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(54) **TRANSCRIPTION FACTOR MODULATING COMPOUNDS AND METHODS OF USE THEREOF**

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ABSTRACT

Substituted benzimidazole compounds useful as anti-infectives that decrease resistance, virulence, or growth of microbes are provided. Methods of using substituted benzimidazole compounds, in, e.g., reducing virulence and infectivity, inhibiting biofilms and treating bacterial infections are also provided.

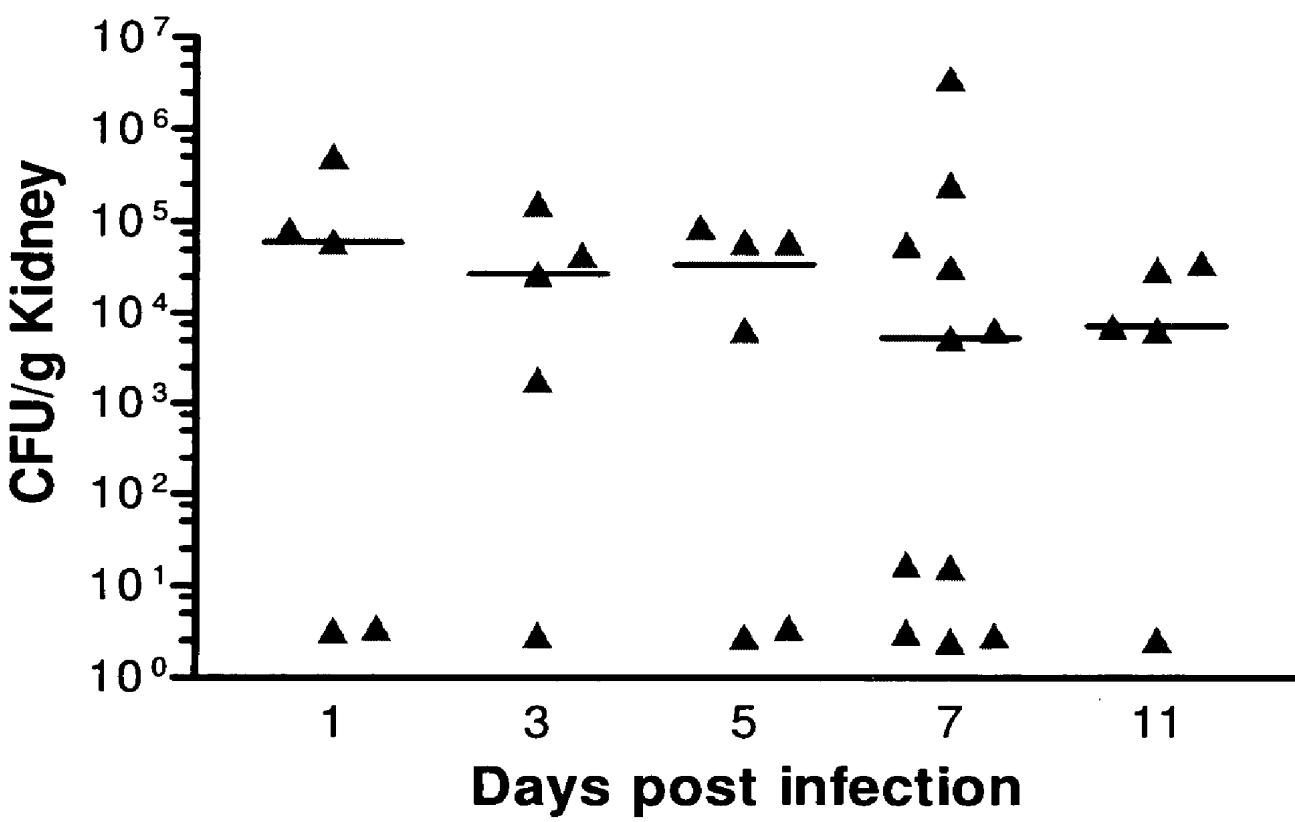


Figure 1

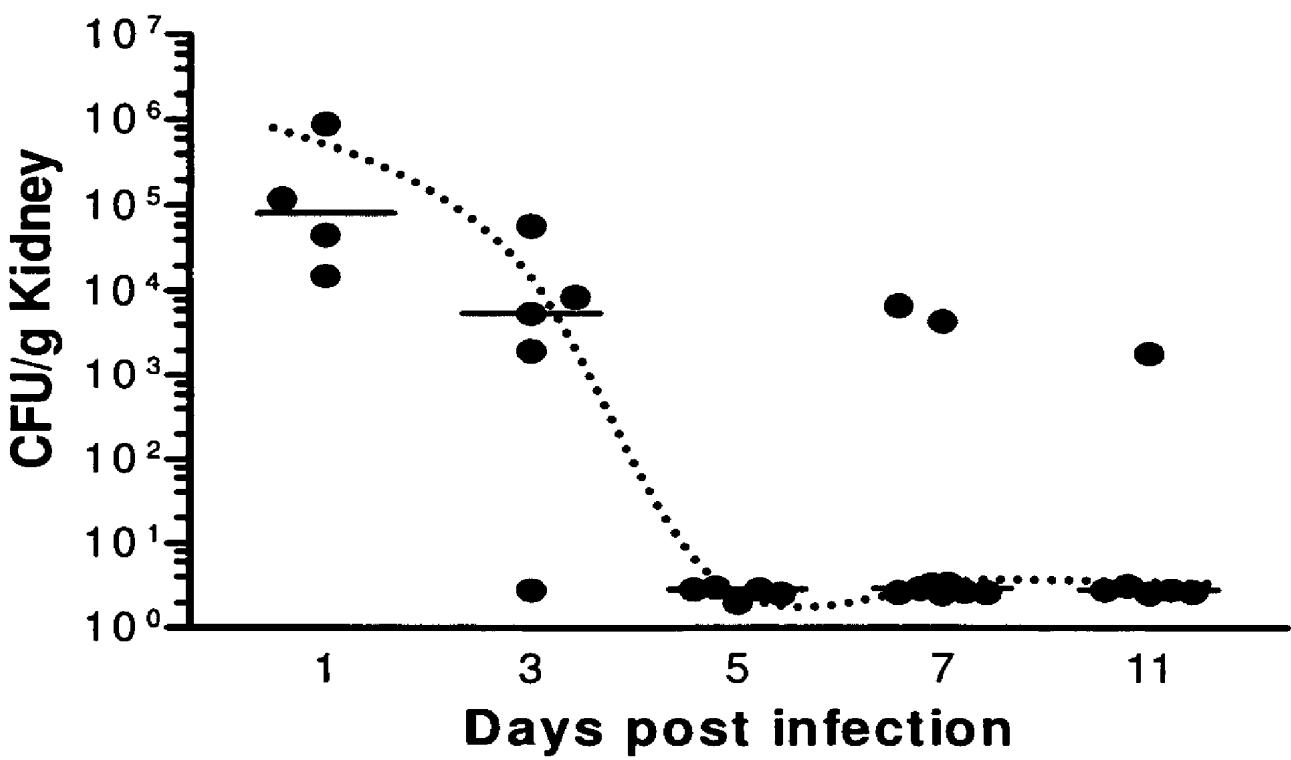


Figure 2

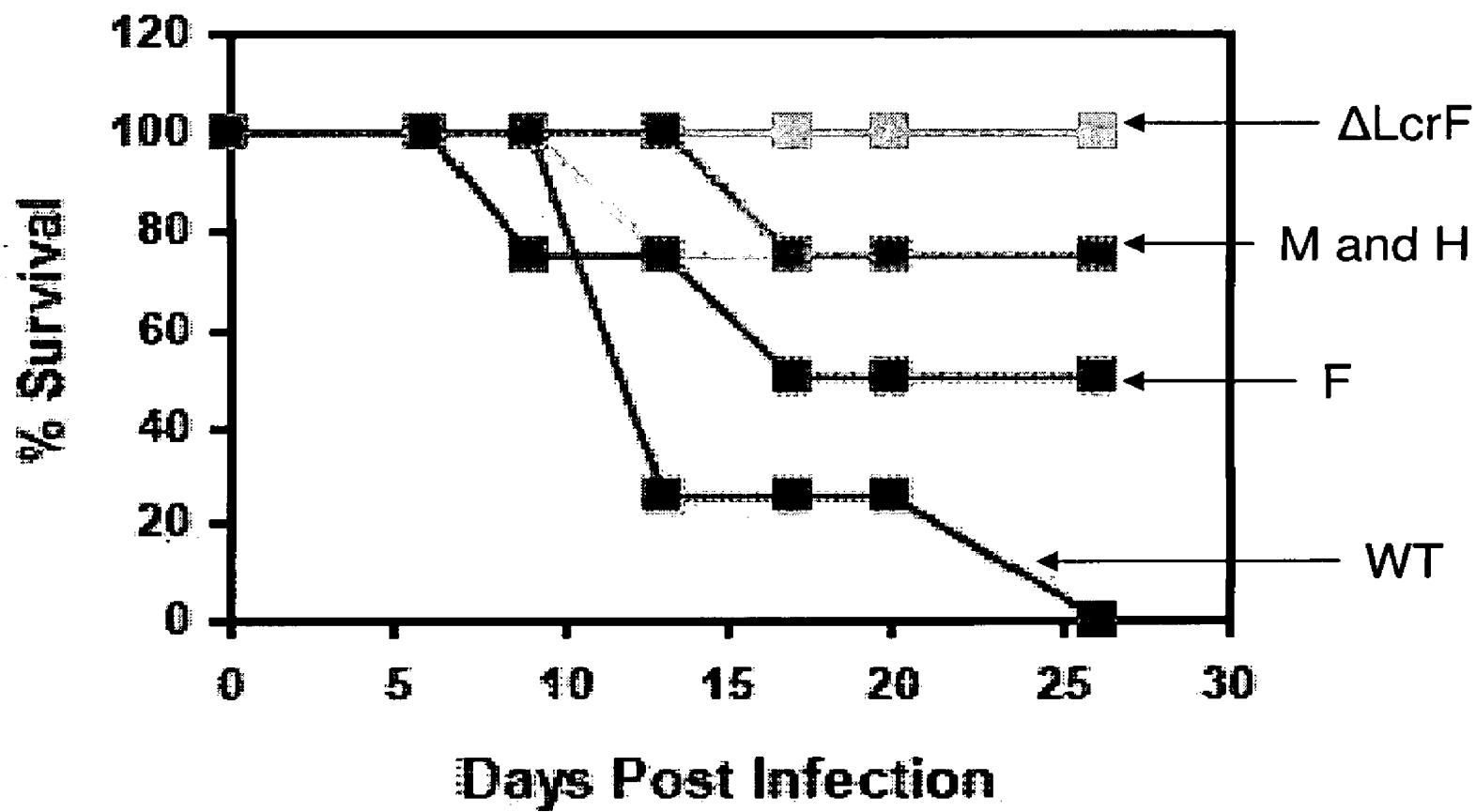


Figure 3

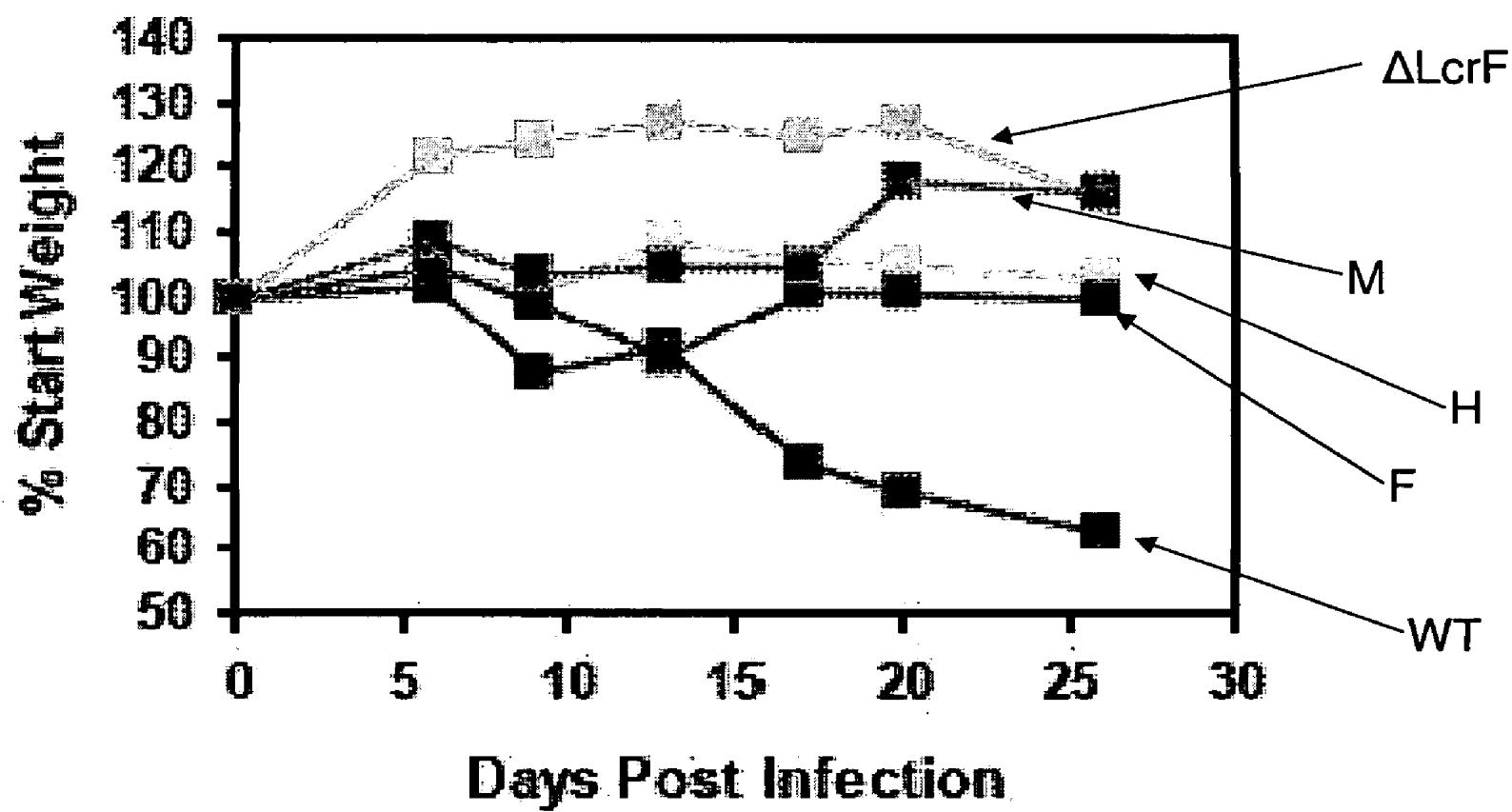


Figure 4

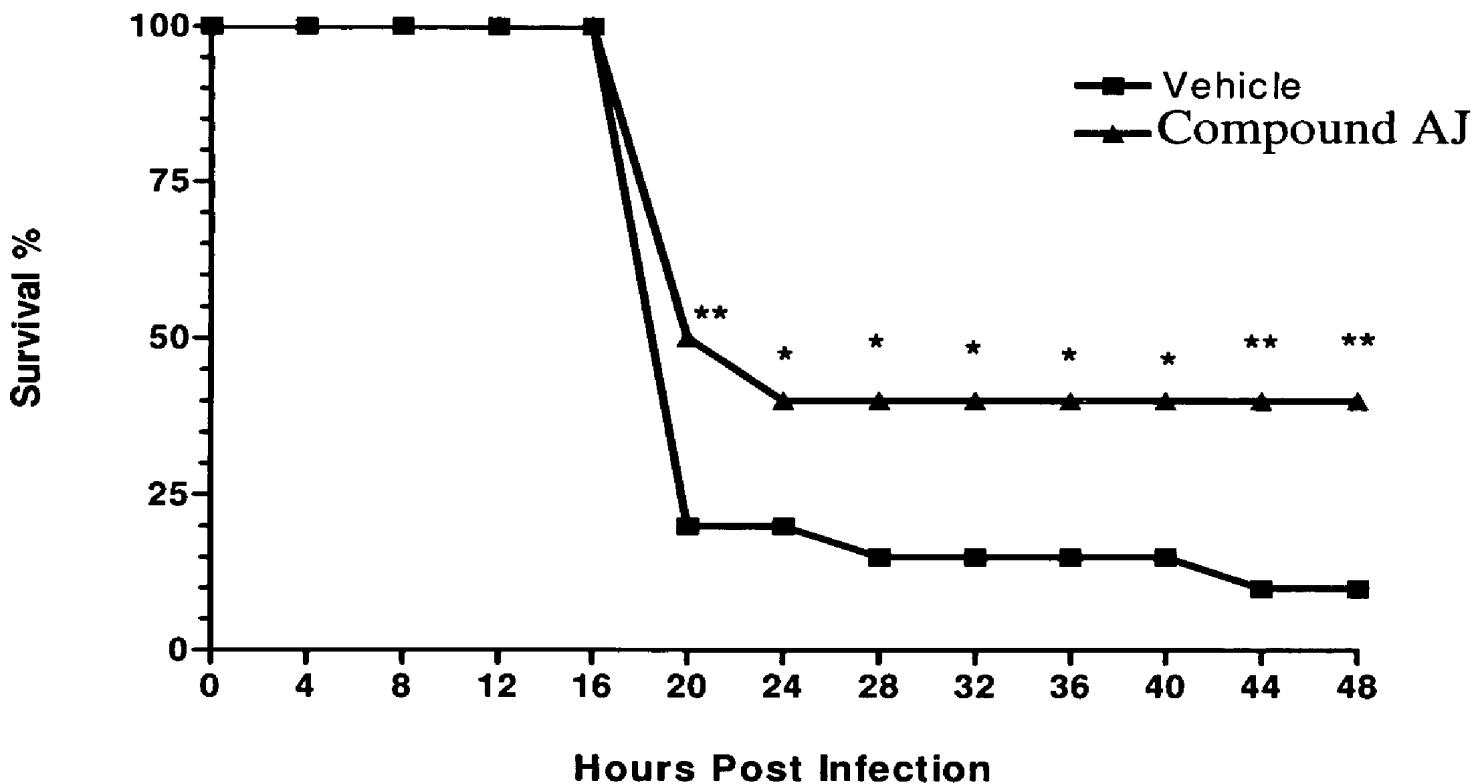


Figure 5

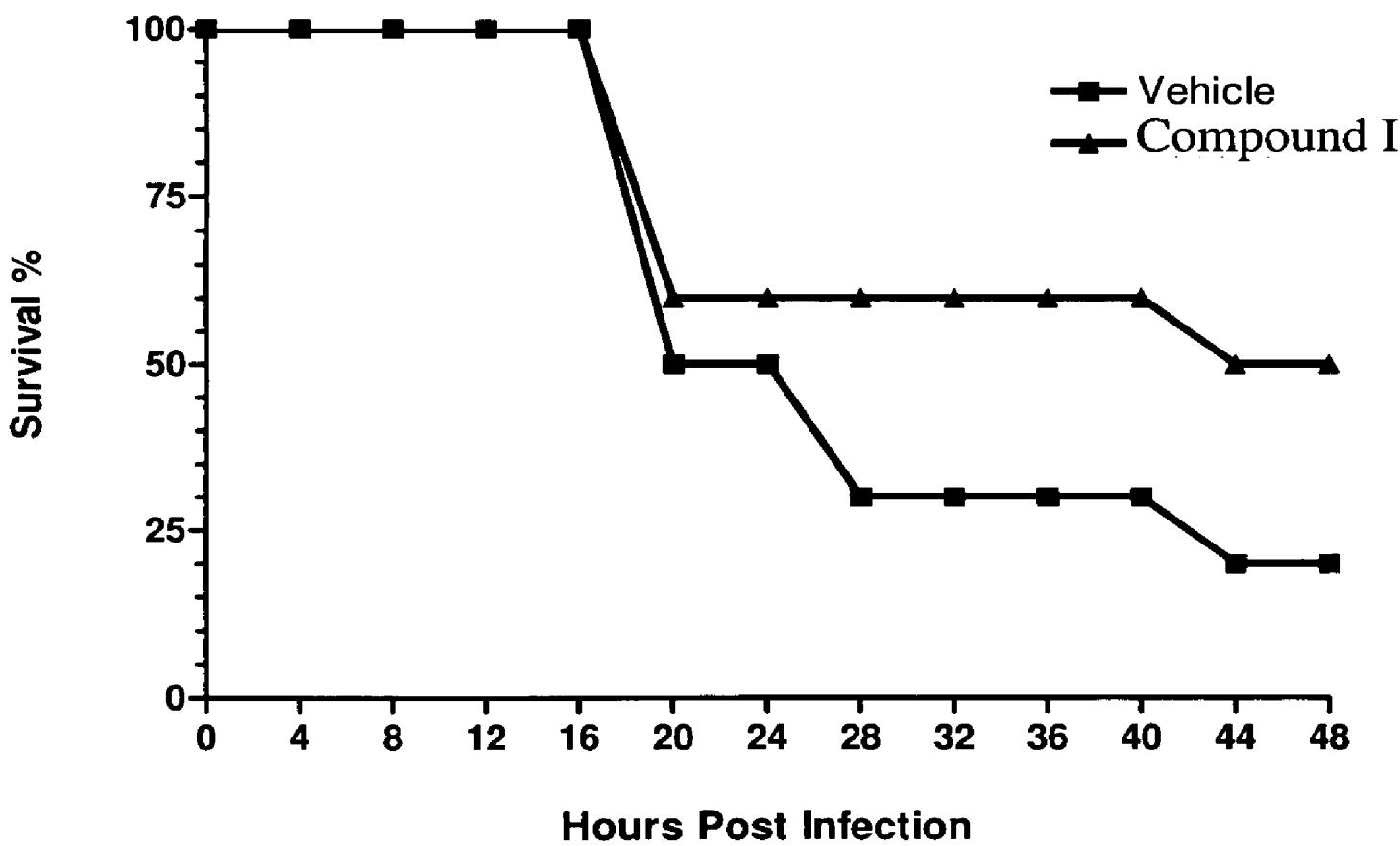


Figure 6

**TRANSCRIPTION FACTOR MODULATING
COMPOUNDS AND METHODS OF USE
THEREOF**

RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application No. 60/920,316, filed on Mar. 27, 2007; U.S. Provisional Patent Application No. 60/931,040, filed on May 21, 2007; U.S. Provisional Patent Application No. 60/934,684, filed on Jun. 15, 2007; U.S. Provisional Patent Application No. 60/973,371, filed on Sep. 18, 2007; U.S. Provisional Patent Application No. 61/016,267, filed on Dec. 21, 2007 and U.S. Provisional Patent Application No. 61/021,136, filed on Jan. 15, 2008. The contents of each of the aforementioned applications are hereby incorporated by reference in their entirety.

**STATEMENT REGARDING FEDERALLY
SPONSORED RESEARCH OR DEVELOPMENT**

[0002] This application was funded, at least in part, by grant NIH NIAID 5R43AI058627-2. The government, therefore, has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Most antibiotics currently used and in development to treat bacterial infections impose selective pressure on microorganisms and have led to the development of widespread antibiotic resistance. Therefore, the development of an alternative approach to treating microbial infections would be of great benefit.

[0004] Multidrug resistance in bacteria is generally attributed to the acquisition of multiple transposons and plasmids bearing genetic determinants for different mechanisms of resistance (Gold et al. 1996. *N. Engl. J. Med.* 335:1445). However, descriptions of intrinsic mechanisms that confer multidrug resistance have begun to emerge. The first of these was a chromosomally encoded multiple antibiotic resistance (mar) locus in *Escherichia coli* (George and Levy, 1983. *J. Bacteriol.* 155:531; George and Levy 1983 *J. Bacteriol.* 155: 541). Mar mutants of *E. coli* arose at a frequency of 10^{-6} to 10^{-7} and were selected by growth on subinhibitory levels of tetracycline or chloramphenicol (George and Levy, supra). These mutants exhibited resistance to tetracyclines, chloramphenicol, penicillins, cephalosporins, puromycin, nalidixic acid, and rifampin (George and Levy, supra). Later, the resistance phenotype was extended to include fluoroquinolones (Cohen et al. 1989. *Antimicrob. Agents Chemother.* 33:1318), oxidative stress agents (Ariza et al. 1994. *J. Bacteriol.* 176: 143; Greenberg et al. 1991. *J. Bacteriol.* 73:4433), and more recently, organic solvents (White et al. 1997. *J. of Bacteriology* 179:6122; Asako, et al. 1997. *J. Bacteriol.* 176:143) and household disinfectants, e.g., pine oil and/or TRICLOSAN® (McMurry et al. 1998. *FEMS Microbiology Letters* 166:305; Moken et al. 1997. *Antimicrobial Agents and Chemotherapy* 41:2770).

[0005] The mar locus consists of two divergently positioned transcriptional units that flank a common promoter/operator region in *E. coli*, *Salmonella typhimurium*, and other *Enterobacteriaceae* (Alekshun and Levy, 1997, *Antimicrobial Agents and Chemother.* 41: 2067). One operon encodes MarC, a putative integral inner membrane protein without any yet apparent function, but which appears to contribute to the Mar phenotype in some strains. The other operon com-

prises marRAB, encoding the Mar repressor (MarR), which binds marO and negatively regulates expression of marRAB (Cohen et al. 1994. *J. Bacteriol.* 175:1484; Martin and Rosner 1995. *PNAS* 92:5456; Seoane and Levy, 1995 *J. Bacteriol.* 177:530), an activator (MarA), which controls expression of other genes on the chromosome, e.g., the mar regulon (Cohen et al. 1994 *J. Bacteriol.* 175:1484; Gambino et. al. 1993. *J. Bacteriol.* 175:2888; Seoane and Levy, 1995 *J. Bacteriol.* 177:530), and a putative small protein (MarB) of unknown function.

[0006] Exposure of *E. coli* to several chemicals, including tetracycline and chloramphenicol (Hachler et al. 1991 *J Bacteriol* 173(17):5532-8; Ariza, 1994, *J Bacteriol*; 176(1):143-8), sodium salicylate and its derivatives (Cohen, 1993, *J Bacteriol*; 175(24):7856-62) and oxidative stress agents (Seoane et al. 1995. *J Bacteriol*; 177(12):3414-9) induces the Mar phenotype. Some of these chemicals act directly at the level of MarR by interacting with the repressor and inactivating its function (Alekshun. 1999. *J. Bacteriol.* 181:3303-3306) while others (antibiotics such as tetracycline and chloramphenicol) appear to induce mar expression by an alternative mechanism (Alekshun. 1999. *J. Bacteriol.* 181:3303-3306) e.g., through a signal transduction pathway.

[0007] Once expressed, MarA activates the transcription of several genes that constitute the *E. coli* mar regulon (Alekshun, 1997, *Antimicrob. Agents Chemother.* 41:2067-2075; Alekshun, 1999, *J. Bacteriol.* 181:3303-3306). With respect to decreased antibiotic susceptibility, the increased expression of the AcrAB/TolC multidrug efflux system (Fralick, 1996, *J. Bacteriol.* 178(19):5803-5; Okusu, 1996 *J Bacteriol*; 178(1):306-8) and decreased synthesis of OmpF (Cohen, 1988, *J. Bacteriol.*; 170(12):5416-22) an outer membrane protein, play major roles. Organic solvent tolerance, however, is attributed to MarA mediating increased expression of AcrAB, TolC, OmpX, and a 77 kDa protein (Aono, 1998, *Extremophiles*; 2(3):239-48; Aono, 1998 *J Bacteriol*; 180(4): 938-44) but is independent of OmpF levels (Asako, 1999, *Appl Environ Microbiol*; 65(1):294-6).

[0008] MarA is a member of the AraC/XylS family of transcriptional activators (Gallegos et al. 1993. *Nucleic Acids Res.* 21:807). There are more than 100 proteins within the AraC/XylS family and a defining characteristic of this group of proteins is the presence of two helix-turn-helix (HTH) DNA binding motifs. Proteins within this family activate many different genes, some of which produce antibiotic and oxidative stress resistance or control microbial metabolism and virulence (Gallegos et al. supra).

[0009] MarA (AraC) family proteins are present in nearly all clinically important bacteria including *Pseudomonas aeruginosa*, *Yersinia* spp., *E. coli* (including enteroaggregative, enterotoxigenic, and enteropathogenic strains), *Klebsiella* spp., *Shigella* spp., *Salmonella* spp., *Vibrio cholerae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* (M.-T. Gallegos et al. 1993. *Nuc. Acids. Res.* 21:807). Inactivation of MarA (AraC) family proteins by mutation attenuates virulence of bacteria in various animal models of infection (P. Casaz et al. 2006. *Microbiol.* 152:3643; G. A. Champion et al. 2003. *Mol. Micro.* 23:323; Y. Flashner et al. 2004. *Infect. Immun.* 72:908; D. S. Bieber et al. 1998. *Sci.* 280:2114).

[0010] MarA, Rob, and SoxS proteins are required for full *E. coli* virulence in a murine ascending pyelonephritis model (P. Casaz et al. 2006. *Microbiol.* 152:3643). Deletion of genes for marA, rob, and soxS from a clinical (intestinal fistula) *E. coli* isolate (KM-D), removed its ability to colonize the kid-

neys. Wild type virulence was restored when the deletion strain (SRM) was complemented with a single chromosomal copy of the *marA*, *soxS*, or *rob* genes.

[0011] The *Y. pseudotuberculosis* MarA (AraC) family protein LcrF (also called VirF in *Y. enterocolitica*) regulates expression of a major virulence determinant, the type III secretion system (TTSS) (G. R. Cornelis and H. Wolf-Watz. 1997. *Mol. Microbiol.* 23:861-867). The TTSS delivers toxins directly into host cells via a needle-like apparatus. Mutants that do not express the TTSS show dramatic attenuation of virulence in whole cell and animal models of infection (G. R. Cornelis and H. Wolf-Watz. 1997. *Mol. Microbiol.* 23:861-867; L. K. Logsdon and J. Mecsas. 2003. *Infect. Immun.* 71:4595-4607; J. Mecsas et al., 2001, *Infect. Immun.*, 69:2779-2787; D. M. Monack et al. 1997. *Proc. Natl. Acad. Sci. U.S.A.* 94:10385-10390). Flashner et al., have recently investigated the effects of lcrF deletion on the pathogenicity of *Y. pestis* in a mouse model of septic infection (Y. Flashner et al. 2004. *Infect. Immun.* 72:908-915). The LD₅₀ (50% lethal dose) of wild type *Y. pestis* in this model is approximately 1 colony forming unit (CFU). When an 1:1 mixture of wild type and lcrF mutant *Y. pestis* was used to infect mice, the competitive index (defined as the ratio of lcrF/wt recovered following infection vs. the ratio of lcrF/wt used for infection) was <10⁻⁷ indicating severe attenuation of the mutant organism.

[0012] The *Pseudomonas aeruginosa* MarA (AraC) family protein ExsA regulates expression of a well established virulence determinant, the type III secretion system (T. L. Yahr et al. 2006. *Mol. Micro.* 62(3):631). Mutants lacking ExsA show dramatically reduced virulence in animal models of *P. aeruginosa* infection (V. J. Finck-Barbancon et al. 1997. *Mol. Micro.* 25(3):547; A. R. Hauser et al. 1998. *Mol. Micro.* 27:807; I. Kudoh et al. 1994. *Am. J. Physiol.* 267:L551; M. A. Laskowski et al. 2004. *Mol. Micro.* 54(4):1090; E. J. Lee et al. 2003. *Invest. Ophthalmol. Vis. Sci.* 44(9):3892; R. S. Smith et al. 2004. *Infect. & Immun.* 72(3):1677). Furthermore, expression of the type III secretion system is correlated with increased severity of disease in clinical pneumonia cases, including ventilator-associated pneumonia (A. R. Hauser et al. 2002. *Crit. Care Med.* 30(3):521; G. S. Schulert et al. 2003. *J. Infect. Dis.* 188:1695; A. Roy-Burman et al. 2001. *J. Infect. Dis.* 183:1767).

SUMMARY OF THE INVENTION

[0013] The present invention pertains, at least in part, to a method for reducing infectivity and/or virulence of a microbial cell by contacting the cell with a transcription factor modulating compound.

[0014] In another embodiment, the present invention pertains, at least in part, to a method for modulating transcription of genes regulated by one or more transcription factors in the MarA (AraC) family. The method includes contacting a transcription factor with a transcription factor modulating compound. Specifically, in one embodiment, the transcription factor is ExsA, LcrF (VirF) or SoxS.

[0015] The present invention also pertains, at least in part, to a method for preventing bacterial growth on a contact lens by administering a composition comprising an acceptable carrier and a transcription factor modulating compound.

[0016] The present invention also pertains, at least in part, to a method for preventing or treating an infection in a patient into which an indwelling device has been implanted (e.g., ventilator-associated pneumonia in patients receiving

mechanical ventilation) by administering a composition comprising a transcription factor modulating compound.

[0017] The present invention also pertains, at least in part, to methods for treating or preventing biofilm formation in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0018] In another embodiment, the present invention pertains, at least in part, to a method for treating or preventing a bacterial infection in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0019] The present invention also pertains, at least in part, to a method for prevention or treatment of a urinary tract infection in a subject by administering to the subject an effective amount of a transcription factor compound.

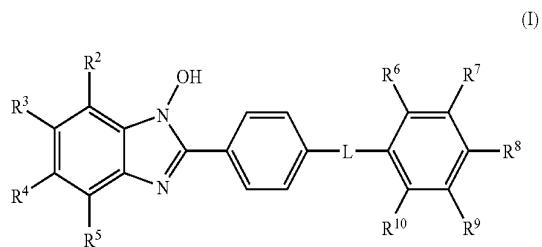
[0020] In yet another embodiment, the invention pertains, at least in part, to a method for treating or preventing pneumonia in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0021] In a further embodiment, the invention pertains, at least in part, to a method for treating burn wounds and corneal ulcers in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0022] In another embodiment, the present invention pertains, at least at part, a method for treating or preventing ascending pyelonephritis or kidney infection in a subject by

[0023] In one embodiment, the present invention pertains, at least in part, to a method for inhibiting a MarA family polypeptide by contacting a Mar family polypeptide with an effective amount of a transcription factor modulating compound.

[0024] In one embodiment, the transcription factor modulating compound is a compound of formula I:



wherein:

[0025] R², R⁴ and R⁵ are each hydrogen;

[0026] R³ is nitro or cyano;

[0027] L is $-\text{NHCO}-$, $-\text{NHCOCO}=\text{CH}-$, $-\text{NHCOCH}_2\text{CH}_2-$, $-\text{NHCOCH}_2-$, $-\text{CH}_2\text{NHCO}-$, or $-\text{C}\equiv\text{C}-$;

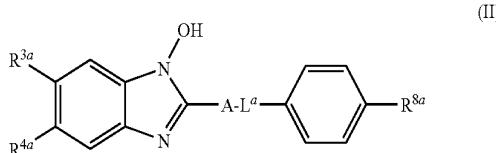
[0028] R⁶ and R¹⁰ are each hydrogen, halogen, alkyl or alkoxy;

[0029] R⁷ and R⁹ are each hydrogen, alkyl or halogen; and
 [0030] R⁸ is hydrogen, hydroxyl, carboxy, alkylcarbonyl,

[0050] K is hydrogen, hydroxyl, carboxy, alkylcarbonylamo, amino, aminosulfonyl, alkylsulfonyl, alkoxy, halogen, alkyl, alkylamino, acylamino, cyano, acyl, heteroaryl or heterocyclic;

[0031] and pharmaceutically acceptable salts thereof.

[0032] In another embodiment, the transcription factor modulating compound is a compound of formula II:



wherein:

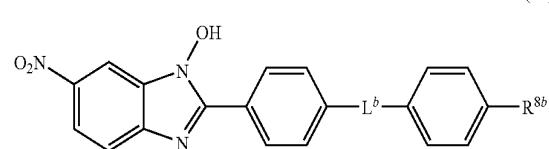
[0033] R^{3a} and R^{4a} are each independently hydrogen, —NO₂, —CN, —F, or —N(CH₃)₂

[0034] A is phenyl or heterocyclic;

[0035] L^a is —NHCO— or —NHCH=CH—; and

[0036] R^{8a} is an electron-donating or an electron-withdrawing group and pharmaceutically acceptable salts thereof.

[0037] In yet another embodiment, the transcription factor modulating compound is a compound of formula III:

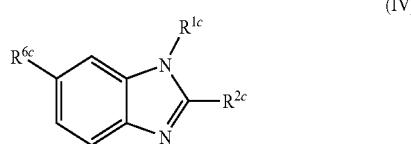


wherein:

[0038] L^b is —NHCO— or —NHCOCH=CH—; and

[0039] R^{8b} is an electron-donating or an electron-withdrawing group and pharmaceutically acceptable salts thereof.

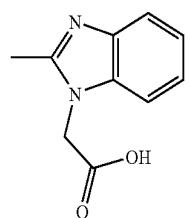
[0040] In one embodiment, the transcription factor modulating compound is a compound of formula IV:



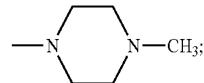
[0041] wherein:

[0042] R^{1c} is —CH₂CO₂H, —OCH₂CO₂Et, —OCH₂CH₂CO₂H, —OCH₂CH₂OH, —OCH₂CN, —OCH₂CH₂CH₃, —OCH₃, —OH, —OCH₂CH₂NH₂ or hydrogen;

[0043] R^{2c} is aryl,

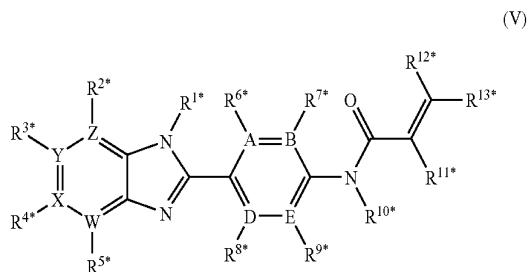


[0044] R^{6c} is hydrogen, —NO₂, H, —COCH₃, —CF₃, —F, —OCH₃, —CO₂H, —CONH₂, —CN, —N(CH₃)₂, —C(CH₃)₃, —SO₂CH₃, —C(CH₃)NOH, or



and pharmaceutically acceptable salts thereof.

[0045] In one embodiment, the transcription factor modulating compound is a compound of formula V:



wherein:

[0046] R^{1*} is hydroxyl, OCOCO₂H; a straight or branched C₁-C₅ alkoxy group; or a straight or branched C₁-C₅ alkyl group;

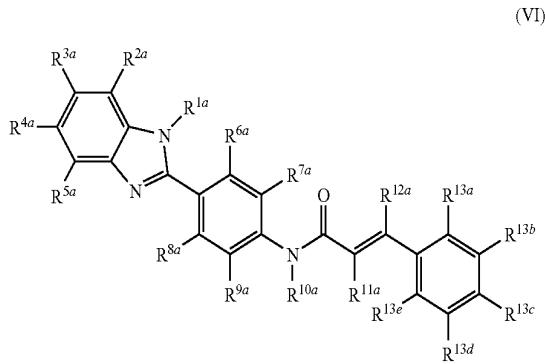
[0047] A, B, D, E, W, X, Y and Z are each independently carbon or nitrogen;

[0048] wherein: R^{2*}, R^{3*}, R^{4*}, R^{5*}, R^{6*}, R^{7*}, R^{8*}, R^{9*} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime or halogen when A, B, D, E, W, X, Y and Z are carbon; or wherein: R^{2*}, R^{3*}, R^{4*}, R^{5*}, R^{6*}, R^{7*}, R^{8*}, R^{9*} are each independently absent or hydroxyl when A, B, D, E, W, X, Y and Z are nitrogen;

[0049] R^{10*}, R^{11*}, R^{12*} and R^{13*} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime or halogen; and pharmaceutically acceptable salts, esters and prodrugs thereof;

[0050] provided that when A, B, C, D, E, W, X, Y and Z are each carbon, one of R^{6*}, R^{7*}, R^{8*}, R^{9*} is not hydrogen.

[0051] In another embodiment, the transcription factor modulating compound is a compound of formula VI:



wherein:

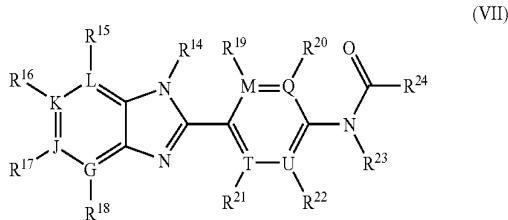
[0052] R^{1a} is hydroxyl, OCOCO_2H , a straight or branched $C_1\text{-}C_5$ alkyloxy group, or a straight or branched $C_1\text{-}C_5$ alkyl group;

[0053] $R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{13b}, R^{13c}, R^{13d}$ and R^{13e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, absent, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen when G, J, K, L, M, Q, T and U are carbon; or $R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}$ and R^{24} are each independently absent or hydroxyl when G, J, K, L, M, Q, T and U are nitrogen;

[0054] provided that when R^{1a} is hydroxyl, R^{3a} is nitro, $R^{2a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{13b}$, and R^{13e} are hydrogen, then R^{13c} is not hydrogen, fluorine, dimethylamino, cyano, hydroxyl, methyl or methoxy; and

[0055] provided that when R^{1a} is hydroxyl, R^{3a} is nitro, $R^{2a}, R^{4a}, R^{5a}, R^{6a}, R^{7a}, R^{8a}, R^{9a}, R^{10a}, R^{11a}, R^{12a}, R^{13a}, R^{13b}$ and R^{13d} are hydrogen, then R^{13c} and R^{13e} are not fluorine.

[0056] In yet another embodiment, the transcription factor modulating compound is a compound of formula VII:



wherein:

[0057] R^{14} is hydroxyl, OCOCO_2H , a straight or branched $C_1\text{-}C_5$ alkyloxy group, or a straight or branched $C_1\text{-}C_5$ alkyl group;

[0058] G, J, K, L, M, Q, T and U are each independently carbon or nitrogen;

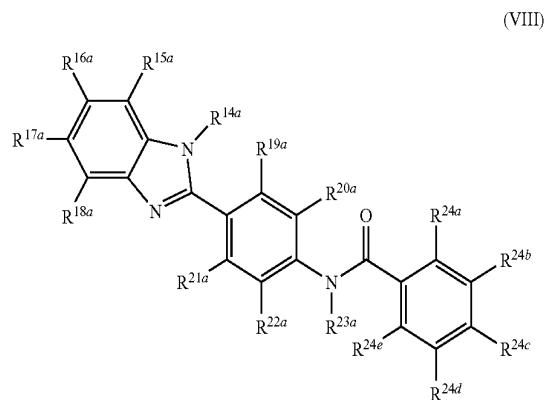
[0059] wherein: $R^1, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}$ and R^{24} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, het-

eroaryl, alkoxy carbonyl, aryloxy carbonyl, heteroaryl oxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, absent, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen when G, J, K, L, M, Q, T and U are carbon; or $R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}$ and R^{24} are each independently absent or hydroxyl when G, J, K, L, M, Q, T and U are nitrogen;

[0060] R^{23} and R^{24} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryl oxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, absent, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and pharmaceutically acceptable salts, esters and prodrugs thereof;

[0061] provided that when G, J, K, L, M, Q, T and U are each carbon, one of $R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}$ and R^{24} , are not hydrogen.

[0062] In a further embodiment, the transcription factor modulating compound is a compound of formula VIII:



wherein:

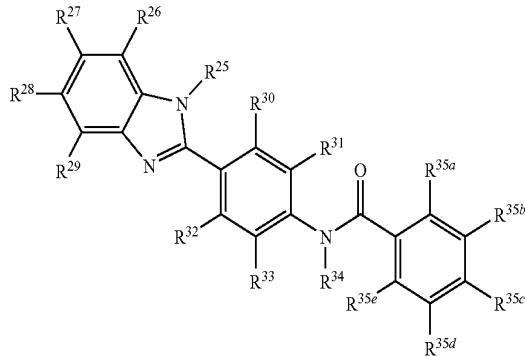
[0063] R^{14a} is hydroxyl, OCOCO_2H , a straight or branched $C_1\text{-}C_5$ alkyloxy group, or a straight or branched $C_1\text{-}C_5$ alkyl group;

[0064] $R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{21a}, R^{22a}, R^{23a}$ and $R^{24a}, R^{24b}, R^{24c}, R^{24d}$ and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, absent, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0065] provided that at least two of $R^{24a}, R^{24b}, R^{24c}, R^{24d}$ and R^{24e} are not hydrogen.

[0066] In another embodiment, the transcription factor modulating compound is a compound of formula IX:

(IX)



wherein:

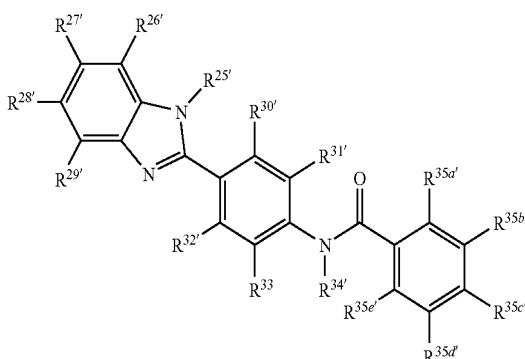
[0067] R²⁵ is hydroxyl, OCOCO₂H, a straight or branched C₁-C₅ alkyloxy group, or a straight or branched C₁-C₅ alkyl group;

[0068] R²⁶, R²⁷, R²⁸, R²⁹, R³⁰, R³¹, R³², R³³, R³⁴, R^{35a}, R^{35b}, R^{35c}, R^{35d}, and R^{35e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0069] provided that at least two of R²⁶, R²⁷, R²⁸ and R²⁹ are not hydrogen.

[0070] In another embodiment, the transcription factor modulating compound is a compound of formula X:

(X)



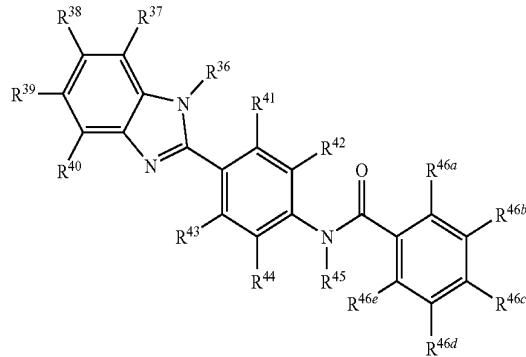
wherein:

[0071] R^{25'} is a substituted straight or branched C₁-C₅ alkyloxy group;

[0072] R^{26'}, R^{27'}, R^{28'}, R^{29'}, R^{30'}, R^{31'}, R^{32'}, R^{33'}, R^{34'}, R^{35a'}, R^{35b'}, R^{35c'}, R^{35d'}, and R^{35e'} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof.

[0073] In one embodiment, the transcription factor modulating compound is a compound of formula (XI):

(XI)



wherein:

[0074] R³⁶ is hydroxyl;

[0075] R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each independently hydrogen, alkyl alketyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryl oxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen;

[0076] R³⁸ is cyano, nitro, oxime, alkyloxime, aryloxime, heteroaryl, amino-oxime, or aminocarbonyl;

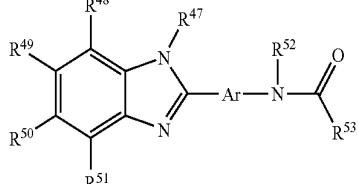
[0077] R^{46c} is hydrogen, acyl, fluorine, pyrimidyl, pyridinyl, cyano, imidazolyl, dialkylaminocarbonyl or dialkylamino; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0078] provided that when R³⁸ is nitro and R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, then R^{46c} is not dialkylamino, acyl or hydrogen; and

[0079] provided that when R³⁸ is cyano and R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, then R^{46c} is not dialkylamino.

[0080] In another embodiment, the transcription factor modulating compound is a compound of formula

(XII)



wherein:

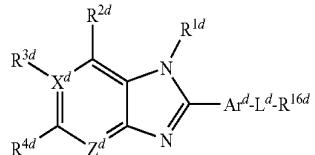
[0081] R⁴⁷ is hydroxyl, OCOCO₂H, a straight or branched C₁-C₅ alkyloxy group, or a straight or branched C₁-C₅ alkyl group;

[0082] R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof.

lamino, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyl oxide, aryloxime, amino-oxime, or halogen; [0083] Ar is aryl; and pharmaceutically acceptable salts, esters and prodrugs thereof.

