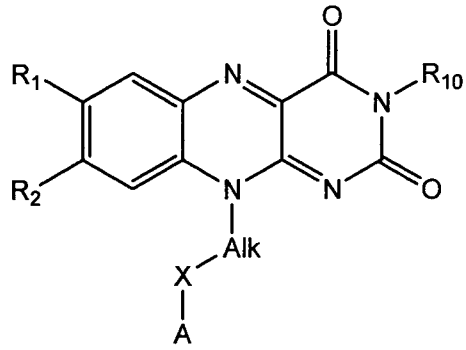
ABSTRACT

The present invention relates novel flavin derivatives and other flavin derivatives, their use and compositions for use as riboswitch ligands and/or anti-infectives. The invention also provides method of making novel flavin derivatives.

CLAIMS

1. A compound of Formula Q(i):



Formula Q(i)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is $-N(R_6)$ and A is:

$-C_{1-4}$alkyl-$N(R_{11})(R_{12})$,

$-C_{0-4}$alkyl-aryl[1] (e.g., phenyl, naphthyl, benzyl), or $-C_{0-4}$alkyl-heteroaryl[1] (e.g., isoxazolyl, (isoxazol-5-yl)methyl, tetrazolyl, pyridyl, for example pyrid-3-yl, (pyrid-5-yl)methyl, indolyl, 1,2,5-oxadiazolyl, pyrrolyl), wherein the alkyl group of said –alkylaryl[1] and –alkylheteroaryl[1] is optionally substituted with hydroxy or another aryl[1] (e.g., phenyl), and the aryl[1] and heteroaryl[1] group of said –alkylaryl[1] and –alkylheteroaryl[1] are independently substituted with one or more:

$-N(R_a)-C(O)-C_{1-4}$alkyl (e.g., $-NHC(O)CH_3$), wherein R_a is H or C_{1-4}alkyl,

-OH,

heteroaryl[1] (e.g., imidazolyl),

heteroC_{3-8}cycloalkyl (e.g., morpholinyl),

aryl[1] (e.g., phenyl),

-O-halo-C_{1-4}alkyl (e.g., $-OCF_3$),

$-NO_2$,

$-N(R_a)(R_b)$, wherein R_a is H or C_{1-4}alkyl and R_b is C_{1-4}alkyl,

-SO_2-C_{1-4}alkyl (e.g., -SO_2-CH_3);

–C_{0-4}alkyl-pyridyl substituted with one or more hydroxy (e.g., 2-hydroxypyrid-4-ylmethyl or 2-hydroxypyrid-3-yl);

–C_{0-4}alkyl-benzotriazolyl (e.g., 1*H*-benzotriazol-5-yl);

–C_{0-4}alkyl-indolyl (e.g., -indol-5-ylmethyl, indol-2-ylmethyl, indol-3-ylethyl);

–C_{0-4}alkyl-tetrazolyl (e.g., 1,2,3,5-tetrazol-4-ylethyl);

–C_{0-4}alkyl-oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl);

–C_{0-4}alkyl-benzodioxolyl (e.g., 1,3-benzodioxol-5-ylmethyl);

–C_{0-4}alkyl-benzimidazolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylbenzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl);

–C_{0-4}alkyl-imidazolyl optionally substituted with C_{1-4}alkyl (e.g., 1-methyl-imidazol-5-ylmethyl);

–C_{0-4}alkyl-pyrrolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylpyrrolidin-2-ylmethyl); or

para-phenylbenzyl;

or

X is a single bond, and A is a monocyclic heteroaryl[2] (e.g., pyrrolyl, for example pyrrol-1-yl; pyridyl, for example pyrid-2-yl, pyrid-4-yl or pyrid-3-yl; tetrazolyl, for example 1,2,3,4-tetrazol-1-yl; imidazolyl, for example imidazol-1-yl; or isoxazolyl, for example isoxazol-5-yl) wherein said monocyclic heteroaryl[2] is optionally substituted with C_{1-4}alkyl (e.g., methyl);

or

X is a single bond, -N(R_6)-, -N(R_6)-CH_2-, -N(R_6)-CH_2CH_2-, -N(R_6)-C(H)(CH_3)-, or -C(O)-; and:

A is a C_{3-8}cycloalkyl[2] (e.g., C_4cycloalkyl[2] or C_{5-6}cycloalkyl[2]) wherein one or more carbon atoms of said cycloalkyl[2] are optionally and independently replaced with N, O, S, $S(O)_2$ or –C(O)-, for example:

cyclobutyl,

cyclopentyl,

cyclohexyl,

1-methylcyclohex-1-yl,

piperidinyl (e.g., piperidin-1-yl),
pyrrolidinyl (e.g., pyrrolidin-1-yl),
morpholinyl (e.g., morpholin-4-yl),
azapanyl (e.g., azapan-1-yl),
piperazinyl
2,5-dioxopiperazin-1-yl,
tetrahydropyranyl (e.g., tetrahydropyran-4-yl),
isoxazolidinyl (isoxazolidin-5-yl),
1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl,
1,1,3-trioxo-1,2,5-thiazolidin-2-yl,
2-oxocyclopentylidenyl,
2-oxooxazolidin-5-yl,
2-oxopyrimidin-1-yl, or
2,4-dioxo-imidazolidin-3-yl);

wherein said cycloalkyl^2 is optionally substituted with one or more

C_{1-4}alkyl (e.g., methyl),
–C(O)OR_7,
-CH_2C(O)OR_7,
-N(R_6)C(O)OR_7,
-OH,
hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl),
C_{1-4}alkoxy (e.g., methoxy),
-CH_2N(R_6)-C(O)OR_7,
aryl^2 (e.g., phenyl) or aryl^2-C_{1-4}alkyl (e.g., benzyl) wherein said aryl^2 group of said aryl^2 or aryl^2-alkyl is optionally substituted with C_{1-4}alkyl (e.g., methyl), for example, 4-methylphenyl, 2-methylphenyl,
heteroaryl^2 (e.g., 2*H*-tetrazol-5-yl),
heteroaryl^2-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl),
-C_{1-4}alkyl-N(R_8)(R_9) (e.g., -methyl-NH_2- or -ethyl-NH_2),
C_{1-4}alkoxy (e.g., methoxy),
–C(O)N(R_6)-S(O)$_2$-C_{1-4}alkyl (e.g., -C(O)N(H)S(O)$_2$-CH_3),
-N(H)-S(O)$_2$-C_{1-4}alkyl (e.g., -N(H)-S(O)$_2$-methyl),

$-S(O)_2-N(R_8)(R_9)$ (e.g., $-S(O)_2-NH_2$),

–C(O)N(H)CN,

$–C(O)N(R_8)(R_9)$, or

$-N(R_8)(R_9)$;

or

A is a 7-11 membered fused cycloalkyl-aryl or spiral compound wherein one or more carbon atoms may be a hetero atom selected from N, O or S and wherein said fused cycloalkyl-aryl or spiral group is optionally substituted with one or more hydroxy, C_{1-4}alkyl (e.g., methyl) or oxo (i.e., =O), for example

3,9-diazaspiro[5.5]undecan-3-yl,

3,9-diazaspiro[5.5]undecan-9-yl,

(6-oxo-7-oxa-2-azaspiro[4.4]nonan-2-yl),

(9-oxo-8-oxa-3-azaspiro[4.4]nonan-3-yl),

(1-oxo-2,8-diazaspiro[4.5]decan-8-yl),

(2,4-dioxo-3,8-diazaspiro[4.5]decan-8-yl),

Indolinyl (e.g., indolin-1-yl),

Indanyl (e.g., indan-1-yl, indan-2-yl or 2-hydroxyindan-1-yl),

tetralinyl (e.g., tetralin-2-yl, tetralin-1-yl),

isoindolinyl (e.g., isoindolin-2-yl),

adamantyl,

3,4-dihydro-1H-isoquinolin-2-yl or 3,4-dihydro-2H-quinolin-1-yl,

1,3,4,5-tetrahydro-2-benzazepin-2-yl,

2,3,4,5-tetrahydro-1-benzazepin-1-yl,

1,2,4,5-tetrahydro-3-benzazepin-3-yl,

(iii) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), $-N(R_4)(R_5)$ or -O-C_{3-8}cycloalkyl (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7,

$aryl^2$ optionally substituted with halo (e.g., 4-fluorophenyl),

$aryl^2$-C_{1-4}alkyl wherein said $aryl^2$ group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -$CH_2OC(O)CH_3$;

(viii) R_8 and R_9 are independently H or C_{1-4}alkyl;

(ix) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$);

(x) R_{11} and R_{12} are independently H or C_{1-4}alkyl,

in free or salt form, provided that:

(a) when R_2 is chloro, Alk is propylene, X is a single bond and A is pyrrolidin-1-yl, then R_1 is C_{1-8} alkyl (e.g., methyl) or R_{10} is -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$), i.e., the compound is not 8-chloro-10-(3-pyrrolidin-1-ylpropyl)benzo[g]pteridine-2,4-dione;

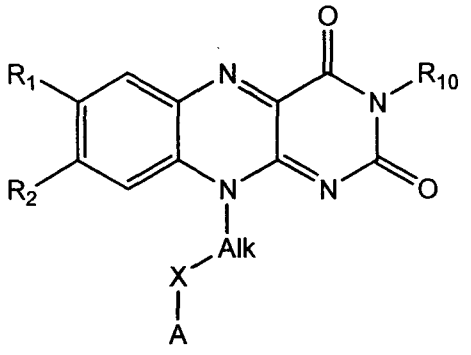
(b) the compound is not 10-[3-(3,6-dioxo-1,4-cyclohexadien-1-yl)propyl)-3,7,8-trimethyl-benzo[g]pteridine-2,4-(3H, 10H)-dione;

(c) A is not purinyl, e.g., the compound is not optionally substituted 10-[2-(9H-purin-9-yl)ethyl]-, 10-[3-(9H-purin-9-yl)propyl]- or 10-[6-(9H-purin-9-yl)hexyl]-7,8-dimethyl-benzo[g]pteridine-2,4-(3H, 10H)-dione;

(d) A is not indol-3-yl, e.g., the compound is not 10-[3-(1H-indol-3-yl)ethyl]- or 10-[3-(1H-indol-3-yl)propyl]-7,8-dimethyl-benzo[g]pteridine-2,4-(3H, 10H)-dione;

(e) –Alk-X-A is not 2-(2-oxocylopentylidene)ethyl,

2. The compound according to claim 1, wherein said compound is a compound of Formula Q-I(i):



Formula Q-I(i)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is a single bond, $-N(R_6)-$, $-N(R_6)-CH_2-$, $-N(R_6)-CH_2CH_2-$, $-N(R_6)-C(H)(CH_3)-$, or $-C(O)-$ and

A is a $-C_{3-8}$cycloalkyl^2 (e.g., C_4cycloalkyl^2 or C_{5-6}cycloalkyl^2) wherein one or more carbon atoms of said cycloalkyl^2 are optionally and independently replaced with N, O, S, $S(O)_2$ or –C(O)-, for example:

cyclobutyl,

cyclopentyl,

cyclohexyl,

1-methylcyclohex-1-yl,

piperidinyl (e.g., piperidin-1-yl),

pyrrolidinyl (e.g., pyrrolidin-1-yl),

morpholinyl (e.g., morpholin-4-yl),

azapanyl (e.g., azapan-1-yl),

piperazinyl,

2,5-dioxopiperazin-1-yl,

tetrahydropyranyl (e.g., tetrahydropyran-4-yl),

isoxazolidinyl (isoxazolidin-5-yl),

1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl,

1,1,3-trioxo-1,2,5-thiazolidin-2-yl,

2-oxocyclopentylidenyl,

2-oxooxazolidin-5-yl,

2-oxopyrimidin-1-yl, or

2,4-dioxo-imidazolidin-3-yl);

wherein said cycloalkyl^2 is optionally substituted with one or more

C_{1-4}alkyl (e.g., methyl),

–C(O)OR_7,

-CH_2C(O)OR_7,

-N(R_6)C(O)OR_7,

-OH,

hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl),

C_{1-4}alkoxy (e.g., methoxy),

-CH_2N(R_6)-C(O)OR_7,

aryl^2 (e.g., phenyl) or aryl^2-C_{1-4}alkyl (e.g., benzyl) wherein said aryl^2 group of said aryl^2 or aryl^2-alkyl is optionally substituted with C_{1-4}alkyl (e.g., methyl), for example, 4-methylphenyl, 2-methylphenyl,

heteroaryl^2 (e.g., 2*H*-tetrazol-5-yl),

heteroaryl^2-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl),

-C_{1-4}alkyl-N(R_8)(R_9) (e.g., -methyl-NH_2- or -ethyl-NH_2),

C_{1-4}alkoxy (e.g., methoxy),

–C(O)N(R_6)-S(O)$_2$-C_{1-4}alkyl (e.g., -C(O)N(H)S(O)$_2$-CH_3),

-N(H)-S(O)$_2$-C_{1-4}alkyl (e.g., -N(H)-S(O)$_2$-methyl),

-S(O)$_2$-N(R_8)(R_9) (e.g., -S(O)$_2$-NH_2),

–C(O)N(H)CN,

–C(O)N(R_8)(R_9), or

-N(R_8)(R_9);

or

A is a 7-11 membered fused cycloalkyl-aryl or spiral compound wherein one or more carbon atoms may be a hetero atom selected from N, O or S and wherein said fused cycloalkyl-aryl or spiral group is optionally substituted with one or more hydroxy, C_{1-4}alkyl (e.g., methyl) or oxo (i.e., =O), for example

3,9-diazaspiro[5.5]undecan-3-yl,

3,9-diazaspiro[5.5]undecan-9-yl,

(6-oxo-7-oxa-2-azaspiro[4.4]nonan-2-yl),

(9-oxo-8-oxa-3-azaspiro[4.4]nonan-3-yl),

(1-oxo-2,8-diazaspiro[4.5]decan-8-yl),

(2,4-dioxo-3,8-diazaspiro[4.5]decan-8-yl),

Indolinyl (e.g., indolin-1-yl),

Indanyl (e.g., indan-1-yl, indan-2-yl or 2-hydroxyindan-1-yl),

tetralinyl (e.g., tetralin-2-yl, tetralin-1-yl),

isoindolinyl (e.g., isoindolin-2-yl),

adamantyl,

3,4-dihydro-1H-isoquinolin-2-yl or 3,4-dihydro-2H-quinolin-1-yl,

1,3,4,5-tetrahydro-2-benzazepin-2-yl,

2,3,4,5-tetrahydro-1-benzazepin-1-yl,

1,2,4,5-tetrahydro-3-benzazepin-3-yl,

(iii) R_1 is H or C_{1-8}alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), $-N(R_4)(R_5)$ or $-O-C_{3-8}$cycloalkyl (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

$-C_{1-4}$alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, $-C(O)OR_7$,

aryl[2] optionally substituted with halo (e.g., 4-fluorophenyl),

aryl[2]-C_{1-4}alkyl wherein said aryl[2] group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

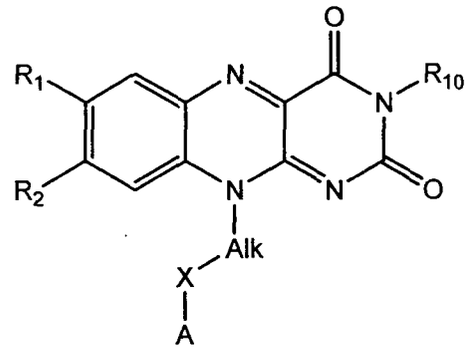
(vii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), $-CH_2OC(O)CH_3$;

(viii) R_8 and R_9 are independently H or C_{1-4}alkyl;

(ix) R_{10} is H or $-C_{1-4}$alkyl-$OC(O)CH_3$ (e.g., $-CH_2OC(O)CH_3$),

in free or salt form.

