

ANTIMICROBIAL AGENTS

RELATED APPLICATIONS

This application claims priority to, and the benefit of, U.S. Provisional Application Serial No.61/452,884, filed March 15, 2011. The entire content of which is incorporated by
5 reference herein.

FIELD OF THE INVENTION

The present invention relates to the field of anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents. More particularly, the invention relates to substituted
10 aromatic compounds, including substituted biphenyl compounds, useful as therapeutic agents.

BACKGROUND

Since the discovery of penicillin in the 1920s and streptomycin in the 1940s, many new compounds have been discovered or specifically designed for use as antibiotic agents. It was once believed that infectious diseases could be completely controlled or eradicated with
15 the use of such therapeutic agents. However, such beliefs have been shaken by the fact that strains of cells or microorganisms resistant to currently effective therapeutic agents continue to evolve. In fact, virtually every antibiotic agent developed for clinical use has ultimately encountered problems with the emergence of resistant bacteria. For example, resistant strains
20 of Gram-positive bacteria such as methicillin-resistant staphylococci, penicillin-resistant streptococci, and vancomycin-resistant enterococci have developed, which can cause serious and even fatal results for patients infected with such resistant bacteria. Bacteria that are resistant to macrolide antibiotics, i.e., antibiotics based on a 14- to 16-membered lactone ring, have developed. Also, resistant strains of Gram-negative bacteria such as *H. influenzae* and *M. catarrhalis* have been identified. See, e.g., F.D. Lowry, "Antimicrobial Resistance: The
25 Example of *Staphylococcus aureus*," *J. Clin. Invest.*, vol. 111, no. 9, pp. 1265-1273 (2003); and Gold, H.S. and Moellering, R.C., Jr., "Antimicrobial-Drug Resistance," *N. Engl. J. Med.*, vol. 335, pp. 1445-53 (1996).

The problem of resistance is not limited to the area of anti-infective agents, resistance has also been encountered with anti-proliferative agents used in cancer chemotherapy.

Therefore, there exists a need for new anti-infective and anti-proliferative agents that are both effective against resistant bacteria and resistant strains of cancer cells.

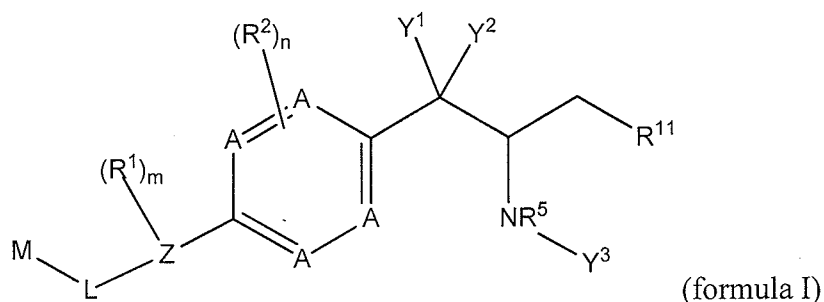
In the antibiotic area, despite the problem of increasing antibiotic resistance, no new major classes of antibiotics have been developed for clinical use since the approval in the United States in 2000 of the oxazolidinone ring-containing antibiotic, N-[[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetamide, which is known as linezolid and is sold under the trade name Zyvox®. See, R.C. Moellering, Jr., "Linezolid: The First Oxazolidinone Antimicrobial," *Annals of Internal Medicine*, vol. 138, no. 2, pp. 135-142 (2003).

Linezolid was approved for use as an anti-bacterial agent active against Gram-positive organisms. Unfortunately, linezolid-resistant strains of organisms are already being reported. See, Tsiodras *et al.*, *Lancet*, vol. 358, p. 207 (2001); Gonzales *et al.*, *Lancet*, vol 357, p. 1179 (2001); Zurenko *et al.*, *Proceedings Of The 39th Annual Interscience Conference On Antibacterial Agents And Chemotherapy (ICAAC)*, San Francisco, CA, USA (September 26-29, 1999). Because linezolid is both a clinically effective and commercially significant anti-microbial agent, investigators have been working to develop other effective linezolid derivatives.

Notwithstanding the foregoing, there is an ongoing need for new anti-infective and anti-proliferative agents. Furthermore, because many anti-infective and anti-proliferative agents have utility as anti-inflammatory agents and prokinetic agents, there is also an ongoing need for new compounds useful as anti-inflammatory and prokinetic agents. Because of these needs for these therapeutic agents there is a corresponding need for processes for making them and key intermediates.

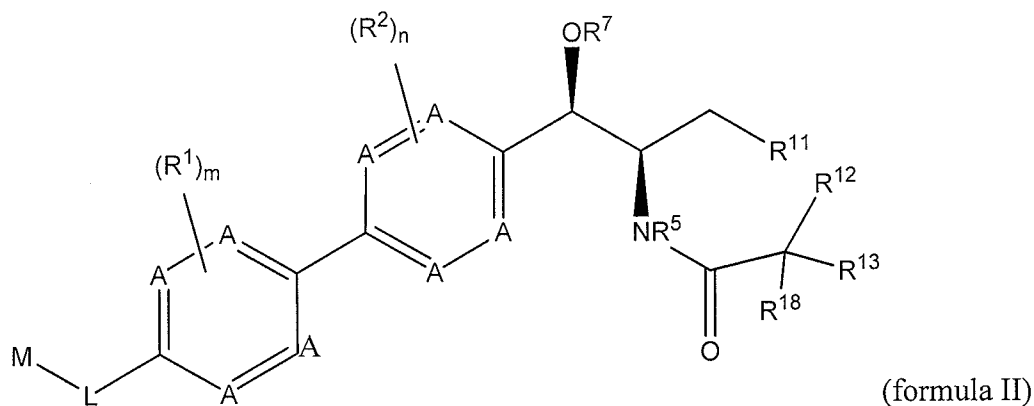
SUMMARY OF THE INVENTION

The present invention provides compounds useful as anti-infective, anti-proliferative, anti-inflammatory, and prokinetic agents. These compounds correspond to the following formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, L, M, R¹, R², R⁵, R¹¹, Y¹, Y², Y³, Z, m, n and the other variables are as defined below.

In one aspect, the invention is directed to compounds that correspond to the following
5 formula:



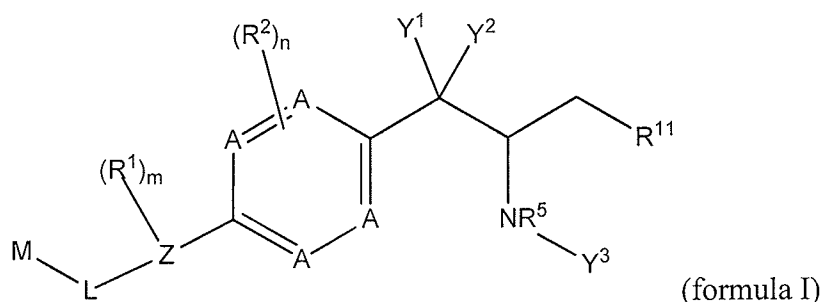
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, L, M, R¹, R², R⁵, R⁷, R¹¹, R¹², R¹³, R¹⁸, m, n, and the other variables are defined below.

10 In addition, the invention provides methods of synthesizing the foregoing compounds. Following synthesis, an effective amount of one or more of the compounds can be formulated with a pharmaceutically acceptable carrier for administration to a mammal or other animals. The compounds or formulations can be administered, for example, *via* oral, parenteral, or topical routes, to provide an effective amount of the compound to the mammal.