[0084] In one embodiment, the transcription factor modulating compounds is a compound of formula XIII:

(XIII)



wherein:

[0085] R^{1d} is hydrogen, —OH, —OCH₂-aryl, —CH₂CH₂CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

[0086] R^{2d} is hydrogen or —NR^{2da}R^{2db};

[0087] R^{2da} and R^{2db} are each independently hydrogen, alkyl or aminoalkyl;

[0088] X^d is CR^{3d}, N or NO;

[0089] R^{3d} is absent when X^d is N or NO—NO₂, hydrogen, acyl, halogen, alkoxy, —CO₂H, —CONR^{3da}R^{3db}; cyano, —NR^{3dc}R^{3dd}, alkyl, —SO₂R^{3de}, —C(R^{3df})NOH, heterocyclic or heteroaryl;

[0090] R^{3da} and R^{3db} are each independently hydrogen or alkyl;

[0091] R^{3dc} and R^{3dd} are each independently hydrogen, alkyl or substituted carbonyl;

[0092] R^{3de} and R^{3df} are each independently alkyl or amino;

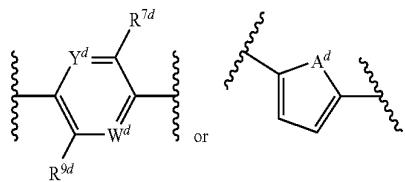
[0093] R^{4d} is hydrogen, alkoxy, —NR^{4da}R^{4db}, alkyl, halogen, —SO₂R^{4dc} or —CO₂H;

[0094] R^{4da} and R^{4db} are each independently hydrogen, alkyl or aminoalkyl;

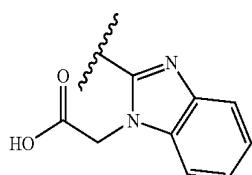
[0095] R^{4dc} is alkyl or amino;

[0096] Z^d is CH, N or NO;

[0097] Ar^d is



when L^d is present or



when L^d and R^{16d} are each absent;

[0098] Y^d is N or CR^{6d};

[0099] W^d is N or CR^{8d};

[0100] R^{6d} is absent when Y^d is N, or hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

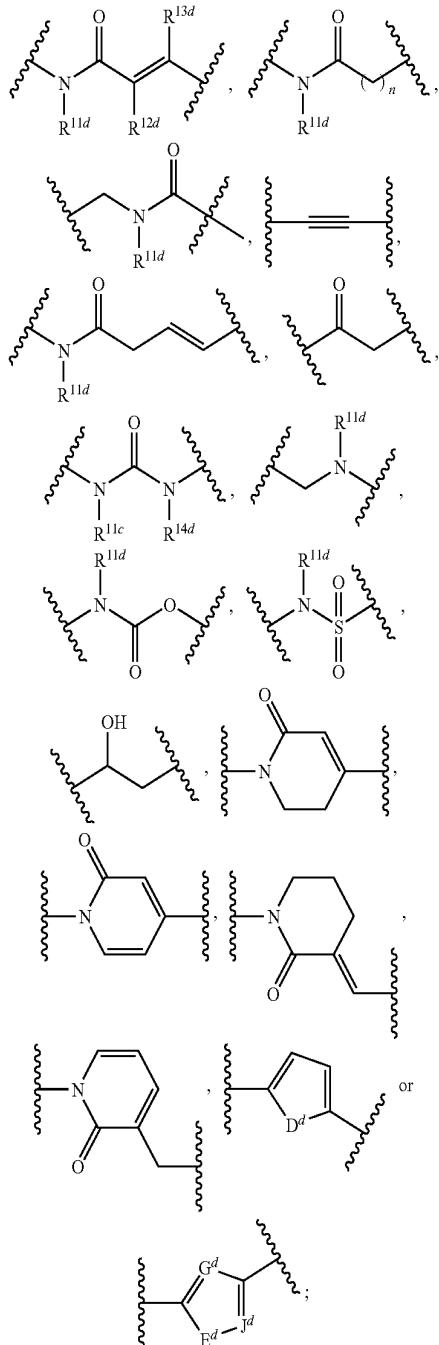
[0101] R^{8d} is absent when W^d is N, or hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

[0102] R^{7d} and R^{9d} are each independently hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

[0103] A^d is O, NR^{10d} or S;

[0104] R^{10d} is hydrogen or alkyl;

[0105] L^d is absent, or L^d is hydrogen or unsubstituted phenyl when R^{16d} is absent, or L^d is —O—, —SO—, —SO₂—, —OCH₂—, —CH₂—, —NR^{15d},



[0106] n is an integer between 0-2;

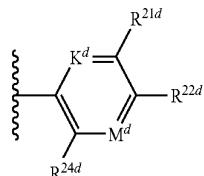
[0107] D^d and E^d are each independently NR^{17d}, O or S

[0108] J^d is N or CR^{18d};

[0109] G^d is N or CR^{19d};

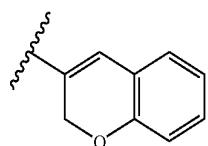
[0110] R^{11d} is hydrogen or alkyl;

- [0111] R^{18d} is absent when J^d is N or hydrogen or alkyl;
 [0112] R^{19d} is absent when G^d is N or hydrogen or alkyl;
 [0113] R^{12d} and R^{13d} are each independently hydrogen, alkyl, halogen or aryl;
 [0114] R^{15d} is hydrogen or alkyl;
 [0115] R^{16d} is hydrogen, alkoxy, hydroxyl, amino, alkyl, $-\text{NO}_2$ or halogen when L^d is absent; or R^{16d} is



when L^d is present;

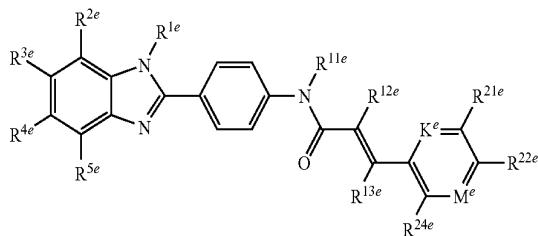
- [0116] K^d is CR^{20d} or N;
 [0117] M^d is CR^{23d} or N;
 [0118] R^{20d} is absent when K^d is N or hydrogen, alkyl, halogen, alkoxy or hydroxyl;
 [0119] R^{21d} is hydrogen, halogen or alkyl;
 [0120] R^{22d} is hydrogen, heteroaryl, halogen, alkoxy, cyano, acyl, $-\text{SO}_2\text{R}^{22da}$ heterocyclic, $-\text{COOH}$, hydroxyl, $-\text{CF}_3$, alkyl, amino, CO_2H , aminocarbonyl or



- [0121] R^{22da} is amino or alkyl;
 [0122] R^{23d} is absent when M^d is N or hydrogen, halogen, alkyl or alkoxy; or R^{22d} and
 [0123] R^{23d} together with the carbon atoms to which they are attached are joined to form a 5- or 6-membered ring;
 [0124] R^{24d} is hydrogen, halogen or alkoxy; and pharmaceutically acceptable salts thereof; and pharmaceutically acceptable salts thereof.

[0125] In one embodiment, the transcription factor modulating compound is a compound of formula XIV:

(XIV)



wherein:

- [0126] R^{1e} is $-\text{OH}$, $-\text{OCH}_2\text{-aryl}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CN}$, $-\text{OCH}_2\text{CH}_2\text{NH}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$, $-\text{OCH}_2\text{COOH}$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{P}(\text{O})(\text{OH})_2$ or $-\text{OCH}_2\text{P}(\text{O})(\text{OCH}_2\text{CH}_3)_2$;

- [0127] $R^{2e}, \text{R}^{4e}, \text{R}^{53}, \text{R}^{11e}, \text{R}^{12e}, \text{R}^{13e}, \text{R}^{21e}, \text{R}^{22e}$, and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkylnyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;
 [0128] R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkylnyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

[0129] R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkylnyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

[0130] R^{3e} is $-\text{NO}_2$, hydrogen, acyl, halogen, alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}^{3da}\text{R}^{3db}$, cyano, $-\text{NR}^{3dc}\text{R}^{3dd}$, alkyl, $-\text{SO}_2\text{R}^{3de}$, $-\text{C}(\text{R}^{3df})\text{NOH}$, heterocyclic or heteroaryl;

[0131] R^{3ea} is alkyl or amino;

[0132] K^e is CR^{20e} or N;

[0133] M^e is CR^{23e} or N; and pharmaceutically acceptable salts thereof.

[0134] The invention also pertains, at least in part, to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a transcription factor modulating compound.

BRIEF DESCRIPTION OF THE DRAWINGS

[0135] FIG. 1 is a graph illustrating the CFU/g of *E. coli* in kidney tissue of CD1 mice inoculated with $\sim 10^7$ CFUs of wild type KM-D *E. coli* (intestinal fistula isolate) over a period of 11 days post infection.

[0136] FIG. 2 is a graph illustrating the CFU/g of *E. coli* in kidney tissue of CD1 mice inoculated with $\sim 10^7$ CFUs of wild type KM-D *E. coli* with null mutations of the marA, rob and soxS genes over a period of 11 days post infection.

[0137] FIG. 3 is a graph illustrating the percent survival of CD1 mice infected with *Y. pseudotuberculosis* dosed with a transcription factor modulating compound of the invention.

[0138] FIG. 4 is a graph illustrating the percent weight loss of CD1 mice infected with *Y. pseudotuberculosis* after dosing with a transcription factor modulating compound of the invention.

[0139] FIGS. 5 and 6 are graphs illustrating the percent survival of Swiss Webster mice infected with *P. aeruginosa* dosed with transcription factor modulating compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0140] The Mar proteins are members of the AraC family of bacterial transcription regulators characterized by two highly conserved helix-turn-helix (HTH) DNA-binding domains. The signaling networks regulating the activity of Mar proteins vary and, while there is high conservation within the DNA binding domains, all Mar proteins bind to distinct DNA sequences in the promoter regions of the genes which they regulate. Mar proteins are present in all clinically important bacteria whose genomes have been examined including *Pseudomonas aeruginosa*, *Yersinia* spp., *E. coli* (including enteroaggregative, enterotoxigenic and enteropathogenic strains), *Klebsiella* spp., *Shigella* spp., *Salmonella* spp., *Vibrio cholerae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*. Mar proteins confer upon bacteria the ability to cause infections, resist antibiotics and adapt to hostile environments. Inactivation of Mar proteins by mutation attenuates the virulence of bacterial pathogens in animal models of infection, but does not affect bacterial growth.

[0141] The invention relates to anti-infective transcription factor modulating compounds that target the virulence and

infectivity of a microbial cell, thus preventing infection or disease in a subject. The invention pertains, at least in part, to a method for reducing the infectivity or virulence of a microbial cell, comprising contacting said cell with a transcription factor modulating compound, e.g. a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2. The term "reducing infectivity" includes decreasing or eliminating the potential of a microbial cell to cause an infection. The term "reducing virulence" includes decreasing or eliminating the ability of a microbial cell to cause disease. Examples of microbial cells, include, but are not limited to *E. coli*, *Y. pseudotuberculosis*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *P. aeruginosa*. A skilled artisan, using routine techniques, would be able to determine whether a microbial cell is infective or virulent.

[0142] In one embodiment, the method of reducing infectivity or virulence of a microbial cell includes reducing the manner in which a microbial cell causes a disease. Without being bound by theory, the methods for reducing infectivity or virulence of a microbial cell may include, for example, the inhibition of the adhesion of a microbial cell to a host cell; the inhibition of the colonization of the microbial cell in the host; the inhibition of the microbial cell from entering host cells and/or entry into the host body; the reduction or elimination of the ability of the microbial cell to produce immune response inhibitors or toxins that may cause tissue damage or damage to the host cells.

[0143] The term "microbe" includes microorganisms that cause disease. For example, in one embodiment, microbes are unicellular and include bacteria, fungi, or protozoa. In another embodiment, microbes suitable for use in the invention are multicellular, e.g., parasites or fungi. In another embodiment, microbes are pathogenic for humans, animals, or plants. In one embodiment, the microbes include prokaryotic organisms. In other embodiments, the microbes include eukaryotic organisms. In a further embodiment, the microbe is antibiotic resistant.

[0144] In one embodiment, microbes against which a transcription factor modulating compound of the invention may be used are bacteria, e.g., Gram negative or Gram positive bacteria. In one embodiment, the microbe includes any bacteria that are shown to become resistant to antibiotics, e.g., display a Mar phenotype or are infectious or potentially infectious. Exemplary bacteria that contain MarA homologs include the following: *E. coli* (e.g., UPEC (uropathogenic) or EPEC (enteropathogenic)), *Salmonella enterica* (e.g., Choleraesuis (septicemia), Enteritidis enteritis, Typhimurium enteritis, Typhimurium (multi-drug resistant)), *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Klebsiella* sp., *Proteus* spp., *Vibrio cholerae*, *Shigella* sp., *Providencia stuartii*, *Neisseria meningitidis*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Bordetella pertussis* and *Bordetella bronchiseptica*.

[0145] Examples of microbes against which a transcription factor modulating compound of the invention may be used include, but are not limited to, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Pseudomonas acidovorans*, *Pseudomonas alcaligenes*, *Pseudomonas putida*, *Stenotrophomonas maltophilia*, *Burkholderia cepacia*, *Aeromonas hydrophilia*, *Escherichia coli*, *Citrobacter freundii*, *Salmonella typhimurium*, *Salmonella typhi*, *Salmonella paratyphi*, *Salmonella enteritidis*, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella sonnei*, *Enterobacter cloacae*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Serratia marcescens*, *Francisella tularensis*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia alcalifaciens*, *Providencia rettgeri*, *Providencia stuartii*, *Acinetobacter calcoaceticus*, *Acinetobacter baumannii*,

Acinetobacter haemolyticus, *Yersinia enterocolitica*, *Yersinia pestis*, *Yersinia pseudotuberculosis*, *Yersinia intermedia*, *Bordetella pertussis*, *Bordetella parapertussis*, *Bordetella bronchiseptica*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Haemophilus haemolyticus*, *Haemophilus parahaemolyticus*, *Haemophilus ducreyi*, *Pasteurella multocida*, *Pasteurella haemolytica*, *Branhamella catarrhalis*, *Helicobacter pylori*, *Campylobacter fetus*, *Campylobacter jejuni*, *Campylobacter coli*, *Borrelia burgdorferi*, *Vibrio cholerae*, *Vibrio parahaemolyticus*, *Legionella pneumophila*, *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Gardnerella vaginalis*, *Bacteroides fragilis*, *Bacteroides distasonis*, *Bacteroides 3452A* homology group, *Bacteroides vulgatus*, *Bacteroides ovalis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides eggerthii*, *Bacteroides splanchnicus*, *Clostridium difficile*, *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium leprae*, *Corynebacterium diphtheriae*, *Corynebacterium ulcerans*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Staphylococcus intermedius*, *Staphylococcus hyicus* subsp. *hyicus*, *Staphylococcus haemolyticus*, *Staphylococcus hominis*, and *Staphylococcus saccharolyticus*.

[0146] In one embodiment, microbes against which a transcription factor modulating compound of the invention may be used are bacteria from the family Enterobacteriaceae. In preferred embodiments, the compound is effective against a bacteria of a genus selected from the group consisting of: *Escherichia*, *Proteus*, *Salmonella*, *Klebsiella*, *Providencia*, *Enterobacter*, *Burkholderia*, *Pseudomonas*, *Aeromonas*, *Haemophilus*, *Yersinia*, *Acinetobacter*, *Neisseria*, and *Mycobacteria*.

[0147] In yet other embodiments, the microbes against which a transcription factor modulating compound of the invention may be used are Gram positive bacteria and are from a genus selected from the group consisting of: *Lactobacillus*, *Azorhizobium*, *Streptomyces*, *Pediococcus*, *Photobacterium*, *Haemophilus*, *Bacillus*, *Enterococcus*, *Staphylococcus*, *Clostridium*, and *Streptococcus*.

[0148] In other embodiments, the microbes against which a transcription factor modulating compound of the invention may be used are fungi. In one embodiment, the fungus is from the genus *Mucor* or *Candida*, e.g., *Mucor racmeosus* or *Candida albicans*.

[0149] In yet other embodiments, the microbes against which a transcription factor modulating compound of the invention may be used are protozoa. In a preferred embodiment the microbe is a malaria or cryptosporidium parasite.

[0150] The term "transcription factor" includes proteins that are involved in gene regulation in both prokaryotic and eukaryotic organisms. Preferably, a transcription factor against which a modulating compound of the invention is effective is present only in a prokaryotic organism. In one embodiment, transcription factors can have a positive effect on gene expression and, thus, may be referred to as an "activator" or a "transcriptional activation factor." In another embodiment, a transcription factor can negatively affect gene expression and, thus, may be referred to as a "repressor" or a "transcription repression factor." Activators and repressors are generally used terms and their functions are discerned by those skilled in the art. In one embodiment, the transcription factor is ExsA, SoxS or LcrF (VirF).

[0151] Some major families of transcription factors found in bacteria include the helix-turn-helix transcription factors (HTH) (Harrison, S. C., and A. K. Aggarwal 1990. *Annual Review of Biochemistry*: 59:933-969) such as AraC, MarA, Rob, SoxS and LysR; winged helix transcription factors (Ga-

jiwala, K. S., and S. K. Burley 2000. 10:110-116), e.g., MarR, Sar/Rot family, and OmpR (Huffman, J. L., and R. G. Brennan 2002. *Curr Opin Struct Biol.* 12:98-106, Martinez-Hackert, E., and A. M. Stock 1997. *Structure.* 5:109-124); and looped-hinge helix transcription factors (Huffman, J. L., and R. G. Brennan 2002 *Curr Opin Struct Biol.* 12:98-106), e.g. the AbrB protein family.

[0152] MarA (AraC) family proteins are present in nearly all clinically important bacteria including *Pseudomonas aeruginosa*, *Yersinia* spp., *E. coli* (including enteroaggregative, enterotoxigenic, and enteropathogenic strains), *Klebsiella* spp., *Shigella* spp., *Salmonella* spp., *Vibrio cholerae*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* (M.-T. Gallegos et al 1993. *Nuc. Acids. Res.* 21:807). MarA (AraC) family proteins confer upon bacteria the ability to cause infections, resist antibiotics, and adapt to hostile environments. Inactivation of MarA (AraC) family proteins by mutation attenuates virulence of bacteria in various animal models of infection (P. Casazza et al. 2006. *Microbiol.* 152:3643; G. A. Champion et al. 2003. *Mol. Micro.* 23:323; Y. Flashner et al. 2004. *Infect. Immun.* 72:908; D. S. Bieber et al. 1998. *Sci.* 280:2114).

[0153] The term “AraC family polypeptide,” “AraC/XylS family polypeptide” or “AraC/XylS family peptide” include an art recognized group of prokaryotic transcription factors which contains more than 100 different proteins (Gallegos et al., (1997) *Micro. Mol. Biol. Rev.* 61: 393; Martin and Rosner, (2001) *Curr. Opin. Microbiol.* 4:132). AraC family polypeptides include proteins defined in the PROSITE (PS) database as profile PS01124. The AraC family polypeptides also include polypeptides described in PS0041, HTH AraC Family 1, and PS01124, and HTH AraC Family 2.

[0154] In an embodiment, the AraC family polypeptides are generally comprised of, at the level of primary sequence, by a conserved stretch of about 100 amino acids, which are believed to be responsible for the DNA binding activity of this protein (Gallegos et al., (1997) *Micro. Mol. Biol. Rev.* 61: 393; Martin and Rosner, (2001) *Curr. Opin. Microbiol.* 4: 132). AraC family polypeptides also may include two helix turn helix DNA binding motifs (Martin and Rosner, (2001) *Curr. Opin. Microbiol.* 4: 132; Gallegos et al., (1997) *Micro. Mol. Biol. Rev.* 61: 393; Kwon et al., (2000) *Nat. Struct. Biol.* 7: 424; Rhee et al., (1998) *Proc. Natl. Acad. Sci. U.S.A.* 95: 10413). The term includes MarA family polypeptides and HTH proteins.

[0155] The term “helix-turn-helix protein,” “HTH protein,” “helix-turn-helix polypeptides,” and “HTH polypeptides,” includes proteins comprising one or more helix-turn-helix domains. Helix-turn-helix domains are known in the art and have been implicated in DNA binding (*Ann Rev. of Biochem.* 1984. 53:293).

[0156] In one embodiment, a helix-turn-helix domain containing protein is a Mar A family polypeptide. The language “MarA family polypeptide” includes the many naturally occurring HTH proteins, such as transcription regulation proteins which have sequence similarities to MarA and which contain the MarA family signature pattern, which can also be referred to as an AraC/XylS signature pattern. MarA family polypeptides have two “helix-turn-helix” domains. This signature pattern was derived from the region that follows the first, most amino terminal, helix-turn-helix domain (HTH1) and includes the totality of the second, most carboxy terminal helix-turn-helix domain (HTH2). (See PROSITE PS00041).

[0157] The MarA family of proteins (“MarA family polypeptides”) represent one subset of AraC/XylS family polypeptides and include proteins like MarA, SoxS, Rob, RamA, AarP, PqrA, etc. The MarA family polypeptides, generally, are involved in regulating resistance to antibiotics, organic solvents, and oxidative stress agents (Alekshun and Levy, (1997) *Antimicrob. Agents. Chemother.* 41: 2067). Like

other AraC/XylS family polypeptides, MarA-like proteins also generally contain two HTH motifs as exemplified by the MarA and Rob crystal structures (Kwon et al., (2000) *Nat. Struct. Biol.* 7: 424; Rhee et al., (1998) *Proc. Natl. Acad. Sci. U.S.A.* 95: 10413). Members of the MarA family can be identified by those skilled in the art and will generally be represented by proteins with homology to amino acids 30-76 and 77-106 of MarA. Preferably, a MarA family polypeptide or portion thereof comprises the first MarA family HTH domain (HTH1) (Brunelle, 1989, *J Mol Biol.* 209(4):607-22). In another embodiment, a MarA polypeptide comprises the second MarA family HTH domain (HTH2) (Caswell, 1992, *Biochem J.* 287:493-509). In a preferred embodiment, a MarA polypeptide comprises both the first and second MarA family HTH domains.

[0158] MarA family polypeptide sequences are “structurally related” to one or more known MarA family members, preferably to MarA. This relatedness can be shown by sequence or structural similarity between two MarA family polypeptide sequences or between two MarA family nucleotide sequences that specify such polypeptides. Sequence similarity can be shown, e.g., by optimally aligning MarA family member sequences using an alignment program for purposes of comparison and comparing corresponding positions. To determine the degree of similarity between sequences, they will be aligned for optimal comparison purposes (e.g., gaps may be introduced in the sequence of one protein for nucleic acid molecule for optimal alignment with the other protein or nucleic acid molecules). The amino acid residues or bases and corresponding amino acid positions or bases are then compared. When a position in one sequence is occupied by the same amino acid residue or by the same base as the corresponding position in the other sequence, then the molecules are identical at that position. If amino acid residues are not identical, they may be similar. As used herein, an amino acid residue is “similar” to another amino acid residue if the two amino acid residues are members of the same family of residues having similar side chains. Families of amino acid residues having similar side chains have been defined in the art (see, for example, Altschul et al. 1990. *J. Mol. Biol.* 215:403) including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan). The degree (percentage) of similarity between sequences, therefore, is a function of the number of identical or similar positions shared by two sequences (i.e., % homology = # of identical or similar positions/total # of positions × 100). Alignment strategies are well known in the art; see, for example, Altschul et al. supra for optimal sequence alignment.

[0159] MarA family polypeptides may share some amino acid sequence similarity with MarA. The nucleic acid and amino acid sequences of MarA as well as other MarA family polypeptides are available in the art. For example, the nucleic acid and amino acid sequence of MarA can be found, e.g., on GeneBank (accession number M96235 or in Cohen et al. 1993. *J. Bacteriol.* 175:1484). In one embodiment, a MarA family polypeptide excludes one or more of XylS, AraC, and MelR. In another embodiment, the MarA family polypeptide is involved in antibiotic resistance. In yet another embodiment, the MarA family polypeptide is selected from the group consisting of: MarA, RamA, AarP, Rob, SoxS, and PqrA.

[0160] Exemplary MarA family polypeptides are shown in Table 1, and at Prosite (PS00041) and include: AarP, Ada, AdaA, AdiY, AfrR, AggR, AppY, AraC, CafR, CelD, CfaD,

CsvR, D90812, EnvY, ExsA, FapR, HrpB, InF, InvF, LcrF, LumQ, MarA, MelR, MixE, MmsR, MsmR, OrfR, Orf_f375, PchR, PerA, PocR, PqrA, RafR, RamA, RhaR, RhaS, Rns, Rob, SoxS, S52856, TetD, TcpN, ThcR, TmbS, U73857, U34257, U21191, UreR, VirF, XylR, XylS, Xys1, 2, 3, 4, Ya52, YbbB, YfiF, YisR, YzcC, and YijO.

TABLE 1

Some Bacterial MarA homologs ^a
Gram-negative bacteria
<i>Escherichia coli</i>
MarA (1)
OrfR (2, 3)
SoxS (4, 5)
AfrR (6)
AraC (7)
CelD (8)
D90812 (9)
FapR (10, 11)
MelR (12)
ORF f375 (13, 14)
RhaR (15, 16, 17)
RhaS (18)
Rob (19)
U73857 (20)
XylR (21)
YijO (22)
<i>Proteus vulgaris</i>
PqrA (23)
<i>Salmonella typhimurium</i>
MarA (24)
InvF (25)
PocR (26)
<i>Klebsiella pneumoniae</i>
RamA (27)
<i>Haemophilus influenzae</i>
Ya52 (28)
<i>Yersinia</i> spp.
CafR (29)
LcrF (30) or VirF (30)
<i>Providencia stuartii</i>
AarP (31)
<i>Pseudomonas</i> spp.
ExsA (32)
MmsR (33)
TmbS (34)
XylS (35)
Xys1, 2, 3, 4 (36, 37)
Cyanobacteria
<i>Synechocystis</i> spp.
LumQ (38)
PchR (38)
Gram-positive bacteria
<i>Lactobacillus helveticus</i>
U34257 (39)
<i>Azorhizobium caulinodans</i>
S52856 (40)
<i>Streptomyces</i> spp.
U21191 (41)
AraL (42)
<i>Streptococcus mutans</i>
MsmR (43)

TABLE 1-continued

Some Bacterial MarA homologs ^a
<i>Pediococcus pentosaceus</i>
RafR (44)
<i>Photobacterium leiognathi</i>
LumQ (45)
<i>Bacillus subtilis</i>
AdaA (46)
YbbB (47)
YifF (48)
YisR (49)
YzcB (50)

^a The smaller MarA homologs, ranging in size from 87 (U34257) to 138 (OrfR) amino acid residues, are represented in boldface. References are given in parentheses and are listed below.

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[0161] The term “transcription factor modulating compound” or “transcription factor modulator” includes compounds which interact with one or more transcription factors, such that the activity of the transcription factor is modulated, e.g., enhanced or inhibited. The term also includes both AraC

family modulating compounds and MarA family modulating compounds (e.g., compounds that modulate transcription factors of the AraC family and compounds that modulate transcription factors of the MarA family, respectively). In another embodiment, the transcription factor modulating compound is a compound which inhibits a transcription factor, e.g., a prokaryotic transcription factor or a eukaryotic transcription activation factor. In one embodiment, the transcription factor modulating compounds modulate the activity of a transcription factor as measured by assays known in the art or LANCE assays such as those described in Example 12. In one embodiment, the transcription factor modulating compound inhibits the binding of a particular transcription factor to its cognate DNA by about 10% or greater, about 40% or greater, about 50% or greater, about 60% or greater, about 70% or greater, about 80% or greater, about 90% or greater, about 95% or greater, or about 100% as compared to the activity in the absence of the transcription factor modulating compound.

[0162] In another embodiment, the transcription factor modulating compound is a MarR family polypeptide inhibitor. In another embodiment, the transcription factor modulating compound is a AraC family polypeptide inhibitor.

[0163] The invention also pertains to a method for preventing bacterial growth on a contact lens. The method includes contacting the contact lenses with a solution of a transcription factor modulating compound, e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2, in an acceptable carrier. The invention also pertains to a solution comprising the compound, packaged with directions for using the solution to clean contact lenses.

[0164] In yet another embodiment, the invention pertains, at least in part, to a method for the prevention or treatment of an infection in a patient into which an indwelling device has been implanted comprising administering a composition comprising a transcription factor modulating compound, e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2. The method includes contacting at least one compound of the invention with a medical indwelling device, such as to prevent or substantially inhibit the formation of a biofilm. Examples of medical indwelling devices include catheters, orthopedic devices, devices associated with endotracheal intubation, devices associated with mechanical ventilation (e.g., a ventilator) and implants.

[0165] In one embodiment, the invention pertains, at least in part, to a method for treating or preventing biofilm formation in a subject, comprising administering to said subject an effective amount of a transcription factor modulating compound, e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2. The biofilm associated states includes disorders which are characterized by the presence or potential presence of a bacterial biofilm and can include, for example, middle ear infections, cystic fibrosis, osteomyelitis, acne, dental cavities, endocarditis, pneumonia and prostatitis. Biofilm is also implicated with, e.g., *Pseudomonas aeruginosa*. Furthermore, the invention also pertains to methods for preventing the formation of biofilms on surfaces or in areas by contacting the area with an effective amount of a transcription factor modulating compound, e.g., a MarA family inhibiting compound, etc. In one embodiment, the biofilm associated state is ventilator associated pneumonia. In yet another embodiment, the invention pertains, at least in part to a method for treating

or preventing pneumonia in a subject where the pneumonia is associated with *Pseudomonas aeruginosa*.

[0166] In another embodiment, the transcription factor modulating compound inhibits biofilm formation, for example, as measured by assays known in the art or the Crystal Violet assay described in Example 11. In one embodiment, the transcription factor modulating compound of the invention inhibits the formation of a biofilm by about 25% or more, 50% or more, 75% or more, 80% or more, 90% or more, 95% or more, 96% or more, 97% or more, 98% or more, 99% or more, 99.9% or more, 99.99% or more, or by 100%, as compared to the formation of a biofilm without the transcription factor modulating compound.

[0167] The term "biofilm" includes biological films that develop and persist at interfaces in aqueous and other environments. Biofilms are composed of microorganisms embedded in an organic gelatinous structure composed of one or more matrix polymers which are secreted by the resident microorganisms. The term "biofilm" also includes bacteria that are attached to a surface in sufficient numbers to be detected or communities of microorganisms attached to a surface (Costerton, J. W., et al. (1987) *Ann. Rev. Microbiol.* 41:435-464; Shapiro, J. A. (1988) *Sci. Am.* 256:82-89; O'Toole, G. et al. (2000) *Annu Rev Microbiol.* 54:49-79).

[0168] In a further embodiment, the invention pertains, at least in part to a method for preventing or treating a bacterial infection in a subject, comprising administering to said subject an effective amount of a transcription factor modulating compound, e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2. The term "bacterial infection" includes states characterized by the presence of bacteria which can be prevented or treated by administering the transcription factor modulating compounds of the invention. The term includes biofilm formation and other infections or the undesirable presence of a bacteria on or in a subject. In one embodiment, the bacterial infection is associated with *Y. pseudotuberculosis* or *P. aeruginosa*. In yet another embodiment, the bacterial infection is associated with burn wounds or corneal ulcers. In another embodiment, the bacterial infection is associated with the implantation of a medical device in a subject (e.g., in the case of mechanical ventilation, endotracheal intubation, catheterization, and the like). In a further embodiment, the bacterial infection is a nosocomial infection.

[0169] In a further embodiment, the invention pertains, at least in part, to a method of treating or preventing pneumonia (e.g., ventilator-associated pneumonia) in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0170] In another embodiment, the invention pertains, at least in part, to a method of inhibiting a MarA family polypeptide by contacting a MarA family polypeptide with an effective amount of a transcription factor modulating compound. Suitable MarA family polypeptides include, but are not limited to, ExsA, LcrF (VirF) or Sox.

[0171] In one embodiment, the invention pertains, at least in part, to a method of treating or preventing burn wounds or corneal ulcers in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0172] In yet another embodiment, the invention pertains, at least in part, to a method for treatment or prevention of a

urinary tract infection in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

[0173] In another embodiment, the invention pertains, at least in part, to a method for treatment or prevention of a kidney infection in a subject by administering to the subject an effective amount of a transcription factor modulating compound.

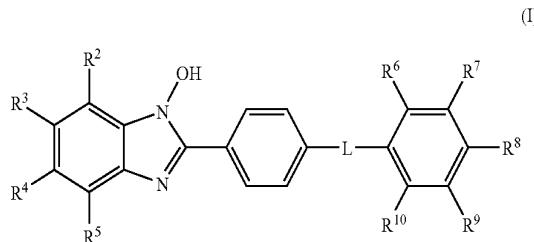
[0174] In an embodiment, the invention pertains, at least in part, to a method for treatment or prevention of acute pyelonephritis in a subject, by administering to the subject an effective amount of a transcription factor modulating compound.

[0175] In one embodiment, the invention pertains, at least in part, to a method of inhibiting bacterial infectivity and/or virulence of a bacteria comprising administering an effective amount of a transcription factor modulating compound.

[0176] In one embodiment, the invention pertains to a method of treating or preventing an infection in a subject by administering an effective amount of a transcription factor modulating compound of the invention. The aforementioned infection includes, but is not limited to, an infection by *Staphylococcus aureus*, *Enterococcus faecium*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Streptococcus pneumoniae*, *Y. pseudotuberculosis* or *P. aeruginosa*.

[0177] In another embodiment, the present invention pertains, at least in part, to a method for modulating transcription of genes regulated by transcription factors in the MarA (AraC) family, comprising contacting a transcription factor with a transcription factor modulating compound. Specifically, in one embodiment, the member of the MarA (AraC) family is ExsA or VirF. AraC family proteins contain a conserved DNA binding domain with two helix-turn-helix motifs. This conserved domain spans 100 amino acids with 17 residues showing a high degree of conservation over that span representing the consensus for the family. The overall similarity of the DNA binding domain is >20% among members of the AraC family. For example, ExsA and VirF are 56% identical, 72% similar across a 266 amino acid overlap and they show 85% identity and 97% similarity in the 100 bp DNA binding domain; VirF and MarA show 23% identity, 42% similarity across a 96 amino acid overlap; and ExsA and MarA show 23% identity, 42% similarity across a 92 amino acid overlap.

[0178] In one embodiment, the transcription factor modulating compounds of the invention are a compound of formula I:



wherein:

[0179] R², R⁴ and R⁵ are each hydrogen;

[0180] R³ is nitro or cyano;

[0181] L is —NHCO—, —NHCOCH=CH—, —NHCOCH₂CH₂—, —NHCOCH₂—, —CH₂NHCO—, or —C≡C—;

[0182] R⁶ and R¹⁰ are each hydrogen, halogen, alkyl or alkoxy;

[0183] R⁷ and R⁹ are each hydrogen, alkyl or halogen; and

[0184] R⁸ is hydrogen, hydroxyl, carboxy, alkylcarbonylamino, amino, aminosulfonyl, alkylsulfonyl, alkoxy, halogen, alkyl, alkylamino, acylamino, cyano, acyl, heteroaryl or heterocyclic;

[0185] and pharmaceutically acceptable salts thereof.

[0186] In one embodiment, the transcription factor modulating compound is a compound of formula I, wherein: R³ is cyano, L is —NHCO—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is acyl.

[0187] In one embodiment, R³ is nitro, L is —CH₂NHCO—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is halogen (e.g., fluorine).

[0188] In another embodiment, R³ is nitro, L is —C≡C—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is halogen (e.g., fluorine). In another embodiment, L is —NHCOCH₂—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen, R⁸ is halogen (e.g., fluorine).

[0189] In yet another embodiment, R³ is nitro, L is —NHCOCH₂CH₂—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is halogen (e.g., fluorine).

[0190] In a further embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen. R⁸ may be, for example, hydrogen, halogen (e.g., fluorine), substituted alkyl (e.g., trifluoromethyl), unsubstituted alkyl (e.g., methyl), alkoxy (e.g., methoxy), carboxy, acyl, heteroaryl (e.g., triazolyl or imidazolyl) or cyano.

[0191] In one embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen and R⁶ is alkoxy (e.g., methoxy).

[0192] In another embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁶, R⁷ or R⁹ are each hydrogen and R⁸ and R¹⁰ are each halogen (e.g., fluorine) or alkoxy (e.g., methoxy).

[0193] In a further embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁶, R⁷ and R¹⁰ are each hydrogen and R⁸ and R⁹ are each halogen (e.g., fluorine).

[0194] In yet another embodiment, R³ is nitro, L is —NHCO—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is hydrogen, alkoxy (e.g., methoxy), halogen (e.g., fluorine), alkyl (e.g., methyl), cyano, acyl, heterocyclic (e.g., imidazolyl, oxazolyl, triazolyl, morpholinyl or pyrazolyl), alkylcarbonylamino (e.g., —NHCOCH₃), hydroxyl, aminosulfonyl (e.g., —SO₂NH₂), alkylsulfonyl (e.g., —SO₂CH₃) or amino (e.g., dialkylamino such as dimethylamino).

[0195] In one embodiment, R³ is nitro, L is —NHCO—, R⁶, R⁸, R⁹ and R¹⁰ are each hydrogen and R⁷ is halogen (e.g., fluorine) or alkyl (e.g., methyl).

[0196] In another embodiment, R³ is nitro, L is —NHCO—, R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen and R⁶ is halogen (e.g., fluorine) or alkyl (e.g., methyl).

[0197] In another embodiment, R⁸ is an electron withdrawing or an electron donating group. In yet another embodiment, R², R³, R⁴, and/or R⁵ comprise a lipophilic group. In another embodiment, R³ is a lipophilic group and R², R⁴ and R⁵ are each hydrogen.

[0198] In one embodiment, the transcription factor modulating compound is a compound of formula I, wherein: R³ is cyano, L is —NHCO—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is acyl.

[0199] In one embodiment, R³ is nitro, L is —CH₂NHCO—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is halogen (e.g., fluorine).

[0200] In another embodiment, R³ is nitro, L is —C≡C—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is halogen (e.g., fluorine). In another embodiment, —NHCOCH₂—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen, R⁸ is halogen (e.g., fluorine).

[0201] In yet another embodiment, R³ is nitro, L is —NHCOCH₂CH₂—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is halogen (e.g., fluorine).

[0202] In a further embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen. R⁸ may be, for example, hydrogen, halogen (e.g., fluorine), substituted alkyl (e.g., trifluoromethyl), unsubstituted alkyl (e.g., methyl), alkoxy (e.g., methoxy), carboxy, acyl, heteroaryl (e.g., triazolyl or imidizolyl) or cyano.

[0203] In one embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen and R⁶ is alkoxy (e.g., methoxy).

[0204] In another embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁶, R⁷ or R⁹ are each hydrogen and R⁸ and R¹⁰ are each halogen (e.g., fluorine) or alkoxy (e.g., methoxy).

[0205] In a further embodiment, R³ is nitro, L is —NHCOCH=CH—, R⁶, R⁷ and R¹⁰ are each hydrogen and R⁸ and R⁹ are each halogen (e.g., fluorine).

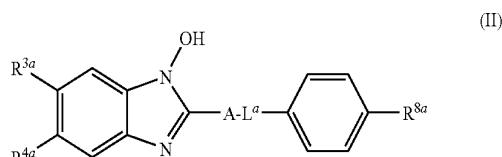
[0206] In yet another embodiment, R³ is nitro, L is —NHCO—, R⁶, R⁷, R⁹ and R¹⁰ are each hydrogen and R⁸ is hydrogen, alkoxy (e.g., methoxy), halogen (e.g., fluorine), alkyl (e.g., methyl), cyano, acyl, heterocyclic (e.g., imidazolyl, oxazolyl, triazolyl, morpholinyl or pyrazolyl), alkyl-carbonylamo (e.g., —NHCOCH₃), hydroxyl, aminosulfonyl (e.g., —SO₂NH₂), alkylsulfonyl (e.g., —SO₂CH₃) or amino (e.g., dialkylamino such as dimethylamino).

[0207] In one embodiment, R³ is nitro, L is —NHCO—, R⁶, R⁸, R⁹ and R¹⁰ are each hydrogen and R⁷ is halogen (e.g., fluorine) or alkyl (e.g., methyl).

[0208] In another embodiment, R³ is nitro, L is —NHCO—, R⁷, R⁸, R⁹ and R¹⁰ are each hydrogen and R⁶ is halogen (e.g., fluorine) or alkyl (e.g., methyl).

[0209] In another embodiment, R⁸ is an electron withdrawing or an electron donating group. In yet another embodiment, R², R³, R⁴, and/or R⁵ comprise a lipophilic group. In another embodiment, R³ is a lipophilic group and R², R⁴ and R⁵ are each hydrogen.

[0210] In one embodiment, the transcription factor modulating compound is a compound of formula II:



wherein:

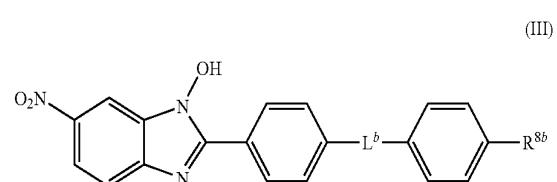
[0211] R^{3a} and R^{4a} are each independently hydrogen, —NO₂, —CN, —F, or —N(CH₃)₂

[0212] A is phenyl or heterocyclic;

[0213] L^a is —NHCO— or —NHCH=CH—; and

[0214] R^{8a} is an electron-donating or an electron-withdrawing group and pharmaceutically acceptable salts thereof.

[0215] In another embodiment, the transcription factor modulating compound is a compound of formula III:

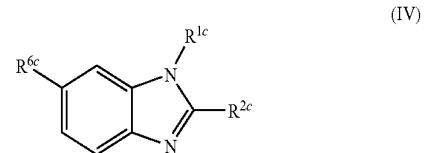


wherein:

[0216] L^b is —NHCO— or —NHCOCH=CH—; and

[0217] R^{8b} is an electron-donating or an electron-withdrawing group and pharmaceutically acceptable salts thereof.

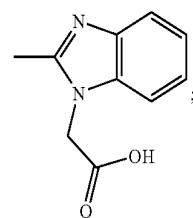
[0218] In one embodiment, the transcription factor modulating compounds of the invention are a compound of formula IV:



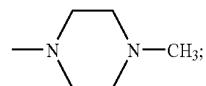
wherein:

[0219] R^{1c} is —CH₂CO₂H, —OCH₂CO₂Et, —OCH₂CH₂CO₂H, —OCH₂CH₂OH, —OCH₂CN, —OCH₂CH₂CH₃, —OCH₃, —OH, —OCH₂CH₂NH₂ or hydrogen;

[0220] R^{2c} is aryl,



[0221] R^{6c} is hydrogen, —NO₂, H, —COCH₃, —CF₃—F, —OCH₃—CO₂H, —CONH₂, —CN, —N(CH₃)₂, —C(CH₃)₃, —SO₂CH₃, —C(CH₃)NOH, or

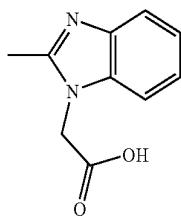


and pharmaceutically acceptable salts thereof.

[0222] In one embodiment, R^{6c} is hydrogen, R^{1c} is —OH or —OCH₂CO₂H and R^{2c} is aryl (e.g., phenyl).

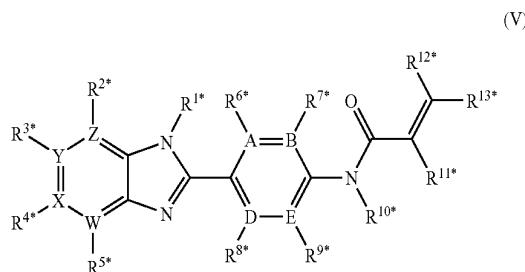
[0223] In another embodiment, R^{6c} is —COCH₃, —CF₃, —F, —OCH₃, —CO₂H, —CONH₂, —CN, —N(CH₃)₂, —C(CH₃)₃, —SO₂CH₃ or —C(CH₃)NOH, R^{1c} is —OH and R^{2c} is aryl (e.g., phenyl or furanyl).

[0224] In yet another embodiment, R^{6c} is —NO₂, R^{1c} is —CH₂CH₂ OH, —OCH₂CO₂ Et, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂CN, —OCH₂CH₂ NH₂ or —OCH₃ and R^{2c} is aryl (e.g., phenyl). Alternatively, R^{1c} is —OH and R^{2c} is



or aryl, such as, for example, furanyl, which may be substituted with phenyl, or phenyl which may be substituted at least one of an ortho, meta or para position. The phenyl may be substituted with alkoxy (e.g., phenoxy or methoxy), hydroxyl, amino, dialkylamino (e.g., dimethylamino), —COOH, halogen (e.g., bromine), aminoalkyl (e.g., aminomethyl), alkylcarbonylamino (e.g., methylcarbonylamino), arylcarbonylamino (e.g., furanycarbonylamino or phenylcarbonylamino) or arylcarbonylaminoalkyl (e.g., phenylcarbonylaminomethyl). The phenylcarbonylamino substituent may be further substituted at least one of an ortho, meta or para position. Examples of suitable substituents include, for example, alkoxy (e.g. methoxy), halogen (e.g., fluorine or chlorine), dialkylamino (e.g., dimethylamino) or alkyl (e.g., t-butyl or methyl).

[0225] In one embodiment, the transcription factor modulating compounds of the invention are a compound of formula V:



wherein:

[0226] R^{1*} is hydroxyl, OCOCO₂H; a straight or branched C₁-C₅ alkoxy group; or a straight or branched C₁-C₅ alkyl group;

[0227] A, B, D, E, W, X, Y and Z are each independently carbon or nitrogen; wherein: R^{2*}, R^{3*}, R^{4*}, R^{5*}, R^{6*}, R^{7*}, R^{8*}, R^{9*} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclcyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime or halogen when A, B, D, E, W, X, Y and Z are carbon; or wherein: R^{2*}, R^{3*}, R^{4*}, R^{5*}, R^{6*}, R^{7*}, R^{8*}, R^{9*} are each independently absent or hydroxyl when A, B, D, E, W, X, Y and Z are nitrogen;

[0228] R^{10*}, R^{11*}, R^{12*} and R^{13*} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclcyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime or halogen; and pharmaceutically acceptable salts, esters and prodrugs thereof;

[0229] provided that when A, B, C, D, E, W, X, Y and Z are each carbon, one of R^{6*}, R^{7*}, R^{8*}, R^{9*} is not hydrogen.

[0230] In one embodiment, A, B, D, E, W, X, Y and Z are each carbon, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is nitro, R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl), R^{6*} is halogen (e.g., fluorine) and R^{7*}, R^{8*} and R^{9*} are hydrogen.

[0231] In another embodiment, A, B, D, E, W, X, Y and Z are each carbon, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is nitro, R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl), R^{6*}, R^{7*} and R^{8*} are hydrogen, and R^{9*} is halogen (e.g., fluorine).

[0232] In a further embodiment, A, B, D, E, W, X, Y and Z are each carbon, R^{1*} is hydroxyl; R^{2*}, R^{4*}, R^{5*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is nitro, R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl), R^{6*}, R^{8*} and R^{9*} are hydrogen, and R^{7*} is substituted alkyl (e.g., morpholinylmethyl) or unsubstituted alkyl (e.g., methyl).

[0233] In yet another embodiment, A, B, D, E, W, X, Y and Z are each carbon, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is nitro, R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl), R^{6*}, R^{7*} and R^{9*} are each hydrogen and R^{8*} is alkoxy (e.g., methoxy).

[0234] In one embodiment, A, B, D, E, W, X, Y and Z are each carbon, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is nitro and R^{13*} is aryl, such as alkyl substituted phenyl (e.g., 4-methylphenyl). In one embodiment, R^{6*}, R^{8*} and R^{9*} are each hydrogen and R^{7*} is alkyl (e.g., ethyl).

[0235] In another embodiment, A, B, D, W, X, Y and Z are each carbon, E is nitrogen, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{6*}, R^{7*}, R^{8*}, R^{10*}, R^{11*} and R^{12*} are hydrogen, R^{3*} is nitro, R^{9*} is absent and R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl or 2,4-fluorophenyl).

[0236] In a further embodiment, B, D, E, W, X, Y and Z are each carbon, A is nitrogen, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{7*}, R^{8*}, R^{9*}, R^{10*}, R^{11*} and R^{12*} are hydrogen, R^{6*} is absent, R^{3*} is nitro and R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl or 2,4-fluorophenyl).

[0237] In yet another embodiment, A, B, D, E, X, Y and Z are each carbon, W is nitrogen, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{7*}, R^{8*}, R^{9*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is nitro, R^{5*} is absent, R^{6*} is halogen (e.g., fluorine) and R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl).

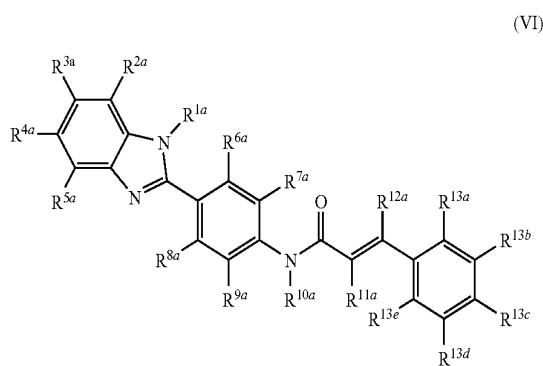
[0238] In one embodiment, A, B, D, E, X, W, and Z are each carbon, Y is nitrogen, R^{1*} is hydroxyl, R^{2*}, R^{4*}, R^{5*}, R^{6*}, R^{7*}, R^{8*}, R^{9*}, R^{10*}, R^{11*} and R^{12*} are each hydrogen, R^{3*} is hydroxyl and R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl).

[0239] In another embodiment, A, B, D, E, X, Y and Z are each carbon, W is nitrogen, R^{1*} is hydroxyl, R^{2*}, R^{3*}, R^{4*},

R^{6*} , R^{7*} , R^{8*} , R^{9*} , R^{10*} , R^{11*} and R^{12*} are each hydrogen, R^{5*} is hydroxyl and R^{13*} is aryl, such as halogen substituted phenyl (e.g., 4-fluorophenyl).

[0240] In a further embodiment, A, B, D, E, W, X and Z are each carbon, Y is nitrogen, R^{1*} is hydroxyl, R^{2*} , R^{4*} , R^{5*} , R^{8*} , R^{7*} , R^{8*} , R^{9*} , R^{10*} , R^{11*} and R^{12*} are each hydrogen, R^{3*} is absent and R^{13*} is aryl (e.g., substituted phenyl, such as 4-fluorophenyl).

[0241] In one embodiment, the transcription factor modulating compounds of the invention include compounds of formula VI:



wherein:

[0242] R^{1*} is hydroxyl, OCOCO₂H, a straight or branched C₁-C₅ alkyloxy group, or a straight or branched C₁-C₅ alkyl group;

[0243] R^{2*} , R^{5*} , R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{5a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13c} , R^{13d} and R^{13e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroarylarnino, oxime, alkylxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0244] provided that when R^{1*} is hydroxyl, R^{3*} is nitro, R^{2*} , R^{4*} , R^{5*} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} , and R^{13e} are hydrogen, then R^{13c} is not hydrogen, fluorine, dimethylamino, cyano, hydroxyl, methyl or methoxy; and

[0245] provided that when R^{1*} is hydroxyl, R^{3*} is nitro, R^{2*} , R^{4*} , R^{5*} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are hydrogen, then R^{13c} and R^{13e} are not fluorine.

[0246] In one embodiment, R^{1*} is hydroxyl and R^{3*} is cyano and R^{2*} , R^{4*} , R^{5*} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13c} , R^{13d} and R^{13e} are each hydrogen.

[0247] In another embodiment, R^{1*} is hydroxyl, R^{3*} is cyano, R^{2*} , R^{4*} , R^{5*} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are each hydrogen and R^{13c} is halogen (e.g., fluorine), alkyl (e.g., methyl) or acyl.

[0248] In yet another embodiment, R^{1*} is hydroxyl and R^{3*} is nitro, R^{2*} , R^{4*} , R^{5*} , R^{6a} , R^{7a} , R^{5a} , R^{9a} , R^{11a} , R^{12a} , R^{13b} , R^{13c} , R^{13d} and R^{13e} are each hydrogen and R^{11a} is aryl (e.g., phenyl), halogen (e.g., fluorine) or alkyl (e.g., methyl).

[0249] In another embodiment, R^{1*} is hydroxyl, R^{3*} is nitro, R^{2*} , R^{2b} , R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{12a} , R^{13a} ,

R^{13b} , R^{13d} and R^{13e} are each hydrogen, R^{13c} is halogen (e.g., fluorine) and R^{11a} is alkyl (e.g., hydroxyethyl or piperazinylmethyl).

[0250] In a further embodiment, R^{1*} is hydroxyl, R^{3*} is nitro, R^{2*} , R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are each hydrogen and R^{13c} is alkyl (e.g., isopropyl), acyl or heteroaryl (e.g., triazole, imidazole or oxazole).

[0251] In one embodiment, R^{1*} is hydroxyl and R^{3*} is nitro, R^{2*} , R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} and R^{13d} are each hydrogen and R^{13c} and R^{13e} are each alkoxy (e.g., methoxy).

[0252] In another embodiment, R^{1*} is hydroxyl and R^{3*} is nitro, R^{2*} , R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{5a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} and R^{13e} are each hydrogen and R^{13b} is alkyl (e.g., alkyl substituted with phosphonic acid or phosphonic acid dialkyl ester) and R^{13e} is halogen (e.g., fluorine).

[0253] In one embodiment, R^{1*} is hydroxyl, R^{3*} is nitro, R^{13c} is halogen (e.g., fluorine), R^{2*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are each hydrogen and R^{4*} is alkylamino (e.g., dimethylamino or dialkylaminoalkylamino), alkyl (e.g., methyl) or alkoxy (e.g., ethoxy, phosphonic acid substituted alkoxy, ether substituted alkoxy, alkylamino substituted alkoxy, or heterocyclic substituted alkoxy, for example, morpholine substituted alkoxy or piperazine substituted alkoxy) or halogen (e.g., fluorine).

