherein X₁ is S and X₂ is =N-.
10. The compound of claim 9, wherein R₂ is substituted with halogen.
11. The compound of claim 1, wherein R₁ is H.
12. The compound of claim 1, wherein Ring D is a 5 or 6 membered heteroaryl.

13. The compound of claim 12, wherein Ring D includes an additional nitrogen atom.
14. The compound of claim 13, wherein Ring D is substituted with a C₁-C₄ aliphatic.
15. The compound of claim 14, wherein Ring D is substituted with methyl.
16. The compound of claim 1, wherein Ring D is a 5 or 6 membered heterocycloaliphatic.
17. The compound of claim 16, wherein Ring D includes an additional nitrogen atom.
18. The compound of claim 17, wherein Ring D is substituted with a C₁-C₄ aliphatic.
19. The compound of claim 18, wherein Ring D is substituted with methyl.
20. The compound of claim 1, wherein Ring D is substituted with a C₁-C₄ aliphatic.
21. The compound of claim 20, wherein Ring D is substituted with methyl.
22. A compound of the formula II



II

or a pharmaceutically acceptable salt thereof, wherein

X₁ is O, S, =CH-, =N-, or -NH-;

X₂ is O, S, -NH-, =N-, or =CH-, provided that at least one of X₁ and X₂ is a heteroatom;

Ring A is optionally substituted with 1-3 of -COOR₆, -CN, -N(R₆)₂, -OR₆, halo, -C(O)N(R₆)₂, -N(R₆)₂C(O)-R₆, -N(R₆)₂C(O)OR₆, -S(O)₂R₆, -S(O)R₆, -SR₆, and -(C₁-C₆)alkyl optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Ring B is optionally substituted with (C₁-C₄)alkyl;

Ring C is optionally substituted with 1-2 of $-\text{COOR}_6$, $-\text{CN}$, $-\text{N(R}_6)_2$, $-\text{OR}_6$, halo, $-\text{C(O)N(R}_6)_2$, $-\text{N(R}_6)_2\text{C(O)-R}_6$, $-\text{N(R}_6)_2\text{C(O)O-R}_6$, and $-(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1-3 halo, hydroxyl, cyano, $\text{N(R}_7)_2$ and nitro;

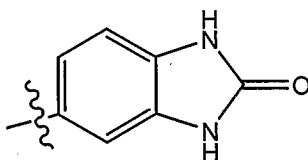
Ring D is a 5 or 6 membered heterocycloaliphatic optionally including an additional hetero atom, or a 5 or 6 membered heteroaryl optionally including an additional hetero atom, each of the 5 or 6 membered heterocycloaliphatic and the 5 or 6 membered heteroaryl is optionally substituted with cycloaliphatic, cycloheteroaliphatic, aryl, heteroaryl, oxo, $-\text{OR}_6$, halo, $-\text{COOR}_6$, $-\text{C(O)N(R}_6)_2$, $-\text{N(R}_6)_2\text{C(O)-R}_6$, $-\text{N(R}_6)_2\text{C(O)O-R}_6$ and $-(\text{C}_1\text{-C}_6)\text{alkyl}$ optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R_1 is independently H or $\text{C}_1\text{-C}_4$ aliphatic optionally substituted with 1-3 halo, hydroxyl, cyano, and nitro;

Each R_6 is independently H, $-(\text{C}_1\text{-C}_6)\text{alkyl}$, cycloaliphatic, aryl, heterocycloalkyl, or heteroaryl ring, wherein each of the $-(\text{C}_1\text{-C}_6)\text{alkyl}$, cycloaliphatic, aryl, heterocyclic, and heteroaryl are optionally substituted with 1-3 substituents selected from halo, hydroxyl, cyano, nitro, OH, and $-\text{N(R}_7)_2$;

Each R_7 is independently H or an unsubstituted $-(\text{C}_1\text{-C}_6)\text{alkyl}$; and provided that the compounds do not include the following:

1. N-[4-amino-3-butylquinolin-7-yl]-5-[4-chlorophenyl]-2-furamide; and
2. Compounds in which Rings C and D together form



; and

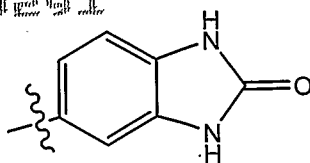
3. N-[2-oxo-benzothiazol-6-yl]-5-[4-chlorophenyl]-3-[2-methylfuramide].

23. The compound of claim 22, wherein X_2 is $=\text{N-}$.
24. The compound of claim 22, wherein Ring A is substituted at either an ortho or para position relative to the attachment between Ring A and Ring B.
25. The compound of claim 22, wherein Ring A is substituted on para relative to the attachment between Ring A and Ring B.