15 The foregoing and other aspects and embodiments of the invention can be more fully understood by reference to the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

each A is individually selected from CH, CR², nitrogen, and nitrogen oxide;

5 Y¹ and Y² are independently selected from: a) H, b) F, c) Cl, d) Br, e) I, f) –CF₃, g) –OR⁷, h) –CN, i) –NO₂, j) –NR⁵R⁵, k) –C(O)R⁵, l) –C(O)OR⁵, m) –OC(O)R⁵, n) –C(O)NR⁵R⁵, o) –NR⁵C(O)R⁵, p) –OC(O)NR⁵R⁵, q) –NR⁵C(O)OR⁵, r) –NR⁵C(O)NR⁵R⁵, s) –C(S)R⁵, t) –C(S)OR⁵, u) –OC(S)R⁵, v) –C(S)NR⁵R⁵, w) –NR⁵C(S)R⁵, x) –OC(S)NR⁵R⁵, y) –NR⁵C(S)OR⁵, z) –NR⁵C(S)NR⁵R⁵, aa) –NR⁵C(NR⁵)NR⁵R⁵, bb) –S(O)_pR⁵, and cc) R⁵;

10 alternatively, Y¹ and Y² taken together form a) =O, b) =S, c) =NR⁵, d) =NOR⁵, or e) =N–NR⁵R⁵;

Y³ is selected from: a) H, b) S(O)_pR⁷, c) C₁₋₆ alkyl, d) C₂₋₆ alkenyl, e) C₂₋₆ alkynyl, f) C(O)–C₁₋₆ alkyl, g) C(O)–C₂₋₆ alkenyl, h) C(O)–C₂₋₆ alkynyl, i) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, j) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, k) C(O)–C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, l) C(O)–3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, m) C(O)C(O)–NR⁵R⁵, and n) C(O)C(O)–OR⁵,

20 wherein any of c) – l) optionally is substituted with one or more R⁵, R¹², R¹³ or R¹⁸, and

any of the carbon atom of c) – h) optionally is replaced with NR⁵, oxygen, or sulfur;

25 alternatively, Y³ and R⁵ taken together form a 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur optionally substituted with one or more R⁷;

alternatively, R^5 and R^{11} taken together form a 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur optionally substituted with one or more R^7 ;

Z is selected from a) bond, b) C_{3-14} saturated, unsaturated, or aromatic carbocycle, c) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, d) C_{1-6} alkyl, e) C_{2-6} alkenyl, and f) C_{2-6} alkynyl,

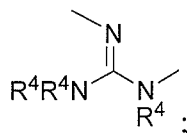
wherein any of b) – f) optionally is substituted with one or more R^5 groups;

M-L is selected from:

- a) M-X, b) $M-L^1$, c) $M-L^1-X$, d) $M-X-L^2$, e) $M-L^1-X-L^2$, f) $M-X-L^1-X-L^2$,
g) $M-L^1-X-L^2-X$, h) $M-X-X$, i) $M-L^1-X-X$, j) $M-X-X-L^2$, and
k) $M-L^1-X-X-L^2$, wherein

X, at each occurrence, independently is selected from:

- a) -O-, b) $-NR^4$ -, c) $-N(O)$ -, d) $-N(OR^4)$ -, e) $-S(O)_p$ -, f) $-SO_2NR^4$ -,
g) $-NR^4SO_2$ -, h) $-NR^4-N=$, i) $=N-NR^4$ -, j) $-O-N=$, k) $=N-O$ -,
l) $-N=$, m) $=N$ -, n) $-NR^4-NR^4$ -, o) $-NR^4C(O)O$ -, p) $-OC(O)NR^4$ -,
q) $-NR^4C(O)NR^4$ -, r) $-NR^4C(NR^4)NR^4$ -, s) $-C(O)$ -, t) $-NR^4C(O)$ -,
u) $-C(O)NR^4$ -, v) $-OC(O)$ -, w) $-C(O)O$ -, and
x)



L^1 is selected from:

- a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups; and

L^2 is selected from:

- a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups;

alternatively, L in M-L is a bond;

M is selected from:

a) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, b) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, c) C₁₋₆ alkyl, d) C₂₋₆ alkenyl, e) C₂₋₆ alkynyl, f) -NH₂, g) -CN, h) H, i) F, j) Cl, k) Br, l) I, m) OH, n) C(O)H, o) C(O)R⁶, p) S(O)_pR⁶, and q) NO₂,

wherein any of a) – e) optionally is substituted with one or more R⁵ groups;

R¹, at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷, j) -C(O)R⁷, k) -C(O)OR⁷, l) -OC(O)R⁷, m) -C(O)NR⁷R⁷, n) -NR⁷C(O)R⁷, o) -OC(O)NR⁷R⁷, p) -NR⁷C(O)OR⁷, q) -NR⁷C(O)NR⁷R⁷, r) -C(S)R⁷, s) -C(S)OR⁷, t) -OC(S)R⁷, u) -C(S)NR⁷R⁷, v) -NR⁷C(S)R⁷, w) -OC(S)NR⁷R⁷, x) -NR⁷C(S)OR⁷, y) -NR⁷C(S)NR⁷R⁷, z) -NR⁷C(NR⁷)NR⁷R⁷, aa) -S(O)_pR⁷, bb) -SO₂NR⁷R⁷, and cc) R⁷;

R², at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷, j) -C(O)R⁷, k) -C(O)OR⁷, l) -OC(O)R⁷, m) -C(O)NR⁷R⁷, n) -NR⁷C(O)R⁷, o) -OC(O)NR⁷R⁷, p) -NR⁷C(O)OR⁷, q) -NR⁷C(O)NR⁷R⁷, r) -C(S)R⁷, s) -C(S)OR⁷, t) -OC(S)R⁷, u) -C(S)NR⁷R⁷, v) -NR⁷C(S)R⁷, w) -OC(S)NR⁷R⁷, x) -NR⁷C(S)OR⁷, y) -NR⁷C(S)NR⁷R⁷, z) -NR⁷C(NR⁷)NR⁷R⁷, aa) -S(O)_pR⁷, bb) -SO₂NR⁷R⁷, and cc) R⁷;

R⁴, at each occurrence, independently is selected from:

a) H, b) F, c) Cl, d) Br, e) I, f) =O, g) =S, h) =NR⁵, i) =NOR⁵, j) =N-NR⁵R⁵, k) -CF₃, l) -OR⁵, m) -CN, n) -NO₂, o) -NR⁵R⁵, p) -C(O)R⁵, q) -C(O)OR⁵, r) -OC(O)R⁵, s) -C(O)NR⁵R⁵, t) -NR⁵C(O)R⁵, u) -OC(O)NR⁵R⁵, v) -NR⁵C(O)OR⁵, w) -NR⁵C(O)NR⁵R⁵, x) -C(S)R⁵, y) -C(S)OR⁵, z) -OC(S)R⁵, aa) -C(S)NR⁵R⁵, bb) -NR⁵C(S)R⁵, cc) -OC(S)NR⁵R⁵, dd) -NR⁵C(S)OR⁵, ee) -NR⁵C(S)NR⁵R⁵, ff) -NR⁵C(NR⁵)NR⁵R⁵, gg) -S(O)_pR⁵, hh) R⁵, and ii) C₁₋₆ alkyl optionally substituted with R⁷;

R⁵, at each occurrence, independently is selected from:

a) H, b) C₁₋₆ alkyl, c) C₂₋₆ alkenyl, d) C₂₋₆ alkynyl, e) -C(O)-C₁₋₆ alkyl, f) -C(O)-C₂₋₆ alkenyl, g) -C(O)-C₂₋₆ alkynyl, h) -C(O)O-C₁₋₆ alkyl, i) -C(O)O-C₂₋₆ alkenyl, j) -C(O)O-C₂₋₆ alkynyl, k) F, l) Cl, m) Br, n) I, o) OH, p) C(O)H, q) C(O)R⁷, r) NR⁷R⁷, s) NR⁷C(O)R⁷, t) C(O)NR⁷R⁷, u)

S(O)_pR⁶, v) CN, w) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, x) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, y) -O-C₁₋₆ alkyl,

5 z) -O-C₂₋₆ alkenyl, aa) -O-C₂₋₆ alkynyl, bb) NR⁷C(=NR⁷)NR⁷R⁷, and cc) NO₂,

wherein any of b) - j) and x) - aa) optionally is substituted with one or more R⁶ groups;

R⁶, at each occurrence, independently is selected from:

10 a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OH, g) -OC₁₋₆ alkyl, h) -SH, i) -SC₁₋₆ alkyl, j) -CN, k) -NO₂, l) -NH₂, m) -NHC₁₋₆ alkyl, n) -N(C₁₋₆ alkyl)₂, o) -C(O)C₁₋₆ alkyl, p) -C(O)OC₁₋₆ alkyl, q) -C(O)NH₂, r) -C(O)NHC₁₋₆ alkyl, s) -C(O)N(C₁₋₆ alkyl)₂, t) -NHC(O)C₁₋₆ alkyl, u) -S(O)_pR⁷, v) NHR⁷, w) NR⁷R⁷, x) C₃₋₁₄ saturated, unsaturated, or aromatic
15 carbocycle, y) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, and z) OR⁸,

wherein any of x) - y) optionally is substituted with one or more R⁸;

R⁷, at each occurrence, independently is selected from:

20 a) H, b) C₁₋₆ alkyl, c) C₂₋₆ alkenyl, d) C₂₋₆ alkynyl, e) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, g) -C(O)C₁₋₆ alkyl, h) -C(O)-C₂₋₆ alkenyl, i) -C(O)-C₂₋₆ alkynyl,
25 j) -C(O)-C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, k) -C(O)-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) -C(O)O-C₁₋₆ alkyl, m) -C(O)O-C₂₋₆ alkenyl, n) -C(O)O-C₂₋₆ alkynyl, o) -C(O)O-C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, and
30 p) -C(O)O-3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^8 groups;

R^8 , at each occurrence, is independently selected from:

- 5 a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) =NR⁹, h) =NOR⁹, i) =N–NR⁹R⁹,
j) –CF₃, k) –OR⁹, l) –CN, m) –NO₂, n) –NR⁹R⁹, o) –C(O)R⁹, p) –C(O)OR⁹,
q) –OC(O)R⁹, r) –C(O)NR⁹R⁹, s) –NR⁹C(O)R⁹, t) –OC(O)NR⁹R⁹,
u) –NR⁹C(O)OR⁹, v) –NR⁹C(O)NR⁹R⁹, w) –C(S)R⁹, x) –C(S)OR⁹,
y) –OC(S)R⁹, z) –C(S)NR⁹R⁹, aa) –NR⁹C(S)R⁹, bb) –OC(S)NR⁹R⁹,
cc) –NR⁹C(S)OR⁹, dd) –NR⁹C(S)NR⁹R⁹, ee) –NR⁹C(NR⁹)NR⁹R⁹,
10 ff) –S(O)_pR⁹, gg) –SO₂NR⁹R⁹, and hh) R⁹;

R^9 , at each occurrence, independently is selected from:

- a) H, b) C₁₋₆ alkyl, c) C₂₋₆ alkenyl, d) C₂₋₆ alkynyl, e) C₃₋₁₄ saturated,
unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated,
or aromatic heterocycle comprising one or more heteroatoms selected from
15 nitrogen, oxygen, and sulfur, g) –C(O)–C₁₋₆ alkyl, h) –C(O)–C₂₋₆ alkenyl, i) –
C(O)–C₂₋₆ alkynyl,
j) –C(O)–C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, k) –C(O)–3-
14 membered saturated, unsaturated, or aromatic heterocycle comprising one
or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) –C(O)O–
20 C₁₋₆ alkyl, m) –C(O)O–C₂₋₆ alkenyl, n) –C(O)O–C₂₋₆ alkynyl, o) –C(O)O–C₃₋₁₄
saturated, unsaturated, or aromatic carbocycle, and p) –C(O)O–3-14 membered
saturated, unsaturated, or aromatic heterocycle comprising one or more
heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more
25 moieties selected from:

- a) F, b) Cl, c) Br, d) I, e) –CF₃, f) –OH, g) –OC₁₋₆ alkyl,
h) –SH, i) –SC₁₋₆ alkyl, j) –CN, k) –NO₂, l) –NH₂,
m) –NHC₁₋₆ alkyl, n) –N(C₁₋₆ alkyl)₂, o) –C(O)C₁₋₆ alkyl,
p) –C(O)OC₁₋₆ alkyl, q) –C(O)NH₂, r) –C(O)NHC₁₋₆ alkyl, s) –
30 C(O)N(C₁₋₆ alkyl)₂, t) –NHC(O)C₁₋₆ alkyl, u) –SO₂NH₂, v) –
SO₂NHC₁₋₆ alkyl, w) –SO₂N(C₁₋₆ alkyl)₂, and
x) –S(O)_pC₁₋₆ alkyl;

R^{11} is selected from a) –OH, b) F, c) H, d) C(O)O–C₁₋₆ alkyl, and e) OC(O)–C₁₋₆ alkyl;

R^{12} and R^{13} are independently selected from a) H, b) C_{1-4} alkyl, c) F, d) Cl, e) Br, f) I, g) CF_3 , h) NH_2 , i) CN, and j) N_3 ;

R^{18} is selected from a) H and b) F;

alternatively, R^{18} is absent and R^{12} and R^{13} together form

a) =O,

b) C_{3-14} saturated, unsaturated, or aromatic carbocycle, or

c) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of a) – b) optionally is substituted with one or more moieties selected from:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OH$, g) $-OC_{1-6}$ alkyl,

h) $-SH$, i) $-SC_{1-6}$ alkyl, j) $-CN$, k) $-NO_2$, l) $-NH_2$,

m) $-NHC_{1-6}$ alkyl, n) $-N(C_{1-6} \text{ alkyl})_2$, o) $-C(O)C_{1-6}$ alkyl,

p) $-C(O)OC_{1-6}$ alkyl, q) $-C(O)NH_2$, r) $-C(O)NHC_{1-6}$ alkyl, s) $-$

$C(O)N(C_{1-6} \text{ alkyl})_2$, t) $-NHC(O)C_{1-6}$ alkyl, u) $-SO_2NH_2$, v) $-$

SO_2NHC_{1-6} alkyl, w) $-SO_2N(C_{1-6} \text{ alkyl})_2$, and

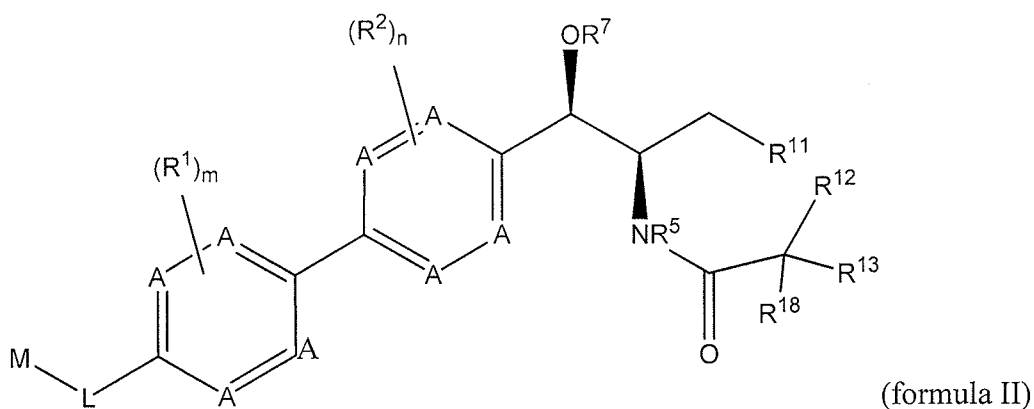
x) $-S(O)_pC_{1-6}$ alkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p, at each occurrence, independently is 0, 1, or 2.