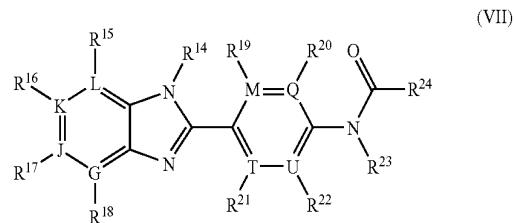
[0254] In yet another embodiment, R^{1*} is hydroxyl, R^{3*} is nitro, R^{13c} is halogen (e.g., fluorine), R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are each hydrogen and R^{2*} is alkylamino (e.g., alkylaminoalkylamino, such as dimethylaminoethylamino).

[0255] In a further embodiment, R^{1*} is a substituted or unsubstituted straight or branched C₁-C₅ alkyloxy group (e.g., phosphonic acid substituted alkoxy or phosphonic acid dialkyl ester alkoxy), R^{3*} is nitro, R^{13c} is halogen (e.g., fluorine), R^{2*} , R^{4*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are each hydrogen.

[0256] In yet another embodiment, R^{1*} is hydroxyl, R^{3*} is nitro, R^{2*} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are hydrogen, R^{13c} is acyl and R^{4*} is alkoxy (e.g., piperazinyl substituted alkoxy or morpholine substituted alkoxy).

[0257] In a further embodiment, R^{1*} is hydroxyl, R^{3*} is heteroaryl (e.g., imidazolyl or pyrazolyl), R^{3a} , R^{4a} , R^{5a} , R^{6a} , R^{7a} , R^{8a} , R^{9a} , R^{10a} , R^{11a} , R^{12a} , R^{13a} , R^{13b} , R^{13d} and R^{13e} are each hydrogen, and R^{3c} is halogen (e.g., fluorine).

[0258] In another embodiment, the transcription factor modulating compounds of the invention include compounds of formula VII:



wherein:

[0259] R^{14} is hydroxyl, OCOCO₂H, a straight or branched C₁-C₅ alkyloxy group, or a straight or branched C₁-C₅ alkyl group;

[0260] G, J, K, L, M, Q, T and U are each independently carbon or nitrogen;

[0261] wherein: R⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³ and R²⁴ are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, absent, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen, when G, J, K, L, M, Q, T and U are carbon; or R⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³ and R²⁴ are each independently absent or hydroxyl when G, J, K, L, M, Q, T and U are nitrogen;

[0262] R²³ and R²⁴ are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, absent, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and pharmaceutically acceptable salts, esters and prodrugs thereof;

[0263] provided that when G, J, K, L, M, Q, T and U are each carbon, one of R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²², R²³ and R²⁴, are not hydrogen.

[0264] In one embodiment, G, J, K, L, M, Q, T and U are each carbon, R¹⁴ is hydroxyl, R¹⁶ is nitro, R²⁴ is aryl (e.g., phenyl, such as acyl substituted phenyl), R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²¹ are hydrogen and R²² is halogen (e.g., fluorine).

[0265] In another embodiment, G, J, K, L, M, Q, T and U are each carbon, R¹⁴ is hydroxyl, R¹⁶ is nitro, R²⁴ is aryl (e.g., phenyl, such as acyl substituted phenyl), R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²¹ and R²² are hydrogen and R²⁰ is alkyl (e.g., methyl or ethyl).

[0266] In yet another embodiment, G, J, K, L, M, Q, T and U are each carbon, R¹⁴ is hydroxyl, R¹⁶ is nitro, R²⁴ is aryl (e.g., phenyl, such as acyl substituted phenyl), R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²² are hydrogen and R²¹ is alkoxy (e.g., methoxy).

[0267] In a further embodiment, G, J, K, L, M, Q, T and U are each carbon, R¹⁴ is hydroxyl, R¹⁶ is nitro, R²⁴ is aryl (e.g., phenyl, such as halogen substituted phenyl, for example, 4-fluorophenyl), R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰ and R²² are hydrogen and R²¹ is halogen (e.g., fluorine) or alkoxy (e.g., methoxy or phosphonic acid substituted alkoxy).

[0268] In one embodiment, G, J, K, L, M, Q, T and U are each carbon, R¹⁴ is hydroxyl, R¹⁶ is nitro, R²⁴ is aryl (e.g., phenyl, such as halogen substituted phenyl, for example, 4-fluorophenyl), R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²¹ and R²² are hydrogen and R²⁰ is alkyl (e.g., ethyl).

[0269] In one embodiment, G, J, K, L, Q, T and U are each carbon, M is nitrogen, R¹⁴ is hydroxyl, R¹⁶ is nitro, R¹⁵, R¹⁷, R¹⁸, R²⁰, R²¹, R²² and R²³ are each hydrogen, R¹⁹ is absent and R²⁴ is aryl, such as, for example, substituted phenyl, and in particular, halogen substituted phenyl (e.g., 4-fluorophenyl) or acyl substituted phenyl (e.g., 4-acyl substituted phenyl).

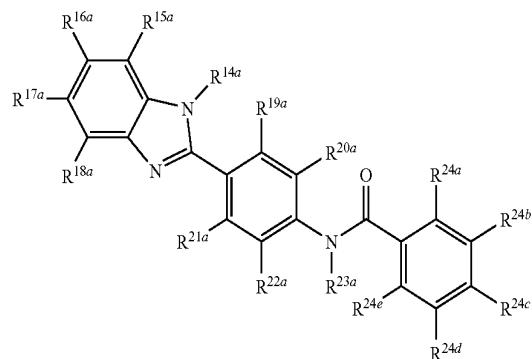
[0270] In another embodiment, G, J, K, L, M, Q and T are each carbon, U is nitrogen, R¹⁴ is hydroxyl, R¹⁶ is nitro, R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, and R²³ are each hydrogen, R²² is absent and R²⁴ is aryl, such as, for example, phenyl such as halogen substituted phenyl (4-fluorophenyl).

[0271] In yet another embodiment, wherein: J, K, L, M, Q, T and U are each carbon, G is nitrogen, R¹⁴ is hydroxyl, R¹⁶ is nitro, R¹⁵, R¹⁷, R¹⁹, R²⁰, R²¹, R²² and R²³ are each hydrogen, R¹⁸ is absent and R²⁴ is aryl, such as, for example, phenyl, which may be substituted with halogen (e.g., 4-fluorophenyl) or acyl (e.g., 4-acylphenyl).

[0272] In one embodiment, G, J, L, M, Q, T and U are each carbon, K is nitrogen, R¹⁴ is hydroxyl, R¹⁶ is absent, R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²¹, R²² and R²³ are each hydrogen and R²⁴ is aryl, such as, for example, phenyl, which may be substituted with halogen (e.g., 4-fluorophenyl).

[0273] In one embodiment, the transcription factor modulating compounds of the invention include compounds of formula VIII:

(VIII)



wherein:

[0274] R^{14a} is hydroxyl, OCOCO₂H, a straight or branched C₁-C₅ alkoxy group, or a straight or branched C₁-C₅ alkyl group;

[0275] R^{15a}, R^{16a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{21a}, R^{22a}, R^{23a} and R^{24a}, R^{24b}, R^{24c}, R^{24d} and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkyl carbonyl, aryl carbonyl, heteroaryl carbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0276] provided that at least two of R^{24a}, R^{24b}, R^{24c}, R^{24d} and R^{24e} are not hydrogen.

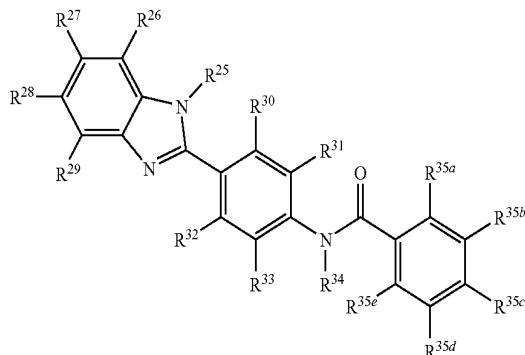
[0277] In one embodiment, R^{14a} is hydroxyl, R^{15a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{21a}, R^{22a}, R^{23a}, R^{24a}, R^{24b} and R^{24e} are hydrogen, R^{16a} is nitro and R^{24c} and R^{24d} are joined to form a ring (e.g., a six membered ring, such as cyclohexanone).

[0278] In another embodiment, R^{14a} is hydroxyl, R^{15a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{21a}, R^{22a}, R^{23a}, R^{24a}, R^{24b} and R^{24e} are hydrogen, R^{16a} is nitro and R^{24c} is halogen (e.g., fluorine) and R^{24d} is halogen (e.g., fluorine), alkyl (e.g., methyl) or alkoxy (e.g., methoxy).

[0279] In yet another embodiment, R^{14a} is hydroxyl, R^{15a}, R^{17a}, R^{18a}, R^{19a}, R^{20a}, R^{21a}, R^{22a}, R^{23a}, R^{24a}, R^{24b} and R^{24e} are hydrogen, R^{16a} is nitro, R^{24c} is halogen (e.g., fluorine) and R^{24e} is alkoxy (e.g., methoxy).

[0280] In another embodiment, the transcription factor modulating compounds of the invention include compounds of formula IX:

(IX)

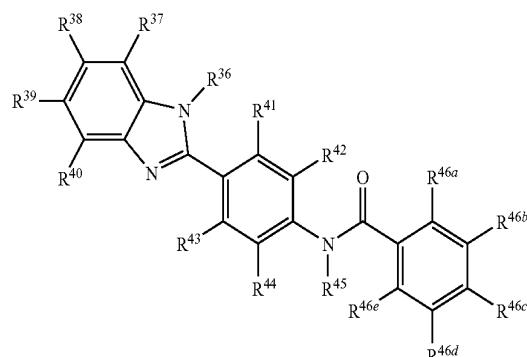


[0287] $R^{26'}, R^{27'}, R^{28'}, R^{29'}, R^{30'}, R^{31'}, R^{32'}, R^{33'}, R^{34'}, R^{35a'}$, $R^{35b'}, R^{35c'}, R^{35d'}$, and $R^{35e'}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino alkylamino, arylamino, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof.

[0288] In one embodiment, $R^{26'}, R^{28'}, R^{29'}, R^{30'}, R^{31'}, R^{32'}, R^{33'}, R^{34'}, R^{35a'}$, $R^{35b'}, R^{35c'}, R^{35d'}$, and $R^{35e'}$ are each hydrogen, $R^{27'}$ is nitro, $R^{35c'}$ is halogen (e.g., fluorine) and $R^{25'}$ phosphonic acid substituted alkoxy, alkyl phosphonic acid substituted alkoxy, carboxylic acid substituted alkoxy or alkylamino substituted alkoxy.

[0289] In a further embodiment, the transcription factor modulating compounds of the invention include compounds of formula XI:

(XI)



wherein:

[0281] R^{25} is hydroxyl, OCOCO_2H , a straight or branched $\text{C}_1\text{-C}_5$ alkoxy group, or a straight or branched $\text{C}_1\text{-C}_5$ alkyl group;

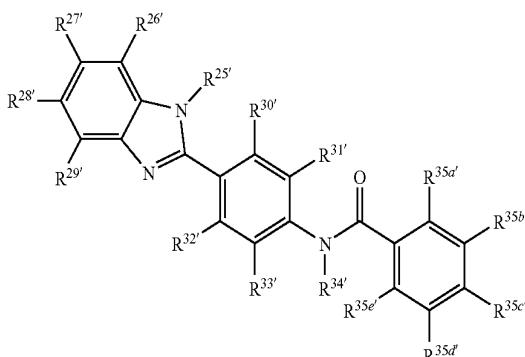
[0282] $R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35a}, R^{35b}, R^{35c}, R^{35d}$, and R^{35e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0283] provided that at least two of R^{26}, R^{27}, R^{28} and R^{29} are not hydrogen.

[0284] In one embodiment, R^{25} is hydroxyl, $R^{26}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, R^{34}, R^{35a}, R^{35b}, R^{35d}$, and R^{35e} are each hydrogen, R^{27} is nitro, R^{28} is alkyl (e.g., methyl) and R^{35c} is acyl or heteroaryl (e.g., oxazole).

[0285] In yet another embodiment, the transcription factor modulating compounds of the invention include compounds of formula X:

(X)



wherein:

[0290] R^{36} is hydroxyl;

[0291] $R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46a}, R^{46b}, R^{46d}$, and R^{46e} are each independently hydrogen, alkyl alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO_2H , cyano, nitro, CONH_2 , heteroaryl amino, oxime, alkyloxime, aryloxime, amino-oxime, or halogen;

[0292] R^{38} is cyano, nitro, oxime, alkyloxime, aryloxime, heteroaryl, amino-oxime, or aminocarbonyl;

[0293] R^{46c} is hydrogen, acyl, fluorine, pyridinyl, pyridinyl, cyano, imidazolyl, dialkylaminocarbonyl or dialkylamino; and esters, prodrugs and pharmaceutically acceptable salts thereof;

[0294] provided that when R^{38} is nitro and $R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46a}, R^{46b}, R^{46d}$, and R^{46e} are each hydrogen, then R^{46c} is not dialkylamino, acyl or hydrogen; and

[0295] provided that when R^{38} is cyano and $R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46a}, R^{46b}, R^{46d}$, and R^{46e} are each hydrogen, then R^{46c} is not dialkylamino.

[0296] In one embodiment, $R^{37}, R^{39}, R^{40}, R^{41}, R^{42}, R^{43}, R^{44}, R^{45}, R^{46a}, R^{46b}, R^{46d}$, and R^{46e} are each hydrogen, and R^{38} is cyano and R^{46c} is acyl, fluorine, cyano or imidazolyl.

wherein:

[0286] $R^{25'}$ is a substituted straight or branched $\text{C}_1\text{-C}_5$ alkoxy group;

[0297] In another embodiment, R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, and R³⁸ is amino-oxime and R^{46c} is fluorine.

[0298] In a further embodiment, R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, and R³⁸ is nitro and R^{46a} is pyrazinyl, pyridinyl or dialkylaminocarbonyl (e.g., dimethylaminocarbonyl).

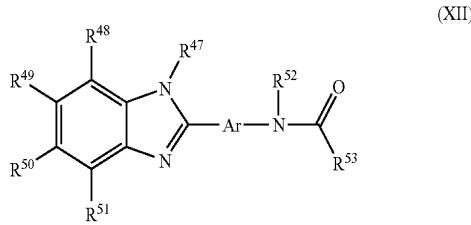
[0299] In another embodiment, R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, and R³⁸ is aminocarbonyl and R^{46c} is halogen (e.g., fluorine).

[0300] In one embodiment, R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, and R³⁸ is oxime and R^{46c} is dialkylamino (e.g., dimethylamino).

[0301] In another embodiment, R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46c}, R^{46d}, and R^{46e} are each hydrogen, and R³⁸ is nitro and R^{46a} is hydroxyl.

[0302] In another embodiment, R³⁷, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R^{46a}, R^{46b}, R^{46d}, and R^{46e} are each hydrogen, and R³⁸ is heteroaryl (e.g., imidazolyl or pyrazolyl) and R^{46c} is acyl.

[0303] In one embodiment, the transcription factor modulating compounds of the invention include compounds of formula XII:



wherein:

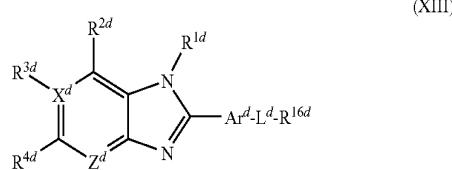
[0304] R⁴⁷ is hydroxyl, OCOCO₂H, a straight or branched C₁-C₅ alkyloxy group, or a straight or branched C₁-C₅ alkyl group;

[0305] R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, alkoxy, aryloxy, heteroaryloxy, alkoxy carbonyl, aryloxycarbonyl heteroaryloxycarbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, acyl, acylamino, amino, alkylamino, arylamino, CO₂H, cyano, nitro, CONH₂, heteroaryl amino, oxime, alkyl oxime, aryloxime, amino-oxime, or halogen;

[0306] Ar is aryl; and pharmaceutically acceptable salts, esters and prodrugs thereof.

[0307] In one embodiment, R⁴⁷ is hydroxyl, R⁴⁸, R⁵⁰, R⁵¹ and R⁵² are each hydrogen, Ar is furanyl, and R⁵³ is alkenyl, which may be substituted with phenyl, such as, for example, halogen substituted phenyl (e.g., fluorophenyl).

[0308] In one embodiment, the transcription factor modulating compounds is a compound of formula XIII:



wherein:

[0309] R^{1d} is hydrogen, —OH, —OCH₂-aryl, —CH₂CH₂CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

[0310] R^{2d} is hydrogen or —NR^{2da}R^{2db};

[0311] R^{2da} and R^{2db} are each independently hydrogen, alkyl or aminoalkyl;

[0312] X^d is CR^{3d}, N or NO;

[0313] R^{3de} is absent when X^d is N or NO—NO₂, hydrogen, acyl, halogen, alkoxy, —CO₂H, —CONR^{3da}R^{3db}; cyano, —NR^{3dc}R^{3dd}, alkyl, —SO₂R^{3de}, —C(R^{3df})NOH, heterocyclic or heteroaryl;

[0314] R^{3da} and R^{3db} are each independently hydrogen or alkyl;

[0315] R^{3dc} and R^{3dd} are each independently hydrogen, alkyl or substituted carbonyl;

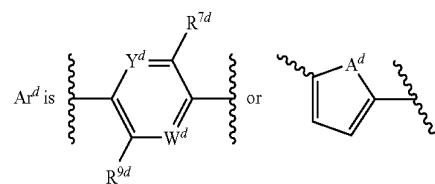
[0316] R^{3de} and R^{3df} are each independently alkyl or amino;

[0317] R^{4d} is hydrogen, alkoxy, —NR^{4da}R^{4db}, alkyl, halogen, —SO₂R^{4d} c or —CO₂H;

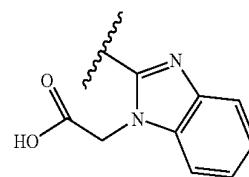
[0318] R^{4da} and R^{4db} are each independently hydrogen, alkyl or aminoalkyl;

[0319] R^{4dc} is alkyl or amino;

[0320] Z^d is CH, N or NO;



when L^d is present or



when L^d and R^{16d} are each absent;

[0321] Y^d is N or CR^{6d}

[0322] W^d is N or CR^{8d}

[0323] R^{6d} is absent when Y^d is N, or hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

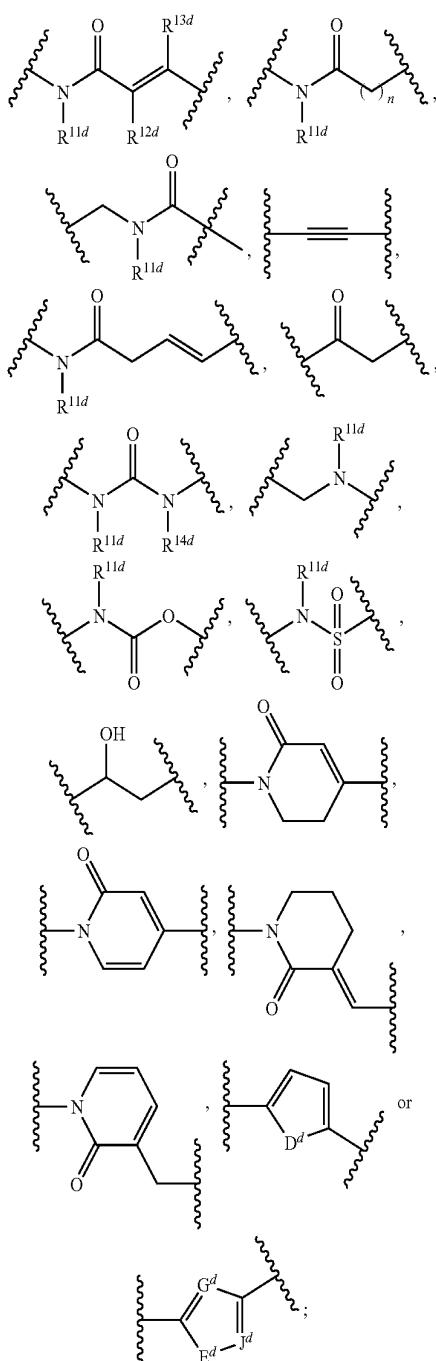
[0324] R^{8d} is absent when W^d is N, or hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

[0325] R^{7d} and R^{9d} are each independently hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

[0326] A^d is O, NR^{10d} or S;

[0327] R^{10d} is hydrogen or alkyl;

[0328] L^d is absent, or L^d is hydrogen or unsubstituted phenyl when R^{16d} is absent, or L^d is —O—, —SO—, —SO₂—, —OCH₂—, —CH₂—, —NR^{15d},



[0329] n is an integer between 0-2;

[0330] D^d and E^d are each independently NR^{17d}; Q or S

[0331] I^d is N or CR^{1a}.

[033?]
G^d is N or CR^{19d}.

[0332] G^- is N or CR_2^- ;

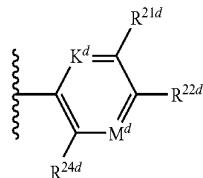
[0333] R^{11a} is hydrogen or alkyl;
 [0334] R^{18d} is absent when J^d is N or hydrogen, or alkyl;

[0334] R^{18d} is absent when J^d is N or hydrogen or alkyl;
 [0335] R^{19d} is absent when C^d is N or hydrogen or all-1-

[0335] R^{19d} is absent when G^d is N or hydrogen or alkyl;
 [0336] R^{12d} and R^{13d} are each independently hydrogen,

alkyl, halogen or aryl;

[0338] R^{16d} is hydrogen, alkoxy, hydroxyl, amino, alkyl, $-NO_2$ or halogen when L^d is absent; or R^{16d} is



when L^d is present;

[0339] K^d is CR^{20d} or N;

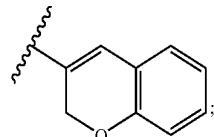
[0340] M^d is CR^{23d} or N;

[0341] R^{20d} is absent when K^d is N or hydrogen, alkyl, halogen, alkoxy or hydroxyl;

[0342] R^{21d} is hydrogen, halogen or alkyl;

[0343] R^{22d} is hydrogen, heteroaryl, halogen, alkoxy, cyano, acyl, $-\text{SO}_2\text{R}^{22da}$ heterocyclic, $-\text{COOH}$, hydroxyl,

—CF₃, alkyl, amino, CO₂H, aminocarbonyl or



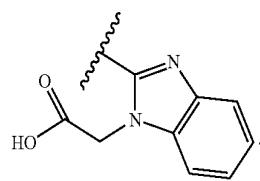
[0344] R^{22da} is amino or alkyl;

[0344] R^{23d} is absent or unity;
 [0345] R^{23d} is absent when M^d is N or hydrogen, halogen, alkyl or alkoxy; or R^{22d} and

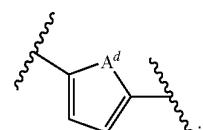
[0346] R^{23d} together with the carbon atoms to which they are attached are joined to form a 5- or 6-membered ring;

[0347] R^{24d} is hydrogen, halogen or alkoxy; and pharmaceutically acceptable salts thereof; and pharmaceutically acceptable salts thereof.

[0348] In one embodiment, L^d and R^{16d} are absent; X^d is CR^{3d} ; Z^d is CH ; R^{2d} and R^{4d} are hydrogen; R^{1d} is $-OH$; R^{3d} is $-NO_2$ and Ar^d is

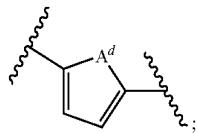


[0349] In another embodiment, Ar^d is



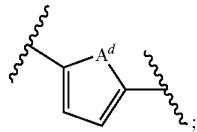
A^d is O; X^d is CR^{3d}; Z^d is CH and R^{2d} and R^{4d} are each hydrogen; R^{1d} is —OH; L^d is hydrogen; R^{3d} is —CONR^{3da}R^{3db} or —NO₂; and R^{3da} and R^{3db} are each hydrogen.

[0350] In one embodiment, Ar^d is



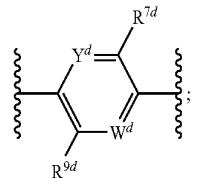
A^d is O; X^d is CR^{3d} ; Z^d is CH and R^{2d} and R^{4d} are each hydrogen; R^{1d} is —OH; L^d is hydrogen; R^{3d} is —NO₂; L^d is —CH₂— and R^{16d} is hydrogen.

[0351] In one embodiment, Ar^d is



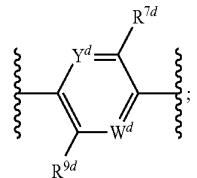
A^d is O; X^d is CR^{3d} ; Z^d is CH and R^{2d} and R^{4d} are each hydrogen; R^{1d} is —OH; L^d is hydrogen; R^{3d} is —NO₂. Alternatively, L^d is unsubstituted phenyl and R^{16d} is hydrogen.

[0352] In one embodiment, Ar^d is



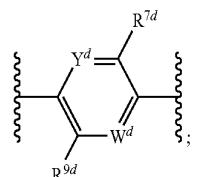
L^d is hydrogen; X^d is CR^{3d} ; Y^d is CR^{6d} and W^d is CR^{8d} ; R^{2d} and R^{4d} are each hydrogen; Z^d is N; R^{3d} is hydrogen and R^{1d} is —OCH₂-aryl (e.g., in which aryl is phenyl, such as alkyl substituted phenyl, for example 4-methylphenyl), and R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen.

[0353] In one embodiment, Ar^d is



L^d is hydrogen; X^d is CR^{3d} ; Y^d is CR^{6d} and W^d is CR^{8d} ; R^{2d} and R^{4d} are each hydrogen; Z^d is CH; R^{1d} is —OH and R^{3d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen.

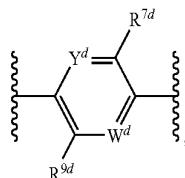
[0354] In one embodiment, Ar^d is



L^d is hydrogen; X^d is CR^{3d} ; Y^d is CR^{6d} and W^d is CR^{8d} ; R^{2d} and R^{4d} are each hydrogen; Z^d is CH, R^{3d} is —NO₂, R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen and R^{1d} is —OH, —OCH₂COOCH₂CH₃, —OCH₂CH₂ OH, —COOH,

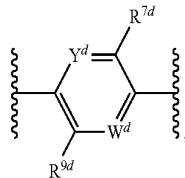
—OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂ OH, —OCH₂CN, —OCH₂CH₂NH₂ or —OCH₃.

[0355] In one embodiment, Ar^d is



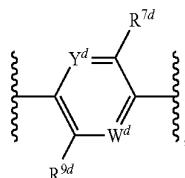
L^d is hydrogen; X^d is CR^{3d} ; Y^d is CR^{6d} and W^d is CR^{8d} ; R^{2d} and R^{4d} are each hydrogen; Z^d is CH; R^{1d} is —OH; R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{3d} is acyl, alkyl (e.g., t-butyl) or halogen substituted alkyl such as —CF₃), halogen (e.g., fluorine), alkoxy (e.g., alkoxy), —CO₂H, —CONR^{3da}R^{3db}, —CN, —NR^{3dc}R^{3dd}, —NO₂, —SO₂R^{3de} or —C(R^{3df})NOH; R^{3da} and R^{3db} are each hydrogen; R^{3dc} and R^{3dd} are each alkyl (e.g., methyl); R^{3de} is alkyl (e.g., methyl) and R^{3df} is alkyl (e.g., methyl).

[0356] In one embodiment, Ar^d is



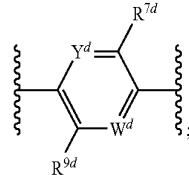
L^d is hydrogen; X^d is CR^{3d} ; Y^d is CR_{6d} and W^d is CR^{8d} ; R^{2d} and R^{4d} are each hydrogen; Z^d is CH; R^{1d} is —OH; R^{3d} is —NO₂; R^{6d} , R^{7d} and R^{9d} are each hydrogen; R^{6d} is amino (e.g., carbonylamino, for example, aryl substituted carbonylamino such as furanyl substituted carbonylamino or alkyl substituted carbonylamino, such as methyl substituted carbonylamino).

[0357] In one embodiment, Ar^d is



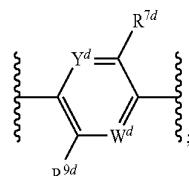
L^d is hydrogen; X^d is CR^{3d} ; Y^d is CR^{6d} and W^d is CR^{8d} ; R^{2d} and R^{4d} are each hydrogen; Z^d is CH; R^{1d} is —OH; R^{3d} is —NO₂; R^{6d} , R^{8d} and R^{9d} are each hydrogen; and R^{7d} is amino (e.g., —NH₂ or dialkylamino, such as dialkylamino, for example, dimethylamino; carbonylamino, such as alkyl substituted carbonylamino, for example, methyl substituted carbonylamino), —CO₂H or alkyl (e.g., aminoalkyl, for example, aminomethyl).

[0358] In one embodiment, L^d is absent; Ar^d is



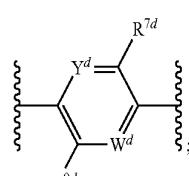
X^d is CH^{3d}; Y^d is CR^{6d}; W^d is CR^{8d} and Z^d is CH; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d} and R^{9d} are each hydrogen; R^{1d} is —OH; R^{3d} is —NO₂; and R^{16d} is alkoxy (e.g., methoxy), amino (e.g., —NH₂), dimethylamino or carbonylamino, alkyl substituted carbonylamino, for example, methyl substituted carbonylamino) or halogen (e.g., bromine).

[0359] In one embodiment, L^d is absent; Ar^d is

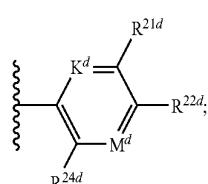


[0360] X^d is CH^{3d}; Y^d is CR^{6d}; W^d is CR^{8d} and Z^d is CH; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d} and R^{9d} are each hydrogen; R^{1d} is —OH; R^{3d} is —NR^{3dc}R^{3dd}; R^{3dc} is hydrogen; R^{16d} is —NO₂; and R^{3dd} is substituted carbonyl (e.g., substituted carbonyl, such as para-fluorophenyl)

[0361] In one embodiment, Ar^d is

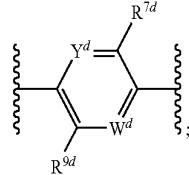


Y^d is CR^{6d} and W is CR^{8d}; X^d is CR^{3d} and Z^d is CH; L^d is —O—; R^{1d} is —OH; R^{3d} is —NO₂ and R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d} and R^{9d} are each hydrogen; R^{16d} is



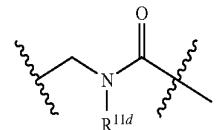
K^d is CR^{20d}; M^d is CR^{23d} and R^{20d}, R^{21d}, R^{22d}, R^{23d} and R^{24d} are each hydrogen.

[0362] In one embodiment A^d is

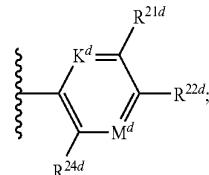


Y^d is CR^{6d} and W is CR^{8d}; X^d is CR^{3d} and Z^d is CH; L^d is

[0363]

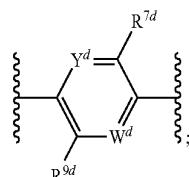


R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d} and R^{11d} are each hydrogen; R^{1d} is —OH; R^{3d} is



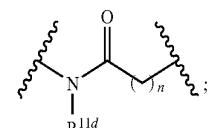
K^d is CR^{20d} and M^d is CR^{23d}; R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen and R^{22d} is hydrogen or halogen (e.g., fluorine).

[0364] In one embodiment, Ar^d is



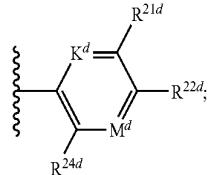
Y^d is CR^{6d} and W is CR^{8d}; X^d is CR^{3d} and Z^d is CH; L^d is

[0365]



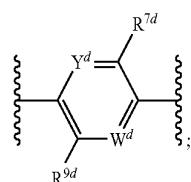
n is 1; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d} and R^{1d} are each hydrogen; R^{1d} is —OH; R^{3d} is —NO₂; R^{16d} is

Y^d is CR^{6d} and W is CR^{8d}, X^d is CR^{3d} and Z^d is CH; L^d is [0369]



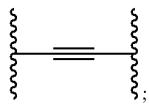
K^d is CR^{20d} and M^d is CR^{23d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine).

[0366] In one embodiment, Ar^d is

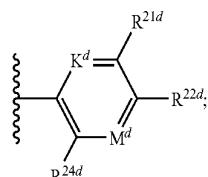


Y^d is CR^{6d} and W is CR^{8d}, X^d is CR^{3d} and Z^d is CH; L^d is

[0367]

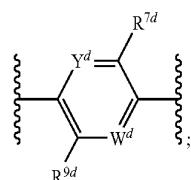


R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d} and R^{11d} and are each hydrogen; R^{1d} is —OH; R^{3d} is —NO₂; R^{16d} is



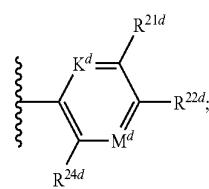
K^d is CR^{20d} and M^d is CR^{23d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen and R^{22d} is halogen (e.g., fluorine).

[0368] In one embodiment Ar^d is



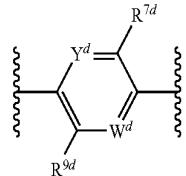
R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d} and R^{11d} are each hydrogen; R^{1d} is —OH; R^{3d} is —NO₂; R^{16d} is

[0369]



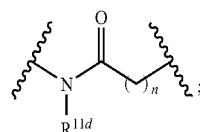
K^d is CR^{20d} and M^d is CR^{23d}, and R^{20d}, R^{21d}, R^{22d}, R^{23d} and R^{24d} are each hydrogen.

[0370] In one embodiment Ar^d is

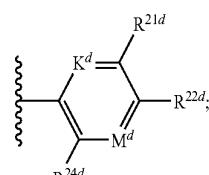


Y^d is CR^{6d} and W is CR^{8d}, X^d is CR^{3d} and Z^d is

[0371]



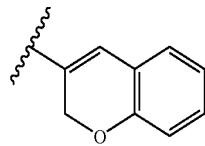
n is 0; R^{1d} is —OH; R^{3d} is —NO₂; R^{11d} is hydrogen; R^{2d} and R^{4d} are each hydrogen; R^{6d}, R^{7d}, R^{8d} and R^{9d} are each hydrogen; R^{16d} is



K^d is CR^{20d} and M^d is CR^{23d}; R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen and R^{22d} is hydrogen, alkoxy (e.g., methoxy), halogen (e.g., chlorine or fluorine), amino (e.g., dialkylamino, such as dimethylamino, or carbonylamino, such as alkyl substituted carbonylamino, for example methyl substituted carbonylamino), alkyl (e.g., methyl or isopropyl),

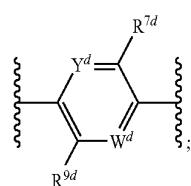
cyano, $-\text{SO}_2\text{R}^{22d}$, acyl, heterocyclic (e.g., morpholinyl), heteroaryl (e.g., pyrazol, isoxazolyl, imidazolyl, triazolyl, pyrimidinyl or pyridinyl), $-\text{CO}_2\text{H}$, hydroxyl,

Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z^d is CH ; L^d is
[0375]



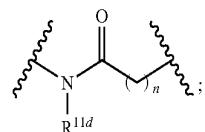
or aminocarbonyl (e.g., dimethylaminocarbonyl); and R^{22d} is amino or alkyl (e.g., methyl).

[0372] In one embodiment, Ar^d is

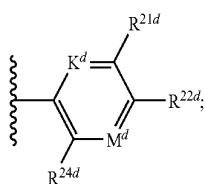


Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z^d is CH ; L^d is

[0373]

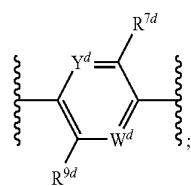


n is 0; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{1d} is hydrogen; R^{2d} and R^{4d} are each hydrogen; R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{16d} is

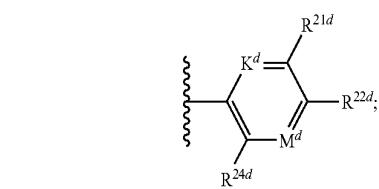
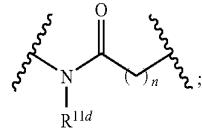


K^d is CR^{20d} and M^d is CR^{23d} ; R^{20d} , R^{22d} , R^{23d} and R^{24d} are each hydrogen and R^{2d} is halogen (e.g., fluorine or chlorine), alkyl (e.g., methyl) or hydroxyl.

[0374] In one embodiment, Ar^d is

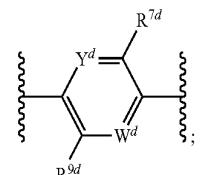


n is 0; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{11d} is hydrogen; R^{2d} and R^{4d} are each hydrogen; R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{16d} is



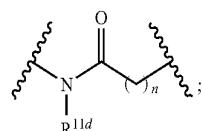
K^d is CR^{20d} and M^d is CR^{23d} ; R^{20d} , R^{21d} and R^{23d} are each hydrogen; R^{22d} and R^{24d} are each alkoxy (e.g., methyl) or R^{22d} is halogen (e.g., fluorine) and R^{24d} is alkoxy (e.g., methoxy).

[0376] In one embodiment Ar^d is

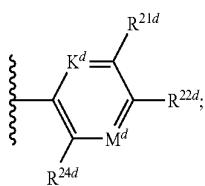


Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z^d is CH ; L^d is

[0377]

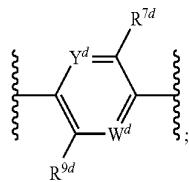


n is 0; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{11d} is hydrogen; R^{2d} and R^{4d} are each hydrogen; R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{16d} is



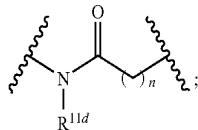
K^d is CR^{20d} and M^d is CR^{23d} ; R^{20d} , R^{21d} and R^{24d} are each hydrogen; R^{22d} and R^{23d} together with the carbon atoms to which they are attached form a 6-membered ring (e.g., a cyclohexanone ring) or R^{22d} is halogen (e.g., fluorine) and R^{23d} is alkyl (e.g., methyl) or alkoxy (e.g., methoxy).

[0378] In one embodiment, Ar^d is



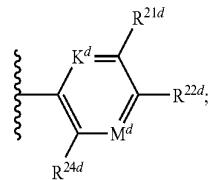
Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z is CH ; L^d is

[0379]



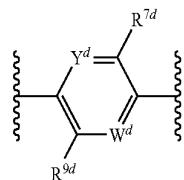
n is 0; R^{1d} is $-OH$; R^{3d} is $-NO_2$; R^{11d} is hydrogen; R^{2d} and R^{4d} are each hydrogen; R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{16d} is

n is 0; R^{1d} is $-OH$; R^{11d} is hydrogen; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{16d} is



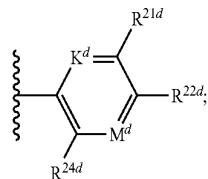
K^d is CR^{20d} and M^d is CR^{23d} ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{3d} is cyano and R^{22d} is halogen (e.g., fluorine), acyl or cyano.

[0382] In one embodiment, Ar^d is



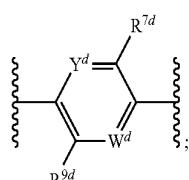
Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z is CH ; L^d is

[0383]



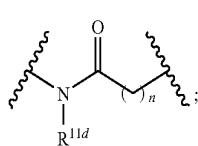
K^d is CR^{20d} and M^d is CR^{23d} ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen and R^{21d} and R^{22d} are each halogen (e.g., fluorine).

[0380] In one embodiment, Ar^d is



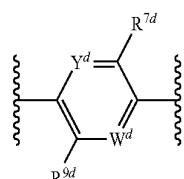
Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z is CH ; L^d is

[0381]

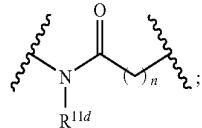


K^d is CR^{20d} and M^d is CR^{23d} ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{3d} is $-C(R^{3df})NOH$; R^{3df} is amino and R^{22d} is halogen (e.g., fluorine).

[0384] In one embodiment Ar^d is

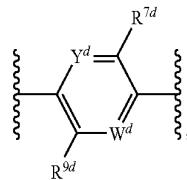


Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z^d is CH ; L^d is
[0385]



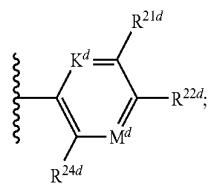
n is 0; R^{1d} is hydrogen; $R^{1d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; R^{16d} is

[0388] In one embodiment Ar^d is



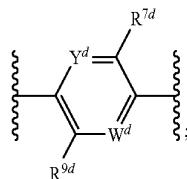
Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z^d is CH ; L^d is

[0389]



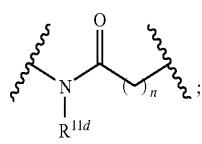
K^d is CR^{20d} and M^d is CR^{23d} ; $R^{20d}, R^{21d}, R^{23d}$ and R^{24d} are each hydrogen; R^{3d} is $-C(R^{3df})NO_2$; R^{3df} is alkyl (e.g., methyl) and R^{22d} is amino (e.g., dialkylamino such as dimethylamino).

[0386] In one embodiment, Ar^d is



Y^d is CR^{6d} and W is CR^{8d} ; X^d is CR^{3d} and Z^d is CH ; L^d is

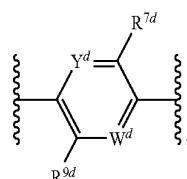
[0387]



n is 0; R^{1d} is OH; R^{11d} is hydrogen; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; R^{16d} is

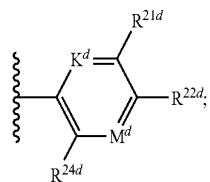
K^d is CR^{20d} and M^d is CR^{23d} ; $R^{20d}, R^{21d}, R^{23d}$ and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine); and R^{1d} is $-OCH_2COOH$, $-OCH_2CH_2N^+(CH_3)_3$, $-OCH_2P(O)(OH)_2$ or $-OCH_2P(O)(OCH_2CH_3)_2$.

[0390] In one embodiment, Ar^d is

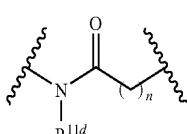


L^d is

[0391]

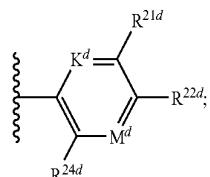
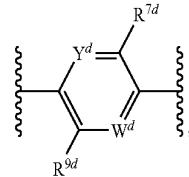


K^d is CR^{20d} and M^d is CR^{23d} ; $R^{20d}, R^{21d}, R^{23d}$ and R^{24d} are each hydrogen; $CONR^{3da}R^{3db}$; R^{3da} and R^{3db} are each hydro-
gen and R^{22b} is halogen (e.g., fluorine).



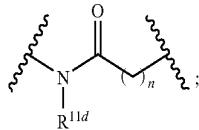
n is 0; R^{1d} is $-\text{OH}$; X^d is CR^{3d} , Y^d is CR^{6d} and W^d is CR^{8d} ; [0396] In one embodiment, Ar^d is R^{16d} is

[0392]

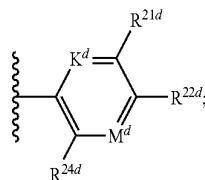
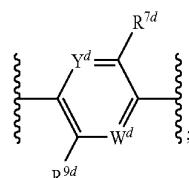
 L^d is

[0397]

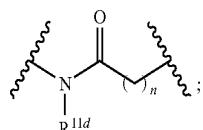
K^d is CR^{20d} , M^d is CR^{23d} , R^{3d} is $-\text{NO}_2$; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} and R^{11d} are each hydrogen; Z^d is N and R^{22d} is halogen (e.g., fluorine) or acyl.

[0393] In one embodiment, Ar^d is n is 0; R^{1d} is $-\text{OH}$; X^d is CR^{3d} , Y^d is CR^{6d} and W^d is

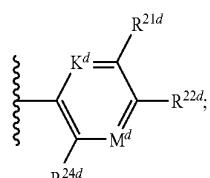
[0398]

 L^d is

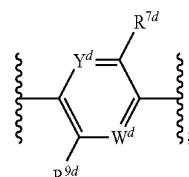
[0394]

 n is 0; R^{1d} is $-\text{OH}$; X^d is CR^{3d} , Y^d is CR^{6d} and W^d is

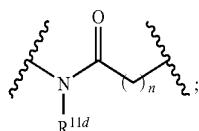
[0395]

 L^d is

[0400]

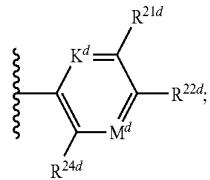


K^d is CR^{20d} , M^d is CR^{23d} ; Z^d is CH; R^{2d} , R^{4d} , R^{11d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{3d} is $-\text{NO}_2$; R^{6d} , R^{8d} and R^{9d} are each hydrogen; R^{7d} is alkyl (e.g., ethyl); and R^{22d} is halogen (e.g., fluorine) or acyl.



n is 0; R^{1d} is —OH; X^d is CR^{3d}; Y^d is CR^{6d} and W^d is

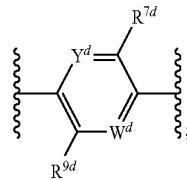
[0401]



K^d is CR^{20d}; M^d is CR^{23d}; Z^d is CH; R^{2d}, R^{4d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{3d} is —NO₂; R^{6d}, R^{7d} and R^{9d} are each hydrogen; R^{8d} is halo en (e.g., fluorine) and R^{22d} is acyl.

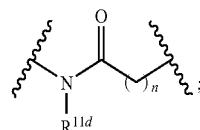
[0402] In one embodiment, Ar^d is

[0405] In one embodiment, Ar^d is



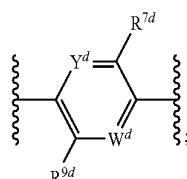
L^d is

[0406]



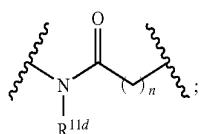
n is 0; R^{1d} is —OH; X^d is CR^{3d} and Z^d is CH; R^{3d} is

[0407]



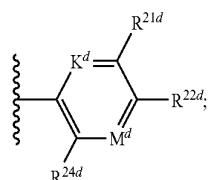
L^d is

[0403]



n is 0; R^d is —OH; X^d is CR^{3d} and Z^d is CH; R^{3d} is —NO₂; R^{16d} is

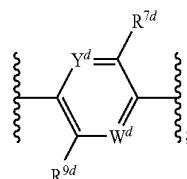
[0404]



X^d is CR^{20d} and M^d is CR^{23d}, R^{2d}, R^{4d}, R^{7d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; W^d is CR^{8d} and R^{8d} is hydrogen; R^{6d} is absent; Y^d is N; and R^{22d} is halogen (e.g., fluorine) or acyl.

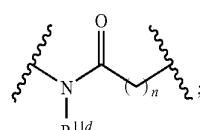
K^d is CR^{20d} and M^d is —CR^{23d}, R^{2d}, R^{4d}, R^{7d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; Y^d is CR^{6d} and R^{6d} is hydrogen; R^{8d} is absent and W^d is N; R^{22d} is halogen (e.g., fluorine).

[0408] In one embodiment, Ar^d is



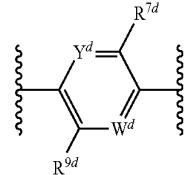
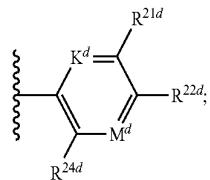
L^d is

[0409]



n is 0; R^{1d} is —OH; X^d is CR^{3d} and Z^d is CH; R^{3d} is —NO₂; R^{16d} is

[0410]

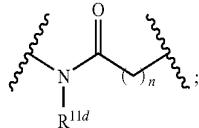


R^{1d} is —OH; Y^d is CR^{6d} and W^d is CR^{8d}; X^d is CR^{3d} and Z^d is CH; L^d is

K^d is CR^{20d} and M^d is CR^{23d}; R^{2d}, R^{6d}, R^{7d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; W^d is CR^{8d} and R^{8d} is hydrogen; Y^d is CR^{6d} and W^d is CR^{8d}; R^{4d} is alkyl (e.g., methyl) and R^{22d} is acyl or heteroaryl (e.g., isoxazolyl).

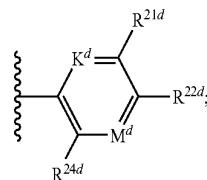
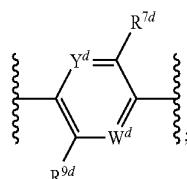
[0411] In one embodiment, Ar^d is

[0415]



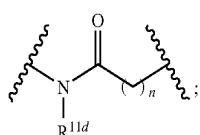
n is 0; R^{16d} is

[0416]



Y^d is CR^{6d} and W^d is CR^{8d}; X^d is CR^{3d} and Z^d is CH; L^d is

[0412]

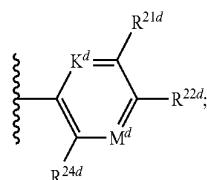
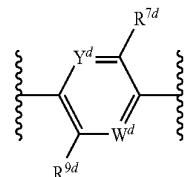


n is 0; R^{1d} is —OH; R^{16d} is

[0413]

K^d is CR^{20d} and M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{3d} is cyano; and R^{22d} is heteroaryl (e.g., imidazolyl).

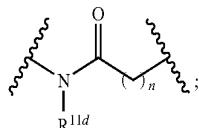
[0417] In one embodiment, Ar^d is



L^d is

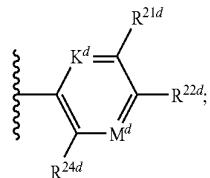
[0418]

K^d is CR^{20d} and M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{3d} is heteroaryl (e.g., imidazolyl or pyrazolyl) and R^{22d} is acyl.

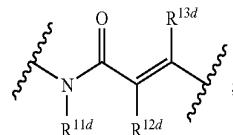


n is 0; and R^{1d} is $-\text{OH}$; Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0419]



[0423] In one embodiment, L^d is

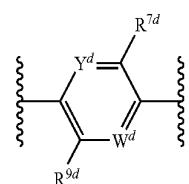
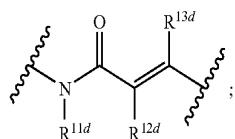


Ar^d is

[0424]

K^d is CR^{20d} ; M^d is CR^{23d} ; R^{3d} is absent and X^d is N ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen and R^{22d} is halogen (e.g., fluorine)

[0420] In one embodiment, L^d is

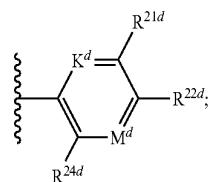
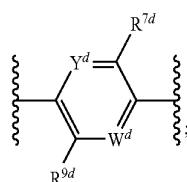


X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0425]

Ar^d is

[0421]

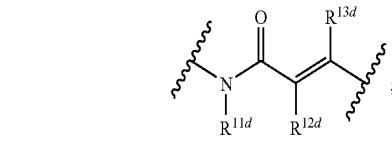
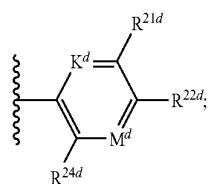


K^d is CR^{20d} and M^d is CR^{23d} , R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{21d} , R^{22d} , R^{23d} and R^{24d} are each hydrogen; and R^{20d} is alkoxy (e.g., methoxy).