3. The compound according to claim 1, whrein said compound is a compound of Formula Q-II(i):



Formula Q-II(i)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is a single bond and A is:

a monocyclic heteroaryl[2] (e.g., pyrrolyl, for example pyrrol-1-yl; pyridyl, for example pyrid-2-yl, pyrid-4-yl or pyrid-3-yl; tetrazolyl, for example 1,2,3,4-tetrazol-1-yl; imidazolyl, for example imidazol-1-yl; or isoxazolyl, for example isoxazol-5-yl); or

wherein said heteroaryl[2] is optionally substituted with one or more C_{1-4}alkyl (e.g., methyl),

(iii) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -N(R_4)(R_5) or -O-C_{3-8}cycloalkyl[2] (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7,

aryl[2] optionally substituted with halo (e.g., 4-fluorophenyl),

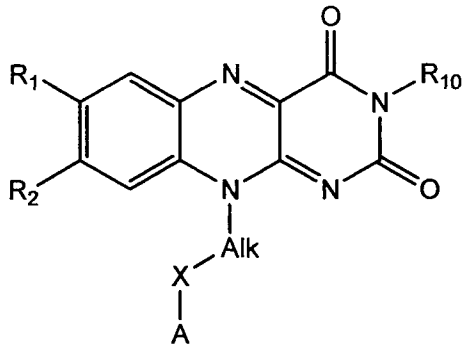
aryl[2]-C_{1-4}alkyl wherein said aryl group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

(vi) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -$CH_2OC(O)CH_3$;

(vii) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$),

in free or salt form.

4. The compound according to claim 1, whrein said compound is a compound of Formula Q-III(i):



Formula Q-III(i)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is $-N(R_6)$ and A is:

$-C_{1-4}$alkyl-$N(R_{11})(R_{12})$,

$-C_{0-4}$alkyl-aryl[1] (e.g., phenyl, naphthyl, benzyl), or $-C_{0-4}$alkyl-heteroaryl[1] (e.g., isoxazolyl, (isoxazol-5-yl)methyl, tetrazolyl, pyridyl, for example pyrid-3-yl, (pyrid-5-yl)methyl, indolyl, 1,2,5-oxadiazolyl, pyrrolyl), wherein the alkyl group of said –alkylaryl[1] and –alkylheteroaryl[1] is optionally substituted with hydroxy or another aryl[1] (e.g., phenyl), and the aryl[1] and heteroaryl[1] group of said –alkylaryl[1] and –alkylheteroaryl[1] are independently substituted with one or more:

$-N(R_a)$-C(O)-C_{1-4}alkyl (e.g., $-NHC(O)CH_3$), wherein R_a is H or C_{1-4}alkyl,

-OH,

heteroaryl[1] (e.g., imidazolyl),

heteroC_{3-8}cycloalkyl[1] (e.g., morpholinyl),

aryl[1] (e.g., phenyl),

-O-halo-C_{1-4}alkyl (e.g., $-OCF_3$),

$-NO_2$,

$-N(R_a)(R_b)$, wherein R_a is H or C_{1-4}alkyl and R_b is C_{1-4}alkyl,

$-SO_2$-C_{1-4}alkyl (e.g., $-SO_2-CH_3$);

–C_{0-4}alkyl-pyridyl substituted with one or more hydroxy (e.g., 2-hydroxypyrid-4-ylmethyl or 2-hydroxypyrid-3-yl);

–C_{0-4}alkyl-benzotriazolyl (e.g., 1*H*-benzotriazol-5-yl);

–C_{0-4}alkyl-indolyl (e.g., -indol-5-ylmethyl, indol-2-ylmethyl, indol-3-ylethyl);

–C_{0-4}alkyl-tetrazolyl (e.g., 1,2,3,5-tetrazol-4-ylethyl);

–C_{0-4}alkyl-oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl);

–C_{0-4}alkyl-benzodioxolyl (e.g., 1,3-benzodioxol-5-ylmethyl);

–C_{0-4}alkyl-benzimidazolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylbenzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl);

–C_{0-4}alkyl-imidazolyl optionally substituted with C_{1-4}alkyl (e.g., 1-methyl-imidazol-5-ylmethyl);

–C_{0-4}alkyl-pyrrolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylpyrrolidin-2-ylmethyl);

para-phenylbenzyl;

(iii) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -N(R_4)(R_5) or -O-C_{3-8}cycloalkyl[2] (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7,

aryl[2] optionally substituted with halo (e.g., 4-fluorophenyl),

aryl[2]-C_{1-4}alkyl wherein said aryl group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

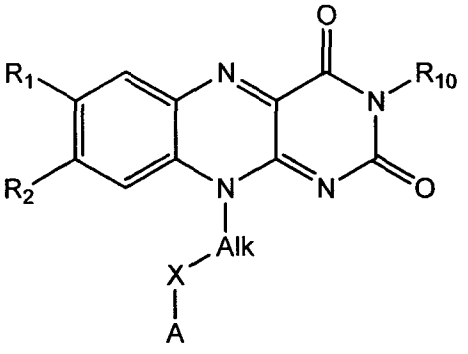
(vii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -$CH_2OC(O)CH_3$;

(viii) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$);

(ix) R_{11} and R_{12} are independently H or C_{1-4}alkyl,

in free or salt form.

5. The compound according to claim 1, whrein said compound is a compound of Formula Q-IV(i):



Formula Q-IV(i)

wherein

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene);

(ii) X is a single bond and A is pyrrolyl, for example pyrrol-1-yl or imidazolyl, for example imidazol-1-yl);

or

X is a single bond and A is a pyrrolidinyl (e.g., pyrrolidin-1-yl) or piperidinyl (e.g., piperidin-1-yl) optionally substituted with another aryl (e.g., phenyl) or aryl-C_{1-4}alkyl (e.g., benzyl);

or

X is $-N(R_6)-$ and A is tetralinyl (e.g., tetralin-2-yl);

(iii) R_1 is H or C_{1-8}alkyl (e.g., methyl);

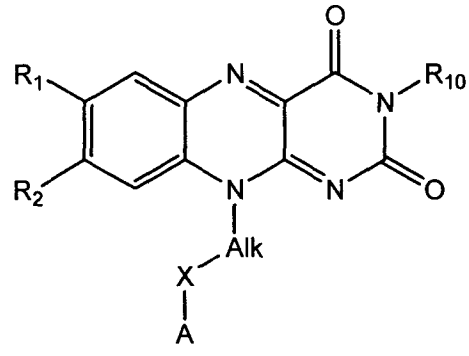
(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl);

(v) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vi) R_{10} is H,

in free or salt form.

6. The compound according to claim 1, whrein said compound is a compound of Formula Q-V(i):



Formula Q-V(i)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene or n-propylene);

(ii) X is a single bond and A is pyrrolyl, for example pyrrol-1-yl, pyrrolidinyl (e.g., pyrrolidin-1-yl) or piperidinyl (e.g., piperidin-1-yl) optionally substituted with another aryl (e.g., phenyl) or aryl-C_{1-4}alkyl (e.g., benzyl);

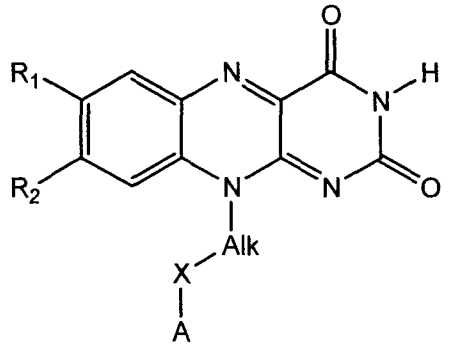
(iii) R_1 is C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is C_{1-4}alkyl (e.g., methyl);

(v) R_{10} is H,

in free or salt form.

7. The compound according to claim 1, wherein said compound is a compound of Formula I(B):



Formula I(B)

wherein:

(i) Alk is C_{1-2}alkylene (e.g., methylene or ethylene);

(ii) X is -N(R_6)-,

(iii) A is selected from a group consisting of:

–C_{1-4}alkyl-N(R_{11})(R_{12}),

–C_{0-4}alkyl-aryl[1] (e.g., phenyl, naphthyl, benzyl), or –C_{0-4}alkyl-heteroaryl[1] (e.g., isoxazolyl, tetrazolyl, pyridyl, indolyl, 1,2,5-oxadiazolyl, pyrrolyl), wherein the alkyl group of said –alkylaryl[1] and –alkylheteroaryl[1] is optionally substituted with hydroxy or another aryl (e.g., phenyl), and the aryl[1] and heteroaryl[1] group of said –alkylaryl[1] and –alkylheteroaryl[1] are independently substituted with one or more:

-$N(R_a)$-C(O)-C_{1-4}alkyl (e.g., -$NHC(O)CH_3$), wherein R_a is H or C_{1-4}alkyl,

-OH,

Heteroaryl[1] (e.g., imidazolyl),

heteroC_{3-8}cycloalkyl[1] (e.g., morpholinyl),

aryl[1] (e.g., phenyl),

-O-halo-C_{1-4}alkyl (e.g., -OCF_3),

-NO_2,

-$N(R_a)(R_b)$, wherein R_a is H or C_{1-4}alkyl and R_b is C_{1-4}alkyl,

-SO_2-C_{1-4}alkyl (e.g., -SO_2-CH_3);

–C_{0-4}alkyl-pyridyl substituted with one or more hydroxy (e.g., 2-hydroxypyrid-4-ylmethyl or 2-hydroxypyrid-3-yl);

–C_{0-4}alkyl-benzotriazolyl (e.g., 1*H*-benzotriazol-5-yl);

–C_{0-4}alkyl-indolyl (e.g., -indol-5-ylmethyl, indol-2-ylmethyl, indol-3-ylethyl);

–C_{0-4}alkyl-tetrazolyl (e.g., 1,2,3,5-tetrazol-4-ylethyl);

–C_{0-4}alkyl-oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl);

–C_{0-4}alkyl-benzodioxolyl (e.g., 1,3-benzodioxol-5-ylmethyl);

–C_{0-4}alkyl-benzimidazolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylbenzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl);

–C_{0-4}alkyl-imidazolyl optionally substituted with C_{1-4}alkyl (e.g., 1-methyl-imidazol-5-ylmethyl);

–C_{0-4}alkyl-pyrrolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylpyrrolidin-2-ylmethyl);

para-phenylbenzyl;

(iv) R_1 is H or C_{1-4}alkyl (e.g., methyl);

(v) R_2 is selected from a group consisting of H, C_{1-4}alkyl (e.g., methyl) and -O-C_{3-8}cycloalkyl[1] (e.g., -O-cyclopentyl);

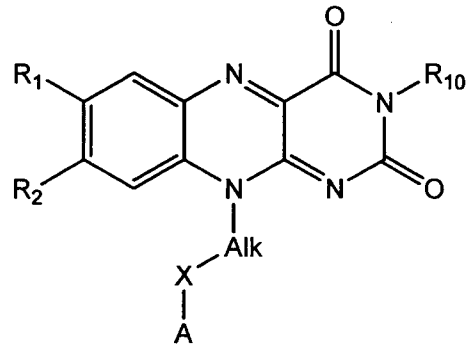
(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vii) R_{11} and R_{12} are independently H or C_{1-4}alkyl (e.g., methyl),

in free or salt form.

8. The compound according to any of claims 1-7, wherein the compound is selected from any of those described in formulae Q.35, Q.36, Q.37, Q.38, Q.39, Q.40 or Q.41, in free or salt form.

9. A compound of Formula I(A)(i):



Formula I(A)(i)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene or ethylene);

(ii) X is a single bond, -N(R_6)-, -N(R_6)-CH_2- or -C(O)-;

(iii) A is a monocyclic heteroaryl (e.g., pyrid-4-yl or pyrid-3-yl) or C_{5-6}cycloalkyl wherein one or more carbon atoms of said cycloalkyl are optionally and independently replaced with N, O, S, or –C(O)-, (for example, piperidinyl (e.g., piperidin-1-yl), pyrrolidinyl (e.g., pyrrolidin-1-yl), piperazinyl (e.g., 2,5-dioxopiperazin-1-yl), isoxazolidinyl (isoxazolidin-5-yl), 1,1-dioxo-1,4-thiazinan-4-yl, C_{3-8}cycloalkyl (e.g., cyclopentyl, cyclohexyl or 2-oxocyclopentylidene), 2-oxopyrimidin-1-yl or 2,4-dioxo-imidazol-3-yl) wherein said heteroaryl and cycloalkyl are independently optionally substituted with one or more –C(O)OR_7, -CH_2C(O)OR_7, -N(R_6)C(O)OR_7, -OH, hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl), -CH_2N(R_6)-C(O)OR_7, heteroaryl (e.g., 2*H*-tetrazol-5-

yl), heteroaryl-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl), amineC_{1-4}alkyl (e.g., amine-ethyl), C_{1-4}alkoxy (e.g., methoxy), –C(O)N(R_6)-S(O)$_2$-C_{1-4}alkyl (e.g., -C(O)N(H)S(O)$_2$-CH_3) or -N(R_8)(R_9);

(iv) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(v) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -N(R_4)(R_5);

(vi) R_4 and R_5 are independently selected from H, C_{3-7} cycloalkyl (e.g., cyclopropyl or cyclopentyl), -C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7, aryl optionally substituted with halo (e.g., 4-fluorophenyl);

(vii) R_6 is H or C_{1-4}alkyl (e.g., methyl);

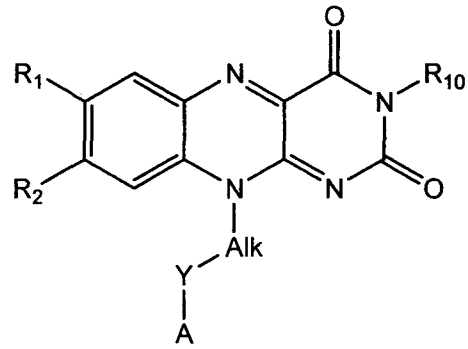
(viii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -CH_2OC(O)CH_3;

(ix) R_8 and R_9 are independently H or C_{1-4}alkyl;

(x) R_{10} is H or -C_{1-4}alkyl-OC(O)CH_3 (e.g., -CH_2OC(O)CH_3),

in free, salt or prodrug form, with the proviso that when R_2 is chloro, Alk is propylene, X is a single bond and A is pyrolidin-1-yl, then R_1 is C_{1-8} alkyl (e.g., methyl) or R_{10} is -C_{1-4}alkyl-OC(O)CH_3 (e.g., -CH_2OC(O)CH_3).