The present invention relates to a compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

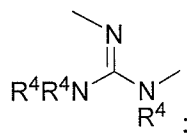
each A is individually selected from CH, CR², nitrogen, and nitrogen oxide;

M-L is selected from:

- a) M-X, b) M-L¹, c) M-L¹-X, d) M-X-L², e) M-L¹-X-L², f) M-X-L¹-X-L²,
 g) M-L¹-X-L²-X, h) M-X-X-, i) M-L¹-X-X-, j) M-X-X-L², and
 k) M-L¹-X-X-L², wherein

X, at each occurrence, independently is selected from:

- a) -O-, b) -NR⁴-, c) -N(O)-, d) -N(OR⁴)-, e) -S(O)_p-, f) -SO₂NR⁴-,
 g) -NR⁴SO₂-, h) -NR⁴-N=, i) =N-NR⁴-, j) -O-N=, k) =N-O-,
 l) -N=, m) =N-, n) -NR⁴-NR⁴-, o) -NR⁴C(O)O-, p) -OC(O)NR⁴-,
 q) -NR⁴C(O)NR⁴-, r) -NR⁴C(NR⁴)NR⁴-, and
 s)



L¹ is selected from:

- a) C₁₋₆ alkyl, b) C₂₋₆ alkenyl, and c) C₂₋₆ alkynyl,

wherein any of a) – c) optionally is substituted with one or more R⁵ groups; and

L² is selected from:

- a) C₁₋₆ alkyl, b) C₂₋₆ alkenyl, and c) C₂₋₆ alkynyl,

wherein any of a) – c) optionally is substituted with one or more R⁵ groups;

alternatively, L in M-L is a bond;

M is selected from:

- a) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, b) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, c) C₁₋₆ alkyl, d) C₂₋₆ alkenyl, e) C₂₋₆ alkynyl, f) -NH₂, and g) -CN, wherein any of a) – e) optionally is substituted with one or more R⁵ groups;

R¹, at each occurrence, independently is selected from:

- a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷,

j) $-C(O)R^7$, k) $-C(O)OR^7$, l) $-OC(O)R^7$, m) $-C(O)NR^7R^7$, n) $-NR^7C(O)R^7$,
 o) $-OC(O)NR^7R^7$, p) $-NR^7C(O)OR^7$, q) $-NR^7C(O)NR^7R^7$, r) $-C(S)R^7$,
 s) $-C(S)OR^7$, t) $-OC(S)R^7$, u) $-C(S)NR^7R^7$, v) $-NR^7C(S)R^7$,
 w) $-OC(S)NR^7R^7$, x) $-NR^7C(S)OR^7$, y) $-NR^7C(S)NR^7R^7$,
 z) $-NR^7C(NR^7)NR^7R^7$, aa) $-S(O)_pR^7$, bb) $-SO_2NR^7R^7$, and cc) R^7 ;

R^2 , at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OR^7$, g) $-CN$, h) $-NO_2$, i) $-NR^7R^7$,
 j) $-C(O)R^7$, k) $-C(O)OR^7$, l) $-OC(O)R^7$, m) $-C(O)NR^7R^7$, n) $-NR^7C(O)R^7$,
 o) $-OC(O)NR^7R^7$, p) $-NR^7C(O)OR^7$, q) $-NR^7C(O)NR^7R^7$, r) $-C(S)R^7$,
 s) $-C(S)OR^7$, t) $-OC(S)R^7$, u) $-C(S)NR^7R^7$, v) $-NR^7C(S)R^7$,
 w) $-OC(S)NR^7R^7$, x) $-NR^7C(S)OR^7$, y) $-NR^7C(S)NR^7R^7$,
 z) $-NR^7C(NR^7)NR^7R^7$, aa) $-S(O)_pR^7$, bb) $-SO_2NR^7R^7$, and cc) R^7 ;

R^4 , at each occurrence, independently is selected from:

a) H, b) F, c) Cl, d) Br, e) I, f) $=O$, g) $=S$, h) $=NR^5$, i) $=NOR^5$, j) $=N-NR^5R^5$,
 k) $-CF_3$, l) $-OR^5$, m) $-CN$, n) $-NO_2$, o) $-NR^5R^5$, p) $-C(O)R^5$, q) $-C(O)OR^5$,
 r) $-OC(O)R^5$, s) $-C(O)NR^5R^5$, t) $-NR^5C(O)R^5$, u) $-OC(O)NR^5R^5$,
 v) $-NR^5C(O)OR^5$, w) $-NR^5C(O)NR^5R^5$, x) $-C(S)R^5$, y) $-C(S)OR^5$,
 z) $-OC(S)R^5$, aa) $-C(S)NR^5R^5$, bb) $-NR^5C(S)R^5$, cc) $-OC(S)NR^5R^5$,
 dd) $-NR^5C(S)OR^5$, ee) $-NR^5C(S)NR^5R^5$, ff) $-NR^5C(NR^5)NR^5R^5$,
 gg) $-S(O)_pR^5$, and hh) R^5 ;

R^5 , at each occurrence, independently is selected from:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) $-C(O)-C_{1-6}$ alkyl,
 f) $-C(O)-C_{2-6}$ alkenyl, g) $-C(O)-C_{2-6}$ alkynyl, h) $-C(O)O-C_{1-6}$ alkyl,
 i) $-C(O)O-C_{2-6}$ alkenyl, and j) $-C(O)O-C_{2-6}$ alkynyl,

wherein any of b) - j) optionally is substituted with one or more R^6 groups;

R^6 , at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OH$, g) $-OC_{1-6}$ alkyl, h) $-SH$,
 i) $-SC_{1-6}$ alkyl, j) $-CN$, k) $-NO_2$, l) $-NH_2$, m) $-NHC_{1-6}$ alkyl,
 n) $-N(C_{1-6} \text{ alkyl})_2$, o) $-C(O)C_{1-6}$ alkyl, p) $-C(O)OC_{1-6}$ alkyl, q) $-C(O)NH_2$, r) $-C(O)NHC_{1-6}$ alkyl, s) $-C(O)N(C_{1-6} \text{ alkyl})_2$, t) $-NHC(O)C_{1-6}$ alkyl, and u) $-S(O)_pC_{1-6}$ alkyl;

R^7 , at each occurrence, independently is selected from:

- a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,
- g) $-C(O)C_{1-6}$ alkyl, h) $-C(O)-C_{2-6}$ alkenyl, i) $-C(O)-C_{2-6}$ alkynyl, j) $-C(O)-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, k) $-C(O)-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) $-C(O)O-C_{1-6}$ alkyl,
- m) $-C(O)O-C_{2-6}$ alkenyl, n) $-C(O)O-C_{2-6}$ alkynyl, o) $-C(O)O-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, and p) $-C(O)O-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^8 groups;

R^8 , at each occurrence, is independently selected from:

- a) F, b) Cl, c) Br, d) I, e) =O, f) =S, g) $=NR^9$, h) $=NOR^9$, i) $=N-NR^9R^9$, j) $-CF_3$, k) $-OR^9$, l) $-CN$, m) $-NO_2$, n) $-NR^9R^9$, o) $-C(O)R^9$, p) $-C(O)OR^9$, q) $-OC(O)R^9$, r) $-C(O)NR^9R^9$, s) $-NR^9C(O)R^9$, t) $-OC(O)NR^9R^9$, u) $-NR^9C(O)OR^9$, v) $-NR^9C(O)NR^9R^9$, w) $-C(S)R^9$, x) $-C(S)OR^9$, y) $-OC(S)R^9$, z) $-C(S)NR^9R^9$, aa) $-NR^9C(S)R^9$, bb) $-OC(S)NR^9R^9$, cc) $-NR^9C(S)OR^9$, dd) $-NR^9C(S)NR^9R^9$, ee) $-NR^9C(NR^9)NR^9R^9$, ff) $-S(O)_pR^9$, gg) $-SO_2NR^9R^9$, and hh) R^9 ;

R^9 , at each occurrence, independently is selected from:

- a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,
- g) $-C(O)-C_{1-6}$ alkyl, h) $-C(O)-C_{2-6}$ alkenyl, i) $-C(O)-C_{2-6}$ alkynyl, j) $-C(O)-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle,

k) $-C(O)-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) $-C(O)O-C_{1-6}$ alkyl, m) $-C(O)O-C_{2-6}$ alkenyl, n) $-C(O)O-C_{2-6}$ alkynyl, o) $-C(O)O-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, and p) $-C(O)O-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more moieties selected from:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OH$, g) $-OC_{1-6}$ alkyl, h) $-SH$, i) $-SC_{1-6}$ alkyl, j) $-CN$, k) $-NO_2$, l) $-NH_2$, m) $-NHC_{1-6}$ alkyl, n) $-N(C_{1-6} \text{ alkyl})_2$, o) $-C(O)C_{1-6}$ alkyl, p) $-C(O)OC_{1-6}$ alkyl, q) $-C(O)NH_2$, r) $-C(O)NHC_{1-6}$ alkyl, s) $-C(O)N(C_{1-6} \text{ alkyl})_2$, t) $-NHC(O)C_{1-6}$ alkyl, u) $-SO_2NH_2-$, v) $-SO_2NHC_{1-6}$ alkyl, w) $-SO_2N(C_{1-6} \text{ alkyl})_2$, and x) $-S(O)_pC_{1-6}$ alkyl;