[0426] In one embodiment, L^d is

X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

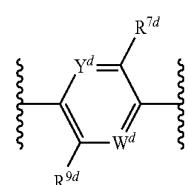
[0422]



Ar is

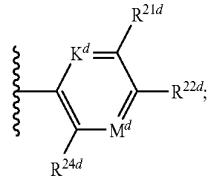
[0427]

K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$ and R^{22d} is heteroaryl (e.g., isoxazolyl, triazolyl, imidazolyl), hydrogen, halogen (e.g., fluorine), alkyl (e.g., methyl or halogen substituted alkyl, such as trifluoromethyl), alkoxy (e.g., methoxy), cyano, hydroxyl, acyl or $-\text{SO}_2\text{R}^{22da}$ and R^{22da} is alkyl (e.g., methyl).



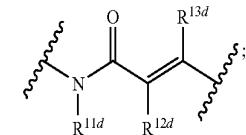
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0428]



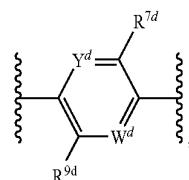
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{20d} , R^{21d} and R^{23d} are each hydrogen and R^{22d} and R^{24d} are each halogen (e.g., fluorine).

[0429] In one embodiment, L^d is



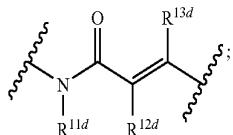
Ar^d is

[0433]



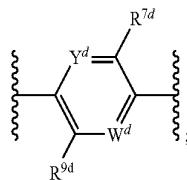
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0434]



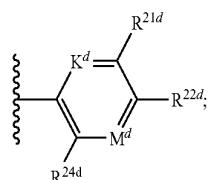
A^d is

[0430]

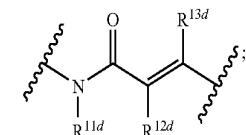


X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0431]

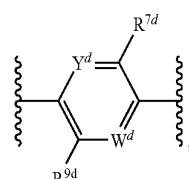


K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{20d} , R^{21d} and R^{23d} are each hydrogen and R^{22d} and R^{24d} are each halogen (e.g., fluorine).



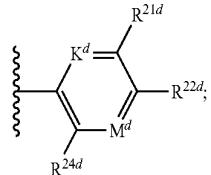
Ar^d is

[0436]



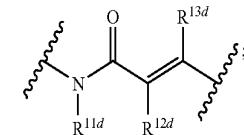
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0437]



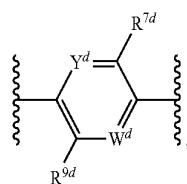
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine); R^{3d} is heteroaryl (e.g., pyrazolyl or imidazolyl).

[0438] In one embodiment, L^d is



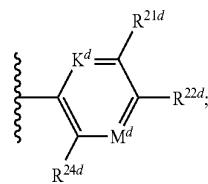
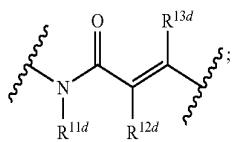
Ar^d is

[0442]



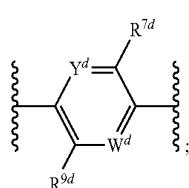
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0443]



A^d is

[0439]

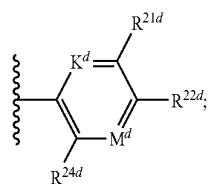
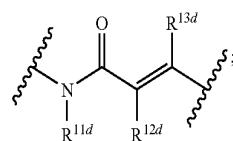


X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0440]

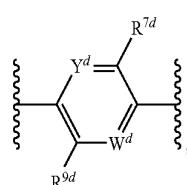
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} and R^{13d} are each hydrogen; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{1d} is $-\text{OH}$ and R^{3d} is NO_2 ; R^{22d} is hydrogen; and R^{12d} is alkyl (e.g., methyl), halogen (e.g., fluorine) or aryl (e.g., phenyl).

[0444] In one embodiment, L^d is



Ar^d is

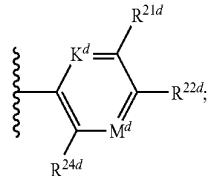
[0445]



K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is cyano; and R^{22d} is hydrogen, halogen (e.g., fluorine) or alkyl (e.g., methyl).

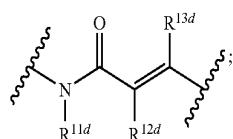
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0446]



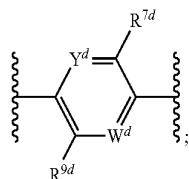
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} and R^{13d} are each hydrogen; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{1d} is $-OH$ and R^{3d} is NO_2 ; R^{22d} is halogen (e.g., fluorine); R^{12d} is alkyl (e.g., heterocyclic substituted alkyl, such as piperazinylmethyl, or hydroxyalkyl, such as hydroxyethyl).

[0447] In one embodiment, L^d is



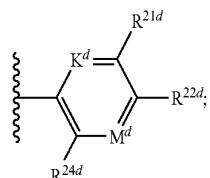
Ar^d is

[0448]



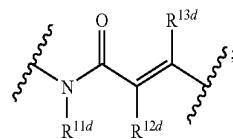
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0449]



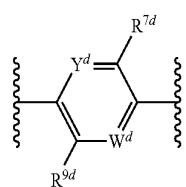
K^d is CR^{20d} and M^d is CR^{23d} ; R^{3d} is $-NO_2$ and R^{1d} is $-OH$; R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine) or acyl; R^{2d} is hydrogen; R^{4d} is halogen (e.g., fluorine) alkyl, (e.g., methyl), alkoxy (e.g., ethoxy, morpholine substituted ethoxy, piperazinyl substituted ethoxy, phosphate substituted alkoxy, dimethylaminoethoxy or methoxyethoxyethoxy) or $-NR^{4da}R^{4db}$; and R^{4da} and R^{4db} are each alkyl (e.g., methyl or dimethylaminoethyl).

[0450] In one embodiment, L^d is



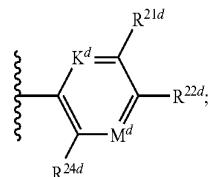
Ar^d is

[0451]



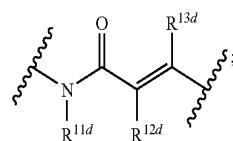
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is

[0452]



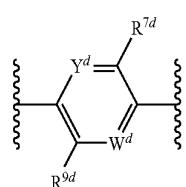
K^d is CR^{20d} and M^d is CR^{23d} ; R^{3d} is $-NO_2$ and R^{1d} is $-OH$; R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine) or acyl; R^{4d} is hydrogen; R^{2d} is $-NR^{2da}R^{2db}$ and R^{2da} and R^{2db} are each alkyl (e.g., methyl or dimethylaminoethyl).

[0453] In one embodiment, L^d is



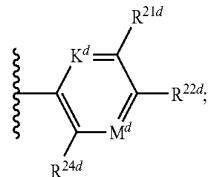
Ar^d is

[0454]



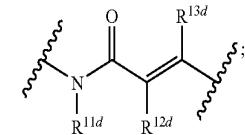
X^d is CR^{3d} , Z^d is CH, Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0455]



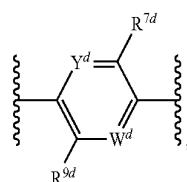
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{3d} is $-\text{NO}_2$; R^{22d} is halogen (e.g., fluorine) and R^{1d} is $-\text{OCH}_2\text{P}(\text{O})(\text{OH})_2$ or $-\text{OCH}_2\text{P}(\text{O})(\text{OCH}_2\text{CH}_3)_2$.

[0456] In one embodiment, L^d is



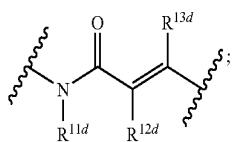
Ar^d is

[0460]



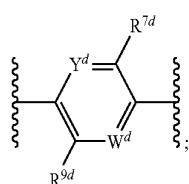
X^d is CR^{3d} , Z^d is CH, Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0461]



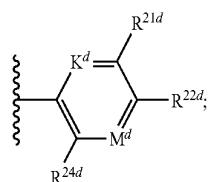
Ar^d is

[0457]



X^d is CR^{3d} , Z^d is CH, Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

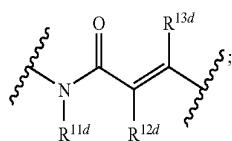
[0458]



K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{8d} and R^{9d} are each hydrogen; R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$ and R^{3d} is NO_2 ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine); and R^{7d} is alkyl (e.g., morpholinyl substituted methyl or methyl).

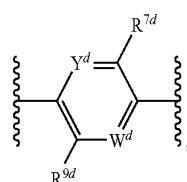
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$ and R^{3d} is NO_2 ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine); R^{7d} , R^{8d} and R^{9d} are each hydrogen and R^{6d} is halogen (e.g., fluorine).

[0462] In one embodiment, L^d is



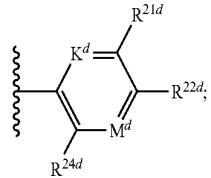
Ar^d is

[0463]



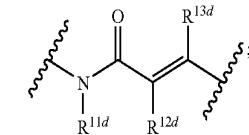
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0464]



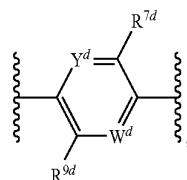
K^d is CR^{20d} and M^d is CR^{23d} , R^{2d} , R^{4d} , R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$ and R^{3d} is NO_2 ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine); R^{6d} , R^{7d} and R^{8d} are each hydrogen and R^{9d} is alkoxy (e.g., methoxy).

[0465] In one embodiment, L^d is



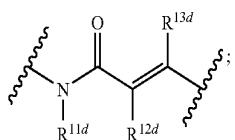
Ar^d is

[0469]



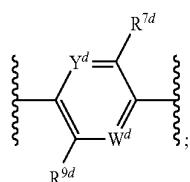
R^{16d} is

[0470]



Ar^d is

[0466]

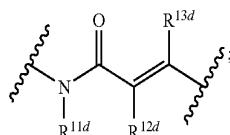


X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is

[0467]

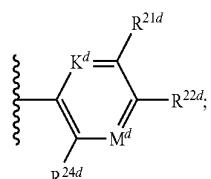
K^d is $-\text{CR}^{20d}$ and M^d is CR^{23d} , X^d is CR^{3d} , Z^d is NO or N , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{1d} is $-\text{OH}$; R^{2d} , R^{3d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; and R^{22d} is halogen (e.g., fluorine).

[0471] In one embodiment, L^d is

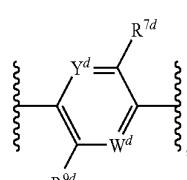


Ar^d is

[0472]

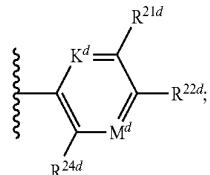


K^d is CR^{20d} and M^d is CR^{23d} , R^{2d} , R^{4d} , R^{11d} , R^{12d} and R^{13d} are each hydrogen; R^{1d} is $-\text{OH}$ and R^{3d} is NO_2 ; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is halogen (e.g., fluorine); R^{6d} , R^{7d} and R^{9d} are each hydrogen and R^{8d} is halogen (e.g., fluorine).

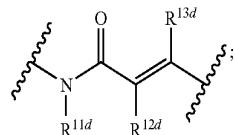


R^{16d} is

[0473]



[0477] In one embodiment, L^d is

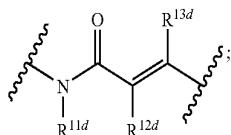


Ar^d is

[0478]

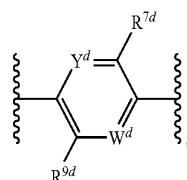
K^d is $-CR^{20d}$ and M^d is CR^{23d} ; R^{3d} is absent; X^d is $-NO$ or N , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^d is $-OH$; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; and R^{22d} is halo en (e.g., fluorine)

[0474] In one embodiment, L^d is



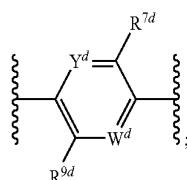
R^{16d} is

[0479]



Ar^d is

[0475]

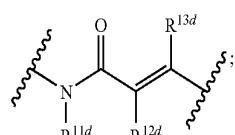
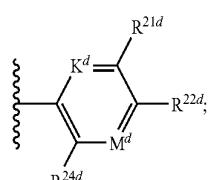


X^d is CR^{3d} and Z^d is CH ; Y^d is $-CR^{6d}$ and R^{8d} is absent; W^d is N ; R^{1d} is $-OH$ and R^{3d} is $-NO_2$; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} are each hydrogen; and R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen and R^{22d} is halogen (e.g., fluorine). Alternatively, R^{20d} and R^{22d} are each hydrogen and R^{21d} , R^{23d} and R^{24d} are each halogen (e.g., fluorine).

[0480] In one embodiment, L^d is

R^{16d} is

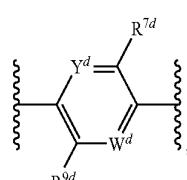
[0476]



Ar^d is

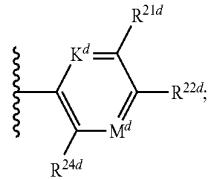
[0481]

X^d ; is CR^{3d} and Z^d is CH ; R^{6d} is absent; Y^d is N and W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} are each hydrogen; R^{1d} and $-OH$ and R^{3d} is $-NO_2$; R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen and R^{22d} is halogen (e.g., fluorine). Alternatively, R^{20d} and R^{22d} are each halogen (e.g., fluorine) and R^{21d} , R^{23d} and R^{24d} are each hydrogen.



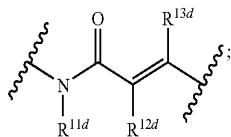
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0482]



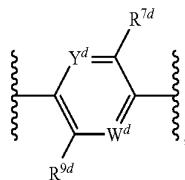
K^d is CR^{20d} and M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{12d} , R^{13d} , R^{20a} , R^{21a} , R^{23a} and R^{24a} are each hydrogen; R^{22d} is acyl; and R^{11d} is alkyl (e.g., carbonyl substituted alkyl, such as $-\text{CH}_2\text{COOH}$ or aminocarbonylmethyl); R^{1d} is $-\text{OH}$ and R^{3d} is $-\text{NO}_2$ or cyano.

[0483] In one embodiment, L^d is



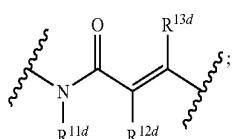
Ar^d is

[0487]



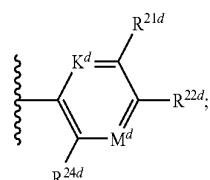
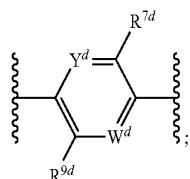
X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

[0488]



Ar^d is

[0484]

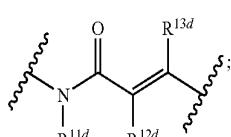
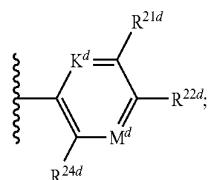


K^d is CR^{20d} and M^d is N ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is cyano and R^{22d} is heteroaryl (e.g., imidazolyl).

[0489] In one embodiment, L^d is

X^d is CR^{3d} , Z^d is CH , Y^d is CR^{6d} and W^d is CR^{8d} ; R^{16d} is

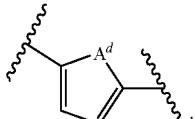
[0485]



Ar^d is

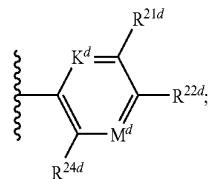
[0490]

K^d is CR^{20d} and M^d is N ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{1d} is $-\text{OH}$; R^{3d} is $-\text{NO}_2$; R^{22d} is acyl, heteroaryl (e.g., imidazolyl) or alkyl (e.g., halogen substituted alkyl, such as trifluoromethyl).



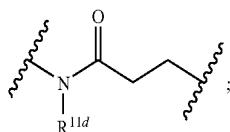
A^d is O; R^{16d} is

[0491]



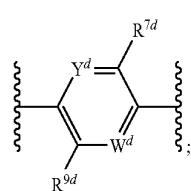
[0492] X^d is CR^{3d} ; Z is CH; K^d is CR^{20d} and M^d is CR^{23d} ; $R^{2d}, R^{4d}, R^{11d}, R^{12d}, R^{13d}, R^{20d}, R^{21d}, R^{23d}$ and R^{24d} are each hydrogen; R^{1d} is —OH, R^{3d} is —NO₂ and R^{22d} is halogen (e.g., fluorine)

[0493] In one embodiment, L^d is



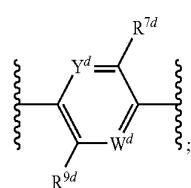
Ar^d is

[0494]



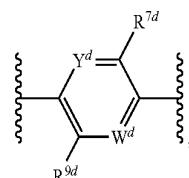
R^{16d} is; X^d is CR^{3d} , Z is CH; Z^d is CH; Y^d is CR^{6d} K^d is — CR^{20d} and M^d is CR^{23d} ; R^{1d} is —OH and R^{3d} is —NO₂; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d}$ and R^{24d} are each hydrogen and R^{22d} is halogen (e.g., fluorine).

[0495] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d} ; Z^d is CH; Ar^d is



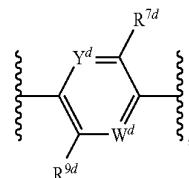
Y^d is CR^{6d} ; W^d is CR^{8d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH, —OCH₂CO₂CH₂CH₃, —OCH₂CH₂CH₃, —OCH₂CH₂ OH, —OCH₂CO₂H, —OCH₂CN, —OCH₂CH₂ NH₂, —OCH₂CH₂ CO₂H or —OCH₃.

[0496] In one embodiment, when R^{3d} is —CN; X^d is CR^{3d} ; Z^d is CH; Ar^d is



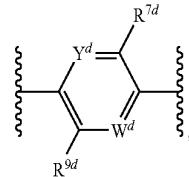
Y^d is CR^{6d} ; W^d is CR^{8d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OCH₂CO₂H.

[0497] In one embodiment, when R^{3d} is F; X^d is CR^{3d} ; Z^d is CH; Ar^d is



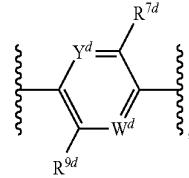
Y^d is CR^{6d} ; W^d is CR^{8d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OCH₂CO₂H.

[0498] In one embodiment, when R^{3d} is H; X^d is CR^{3d} ; Z^d is CH; Ar^d is



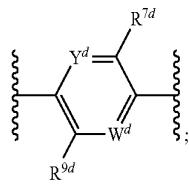
Y^d is CR^{6d} ; W^d is CR^{8d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH or —CH₂CO₂H.

[0499] In one embodiment, when R^{3d} is Cl; X^d is CR^{3d} ; Z^d is CH; Ar^d is



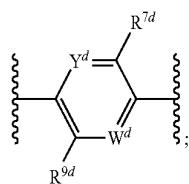
Y^d is CR^{6d} ; W^d is CR^{8d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}$ and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OCH₂CH₂CH₂CH₃ or —OCH₂CO₂H.

[0500] In one embodiment, when R^{3d} is acyl, methoxy, $-\text{CONH}_2$, $-\text{CO}_2\text{H}$ or t-butyl; X^d is CR^{3d} ; W^d is CH; Ar^d is



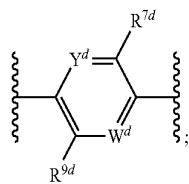
Y^d is CR^{6d} ; Z^d is CR^{8d} , R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OCH}_2\text{CO}_2\text{H}$.

[0501] In one embodiment, when R^{1d} is $-\text{OH}$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



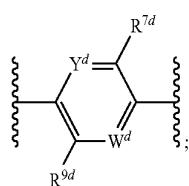
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{3d} is not acyl, $-\text{CF}_3$, F, methoxy, $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NHCOCO}_2\text{H}$, cyano, dimethylamino, t-butyl, $-\text{SO}_2\text{CH}_3$, SO_2NHCH_2 , furanyl, or $-\text{C}(\text{CH}_3)\text{NOH}$.

[0502] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



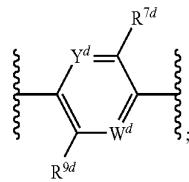
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{4d} is $-\text{NH}_2$, R^{2d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ or $-\text{OCH}_2\text{CO}_2\text{H}$.

[0503] In one embodiment, when R^{3d} is H; X^d is CR^{3d} ; Z^d is CH; Ar^d is



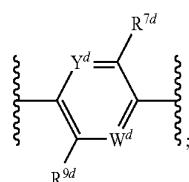
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is chlorine, then R^{1d} is not $-\text{OH}$.

[0504] In one embodiment, when R^{3d} is Cl; X^d is CR^{3d} ; Z^d is CH; Ar^d is



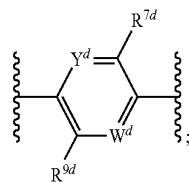
Y^d is CR^{6d} ; W^d is CR^{8d} , R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is chlorine, then R^{1d} is not $-\text{OCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ or $-\text{OCH}_2\text{CO}_2\text{H}$.

[0505] In one embodiment, when R^{3d} is Cl; X^d is CR^{3d} ; Z^d is CH; Ar^d is



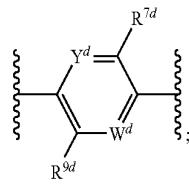
Y^d is CR^{6d} ; W^d is CR^{8d} , R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is methoxy, then R^{1d} is not $-\text{OCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$ or $-\text{OCH}_2\text{CO}_2\text{H}$.

[0506] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



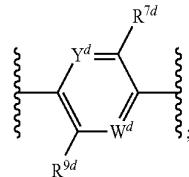
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{4d} is $-\text{NH}_2$, R^{2d} , R^{6d} , R^{7d} and R^{9d} are each hydrogen; R^{8d} is methoxy, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0507] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



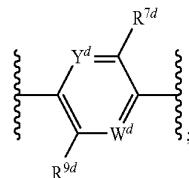
Y^d is CR^{6d} ; W^d is N; R^8 is absent; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$ or $-\text{OCH}_2\text{CO}_2\text{H}$.

[0508] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



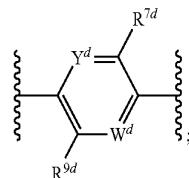
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{8d} and R^{9d} are each hydrogen; R^{7d} is trifluoromethyl, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0509] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



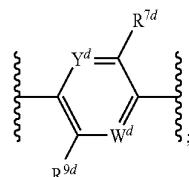
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is methoxy, then R^{1d} is not $-\text{OH}$.

[0510] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



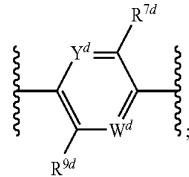
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} and R^{9d} are each hydrogen; R^{7d} and R^{8d} are each fluorine, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0511] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



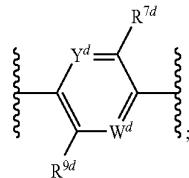
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydroxy, then R^{1d} is not $-\text{OH}$.

[0512] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



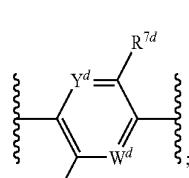
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is $-\text{NH}_2$, then R^{1d} is not $-\text{OH}$.

[0513] In one embodiment, when R^{3d} is cyano or NO_2 ; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



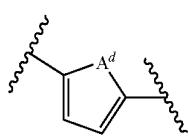
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{7d} is $-\text{NH}_2$, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0514] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



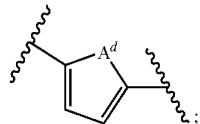
R^{6d} is absent; Y^d is N; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0515] In one embodiment, when R^{3d} is $-\text{NO}_2$, CO_2H , cyano CONH_2 hydrogen, acyl, fluorine or trifluoromethyl; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



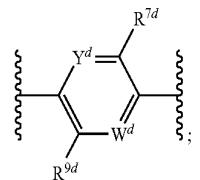
A^d is O; R^{2d} and R^{4d} are each hydrogen, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0516] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



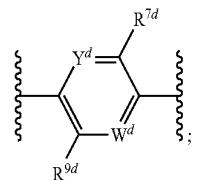
A^d is S; R^{2d} and R^{4d} are each hydrogen, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0517] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



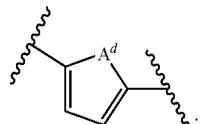
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{8d} and R^{9d} are each hydrogen; R^{7d} is methoxy; and L^d is absent and R^{16d} is $-\text{OH}$, then R^{1d} is not $-\text{OH}$.

[0518] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



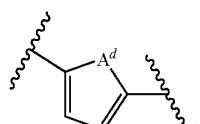
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{6d} is $-\text{NH}_2$, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0519] In one embodiment, when R^{3d} is hydrogen; X^d is CR^{3d} ; Z^d is CH; Ar^d is



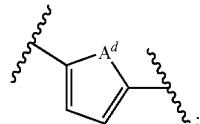
A^d is O; R^{2d} is hydrogen and R^{4d} is fluorine, and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0520] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



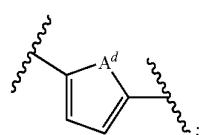
A^d is O; R^{2d} and R^{4d} are each hydrogen, and L^d is absent and R^{16d} is methyl, then R^{1d} is not $-\text{OH}$.

[0521] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



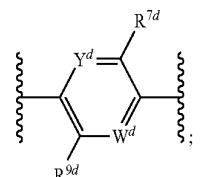
A^d is O; R^{2d} and R^{4d} are each hydrogen, and L^d is unsubstituted phenyl, then R^{1d} is not $-\text{OH}$.

[0522] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



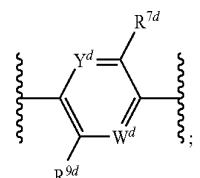
A^d is S; R^{2d} and R^{4d} are each hydrogen, and L^d is absent and R^{16d} is methyl or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0523] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



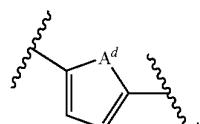
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is $-\text{N}(\text{CH}_3)_2$, then R^{1d} is not $-\text{OH}$.

[0524] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



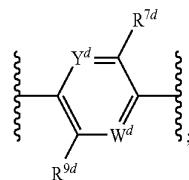
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{8d} and R^{9d} are each hydrogen; R^{7d} is $-\text{NHCOCH}_2$, $-\text{CO}_2\text{H}$ or $-\text{N}(\text{CH}_3)_2$ and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0525] In one embodiment, when R^{3d} is bromine; X^d is CR^{3d} ; Z^d is CH; Ar^d is



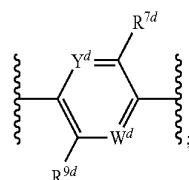
A^d is O; R^{2d} and R^{4d} are each hydrogen and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH.

[0526] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



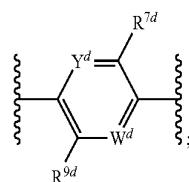
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} and R^{8d} are each hydrogen; R^{9d} is methyl; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH.

[0527] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



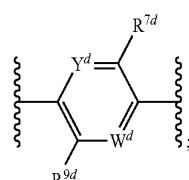
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{6d} is NHCOCH_3 ; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH.

[0528] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



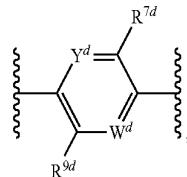
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; R^{6d} is — $\text{NHCO}\text{furanyl}$; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH.

[0529] In one embodiment, when R^{3d} is NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



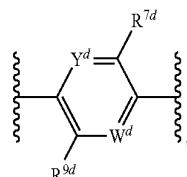
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{8d} and R^{9d} are each hydrogen; R^{7d} is — NHCH_2Ph , methyl, — NHCOPh , — CH_2NH_2 ; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not —OH.

[0530] In one embodiment, when R^{3d} is — NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



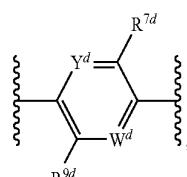
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent and R^{16d} is bromine or — $\text{CH}_2\text{NHCH}_2\text{Ph}$, then R^{1d} is not —OH.

[0531] In one embodiment, when R^{3d} is — NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



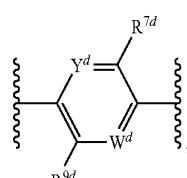
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is — CH_2 ; R^{16d} is — NHCH_2Ph , then R^{1d} is not —OH.

[0532] In one embodiment, when R^{3d} is — NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



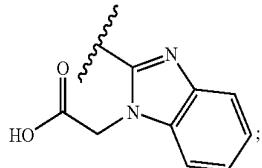
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} and R^{15d} are each hydrogen; and L^d is — NR^{15d} ; R^{16d} is — CH_2PH , then R^{1d} is not —OH.

[0533] In one embodiment, when R^{3d} is — NO_2 ; X^d is CR^{3d} ; Z^d is CH; Ar^d is



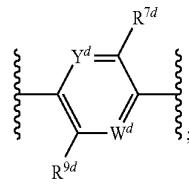
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and L^d is absent; R^{16d} is — NHCH_2Ph , — CH_2NH_2 or — NHCOCH_3 , then R^{1d} is not —OH.

[0534] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



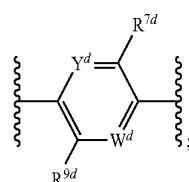
R^{2d} and R^{4d} are each hydrogen, then R^{1d} is not $-\text{OH}$.

[0535] In one embodiment, when R^{3d} is $-\text{CONH}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



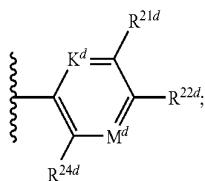
Y^d is CR^{6d} ; W^d is CR^{8d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} and R^{8d} are each hydrogen; R^{9d} is $-\text{NH}_2$; and L^d is absent and R^{16d} is hydrogen or L^d is hydrogen, then R^{1d} is not $-\text{OH}$.

[0536] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



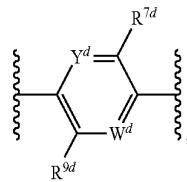
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is $-\text{O}-$; R^{16d} is

[0537]



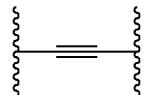
K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{20d} , R^{21d} , R^{22d} , R^{23d} and R^{24d} are each hydrogen; then R^{1d} is not $-\text{OH}$.

[0538] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



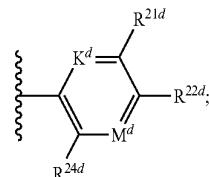
Y^d , d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0539]



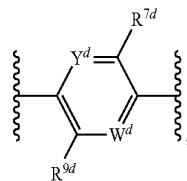
R^{16d} is

[0540]



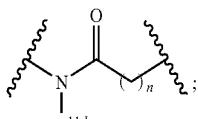
K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{20d} , R^{21d} , R^{22d} and R^{23d} are each hydrogen; R^{22d} is hydrogen, methoxy or fluorine; then R^{1d} is not $-\text{OH}$.

[0541] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



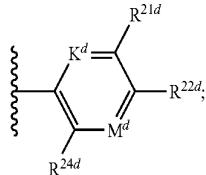
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0542]

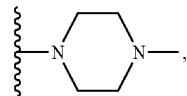


n is 0; R^{6d} is

[0543]

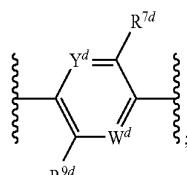


K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{22d} is hydrogen, methoxy, chlorine, fluorine,



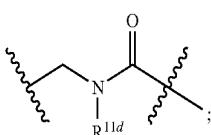
trifluoromethoxy, cyclohexyl, —NHC(O)CH₃, cyano, —CF₃, morpholinyl, —SO₂ NH₂, acyl, —SO₂ CH₃, pyrazolyl, diethylamino, —COOH, —CH₂N(CH₃)₂, isoxazolyl, imidazolyl, triazolyl, t-butyl, methyl, hydroxyl, or dimethylamino; then R^{1d} is not —OH.

[0544] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d}; Z^d is CH; Ar^d is



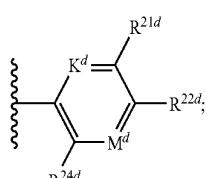
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0545]



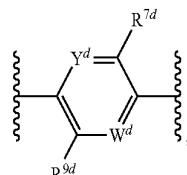
R^{16d} is

[0546]



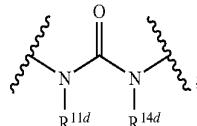
K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; then R^{1d} is not —OH.

[0547] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d}; Z^d is CH; Ar^d is



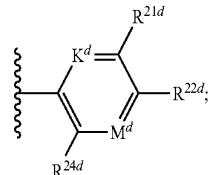
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0548]



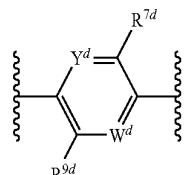
R^{16d} is

[0549]



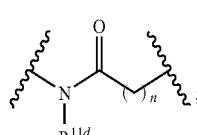
K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{14d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{22d} is hydrogen or dimethylamino, then R^{1d} is not —OH.

[0550] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d}; Z^d is CH; Ar^d is



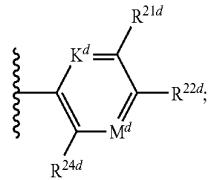
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0551]



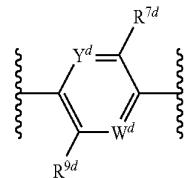
n is 0; R^{16d} is

[0552]



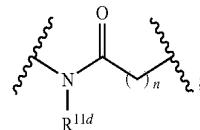
K^d is N; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{21d}, R^{22d}, R^{23d} and R^{24d} are each hydrogen; and R^{20d} is chlorine, methoxy, methyl or fluorine, then R^{1d} is not —OH.

[0553] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d}; Z^d is CH; Ar^d is



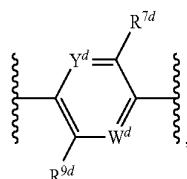
Y^d is CR^{6d}; W^d is CR^{8d}; L is

[0557]



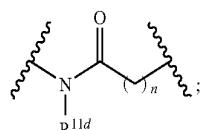
n is 0-2; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d} and R^{11d} are each hydrogen; and R^{16d} is piperidinyl; —CH₂CH₂-piperidine or —CH₂-piperidine, then R^{1d} is not —OH.

[0558] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d}; Z^d is CH; Ar^d is



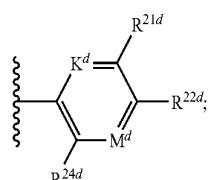
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0554]

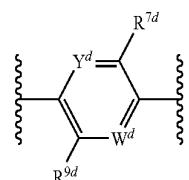


n is 1; R^{16d} is

[0555]

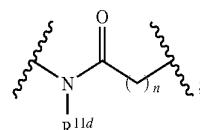


K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{22d} is hydrogen, fluorine, methoxy, methyl, dimethylamino, chlorine, then R^{1d} is not —OH.



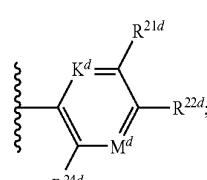
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0559]



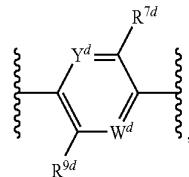
n is 1; R^{16d} is

[0560]



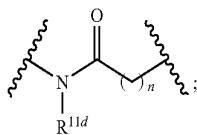
K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{22d}, R^{23d} and R^{24d} are each hydrogen; R^{21d} is chlorine, then R^{1d} is not —OH.

[0561] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



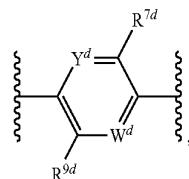
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0562]



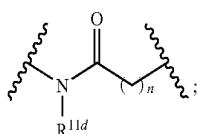
n is 0-2; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}$ and R^{11d} are each hydrogen; and R^{16d} is diethylamino; $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$ or $-\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, then R^{1d} is not $-\text{OH}$.

[0563] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



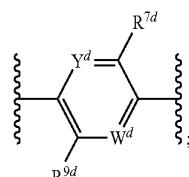
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0564]



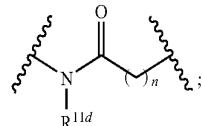
n is 1-2; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}$ and R^{11d} are each hydrogen; and R^{16d} is $-\text{CH}_2\text{CH}_2\text{Ph}$ or $-\text{CH}_2\text{Ph}$, then R^{1d} is not $-\text{OH}$.

[0565] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



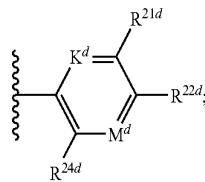
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0566]



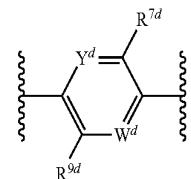
n is 0; R^{16d} is

[0567]



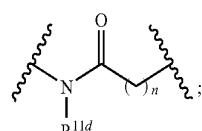
K^d is CR^{20d} ; M^d is CR^{23d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}, R^{23d}, R^{22d}$ and R^{24d} are each hydrogen; R^{21d} is chlorine, methoxy or dimethylamino; then R^{1d} is not $-\text{OH}$.

[0568] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



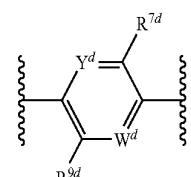
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0569]



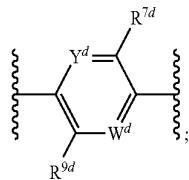
n is 0; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}$ are each hydrogen; and R^{16d} is methyl; then R^{1d} is not $-\text{OH}$.

[0570] In one embodiment, when R^{3d} is $-\text{NO}_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



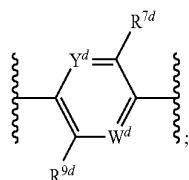
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is absent; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and R^{16d} is $-NHCOCH_3$; then R^{1d} is not $-OH$.

[0571] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



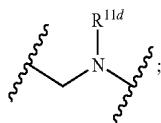
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is $-CH_2-$; R^{16d} is R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} and R^{9d} are each hydrogen; and R^{16d} is $-NH_2$; then R^{1d} is not $-OH$.

[0572] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



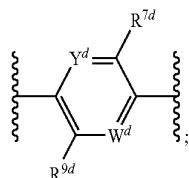
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0573]



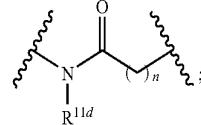
R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} and R^{16d} are each hydrogen; then R^{1d} is not $-OH$.

[0574] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



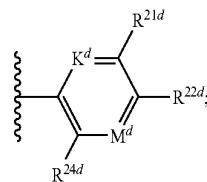
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0575]



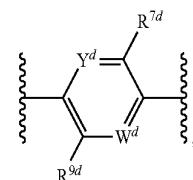
n is 0; R^{16d} is

[0576]



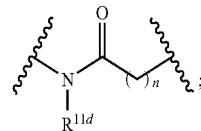
K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{21d} , R^{22d} , R^{23d} and R^{24d} are each hydrogen; R^{20d} is chlorine; then R^{1d} is not $-OH$.

[0577] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



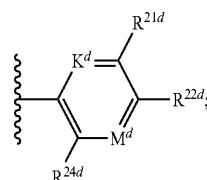
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0578]



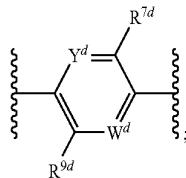
n is 0; R^{16} is

[0579]



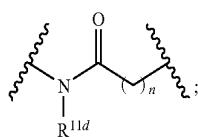
K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{20d} and R^{22d} is chlorine; then R^{1d} is not $-OH$.

[0580] In one embodiment, when R^{3d} is $-NO_2$; X^d is Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is CR^{3d} , Z^d is CH ; Ar^d is [0585]



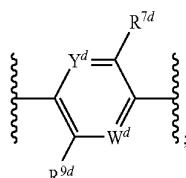
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0581]



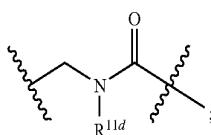
n is 0; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d} and R^{11d} are each hydrogen; and R^{16d} is t-butyl; then R^{1d} is not —OH.

[0582] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



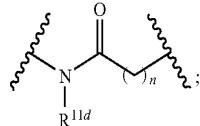
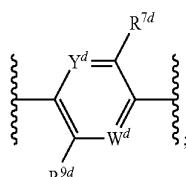
Y^d ; is CR^{6d}; W^d is CR^{8d}; L^d is

[0583]



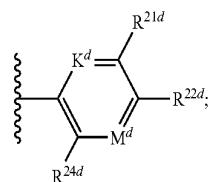
n is 0; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} are each hydrogen; and R^{16d} is t-butylmethoxy; then R^{1d} is not $-OH$.

[0584] In one embodiment, when R^{3d} is bromine, fluorine, $-CF_3$, cyano, $-CO_2H$, dimethylamino, acyl or hydrogen; X^d is CR^{3d} ; Z^d is $CH:Ar^d$ is



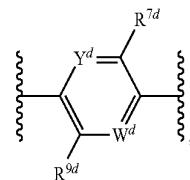
n is 0; R^{16d} is

[0586]



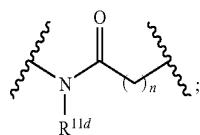
K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}; R^{20d}, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{22d} is dimethylamino; then R^{1d} is not —OH.

[0587] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



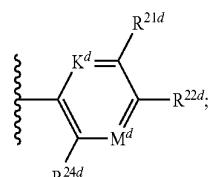
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0588]



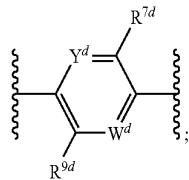
n is 0; R^{16d} is

[0589]



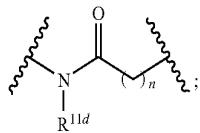
K^d is CR^{20d} ; M^d is CR^{23d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}$; R^{20d} , R^{22d} , R^{23d} and R^{24d} are each hydrogen; R^{21d} is fluorine, methyl or cyano; then R^{1d} is not $-OH$.

[0590] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



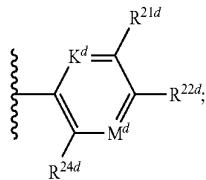
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0591]



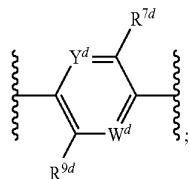
n is 0; R^{16d} is

[0592]



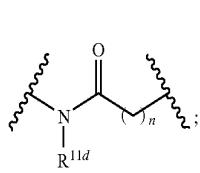
K^d is CR^{20d} ; M^d is CR^{23d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}$; $R^{21d}, R^{22d}, R^{23d}$ and R^{24d} are each hydrogen; R^{20d} is fluorine or methyl; then R^{1d} is not $-OH$.

[0593] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



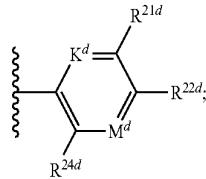
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0594]



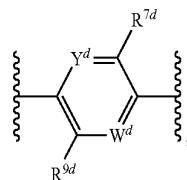
n is 1; R^{16d} is

[0595]



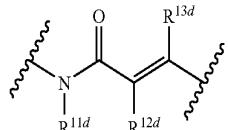
K^d is CR^{20d} ; M^d is N; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{20d}$, $R^{21d}, R^{22d}, R^{23d}$ and R^{24d} are each hydrogen; then R^{1d} is not $-OH$.

[0596] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d



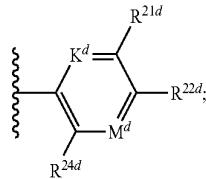
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0597]



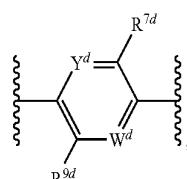
R^{16d} is

[0598]

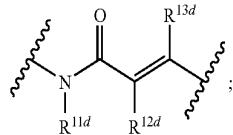


K^d is CR^{20d} ; M^d is CR^{23d} ; $R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}$, $R^{12d}, R^{13d}, R^{20d}$, R^{21d}, R^{23d} and R^{24d} are each hydrogen; R^{22d} is fluorine, dimethylamino, methyl, methoxy, cyano, $-CF_3$, hydroxyl or hydrogen, then R^{1d} is not $-OH$.

[0599] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH; Ar^d is



Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is
[0600]

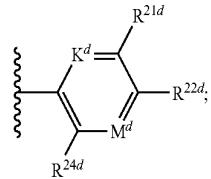
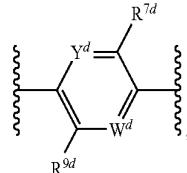


R^{16d} is

[0601]

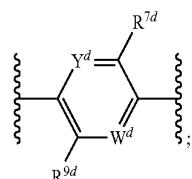
K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} are each hydrogen; R^{22d} is fluorine or methyl, then R^{1d} is not $-OH$.

[0605] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



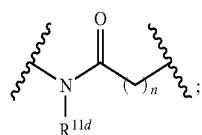
K^d is CR^{20d} ; M^d is N ; R^{23d} is absent; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{22d} and R^{24d} are each hydrogen; then R^{1d} is not $-OH$.

[0602] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is



Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0603]

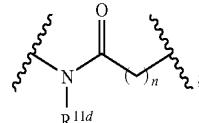


n is 2; R^{16d} is

[0604]

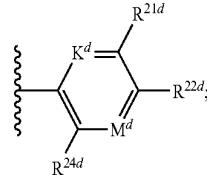
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0606]



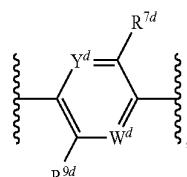
n is 2; R^{16d} is

[0607]



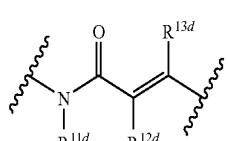
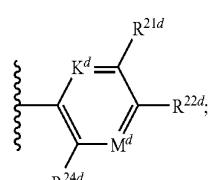
K^d is CR^{20d} ; M^d is N ; R^{23d} is absent; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{22d} and R^{24d} are each hydrogen; then R^{1d} is not $-OH$.

[0608] In one embodiment, when R^{3d} is $-NO_2$; X^d is CR^{3d} , CH ; Ar^d is



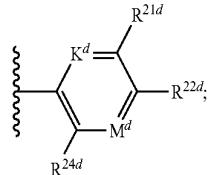
Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0609]

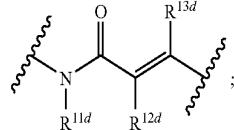


R^{16d} is

[0610]

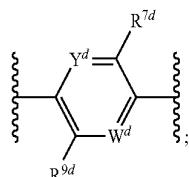
 Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0615]

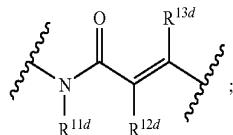


K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{21d} , R^{22d} , R^{23d} and R^{24d} are each hydrogen; R^{20d} is methoxy, then R^{1d} is not $—OH$.

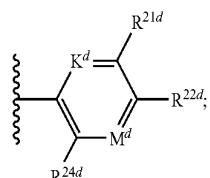
[0611] In one embodiment, when R^{3d} is $—NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is

 Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0612]

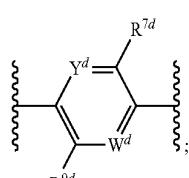
 R^{16d} is

[0613]

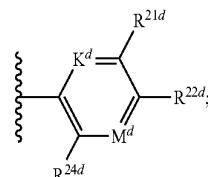


K^d is CR^{20d} ; M^d is CR^{23d} ; R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} and R^{23d} each hydrogen; R^{22d} and R^{24d} are each fluorine, then R^{1d} is not $—OH$.

[0614] In one embodiment, when R^{3d} is $—NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is

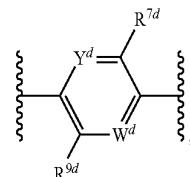
 R^{16d} is

[0616]

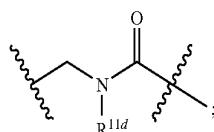


K^d is CR^{20d} ; M^d is CR^{23d} , R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} and R^{24d} each hydrogen; R^{22d} and R^{23d} are each fluorine, then R^{1d} is not $—OH$.

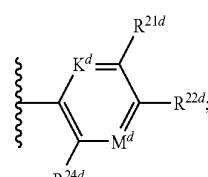
[0617] In one embodiment, when R^{3d} is $—NO_2$; X^d is CR^{3d} ; Z^d is CH ; Ar^d is

 Y^d is CR^{6d} ; W^d is CR^{8d} ; L^d is

[0618]

 R^{16d} is

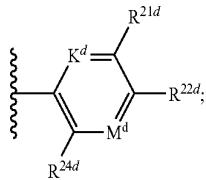
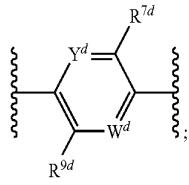
[0619]



K^d is CR^{20d} ; M^d is CR^{23d} , R^{2d} , R^{4d} , R^{6d} , R^{7d} , R^{8d} , R^{9d} , R^{11d} , R^{12d} , R^{13d} , R^{20d} , R^{21d} , R^{23d} and R^{24d} each hydrogen; R^{22d} is cyano, fluorine, methoxy, dimethylamino or acyl, then R^{1d} is not $—OH$.

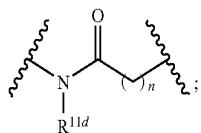
[0620] In one embodiment, when R^{3d} is hydrogen; X^d is CR^{3d}; Z^d is CH; Ar^d is n is 0; R^{16d} is

[0625]



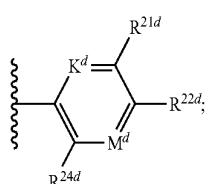
Y^d is R^{6d}; W^d is CR^{6d}; L^d is CR^d; R^{16d} is

[0621]



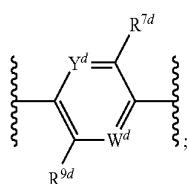
n is 0; R^{16d} is

[0622]



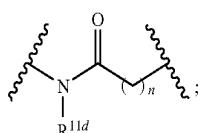
K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{12d}, R^{13d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} each hydrogen; R^{22d} is dimethylamino; R^{1d} is methyl or —COOH, then R^{1d} is not —OH.

[0623] In one embodiment, when R^{3d} is dimethylamino; X^d is CR^{3d}; Z^d is CH; Ar^d is



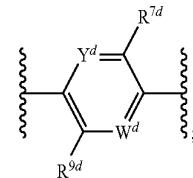
Y^d is CR^{6d}; W^d is CR^{8d}; L^d is

[0624]



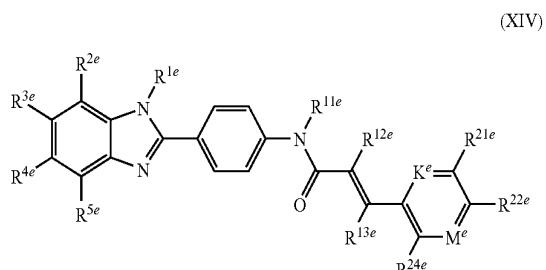
K^d is CR^{20d}; M^d is CR^{23d}; R^{2d}, R^{4d}, R^{6d}, R^{7d}, R^{8d}, R^{9d}, R^{11d}, R^{12d}, R^{13d}, R^{20d}, R^{21d}, R^{23d} and R^{24d} each hydrogen; R^{22d} is fluorine; then R^{1d} is not —OH.