10. A compound of Formula II(A):



Formula II(A)

wherein

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, pentylene);

(ii) Y is -N(R_6)-C(O)- or –C(O)-N(R_6)-;

(iii) A is heteroaryl (e.g., pyrid-3-yl) optionally substituted with one or more –C(O)OR_7, -CH_2C(O)OR_7, -N(R_6)C(O)OR_7, -OH, hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl), -CH_2N(R_6)-C(O)OR_7, heteroaryl (e.g., 2*H*-

tetrazol-5-yl), heteroaryl-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl), amineC_{1-4}alkyl (e.g., amine-ethyl), C_{1-4}alkoxy (e.g., methoxy), –$C(O)N(R_6)$-$S(O)_2$-C_{1-4}alkyl (e.g., -$C(O)N(H)S(O)_2$-CH_3) or -$N(R_8)(R_9)$;

(iv) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(v) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -$N(R_4)(R_5)$;

(vi) R_4 and R_5 are independently selected from H, C_{3-7} cycloalkyl (e.g., cyclopropyl or cyclopentyl), -C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, $-C(O)OR_7$, aryl optionally substituted with $_{halo}$ (e.g., 4-fluorophenyl);

(vii) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(viii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -$CH_2OC(O)CH_3$;

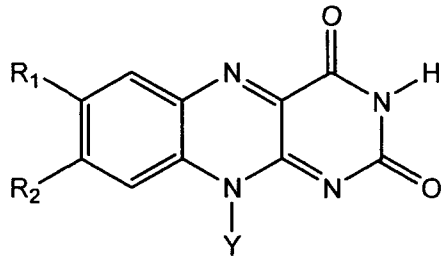
(ix) R_8 and R_9 are independently H, C_{1-4}alkyl;

(x) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$),

in free, salt or prodrug form.

11. The compound according to claim 10 selected from any one described in formula 2.8, in free, pharmaceutically acceptable salt form.

12. A compound of Formula II(B):



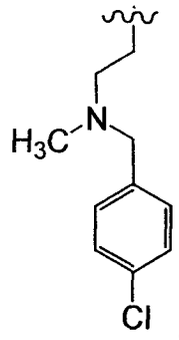
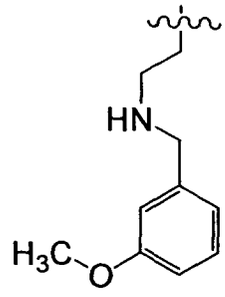
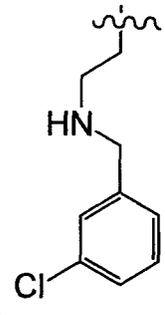
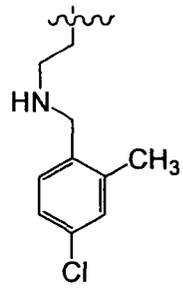
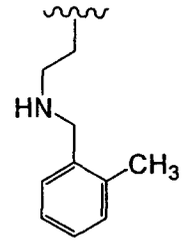
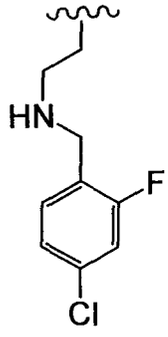
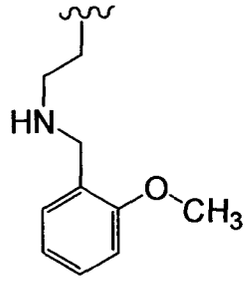
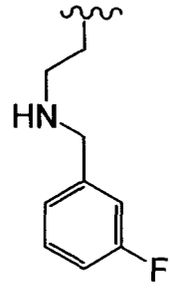
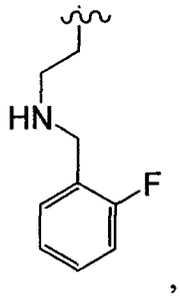
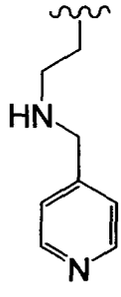
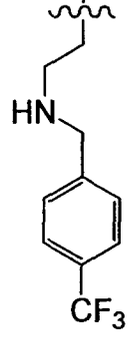
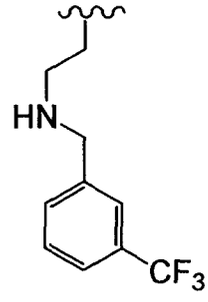
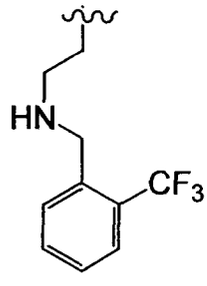
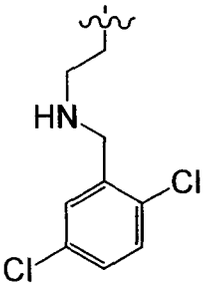
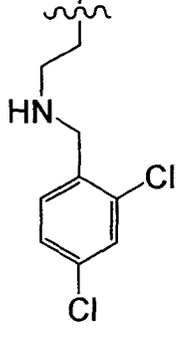
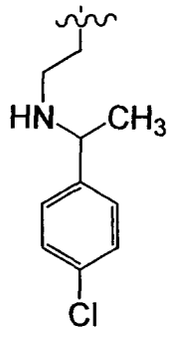
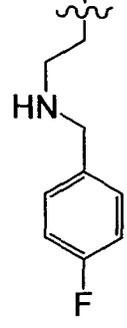
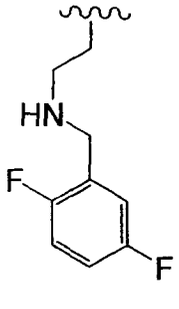
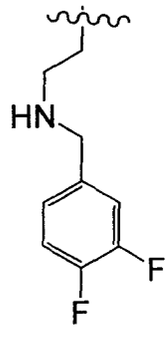
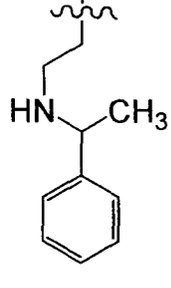
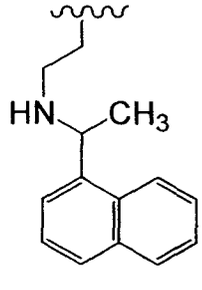
Formula II(B)

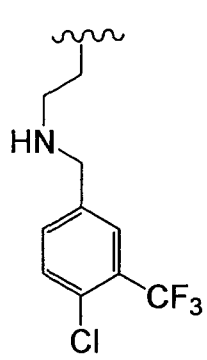
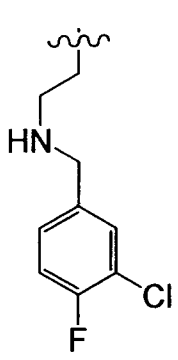
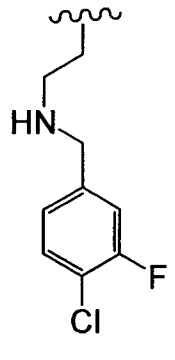
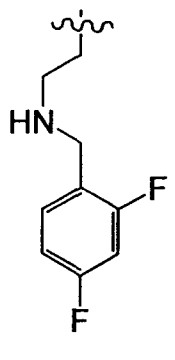
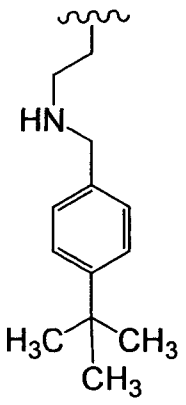
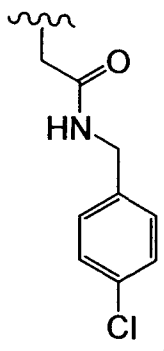
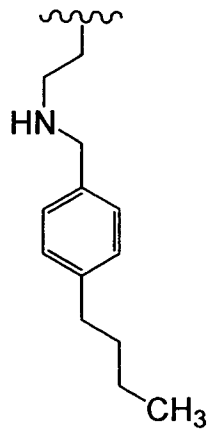
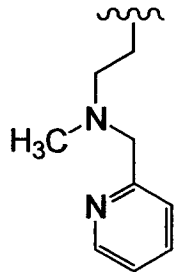
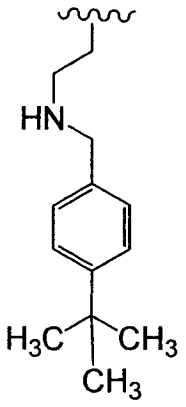
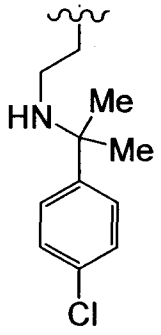
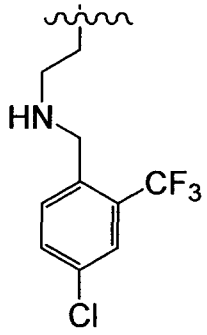
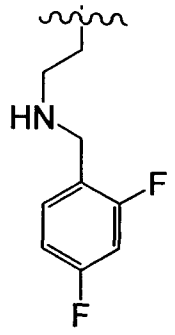
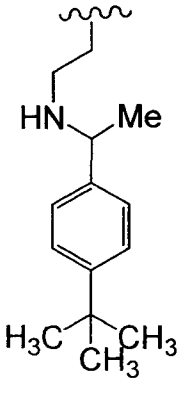
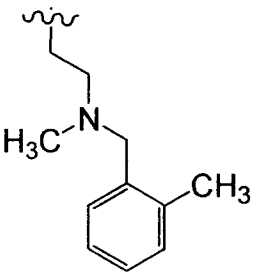
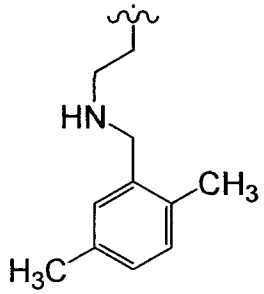
wherein:

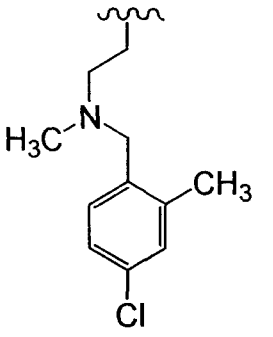
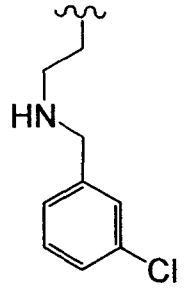
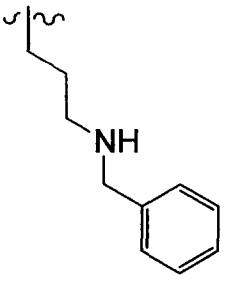
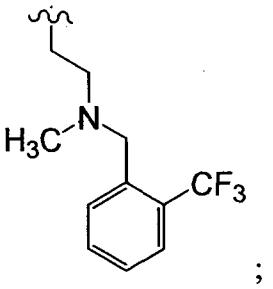
(i) R_1 is H or C_{1-4}alkyl (e.g., methyl)

(ii) R_2 is selected from a group consisting of H, C_{1-4}alkyl (e.g., methyl) and -O-C_{3-8}cycloalkyl[1] (e.g., -O-cyclopentyl);

(iii) Y is selected from a group consisting of:

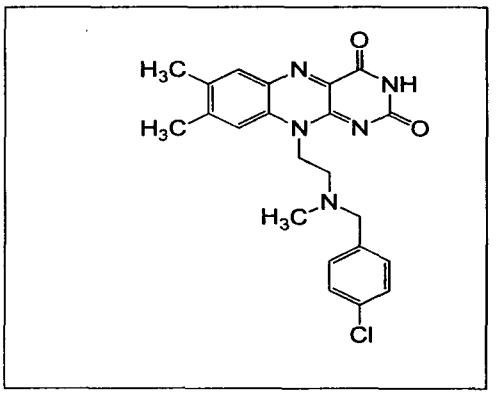
















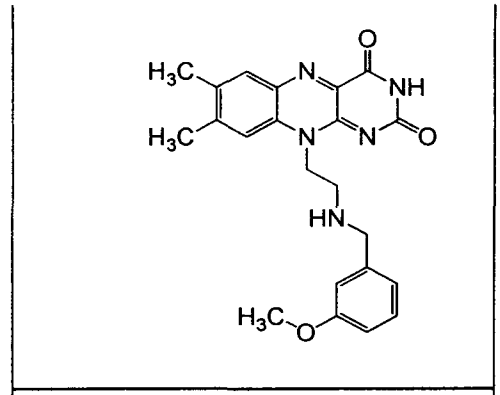





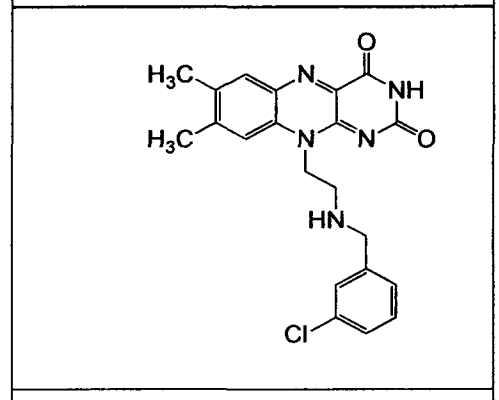
in free or salt form.

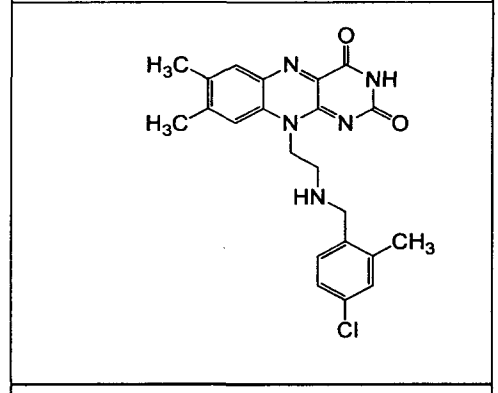
13. The compound according to claim 12, wherein said compound of Formula II(B) is selected from any compounds described in formulae 3.51, 3.52, 3.53 or 3.54 in free or salt form.