R^{11} is selected from a) $-OH$, and b) F;

R^{12} and R^{13} are independently selected from a) H, b) C_{1-4} alkyl, c) F, d) Cl, e) Br, f) I, g) CF_3 , h) NH_2 , i) CN , and j) N_3 ;

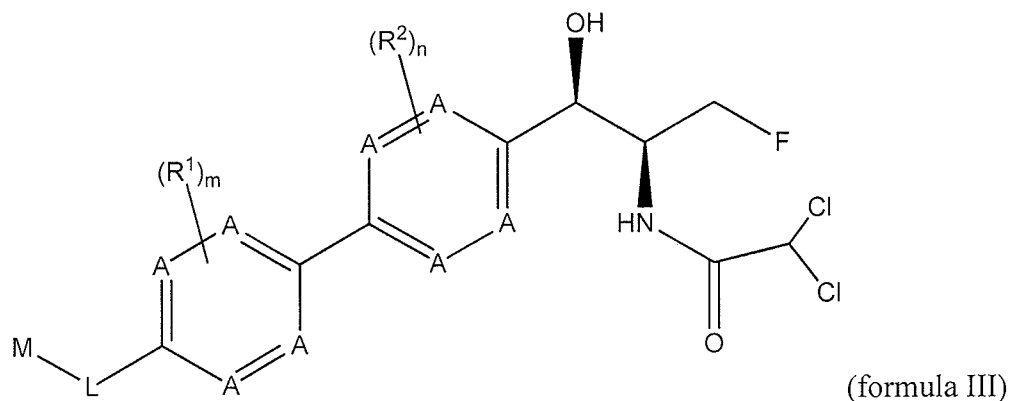
R^{18} is selected from a) H, and b) F,

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

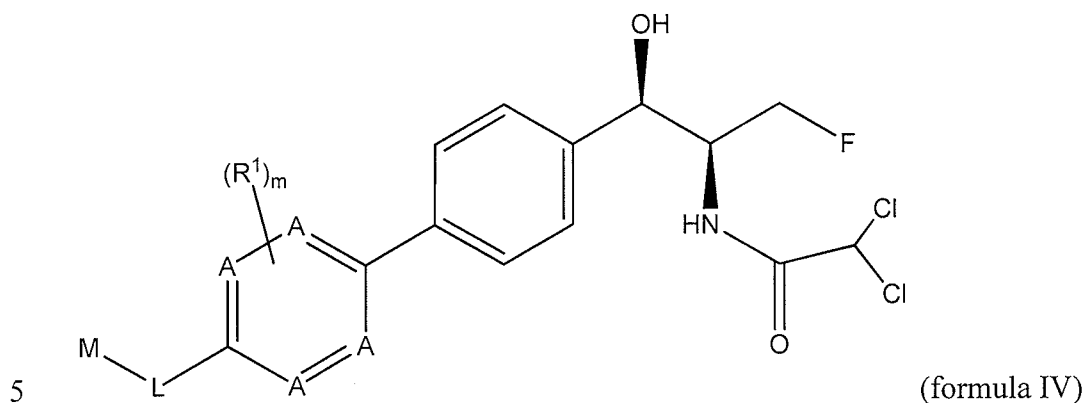
p, at each occurrence, independently is 0, 1, or 2.

In one aspect, the present invention relates to a compound having the formula:



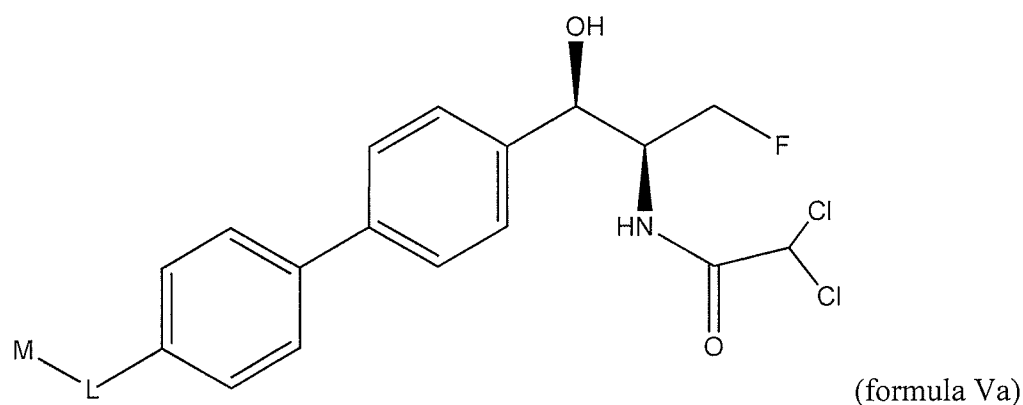
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, M, L, R¹, R², m and n are as defined herein.

In one aspect, the present invention relates to a compound having the formula:



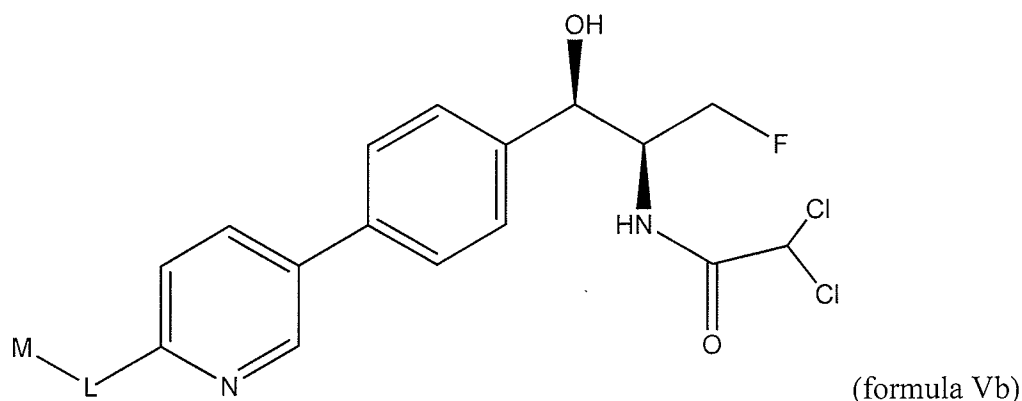
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein A, M, L, R¹, and m are as defined herein.

In one aspect, the present invention relates to a compound having the formula:



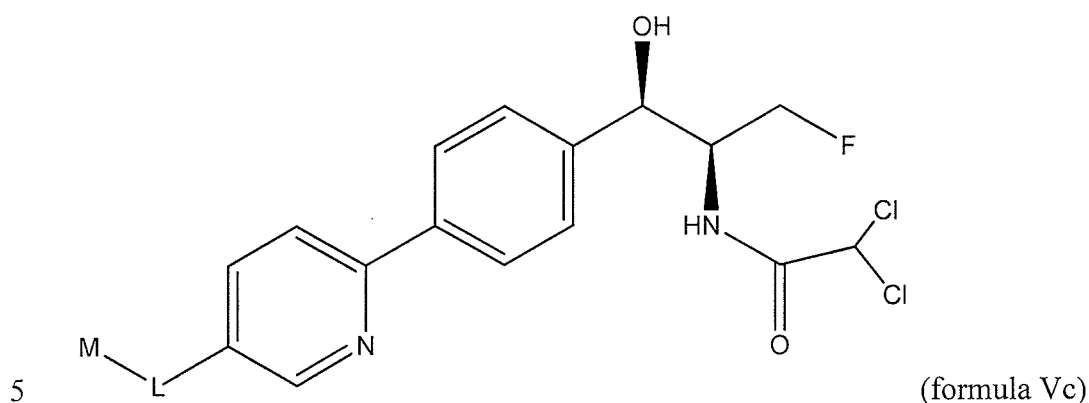
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein M and L are as defined herein.