[0626] In one embodiment, when R^{3d} is —NO₂; X^d is CR^{3d}; Z^d is CH; Ar^d is



Y^d is CR^{6d}; W^d is CR^{8d}; L^d is absent R^{2d}, R^{4d}, R^{6d}, R^{8d} R^{9d} and R^{16d} are each hydrogen; and R^{7d}—NHCO-4-fluorophenyl, then R^{1d} is not —OH.

[0627] In another embodiment, the transcription factor modulating compound is a compound of formula XIV:



wherein:

[0628] R^{1e} is —OH, —OCH₂-aryl, —CH₂CH₂ CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂ NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

[0629] R^{2e}, R^{4e}, R⁵³, R^{11e}, R^{12e}, R^{13e}, R^{21e}, R^{22e}, and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

[0630] R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

[0631] R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

[0632] R^{3e} is $-\text{NO}_2$, hydrogen, acyl, halogen, alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}^{3da}\text{R}^{3db}$; cyano, $-\text{NR}^{3dc}\text{R}^{3dd}$, alkyl, $-\text{SO}_2\text{R}^{3de}$, $-\text{C}(\text{R}^{3df})\text{NOH}$, heterocyclic or heteroaryl;

[0633] R^{3ea} is alkyl or amino;

[0634] K^e is CR^{20e} or N;

[0635] M^e is CR^{23e} or N; and pharmaceutically acceptable salts thereof.

[0636] In one embodiment, R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is acyl; and R^{3e} is CO_2H , acyl, $-\text{SO}_2\text{R}^{3ea}$, hydrogen, $-\text{CF}_3$ or halogen (e.g., bromine or fluorine), and R^{3ea} is alkyl (e.g., methyl) or amino.

[0637] In one embodiment, R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{3e} is nitro; and R^{22e} is alkylsulfonyl.

[0638] In one embodiment, R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{22e} is acyl; R^{3e} is cyano or nitro and R^{11e} is alkyl (e.g., $-\text{CH}_2\text{COOH}$ or aminocarbonylmethyl).

[0639] In one embodiment, R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is N; R^{23e} is absent; R^{11e} is hydrogen; R^{3e} is $-\text{NO}_2$ and R^{22e} is acyl, aryl (e.g., imidazolyl) or alkyl (e.g., halogen substituted alkyl, such as trifluoromethyl).

[0640] In one embodiment, R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is N; R^{23e} is absent; R^{11e} is hydrogen; R^{3e} is cyano and R^{22e} is aryl (e.g., imidazolyl).

[0641] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is dimethylamino, fluorine, methyl, methoxy, cyano, $-\text{CF}_3$, hydroxyl, isopropyl, hydrogen, imidazolyl, triazolyl, acyl or oxazolyl, then R^{3e} is not $-\text{NO}_2$.

[0642] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{22e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is N; R^{23e} is absent; R^{11e} is hydrogen; then R^{3e} is not $-\text{NO}_2$.

[0643] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{22e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; and R^{21e} is methoxy, then R^{3e} is not $-\text{NO}_2$.

[0644] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} and R^{23e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; and R^{22e} and R^{24e} and are each fluorine, then R^{3e} is not $-\text{NO}_2$.

[0645] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is CR^{23e} ; R^{11e} is hydrogen; and R^{22e} and R^{23e} and are each fluorine, then R^{3e} is not $-\text{NO}_2$.

[0646] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is hydrogen, fluorine, acyl, cyano or methyl, then R^{3e} is not cyano.

[0647] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is fluorine;

[0648] R^{4e} is fluorine, dimethylamino, methyl, ethoxy, $-\text{OCH}_2\text{CH}_2\text{P}(\text{O})(\text{OH})_2$, $-\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2$ morpholinyl, $-\text{OCH}_2\text{CH}_2$ -4-methylpyrazinyl, $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ or $-\text{OCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ then R^{3e} is not $-\text{NO}_2$.

[0649] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is acyl; R^{4e} is fluorine, dimethylamino, methyl, ethoxy, $-\text{OCH}_2\text{CH}_2$ morpholinyl or $-\text{OCH}_2\text{CH}_2$ -methylpyrazinyl, then R^{3e} is not $-\text{NO}_2$.

[0650] In one embodiment, when R^e is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is fluorine, then R^{3e} is not pyrazolyl or imidazolyl.

[0651] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is CR^{23e} ; R^{11e} is hydrogen; and R^{21e} is $-\text{CH}_2\text{P}(\text{O})(\text{OH})_2$ or $-\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$ and R^{22e} is fluorine, then R^{3e} is not $-\text{NO}_2$.

[0652] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} and R^{23e} are each hydrogen; K^e is CR^{20e} and Me is CR^{23e} ; R^{11e} is hydrogen; and R^{22e} and R^{24e} are each methoxy, then R^{3e} is not $-\text{NO}_2$.

[0653] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{22e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; and R^{12e} is phenyl, fluorine or methyl, then R^{3e} is not $-\text{NO}_2$.

[0654] In one embodiment, when R^{1e} is $-\text{OH}$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and Me is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is fluorine, and R^{12e} is $-\text{CH}_2$ -4-methylpiperazine or hydroxyethyl, then R^{3e} is not $-\text{NO}_2$.

[0655] In one embodiment, when R^{1e} is $-\text{OH}$, R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is acyl or fluorine; R^{2e} is $-\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, then R^{3e} is not $-\text{NO}_2$.

[0656] In one embodiment, when R^{1e} is $-\text{OCH}_2\text{P}(\text{O})(\text{OH})_2$ or $-\text{OCH}_2\text{P}(\text{O})(\text{OEt})_2$, R^{2e} , R^{4e} , R^{5e} , R^{12e} , R^{13e} , R^{20e} , R^{21e} , R^{23e} and R^{24e} are each hydrogen; K^e is CR^{20e} and M^e is CR^{23e} ; R^{11e} is hydrogen; R^{22e} is fluorine, then R^{3e} is not $-\text{NO}_2$.

[0657] In one embodiment, the transcription factor modulating compound is a compound of Table 2, or a pharmaceutically acceptable salt thereof.

TABLE 2

Compound Code	Compound
A	

TABLE 2-continued

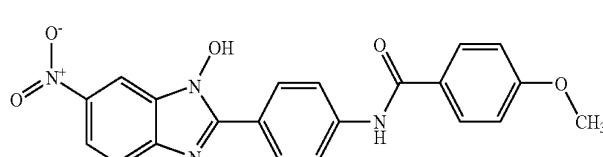
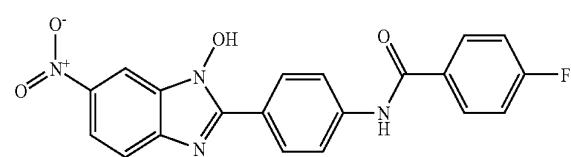
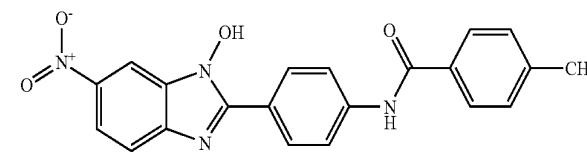
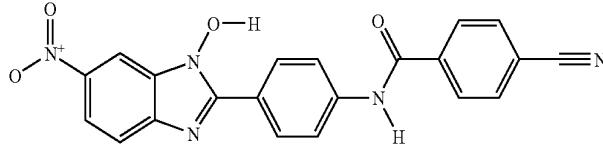
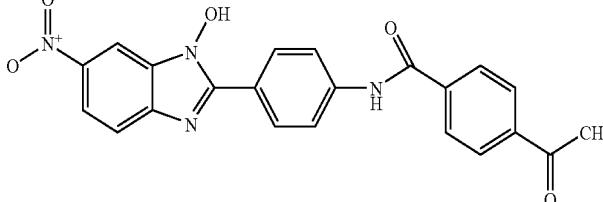
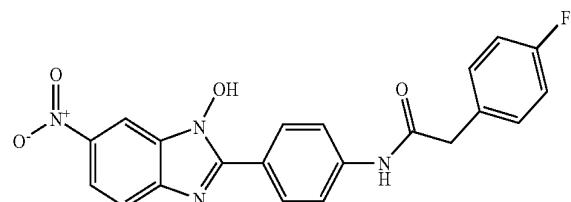
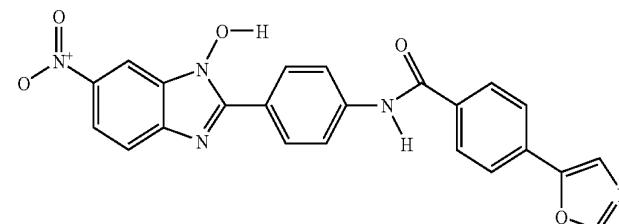
Compound Code	Compound
B	
C	
D	
E	
F	
G	
H	

TABLE 2-continued

TABLE 2-continued

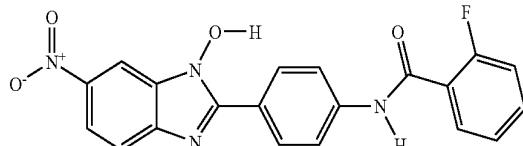
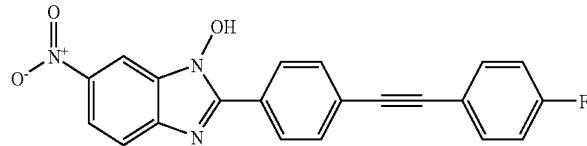
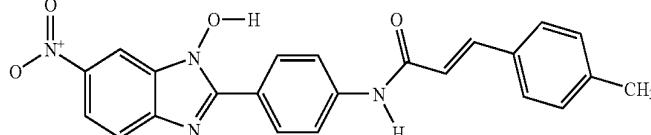
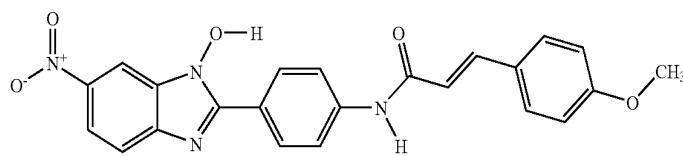
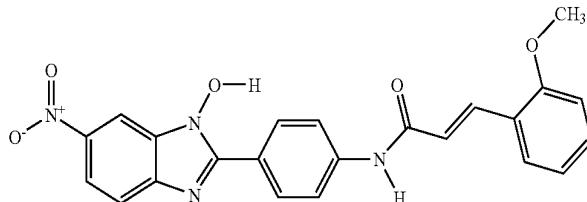
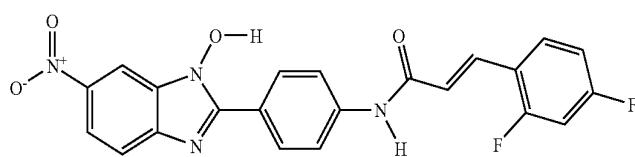
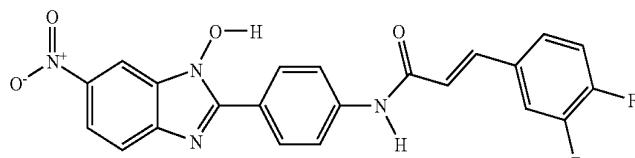
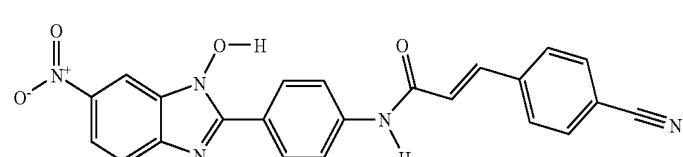
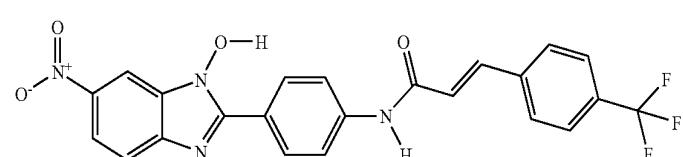
Compound Code	Compound
Q	
R	
S	
T	
U	
V	
W	
X	
Y	

TABLE 2-continued

Compound Code	Compound
Z	
AA	
AB	
AC	
AD	
AE	
AF	

TABLE 2-continued

Compound Code	Compound
AG	
AH	
AI	
AJ	
AK	
AM	
AN	
AO	

TABLE 2-continued

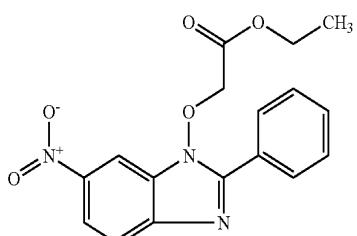
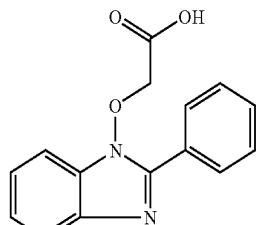
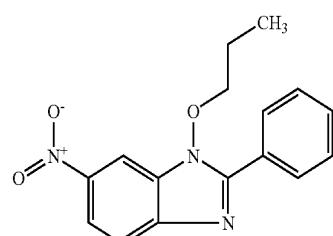
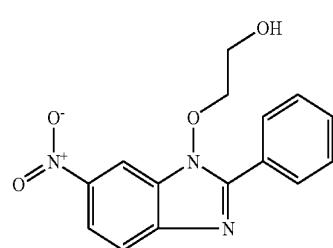
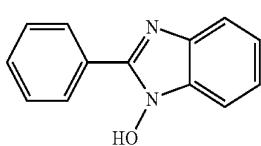
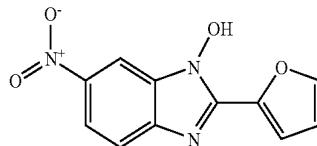
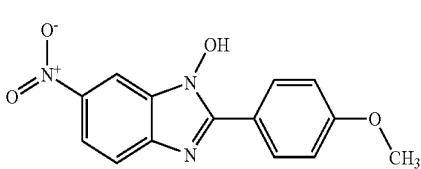
Compound Code	Compound
AP	
AQ	
AR	
AS	
AT	
AU	
AV	

TABLE 2-continued

Compound Code	Compound
AW	
AX	
AY	
AZ	
BA	
BB	
BC	
BD	

TABLE 2-continued

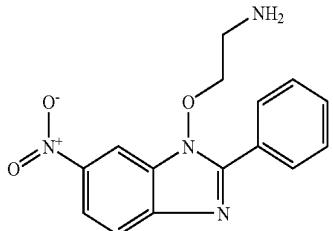
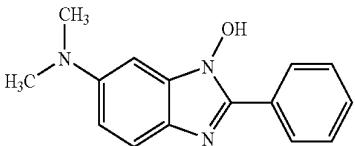
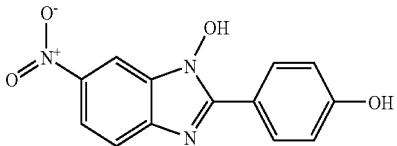
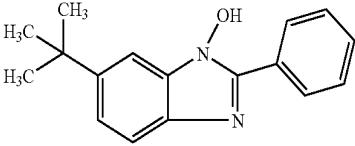
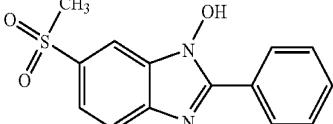
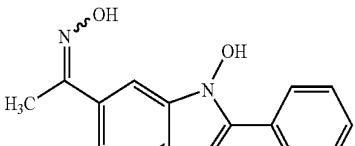
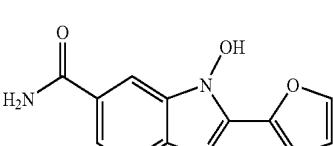
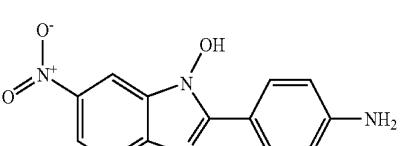
Compound Code	Compound
BE	
BF	
BG	
BH	
BI	
BJ	
BK	
BL	

TABLE 2-continued

Compound Code	Compound
BN	
BO	
BP	
BQ	
BR	
BS	
BT	
BU	

TABLE 2-continued

Compound Code	Compound
BV	
BW	
BX	
BZ	
CA	
CB	
CD	
CE	

TABLE 2-continued

Compound Code	Compound
CG	
CH	
CJ	
CK	
CL	
CM	
CO	
CP	
CQ	

TABLE 2-continued

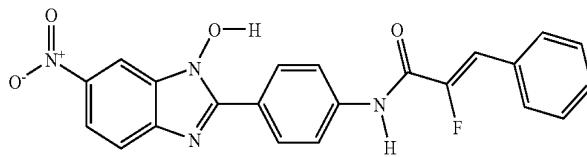
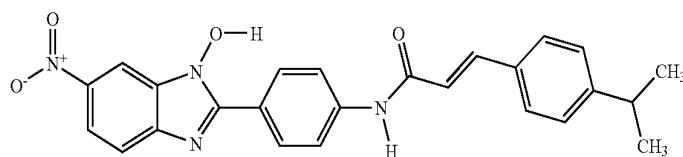
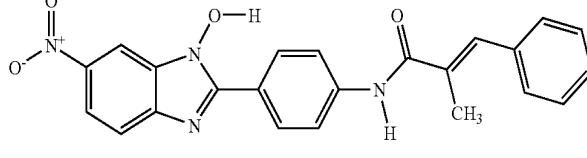
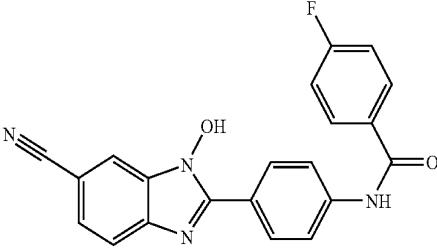
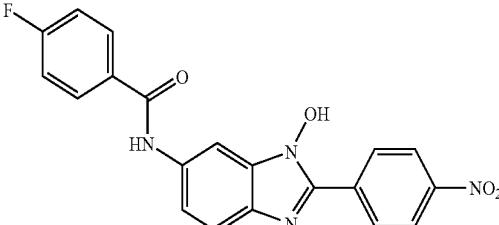
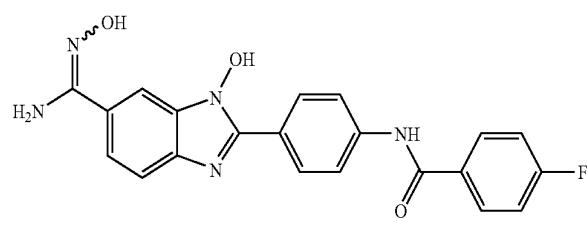
Compound Code	Compound
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CS	
CT	
CV	
CW	
CX	

TABLE 2-continued

Compound Code	Compound
CY	
CZ	
DA	
DB	
DC	
DD	

TABLE 2-continued

Compound Code	Compound
DE	
DF	
DG	
DH	
DI	
DJ	
DK	

TABLE 2-continued

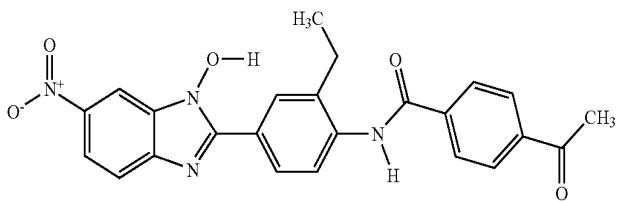
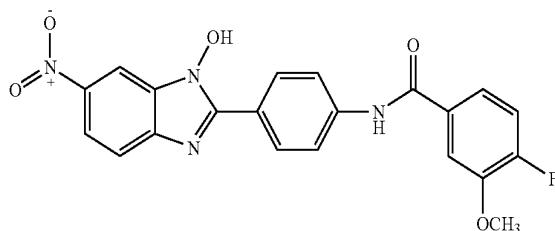
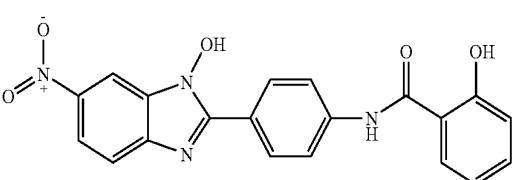
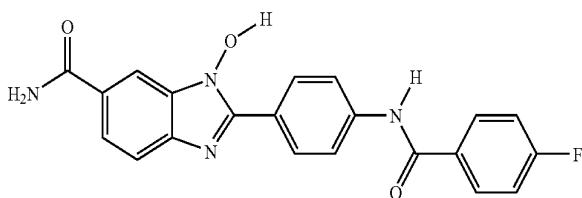
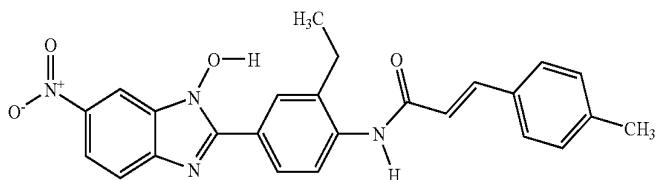
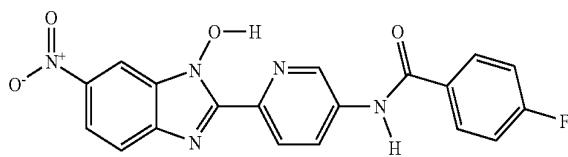
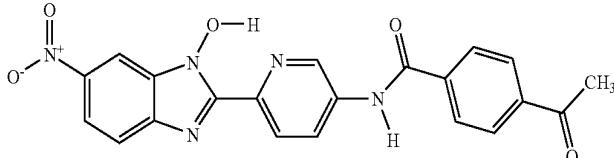
Compound Code	Compound
DL	
DM	
DN	
DO	
DP	
DQ	
DR	

TABLE 2-continued

Compound Code	Compound
DS	
DT	
DU	
DV	
DW	
DX	
DY	

TABLE 2-continued

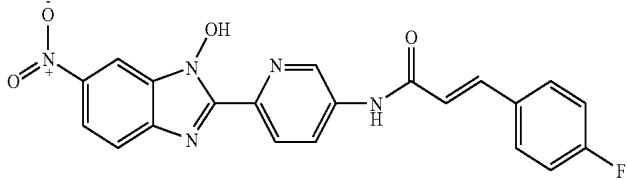
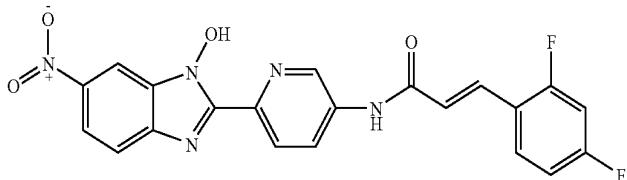
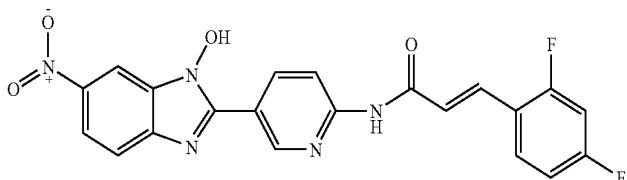
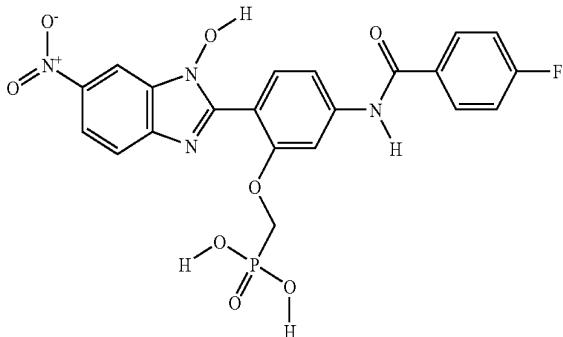
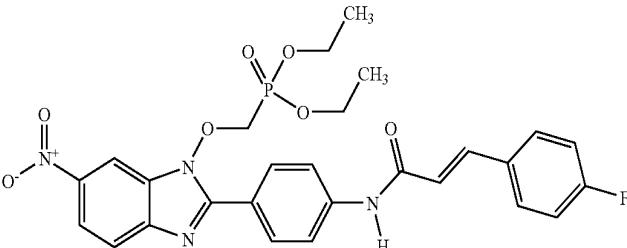
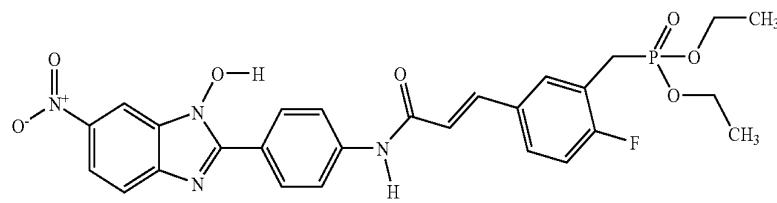
Compound Code	Compound
DZ	
EA	
EB	
EC	
ED	
EF	

TABLE 2-continued

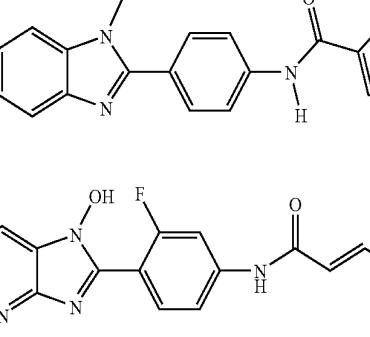
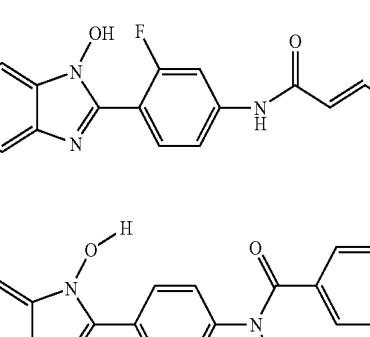
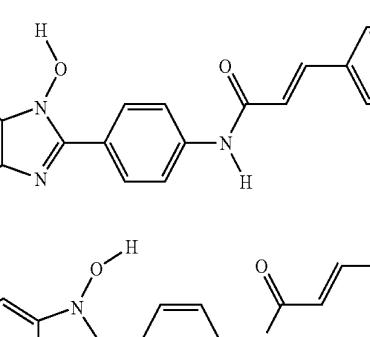
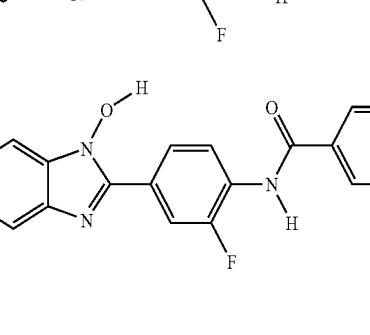
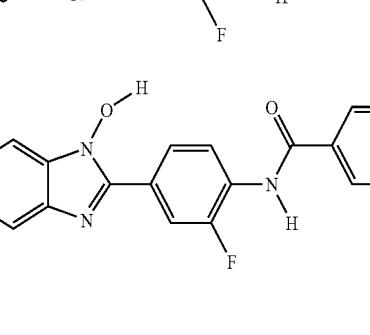
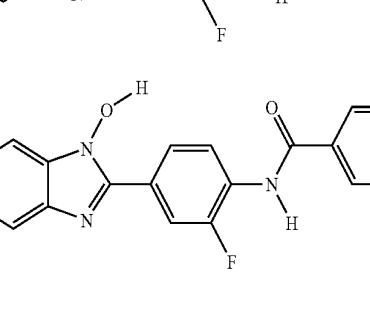
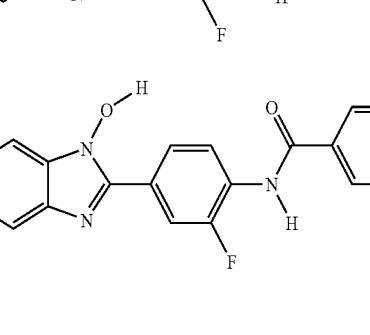
Compound Code	Compound
EG	
EH	
EI	
EJ	
EK	
EL	
EM	

TABLE 2-continued

TABLE 2-continued

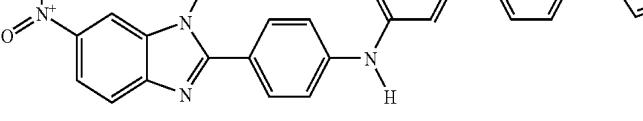
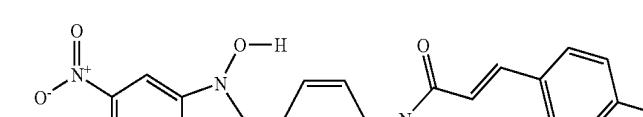
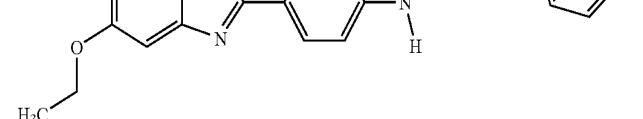
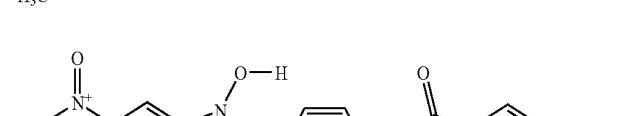
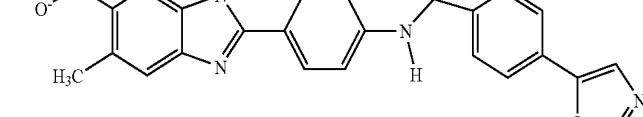
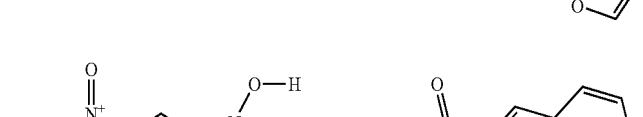
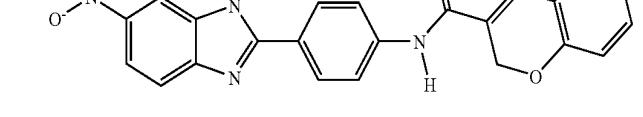
Compound Code	Compound
EU	
EV	
EX	
EY	
EZ	
FA	
FB	

TABLE 2-continued

Compound Code	Compound
FD	
FE	
FF	
FG	
FH	
FI	

TABLE 2-continued

TABLE 2-continued

Compound Code	Compound
FQ	
FR	
FS	
FT	
FU	

TABLE 2-continued

Compound Code	Compound
FV	
FW	
FX	
FY	
FZ	
GA	
GB	
GC	

TABLE 2-continued

Compound Code	Compound
GD	
GE	
GF	
GH	
GI	
GK	

TABLE 2-continued

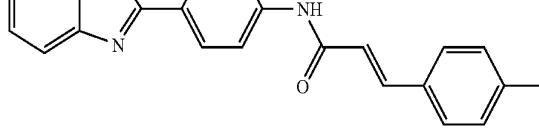
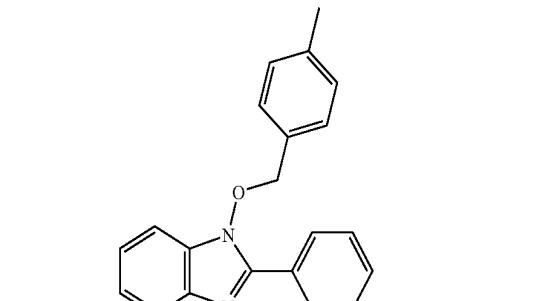
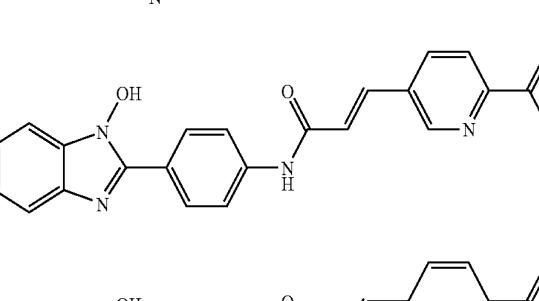
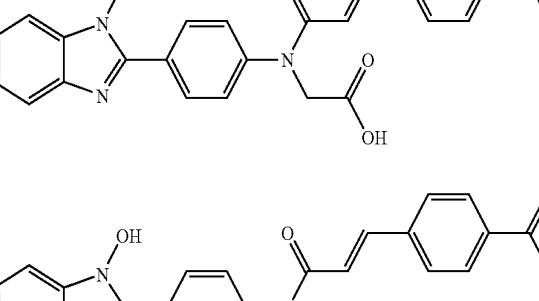
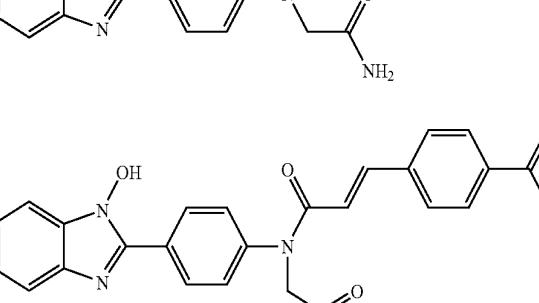
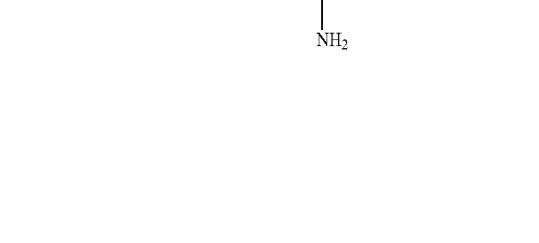
Compound Code	Compound
GL	
GM	
GN	
GO	
GP	
GQ	

TABLE 2-continued

[0658] In one embodiment, the pharmaceutically acceptable salt is sodium or potassium.

[0659] The EC₅₀ of a transcription factor modulating compound can be measured using the assay described in Example 2. In a further embodiment, the transcription factor modulating compound has an EC₅₀ activity against SoxS of less than about 10 μ M, less than about 5 μ M, or less than about 1 μ M, as described in Examples 3, 14 and 15. In a further embodiment, the transcription factor modulating compound can have an EC₅₀ activity against MarA of less than about 10 μ M, less than about 5 μ M, or less than about 1 μ M. In yet another embodiment, the transcription factor modulating compound can have an EC₅₀ against LcrF (VirF) of less than about 10 μ M, less than about 5 μ M, or less than about 1 μ M, as described in Examples 5 and 15. In a further embodiment, the transcription factor modulating compound can have an EC₅₀ against ExsA of less than about 10 jtM, less than about 5 jtM,

[0660] In one embodiment, the invention pertains, at least in part, to a method for reducing or preventing the spread of microbial cells from one or more organs (e.g., liver, kidney, lungs, brain or spleen) to another organ or organs in a subject

by administering to the subject an effective amount of a transcription factor modulating compound (e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV or a compound of Table 2). In another embodiment, the invention pertains, at least in part, to a method for reducing the bacterial burden (e.g., the amount of bacteria) in one or more organs in the subject's body (e.g., lungs, brain, liver, spleen and kidneys) by administering an effective amount of a transcription factor modulating compound compound (e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV or a compound of Table 2).

[0661] In another embodiment, the transcription factor modulating compound causes a log decrease in CFU/g of a tissue in an animal compared to control tissue, for example, in lung tissue or kidney tissue. This can be measured using the assay described Example 3 and 7. In one embodiment, the transcription factor modulating compound cause a log decrease in CFU/g of tissue of greater than 1.0 CFU/g. In a further embodiment, the compound causes a log decrease in CFU/g of tissue greater than 2.5 CFU/g. In one embodiment, the transcription factor modulating compound that cause a log decrease in CFU/g is compound E, F, H, M, BO or CG.

[0662] In another embodiment, the transcription factor modulating compound (e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII or XIV or a compound of Table 2) induces a decrease in the cytotoxicity of a microbial agent (e.g., the ability of a microbial agent to kill a cell). In one embodiment, the transcription factor modulating compound inhibits the cytotoxicity of a microbe compared to a control, as described in Examples 6 and 9. In one embodiment, the cytotoxicity is inhibited by about 10%, by about 20%, by about 30%, about 40%, by about 50%, by about 60%, by about 70%, by about 80%, by about 90% or about 100%.

[0663] In another embodiment, the transcription factor modulating compound effective against *Pseudomonas aeruginosa* is compound A, C, D, E, F, H, I, J, K, M, S, T, U, V, W, X, Y, AB, AC, AD, AE, AJ, AK, AL, AM or AN.

[0664] In a further embodiment, the transcription factor modulating compound effective against *Yersinia pseudotuberculosis* is compound A, B, C, D, E, F, H, I, J, K, M, S, T, U, V, W, X or Y.

[0665] In a further embodiment, the transcription factor modulating compound is not apigenin.

[0666] The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C₁-C₆ includes alkyl groups containing 1 to 6 carbon atoms.

[0667] Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, —COOH, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclcyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

[0668] The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl,

pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, e.g., tricyclic, bicyclic, e.g., naphthalene, benzoxazole, benzo-dioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles," "heterocycles," "heteroaryls" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, —COOH, alkylcarbonyl, alkylaminocarbonyl, arylalkyl aminocarbonyl, alkylaminocarbonyl, alkylcarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclcyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (e.g., tetralin).

[0669] The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

[0670] For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ or straight chain, C₃-C₆ for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C₂-C₆ includes alkenyl groups containing 2 to 6 carbon atoms.

[0671] Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls," the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, —COOH, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino,

arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0672] The term “alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

[0673] For example, the term “alkynyl” includes straight-chain alkynyl groups (e.g., ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (e.g., C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term C₂-C₆ includes alkynyl groups containing 2 to 6 carbon atoms.

[0674] Moreover, the term alkynyl includes both “unsubstituted alkynyls” and “substituted alkynyls,” the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, —COOH, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0675] Unless the number of carbons is otherwise specified, “lower alkyl” as used herein means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. “Lower alkenyl” and “lower alkynyl” have chain lengths of, for example, 2-5 carbon atoms.

[0676] The term “acyl” includes compounds and moieties which contain the acyl radical (CH₃ CO—) or a carbonyl group. It includes substituted acyl moieties. The term “substituted acyl” includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, —COOH, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0677] The term “acylamino” includes moieties wherein: an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0678] The term “aryl” includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aryl groups include phenylcarboxy, naphthyl carboxy, etc.

[0679] The terms “alkoxyalkyl,” “alkylaminoalkyl” and “thioalkoxyalkyl” include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, e.g., oxygen, nitrogen or sulfur atoms.

[0680] The term “alkoxy” includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropoxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxycarbonyloxy, —COOH, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

[0681] The term “amine” or “amino” includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term includes “alkyl amino” which comprises groups and compounds wherein: the nitrogen is bound to at least one additional alkyl group. The term “dialkyl amino” includes groups wherein: the nitrogen atom is bound to at least two additional alkyl groups. The term “aryl amino” and “diaryl amino” include groups wherein: the nitrogen is bound to at least one or two aryl groups, respectively. The term “alkylarylamino,” “alkylaminocarbonyl” or “arylaminoalkyl” refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term “alkaminoalkyl” refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

[0682] The term “amide,” “amido” or “aminocarbonyl” includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes “alkaminocarbonyl” or “alkylaminocarbonyl” groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms “alkylaminocarbonyl,” “alkenylaminocarbonyl,” “alkynylaminocarbonyl,” “arylamino carbonyl,” “alkylcarbonylamino,” “alkenylcarbonylamino,” “alkynylcarbonylamino,” and “arylcarbonyl”

lmino” are included in term “amide.” Amides also include urea groups (aminocarbonylaminol) and carbamates (oxycarbonylaminol).

[0683] The term “carbonyl” or “carboxy” includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. The carbonyl can be further substituted with any moiety which allows the compounds of the invention to perform its intended function. For example, carbonyl moieties may be substituted with alkyls, alkenyls, alkynyls, aryls, alkoxy, aminos, etc. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc. The term “carboxy” further includes the structure of —COOH and —COO⁻.

[0684] The term “oximyl” includes compounds and moieties that contain a carbon connected with a double bond to a nitrogen atom, which is, in turn connected to a hydroxyl or an alkoxy group. The term “hydrazinyl” includes compounds and moieties that contain a carbon connected with a double bond to a nitrogen atom, which is, in turn, connected to an amino group.

[0685] The term “thiocarbonyl” or “thiocarboxy” includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0686] The term “ether” includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes “alkoxyalkyl” which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group.

[0687] The term “ester” includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term “ester” includes alkoxy carboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxy carbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above.

[0688] The term “thioether” includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term “alkthioalkyls” include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term “alkthioalkenyls” and alkthioalkynyls” refer to compounds or moieties wherein: an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0689] The term “hydroxyl” or “hydroxyl” includes groups with an —OH or —O—.

[0690] The term “halogen” includes fluorine, bromine, chlorine, iodine, etc. The term “perhalogenated” generally refers to a moiety wherein: all hydrogens are replaced by halogen atoms.

[0691] The terms “polycyclol” or “polycyclic radical” refer to two or more cyclic rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclols) in which two or more carbons are common to two adjoining rings, e.g., the rings are “fused rings.” Rings that are joined through non-adjacent atoms are termed “bridged” rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy carbonyloxy, aryloxy carbonyloxy, —COOH, alkylcarbonyl, alkoxy carbonyl,

alkylamino carbonyl, arylalkylaminocarbonyl, alkenylamino carbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amido, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonyl amino, arylcarbonyl amino, carbamoyl and ureido), amidino, imino, sulphydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclol, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0692] The term “heteroatom” includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

[0693] The term “electron withdrawing substituent” includes substituents which tend to withdraw electron density away from the aromatic ring. Examples of such groups include, but are not limited to, ammonium (including alkylammonium, arylammonium, and heteroaryl ammonium), sulfonyl (including, but not limited to, alkylsulfonyl, arylsulfonyl, and heteroaryl sulfonyl), halogen, perhalogenated alkyl, cyano, oxime, carbonyl (including alkylcarbonyl, arylcarbonyl, and heteroaryl carbonyl), and nitro.

[0694] The term “electron donating substituent” includes substituents which provide additional electron density to the aromatic ring. Example of electron donating substituents include O—, amines, amides, hydroxyl, alkoxy, amides, esters, alkenyl, alkyl, and aryl groups.

[0695] The term “lipophilic groups” include groups which are substantially non-polar. Examples of lipophilic groups include alkyl, alkenyl, aryl, halogens, nitro, cyano, and alkoxy groups. The groups can further be substituted with one or more halogens.

[0696] The invention provides compositions which include a therapeutically-effective amount or dose of a transcription factor modulating compound and/or a compound identified in any of the instant assays and one or more carriers (e.g., pharmaceutically acceptable additives and/or diluents). The pharmaceutical compositions of the invention may comprise any compound described in this application as a transcription factor modulating compound, an AraC family polypeptide modulating compound, a MarA family polypeptide modulating compound, a MarA family inhibiting compound, a MarA inhibiting compound, compounds of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2. Each of these compounds may be used alone or in combination as a part of a pharmaceutical composition of the invention. Furthermore, a composition can also include a second antimicrobial agent, e.g., an antibiotic.

[0697] The invention pertains to pharmaceutical compositions comprising an effective amount of a transcription factor modulating compound (e.g., a MarA family polypeptide modulating compound or an AraC family polypeptide modulating compound), and a pharmaceutically acceptable carrier. In one embodiment, the transcription factor modulating compound is of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2.

[0698] In one embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a transcription factor modulating compound, wherein: said compound is of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2. In another embodiment, the pharmaceutical composition can further comprise an antibiotic.

[0699] In one embodiment, the transcription factor modulating compound (e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2) is administered in combination with an antibiotic. The language “in combination with” an antibiotic includes co-administration of the transcription factor modulating compound and with an antibiotic, administration of the transcription factor modulating compound first, followed by administration of an antibiotic, and administration of the antibiotic first, followed by administration of the transcription factor modulating compound. The transcription factor modulating compound can be administered substantially at the same time as the antibiotic or at substantially different times as the antibiotic. Optimal administration rates for a given protocol of administration of the transcription factor modulating and/or the antibiotic can be readily ascertained by those skilled in the art using conventional dosage determination tests conducted with regard to the specific compounds being utilized, the particular compositions formulated, the mode of application, the particular site of administration and the like.

[0700] The term “antibiotic” refers to chemotherapeutic agents that inhibit or abolish the growth of microbial cells (e.g., bacteria or fungi). Suitable antibiotics include, but are not limited, aminoglycosides, ancimycins, carbacephams, cephalosporins, glycopeptides, macrolides, monobactems, penicillins, polypeptides, quinolines, sulphonamides, tetracyclines and the like. One of skill in the art using conventional medical diagnoses would be able to determine the appropriate antibiotic agent to administer in combination with the transcription factor modulating compounds of the invention.

[0701] The language “effective amount” of the compound is that amount necessary or sufficient to treat, prevent or ameliorate a bacterial infection (e.g., pneumonia, urinary tract infection, kidney infection), biofilm formation, bacterial growth (e.g., on a contact lens), corneal ulcers and burn wounds in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, etc. One of ordinary skill in the art would be able to study the aforementioned factors and make the determination regarding the effective amount of the transcription factor modulating compounds without undue experimentation.

[0702] The term “subject” includes plants and animals (e.g., vertebrates, amphibians, fish, mammals, e.g., cats, dogs, horses, pigs, cows, sheep, rodents, rabbits, squirrels, bears, primates (e.g., chimpanzees, gorillas, and humans) which are capable of suffering from a bacterial associated disorder. The term “subject” also comprises immunocompromised subjects, who may be at a higher risk for infection.

[0703] The terms “preventing” and “prevention” include the administration of an effective amount of the transcription factor modulating compound to prevent a bacterial infection (e.g., pneumonia, urinary tract infection, kidney infection), biofilm formation, bacterial growth (e.g., on a contact lens or a medical indwelling device) from occurring.

[0704] The terms “treating” and “treatment” include the administration to a subject an effective amount of the transcription factor modulating compound to treat the subject for a bacterial infection (e.g., pneumonia, urinary tract infection), biofilm formation, bacterial growth (e.g., on a contact lens), corneal ulcers and burn wounds.

[0705] The transcription factor modulating compounds of the invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids.

The acids that may be used to prepare pharmaceutically acceptable acid addition salts of the transcription factor modulating compounds of the invention that are basic in nature are those that form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and palmoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Although such salts must be pharmaceutically acceptable for administration to a subject, e.g., a mammal, it is often desirable in practice to initially isolate a transcription factor modulating compound of the invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The preparation of other transcription factor modulating compounds of the invention not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

[0706] The transcription factor modulating compounds of the invention that are acidic in nature are capable of forming a wide variety of base salts. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those transcription factor modulating compounds of the invention that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmaceutically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines. The pharmaceutically acceptable base addition salts of transcription factor modulating compounds of the invention that are acidic in nature may be formed with pharmaceutically acceptable cations by conventional methods. Thus, these salts may be readily prepared by treating the transcription factor modulating compounds of the invention with an aqueous solution of the desired pharmaceutically acceptable cation and evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, a lower alkyl alcohol solution of the transcription factor modulating compounds of the invention may be mixed with an alkoxide of the desired metal and the solution subsequently evaporated to dryness.

[0707] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microbes may be ensured by the inclusion of various antibacterial and anti-fungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include

isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0708] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[0709] Pharmaceutical compositions of the present invention may be administered to epithelial surfaces of the body orally, parenterally, topically, rectally, nasally, intravaginally, intracisternally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, etc., administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal or vaginal suppositories.

[0710] The phrases "parenteral administration" and "administered parenterally" as used herein mean modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0711] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a sucrose octasulfate and/or an antibacterial, drug or other material other than directly into the central nervous system, such that it enters the subject's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[0712] In some methods, the compositions of the invention can be topically administered to any epithelial surface. An "epithelial surface" according to this invention is defined as an area of tissue that covers external surfaces of a body, or which lines hollow structures including, but not limited to, cutaneous and mucosal surfaces. Such epithelial surfaces include oral, pharyngeal, esophageal, pulmonary, ocular, aural, nasal, buccal, lingual, vaginal, cervical, genitourinary, alimentary, and anorectal surfaces.

[0713] Compositions can be formulated in a variety of conventional forms employed for topical administration. These include, for example, semi-solid and liquid dosage forms, such as liquid solutions or suspensions, suppositories, douches, enemas, gels, creams, emulsions, lotions, slurries, powders, sprays, lipsticks, foams, pastes, toothpastes, ointments, salves, balms, douches, drops, troches, chewing gums, lozenges, mouthwashes, rinses.

[0714] Conventionally used carriers for topical applications include pectin, gelatin and derivatives thereof, polyactic acid or polyglycolic acid polymers or copolymers thereof, cellulose derivatives such as methyl cellulose, carboxymethyl cellulose, or oxidized cellulose, guar gum, acacia gum, karaya gum, tragacanth gum, bentonite, agar, carbomer, blad-

derwrack, ceratonia, dextran and derivatives thereof, ghatti gum, hectorite, ispaghula husk, polyvinylpyrrolidone, silica and derivatives thereof, xanthan gum, kaolin, talc, starch and derivatives thereof, paraffin, water, vegetable and animal oils, polyethylene, polyethylene oxide, polyethylene glycol, polypropylene glycol, glycerol, ethanol, propanol, propylene glycol (glycols, alcohols), fixed oils, sodium, potassium, aluminum, magnesium or calcium salts (such as chloride, carbonate, bicarbonate, citrate, gluconate, lactate, acetate, gluceptate or tartrate).

[0715] Such compositions can be particularly useful, for example, for treatment or prevention of an unwanted cell, e.g., vaginal *Neisseria gonorrhoeae*, or infections of the oral cavity, including cold sores, infections of eye, the skin, or the lower intestinal tract. Standard composition strategies for topical agents can be applied to the antiinfective compounds or a pharmaceutically acceptable salt thereof in order to enhance the persistence and residence time of the drug, and to improve the prophylactic efficacy achieved.

[0716] For topical application to be used in the lower intestinal tract or vaginally, a rectal suppository, a suitable enema, a gel, an ointment, a solution, a suspension or an insert can be used. Topical transdermal patches may also be used. Transdermal patches have the added advantage of providing controlled delivery of the compositions of the invention to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium.

[0717] Compositions of the invention can be administered in the form of suppositories for rectal or vaginal administration. These can be prepared by mixing the agent with a suitable non-irritating carrier which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum or vagina to release the drug. Such materials include cocoa butter, beeswax, polyethylene glycols, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent.

[0718] Compositions which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, films, or spray compositions containing such carriers as are known in the art to be appropriate. The carrier employed in the sucrose octasulfate/contraceptive agent should be compatible with vaginal administration and/or coating of contraceptive devices. Combinations can be in solid, semi-solid and liquid dosage forms, such as diaphragm, jelly, douches, foams, films, ointments, creams, balms, gels, salves, pastes, slurries, vaginal suppositories, sexual lubricants, and coatings for devices, such as condoms, contraceptive sponges, cervical caps and diaphragms.

[0719] For ophthalmic applications, the pharmaceutical compositions can 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 compositions can be formulated in an ointment such as petrolatum. Exemplary ophthalmic compositions include eye ointments, powders, solutions and the like.

[0720] Powders and sprays can contain, in addition to sucrose octasulfate and/or antibiotic or contraceptive agent(s), carriers such as lactose, talc, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0721] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular compound, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0722] Compositions of the invention can also be orally administered in any orally-acceptable dosage form including, but not limited to, capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of sucrose octasulfate and/or antibiotic or contraceptive agent(s) as an active ingredient. A compound may also be administered as a bolus, electuary or paste. 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 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.