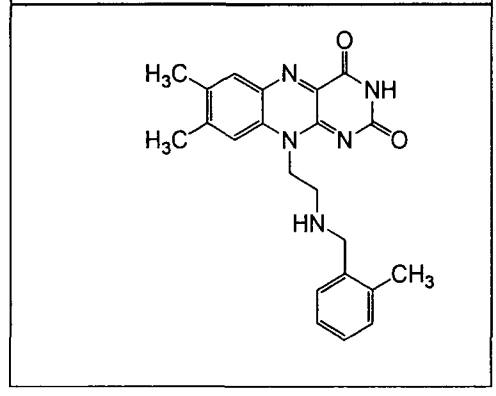
14. The compound according to claim 12 or 13, wherein said compound of Formula II(B) is selected from any of the following:

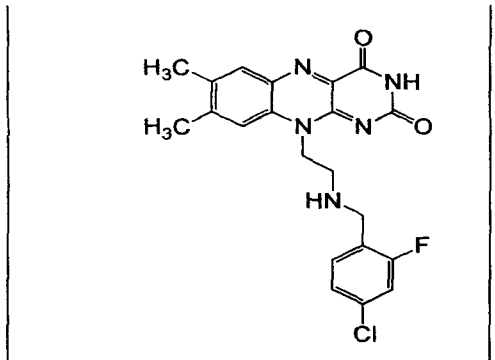


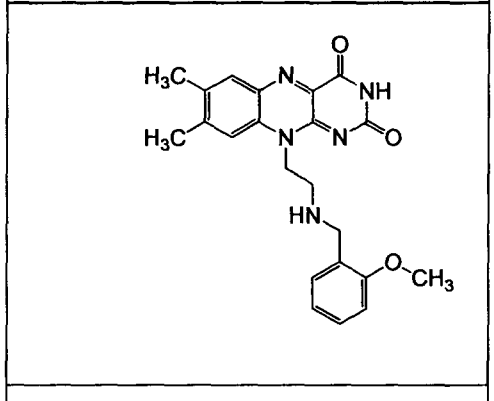


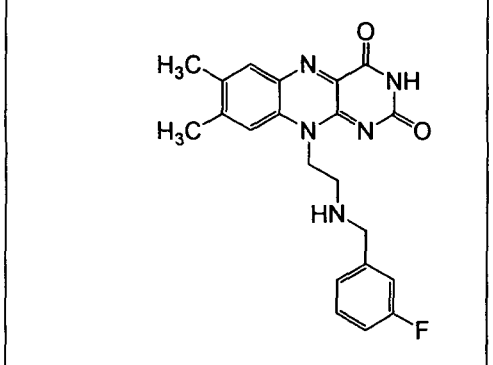


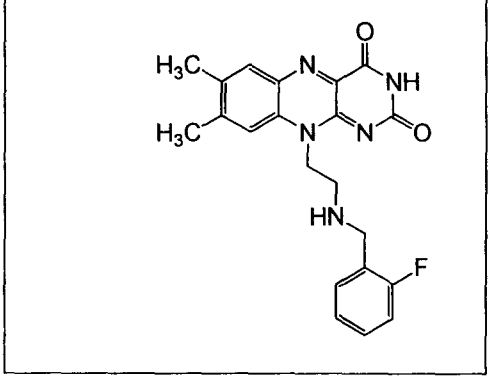


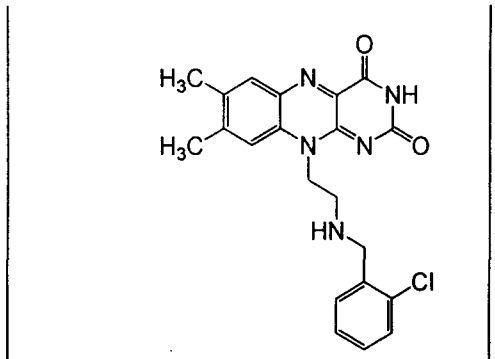


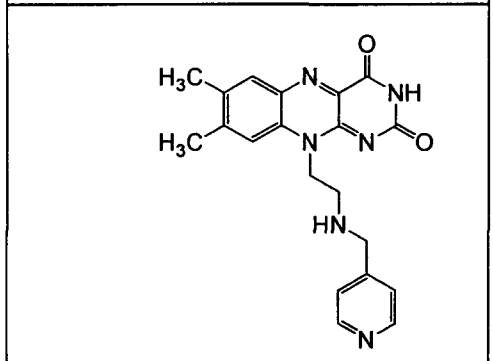


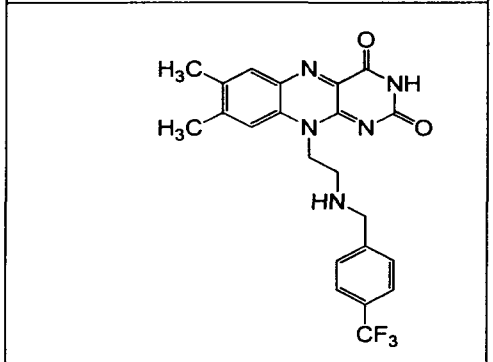


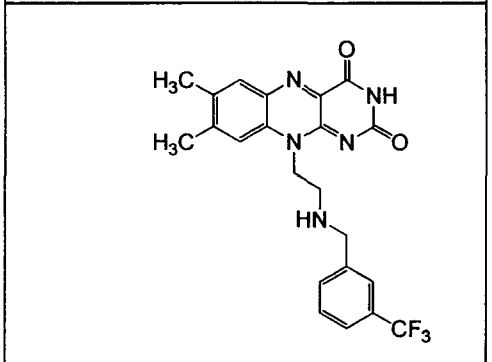


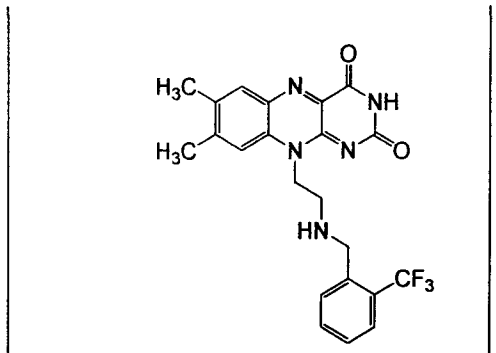


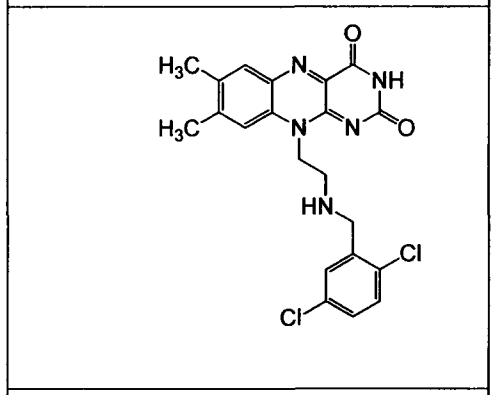


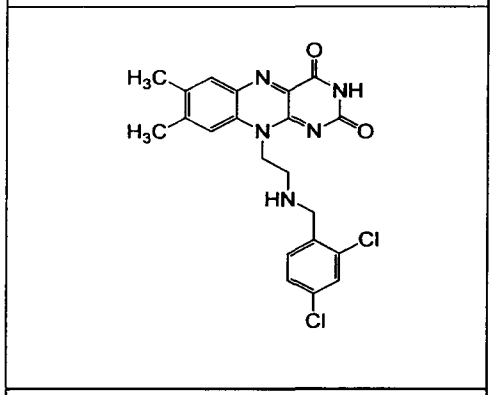


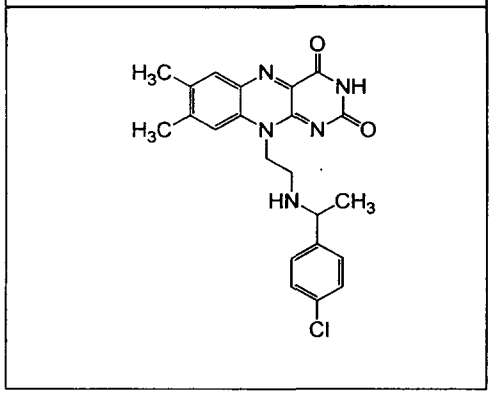


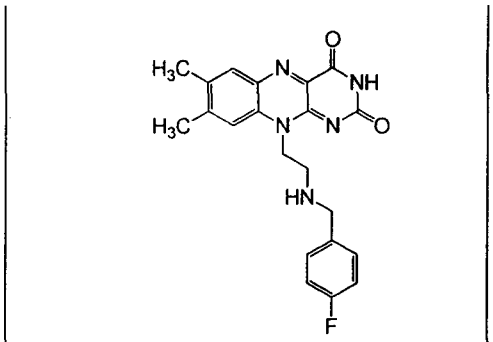


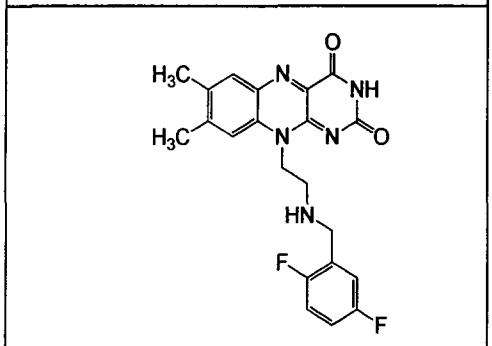


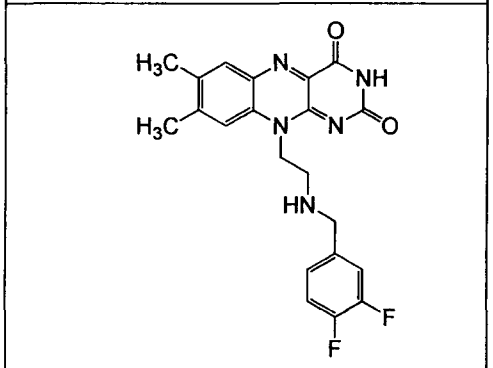


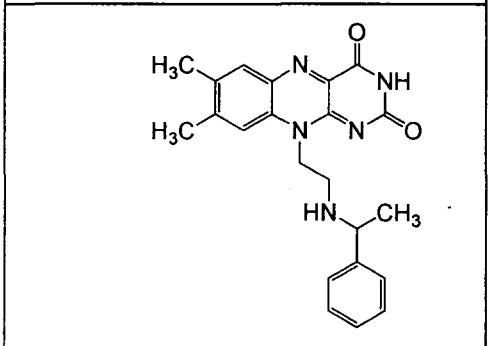


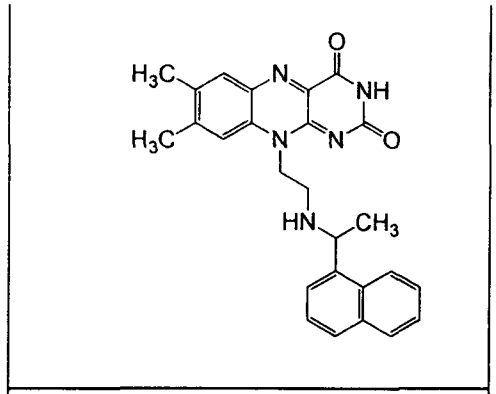


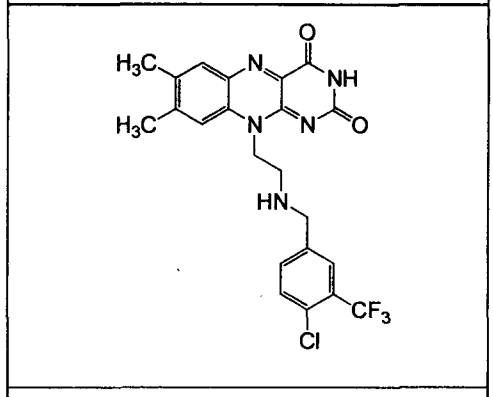


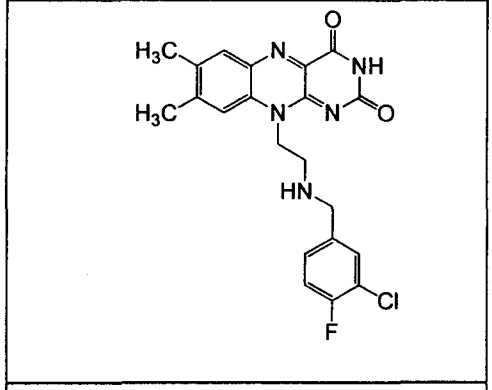


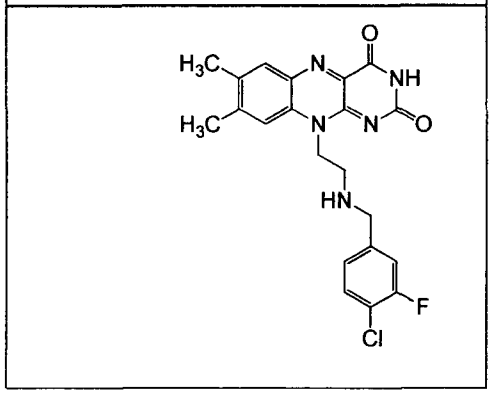


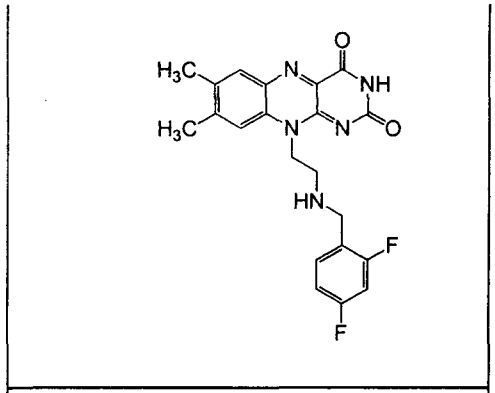


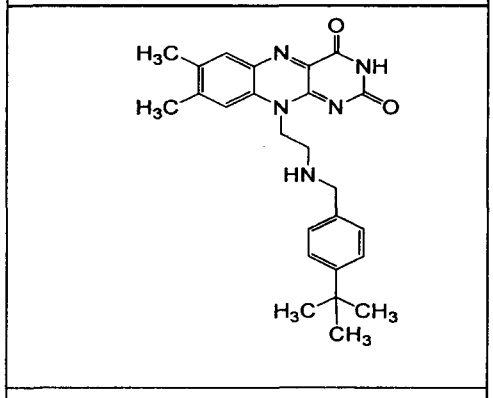


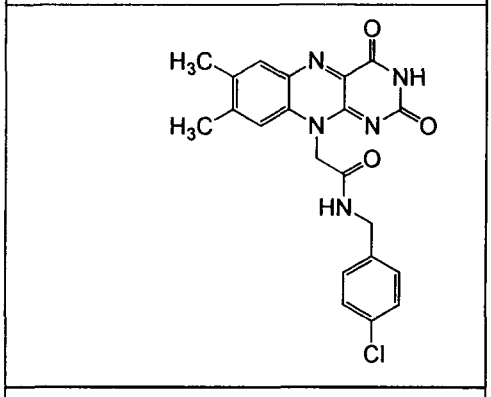


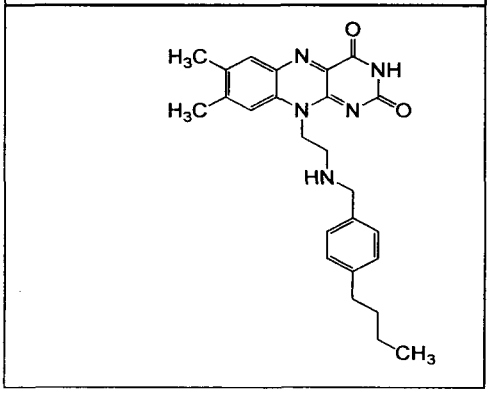


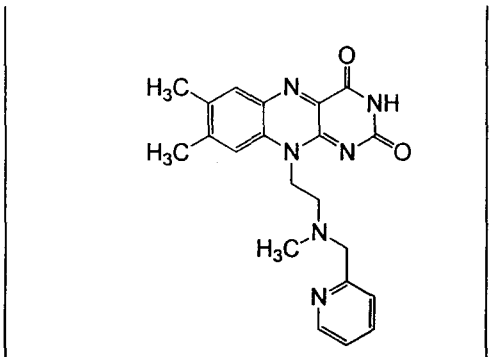


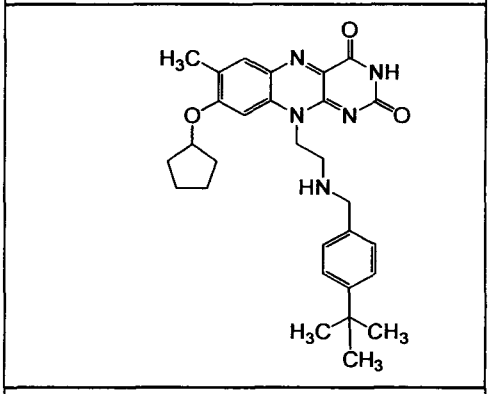


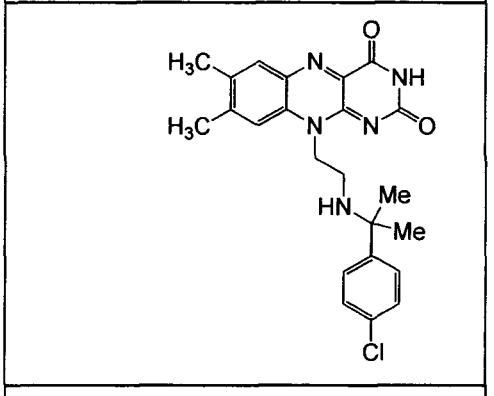