In one aspect, the present invention relates to a compound having the formula:



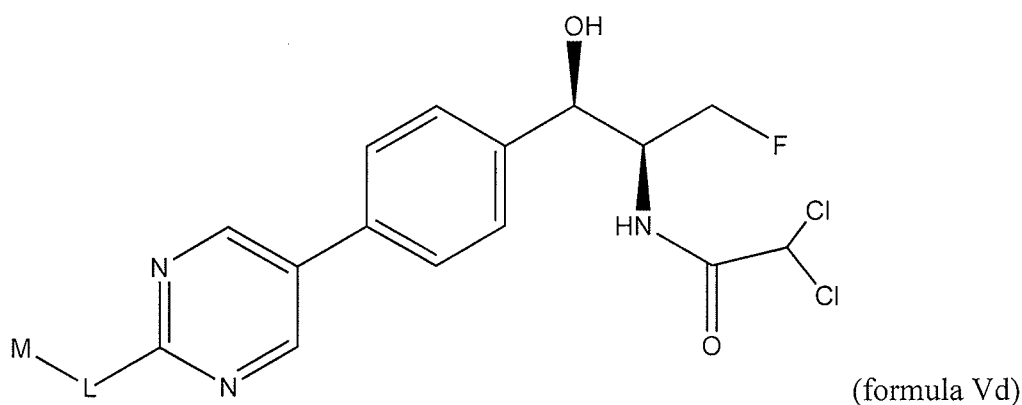
or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein M and L are as defined herein.

In one aspect, the present invention relates to a compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein M and L are as defined herein.

In one aspect, the present invention relates to a compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein M and L are as defined herein.

In one aspect, the present invention relates to a compound of formula I, wherein Z is a 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more

heteroatoms selected from nitrogen, oxygen, and sulfur. In another aspect, Z is a 6-membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur. In another aspect, Z is a 5-membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from
5 nitrogen, oxygen, and sulfur.

In one aspect, the present invention relates to a compound of formulae I, II, III, IV, V, Va, Vb, Vc, or Vd, wherein L in M-L is a bond.

In one aspect, the present invention relates to a compound having a structure corresponding to any one of the compounds listed in Table 1, Table 2, Table 3, Table 4, Table
10 5, Table 6, Table 7, or Table 8, or a pharmaceutically acceptable salt, ester, or prodrug thereof.

In one aspect, the present invention relates to a use of one or more compounds in the manufacture of a medicament for the treatment of a disorder or disease selected from microbial infection, fungal infection, parasitic disease, proliferative disease, viral infection,
15 inflammatory disease, and gastrointestinal motility disorder in a mammal.

In one aspect, the present invention relates to a use of one or more compounds in the manufacture of medicament for the treatment of a disorder, wherein the disorder is selected from:

a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal
20 infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

25 In one aspect, the compound is administered orally, parenterally, or topically.

The compounds of the present invention are useful as pharmaceutical agents, particularly as anti-infective agents and/or as anti-proliferative agents, for treating humans and animals, particularly for treating humans and other mammals. The compounds can be used without limitation, for example, as anti-cancer, anti-microbial, anti-bacterial, anti-
30 fungal, anti-parasitic and/or anti-viral agents. Further, the present invention provides a family of compounds that can be used without limitation as anti-inflammatory agents, for example, for use in treating chronic inflammatory airway diseases, and/or as prokinetic

agents, for example, for use in treating gastrointestinal motility disorders such as gastroesophageal reflux disease, gastroparesis (diabetic and post surgical), irritable bowel syndrome, and constipation. Further, the compounds can be used to treat or prevent a disease state in a mammal caused or mediated by a nonsense or missense mutation.

5 Following synthesis, a therapeutically effective amount of one or more of the compounds can be formulated with a pharmaceutically acceptable carrier for administration to a human or an animal. Accordingly, the compounds or the formulations can be administered, for example, *via* oral, parenteral, or topical routes, to provide an effective amount of the compound. In alternative embodiments, the compounds prepared in
10 accordance with the present invention can be used to coat or impregnate a medical device, e.g., a stent.

 Compounds synthesized according to the methods of the invention can be used to treat a disorder in a mammal, particularly humans, by administering to the mammal an effective amount of one or more compounds of the invention thereby to ameliorate a
15 symptom of a particular disorder. Such a disorder can be selected from a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-
20 resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

1. Definitions

 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable
25 compound. When a substituent is keto (i.e. =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

 The present invention is intended to include all isotopes of atoms occurring in the
30 present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

The compounds described herein can have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom can be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and can be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic, and geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All tautomers of shown or described compounds are also considered to be part of the present invention.

When any variable (e.g., R^1) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^1 moieties, then the group can optionally be substituted with up to two R^1 moieties and R^1 at each occurrence is selected independently from the definition of R^1 . Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent can be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent can be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

When an atom or chemical moiety is followed by a subscripted numeric range (e.g., C_{1-6}), the invention is meant to encompass each number within the range as well as all intermediate ranges. For example, " C_{1-6} alkyl" is meant to include alkyl groups with 1, 2, 3, 4, 5, 6, 1-6, 1-5, 1-4, 1-3, 1-2, 2-6, 2-5, 2-4, 2-3, 3-6, 3-5, 3-4, 4-6, 4-5, and 5-6 carbons.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_{1-6} alkyl is intended to include C_1 , C_2 , C_3 , C_4 , C_5 , and C_6 alkyl groups. Examples

of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl, and n-hexyl.

As used herein, "alkenyl" is intended to include hydrocarbon chains of either straight or branched configuration having one or more carbon-carbon double bonds occurring at any stable point along the chain. For example, C₂₋₆ alkenyl is intended to include C₂, C₃, C₄, C₅, and C₆ alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

As used herein, "alkynyl" is intended to include hydrocarbon chains of either straight or branched configuration having one or more carbon-carbon triple bonds occurring at any stable point along the chain. For example, C₂₋₆ alkynyl is intended to include C₂, C₃, C₄, C₅, and C₆ alkynyl groups. Examples of alkynyl include, but are not limited to, ethynyl and propynyl.

As used herein, "halo" or "halogen" refers to fluoro, chloro, bromo, and iodo.

"Counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

As used herein, "carbocycle" or "carbocyclic ring" is intended to mean any stable monocyclic, bicyclic, or tricyclic ring having the specified number of carbons, any of which can be saturated, unsaturated, or aromatic. For example a C₃₋₁₄ carbocycle is intended to mean a mono-, bi-, or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, and [2.2.2]bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring can also be present on the bridge. Fused (e.g., naphthyl and tetrahydronaphthyl) and spiro rings are also included.

As used herein, the term "heterocycle" or "heterocyclic" is intended to mean any stable monocyclic, bicyclic, or tricyclic ring which is saturated, unsaturated, or aromatic and

comprises carbon atoms and one or more ring heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. A bicyclic or tricyclic heterocycle can have one or more heteroatoms located in one ring, or the heteroatoms can be located in more than one ring. The nitrogen and sulfur heteroatoms can optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). When a nitrogen atom is included in the ring it is either N or NH, depending on whether or not it is attached to a double bond in the ring (i.e., a hydrogen is present if needed to maintain the tri-valency of the nitrogen atom). The nitrogen atom can be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle can optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more atoms (i.e., C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Bridges include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring can also be present on the bridge. Spiro and fused rings are also included.