[0723] Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0724] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tet-

rahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[0725] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[0726] Suspensions, in addition to the antiinfective agent(s) may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0727] Sterile injectable forms of the compositions of this invention can 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. Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0728] The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic 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. 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.

[0729] The transcription factor modulating compound or a pharmaceutically acceptable salt thereof will represent some percentage of the total dose in other dosage forms in a material forming a combination product, including liquid solutions or suspensions, suppositories, douches, enemas, gels, creams, emulsions, lotions slurries, soaps, shampoos, detergents, powders, sprays, lipsticks, foams, pastes, toothpastes, ointments, salves, balms, douches, drops, troches, lozenges, mouthwashes, rinses and others. Creams and gels for example, are typically limited by the physical chemical properties of the delivery medium to concentrations less than 20% (e.g., 200 mg/gm). For special uses, far less concentrated preparations can be prepared, (e.g., lower percent formulations for pediatric applications). For example, the pharmaceutical composition of the invention can comprise sucrose octasulfate in an amount of 0.001-99%, typically 0.01-75%, more typically 0.1-20%, especially 1-10% by weight of the total preparation. In particular, a preferred concentration thereof in the preparation is 0.5-50%, especially 0.5-25%, such as 1-10%. It can be suitably applied 1-10 times a day, depending on the type and severity of the condition to be treated or prevented.

[0730] Given the low toxicity of an antiinfective agent or a pharmaceutically acceptable salt thereof over many decades of clinical use as an anti-ulcerant [W. R. Garnett, *Clin. Pharm.* 1:307-314 (1982); R. N. Brogden et al., *Drugs* 27:194-209 (1984); D. M. McCarthy, *New Eng J. Med.*, 325:1017-1025 (1991), an upper limit for the therapeutically effective dose is not a critical issue.

[0731] In one embodiment, the transcription factor modulating compounds of the invention may be administered prophylactically. For prophylactic applications, the pharmaceutical composition of the invention can be applied prior to potential infection. The timing of application prior to potential infection can be optimized to maximize the prophylactic effectiveness of the compound. The timing of application will vary depending on the mode of administration, doses, the stability and effectiveness of composition, the frequency of the dosage, e.g., single application or multiple dosage. One skilled in the art will be able to determine the most appropriate time interval required to maximize prophylactic effectiveness of the compound.

[0732] A transcription factor modulating compound, e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2, when present in a composition will generally be present in an amount from about 0.000001% to about 100%, more preferably from about 0.001% to about 50%, and most preferably from about 0.01% to about 25%.

[0733] For compositions of the present invention comprising a carrier, the composition comprises, for example, from about 1% to about 99%, preferably from about 50% to about 99%, and most preferably from about 75% to about 99% by weight of at least one carrier.

[0734] The transcription factor modulating compounds of the invention may be formulated in a composition suitable for use in environments including industry, pharmaceuticals, household, and personal care. In an embodiment, the compounds of the invention are soluble in water. The modulating compounds may be applied or delivered with an acceptable carrier system. The composition may be applied or delivered with a suitable carrier system such that the active ingredient (e.g., formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2) may be dispersed or dissolved in a stable manner so that the active ingredient, when it is administered directly or indirectly, is present in a form in which it is available in a advantageous way.

[0735] Also, the separate components of the compositions of the invention may be preblended or each component may be added separately to the same environment according to a predetermined dosage for the purpose of achieving the desired concentration level of the treatment components and so long as the components eventually come into intimate admixture with each other. Further, the present invention may be administered or delivered on a continuous or intermittent basis.

[0736] The transcription factor modulating compound (e.g., a compound of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2) may be formulated with any suitable carrier and prepared for delivery in forms, such as, solutions, microemulsions, suspensions or aerosols. Generation of the aerosol or any other means of delivery of the present invention may be accomplished by any of the methods known in the art. For example, in the case of aerosol delivery, the compound is supplied in a finely divided form along with any suitable carrier with a propellant. Liquidified propellants are typically gases at ambient conditions and are condensed under pressure. The propellant may be any acceptable and known in the art including propane and butane, or other lower alkanes, such as those of up to 5 carbons. The composition is held within a container with an appropriate propellant and valve, and maintained at elevated pressure until released by action of the valve.

[0737] The compositions of the invention may be prepared in a conventional form suitable for, but not limited to topical or local application such as an ointment, paste, gel, spray and liquid, by including stabilizers, penetrants and the carrier or diluent with the compound according to a known technique in the art. These preparations may be prepared in a conventional form suitable for enteral, parenteral, topical or inhalational applications.

[0738] The present invention may be used in compositions suitable for household use. For example, compounds of the present invention are also useful as active antimicrobial ingredients in household products such as cleansers, detergents, disinfectants, dishwashing liquids, soaps and detergents. In an embodiment, the transcription factor modulating compound of the present invention may be delivered in an amount and form effective for the prevention of colonization, removal or death of microbes.

[0739] The compositions of the invention for household use comprise, for example, at least one transcription factor modulating compound of the invention and at least one suitable carrier. For example, the composition may comprise from about 0.00001% to about 50%, preferably from about 0.0001% to about 25%, most preferably from about 0.0005% to about 10% by weight of the modulating compound based on the weight percentage of the total composition.

[0740] The transcription factor modulating compounds of the present invention may also be used in hygiene compositions for personal care. For instance, compounds of the invention can be used as an active ingredient in personal care products such as facial cleansers, astringents, body wash, shampoos, conditioners, cosmetics and other hygiene products. The hygiene composition may comprise any carrier or vehicle known in the art to obtain the desired form (such as solid, liquid, semisolid or aerosol) as long as the effects of the compound of the present invention are not impaired. Methods of preparation of hygiene compositions are not described herein in detail, but are known in the art. For its discussion of such methods, *The CTFA Cosmetic Ingredient Handbook*, Second Edition, 1992, and pages 5-484 of *A Formulary of Cosmetic Preparations* (Vol. 2, Chapters 7-16) are incorporated herein by reference.

[0741] The hygiene composition for use in personal care comprise generally at least one modulating compound of the present application and at least one suitable carrier. For example, the composition may comprise from about 0.00001% to about 50%, preferably from about 0.0001% to about 25%, more preferably from about 0.0005% to about 10% by weight of the transcription factor modulating compound of the invention based on the weight percentage of the total composition.

[0742] The transcription factor modulating compounds of the present invention may be used in industry. In the industrial setting, the presence of microbes can be problematic, as microbes are often responsible for industrial contamination and biofouling. Compositions of the invention for industrial applications may comprise an effective amount of the compound of the present invention in a composition for industrial use with at least one acceptable carrier or vehicle known in the art to be useful in the treatment of such systems. Such carriers or vehicles may include diluents, deflocculating agents, penetrants, spreading agents, surfactants, suspending agents, wetting agents, stabilizing agents, compatibility agents, sticking agents, waxes, oils, co-solvents, coupling agents, foams, antifoaming agents, natural or synthetic polymers,

elastomers and synergists. Methods of preparation, delivery systems and carriers for such compositions are not described here in detail, but are known in the art. For its discussion of such methods, U.S. Pat. No. 5,939,086 is herein incorporated by reference. Furthermore, the preferred amount of the composition to be used may vary according to the active ingredient(s) and situation in which the composition is being applied. [0743] The transcription factor modulating compounds, e.g., compounds of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2, may be useful in nonaqueous environments. Such nonaqueous environments may include, but are not limited to, terrestrial environments, dry surfaces or semi-dry surfaces in which the compound or composition is applied in a manner and amount suitable for the situation.

[0744] The transcription factor modulating compounds, e.g., compounds of formula I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV or a compound of Table 2, of the present invention may be used to form coatings or layers on a variety of substrates including personal care products (such as toothbrushes, contact lens cases and dental equipment), healthcare products, household products, food preparation surfaces and packaging, and laboratory and scientific equipment. Further, other substrates include medical devices such as catheters, urological devices, blood collection and transfer devices, tracheotomy devices, intraocular lenses, wound dressings, sutures, surgical staples, membranes, shunts, gloves, tissue patches, prosthetic devices (e.g., heart valves) and wound drainage tubes. Still further, other substrates include textile products such as carpets and fabrics, paints and joint cement. A further use is as an antimicrobial soil fumigant.

[0745] The transcription factor modulating compounds of the invention may also be incorporated into polymers, such as polysaccharides (cellulose, cellulose derivatives, starch, pectins, alginate, chitin, guar, carrageenan), glycol polymers, polyesters, polyurethanes, polyacrylates, polyacrylonitrile, polyamides (e.g., nylons), polyolefins, polystyrenes, vinyl polymers, polypropylene, silks or biopolymers. The modulating compounds may be conjugated to any polymeric material such as those with the following specified functionality: 1) carboxy acid, 2) amino group, 3) hydroxyl group and/or 4) haloalkyl group.

[0746] The composition for treatment of nonaqueous environments may comprise at least one transcription factor modulating compound of the present application and at least one suitable carrier. In an embodiment, the composition comprises from about 0.001% to about 75%, advantageously from about 0.01% to about 50%, and preferably from about 0.1% to about 25% by weight of a transcription factor modulating compound of the invention based on the weight percentage of the total composition.

[0747] The transcription factor modulating compounds and compositions of the invention may also be useful in aqueous environments. "Aqueous environments" include any type of system containing water, including, but not limited to, natural bodies of water such as lakes or ponds; artificial, recreational bodies of water such as swimming pools and hot tubs; and drinking reservoirs such as wells. The compositions of the present invention may be useful in treating microbial growth in these aqueous environments and may be applied, for example, at or near the surface of water.

[0748] The compositions of the invention for treatment of aqueous environments may comprise at least one transcription factor modulating compound of the present invention and

at least one suitable carrier. In an embodiment, the composition comprises from about 0.001% to about 50%, advantageously from about 0.003% to about 15%, preferably from about 0.01% to about 5% by weight of the compound of the invention based on the weight percentage of the total composition.

[0749] The present invention also provides a process for the production of an antibiofouling composition for industrial use. Such process comprises bringing at least one of any industrially acceptable carrier known in the art into intimate admixture with a transcription factor modulating compound of the present invention. The carrier may be any suitable carrier discussed above or known in the art.

[0750] The suitable antibiofouling compositions may be in any acceptable form for delivery of the composition to a site potentially having, or having at least one living microbe. The antibiofouling compositions may be delivered with at least one suitably selected carrier as hereinbefore discussed using standard formulations. The mode of delivery may be such as to have a binding inhibiting effective amount of the antibiofouling composition at a site potentially having, or having at least one living microbe. The antibiofouling compositions of the present invention are useful in treating microbial growth that contributes to biofouling, such as scum or slime formation, in these aqueous environments. Examples of industrial processes in which these compounds might be effective include cooling water systems, reverse osmosis membranes, pulp and paper systems, air washer systems and the food processing industry. The antibiofouling composition may be delivered in an amount and form effective for the prevention, removal or termination of microbes.

[0751] The antibiofouling composition of the present invention generally comprise at least one compound of the invention. The composition may comprise from about 0.001% to about 50%, more preferably from about 0.003% to about 15%, most preferably from about 0.01% to about 5% by weight of the compound of the invention based on the weight percentage of the total composition.

[0752] The amount of antibiofouling composition may be delivered in an amount of about 1 mg/l to about 1000 mg/l, advantageously from about 2 mg/l to about 500 mg/l, and preferably from about 20 mg/l to about 140 mg/l.

[0753] Antibiofouling compositions for water treatment generally comprise transcription factor modulating compounds of the invention in amounts from about 0.001% to about 50% by weight of the total composition. Other components in the antibiofouling compositions (used at 0.1% to 50%) may include, for example, 2-bromo-2-nitropropane-1, 3-diol (BNPD), β -nitrostyrene (BNS), dodecylguanidine hydrochloride, 2,2-dibromo-3-nitrilopropionamide (DB-NPA), glutaraldehyde, isothiazolin, methylene bis(thiocyanate), triazines, n-alkyl dimethylbenzylammonium chloride, trisodium phosphate-based antimicrobials, tributyltin oxide, oxazolidines, tetrakis(hydroxymethyl)phosphonium sulfate (THPS), phenols, chromated copper arsenate, zinc or copper pyrithione, carbamates, sodium or calcium hypochlorite, sodium bromide, halohydantoin (Br, Cl), or mixtures thereof.

[0754] Other possible components in the compositions of the invention include biocides (about 0.1% to about 15% by weight of the total composition), water, glycols (about 20-30%) or Pluronic (at approximately 7% by weight

of the total composition). The concentration of antibiofouling composition for continuous or semi-continuous use is about 5 to about 70 mg/l.

[0755] Antibiofouling compositions for industrial water treatment may comprise compounds of the invention in amounts from about 0.001% to about 50% based on the weight of the total composition. The amount of compound of the invention in antibiofouling compositions for aqueous water treatment may be adjusted depending on the particular environment. Shock dose ranges are generally about 20 to about 140 mg/l; the concentration for semi-continuous use is about 0.5× of these concentrations.

[0756] The invention also pertains, at least in part, to a method of regulating biofilm development. The method includes administering a composition which contains a transcription factor modulating compound of the invention. The composition can also include other components which enhance the ability of the composition to degrade biofilms.

[0757] The composition can be formulated as a cleaning product, e.g., a household or an industrial cleaner to remove, prevent, inhibit, or modulate biofilm development. Advantageously, the biofilm is adversely affected by the administration of the compound of the invention, e.g., biofilm development is diminished. These compositions may include compounds such as disinfectants, soaps, detergents, as well as other surfactants. Examples of surfactants include, for example, sodium dodecyl sulfate; quaternary ammonium compounds; alkyl pyridinium iodides; TWEEN 80, TWEEN 85, TRITON X-100; BRIJ 56; biological surfactants; rhamnolipid, surfactin, viscosin, and sulfonates. The composition of the invention may be applied in known areas and surfaces where disinfection is required, including but not limited to drains, shower curtains, grout, toilets and flooring. A particular application is on hospital surfaces and medical instruments. The disinfectant of the invention may be useful as a disinfectant for bacteria such as, but not limited to, *Pseudomonadaceae*, *Azatobacteraceae*, *Rhizobiaceae*, *Mthylococcaceae*, *Halobacteriaceae*, *Acetobacteraceae*, *Legionellaceae*, *Neisseriaceae*, and other genera.

[0758] A dentifrice or mouthwash containing the compounds of the invention may be formulated by adding the compounds of the invention to dentifrice and mouthwash formulations, e.g., as set forth in *Remington's Pharmaceutical Sciences*, 18th Ed., Mack Publishing Co., 1990, Chapter 109 (incorporated herein by reference in its entirety). The dentifrice may be formulated as a gel, paste, powder or slurry. The dentifrice may include binders, abrasives, flavoring agents, foaming agents and humectants. Mouthwash formulations are known in the art, and the compounds of the invention may be advantageously added to them.

[0759] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of cell biology, cell culture, molecular biology, genetics, microbiology, recombinant DNA, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature. See, for example, Genetics; Molecular Cloning A Laboratory Manual, 2nd Ed., ed. by Sambrook, J. et al. (Cold Spring Harbor Laboratory Press (1989)); Short Protocols in Molecular Biology, 3rd Ed., ed. by Ausubel, F. et al. (Wiley, NY (1995)); DNA Cloning, Volumes I and II (D. N. Glover ed., 1985); Oligonucleotide Synthesis (M. J. Gait ed. (1984)); Mullis et al. U.S. Pat. No. 4,683,195; Nucleic Acid Hybridization (B. D. Hames & S. J. Higgins eds. (1984)); the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.);

Immunochemical Methods In Cell And Molecular Biology (Mayer and Walker, eds., Academic Press, London (1987)); Handbook Of Experimental Immunology, Volumes 1-IV (D. M. Weir and C. C. Blackwell, eds. (1986)); and Miller, J. Experiments in Molecular Genetics (Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (1972)).

[0760] The contents of all references, patent applications and patents, cited throughout this application are hereby expressly incorporated by reference. Each reference disclosed herein is incorporated by reference herein in its entirety. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety.

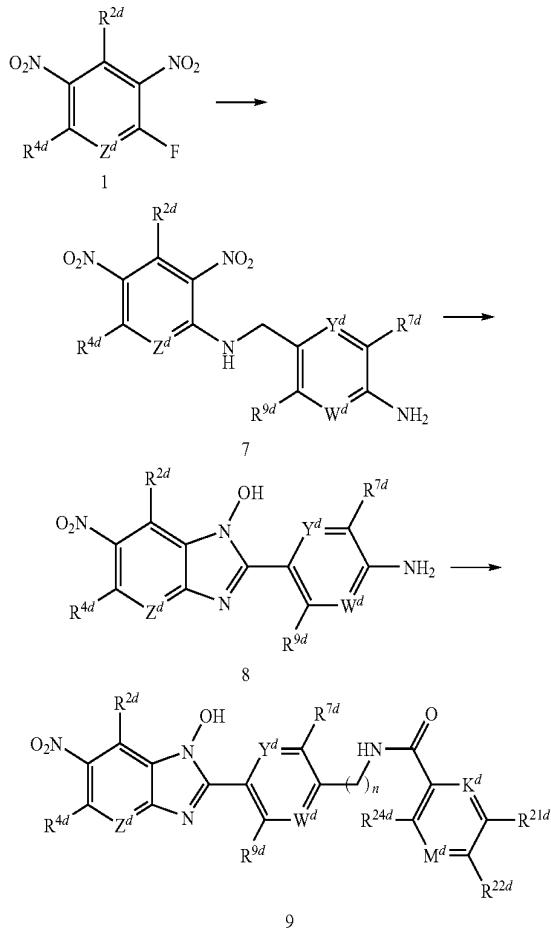
EXEMPLIFICATION OF THE INVENTION

Example 1

Synthesis of Selected Compounds of the Invention

[0761]

Scheme 1



$Y = \text{substituted or unsubstituted phenyl, substituted or unsubstituted heterocycle (5 or 6 membered rings), etc.}$

Preparation of N-(4-aminobenzyl)-2,4-dinitroaniline (7)

[0762] To a solution of 4-aminobenzylamine (25.5 mL, 225 mmol) and powdered NaHCO₃ (94.5 g, 1125 mmol) in anhy-

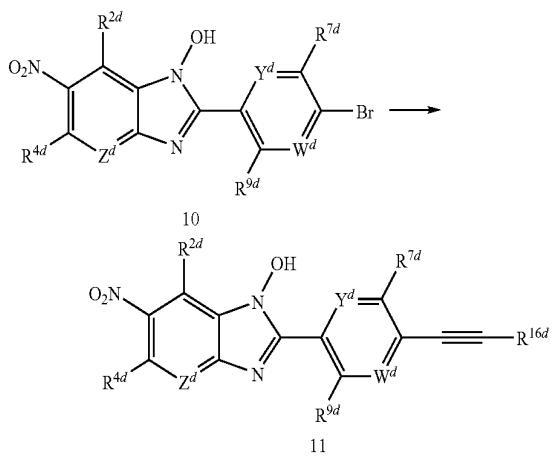
drous DMF (300 mL) was added 2,4-dinitrofluorobenzene (1) (18.8 mL, 150 mmol) dropwise at room temperature. After 2 hours, the solution was slowly diluted with water (1000 mL) to precipitate the product, which was collected on a fritted funnel while rinsing with water until the eluent was colorless. The solid was further dried under high vacuum to afford 43.0 g as a bright orange solid in 99% yield.

Preparation of 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole (8)

[0763] To a solution of N-(4-aminobenzyl)-2,4-dinitroaniline (7) (21.6 g, 74.9 mmol) in anhydrous EtOH (300 mL) and anhydrous DMF (75 mL) was slowly added sodium methoxide (30% w/w) (69.1 g, 375 mmol) at room temperature under argon atmosphere, followed by heating to 60° C. for 2 hours. After cooling to ambient temperature, the solution was diluted with water (700 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product was recrystallized in hot EtOH to afford 18.1 g as a brown solid in 90% yield.

[0764] General procedure for the preparation of N-acyl-6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazoles (9) To a solution of 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole (8) (270 mg, 1.00 mmol) in anhydrous pyridine (2.0 mL) was added acid chlorides (2.5 mmol) or the in situ mixed anhydrides at room temperature. (The mixed anhydride was prepared by adding trimethylacetyl chloride (2.5 mmol) dropwise to a solution of the carboxylic acid (2.55 mmol) in anhydrous pyridine at 0° C. After 1 hour, 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole was added in one portion.) After stirring for 2-3 hours at room temperature, the solution was diluted with 3M NaOH (6.0 mL) and stirred for another hour. The deep amber solution was diluted with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product was further purified by either preparatory HPLC or by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform.

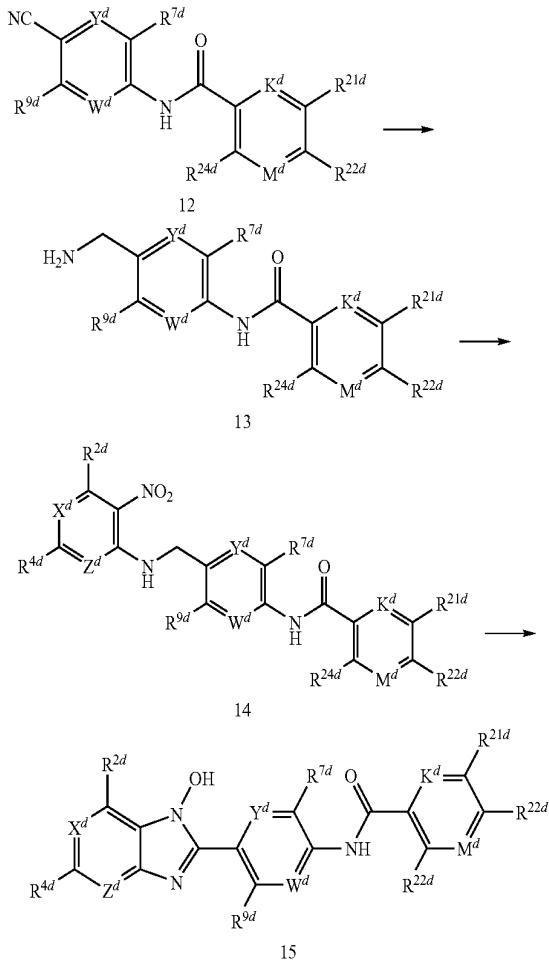
Scheme 2



Preparation of 6-nitro-2-(4-phenylethynyl-phenyl)-1-hydroxybenzimidazoles (11)

[0765] A solution of 6-nitro-2-(4-bromophenyl)-1-hydroxybenzimidazole (10) (334 mg, 1 mmol) in DMF (2 mL) and Et₃N (1 mL) was degassed with argon for 30 minutes. Phenylacetylene (408 mg), 4 mmol, CuI (38 mg, 0.2 mmol), and Pd(PPh₃)₄ (116 mg, 0.1 mmol) were added. Degassing was continued for another 5 minutes and the reaction vial was placed in a sand bath preheated to 100° C. overnight. The reaction was cooled and diluted with 50 mL of water and the pH was adjusted to pH 4 with 10% aqueous HCl. The solids were filtered and triturated successively with 1,2-dichloroethane and warm methanol. The resultant yellow solid was further purified by passing through a silica gel flash column eluting with EtOAc:Hexanes (1:1). Fractions containing the product were pooled and evaporated to provide 27 mg of a yellow solid.

Scheme 3



Preparation of 4-phenylamidobenzylamine (13)

[0766] In a pressure reaction, 4-dimethylaminophenylamidobenzonitrile (12) (26 g, 98 mmol) was dissolved in anhydrous THF (940 mL), and the solution was purged with argon for 2-3 minutes, followed by the addition of 11 mL of uniformly suspended catalyst (Raney® nickel 2400, suspension

in water). After addition of a small amount of methanol to the suspension, the reactor was pressurized at 55 psi H₂ while stirring vigorously for 2.5 hours. The reaction mixture was filtered over a bed of diatomaceous earth (e.g. Celite®), and washed 3×100 mL of anhydrous THF. The combined filtrates were evaporated to dryness, and further dried under high vacuum to afford 25.1 g of white solid.

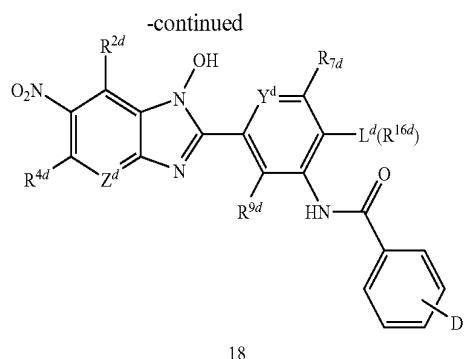
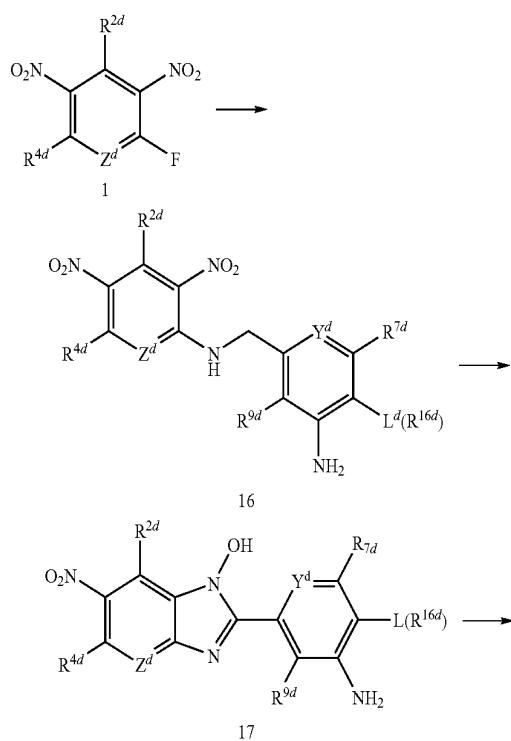
**Preparation of
4-[(2-nitro-phenylamino)-methyl]-phenylbenzamide
(14)**

[0767] To a solution of 4-phenylamidobenzylamine (13) (225 mmol) and powdered NaHCO₃ (1125 mmol) in anhydrous DMF (300 mL) was added substituted 4-nitrofluorobenzene (150 mmol) dropwise at room temperature. After 2 h, the solution was slowly diluted with water (1000 mL) to precipitate the product, which was collected on a fritted funnel while rinsing with water until the eluent was colorless. The solid was further dried under high vacuum to afford the product.

**Preparation of
4-(benzimidazol-2-yl)-phenylbenzamide (15)**

[0768] To a solution of 4-[(2-nitro-phenylamino)-methyl]-phenylbenzamide (14) (74.9 mmol) in anhydrous EtOH and anhydrous DMF (75 mL) was slowly added sodium methoxide (30% w/w) (375 mmol) at room temperature under argon atmosphere, followed by heating to 60° C. for 2 h. After cooling to ambient temperature, the solution was diluted with water (700 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product was recrystallized in hot EtOH.

Scheme 4



**Preparation of 3-aminobenzylidinitrophenylamine
(16)**

[0769] To a solution of 3-aminobenzylamine (225 mmol) and powdered NaHCO₃ (1125 mmol) in anhydrous DMF (300 mL) was added 2,4-dinitrofluorobenzene (1) (18.8 mL, 150 mmol) dropwise at room temperature. After 2 hours, the solution was slowly diluted with water (1000 mL) to precipitate the product, which was collected on a fritted funnel while rinsing with water until the eluent was colorless. The solid was further dried under high vacuum.

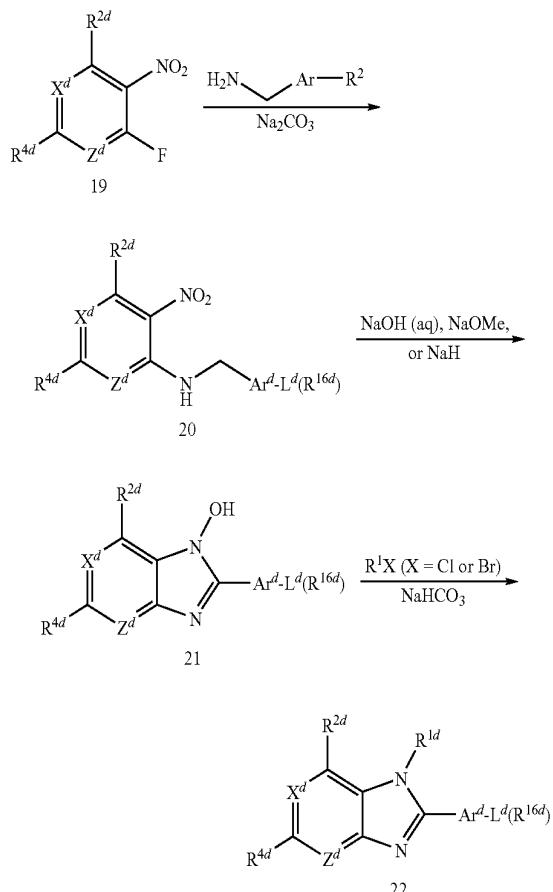
Preparation of 1-hydroxy-2-(3-Amino-phenyl)-6-nitro benzoimidazole (17)

[0770] To a solution of 3-aminobenzylidinitrophenylamine (16) (74.9 mmol) in anhydrous EtOH (300 mL) and anhydrous DMF (75 mL) was slowly added sodium methoxide (30% w/w) (375 mmol) at room temperature under argon atmosphere, followed by heating to 60° C. for 2 h. After cooling to ambient temperature, the solution was diluted with water (700 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product was recrystallized in hot EtOH.

**Preparation of 4-(benzoimidazolyl)phenylbenzamide
(18)**

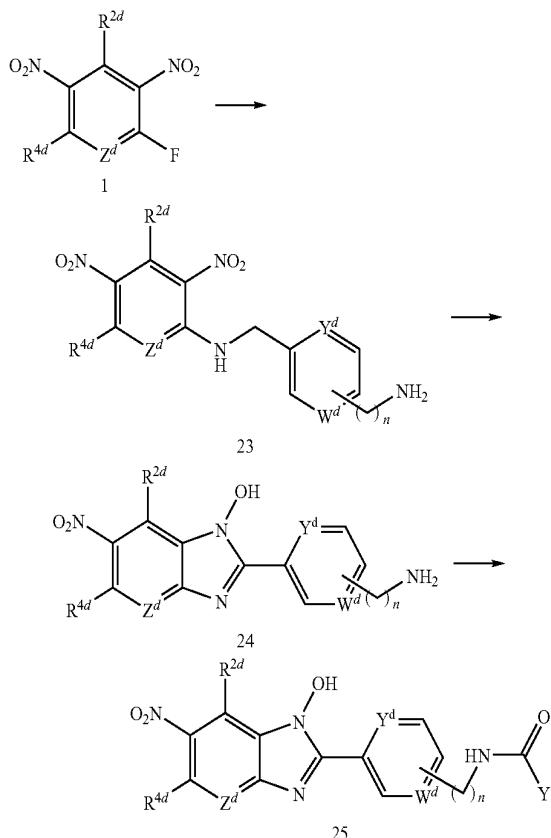
[0771] To a solution of 3-aminonitrobenzoimidazolol (17) (1.00 mmol) in anhydrous pyridine (2.0 mL) was added acid chlorides (2.5 mmol) or the in situ mixed anhydrides at room temperature. (The mixed anhydride was prepared by adding trimethylacetyl chloride (2.5 mmol) dropwise to a solution of the carboxylic acid (2.55 mmol) in anhydrous pyridine at 0° C., After 1 hour, 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole was added in one portion.) After stirring for 2-3 h at room temperature, the solution was diluted with 3M NaOH (6.0 mL) and stirred for another 1 h. The deep amber solution was diluted with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product was further purified by either preparatory HPLC or by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform.

Scheme 5



[0772] The general synthesis of benzimidazole compounds are seen in Scheme 5. To a solution of 4-aminobenzylamine (35.4 mL, 313 mmol) and powdered NaHCO_3 (158 g, 1875 mmol) in anhydrous DMF (500 mL) at room temperature was added a solution of 2,4-dinitrofluorobenzene (19) (46.5 g or 31.4 mL, 250 mmol) in anhydrous DMF (50 mL) dropwise via addition funnel over a 2 hours period. After another 4 hours or as determined complete by HPLC, the solution comprising compound 20 was diluted with anhydrous absolute EtOH (1000 mL), then powdered t-BuOK was added (140 g, 1250 mmol). The resulting solution was heated to 60° C. for 6 hours or as judged complete by HPLC to form compounds of formula 21. After cooling to room temperature, the EtOH was removed under reduced pressure. The resulting solution was poured into vigorously stirred water (4 L) and cooled to 0° C. by means of an ice bath. The amber solution was adjusted to a pH 6 with 4M HCl, which resulted in the precipitation of the desired product. The suspended products of formula 22 were collected on a fine fritted funnel, while rinsing with cold water until the eluent was colorless. The dark orange solid was further dried under high vacuum over P_2O_5 to afford the desired product in sufficient purity for further reactions. Compounds AO, AP, AQ, AR, AS, AT, AU, AV, AW, AX, AY, AZ, BI, BB, BC, BD, BE, BF, BG, BH, BI, BJ, BK, BL, BN, BO, BP, BQ, BR, BU, BV, BW, CA and CB may be prepared in this manner.

Scheme 6



[0773] General syntheses of N-acyl-6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazoles is seen in Scheme 2 and 3. Compounds B, C, D, AH, BM, BT, BX, BZ, CD, CE, CG, CH, and CK may be synthesized in this manner.

Preparation of N-(4-aminobenzyl)-2,4-dinitroaniline (23)

[0774] To a solution of 4-aminobenzylamine (25.5 mL, 225 mmol) (1) and powdered NaHCO_3 (94.5 g, 1125 mmol) in anhydrous DMF (300 mL) was added 2,4-dinitrofluorobenzene (1) (18.8 mL, 150 mmol) dropwise at room temperature. After 2 hours, the solution was slowly diluted with water (1000 mL) to precipitate the product, which was collected on a fritted funnel while rinsing with water until the eluent was colorless. The solid 23 was further dried under high vacuum to afford 43.0 g as a bright orange solid in 99% yield.

Preparation of 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole (24)

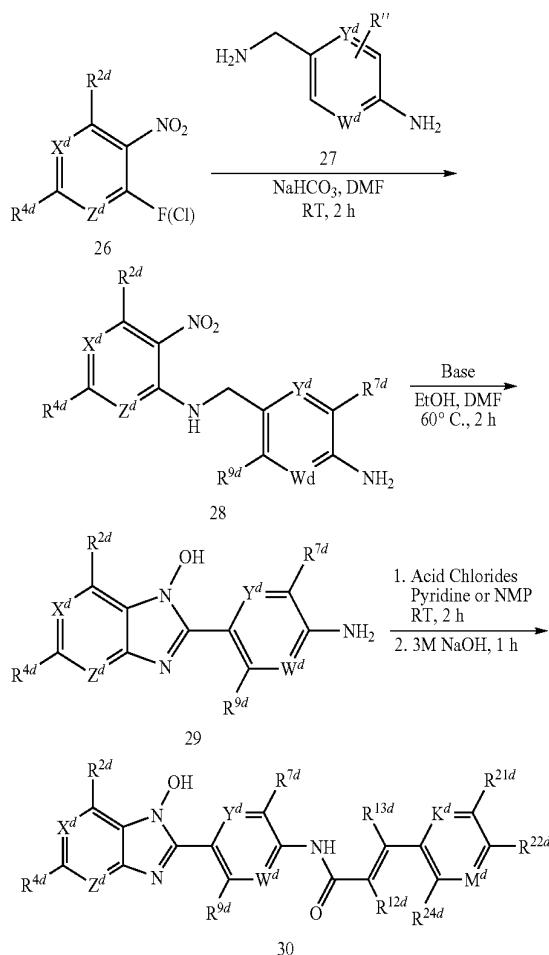
[0775] To a solution of N-(4-aminobenzyl)-2,4-dinitroaniline (23) (21.6 g, 74.9 mmol) in anhydrous EtOH (300 mL) and anhydrous DMF (75 mL) was slowly added sodium methoxide (30% w/w) (69.1 g, 375 mmol) at room temperature under argon atmosphere, followed by heating to 60° C. for 2 hours. After cooling to ambient temperature, the solution was diluted with water (700 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product 24 was recrystallized in hot EtOH to afford 18.1 g as a brown solid in 90% yield.

General procedure for the preparation of N-acyl-6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazoles (25)

[0776] To a solution of 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole (24) (270 mg, 1.00 mmol) in anhydrous pyridine (2.0 mL) was added acid chlorides (2.5 mmol) or the in situ mixed anhydrides at room temperature. (The mixed anhydride was prepared by adding trimethylacetyl chloride (2.5 mmol) dropwise to a solution of the carboxylic acid (2.55 mmol) in anhydrous pyridine at 0° C.)

[0777] After 1 hour, 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole was added in one portion.) After stirring for 2-3 hours at room temperature, the solution was diluted with 3M NaOH (6.0 mL) and stirred for another hour. The deep amber solution was diluted with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel while rinsing with water. The crude product was further purified by either preparatory HPLC or by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform.

Scheme 7



Preparation of
4-aminobenzyl-(2,4-dinitro-phenyl)-amine
derivatives (28)

[0778] To a solution of 4-aminobenzyl amine derivatives (27) (225 mmol) and powdered NaHCO₃ (1125 mmol) in

anhydrous DMF (300 mL) was added 2,4-dinitrofluoro benzene (26) (150 mmol) dropwise at room temperature. After 2 hours, the solution was slowly diluted with water (1000 mL) to precipitate the product, which was collected on a fritted funnel rinsing with water until the eluent was colorless. The solid was further dried under high vacuum to afford a bright orange solid.

Preparation of
6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole
derivatives (29)

[0779] To a solution of N-(4-aminobenzyl)-2,4-dinitroaniline derivative (28) (74.9 mmol) in anhydrous EtOH (300 mL) and anhydrous DMF (75 mL) was slowly added sodium methoxide (30% w/w, 375 mmol) at room temperature under Argon atmosphere. After the addition, the solution was warmed to 60° C. for 2 hours. After cooling to ambient temperature, the solution was transferred to an Erlenmeyer flask or tall beaker through dilution with water (700 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was purified by recrystallization in hot EtOH to afford a brown solid.

Preparation of N-acyl-6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole derivatives (30)

[0780] To a solution of 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole derivative (29) (1.00 mmol) in anhydrous pyridine (2.0 mL) was added acid chlorides (2.50 mmol) or the in situ formed mixed anhydrides at room temperature. After stirring for 2-3 hours, the solution was diluted with 3M NaOH (6.0 mL) and stirred for another hour. The deep amber solution was transferred to an Erlenmeyer flask or beaker through dilution with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was further purified either by preparatory HPLC, or by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform.

(E)-N-[4-(1-Hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-3-(4-[1,2,4]triazol-1-yl-phenyl)-acrylamide (Compound EU)

[0781] ¹H NMR (300 MHz, DMSO-d₆): δ 10.60 (s, 1H), 9.38 (s, 1H), 8.36-8.32 (d, 3H), 8.28 (s, 1H), 8.15-8.11 (d, 1H), 7.99-7.93 (t, 4H), 7.87-7.82 (m, 3H), 7.73-7.68 (d, 1H), 6.96-6.91 (d, 1H). MS (M+1)=375.05.

(E)-N-[4-(1-Hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-3-(4-imidazol-1-yl-phenyl)-acrylamide (Compound AM)

[0782] ¹H NMR (300 MHz, DMSO-d₆): δ 10.77 (s, 1H), 9.77 (s, 1H), 8.37-8.34 (m, 4H), 8.15-8.12 (dd, 1H), 7.98-7.92 (m, 7H), 7.85-7.82 (d, 1H), 7.76-7.71 (d, 1H), 7.08-7.03 (d, 1H). MS (M+1)=467.20.

2-[4-(4-Fluoro-benzoylamino)-phenyl]-3-hydroxy-3H-benzoimidazole-5-carboxylic acid amide (Compound DO)

[0783] ¹H NMR (300 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.30 (d, 2H), 8.18-7.96 (m, 6H), 7.87 (d, 1H), 7.70 (d, 1H), 7.39 (t, 3H), 6.78 (d, 2H), 3.02 (s, 6H). MS (M+1)=391.20.

(E)-N-[2-Fluoro-4-(1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-3-(4-fluoro-phenyl)-acrylamide:
(Compound EL)

[0784] ^1H NMR (300 MHz, DMSO-d₆): δ 10.23 (s, 1H), 8.49-8.39 (t, 1H), 8.38 (s, 1H), 8.22-8.12 (m, 3H), 7.87-7.84 (d, 1H), 7.72-7.63 (m, 3H), 7.33-7.28 (t, 2H), 7.14-7.09 (d, 1H). MS (M+1)=375.05.

4-Acetyl-N-[2-fluoro-4-(1-hydroxy-6-nitro-H-benzoimidazol-2-yl)-phenyl]-benzamide (Compound EM)

[0785] ^1H NMR (300 MHz, DMSO-d₆): δ 12.81 (br s, 1H), 10.57 (s, 1H), 8.42 (s, 1H), 8.41-8.13 (m, 7H), 7.98 (t, 1H), 7.89-7.86 (d, 1H), 2.66 (s, 3H). MS (M+1)=435.10.

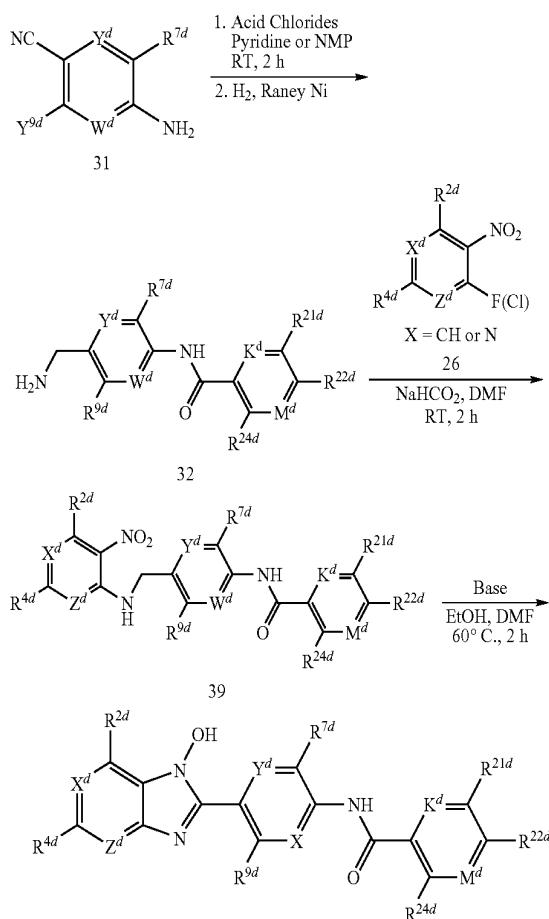
(E)-3-(4-Acetyl-phenyl)-N-[4-(1-hydroxy-6-nitro-H-benzoimidazol-2-yl)-phenyl]-acrylamide (Compound AJ)

[0786] ^1H NMR (300 MHz, DMSO-d₆): δ 12.65 (s, 1H), 10.65 (s, 1H), 8.33-8.36 (m, 3H), 8.13 (dd, 1H), 8.03 (d, 2H), 7.94 (d, 2H), 7.78-7.84 (m, 3H), 7.7 (d, 1H), 7.0 (d, 1H), 2.6 (s, 3H). MS (M-1)=441.

Preparation of 4-phenylamidobenzylamine derivatives (32)

[0787] To a solution of 4-cyanoaniline derivative (31) (225 mmol) in N-methylpyrrolidone (180 mL), was added an acid chloride (225.4 mmol) over a period of 3-5 minutes with vigorous stirring. After stirring the reaction mixture for about 5 hours (until the HPLC monitoring of the reaction indicated a complete consumption of the starting materials), it was poured into about 1400 mL of water at room temperature and the resulting suspension was stirred for about 1 hour. The precipitate was filtered, washed with 4×500 mL portions of water, and dried. A second crop of solid can be obtained from the filtrate and washings. In a pressure reactor, 4-phenylamido benzonitrile intermediate (98 mmol) was dissolved in anhydrous THF (940 mL), and the solution was purged with argon for 2-3 minutes, followed by the addition of 11 mL of the uniformly suspended catalyst (Raney® nickel 2400, suspension in water). After addition of a small amount of methanol to the suspension, the reactor was pressurized at 55 psi of H₂ while stirring vigorously. LC-MS monitoring of the reaction indicated a complete conversion of the starting material to the corresponding amine within 2.5 hours. The reaction mixture was filtered over a bed of diatomaceous earth (e.g., Celite®), and washed with 3×100 mL portions of anhydrous THF. The combined filtrates were evaporated to dryness, and further dried under high vacuum to afford white colored solid.

Scheme 8



Preparation of N-[4-[(2,4-dinitrophenylamino)-methyl]-phenyl]-benzamide derivatives (39)

[0788] To a solution of 4-phenylamidobenzylamine derivatives (32) (225 mmol) and powdered NaHCO₃ (1125 mmol) in anhydrous DMF (300 mL) was added 2,4-dinitrofluorobenzene (26) (150 mmol) dropwise at room temperature. After 2 hours, the solution was slowly diluted with water (1000 mL) to precipitate the product, which was collected on a fritted funnel rinsing with water until the eluent was colorless. The solid was further dried under high vacuum to afford the product as a bright orange solid.

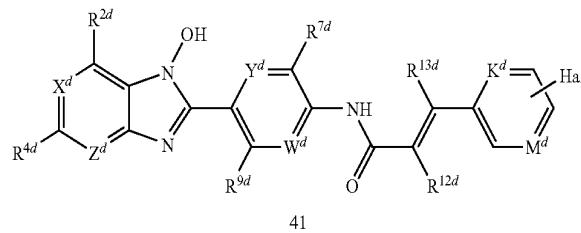
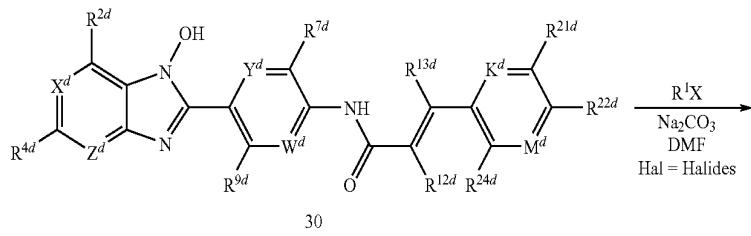
Preparation of N-[4-(1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-benzamide derivatives (40)

[0789] To a solution of N-[4-[(2,4-dinitrophenylamino)-methyl]-phenyl]-benzamide derivatives (39) (74.9 mmol) in anhydrous EtOH (300 mL) and anhydrous DMF (75 mL) was slowly added sodium methoxide (30% w/w) (69.1 g, 375 mmol) at room temperature under Argon atmosphere. After the addition, the solution was warmed to 60° C. for 2 hours. After cooling to ambient temperature, the solution was transferred to an Erlenmyer flask or tall beaker through dilution with water (700 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was purified by recrystallization in hot EtOH.

[5-(4-Fluoro-benzoylamino)-2-(1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenoxy-methyl]-phosphonic acid: (Compound EC)

[0790] ^1H NMR (300 MHz, DMSO-d₆): δ 10.57 (s, 1H), 8.30 (s, 1H), 8.29-8.06 (m, 3H), 7.86-7.83 (d, 2H), 7.67-7.44 (t, 2H), 7.41-7.38 (t, 2H), 4.36-4.32 (d, 2H). MS (M-1)=501.

Scheme 9



Preparation of N-[4-(1-alkyloxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-benzamide derivatives (9)

A suspension of N-[4-(1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-benzamide derivatives (30) (0.19 mmol) and anhydrous sodium carbonate (0.96 mmol) in 3 mL of DMF, was treated with substituted alkyl halide derivatives (0.25 mmol) and stirred at room temperature. After 24 hours, the reaction mixture was poured into 20 mL of water and stirred for 2 hours. The precipitate formed was filtered, washed with 4×10 mL portions of water and dried under vacuum to afford the product.

(2-{2-[4-(4-Fluoro-benzoylamino)-phenyl]-6-nitro-benzoimidazol-1-yloxy}-ethyl)-trimethyl-ammonium (Compound DH)

[0791] ^1H NMR (300 MHz, DMSO-d₆): δ 10.62 (s, 1H), 8.72 (s, 1H), 8.22 (t, 3H), 8.15-8.12 (m, 4H), 7.93 (d, 1H), 7.41 (t, 2H), 4.78 (t, 2H), 3.99 (t, 2H), 3.21 (s, 9H). MS (m/z, M)=478.39.

{2-[4-(4-Fluoro-benzoylamino)-phenyl]-6-nitro-benzoimidazol-1-yloxy}-acetic acid (Compound DG)

[0792] ^1H NMR (300 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.78 (d, 1H), 8.30 (d, 2H), 8.20-8.00 (m, 5H), 7.85 (d, 1H), 7.41 (t, 2H), 5.02 (s, 2H). MS (M+1)=451.20.

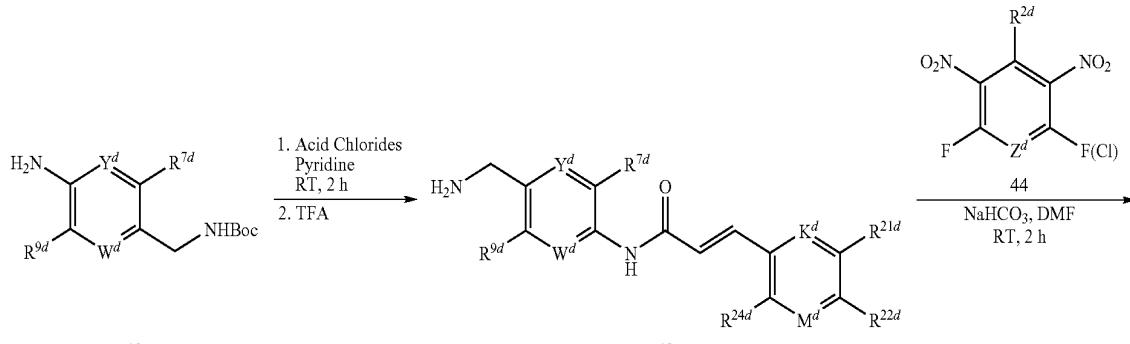
(2-{4-[{(E)}-3-(4-Fluoro-phenyl)-acryloylamino]-phenyl}-6-nitro-benzoimidazol-1-yloxymethyl)-phosphonic acid diethyl ester (Compound ED)

[0793] ^1H NMR (300 MHz, DMSO-d₆): δ 10.62 (s, 1H), 8.60 (d, 1H), 8.30 (d, 2H), 8.23 (dd, 1H), 7.99 (d, 2H), 7.91 (d, 1H), 7.79~7.67 (m, 3H), 7.34 (dd, 2H), 6.86 (d, 1H), 4.95 (d, 2H), 4.19 (q, 4H), 1.33 (t, 6H). MS (M-1)=567.