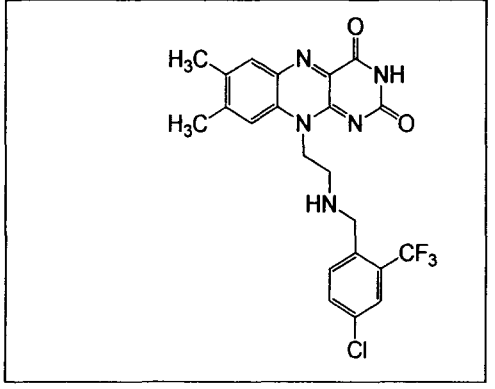


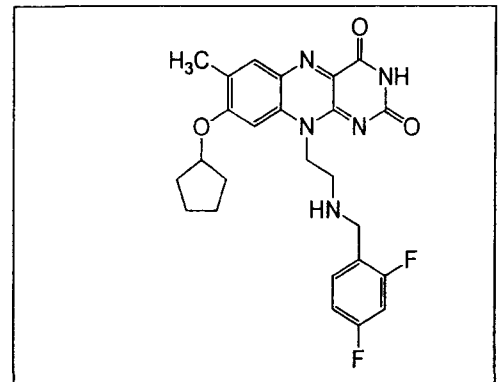


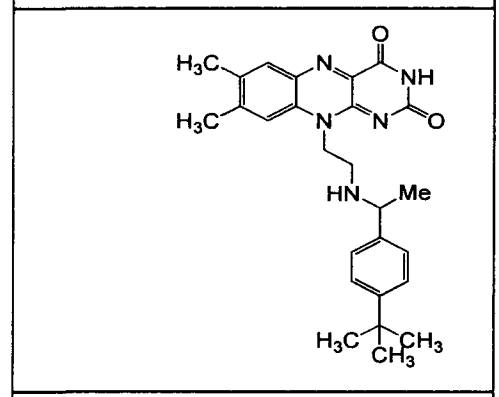


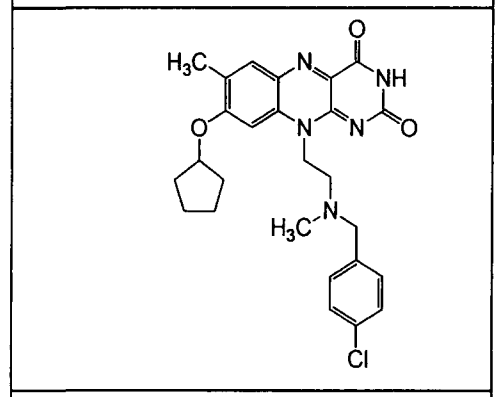


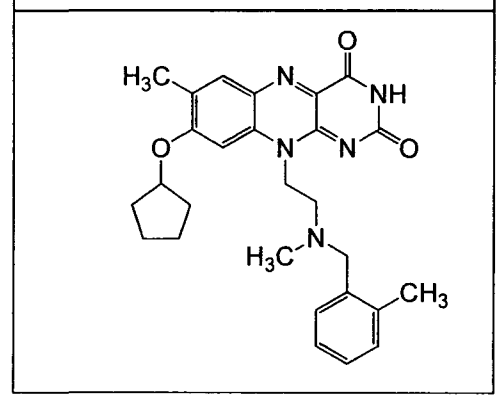


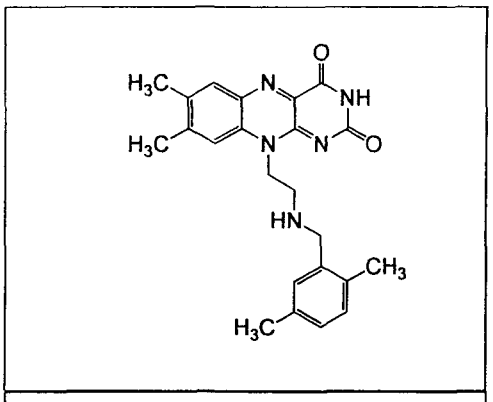


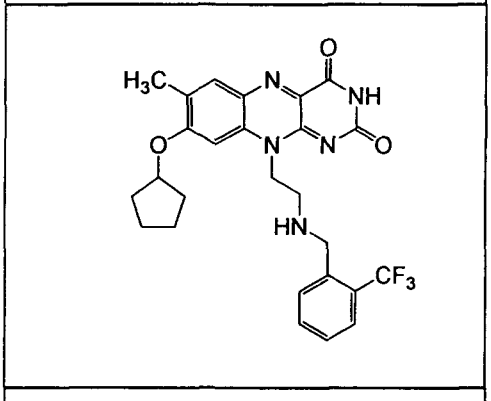


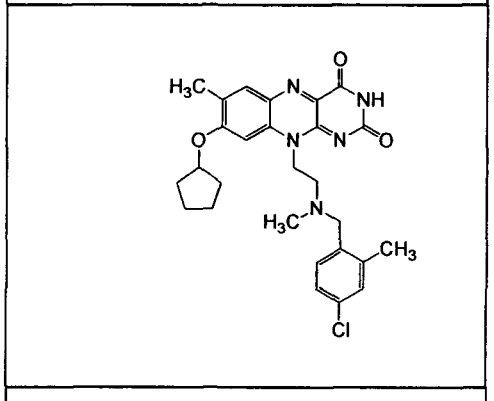


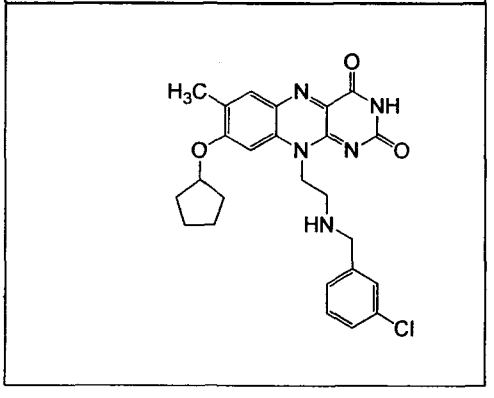


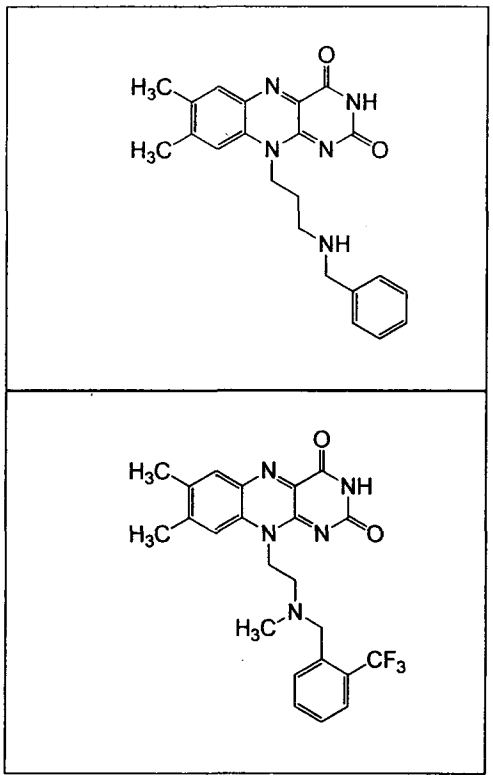






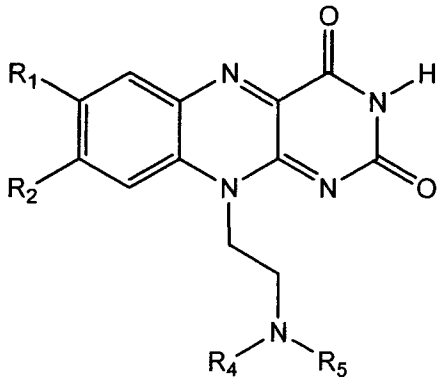






in free or salt form.

15. A compound of Formula III(B):



Formula III(B)

wherein:

(i) R_1 is H or C_{1-4}alkyl (e.g., methyl);

(ii) R_2 is selected from a group consisting of H, C_{1-4}alkyl (e.g., methyl) and -O-C_{3-8}cycloalkyl (e.g., -O-cyclopentyl);

(iii) R_4 is benzyl;

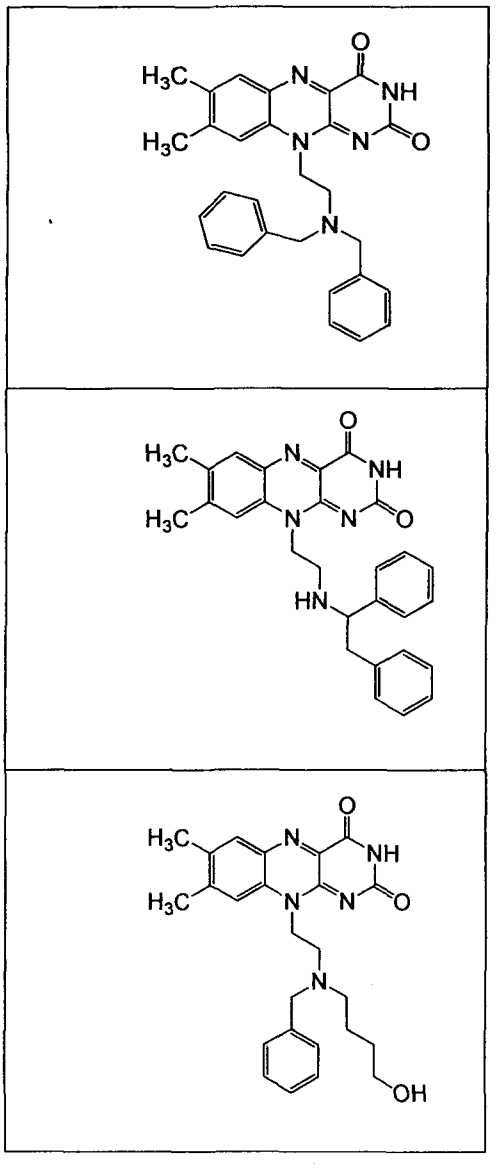
(iv) R_5 is selected from aryl[1]-C_{0-4}alkyl (e.g., phenyl, benzyl, phenylpropyl), hydroxyC_{1-4}alkyl (hydroxybutyl), C_{1-4}alkyl (e.g., n-butyl), C_{3-8}cycloalkyl[1] (e.g., cyclopentyl), wherein R_5 is optionally substituted with one or more

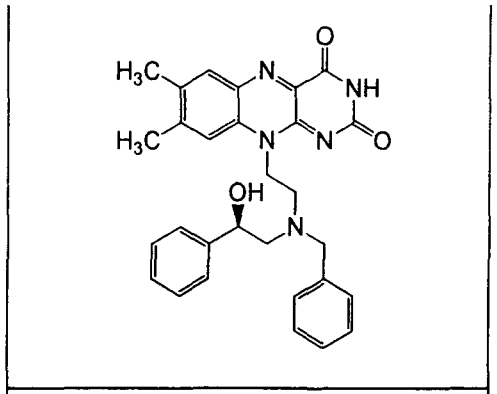
hydroxy or C_{1-4}alkyl (e.g., methyl);

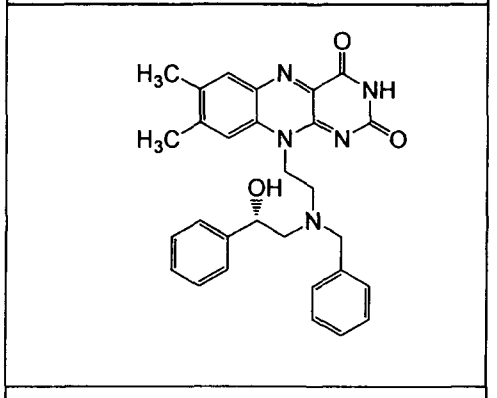
(v) or R_4 is H and R_5 is 1,2-diphenylethyl or 1-hydroxy-2-hydroxymethyl-2-phenyl (-C(H)(CH_2OH)-C(H)(OH)-C_6H_5);

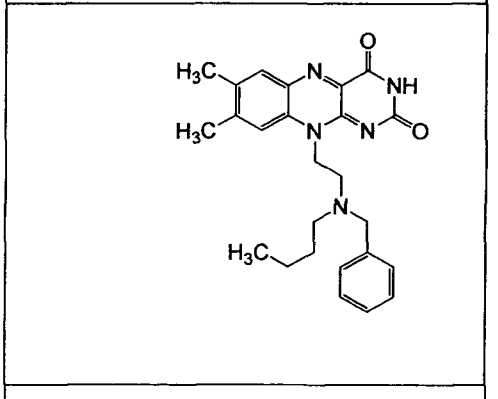
in free or salt form.