As used herein, the term "aromatic heterocycle" or "heteroaryl" is intended to mean a stable 5, 6, or 7-membered monocyclic or bicyclic aromatic heterocyclic ring or 7, 8, 9, 10, 11, or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, e.g., 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. In the case of bicyclic heterocyclic aromatic rings, only one of the two rings needs to be aromatic (e.g., 2,3-dihydroindole), though both can be (e.g., quinoline). The second ring can also be fused or bridged as defined above for heterocycles. The nitrogen atom can be substituted or unsubstituted (i.e., N or NR wherein R is H or another substituent, as defined). The nitrogen and sulfur heteroatoms can optionally be oxidized (i.e., $N \rightarrow O$ and $S(O)_p$, where $p = 1$ or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxindolyl, pyrimidinyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, piperidonyl, 4-piperidonyl, piperonyl, pteridiny, puriny, pyranyl, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2*H*-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4*H*-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6*H*-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

As used herein, the term "amine protecting group" is intended to mean a functional group that converts an amine, amide, or other nitrogen-containing moiety into a different chemical group that is substantially inert to the conditions of a particular chemical reaction. Amine protecting groups are preferably removed easily and selectively in good yield under conditions that do not affect other functional groups of the molecule. Examples of amine protecting groups include, but are not limited to, benzyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, *t*-butyloxycarbonyl, *p*-methoxybenzyl, methoxymethyl, tosyl, trifluoroacetyl, trimethylsilyl, fluorenyl-methyloxycarbonyl, 2-trimethylsilyl-ethyloxycarbonyl, 1-methyl-1-(4-biphenyl) ethyloxycarbonyl, allyloxycarbonyl, and benzyloxycarbonyl. Other suitable amine protecting groups are straightforwardly identified by those of skill in the art, e.g., by reference to Green & Wuts, *Protective Groups in Organic Synthesis*, 3d Ed. (1999, John Wiley & Sons, Inc.).

“Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

As used herein, the phrase “pharmaceutically acceptable” refers to those compounds,
5 materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, “pharmaceutically acceptable salts” refer to derivatives of the
10 disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound
15 formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic,
20 hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, and toluene sulfonic.

25 The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl
30 acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990). For example, salts can include, but are not limited to, the hydrochloride and acetate salts of the

aliphatic amine-containing, hydroxyl amine-containing, and imine-containing compounds of the present invention. A nonlimiting example of a salt of a compound of the present invention is the monohydrochloride salt of compound 7. This salt is exemplified in the Examples.

5 Additionally, the compounds of the present invention, and particularly the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

10 Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers that
15 release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is
20 bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

25 "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

 As used herein, "treating" or "treatment" means the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from
30 occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting its

development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

As used herein, "mammal" refers to human and non-human patients.

As used herein, the term "effective amount" refers to an amount of a compound, or a combination of compounds, of the present invention effective when administered alone or in
5 combination as an anti-proliferative and/or anti-infective agent. In particular, an effective amount refers to an amount of the compound present in or on a recipient sufficient to elicit biological activity, for example, anti-infective activity (e.g., anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity) and/or anti-proliferative activity.

10 The combination of compounds optionally is a synergistic combination. Synergy, as described, for example, by Chou and Talalay, *Adv. Enzyme Regul.* vol. 22, pp. 27-55 (1984), occurs when the effect of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at sub-optimal concentrations of the
15 compounds. Synergy can be in terms of lower cytotoxicity, increased anti-proliferative and/or anti-infective effect, or some other beneficial effect of the combination compared with the individual components.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

Throughout the description, where compositions are described as having, including,
20 or comprising specific components, it is contemplated that compositions also consist essentially of, or consist of, the recited components. Similarly, where processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the
25 invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

All percentages and ratios used herein, unless otherwise indicated, are by weight.

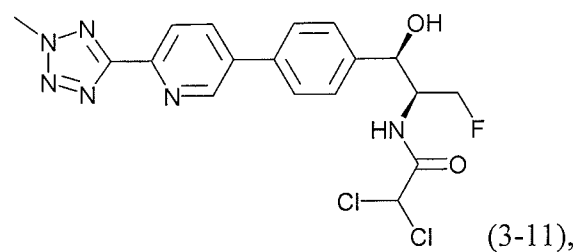
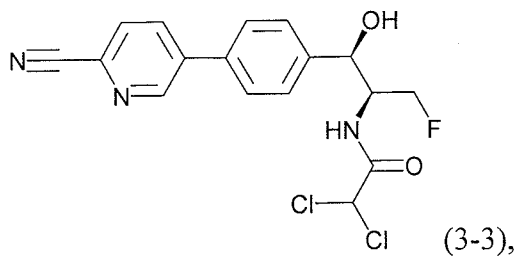
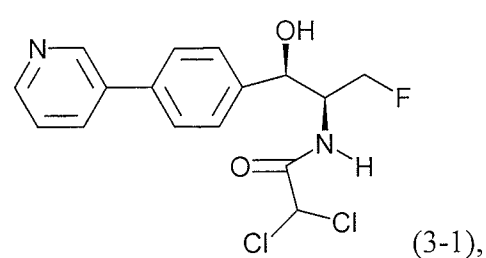
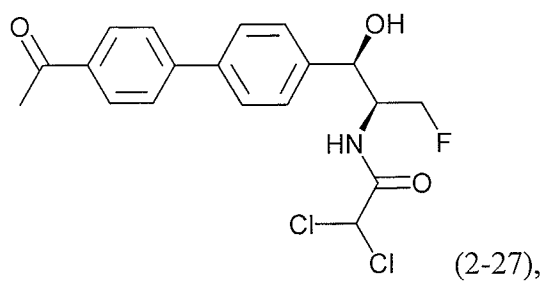
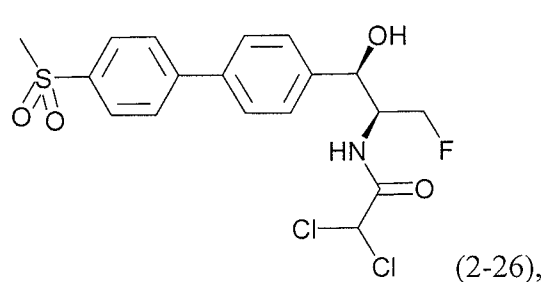
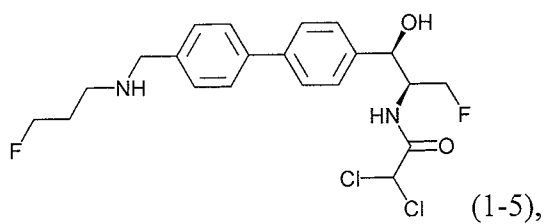
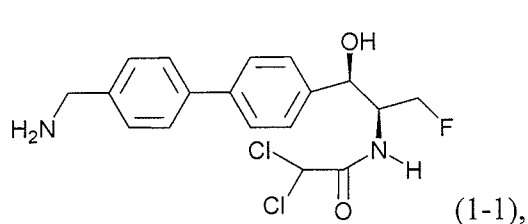
Throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also consist
30 essentially of, or consist of, the recited components. Similarly, where processes are described as having, including, or comprising specific process steps, the processes also consist