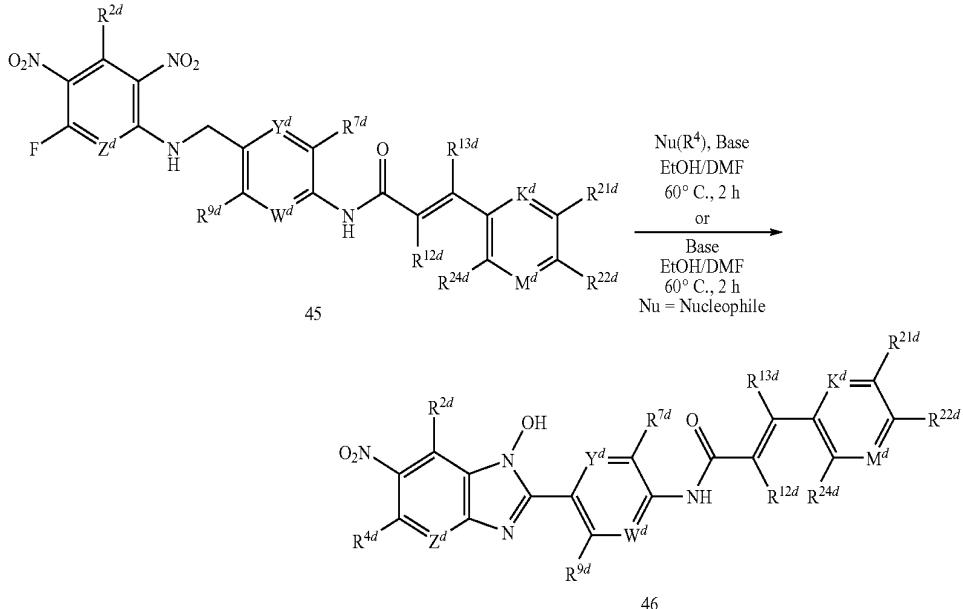
(2-{4-[{(E)}-3-(4-Fluoro-phenyl)-acryloylamino]-phenyl}-6-nitro-benzoimidazol-1-yloxymethyl)-phosphonic acid (Compound DW)

[0794] ^1H NMR (300 MHz, DMSO-d₆): δ 10.55 (s, 1H), 8.56 (d, 1H), 8.32 (d, 2H), 8.17 (dd, 1H), 7.92 (d, 2H), 7.86 (d, 1H), 7.74~7.61 (m, 3H), 7.30 (dd, 2H), 6.80 (d, 1H), 4.50 (d, 2H). MS (M-1)=511.

Scheme 10



-continued



Preparation of (E)-N-(4-Aminomethyl-phenyl)-3-phenyl-acrylamide derivatives (43)

[0795] To a solution of 4-(tert-butoxycarbonyl-aminomethyl)-aniline derivative (42, 0.94 mmol) in 7 mL of NMP, an acid chloride derivative (1.0 mmol) was added and the reaction was stirred at room temperature for 40 minutes. It was then poured in 100 mL of water while stirring. The precipitate was filtered, washed with water (5×15 mL) and dried to give the boc-protected product. A solution of the Boc-protected product (0.83 mmol) in 10 mL of TFA was stirred at room temperature for 20 minutes. It was then diluted with 200 mL of diethyl ether and the suspension stirred for another 10 minutes. The precipitate was filtered, washed with 3×20 mL of diethyl ether, and dried under vacuum for 6 hours to give the product (43) as its TFA salt.

Preparation of (E)-N-[4-[(5-Fluoro-2,4-dinitro-phenylamino)-methyl]-phenyl]-3-phenyl-acrylamide (45)

[0796] To a solution of 1,5-difluoro-2,4-dinitrobenzene (44) (2.0 mmol) in 8 mL of DMF, was added sodium bicarbonate (10.0 mmol) and the compound (43) (2.0 mmol) and the reaction mixture was refluxed for 10 hours. The reaction was poured in ice-water to give a precipitate. The precipitate was filtered, washed with water, and dried under vacuum to give the desired product.

Preparation of (E)-N-[4-(5-ethoxy-1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-3-phenylacrylamide (46)

[0797] To a solution of (E)-N-[4-[(5-Fluoro-2,4-dinitrophenylamino)-methyl]-phenyl]-3-phenyl-acrylamide (45) (0.44 mmol) in ethanol (10 mL) and DMF (10 mL), was added sodium hydride (2.2 mmol). The reaction mixture was heated at 60° C. for 3 hours. After cooling to room temperature, it was poured into ice-water, and acidified with aqueous

citric acid. The resulting precipitation was collected, washed with water, and dried in vacuo to yield the product as a yellow solid.

(E)-3-(4-Fluoro-phenyl)-N-[4-(1-hydroxy-5-methyl-6-nitro-1H-benzimidazol-2-yl)-phenyl]-acrylamide
(Compound EO)

[**0798**] ^1H NMR (300 MHz, DMSO- d_6): δ 12.57 (s, 1H), 10.52 (s, 1H), 8.31 (d, 2H), 8.16 (s, 1H), 7.91 (d, 2H), 7.74-7.62 (m, 4H), 7.30 (dd, 2H), 6.82 (d, 1H), 2.63 (s, 3H). MS (M+1)=433.

(E)-N-[4-(5-Ethoxy-1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-3-(4-fluoro-phenyl)-acrylamide (Compound EV)

[0799] ^1H NMR (300 MHz, DMSO- d_6): δ 12.41 (s, 1H), 10.51 (s, 1H), 8.28 (d, 2H), 8.05 (s, 1H), 7.91 (d, 2H), 7.72 (dd, 2H), 7.64 (d, 1H), 7.49 (s, 1H), 7.30 (dd, 2H), 6.82 (d, 1H), 4.22 (q, 2H), 1.36 (t, 3H), MS ($M+1$) = 463

N-[4-(1-Hydroxy-5-methyl-6-nitro-1H-benzimidazol-2-yl)-phenyl]-4-oxazol-5-v-benzamide (Compound EX)

[0800] ^1H NMR (300 MHz, DMSO- d_6): δ 12.47 (s, 1H), 10.67 (s, 1H), 8.50 (s, 1H), 8.32 (d, 2H), 8.18 (s, 1H), 8.10 (d, 2H), 8.01 (d, 2H), 7.88 (d, 2H), 7.84 (s, 1H), 7.69 (s, 1H), 2.62 (s, 3H). MS (M+1)=456.

N-[4-(5-Dimethylamino-1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-3-(4-fluorocinnamyl)-amide; (Compound EZ)

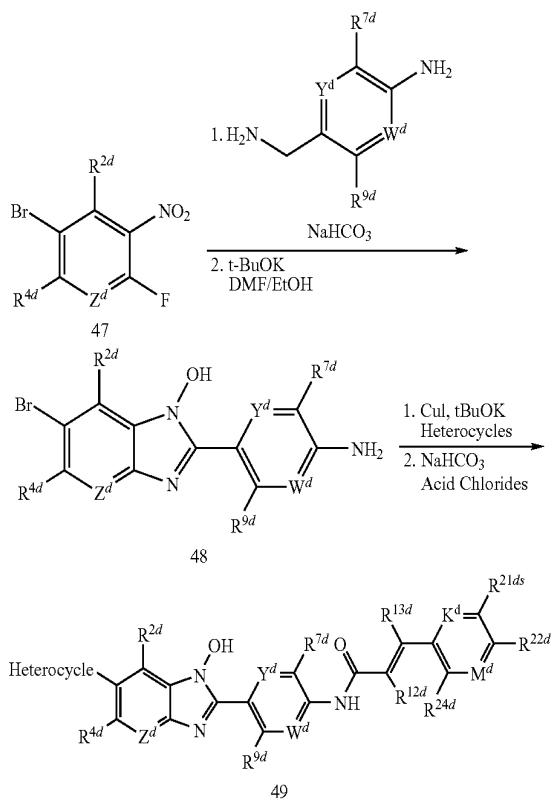
[0801] ^1H NMR (300 MHz, DMSO- d_6): δ 12.32 (s, 1H), 10.51 (s, 1H), 8.27 (d, 2H), 7.97 (s, 1H), 7.90 (d, 2H), 7.71

(dd, 2H), 7.65 (d, 1H), 7.49 (s, 1H), 7.30 (dd, 2H), 6.82 (d, 1H), 2.75 (s, 6H). MS (M+1)=462.

**N-[4-(5-Fluoro-1-hydroxy-6-nitro-1H-benzimidazol-2-yl)-phenyl]-3-(4-fluoro-cinnamyl)-amide
(Compound FA)**

[0802] ^1H NMR (300 MHz, DMSO-d₆): δ 12.72 (s, 1H), 10.55 (s, 1H), 8.33 (d, 2H), 8.28 (d, 1H), 7.92 (d, 2H), 7.81 (d, 1H), 7.75-7.70 (m, 2H), 7.64 (d, 1H), 7.30 (dd, 2H), 6.82 (d, 1H). MS (M+1)=437

Scheme 11



**Preparation of
6-bromo-2-(4-aminophenyl)-1-hydroxybenzimidazole
(48)**

[0803] To a solution of 4-aminobenzyl amine (35.4 mL, 313 mmol) and powdered NaHCO₃ (158 g, 1875 mmol) in anhydrous DMF (500 mL) at room temperature was added a solution of 4-bromo-1-fluoro-2-nitrobenzene (47) (31.4 mL, 250 mmol) in anhydrous DMF (50 mL) dropwise via addition funnel over a 1 hour period. After another 4 hours or as determined complete by HPLC, the solution was diluted with anhydrous absolute ethanol (1000 mL) and powdered potassium tert-butoxide (140 g, 1250 mmol) was added in portions. This solution was subsequently heated to 60° C. for 6 hours. After cooling to room temperature, the solution was poured into stirring solution of water (4 L), then adjusted to pH 6 with 1M HCl. The slowly stirring suspension was cooled with an ice bath to facilitate solidification. The suspended product

was collected on a fine fritted funnel rinsing with water until the eluent was colorless. The orange solid was further dried under high vacuum.

Preparation of 6-pyrazole-2-(4-aminophenyl)-1-hydroxybenzimidazole (49)

[0804] A 20 mL Biotage microwave vial was charged with 6-bromo-2-(4-aminophenyl)-1-hydroxybenzimidazole (48) (1.52 g, 5.00 mmol), N,N'-dimethylethylenediamine (1.10 mL, 10.0 mmol), CuI (0.952 g, 5.00 mmol), pyrazole (1.36 g, 20.0 mmol) and potassium tert-butoxide (2.24 g, 20.0 mmol) and anhydrous DMSO (20 mL). The secured vial was placed into a Biotage microwave reactor with a temperature setting of 195° C. for 45 minutes. After cooling, the vial was opened and poured into a rapidly stirring water solution. The resulting suspension was filtered through a plug of Celite rinsing with 0.5M NaOH. The water solution was loaded onto a prepared DVB column. After loading, the product was eluted with CH₃ CN. The CH₃ CN was removed under reduced pressure. The resulting water solution was cooled to 0° C. by an ice bath then adjusted to pH 6 with 1M HCl to precipitate the product 49. The resulting solid was collected onto a fine fritted funnel rinsing with cold water to afford a light brown solid to afford 1.52 g in 70% yield. The product was further dried under high vacuum.

Preparation (E)-3-(4-Fluoro-phenyl)-N-[4-(1-hydroxy-6-pyrazol-1-yl-1H-benzimidazol-2-yl)-phenyl]-acrylamide (Compound FX)

[0805] To a solution of 6-pyrazole-2-(4-aminophenyl)-1-hydroxybenzimidazole (0.78 g, 2.50 mmol) and NaHCO₃ (0.84 g, 10.0 mmol) in anhydrous CH₃ CN (20 mL) and DMPU (5 mL) at room temperature was added 4-fluorocinnamoyl chloride (1.15 g, 6.25 mmol). After 6 hours, the solution was diluted with 3M NaOH (25 mL) and stirred for another 2 hours. The solution was transferred to another flask through dilution with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was further purified by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform. ^1H NMR (DMSO-d₆) δ 10.49 (s, 1H), 8.61 (s, 1H), 8.33 (m, 2H), 7.94-7.63 (m, 9H), 7.32 (m, 2H), 6.84 (m, 1H), 6.55 (s, 1H). MS (M+1)=440.

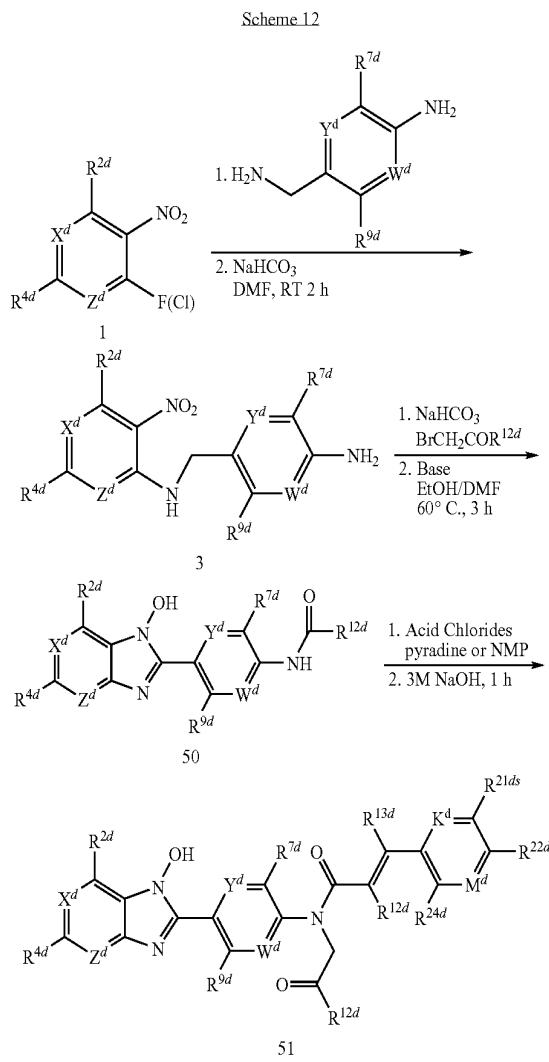
**Preparation of 4-Acetyl-N-[4-(1-hydroxy-6-pyrazol-1-yl-1H-benzimidazol-2-yl)-phenyl]-benzamide
(Compound FY)**

[0806] To a solution of 6-pyrazole-2-(4-aminophenyl)-1-hydroxybenzimidazole (0.78 g, 2.50 mmol) and NaHCO₃ (0.84 g, 10.0 mmol) in anhydrous CH₃ CN (20 mL) and DMPU (5 mL) at room temperature was added 4-acetylbenzoyl chloride (1.14 g, 6.25 mmol). After 6 hours, the solution was diluted with 3M NaOH (25 mL) and stirred for another 2 hours. The solution was transferred to another flask through dilution with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was further purified by recrystallization in hot ethanol or a mixture of hot

ethanol and chloroform. ^1H NMR (DMSO-d₆) δ 10.61 (s, 1H), 8.69-7.77 (m, 13H), 6.60 (1, 1H), 2.63 (s, 3H). MS (M+1)=438.

Preparation of 4-Acetyl-N-[4-(1-hydroxy-6-imidazol-1-yl-1H-benzoimidazol-2-yl)-phenyl]-benzamide:
(Compound FZ)

[0807] To a solution of 6-imidazole-2-(4-aminophenyl)-1-hydroxybenzimidazole (0.78 g, 2.50 mmol) and NaHCO₃ (0.84 g, 10.0 mmol) in anhydrous CH₃ CN (20 mL) and DMPU (5 mL) at room temperature was added 4-acetylbenzoyl chloride (1.14 g, 6.25 mmol). After 6 hours, the solution was diluted with 3M NaOH (25 mL) and stirred for another 2 hours. The solution was transferred to another flask through dilution with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was further purified by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform. ^1H NMR (DMSO-d₆) δ 10.63 (s, 1H), 8.32-7.46 (m, 13H), 7.13 (1, 1H), 2.68 (s, 3H). MS (M+1)=438.



Preparation of N-Alkylhydroxybenzimidazole Intermediate (50)

[0808] To a solution of N-(4'-aminobenzylamine)-2,4-dinitroaniline (3) (25.0 mmol), powdered NaHCO₃ (6.30 g, 75.0 mmol) in anhydrous DMF at room temperature (75 mL) was added with the alkylating agent (26.3 mmol). After 12 hours, the solution was diluted with EtOH (225 mL) then powdered potassium tert-butoxide (14.0 g, 125 mmol) was added. The solution was heated to 60° C. for 3 hours. After cooling to ambient temperature, the solution was poured into cold 10% citric acid solution to precipitate product. The product was collected on a sintered funnel rinsing with cold water. The product was further dried under high vacuum and used as is in the following reaction.

Preparation of N-acyl-6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole derivatives (51)

[0809] To a solution of 6-nitro-2-(4-aminophenyl)-1-hydroxybenzimidazole derivative (50) (1.00 mmol) in anhydrous pyridine (2.0 mL) was added acid chlorides (2.50 mmol) or the in situ formed mixed anhydrides at room temperature. After stirring for 2-3 hours, the solution was diluted with 3M NaOH (6.0 mL) and stirred for another hour. The deep amber solution was transferred to an Erlenmeyer flask or beaker through dilution with water (100 mL) and then acidified with saturated citric acid. The resulting precipitate was collected on a sintered funnel rinsing with water. The crude product was further purified either by preparatory HPLC, or by recrystallization in hot ethanol or a mixture of hot ethanol and chloroform.

{[(E)-3-(4-Acetyl-phenyl)-acryloyl]-[4-(6-cyano-1-hydroxy-1H-benzoimidazol-2-yl)-phenyl]-acetic acid (Compound GO)}

[0810] ^1H NMR (300 MHz, DMSO-d₆) δ 8.41-8.32 (m, 2H), 8.13 (s, 1H), 7.92-7.80 (m, 3H), 7.69-7.54 (m, 6H), 7.74-7.60 (br s, 1H), 4.52 (s, 2H), 2.50 (s, 3H). MS (M+1)=481.

(E)-3-(4-Acetyl-phenyl)-N-carbamoylmethyl-N-[4-(1-hydroxy-6-nitro-1H-benzoimidazol-2-yl)-phenyl]-acrylamide (Compound GP)

[0811] ^1H NMR (300 MHz, DMSO-d₆) δ 12.88-12.57 (brs, 1H), 8.57-7.48 (m, 12H), 7.21-7.13 (m, 1H), 6.80-6.57 (m, 1H), 4.47 (s, 2H), 2.52 (s, 3H). MS (M+1)=500.

Example 2

Development of Luminescence Assays

[0812] A quantitative chemiluminescence-based assay was used to measure the DNA binding activity of various MarA (AraC) family members. With this technique, biotinylated double-stranded DNA molecules (2 nM) were incubated with a MarA (AraC) protein (20 nM) fused to 6-histidine (6-His) residues in a streptavidin coated 96-well microtiter (white) plate (Pierce Biotechnology, Rockford, Ill.). Unbound DNA and protein was removed by washing and a primary monoclonal anti-6His antibody was subsequently added. A second washing was performed and a secondary HRP-conjugated antibody was then added to the mixture. Excess antibody was removed by a third wash step and a chemiluminescence substrate (Cell Signaling Technology, Beverly, Mass.) was added to the plate. Luminescence was read immediately using a Victor V plate reader (PerkinElmer Life Sciences, Wellesley, Mass.). Compounds that inhibited the binding of the protein

to the DNA resulted in a loss of protein from the plate at the first wash step and were identified by a reduced luminescence signal. The concentration of compound necessary to reduce signal by 50% (EC_{50}/IC_{50}) was calculated using serial dilutions of the inhibitory compounds. Also, single transcription factor modulators that affect different transcription factors were identified.

Example 3

In vivo Activity of Select Transcription Factor Modulating Compounds in an Ascending Pyelonephritis Model of Infection

[0813] Using an animal model of ascending pyelonephritis caused by *E. coli*, transcription factor modulating compounds were judged for the ability to affect kidney infection. Previous studies using this urinary tract infection model have shown that *E. coli* mutants with a soxS gene deletion colonize the mouse kidney in numbers approximately 1-log fewer than the wild type strain. Groups of female CD1 mice (n=6) were diuresed and infected with *E. coli* UPEC strain C189 via intravesicular inoculation. Subsequently, mice were dosed with a transcription factor modulator (25 or 50 µg/ml), a control compound, e.g., SXT, or vehicle alone (0 mg/kg), via an oral route of administration at the time of infection and once a day for 4 days thereafter, to maintain a constant level of drug in the mice. After a 5-day period of infection and prior to sacrifice via CO₂/O₂ asphyxiation, a urine sample was taken by gentle compression of the abdomen. Following asphyxiation, the bladder and kidneys were removed aseptically. Urine volumes and individual organ weights are recorded, the organs were suspended in sterile PBS containing 0.025% Triton X-100, and then homogenized. Serial 10-fold dilutions of the urine samples and homogenates were plated onto McConkey agar plates to determine CFU/ml (CFU=colony forming units) of urine or CFU/gram of organ. **[0814]** Efficacy in these experiments was defined as a ≥ 2 -log decrease in CFU/g organ. The CFU/g for the compounds of the invention are summarized in Table 3 below. Compounds which exhibited a 0-1.0 log decrease in CFU/g are indicated with “***,” compounds which exhibited a 1.1-2.0 log decrease in CFU/g are indicated with “**,” and compounds which exhibited no decrease in CFU/g are indicated with “*.” This data was compared to the in vitro inhibition of SoxS activity or to the concentration necessary to inhibit DNA-protein binding by 50% (EC_{50}). Transcription factor modulating compounds that inhibited the binding of SoxS to DNA by greater than 70% are shown by “***,” compounds that inhibited the binding of SoxS between about 30% and 69% are shown by “**,” compounds that inhibited the binding of SoxS by less than 29% are shown by “*.” Compounds that gave an IC_{50} of greater than 5 µM are represented by “*,” compounds that gave an IC_{50} of between about 1 and 4.9 µM are represented by “**,” and compounds exhibiting IC₅₀’s of less than 0.9 µM are represented by “***.”

TABLE 3

Compound	Efficacy ^a	in vitro SoxS activity
A	*	NT
B	***	*** ^b
D	*	** ^c
E	**	NT

TABLE 3-continued

Compound	Efficacy ^a	in vitro SoxS activity
F	**	NT
H	**	NT
M	***	NT
AH	*	*** ^c
BO	*	* ^b
BP	***	* ^c
BQ	**	* ^c
BS	***	** ^c
BU	***	* ^c
CE	*	*** ^d
CG	*	** ^c
CK	***	*** ^d
GC	**	** ^b

^a Represents the log₁₀ decrease in the CFU/g kidney tissue.

^b Percent inhibition of DNA-protein binding at a compound screening concentration of 50 µg/ml.

^c Concentration necessary to inhibit DNA-protein binding by 50% (EC_{50}) as determined using a dose response analysis.

^d Percent inhibition of DNA-protein binding at a compound screening concentration of 25 µg/ml.

Example 4

Efficacy of Compound GM in an *E. coli* Ascending Pyelonephritis Model

[0815] The closely related *E. coli* MarA, Rob and SoxS proteins have overlapping roles in the regulation of resistance to multiple antibiotics, oxidative stress agents and organic solvents. Multi-drug resistant clinical isolates of *E. coli* have been identified that constitutively express these proteins. As shown in FIGS. 1 and 2, it has been demonstrated that the MarA, Rob and SoxS proteins are also required for full *E. coli* virulence in a murine ascending pyelonephritis model. FIG. 1 illustrates that kidney tissue of diuresed CD1 mice inoculated intravesicularly with $\sim 10^7$ colony forming units (CFU) of wild type KM-D *E. coli* (intestinal fistula isolate) had a constant CFU level for up to 11 days post infection. In contrast, deletion of genes for marA, rob and soxS from a clinical (intestinal fistula) *E. coli* isolate (KM-D) removed its ability to colonize the kidneys (FIG. 2).

[0816] Diuresed CD1 mice were inoculated intravesically with $\sim 10^7$ colony forming units (CFU) of *E. coli* C189 (clinical cystitis isolate). The kidneys were harvested at 5 days post infection. When compound GM was administered as a single dose at the time of infection, a statistically significant difference ($p<0.003$) was noted between the vehicle treated dose group and the 100 mg/kg compound GM dose group. When compound GM was administered subcutaneously at 0, 6, 24, 30, 48, 54, 72 and 96 hours post-infection, a statistically significant difference ($p<0.05$) was noted between the untreated (vehicle) and the 1, 5 and 20 mg/kg dose groups.

Example 5

In vitro Activity of Select Transcription Factor Modulating Compounds Against LcrF (VirF) from *Y. pseudotuberculosis*

[0817] The *Y. pseudotuberculosis* protein LcrF (also called VirF in *Y. enterocolitica*) regulates expression of a major virulence determinant, the type III secretion system (TTSS). The TTSS delivers toxins directly into host cells, and mutants

that do not express the TTSS show dramatic attenuation of virulence in whole cell and animal models of infection. In order to determine the inhibition of LcrF-DNA binding by the transcription factor modulating compounds of the invention, the MarA (AraC) family member LcrF (VirF) was cloned, expressed and purified from *Y. pseudotuberculosis*. The purified protein was used in a cell-free system to monitor DNA-protein interactions in vitro, methods as in Example 2. The EC₅₀'s for inhibition of LcrF(VirF)-DNA binding by the compounds of the invention are summarized in Table 4 below. Compounds with excellent inhibition (less than 10 µM) are indicated with “***,” very good inhibition (greater than 10.0 and less than 25.0 µM) with “**,” good inhibition (greater than 25.0 µM) with “*” and compounds that were not active are indicated with “--”

TABLE 4

Compound	EC ₅₀ (µM)
A	**
B	**
C	**
D	**
E	**
F	**
G	*
H	**
I	***
J	***
K	**
L	*
M	***
N	*
O	*
P	*
Q	*
R	*
S	***
T	***
U	**
V	***
W	**
X	**
Y	***
Z	*
AA	*
AC	**
AJ	**
AK	*
AM	--
CL	**
CM	***
CN	*
CO	***
CP	**
CQ	***
CR	**
CS	*
CT	*
CV	*
CW	--
CX	*
CY	*
DA	**
DC	*
DD	**
DE	***
DF	*
DG	*
DI	**
DJ	**
DK	**
DL	**
DM	**

TABLE 4-continued

Compound	EC ₅₀ (µM)
DN	**
DO	--
DP	***
DQ	*
DR	*
DS	**
DT	*
DU	**
DV	--
DW	***
DX	**
DY	***
DZ	**
EA	***
EB	***
EC	--
ED	*
EF	***
EG	--
EH	***
EI	***
EJ	--
EK	--
EL	**
EM	**
EN	**
EO	***
EP	*
EQ	***
ER	--
ES	*
ET	**
EU	*
EV	**
EX	*
EY	**
EZ	*
FA	--
FB	--
FQ	***
FR	***
FT	*
FU	***
FV	--
FW	**
FX	*
FY	--
GA	**

Example 6

Inhibition of *Y. pseudotuberculosis* Cytotoxic Activity by Select Transcription Factor Modulating Compounds in a Whole Cell Assay

[0818] In order to demonstrate that the transcription factor modulating compounds of the invention inhibit LcrF(VirF)-dependent cytotoxicity of *Y. pseudotuberculosis*, select compounds were screened in a whole cell system. Type III secretion, the process whereby cytotoxic proteins (Yops) are secreted from a bacterium into a host cell, in pathogenic *Yersinia* spp. is regulated by LcrF. Wild type *Y. pseudotuberculosis* are toxic toward J774 tissue culture cells whereas bacteria bearing a mutation in either yopJ (a Yop that inhibits eukaryotic signaling pathways) or lcrF are not. The cytotoxicity of wild type *Y. pseudotuberculosis* was exploited in order to screen compounds for their ability to penetrate the intact bacterial cell and prevent type III secretion by binding to an inactivating LcrF function.

[0819] The CytoTox 96® assay kit from Promega was used for this assay. Briefly, J774 macrophages were plated out at 2×10^4 cells per well in 96-well plates on the day prior to infection. *Yersinia pseudotuberculosis* were grown overnight at 26° C. in 2×YT media and then diluted 1:25 or 1:40 the following morning into 2×YT supplemented with 20 mM MgCl₂ and 20 mM sodium oxalate. The cultures were grown for a further 90 min at 26° C. and then shifted to 37° C. for 90 minutes. The temperature shift and the sodium oxalate, which chelates calcium, lead to induction of LcrF expression. Later experiments also included the YPIIIpIB1ΔJ (YopJ mutant) and YPIIIpIB1ΔLcrF (LcrF mutant). YPIIIpIB1ΔJ is a YopJ deletion mutant and any cytotoxicity that is unrelated to YopJ (i.e. lps-mediated) will be seen with this strain. The OD600 was measured and the culture adjusted to an OD600 of 1.0. This should correspond to approximately 1.25×10^9 cells/mL. Dilutions were prepared in DMEM (the J774 culture media) at different multiplicity of infections (MOIs), assuming J774 cell density of 2×10^4 . *Yersinia pseudotuberculosis* were added in 10 µl aliquots and cells were incubated at 37° C. either in a chamber with a CO₂ generating system, or later, in a tissue culture incubator with 5% CO₂ for 2 hours. Gentamicin was then added to a final concentration of 50 µg/ml and the incubations were continued either for a further 2-3 h or overnight. Controls were included for media alone, target cell spontaneous lysis, target cell maximum lysis and effector cell spontaneous lysis. For maximum lysis, triton X-100 was added to a final concentration of 0.8% 45 minutes prior to termination of the experiment. Supernatants containing released LDH were harvested following centrifugation at 1,000 rpm for 5 minutes. Supernatants were either frozen overnight or assayed immediately. 50 µl of supernatant was mixed with 50 µl fresh assay buffer and incubated in the dark for 30 minutes 501 of stop solution was added to each well and the plates were read at 490 nm. In Table 5 below, compounds that reduced *Y. pseudotuberculosis* cytotoxicity to 99-75% of untreated, wild type levels at 50 µg/mL are indicated with “**.” Compounds that reduced *Y. pseudotuberculosis* cytotoxicity to below 75% of untreated, wild type levels at 50 µg/mL are indicated with “*.” The percent cytotoxicity was measured relative to vehicle treated cells infected with wild type *Y. pseudotuberculosis*. Incubation with wild type *Y. pseudotuberculosis* yields $\geq 75\%$ toxicity.

TABLE 5

Compound	% Cytotoxicity
B	*
C	**
D	*
E	*
F	*
H	*
J	*
K	*
M	*
T	*
W	*
X	*
AA	*
AC	*
AK	**
AM	**
CL	*
CM	**
CO	**
CP	**

TABLE 5-continued

Compound	% Cytotoxicity
CQ	*
CR	*
CS	*
CT	*
CV	*
CW	*
CX	*
CY	*
DA	*
DC	**
DD	*
DE	**
DF	*
DG	*
DI	*
DJ	*
DK	*
DL	*
DM	*
DN	*
DO	*
DP	*
DQ	*
DR	*
DS	*
DT	*
DU	*
DV	*
DW	**
DX	*
DY	*
DZ	*
EA	*
EB	*
EC	*
ED	*
EF	*
EG	*
EH	*
EI	**
EJ	*
EK	*
EL	*
EM	*
EN	*
EO	**
EP	*
EQ	*
ER	*
ES	*
ET	*
EU	**
EV	**
EX	**
EY	*
EZ	**
FB	*

Example 7

Efficacy of Select Transcription Factor Modulating Compounds in a *Y. pseudotuberculosis* Pneumonia Model

[0820] The transcription factor modulating compounds of the invention that reduced *Y. pseudotuberculosis* cytotoxicity were then tested in lethal and sublethal murine *Y. pseudotuberculosis* murine models. Groups of 4 CD1 mice (7-8 week old males) were dosed subcutaneously with either vehicle or compound (25 mg/kg) 1 day prior to infection, at the time of infection, at 8 hours and then daily for 8 days following

intranasal infection with approximately 120 CFU of wild type (WT, IP2666pIB1) or Δ LcrF (JMB155) *Y. pseudotuberculosis*. The percent survival of infected mice following treatment with a transcription factor modulating compound, as illustrated in FIG. 3, was, after 25 days, increased to 60% for mice treated with compound F and increased to 80% for mice treated with compounds M and H when compared to non-treated mice. The percent of the starting weight of the infected mice following treatment with a transcription factor modulating compound, as illustrated in FIG. 4, was, after 25 days, approximately 100% for mice treated with compounds H and F, and approximately 120% for mice treated with compound M, while untreated mice lost approximately 40% of their starting weight.

[0821] Another assay was performed in which groups of 4 CD-1 mice were treated with a single subcutaneous dose of vehicle or LcrF inhibitor (25 mg/kg) one day prior to infection, at the time of infection, at 8 hours post infection, then once daily for a further 2 days. Mice were infected intranasally with 728 CFU of wild type (IP2666pIB1) or 752 CFU Δ LcrF (JMB155) *Y. pseudotuberculosis*. The mice were sacrificed 3 days post infection and serial dilutions of lung tissue homogenates were plated. The results are shown in Table 6, where the decrease is relative to vehicle treated mice infected with wild type *Y. pseudotuberculosis*. Compounds that exhibited a 0-1.0 log decrease in the CFU/g of LcrF in lung tissue are represented by “***,” compounds that exhibited a 1.1-2.0 log decrease in the CFU/g of LcrF in lung tissue are represented by “**” and compounds that exhibited no efficacy are represented by “--.” In particular, the control Δ LcrF bacteria showed dramatically attenuated virulence with a 2-log decrease in bacterial burden in the lungs compared to wild type in sublethal infections and 100% survival in infections where comparable numbers of wild type bacteria were lethal. Treatment with select transcription factor modulating compounds markedly reduced bacterial burden in the lung and decreased mortality in these mouse models of pneumonia.

TABLE 6

Compound	Log Decrease in CFU/g Lung Tissue
C	--
F	**
H	***
M	**
AA	--
AC	--
Δ LcrF	**

Example 8

In vitro Activity of Select Transcription Factor Modulating Compounds Against ExsA from *Pseudomonas aeruginosa*

[0822] ExsA regulates the expression of a major virulence determinant, the type III secretion system (TTSS). It has been shown that mutants that lack the exsA gene do not express the TTSS and these mutants show dramatically reduced virulence in whole cell assays and animal models of *P. aeruginosa* infection. The vast majority of clinical *P. aeruginosa* strains have the TTSS and expression of the TTSS is correlated with increased severity of disease in clinical pneumonia cases, including ventilator associated pneumonia. Several transcrip-

tion factor modulating compounds with high activity against LcrF also showed good inhibition of ExsA-DNA binding in vitro. The MarA (AraC) family member ExsA was cloned, expressed and purified from *P. aeruginosa*. The purified protein was used in a cell-free system to monitor DNA-protein interactions in vitro, methods as in Example 2. The EC₅₀’s for inhibition of ExsA-DNA binding by the compounds of the invention are summarized in Table 7 below. Compounds with excellent inhibition (less than 10 μ M) are indicated with “***,” very good inhibition (greater than 10.0 and less than 25.0 μ M) with “**,” good inhibition (greater than 25.0 μ M) with “*” and compounds that were not active are indicated with “--.”

TABLE 7

Compound	ExsA EC ₅₀ (μ M)
A	**
B	*
C	***
D	***
E	**
F	**
G	*
H	***
I	**
J	***
K	***
L	*
M	***
R	*
S	***
T	***
U	***
V	***
W	**
X	***
Y	**
Z	*
AA	***
AB	***
AC	***
AD	**
AE	**
AF	*
AG	*
AH	*
AI	*
AJ	***
AK	***
AM	***
AN	**
CC	*
CL	**
CM	***
CO	***
CP	***
CQ	*
CR	***
CS	*
CT	--
CV	**
CX	*
DA	**
DC	**
DD	**
DE	***
DF	*
DI	**
DJ	***
DK	*
DL	**
DM	**
DN	**

Example 9

TABLE 7-continued

Compound	ExsA EC ₅₀ (μM)
DO	—
DP	***
DQ	*
DR	**
DS	**
DT	**
DU	**
DV	—
DW	***
DX	**
DY	***
DZ	***
EA	***
EB	***
EC	—
ED	***
EF	***
EG	—
EH	***
EI	**
EJ	—
EK	—
EL	**
EM	***
EN	*
EO	***
EP	*
EQ	***
ER	***
ES	**
ET	**
EU	***
EV	***
EW	***
EX	***
EY	**
EZ	**
FA	**
FB	—
FQ	***
FR	***
FS	*
FT	**
FU	***
FV	—
FW	**
FX	*
FY	—
FZ	—
GA	**
GD	***
GE	**
GF	**
GH	**
GI	*
GK	*
GL	*
GN	***
GO	*
GP	*
GQ	*
GR	**
GS	**
GT	***
GU	***
GV	*

Inhibition of *P. aeruginosa* Cytotoxicity by Select Transcription Factor Modulating Compounds in a Whole Cell Assay

[0823] Transcription factor modulating compounds that exhibited measurable inhibition of ExsA-DNA binding, as described in Example 8, were screened for inhibition of ExsA-dependent *P. aeruginosa* cytotoxicity to macrophages in a whole cell system. In pathogenic *P. aeruginosa*, type III secretion is regulated by ExsA. Type III secretion is the process in which cytotoxic proteins (ExoU, ExoT, etc.) are secreted from a bacterium into a host cell. Wild type *P. aeruginosa* are toxic toward J774 tissue culture cells whereas bacteria bearing a mutation in exsA are not. In this example, the cytotoxicity of wild type *P. aeruginosa* was exploited to screen compounds for their ability to penetrate the intact bacterial cell and prevent type III secretion by binding to an inactivating ExsA function.

[0824] The CytoTox 96® assay kit from Promega was used for this assay. Briefly, J774 macrophage-like cells were plated out at 5×10^4 cells per well in 96-well plates on the day prior to infection. *P. aeruginosa* were grown overnight at 37° C. in Luria Broth and then diluted 1:25 in MinS, a minimal salt media containing the calcium chelator trisodium nitriloacetate. Experiments also included the WT ExsA mutants, in which the entire exsA coding sequence has been deleted. Mar inhibitors were added to the MinS cultures at a concentration of 50 μg/mL and the cultures were grown for a further 3 hours at 37° C. The shift to a calcium free media leads to induction of ExsA expression. Cultures were grown to an OD600 of 1.0, approximately 1×10^9 cells/mL. Dilutions were prepared in DMEM (the J774 culture media) at different multiplicity of infections (MOIs), assuming J774 cell density of 5×10^4 . Media in the J774 cell wells was replaced with DMEM containing 50 μg/mL of Mar inhibitors. *P. aeruginosa* were added to J774 cells in 10 μL aliquots, plates were centrifuged at 1,000 rpm for 5 minutes to synchronize infection and then incubated in a tissue culture incubator with 5% CO₂ for 2 h. Controls were included for media alone, target cell spontaneous lysis, target cell maximum lysis, and Mar inhibitors with J774 cells alone. For target cell maximum lysis, 101 of the CytoTox 96® assay kit lysis solution was added to untreated J774 cells 30 minutes prior to termination of the experiment. Supernatants containing released LDH were harvested following centrifugation at 1,000 rpm for 5 minutes. Supernatants were stored frozen overnight or assayed immediately. 50 μL of supernatant was mixed with 50 μL fresh LDH substrate solution and incubated in the dark for 30 minutes. 50 μL of stop solution was added to each well and the plates were read at 490 nm. In Table 8 below, compounds that reduced *P. aeruginosa* cytotoxicity to 99-75% of untreated, wild type levels at 50 mg/mL are indicated with “*.” Compounds that reduced *P. aeruginosa* cytotoxicity below 75% of untreated, wild type levels at 50 mg/mL are indicated with “**.” The percent cytotoxicity was relative to vehicle treated cells infected with wild type *P. aeruginosa*. Incubation with wild type *P. aeruginosa* yielded ≥75% toxicity. In addition, an exsA null mutant was completely non-cytotoxic.

TABLE 8

Compound	Cytotoxicity at 50 µg/mL <i>Pseudomonas</i>
AA	**
AK	*
AM	**
AJ	**
CL	*
CM	**
CO	*
CP	*
CQ	**
CR	**
CV	*
CY	*
DA	*
DC	*
DD	*
DE	*
DI	*
DJ	*
DL	*
DM	*
DN	*
DP	*
DR	*
DS	*
DT	*
DU	*
DW	*
DX	*
DY	*
DZ	*
EA	*
EB	*
ED	*
EF	*
EH	*
EI	*
EL	*
EM	*
EO	**
EQ	*
ES	**
ET	*
EU	**
EV	**
EW	**
EX	**
EY	*
EZ	**
FA	**
FB	*
FC	**
FQ	**
FR	*
FS	*
FT	*
FU	**
FV	**
FW	**
FX	*
FY	*
FZ	*
GA	**
GD	*
GE	*
GF	*
GH	*
GI	*
GK	*
GL	**
GN	**
GO	*
GP	*

TABLE 8-continued

Compound	Cytotoxicity at 50 µg/mL <i>Pseudomonas</i>
GQ	*
GR	*
GS	**
GT	**
GU	**
GV	**

Example 10

Efficacy of Select Transcription Factor Modulating Compounds in a Lethal *P. aeruginosa* Pneumonia Model

[0825] Transcription factor modulating compounds that substantially inhibited *P. aeruginosa* cytotoxicity were tested in a lethal model of murine acute pneumonia. In this model, infection with $\sim 1 \times 10^6$ CFU of wild type bacteria causes >90% mortality within 48-72 hours, whereas mice infected with the same number of an exsA null mutant bacteria survive indefinitely. The efficacy of two transcription factor modulating compounds, AJ and I, were tested in vivo for their efficacy against *P. aeruginosa* PA103 in a mouse model of pneumonia (10^6 organisms inoculated intranasally). Compound AJ was administered IP at 25 mg/kg at -18, -1, 2, 5, 20, 26 and 44 hours post-infection and mortality was assessed at various times post infection. As shown in FIG. 5, a statistically significant difference was noted between the untreated (vehicle) and the AJ treated groups ($p^{**} p<0.05$, * $p<0.1$ by Chi-Square analysis, $n=22$ mice/group). The AJ treated groups had an approximately 40% survival rate over 48 hours post infection compared to an approximately 20% survival rate over 48 hours in the untreated group.

[0826] Compound I was also administered IP at 25 mg/kg at -18, -1, 5, 20, 26 and 44 hours post infection. As shown in FIG. 5, 40.9% of mice treated with compound AJ survived at 48 hours post infection, which was significantly higher than the 9.5% survival of vehicle treated mice ($P<0.05$). Treatment with a second compound I increased survival at 48 hours post infection to 50% versus 15.7% for vehicle treated mice (FIG. 6). However, the numbers of mice were not sufficient to show statistical significance in the second experiment ($n=6-8$ mice/group).

Example 11

E. coli Biofilm Assay

[0827] The biofilm assay screens test compounds for their ability to inhibit bacteria from forming a biofilm.

Materials:

[0828] The M9 media ("M9") contained M9, casamino acids, and glucose. The test compound was dissolved in 10 mg/mL DMSO stock solution.

Method:

Preparation of Inoculum

[0829] Inoculum was started the day of the experiment by adding a colony or glycerol stock stab to 2 mL M9. The tube was placed in the 37° C. shaker incubator for approximately 4-6 hours. This inoculum was referred to as the "Starter

inoculum." The inoculum was then removed from the shaker incubator and diluted to 1×10^6 cells/mL in M9.

Preparation of Controls

[0830] Typically, there were eight of each control, including a positive and negative control. For both the positive and negative controls, 2.5 μL of DMSO was added to 200 μL of M9. 25 μL of the diluted DMSO was added to 50 μL of M9 in the assay plate.

Preparation of Test Compounds

[0831] The test compounds were screened at 20 $\mu\text{g}/\text{mL}$. 2.5 μL of the test compound were taken from a plate containing 10 $\mu\text{g}/\text{mL}$ stock and added to 200 μL of M9 and mixed. 25 μL of the diluted test compound was added to 50 μL of M9 in the assay plate. The resulting concentration of the test compound was 40 $\mu\text{g}/\text{mL}$.

Preparation of Plate

[0832] 75 μL of the inoculum at 1×10^6 cells/mL was added to each well containing compound and the positive controls. 75 μL M9 was added to the negative controls. The final concentration of the test compound was 20 $\mu\text{g}/\text{mL}$ and the final concentration of the inoculum was 2×10^6 cells/mL. The plates were then placed in a microplate reader (Wallac Victor² V) and read OD₅₃₅ ("Initial growth reading"). The plates were then placed in an incubator overnight at 35° C. In the morning, the plates were read in a microplate reader at OD₅₃₅ ("Final growth reading.")

Addition of Crystal Violet

[0833] The inoculum was then removed from the wells and the plates were washed several times with tap water. 150 μL of Crystal Violet (0.02% Crystal Violet dissolved in water) was then added to each well.

Addition of Ethanol

[0834] The crystal violet was then removed and the plates were washed several times with tap water. 150 μL of ethanol were then added to each well, after mixing. The plates were then placed in a microplate reader and read the OD₅₃₅. This was referred to as the "Crystal Violet" reading.

Data Analysis

[0835] To determine whether a test compound inhibited growth, the Initial growth reading was subtracted from the Final growth reading ("Subtracted Growth"). The same was done for the positive controls and averaged. The % inhibition of growth was determined by the following formula:

$$\frac{100 - (100 * \text{Subtracted growth of sample} / \text{Average growth of Pos Controls})}{100}$$

[0836] To determine whether a test compound inhibited Biofilm formation, the % Inhibition of Biofilm Formation was determined using the following formula:

$$\frac{100 - (100 * \text{Crystal Violet read of sample} / \text{Average crystal violet read of Pos Controls})}{100}$$

Example 12

LANCE Screening Assay for Select Transcription Factor Modulating Compound Inhibitors of SoxS, ExsA, VirF and SlyA DNA-Binding

[0837] This example describes a method for the identification of test compounds that inhibit the interactions of purified

transcription factor such as SoxS, ExsA and/or VirF with a target DNA sequence in an in vitro system.

Materials

[0838] The 6His-tagged SoxS, ExsA and VirF purified according to respective protocol. The N-term-biotinylated double-stranded DNA has a sequence of CCG ATT TAG CAA AAC GTG GCA TCG GTC (SEQ ID NO. 1). The antibody used was the LANCE Eu-labeled anti-6xHis Antibody (Eu- α His) (Perkin Elmer cat #AD0110) which had at least 6 Europium molecules per antibody. Streptavidin conjugated to SureLightTM-Allophycocyanin (SA-APC) was obtained from Perkin Elmer (cat #CR130-100). The Assay buffer contained 20 mM Hepes pH 7.6, 1 mM EDTA, 10 mM (NH₄)₂SO₄, and 30 mM KCl, and 0.2% Tween-20.

Method

[0839] The plates or vials of the compounds to be tested were thawed. These stocks were at a concentration of 10 mg/ml in DMSO. The solutions were allowed to thaw completely, and the plates were briefly shaken on the Titermix to redissolve any precipitated compound. Thawed aliquots of SoxS, ExsA and VirF protein from the stock stored at -80° C. and 1M stock of dithiothreitol stored at -20° C. were then placed on ice.

[0840] Dilutions at 1:100 of the compounds were made into a fresh 96-well polystyrene plate. The dilutions were prepared with 100% DMSO to give a final concentration of 100 $\mu\text{g}/\text{ml}$ solutions. The dilutions were vortexed on a Titermix.

[0841] Fresh DTT was added to 25-50 mL of assay buffer to produce a 1 mM final concentration. Next, 901 of assay buffer was added to each of the 10 μl protein aliquots, and the solution was mixed by pipetting. These proteins were diluted to give the required amount of each of the diluted proteins, resulting in 201 of diluted protein per well. In preparing the solutions, 20% excess was made to allow enough for control wells. Typically, depending on the protein preps and the initial binding curves that were performed, 1000-2000 fmoles of each protein was required per well. The diluted protein solutions were then placed on ice.

[0842] Three tests plates per plate of compound (for SoxS, ExsA and VirF) were prepared. Using a multichannel pipet, 5 μl of the compound was added to each well. 5 μl of DMSO was added to the blank and control wells, and 5 μl of the control inhibitor was added to the respective wells.

[0843] Using the multichannel pipet, 201 of protein was added to all wells except those designated "blank". To these blank wells, 201 of assay buffer was added. The plates were covered with a plate sealer and incubated at room temperature, shaking on the Titermix, for 30 minutes.

[0844] Next, the DNA solution was prepared, with enough for at least 20% more wells than were tested. 15 μl (0.4 fmoles) was added per well. Then the DNA was diluted in assay buffer, and vortexed briefly to mix. The plate sealer was removed, and 15 μl of DNA solution was added to all of the wells. The plates were then resealed, and returned to the Titermix for a further 30 minutes.

[0845] After 25 minutes, the antibody solution was prepared. 0.4 fmoles of SA-APC and 0.125 fmoles of Eu- α His were added per well in a total volume of 10 μl . Amounts were prepared sufficient for at least 20% excess. The plate sealer was removed and 10 μl of antibody solution was added to every well. The plates were subsequently resealed, placed on the Titermix, and covered with aluminum foil. The plates were mixed for 1 hour. The plates were then read on the Wallac Victor V, using the LANCE 615/665 protocol.

Data Processing

[0846] For each plate, the mean control (i.e. signal from protein and DNA without inhibition), mean blank (background signal without protein) and mean inhibitor (P001407) LANCE₆₆₅ counts were determined. The percentage inhibition by each molecule (each test well) was then determined according to the following equation:

$$\% \text{ Inhibition} = 100 - (((\text{test} - \text{mean blank}) / (\text{mean control} - \text{mean blank})) * 100)$$

[0847] Compounds that gave 40% or greater inhibition were identified as hits and screened again for EC₅₀.

EC₅₀ Screening

[0848] The protocol used was identical to that outlined above, except that only 10 compounds were assayed per plate. The testing concentrations started at 10 µg/ml and were diluted two-fold from 10 to 0.078 µg/ml.

EC₅₀ Data Processing

[0849] Percent inhibition was calculated as shown above. Percent inhibition was then plotted vs. log (conc. Inhibitor) using Graph pad Prism software.

Example 13

Cell Free Protein-DNA Binding Assays

[0850] An electrophoretic mobility shift assay (EMSA) using 0.1M (³³P)DNA, 5 nM SoxS and 50 µg/ml of transcription factor modulating compound was used to study activity of the compound to interrupt DNA-protein interactions in vitro. Different compounds had varying activities against SoxS in vitro in an EMSA. For example, compound AU was very active, BB was moderately active, and compound BK lacked activity.

[0851] The measurement of the ability of the transcription factor modulating compounds of the invention to intercalate DNA was performed by a qualitative agarose gel assay. The assay consisted of 100 ng uncut plasmid DNA, DMSO, which relieves DNA supercoiling and converts the plasmid DNA to a single form, and transcription factor modulating compounds AU, BP, BQ, BX and a known DNA intercalator. Unlike the known DNA intercalator, the transcription factor modulating compounds were not found to intercalate DNA.