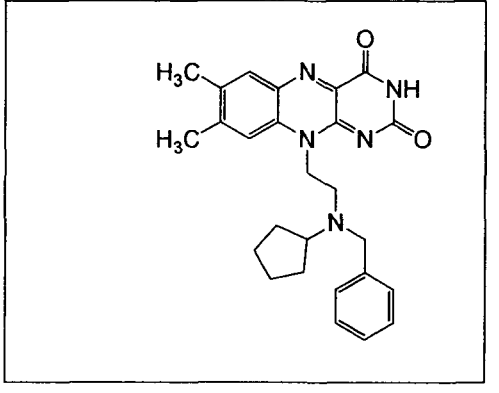
16. The compound according to claim 15, wherein said compound of Formula III(B) is selected from any of the following:

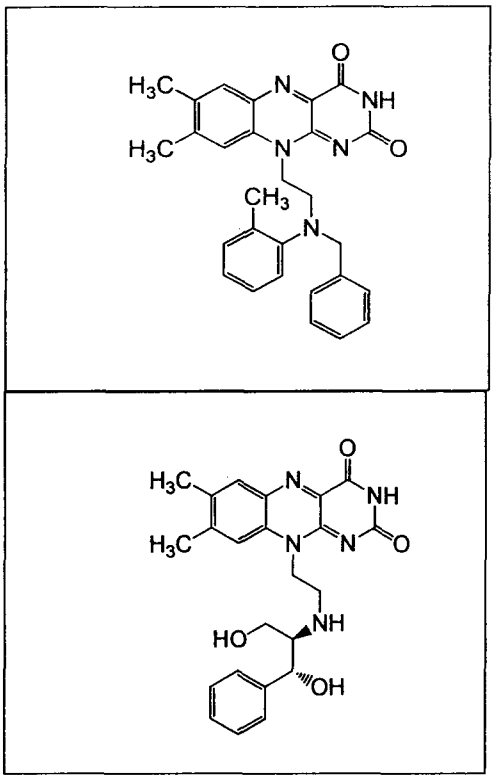






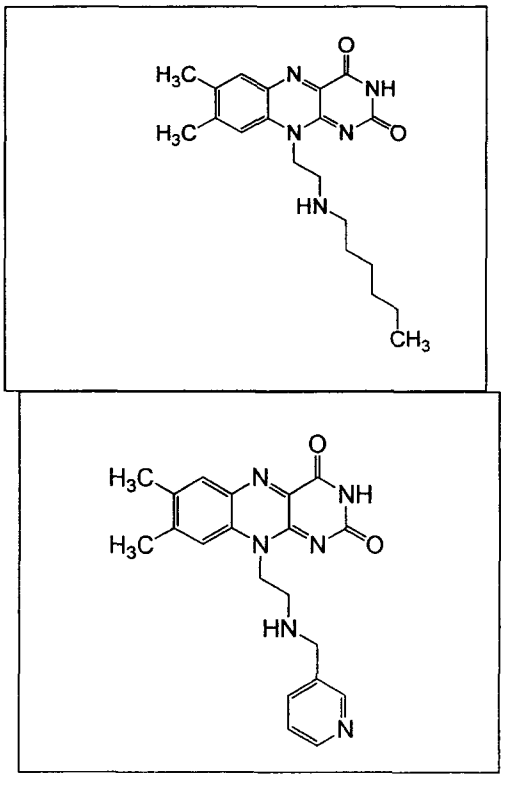






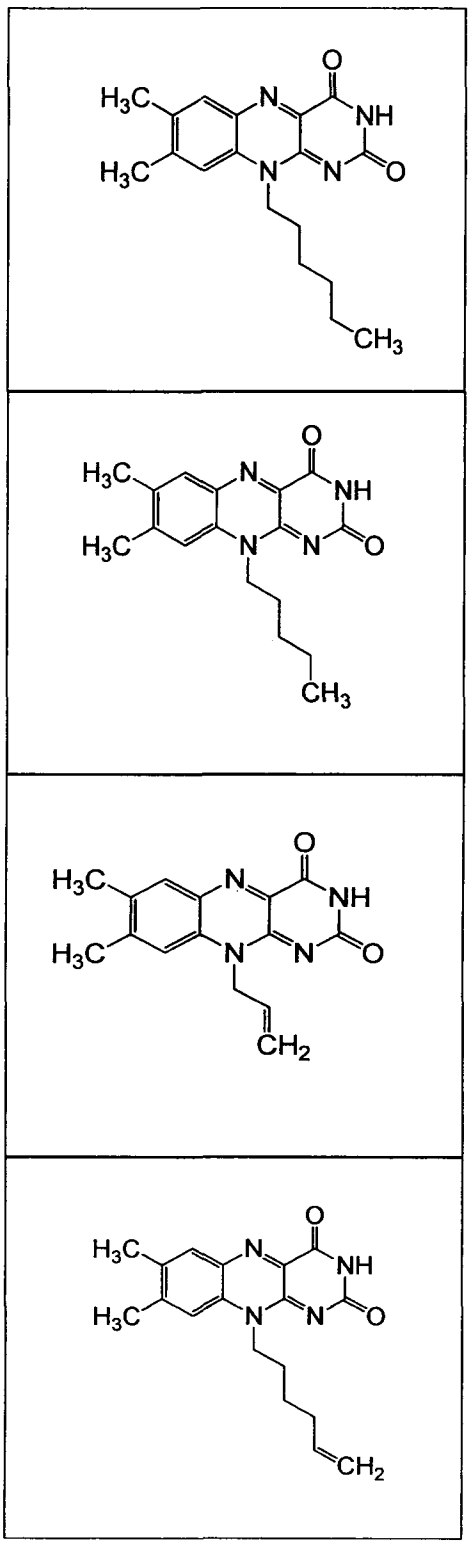
in free or salt form.

17. A compound of Formula IV(B) selected from any of the following:



in free or salt form.

18. A compound of Formula V(B) selected from any of the following:

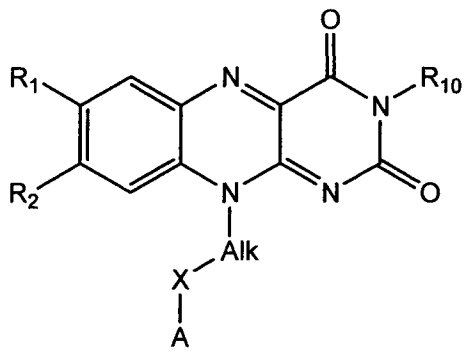


in free or salt form.

19. A method for the treatment or prophylaxis of a bacterial infection comprising administering to a patient in need of such treatment an effective amount of a

compound selected from any of the following:

a) a compound of Formula Q:



Formula Q

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is $-N(R_6)$ and A is:

$-C_{1-4}$alkyl-$N(R_{11})(R_{12})$,

$-C_{0-4}$alkyl-aryl[1] (e.g., phenyl, naphthyl, benzyl), or $-C_{0-4}$alkyl-heteroaryl[1] (e.g., isoxazolyl, (isoxazol-5-yl)methyl, tetrazolyl, pyridyl, for example pyrid-3-yl, (pyrid-5-yl)methyl, indolyl, 1,2,5-oxadiazolyl, pyrrolyl), wherein the alkyl group of said –alkylaryl[1] and –alkylheteroaryl[1] is optionally substituted with hydroxy or another aryl[1] (e.g., phenyl), and the aryl[1] and heteroaryl[1] group of said –alkylaryl[1] and –alkylheteroaryl[1] are independently substituted with one or more:

$-N(R_a)$-C(O)-C_{1-4}alkyl (e.g., $-NHC(O)CH_3$), wherein R_a is H or C_{1-4}alkyl,

-OH,

heteroaryl[1] (e.g., imidazolyl),

heteroC_{3-8}cycloalkyl (e.g., morpholinyl),

aryl[1] (e.g., phenyl),

-O-halo-C_{1-4}alkyl (e.g., $-OCF_3$),

$-NO_2$,

$-N(R_a)(R_b)$, wherein R_a is H or C_{1-4}alkyl and R_b is C_{1-4}alkyl,

$-SO_2-C_{1-4}$alkyl (e.g., $-SO_2-CH_3$);

–C_{0-4}alkyl-pyridyl substituted with one or more hydroxy (e.g., 2-hydroxypyrid-4-ylmethyl or 2-hydroxypyrid-3-yl);

–C_{0-4}alkyl-benzotriazolyl (e.g., 1*H*-benzotriazol-5-yl);

–C_{0-4}alkyl-indolyl (e.g., -indol-5-ylmethyl, indol-2-ylmethyl, indol-3-ylethyl);

–C_{0-4}alkyl-tetrazolyl (e.g., 1,2,3,5-tetrazol-4-ylethyl);

–C_{0-4}alkyl-oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl);

–C_{0-4}alkyl-benzodioxolyl (e.g., 1,3-benzodioxol-5-ylmethyl);

–C_{0-4}alkyl-benzimidazolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylbenzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl);

–C_{0-4}alkyl-imidazolyl optionally substituted with C_{1-4}alkyl (e.g., 1-methyl-imidazol-5-ylmethyl);

–C_{0-4}alkyl-pyrrolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylpyrrolidin-2-ylmethyl); or

para-phenylbenzyl;

or

X is a single bond, and A is a monocyclic heteroaryl^2 (e.g., pyrrolyl, for example pyrrol-1-yl; pyridyl, for example pyrid-2-yl, pyrid-4-yl or pyrid-3-yl; tetrazolyl, for example 1,2,3,4-tetrazol-1-yl; imidazolyl, for example imidazol-1-yl; or isoxazolyl, for example isoxazol-5-yl) wherein said monocyclic heteroaryl^2 is optionally substituted with C_{1-4}alkyl (e.g., methyl);

or

X is a single bond, $-N(R_6)-$, $-N(R_6)-CH_2-$, $-N(R_6)-CH_2CH_2-$, $-N(R_6)-C(H)(CH_3)-$, or $-C(O)-$; and:

A is a C_{3-8}cycloalkyl^2 (e.g., C_4cycloalkyl^2 or C_{5-6}cycloalkyl^2) wherein one or more carbon atoms of said cycloalkyl^2 are optionally and independently replaced with N, O, S, $S(O)_2$ or –C(O)-, for example:

cyclobutyl,

cyclopentyl,

cyclohexyl,

1-methylcyclohex-1-yl,

piperidinyl (e.g., piperidin-1-yl),

pyrrolidinyl (e.g., pyrrolidin-1-yl),

morpholinyl (e.g., morpholin-4-yl),

azapanyl (e.g., azapan-1-yl),

piperazinyl

2,5-dioxopiperazin-1-yl,

tetrahydropyranyl (e.g., tetrahydropyran-4-yl),

isoxazolidinyl (isoxazolidin-5-yl),

1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl,

1,1,3-trioxo-1,2,5-thiazolidin-2-yl,

2-oxocyclopentylidenyl,

2-oxooxazolidin-5-yl,

2-oxopyrimidin-1-yl, or

2,4-dioxo-imidazolidin-3-yl);

wherein said cycloalkyl^2 is optionally substituted with one or more

C_{1-4}alkyl (e.g., methyl),

$-C(O)OR_7$,

$-CH_2C(O)OR_7$,

$-N(R_6)C(O)OR_7$,

-OH,

hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl),

C_{1-4}alkoxy (e.g., methoxy),

$-CH_2N(R_6)-C(O)OR_7$,

aryl^2 (e.g., phenyl) or aryl^2-C_{1-4}alkyl (e.g., benzyl) wherein said aryl^2 group of said aryl^2 or aryl^2-alkyl is optionally substituted with C_{1-4}alkyl (e.g., methyl), for example, 4-methylphenyl, 2-methylphenyl,

heteroaryl^2 (e.g., 2*H*-tetrazol-5-yl),

heteroaryl^2-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl),

$-C_{1-4}$alkyl-$N(R_8)(R_9)$ (e.g., -methyl-NH_2- or -ethyl-NH_2),

C_{1-4}alkoxy (e.g., methoxy),

$-C(O)N(R_6)-S(O)_2-C_{1-4}$alkyl (e.g., $-C(O)N(H)S(O)_2-CH_3$),

$-N(H)-S(O)_2-C_{1-4}$alkyl (e.g., $-N(H)-S(O)_2$-methyl),

$-S(O)_2-N(R_8)(R_9)$ (e.g., $-S(O)_2-NH_2$),

–C(O)N(H)CN,

$–C(O)N(R_8)(R_9)$, or

$-N(R_8)(R_9)$;

or

A is a 7-11 membered fused cycloalkyl-aryl or spiral compound wherein one or more carbon atoms may be a hetero atom selected from N, O or S and wherein said fused cycloalkyl-aryl or spiral group is optionally substituted with one or more hydroxy, C_{1-4}alkyl (e.g., methyl) or oxo (i.e., =O), for example

3,9-diazaspiro[5.5]undecan-3-yl,

3,9-diazaspiro[5.5]undecan-9-yl,

(6-oxo-7-oxa-2-azaspiro[4.4]nonan-2-yl),

(9-oxo-8-oxa-3-azaspiro[4.4]nonan-3-yl),

(1-oxo-2,8-diazaspiro[4.5]decan-8-yl),

(2,4-dioxo-3,8-diazaspiro[4.5]decan-8-yl),

Indolinyl (e.g., indolin-1-yl),

Indanyl (e.g., indan-1-yl, indan-2-yl or 2-hydroxyindan-1-yl),

tetralinyl (e.g., tetralin-2-yl, tetralin-1-yl),

isoindolinyl (e.g., isoindolin-2-yl),

adamantyl,

3,4-dihydro-1H-isoquinolin-2-yl or 3,4-dihydro-2H-quinolin-1-yl,

1,3,4,5-tetrahydro-2-benzazepin-2-yl,

2,3,4,5-tetrahydro-1-benzazepin-1-yl,

1,2,4,5-tetrahydro-3-benzazepin-3-yl,

(iii) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), $-N(R_4)(R_5)$ or $-O-C_{3-8}$cycloalkyl (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –$C(O)OR_7$,

aryl^2 optionally substituted with halo (e.g., 4-fluorophenyl),

aryl^2-C_{1-4}alkyl wherein said aryl^2 group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