26. The compound of claim 22, wherein Ring A is substituted with halogen.
27. The compound of claim 26, wherein Ring A is substituted with chloro.
28. The compound of claim 1, wherein R₂ is substituted with C₁-C₆ aliphatic.
29. The compound of claim 28, wherein Ring A is substituted with methyl.
30. The compound of claim 22, wherein X₁ is S and X₂ is =N-.
31. The compound of claim 22, wherein R₁ is H.
32. The compound of claim 22, wherein Ring D is a 5 or 6 membered heteroaryl.
33. The compound of claim 32, wherein Ring D includes an additional nitrogen atom.
34. The compound of claim 33, wherein Ring D is substituted with a C₁-C₄ aliphatic.
35. The compound of claim 34, wherein Ring D is substituted with methyl.
36. The compound of claim 22, wherein Ring D is a 5 or 6 membered heterocycloaliphatic.
37. The compound of claim 36, wherein Ring D includes an additional nitrogen atom.
38. The compound of claim 37, wherein Ring D is substituted with a C₁-C₄ aliphatic.
39. The compound of claim 38, wherein Ring D is substituted with methyl.
40. The compound of claim 22, wherein Ring D is substituted with a C₁-C₄ aliphatic.
41. The compound of claim 40, wherein Ring D is substituted with methyl.
42. The compound of claims 1 or 22, wherein X₂ is O.

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43. The compound of claim 42, wherein X_1 is $=CH-$.
44. The compound of claims 1 or 22, wherein X_1 is O.
45. The compound of claim 44, wherein X_2 is $=CH-$.
46. A compound selected from
- 5-(4-chlorophenyl)-N-(quinolin-6-yl)furan-2-carboxamide;
 - 5-(4-chlorophenyl)-N-(1H-indazol-5-yl)furan-2-carboxamide;
 - 2-(4-chlorophenyl)-4-methyl-N-(2-methyl-1H-indol-5-yl)thiazole-5-carboxamide;
 - 5-(pyridin-2-yl)-N-(quinolin-6-yl)thiophene-2-carboxamide;
 - 5-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)furan-2-carboxamide;
 - 2-(4-chlorophenyl)-N-(1H-indol-5-yl)thiazole-4-carboxamide;
 - 2-(4-chlorophenyl)-4-methyl-N-(quinolin-6-yl)thiazole-5-carboxamide;
 - N-(2-methyl-1H-indol-5-yl)-5-(pyridin-2-yl)thiophene-2-carboxamide;
 - N-(1H-benzo[d]imidazol-5-yl)-2-(4-chlorophenyl)thiazole-4-carboxamide;
 - 2-(4-chlorophenyl)-N-(2-methyl-1H-indol-5-yl)thiazole-4-carboxamide;
 - N-(1H-indazol-5-yl)-2-p-tolylthiazole-4-carboxamide;
 - 2-(4-chlorophenyl)-N-(quinolin-6-yl)thiazole-4-carboxamide;
 - 2-(4-chlorophenyl)-N-(1H-indazol-5-yl)thiazole-4-carboxamide;
 - N-(1H-indazol-5-yl)-2-phenylthiazole-4-carboxamide; and
 - N-(quinolin-6-yl)-2-p-tolylthiazole-4-carboxamide.
47. A pharmaceutical composition comprising a pharmaceutical carrier and any of the compounds from claims 1-46.
48. A method of modulating a bacterial biofilm, comprising contacting bacteria with a compound of any of claims 1-46.
49. The method claim 48, wherein the compounds further include the following:
1. N-[4-amino-3-butylquinolin-7-yl]-5-[4-chlorophenyl]-2-furamide; and
 2. Compounds in which Rings C and D together form



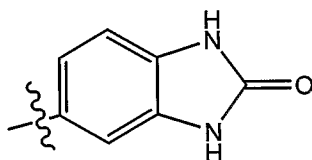
; and

3. N-[2-oxo-benzothiazol-6-yl]-5-[4-chlorophenyl]-3-[2-methylfuramide].

50. An implantable or indwelling device comprising a compound of any of claims 1-46.

51. The implantable device of claim 50, wherein the compounds further include the following:

1. N-[4-amino-3-butylquinolin-7-yl]-5-[4-chlorophenyl]-2-furamide; and
2. Compounds in which Rings C and D together form



; and

3. N-[2-oxo-benzothiazol-6-yl]-5-[4-chlorophenyl]-3-[2-methylfuramide].