Example 14

Inhibition of SoxS binding to its cognate DNA by Select Transcription Factor Modulating Compounds

[0852] A quantitative chemiluminescence-based assay was used to measure the DNA binding activity of various MarA (AraC) family members. With this technique, biotinylated double-stranded DNA molecule (2 nM) was incubated with a MarA (AraC) protein (20 nM) fused to 6-histidine (6-His) residues in a streptavidin coated 96-well microtiter (white) plate (Pierce Biotechnology, Rockford, Ill.). Unbound DNA and protein was removed by washing and a primary monoclonal anti-6His antibody was subsequently added. A second washing was performed and a secondary HRP-conjugated antibody was then added to the mixture. Excess antibody was removed by a third wash step and a chemiluminescence substrate (Cell Signaling Technology, Beverly, Mass.) was added to the plate. Luminescence was read immediately using a Victor V plate reader (PerkinElmer Life Sciences, Wellesley, Mass.). Compounds that inhibited the binding of the protein to the DNA resulted in a loss of protein from the plate at the first wash step and were identified by a reduced luminescence

signal. The results of this assay are shown in Table 9, which shows data on the inhibition of SoxS from binding the DNA. Transcription factor modulating compounds that inhibited the binding of SoxS to DNA by greater than 70% are represented by “***,” compounds that inhibited the binding of SoxS between about 30% and 69% are represented by “**,” compounds that inhibited the binding of SoxS by less than 29% are represented by “*,” and compounds that exhibited no inhibition are represented by “-.”

TABLE 9

Compounds	% Inhibition ^a
A	***
AO	-
AP	-
AQ	*
AR	-
AS	-
AT	-
AV	*
AW	**
AX	*
AY	*
AZ	-
BA	*
BB	*
BC	**
BD	*
BE	-
BF	*
BG	**
BH	-
BI	**
BJ	**
BL	***
BN	*
BO	**
BP	***
BR	*
BT	**
BV	*
BW	*
BX	**
CA	*
CD	**
CH	***
GB	**

^aValues are means of three experiments, standard deviation is less than 15%. Compounds screened at 50 µg/mL.

[0853] The EC₅₀'s of several transcription factor modulating compounds for the inhibition of SoxS binding to the DNA target were also calculated and the results are given in Table 11. Compounds that gave an IC₅₀ of greater than 5 µM are represented by “***,” compounds that gave an IC₅₀ of between about 1 and 4.9 µM are represented by “**,” and compounds exhibiting IC₅₀'s of less than 0.9 µM are represented by “*.”

Example 15

Inhibition of a Series of Transcription Factors to Their Cognate DNA by Select Transcription Factor Modulating Compounds

[0854] Using the chemiluminescence-based assay described above in Example 2, in vitro EC₅₀ (µM) values for the transcription factor modulating compounds were obtained for several AraC family members: MarA, SoxS and Rob (*E. coli*), ExsA (*P. aeruginosa*), Rma (*S. typhimurium*), PqrA (*P. mirabilis*) and SlyA, which is a member of a different superfamily (the MarR protein). Although SlyA contains a helix-turn-helix DNA binding motif, it is not related to

members of the MarA protein family. The results are given in Table 10. Compounds that gave an EC₅₀ of greater than 5 μM are represented by “*”, compounds that gave an EC₅₀ of between about 1 and 4.9 μM are represented by “**”, and compounds exhibiting EC₅₀’s of less than 0.9 μM are represented by “***”, and compounds that were not tested are represented by “—.”

TABLE 10

Compds.	EC50 (μM) ^a						
	SlyA	MarA	SoxS	Rob	ExsA	Rma	PqrA
C	—	—	**	**	**	**	—
AH	*	**	***	**	**	**	**
BQ	*	*	**	*	*	*	*

^aStandard error <15% for all values

[0855] Results of a subsequent assay including VirF of *Y. pseudotuberculosis* are shown in Table 11. Compounds that gave EC₅₀’s of less than about 5 μM are shown by “*”; compounds with EC₅₀’s of between about 5.1 and 15 μM are shown by “**”; and compounds with EC₅₀’s of greater than 15.1 μM are shown by “***”.

TABLE 11

Compound	EC50 (μM)	<i>Y. pseudo-tuberculosis</i>		<i>P. aeruginosa</i>		EC50 (μM)
		<i>E. coli</i> SoxS	VirF	<i>E. coli</i> ExsA	(non-MAR) SlyA	
S	*	*	*	*	***	
V	*	*	*	*	***	
AJ	**	*	*	*	***	
CM	**	**	*	*	***	
DE	*	*	*	*	***	
DP	*	*	**	*	***	
EH	**	*	*	*	***	

Example 16

Acute *P. aeruginosa* Pneumonia Models

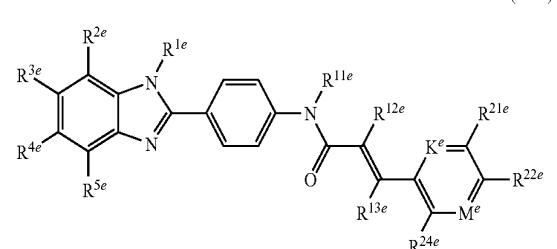
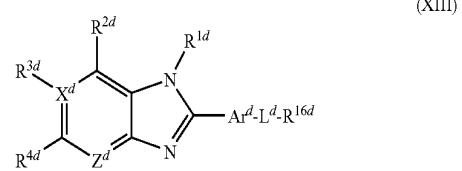
[0856] Approximately 30 Swiss Webster mice (females, 18-24 grams) are randomized to one of 4 groups of 5-10 mice per group. Animals are briefly anesthetized by isoflurane inhalation for 10-30 seconds in order to minimize the stress during intranasal inoculation. The mice are infected intranasally with 1×10⁶ *P. aeruginosa* bacteria diluted in room temperature sterile phosphate buffered saline (PBS) in a volume of 50 μL; a control group receives intranasal PBS with no bacteria. The mice are allowed to recover in an inclined position to improved infection efficacy. The mice are dosed IP with 25 mg/kg of the test compound in a maximum volume of 10 mL/kg (or equal volume of 5% PEG400, 95% H₂O vehicle alone) at -1, 2, 5, 20, 26, 44 and 50 hours post-infection. Infected mice are monitored for morbidity and survival twice daily over the course of 7 days. Any mice exhibiting signs of severe illness, e.g., 20% loss of their starting body weight, severe ataxia, shaking, labored breathing, unresponsiveness, etc., are painlessly euthanized by CO₂ narcoses and cervical dislocation and marked as dead. Mice infected with this inoculum of wild type *P. aeruginosa* (PA103) typically succumb to the infection within 48-72 hours, whereas mice infected with an ExsA null mutant strain (PA103 ΔExsA) survive indefinitely. Compounds are also tested by IV or PO administration with dose level and schedule determined from PK evaluation by these routes.

[0857] In experiments where the determination of bacterial burden in individual organs is desired, mice are infected intranasally with ~4×10⁵ *P. aeruginosa* bacteria and receive the -1, 2, and 5 hour doses of compound or vehicle control. At 18 hours post infection, all mice are euthanized by CO₂ narcoses and cervical dislocation. Blood is collected immediately via cardiac puncture, and the liver, spleen and lungs are collected and weighed aseptically. Organs are homogenized in sterile PBS, and tissue and blood are plated in serial dilutions on rich media, and incubated at 37° C. for 24 hours to determine bacterial counts. In this model, infection with wild type (PA103) *P. aeruginosa* results in a lung bacterial burden greater than the inoculum with detectable dissemination to the peripheral tissues. Mice are not expected to develop pronounced illness in this model, but if any animals become severely moribund, they are euthanized immediately (as described previously) and marked as dead. In this model, the bacterial counts in the lungs and peripheral organs in mice infected with ExsA null mutant bacteria (PA103ΔExsA) are typically at least 2 logs lower than for mice infected with wild type (PA103) bacteria.

EQUIVALENTS

[0858] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific polypeptides, nucleic acids, methods, assays and reagents described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

1. A method for reducing infectivity and/or virulence of a microbial cell, comprising contacting the cell with an effective amount of a transcription factor modulating compound of formula XIII or XIV:



wherein:

R^{1d} is hydrogen, —OH, —OCH₂-aryl, —CH₂CH₂CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

R^{2d} is hydrogen or —NR^{2da}R^{2db};

R^{2da} and R^{2db} are each independently hydrogen, alkyl or aminoalkyl;

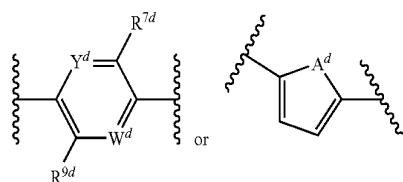
X^d is CR^{3d}, N or NO;

R^{3d} is absent when X^d is N or NO—NO₂, hydrogen, acyl,

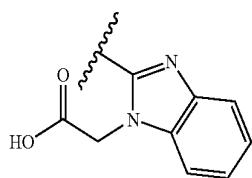
halogen, alkoxy, —CO₂H, —CONR^{3da}R^{3db}, cyano,

—NR^{3d}R^{3dd}, alkyl, —SO₂R^{3de}, —C(R^{3df})NOH, heterocyclic or heteroaryl;

R^{3da} and R^{3db} are each independently hydrogen or alkyl;
 R^{3dc} and R^{3dd} are each independently hydrogen, alkyl or substituted carbonyl;
 R^{3de} and R^{3df} are each independently alkyl or amino;
 R^{4d} is hydrogen, alkoxy, $—NR^{4da}R^{4db}$, alkyl, halogen, $—SO_2R^{4dc}$ or $—CO_2H$;
 R^{4d} and R^{4db} are each independently hydrogen, alkyl or aminoalkyl;
 R^{4dc} is alkyl or amino;
 Z^d is CH, N or NO;
 Ar^d is



when L^d is present or



when L^d and R^{16d} are each absent;

Y^d is N or CR^{6d} ;

W^d is N or CR^{8d} ;

R^{6d} is absent when Y^d is N, or hydrogen, alkyl, amino, $—CO_2H$, $—OCH_2P(O)(OH)_2$ or alkyl;

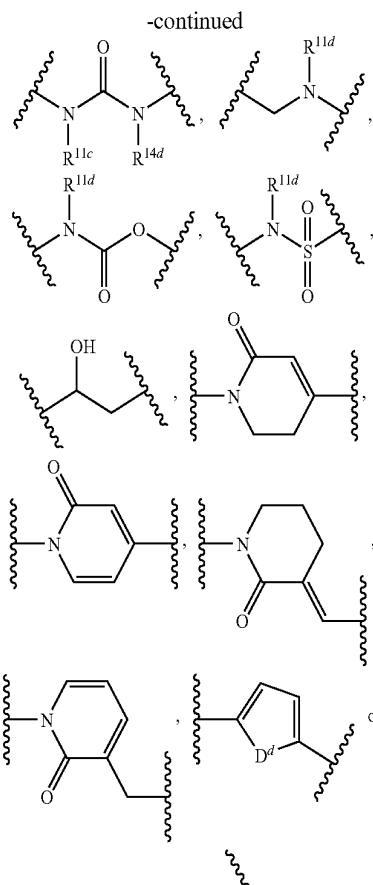
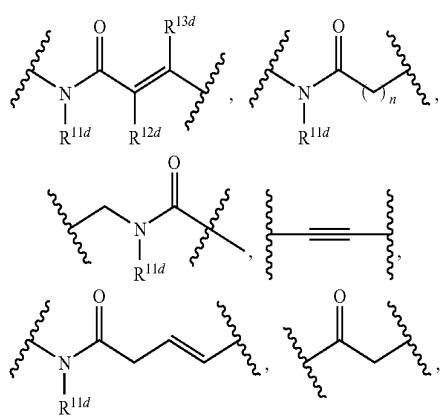
R^{8d} is absent when W^d is N, or hydrogen, alkyl, amino, $—CO_2H$, $—OCH_2P(O)(OH)_2$ or alkyl;

R^{7d} and R^{9d} are each independently hydrogen, alkyl, amino, $—CO_2H$, $—OCH_2P(O)(OH)_2$ or alkyl;

A^d is O, NR^{10d} or S;

R^{10d} is hydrogen or alkyl;

L^d is absent, or L^d is hydrogen or unsubstituted phenyl when R^{16d} is absent, or L^d is $—O—$, $—SO—$, $—SO_2—$, $—OCH_2—$, $—CH_2—$, $—NR^{15d}$,



n is an integer between 0-2;

D^d and E^d are each independently NR^{17d} ; O or S

J^d is N or CR^{18d} ;

G^d is N or CR^{19d} ;

R^{11d} is hydrogen or alkyl;

R^{18d} is absent when J^d is N or hydrogen or alkyl;

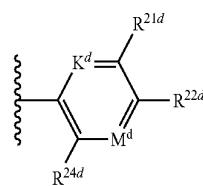
R^{19d} is absent when G^d is N or hydrogen or alkyl;

R^{12d} and R^{13d} are each independently hydrogen, alkyl, halogen or aryl;

R^{15d} is hydrogen or alkyl;

R^{16d} is hydrogen, alkoxy, hydroxyl, amino, alkyl, $—NO_2$ or halogen when L^d is absent; or

R^{16d} is



when L^d is present;

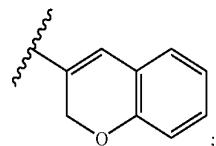
K^d is CR^{20d} or N;

M^d is CR^{23d} Or N;

R^{20d} is absent when K^d is N or hydrogen, alkyl, halogen, alkoxy or hydroxyl;

R^{21d} is hydrogen, halogen or alkyl;

R^{22d} is hydrogen, heteroaryl, halogen, alkoxy, cyano, acyl, $-\text{SO}_2\text{R}^{22da}$, heterocyclic, $-\text{COOH}$ hydroxyl, $-\text{CF}_3$, alkyl, amino, CO_2H , aminocarbonyl or



R^{22da} is amino or alkyl;

R^{23d} is absent when M^d is N or hydrogen, halogen, alkyl or alkoxy; or R^{22d} and R^{23d} together with the carbon atoms to which they are attached are joined to form a 5- or 6-membered ring;

R^{24d} is hydrogen, halogen or alkoxy;

R^{1e} is $-\text{OH}$, $-\text{OCH}_2\text{-aryl}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CN}$, $-\text{OCH}_2\text{CH}_2\text{NH}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$, $-\text{OCH}_2\text{COOH}$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{P(O)(OH)}_2$ or $-\text{OCH}_2\text{P(O)(OCH}_2\text{CH}_3)_2$;

R^{2e} , R^{4e} , R^{53} , R^{11e} , R^{12e} , R^{13e} , R^{21e} , R^{22e} , and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{3e} is $-\text{NO}_2$, hydrogen, acyl, halogen, alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}^{3da}\text{R}^{3db}$; cyano, $-\text{NR}^{3dc}\text{R}^{3dd}$, alkyl, $-\text{SO}_2\text{R}^{3de}$, $-\text{C}(\text{R}^{3df})\text{NOH}$, heterocyclic or heteroaryl;

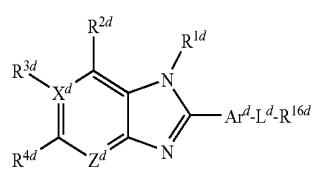
R^{3ea} is alkyl or amino;

K^e is CR^{20e} or N;

M is CR^{23e} or N; and pharmaceutically acceptable salts thereof: such that said infectivity and/or virulence or the microbial cell is reduced.

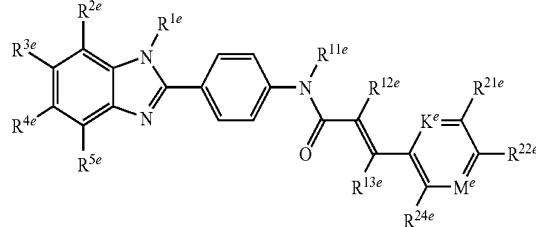
2. A method for modulating transcription of genes regulated by one or more transcription factors in the MarA (AraC) family, comprising contacting a transcription factor with an effective amount of a transcription factor modulating compound of formula XIII or XIV:

(XIII)



-continued

(XIV)



wherein:

R^{1d} is hydrogen, $-\text{OH}$, $-\text{OCH}_2\text{-aryl}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CN}$, $-\text{OCH}_2\text{CH}_2\text{NH}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$, $-\text{OCH}_2\text{COOH}$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{P(O)}$ (OH)₂ or $-\text{OCH}_2\text{P(O)(OCH}_2\text{CH}_3)_2$;

R^{2d} is hydrogen or $-\text{NR}^{2da}\text{R}^{2db}$;

R^{2d} and R^{2db} are each independently hydrogen, alkyl or aminoalkyl;

X^d is CR^{3d} , N or NO;

R^{3d} is absent when X^d is N or NO— NO_2 , hydrogen, acyl, alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}^{3da}\text{R}^{3db}$; cyano, $-\text{NR}^{3dc}\text{R}^{3dd}$, alkyl, $-\text{S}_2\text{R}^{3de}$, $-\text{C}(\text{R}^{3df})\text{NOH}$, heterocyclic or heteroaryl;

R^{3d} and R^{3db} are each independently hydrogen or alkyl;

R^{3de} and R^{3dd} are each independently hydrogen, alkyl or substituted carbonyl;

R^{3de} and R^{3df} are each independently alkyl or amino;

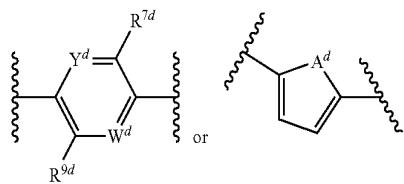
R^{4d} is hydrogen, alkoxy, $-\text{NR}^{4da}\text{R}^{4db}$, alkyl, halogen, $-\text{SO}_2\text{R}^{4d}$, or $-\text{CO}_2\text{H}$;

R^{4d} and R^{4db} are each independently hydrogen, alkyl or aminoalkyl;

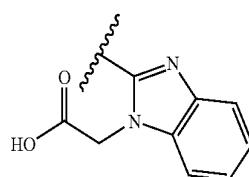
R^{4dc} is alkyl or amino;

Z^d is CH, N or NO;

Ar^d is



when L^d is present or



when L^d and R^{16d} are each absent;

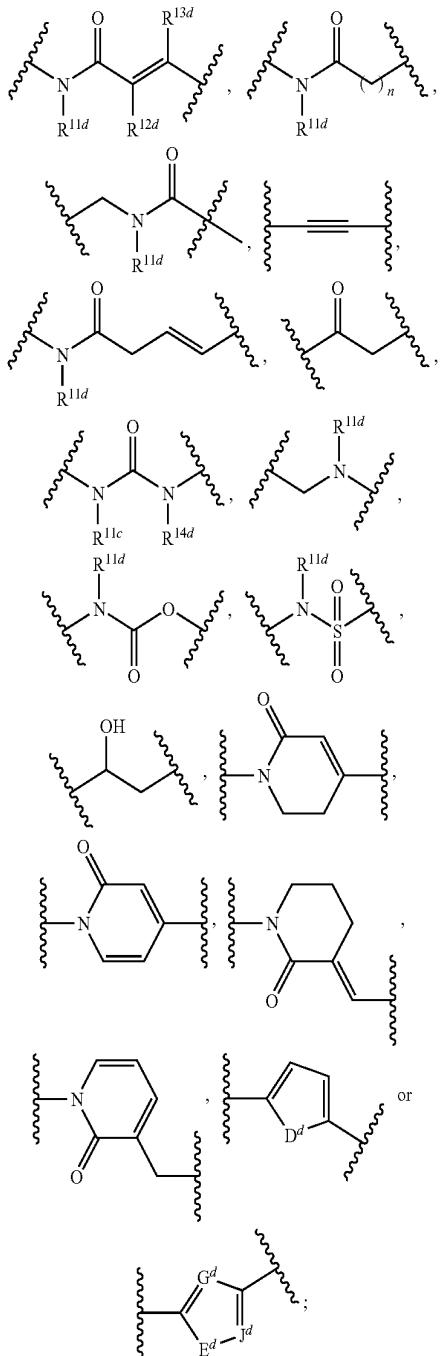
Y^d is N or CR^{6d} ;

W^d is N or CR^{8d} ;

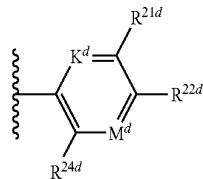
R^{6d} is absent when Y^d is N, or hydrogen, alkyl, amino, $-\text{CO}_2\text{H}$, $-\text{OCH}_2\text{P(O)(OH)}_2$ or alkyl;

R^{8d} is absent when W^d is N, or hydrogen, alkyl, amino, $-\text{CO}_2\text{H}$, $-\text{OCH}_2\text{P}(\text{O})(\text{OH})_2$ or alkyl;
 R^{7d} and R^{9d} are each independently hydrogen, alkyl, amino, $-\text{CO}_2\text{H}$, $-\text{OCH}_2\text{P}(\text{O})(\text{OH})_2$ or alkyl;
 A^d is O, NR^{10d} or S;
 R^{10d} is hydrogen or alkyl;
 L^d is absent, or L^d is hydrogen or unsubstituted phenyl when R^{16d} is absent, or L^d is $-\text{O}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{OCH}_2-$, $-\text{CH}_2-$, $-\text{NR}^{15d}$

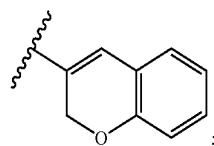
G^d is N or CR^{19d},
 R^{11d} is hydrogen or alkyl;
 R^{18d} is absent when J^d is N or hydrogen or alkyl;
 R^{19d} is absent when G^d is N or hydrogen or alkyl;
 R^{12d} and R^{13d} are each independently hydrogen, alkyl, halogen or aryl;
 R^{15d} is hydrogen or alkyl;
 R^{16d} is alkoxy, hydroxyl, amino, alkyl, $-\text{NO}_2$ or halogen when L^d is absent; or
 R^{16d} is



n is an integer between 0-2;
 D^d and E^d are each independently NR^{17d}, O or S
 J^d is N or CR^{18d};



when L^d is present;
 K^d is CR^{20d} or N;
 M^d is CR^{23d} or N;
 R^{20d} is absent when K^d is N or hydrogen, alkyl, halogen, alkoxy or hydroxyl;
 R^{21d} is hydrogen, halogen or alkyl;
 R^{22d} is hydrogen, heteroaryl, halogen, alkoxy, cyano, acyl, $-\text{SO}_2\text{R}^{22da}$, heterocyclic; $-\text{COOH}$, hydroxyl, $-\text{CF}_3$, alkyl, amino, CO_2H , aminocarbonyl or



R^{22da} is amino or alkyl;
 R^{23d} is absent when M^d is N or hydrogen, halogen, alkyl or alkoxy; or R^{22d} and R^{23d} together with the carbon atoms to which they are attached are joined to form a 5- or 6-membered ring;
 R^{24d} is hydrogen, halogen or alkoxy;

R^{1e} is $-\text{OH}$, $-\text{OCH}_2\text{aryl}$, $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{OCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CN}$, $-\text{OCH}_2\text{CH}_2\text{NH}_2$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3$, $-\text{OCH}_2\text{COOH}$, $-\text{OCH}_2\text{CH}_2\text{CH}_3$, $-\text{OCH}_2\text{CH}_2\text{OH}$, $-\text{OCH}_2\text{P}(\text{O})(\text{OH})_2$ or $-\text{OCH}_2\text{P}(\text{O})(\text{OCH}_2\text{CH}_2)_2$;

R^{2e} , R^{4e} , R^{53} , R^{11e} , R^{12e} , R^{13e} , R^{21e} , R^{22e} , and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

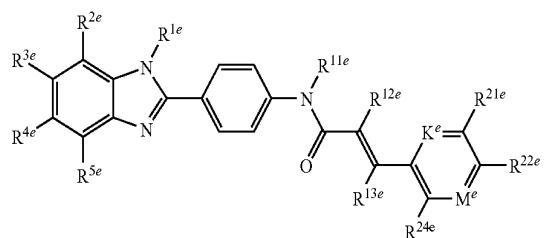
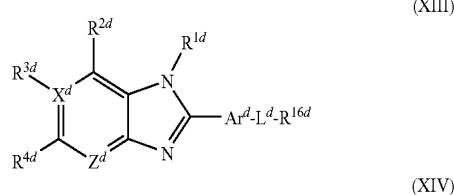
R^{3e} is $-\text{NO}_2$, hydrogen, acyl, halogen, alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}^{3da}\text{R}^{3db}$; cyano, $-\text{NR}^{3dc}\text{R}^{3dd}$, alkyl, $-\text{SO}_2\text{R}^{3de}$, $-\text{C}(\text{R}^{3df})\text{NOH}$, heterocyclic or heteroaryl;

R^{3ea} is alkyl or amino;

K^e is CR^{2de} or N;

Me is CR^{23e} or N; and pharmaceutically acceptable salts thereof, such that said transcription of genes is modulated.

3. A method for preventing bacterial growth on a contact lens comprising administering a composition comprising an acceptable carrier and an effective amount of a transcription factor modulating compound of formula XIII or XIV:



wherein:

R^{1d} is hydrogen, —OH, —OCH₂-aryl, —CH₂CH₂CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

R^{2d} is hydrogen or —NR^{2da}R^{2db};

R^{2da} and R^{2db} are each independently hydrogen, alkyl or aminoalkyl;

X^d is CR^{3d}, N or NO;

R^{3d} is absent when X^d is N or NO—NO₂, hydrogen, acyl, halogen, alkoxy, —CO₂H, —CONR^{3da}R^{3db}; cyano, —NR^{3dc}R^{3dd}, alkyl, —SO₂R^{3de}, —C(R^{3df})NOH, heterocyclic or heteroaryl;

R^{3d} and R^{3db} are each independently hydrogen or alkyl;

R^{3d} , and R^{3dd} are each independently hydrogen, alkyl or substituted carbonyl;

R^{3de} and R^{3df} are each independently alkyl or amino;

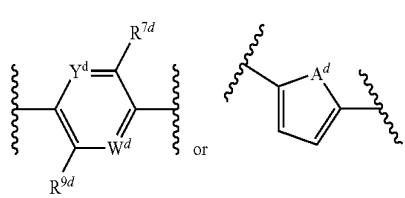
R^{4d} is hydrogen, alkoxy, —NR^{4da}R^{4db}, alkyl, halogen, —SO₂R^{4de} or —CO₂H;

R^{4da} and R^{4db} are each independently hydrogen, alkyl or aminoalkyl;

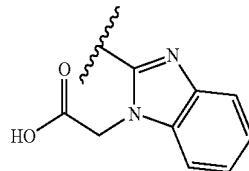
R^{4de} is alkyl or amino;

Z^d is CH, N or NO;

Ar^d is



when L^d is present or



when L^d and R^{16d} are each absent;

Y^d is N or CR^{6d},

W^d is N or CR^{8d},

R^{6d} is absent when Y^d is N, or hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

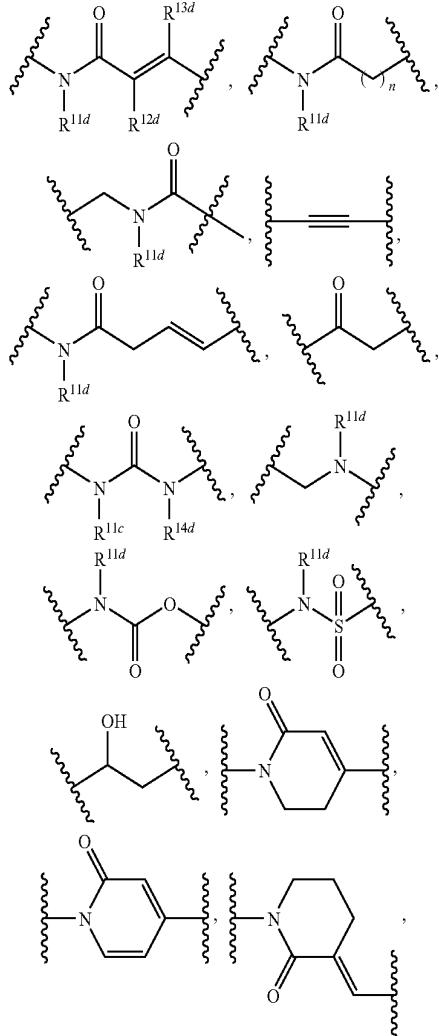
R^{8d} is absent when W^d is N, or hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

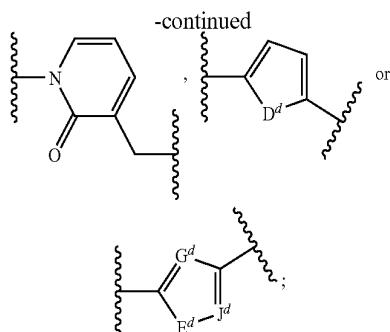
R^{7d} and R^{9d} are each independently hydrogen, alkyl, amino, —CO₂H, —OCH₂P(O)(OH)₂ or alkyl;

A^d is O, NR^{10d} or S;

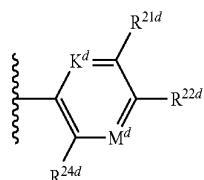
R^{10d} is hydrogen or alkyl;

L^d is absent, or L^d is hydrogen or unsubstituted R^{16d} or L^d is —O—, —SO—, —SO₂—, —OCH₂—, —CH₂—, —NR^{15d},

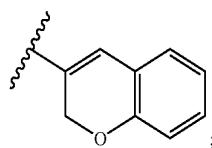




n is an integer between 0-2;
 D^d and E^d are each independently NR^{17d} , O or S
 J^d is N or CR^{18d} ;
 G^d is N or CR^{19d} ;
 R^{11d} is hydrogen or alkyl;
 R^{18d} is absent when J^d is N or hydrogen or alkyl;
 R^{19d} is absent when G^d is N or hydrogen or alkyl;
 R^{12d} and R^{13d} are each independently hydrogen, alkyl, halogen or aryl;
 R^{15d} is hydrogen or alkyl;
 R^{16d} is hydrogen, alkoxy, hydroxyl, amino, alkyl, $—NO_2$ or halogen when L^d is absent; or
 R^{16d} is



when L^d is present;
 K^d is CR^{20d} or N;
 M^d is CR^{23d} or N;
 R^{20d} is absent when K^d is N or hydrogen, alkyl, halogen, alkoxy or hydroxyl;
 R^{21d} is hydrogen, halogen or alkyl;
 R^{22d} is hydrogen, heteroaryl, halogen, alkoxy, cyano, acyl, SO_2R^{22da} , heterocyclic, $—COOH$, hydroxyl, $—CF_3$, alkyl, amino, CO_2H , aminocarbonyl or



R^{22da} is amino or alkyl;
 R^{23d} is absent when M^d is N or hydrogen, halogen, alkyl or alkoxy; or R^{22d} and R^{23d} together with the carbon atoms to which they are attached are joined to form a 5- or 6-membered ring;
 R^{23d} is hydrogen, halogen or alkoxy;
 R^{1e} is $—OH$, $—OCH_2$ -aryl, $—CH_2CH_2CO_2H$, $—OCH_2CO_2CH_2CH_3$, $—OCH_2CN$, $—OCH_2CH_2NH_2$, $—OCH_3$, $—OCH_2CH_2N^+(CH_3)_3$, $—OCH_2COOH$, $—OCH_2CH_2CH_3$, $—OCH_2CH_2OH$, $—OCH_2P(O)(OH)_2$ or $—OCH_2P(O)(OCH_2CH_3)_2$;
 $R^{2e}, R^{4e}, R^{53}, R^{11e}, R^{12e}, R^{13e}, R^{21e}, R^{22e}$ and R^{23e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl,

alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino CO_2H , cyano, nitro or halogen;

R^{20e} is absent when K_e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{23a} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{3e} is $—NO_2$, hydrogen, acyl, halogen, alkoxy, $—CO_2H$, $—CONR^{3da}R^{3db}$, cyano, $—NR^{3de}R^{3dd}$, alkyl, $—SO_2R^{3de}$, $—C(R^{3df})NQH$, heterocyclic or heteroaryl, R^{3ea} is alkyl or amino;

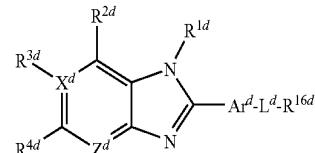
K^d is CR^{20e} or N;

M^e is CR^{23e} or N; and pharmaceutically acceptable salts thereof; such that said bacterial growth is prevented.

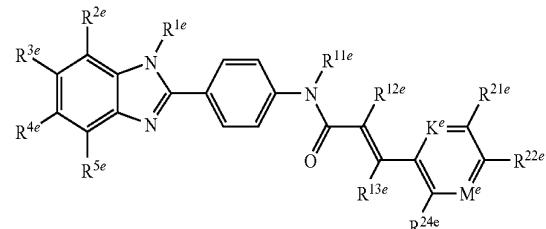
4. (canceled)

5. A method for preventing biofilm formation in a subject for treating or preventing a bacterial infection in a subject, for treating burn wounds in a subject, for treating or preventing corneal ulcers in a subject, for treating ascending pyelonephritis in a subject or for treating a kidney infection in a subject, comprising administering to said subject an effective amount of a transcription factor modulating compound of formula XII or XIV:

(XIII)



(XIV)



wherein:

R^{1d} is hydrogen, $—OH$, $—OCH_2$ -aryl, $—CH_2CH_2CO_2H$, $—OCH_2CO_2CH_2CH_3$, $—OCH_2CN$, $—OCH_2CH_2NH_2$, $—OCH_3$, $—OCH_2CH_2N^+(CH_3)_3$, $—OCH_2COOH$, $—OCH_2CH_2CH_3$, $—OCH_2CH_2OH$, $—OCH_2P(O)(OH)_2$ or $—OCH_2P(O)(OCH_2CH_3)_2$;

R^{2d} is hydrogen or $NR^{2da}R^{2db}$;

R^{2da} and R^{2db} are each independently hydrogen, alkyl or aminoalkyl;

X^d is CR^{3d} , N or NO;

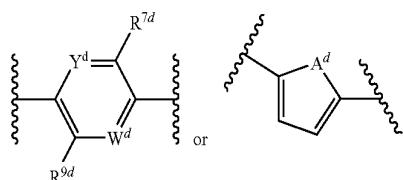
R^{3d} is absent when X^d is N or NO— NO_2 , hydrogen, acyl, halogen, alkoxy, $—CO_2H$, $—CONR^{3da}R^{3db}$, cyano, $—NR^{3dc}R^{3dd}$, alkyl, $—SO_2R^{3de}$, $—C(R^{3df})NOH$, heterocyclic or heteroaryl;

R^{3da} and R^{3db} are each independently hydrogen or alkyl;

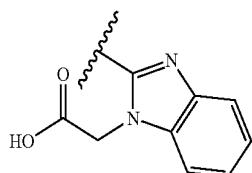
R^{3dc} and R^{3dd} are each independently hydrogen, alkyl or substituted carbonyl;

R^{3de} and R^{3df} are each independently alkyl or amino;

R^{4d} is hydrogen, alkoxy, $-NR^{4da}R^{4db}$, alkyl, halogen, $-SO_2R^{4dc}$ or $-CO_2H$;
 R^{4da} and R^{4db} are each independently hydrogen, alkyl or aminoalkyl;
 R^{4dc} is alkyl or amino;
 Z^d is CH, N or NO;
 Ar^d is



when L^d is present or



when L^d and R^{16d} are each absent;

Y^d is N or CR^{6d} ;
 W^d is N or CR^{8d} ;

R^{6d} is absent when Y^d is N, or hydrogen, alkyl, amino, $-CO_2H$, $-OCH_2P(O)(OH)_2$ or alkyl;

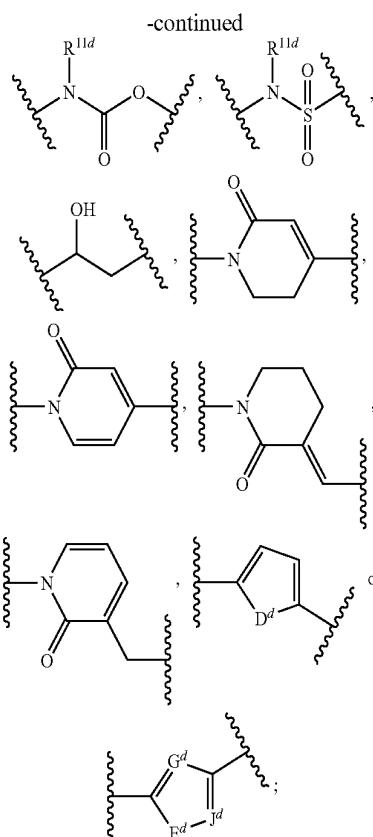
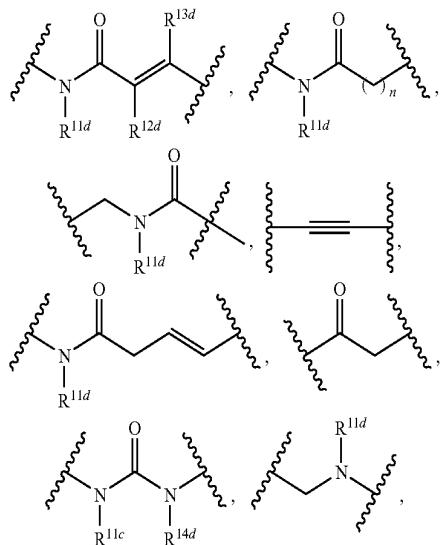
R^{8d} is absent when W^d is N, or hydrogen, alkyl, amino, $-CO_2H$, $-OCH_2P(O)(OH)_2$ or alkyl;

R^{7d} and R^{9d} are each independently hydrogen, alkyl, amino, $-CO_2H$, $-OCH_2P(O)(OH)_2$ or alkyl;

A^d is O, NR^{10d} or S;

R^{10d} is hydrogen or alkyl;

L^d is absent, or L^d is hydrogen or unsubstituted phenyl when R^{16d} or L^d is $-O-$, $-SO-$, $-SO_2-$, $-OCH_2-$, $-CH_2-$, NR^{15d}



n is an integer between 0-2;

D^d and E^d are each independently NR^{17d} ; O or S

J^d is N or CR^{18d} ;

G^d is N or CR^{19d} ;

R^{11d} is hydrogen or alkyl;

R^{18d} is absent when J^d is N or hydrogen or alkyl;

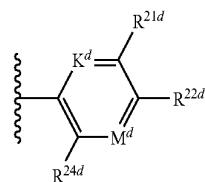
R^{19d} is absent when G^d is N or hydrogen or alkyl;

R^{12d} and R^{13d} are each independently hydrogen, alkyl, halogen or aryl;

R^{15d} is hydrogen or alkyl;

R^{16d} is hydrogen, alkoxy, hydroxyl, amino, alkyl, $-NO_2$ or halogen when L^d is absent; or

R^{16d} is



when L^d is present;

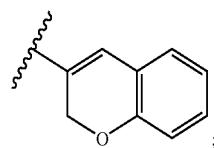
K^d is CR^{20d} or N;

M^d is CR^{23d} or N;

R^{20d} is absent when K^d is N or hydrogen, alkyl, halogen, alkoxy or hydroxyl;

R^{21d} is hydrogen, halogen or alkyl;

R^{22d} is hydrogen, heteroaryl, halogen, alkoxy, cyano, acyl, $-SO_2R^{22da}$, heterocyclic, $-COOH$, hydroxyl, $-CF_3$, alkyl, amino, CO_2H , aminocarbonyl or



- R^{22da} is amino or alkyl;
 R^{23d} is absent when M^e is N or hydrogen, halogen, alkyl or alkoxy; or R^{22d} and R^{23d} together with the carbon atoms to which they are attached are joined to form a 5- or 6-membered ring;
 R^{24d} is hydrogen, halogen or alkoxy;
 R^{1e} is —OH, —OCH₂-aryl, —CH₂CH₂CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;
 R^{2e} , R^{4e} , R^{53} , R^{11e} , R^{12e} , R^{13e} , R^{21e} , R^{22e} , and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;
 R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;
 R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;
 R^{3e} is —NO₂, hydrogen, acyl, halogen, alkoxy, —CO₂H, —CONR^{3da}R^{3db}; cyano —NR^{3dc}R^{3dd}, alkyl, —SO₂R^{3de}—C(R^{3df})NOH, heterocyclic or heteroaryl;
 R^{3ea} is alkyl or amino;
 K^e is CR^{20e} or N;
 M^e is CR^{23e} or N; and pharmaceutically acceptable salts thereof, such that said biofilm formation is prevented, said burn wounds are treated, said bacterial infection is treated or prevented, said corneal ulcers are treated, said ascending pyelonephritis is treated or said kidney infection is treated.
- 6.-291.** (canceled)
- 292.** The method of any one of claims 1-3 and 5, wherein said transcription factor modulating compound is a compound of Table 2 or a pharmaceutically acceptable salt thereof.
- 293.** The method of claim 292, wherein said pharmaceutically acceptable salt is a potassium salt or a sodium salt.
- 294.** The method of claim 2, wherein said transcription factor is a transcriptional activation factor.
- 295.** The method of claim 294, wherein said transcriptional activation factor is an AraC family polypeptide or a MarA family polypeptide.
- 296.** (canceled)
- 297.** (canceled)
- 298.** The method of claim 295, wherein said MarA family polypeptide is MarA, SoxS, Rob or LcrF (VirF) or ExsA.
- 299.** The method of any one of claims 1-3 and 5, wherein said transcription factor modulating compound has an EC₅₀ activity against SoxS, LcrF (VirF) or ExsA of less than 10 μM, less than 5 μM, or less than 1 μM.
- 300.-309.** (canceled)

310. The method of claim 1, wherein said microbial cell is *P. aeruginosa* or *Y. pseudotuberculosis*.

311. The method of claim 5, wherein said bacterial infection is a urinary tract infection, pneumonia or an infection associated with indwelling devices.

312. The method of claim 311, wherein said pneumonia is ventilator associated pneumonia.

313. The method of claim 311, wherein said infection is associated with *Pseudomonas aeruginosa*.

314. The method of claim 311, wherein said indwelling device is selected from the group consisting of catheters, orthopedic devices, devices associated with endotracheal intubation, devices associated with mechanical ventilation, and implants.

315. The method of claim 3, wherein said bacterial growth is associated with *Y. pseudotuberculosis* or *P. aeruginosa*.

316. The method of claim 5, wherein said biofilm is associated with *Y. pseudotuberculosis* or *P. aeruginosa*.

317. The method of claim 5, wherein said burn wounds or corneal ulcers are associated with a bacterial infection.

318. The method of claim 317, wherein said bacterial infection is associated with *Y. pseudotuberculosis* or *P. aeruginosa*.

319. The method of claim 5, wherein said bacterial infection is a nosocomial infection.

320. The method of any one of claims 1-3 and 5, wherein said transcription factor modulating compound is administered with a pharmaceutically acceptable carrier.

321. (canceled)

322. The method of any one of claims 1-3 and 5, wherein said subject is a mammal.

323. The method of claim 322, wherein said subject is a human.

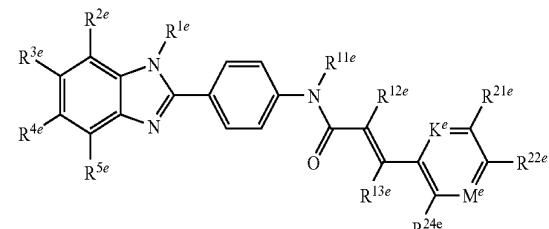
324. (canceled)

325. (canceled)

326. A kit comprising a solution comprising a transcription factor modulating compound and directions for using the solution to clean contact lenses.

327. A transcription factor modulating compound of formula XIV:

(XIV)



wherein:

R^{1e} is —OH, —OCH₂-aryl, —CH₂CH₂CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

R^{2e} , R^{4e} , R^{53} , R^{11e} , R^{12e} , R^{13e} , R^{21e} , R^{22e} , and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO_2H , cyano, nitro or halogen;

R^{3e} is $-\text{NO}_2$, hydrogen, acyl, halogen, alkoxy, $-\text{CO}_2\text{H}$, $-\text{CONR}^{3da}\text{R}^{3db}$, cyano, $-\text{NR}^{3c}\text{R}^{3dd}$, alkyl, $-\text{SO}_2\text{R}^{3e}$, $-\text{C}(\text{R}^{3df})\text{NOH}$, heterocyclic or heteroaryl;

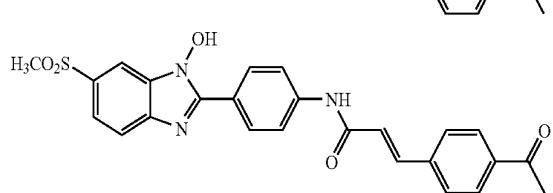
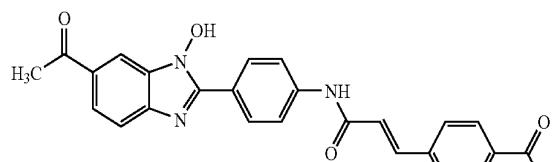
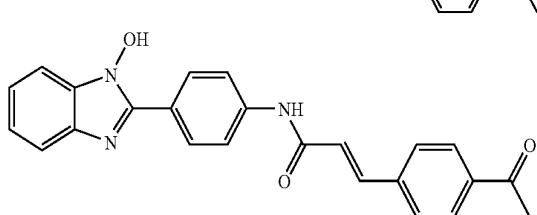
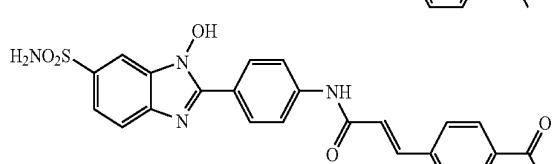
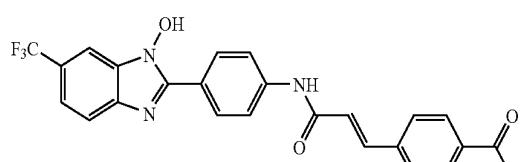
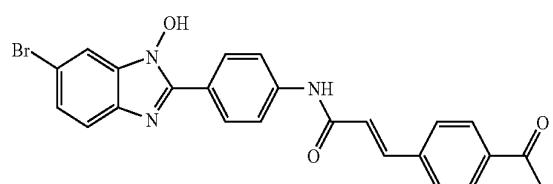
R^{3ea} is alkyl or amino;

K^e is CR^{20e} or N;

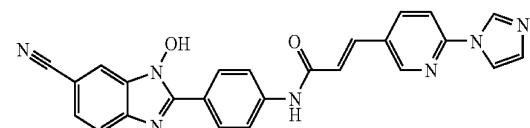
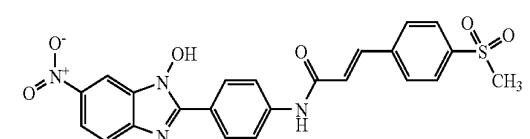
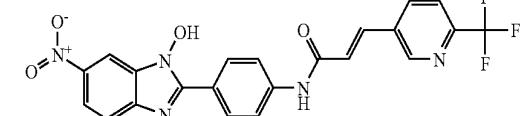
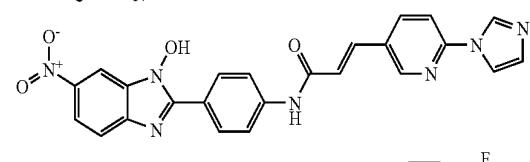
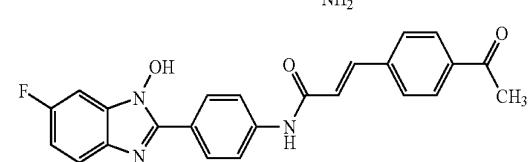
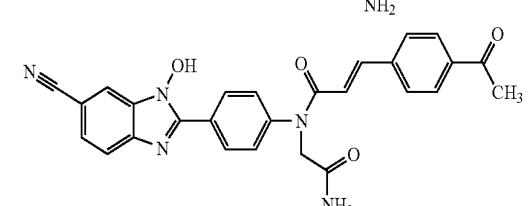
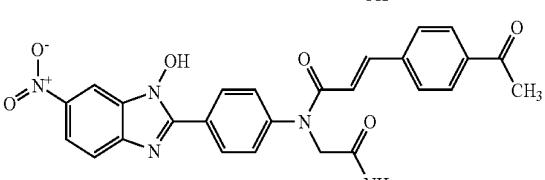
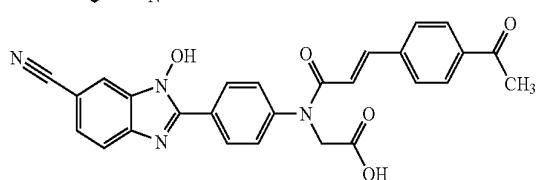
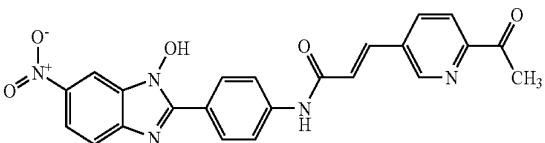
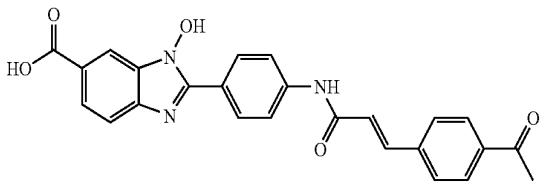
M^e is CR^{23e} or N; and pharmaceutically acceptable salts thereof.

328.-356. (canceled)

357. A transcription factor modulating compound selected from the group consisting of:



-continued

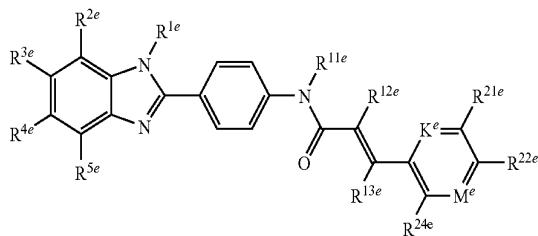


and pharmaceutically acceptable salts thereof.

358.-365. (canceled)

366. A pharmaceutical composition comprising a compound of formula XIV:

(XIV)



wherein:

R^{1e} is —OH, —OCH₂-aryl, —CH₂CH₂ CO₂H, —OCH₂CO₂CH₂CH₃, —OCH₂CN, —OCH₂CH₂NH₂, —OCH₃, —OCH₂CH₂N⁺(CH₃)₃, —OCH₂COOH, —OCH₂CH₂CH₃, —OCH₂CH₂ OH, —OCH₂P(O)(OH)₂ or —OCH₂P(O)(OCH₂CH₃)₂;

R^{2e}, R^{4e}, R^{5e}, R^{11e}, R^{12e}, R^{13e}, R^{21e}, R^{22e}, and R^{24e} are each independently hydrogen, alkyl, alkenyl, alkynyl,

aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

R^{20e} is absent when K^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

R^{23e} is absent when M^e is N or hydrogen, alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, carbonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, acyl, amino, CO₂H, cyano, nitro or halogen;

R^{3e} is —NO₂, hydrogen, acyl, halogen, alkoxy, —CO₂H, —CONR^{3da}R^{3db}; cyano, —NR^{3dc}R^{3dd}, alkyl, —SO₂R^{3de}, —C(R^{3df})NOH, heterocyclic or heteroaryl;

R^{3ea} is alkyl or amino;

K^e is CR^{20e} or N;

M^e is CR^{23e} or N; and pharmaceutically acceptable salts thereof;

and a pharmaceutically acceptable carrier.

367. The method of any one of claims 1-3 and 5, wherein said transcription factor modulating compound is administered orally, topically or parenterally.

* * * * *