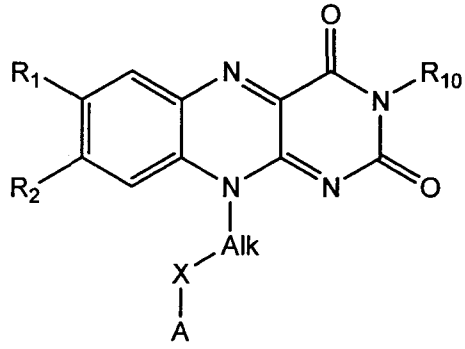
(vii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), $-CH_2OC(O)CH_3$;

(viii) R_8 and R_9 are independently H or C_{1-4}alkyl;

(ix) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., $-CH_2OC(O)CH_3$);

(x) R_{11} and R_{12} are independently H or C_{1-4}alkyl,

b) a compound of Formula Q-I:



Formula Q-I

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is a single bond, -$N(R_6)$-, -$N(R_6)$-CH_2-, -$N(R_6)$-CH_2CH_2-, -$N(R_6)$-$C(H)(CH_3)$-, or -C(O)- and

A is a -C_{3-8}cycloalkyl^2 (e.g., C_4cycloalkyl^2 or C_{5-6}cycloalkyl^2) wherein one or more carbon atoms of said cycloalkyl^2 are optionally and independently replaced with N, O, S, $S(O)_2$ or –C(O)-, for example:

cyclobutyl,

cyclopentyl,

cyclohexyl,

1-methylcyclohex-1-yl,

piperidinyl (e.g., piperidin-1-yl),
pyrrolidinyl (e.g., pyrrolidin-1-yl),
morpholinyl (e.g., morpholin-4-yl),
azapanyl (e.g., azapan-1-yl),
piperazinyl,
2,5-dioxopiperazin-1-yl,
tetrahydropyranyl (e.g., tetrahydropyran-4-yl),
isoxazolidinyl (isoxazolidin-5-yl),
1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl,
1,1,3-trioxo-1,2,5-thiazolidin-2-yl,
2-oxocyclopentylidenyl,
2-oxooxazolidin-5-yl,
2-oxopyrimidin-1-yl, or
2,4-dioxo-imidazolidin-3-yl);

wherein said cycloalkyl^2 is optionally substituted with one or more

C_{1-4}alkyl (e.g., methyl),
–C(O)OR_7,
-CH_2C(O)OR_7,
-N(R_6)C(O)OR_7,
-OH,
hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl),
C_{1-4}alkoxy (e.g., methoxy),
-CH_2N(R_6)-C(O)OR_7,
aryl^2 (e.g., phenyl) or aryl^2-C_{1-4}alkyl (e.g., benzyl) wherein said aryl^2 group of said aryl^2 or aryl^2-alkyl is optionally substituted with C_{1-4}alkyl (e.g., methyl), for example, 4-methylphenyl, 2-methylphenyl,
heteroaryl^2 (e.g., 2*H*-tetrazol-5-yl),
heteroaryl^2-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl),
-C_{1-4}alkyl-N(R_8)(R_9) (e.g., -methyl-NH_2- or -ethyl-NH_2),
C_{1-4}alkoxy (e.g., methoxy),
–C(O)N(R_6)-S(O)$_2$-C_{1-4}alkyl (e.g., -C(O)N(H)S(O)$_2$-CH_3),
-N(H)-S(O)$_2$-C_{1-4}alkyl (e.g., -N(H)-S(O)$_2$-methyl),

$-S(O)_2-N(R_8)(R_9)$ (e.g., $-S(O)_2-NH_2$),

–C(O)N(H)CN,

$–C(O)N(R_8)(R_9)$, or

$-N(R_8)(R_9)$;

or

A is a 7-11 membered fused cycloalkyl-aryl or spiral compound wherein one or more carbon atoms may be a hetero atom selected from N, O or S and wherein said fused cycloalkyl-aryl or spiral group is optionally substituted with one or more hydroxy, C_{1-4}alkyl (e.g., methyl) or oxo (i.e., =O), for example

3,9-diazaspiro[5.5]undecan-3-yl,

3,9-diazaspiro[5.5]undecan-9-yl,

(6-oxo-7-oxa-2-azaspiro[4.4]nonan-2-yl),

(9-oxo-8-oxa-3-azaspiro[4.4]nonan-3-yl),

(1-oxo-2,8-diazaspiro[4.5]decan-8-yl),

(2,4-dioxo-3,8-diazaspiro[4.5]decan-8-yl),

Indolinyl (e.g., indolin-1-yl),

Indanyl (e.g., indan-1-yl, indan-2-yl or 2-hydroxyindan-1-yl),

tetralinyl (e.g., tetralin-2-yl, tetralin-1-yl),

isoindolinyl (e.g., isoindolin-2-yl),

adamantyl,

3,4-dihydro-1H-isoquinolin-2-yl or 3,4-dihydro-2H-quinolin-1-yl,

1,3,4,5-tetrahydro-2-benzazepin-2-yl,

2,3,4,5-tetrahydro-1-benzazepin-1-yl,

1,2,4,5-tetrahydro-3-benzazepin-3-yl,

(iii) R_1 is H or C_{1-8}alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), $-N(R_4)(R_5)$ or $-O-C_{3-8}$cycloalkyl (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7,

aryl^2 optionally substituted with halo (e.g., 4-fluorophenyl),

aryl^2-C_{1-4}alkyl wherein said aryl^2 group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

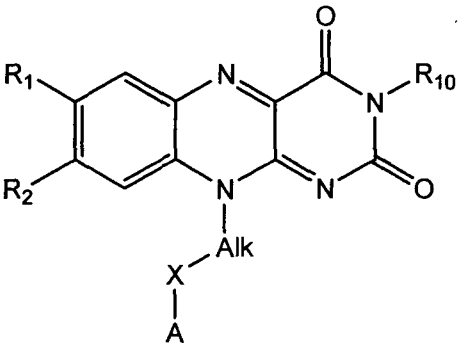
(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -$CH_2OC(O)CH_3$;

(viii) R_8 and R_9 are independently H or C_{1-4}alkyl;

(ix) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$),

c) a compound of Formula Q-II:



Formula Q-II

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is a single bond and A is:

a monocyclic heteroaryl^2 (e.g., pyrrolyl, for example pyrrol-1-yl; pyridyl, for example pyrid-2-yl, pyrid-4-yl or pyrid-3-yl; tetrazolyl, for example 1,2,3,4-tetrazol-1-yl; imidazolyl, for example imidazol-1-yl; or isoxazolyl, for example isoxazol-5-yl); or

wherein said heteroaryl^2 is optionally substituted with one or more C_{1-4}alkyl (e.g., methyl),

(iii) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -$N(R_4)(R_5)$ or -O-C_{3-8}cycloalkyl^2 (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7,

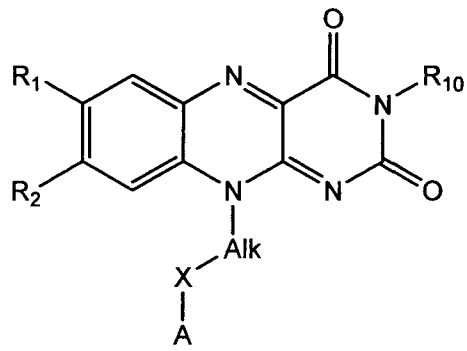
aryl[2] optionally substituted with halo (e.g., 4-fluorophenyl),

aryl[2]-C_{1-4}alkyl wherein said aryl group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

(vi) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -$CH_2OC(O)CH_3$;

(vii) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., -$CH_2OC(O)CH_3$),

d) a compound of Formula Q-III:



Formula Q-III

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene, n-butylene or n-pentylene);

(ii) X is –N(R_6) and A is:

–C_{1-4}alkyl-N(R_{11})(R_{12}),

–C_{0-4}alkyl-aryl[1] (e.g., phenyl, naphthyl, benzyl), or –C_{0-4}alkyl-heteroaryl[1] (e.g., isoxazolyl, (isoxazol-5-yl)methyl, tetrazolyl, pyridyl, for example pyrid-3-yl, (pyrid-5-yl)methyl, indolyl, 1,2,5-oxadiazolyl, pyrrolyl), wherein the alkyl group of said –alkylaryl[1] and –alkylheteroaryl[1] is optionally substituted with hydroxy or another aryl[1] (e.g., phenyl), and the aryl[1] and heteroaryl[1] group of said –alkylaryl[1] and –alkylheteroaryl[1] are independently substituted with one or more:

-$N(R_a)$-C(O)-C_{1-4}alkyl (e.g., -$NHC(O)CH_3$), wherein R_a is H or C_{1-4}alkyl,

-OH,

heteroaryl[1] (e.g., imidazolyl),

heteroC_{3-8}cycloalkyl[1] (e.g., morpholinyl),

aryl[1] (e.g., phenyl),

-O-halo-C_{1-4}alkyl (e.g., -OCF_3),

-NO_2,

-$N(R_a)(R_b)$, wherein R_a is H or C_{1-4}alkyl and R_b is C_{1-4}alkyl,

-SO_2-C_{1-4}alkyl (e.g., -SO_2-CH_3);

–C_{0-4}alkyl-pyridyl substituted with one or more hydroxy (e.g., 2-hydroxypyrid-4-ylmethyl or 2-hydroxypyrid-3-yl);

–C_{0-4}alkyl-benzotriazolyl (e.g., 1*H*-benzotriazol-5-yl);

–C_{0-4}alkyl-indolyl (e.g., -indol-5-ylmethyl, indol-2-ylmethyl, indol-3-ylethyl);

–C_{0-4}alkyl-tetrazolyl (e.g., 1,2,3,5-tetrazol-4-ylethyl);

–C_{0-4}alkyl-oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl);

–C_{0-4}alkyl-benzodioxolyl (e.g., 1,3-benzodioxol-5-ylmethyl);

–C_{0-4}alkyl-benzimidazolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylbenzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl);

–C_{0-4}alkyl-imidazolyl optionally substituted with C_{1-4}alkyl (e.g., 1-methyl-imidazol-5-ylmethyl);

–C_{0-4}alkyl-pyrrolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylpyrrolidin-2-ylmethyl);

para-phenylbenzyl;

(iii) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -$N(R_4)(R_5)$ or -O-C_{3-8}cycloalkyl[2] (e.g., -O-cyclopentyl);

(v) R_4 and R_5 are independently selected from

H,

C_{3-7}cycloalkyl[2] (e.g., cyclopropyl or cyclopentyl),

-C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –$C(O)OR_7$,

$aryl^2$ optionally substituted with halo (e.g., 4-fluorophenyl),

$aryl^2$-C_{1-4}alkyl wherein said aryl group is optionally substituted with halo (e.g., fluoro), for example, 4-fluorophenylethyl;

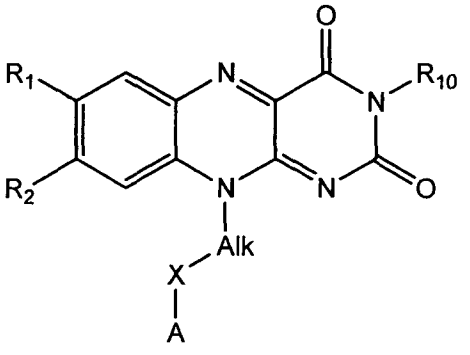
(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), $-CH_2OC(O)CH_3$;

(viii) R_{10} is H or -C_{1-4}alkyl-$OC(O)CH_3$ (e.g., $-CH_2OC(O)CH_3$);

(ix) R_{11} and R_{12} are independently H or C_{1-4}alkyl,

e) a compound of Formula Q-IV:



Formula Q-IV

wherein

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene, n-propylene);

(ii) X is a single bond and A is pyrrolyl, for example pyrrol-1-yl or imidazolyl, for example imidazol-1-yl);

or

X is a single bond and A is a pyrrolidinyl (e.g., pyrrolidin-1-yl) or piperidinyl (e.g., piperidin-1-yl) optionally substituted with another aryl (e.g., phenyl) or aryl-C_{1-4}alkyl (e.g., benzyl);

or

X is $–N(R_6)$- and A is tetralinyl (e.g., tetralin-2-yl);

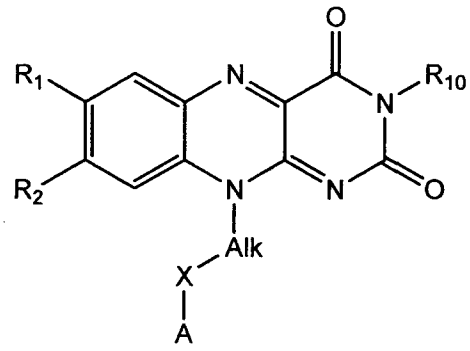
(iii) R_1 is H or C_{1-8}alkyl (e.g., methyl);

(iv) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl);

(v) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vi) R_{10} is H,

f) a compound of Formula Q-V:



Formula Q-V

wherein:

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene, ethylene or n-propylene);

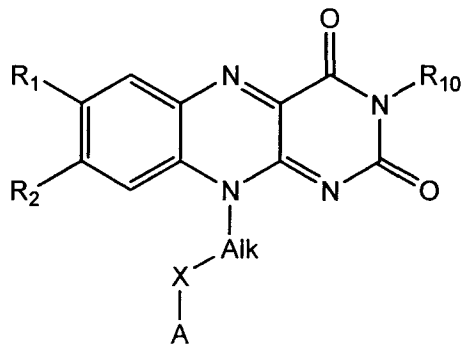
(ii) X is a single bond and A is pyrrolyl, for example pyrrol-1-yl, pyrrolidinyl (e.g., pyrrolidin-1-yl) or piperidinyl (e.g., piperidin-1-yl) optionally substituted with another aryl (e.g., phenyl) or aryl-C_{1-4}alkyl (e.g., benzyl);

(iii) R_1 is C_{1-8} alkyl (e.g., methyl);

(iv) R_2 is C_{1-4}alkyl (e.g., methyl);

(v) R_{10} is H,

g) a compound of Formula I(A):



Formula I(A)

wherein:

(i) Alk is C_{1-6}alkylene (e.g., methylene or ethylene);

(ii) X is a single bond, -N(R_6)-, -N(R_6)-CH_2- or -C(O)-;

(iii) A is a monocyclic heteroaryl (e.g., pyrid-4-yl or pyrid-3-yl) or C_{5-6}cycloalkyl wherein one or more carbon atoms of said cycloalkyl are optionally and independently replaced with N, O, S, or –C(O)-, (for example, piperidinyl (e.g., piperidin-1-yl), pyrrolidinyl (e.g., pyrrolidin-1-yl), piperazinyl (e.g., 2,5-dioxopiperazin-1-yl), isoxazolidinyl (isoxazolidin-5-yl), 1,1-dioxo-1,4-thiazinan-4-yl, C_{3-8}cycloalkyl (e.g., cyclopentyl, cyclohexyl or 2-oxocyclopentylidene), 2-oxopyrimidin-1-yl or 2,4-dioxo-imidazol-3-yl) wherein said heteroaryl and cycloalkyl are independently optionally substituted with one or more –C(O)OR_7, -CH_2C(O)OR_7, -N(R_6)C(O)OR_7, -OH, hydroxy-C_{1-4}alkyl (e.g., hydroxymethyl), -CH_2N(R_6)-C(O)OR_7, heteroaryl (e.g., 2*H*-tetrazol-5-yl), heteroaryl-C_{1-4}alkyl (e.g., 2*H*-tetrazol-5-yl-methyl), amineC_{1-4}alkyl (e.g., amine-ethyl), C_{1-4}alkoxy (e.g., methoxy), –C(O)N(R_6)-S(O)$_2$-C_{1-4}alkyl (e.g., -C(O)N(H)S(O)$_2$-CH_3) or -N(R_8)(R_9);

(iv) R_1 is H or C_{1-8} alkyl (e.g., methyl);

(v) R_2 is H, halo (e.g., chloro), C_{1-4}alkyl (e.g., methyl), -N(R_4)(R_5);

(vi) R_4 and R_5 are independently selected from H, C_{3-7} cycloalkyl (e.g., cyclopropyl or cyclopentyl), -C_{1-4}alkyl (e.g., methyl or ethyl), wherein said alkyl is optionally substituted with one or more groups selected from –OH, –C(O)OR_7, aryl optionally substituted with halo (e.g., 4-fluorophenyl);

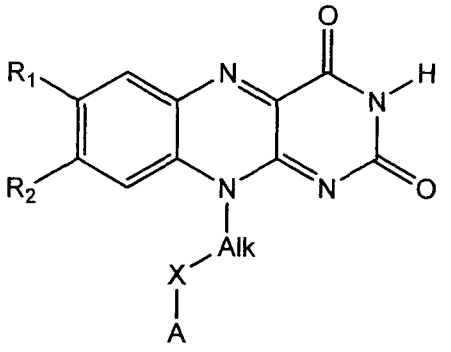
(vii) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(viii) R_7 is H, C_{1-4}alkyl (e.g., methyl, ethyl or *tert*-butyl), -CH_2OC(O)CH_3;

(ix) R_8 and R_9 are independently H or C_{1-4}alkyl;

(x) R_{10} is H or -C_{1-4}alkyl-OC(O)CH_3 (e.g., -CH_2OC(O)CH_3),

h) a compound of Formula I(B):



Formula I(B)

wherein:

(i) Alk is C_{1-2}alkylene (e.g., methylene or ethylene);

(ii) X is -N(R_6)-,

(iii) A is selected from a group consisting of:

–C_{1-4}alkyl-N(R_{11})(R_{12}),

–C_{0-4}alkyl-aryl[1] (e.g., phenyl, naphthyl, benzyl), or –C_{0-4}alkyl-heteroaryl[1] (e.g., isoxazolyl, tetrazolyl, pyridyl, indolyl, 1,2,5-oxadiazolyl, pyrrolyl), wherein the alkyl group of said –alkylaryl[1] and –alkylheteroaryl[1] is optionally substituted with hydroxy or another aryl (e.g., phenyl), and the aryl[1] and heteroaryl[1] group of said –alkylaryl[1] and –alkylheteroaryl[1] are independently substituted with one or more:

-N(R_a)-C(O)-C_{1-4}alkyl (e.g., -NHC(O)CH_3), wherein R_a is H or C_{1-4}alkyl,

-OH,

Heteroaryl[1] (e.g., imidazolyl),

heteroC_{3-8}cycloalkyl[1] (e.g., morpholinyl),

aryl[1] (e.g., phenyl),

-O-halo-C_{1-4}alkyl (e.g., -OCF_3),

-NO_2,

-N(R_a)(R_b), wherein R_a is H or C_{1-4}alkyl and R_b is C_{1-4}alkyl,

-SO_2-C_{1-4}alkyl (e.g., -SO_2-CH_3);

–C_{0-4}alkyl-pyridyl substituted with one or more hydroxy (e.g., 2-hydroxypyrid-4-ylmethyl or 2-hydroxypyrid-3-yl);

–C_{0-4}alkyl-benzotriazolyl (e.g., 1*H*-benzotriazol-5-yl);

–C_{0-4}alkyl-indolyl (e.g., -indol-5-ylmethyl, indol-2-ylmethyl, indol-3-ylethyl);

–C_{0-4}alkyl-tetrazolyl (e.g., 1,2,3,5-tetrazol-4-ylethyl);

–C_{0-4}alkyl-oxadiazolyl (e.g., 1,2,5-oxadiazol-3-yl);

–C_{0-4}alkyl-benzodioxolyl (e.g., 1,3-benzodioxol-5-ylmethyl);

–C_{0-4}alkyl-benzimidazolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylbenzimidazol-2-ylmethyl, benzimidazol-5-ylmethyl);

–C_{0-4}alkyl-imidazolyl optionally substituted with C_{1-4}alkyl (e.g., 1-methyl-imidazol-5-ylmethyl);

–C_{0-4}alkyl-pyrrolyl optionally substituted with –C_{0-4}alkyl (e.g., 1-methylpyrrolidin-2-ylmethyl);

para-phenylbenzyl;

(iv) R_1 is H or C_{1-4}alkyl (e.g., methyl);

(v) R_2 is selected from a group consisting of H, C_{1-4}alkyl (e.g., methyl) and -O-C_{3-8}cycloalkyl[1] (e.g., -O-cyclopentyl);

(vi) R_6 is H or C_{1-4}alkyl (e.g., methyl);

(vii) R_{11} and R_{12} are independently H or C_{1-4}alkyl (e.g., methyl)

or

i) a compound according to any of claims 8-18,

in free or pharmaceutically acceptable salt form.

20. The method according to claim 19, wherein the infection is a Gram-positive or Gram-negative bacterial infection.

21. The method according to any of claims 19-20, wherein the bacterial infection is selected from a group consisting of *Clostridium difficile, Moraxella catarrhalis, Klebsiella pneumoniae, Staphylococcus epidermidis, Streptococcus viridans, Enterococcus faecium, Staphylococcus aureus, Bacillus anthracis, Francisella tularensis, Streptococcus pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Brucella melitensis, Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Salmonella enterica, Vibrio cholerae, Enterococcus faecalis, Yersinia pestis, Bacillus subtilis, Streptococcus pyogenes* and *Borrelia burgdorferi.*

22. The method according to any of claims 19-21, wherein the bacterial infection is a *Clostridium difficile* infection.

23. The method according to any of claims 19-21, wherein the bacterial infection is *Staphylococcus aureus* infection.

24. The method according to any of claims 19-23, wherein said infection is by an infectious agent which is resistant to a drug that is not a riboswitch ligand.

25. The method according to any of claims 19-24, wherein the infection is an infection which is resistant to one or more drugs selected from a group consisting of a penicillin, vancomycin, cephalosporin and methicillin.

26. The method according to claim 25, wherein the infection is a methicillin-resistant *Staphylococcus aureus* infection.

27. The method according to any of claims 19-24, wherein the infection is a fluoroquinolone-resistant (e.g., ciprofloxacin- and/or levofloxacin-resistant), metronidazole and/or vancomycin--resistant *C. difficile* infection.

28. The method according to any of claims 19-27, wherein the compound is a compound of Formula Q in free or pharmaceutically acceptable salt form.

29. The method according to any of claims 19-27, wherein the compound is selected from a group consisting of those described in any of formulae Q.35, Q.36, Q.37, Q.38, Q.39, Q.40 or Q.41, in free or pharmaceutically acceptable salt form.

30. The method according to any of claims 19-27, wherein the compound is selected from a group consisting of those described in formula Q.41, in free or pharmaceutically acceptable salt form.

31. The method according to any of claims 19-27, wherein the compound is a compound of Formula II, in free or pharmaceutically acceptable salt form.

32. A pharmaceutical composition comprising compound according to any of claims 1-18,

in free or pharmaceutically acceptable salt form, in admixture with a pharmaceutically acceptable diluent or carrier.

33 .The compound as claimed in any of the preceding claims or the compounds of Formula Q, Q-I, Q-II, Q-III, Q-IV, Q-V, I(A), I(B), or a pharmaceutical composition according to claim 32 as and when used in the manufacture of a medicament for the treatment or prophylaxis of bacterial infection"

34. Compound as claimed in claim 33, wherein the infection is an infection by one or more of the following bacteria: *Clostridium difficile, Moraxella catarrhalis, Klebsiella pneumoniae, Staphylococcus epidermidis, Streptococcus viridans, Enterococcus faecium, Staphylococcus aureus, Bacillus anthracis, Francisella tularensis, Streptococcus pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Brucella melitensis, Escherichia coli, Haemophilus influenzae, Listeria monocytogenes, Salmonella enterica, Vibrio cholerae, Enterococcus faecalis, Yersinia pestis, Bacillus subtilis, Streptococcus pyogenes* and *Borrelia burgdorferi.*

35. A compound as described in any of claims 19, or a pharmaceutical composition according to claim 32 for use in the manufacture of a medicament for the treatment of a disease, condition or infection selected from a group consisting of anthrax, staphylococcal scalded skin syndrome (staph infections), pneumonia, impetigo, boils, cellulitis folliculitis, furuncles, carbuncles, scalded skin syndrome, abscesses, meningitis, osteomyelitis endocarditis, Toxic Shock Syndrome (TSS), septicemia, acute sinusitis, otitis media, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis, brain abscess, tularemia, urinary tract infection, empyema, food poisoning, diarrhea, conjunctivitis and clostridium difficile associated disease (CDAD).

36. A method for the treatment or prophylaxis of a bacterial infection in a plant comprising administering to said plant an effective amount of a compound according of any of claims 19, in free or pharmaceutically acceptable salt form.

Dated this 27/01/2012

HRISHIKESH RAY CHAUDHURY
OF REMFRY & SAGAR
ATTORNEY FOR THE APPLICANTS

FLAVIN DERIVATIVES

This application claims priority from provisional application number 61/221,937 filed June 30, 2009, and provisional application number 61/303,237, filed February 10, 2010, the contents of each of which are incorporated by reference in their entirety.

TECHNICAL FIELD

[0001] The present invention relates to flavin derivatives and their use and compositions for use as riboswitch ligands and/or anti-infectives. The invention also provides methods of making novel flavin derivatives.

BACKGROUND OF THE INVENTION

[0002] The fast growing rate of antibiotic resistance over the past decades has raised serious concerns that the antibiotic treatment options currently available will soon be ineffective. With the widespread usage of antibiotics in combination with the rapid growing rate of bacterial resistance in stark contrast with the decade-old chemical scaffolds available for their treatment, it is imperative that new drugs are developed in the battle against bacterial pathogens.

[0003] In many bacteria and fungi, RNA structures termed riboswitches regulate the expression of various genes crucial for survival or virulence. Typically located within the 5'-untranslated region (5'-UTR) of certain mRNAs, members of each known class of riboswitch can fold into a distinct, three-dimensionally structured receptor that recognizes a specific organic metabolite. When the cognate metabolite is present at sufficiently high concentrations during transcription of the mRNA, the riboswitch receptor binds to the metabolite and induces a structural change in the nascent mRNA that prevents expression of the open reading frame (ORF), thereby altering gene expression. In the absence of the cognate metabolite, the riboswitch folds into a structure that does not interfere with the expression of the ORF.

[0004] Sixteen different classes of riboswitches have been reported. Members of each class of riboswitch bind to the same metabolite and share a highly conserved sequence and secondary structure. Riboswitch motifs have been identified that bind to thiamine pyrophosphate (TPP), flavin mononucleotide (FMN), glycine, guanine, 3'-5'-cyclic diguanylic acid (c-di-GMP), molybdenum cofactor, glucosamine-6-phosphate (GlcN6P), lysine, adenine, and adocobalamin (AdoCbl) riboswitches. Additionally, four dinstinct

riboswitch motifs have been identified that recognize *S*-adenosylmethionine (SAM) I, II and III, IV and two distinct motifs that recognize pre-queosine-1 (PreQ1). Several antimetabolite ligands have also been identified that bind to known riboswitch classes, including pyrithiamine pyrophosphate (PTPP) which binds TPP riboswitches, *L*-aminoethylcysteine (AEC) and *DL*-4-oxalysine which bind to lysine riboswitches and roseoflavin and FMN which bind to FMN riboswitches.The riboswitch-receptors bind to their respective ligands in an interface that approaches the level of complexity and selectivity of proteins. This highly specific interaction allows riboswitches to discriminate against most intimately related analogs of ligands. For instance, the receptor of a guanine-binding riboswitch from *Bacillus subtilis* forms a three-dimensional structure such that the ligand is almost completely enveloped. The guanine is positioned between two aromatic bases and each polar functional group of the guanine hydrogen bonds with four additional riboswitch nucleotides surrounding it. This level of specificity allows the riboswitch to discriminate against most closely related purine analogs. Similarly, studies of the SAM-binding riboswitches reveal that nearly every functional group of SAM is critical in binding the ligands, allowing it to discriminate highly similar compounds such as *S*-adenosylhomocysteine (SAH) and *S*-adenosylmethionine (SAM), which only differ by a single methyl group. Likewise, TPP riboswitches comprise one subdomain that recognizes every polar functional group of the 4-amino-5-hydroxymethyl-2-methylpyrimidine (HMP) moiety, albeit not the thiazole moiety, and another subdomain that coordinates two metal ions and several water molecules to bind the negatively charged pyrophosphate moiety of the ligand. Similar to TPP, guanine and SAM riboswitches, FMN riboswitches form receptor structures that are highly specific for the natural metabolite FMN. It is by this highly specific interaction that allows for the design of small molecules for the regulation of specific genes.

FMN riboswitches are of particular interest of this invention because it is believed that the riboswitch binds to flavin mono-nucleotide (FMN) and represses the expression of enzymes responsible for riboflavin and FMN biosynthesis. Riboflavin is a water-soluble vitamin that is converted by flavokinases and FAD synthases to co-factors FMN and FAD, which are indispensable cofactors involved in energy metabolism and metabolism of fats, ketones, carbohydrates and proteins crucial for all living organisms. Although vertebrates rely on uptake of vitamin from their gut for riboflavin sources, most prokaryotes, fungi and plants synthesize the necessary riboflavin for survival. It is therefore suggested that