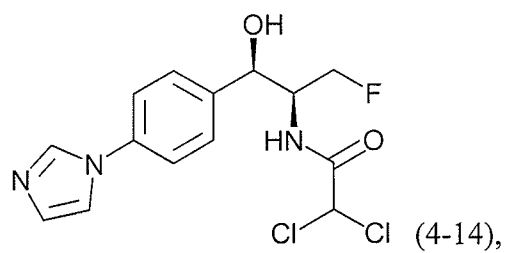
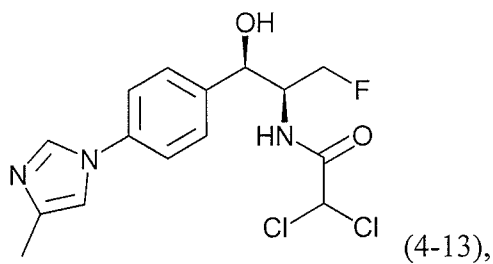
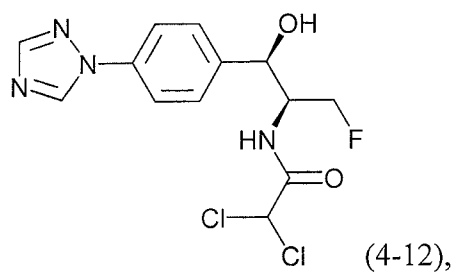
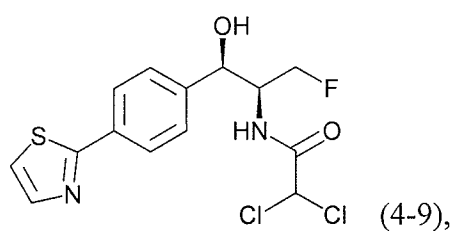
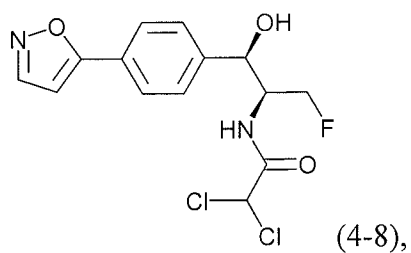
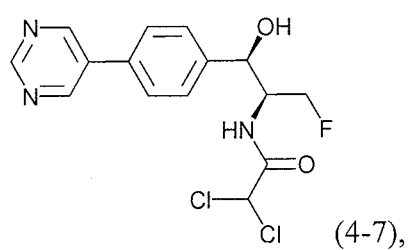
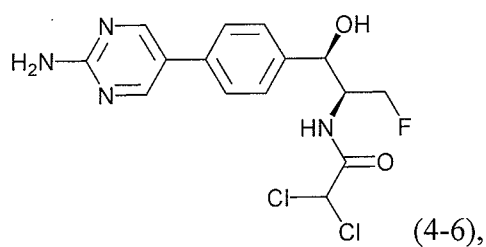
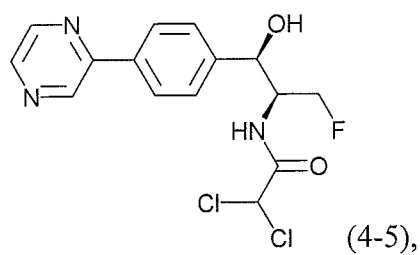
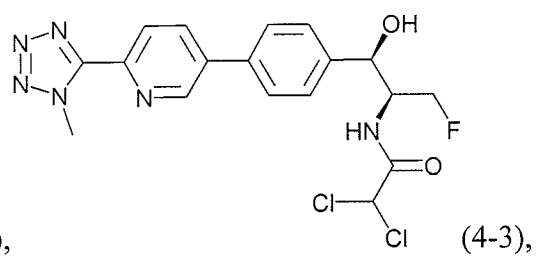
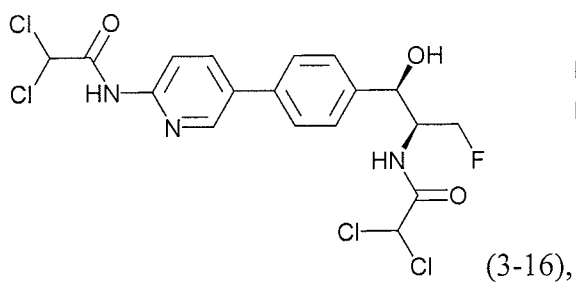
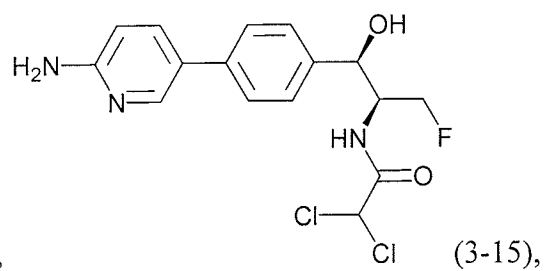
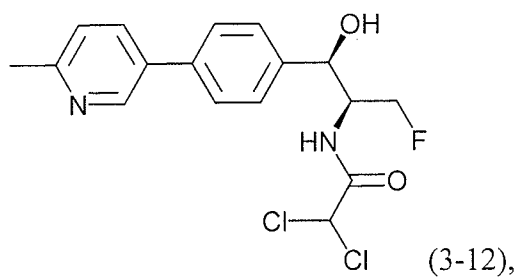
essentially of, or consist of, the recited processing steps. Further, the process steps are numbered for convenience in a claim or group of dependent claims. Moreover, two or more steps or actions can be conducted simultaneously.

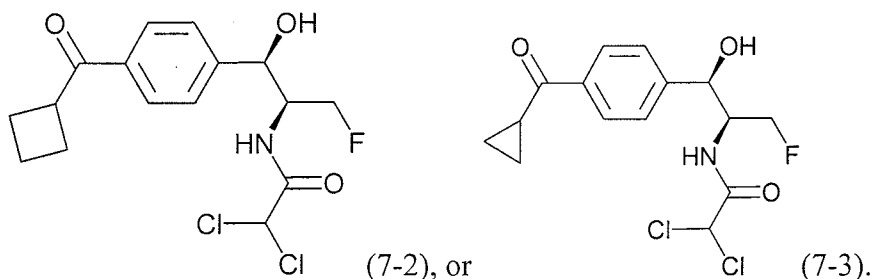
2. Compounds

5 In another aspect, the invention provides a pharmaceutically acceptable salt, ester, or prodrug of a compound listed in Tables 1 to 8 below.

In another aspect, the invention is not the compound:







In another aspect, the invention does include pharmaceutically acceptable salts, esters, or prodrugs of the compounds listed directly above (1-1, 1-5, 2-26, 2-27, 3-1, 3-3, 3-11, 3-12, 3-15, 3-16, 4-3, 4-5, 4-6, 4-7, 4-8, 4-9, 4-12, 4-13, 4-14, 7-2, or 7-3).

5 The invention further provides methods for synthesizing any one of the foregoing compounds, including pharmaceutically acceptable salts, esters, or prodrugs of these compounds.

Yet another aspect of the invention provides a pharmaceutical composition comprising an effective amount of one or more of the foregoing compounds and a pharmaceutically
10 acceptable carrier.

One or more of the foregoing compounds can also be incorporated into a medical device. For example, a medical device, such as a medical stent, can contain or be coated with one or more of the compounds of the invention.

In still another aspect, the invention provides a method for treating a microbial
15 infection, a fungal infection, a viral infection, a parasitic disease, a proliferative disease, an inflammatory disease, or a gastrointestinal motility disorder in a mammal. The method involves administering an effective amount of one or more compounds or pharmaceutical compositions of the invention, for example, via oral, parenteral or topical routes.

In another aspect, the invention is not a method for treating respiratory tract infections
20 (RTI). In another aspect, the invention is a method for treating a microbial infections wherein the bacterial strain is not *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenza* and *MRSA*.

In addition, the present invention provides the use of a compound according to the
25 present invention in the manufacture of a medicament useful for the methods of the present invention.

The invention provides a method of treating a disorder in a mammal comprising the step of administering to the mammal an effective amount of one or more compounds of the invention thereby to ameliorate a symptom of a particular disorder. Such a disorder can be selected from a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal
5 infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

10 3. Characterization of Compounds of the Invention

Compounds designed, selected and/or optimized by methods described above, after being produced, can be characterized using a variety of assays known to those skilled in the art to determine whether the compounds have biological activity. For example, the compounds can be characterized by conventional assays, including but not limited to those
15 assays described below, to determine whether the compounds have a predicted activity, binding activity and/or binding specificity.

Furthermore, high-throughput screening can be used to speed up analysis using such assays. As a result, it can be possible to screen rapidly the molecules described herein for activity, for example, as anti-cancer, anti-bacterial, anti-fungal, anti-parasitic or anti-viral
20 agents. Also, it can be possible to assay how the compounds interact with a ribosome or ribosomal subunit and/or are effective as modulators (for example, inhibitors) of protein synthesis using techniques known in the art. General methodologies for performing high-throughput screening are described, for example, in Devlin, *High Throughput Screening*, (Marcel Dekker, 1998); and U.S. Patent No. 5,763,263. High-throughput assays can use one
25 or more different assay techniques including, but not limited to, those described below.

(1) *Surface Binding Studies*. A variety of binding assays can be useful in screening new molecules for their binding activity. One approach includes surface plasmon resonance (SPR) that can be used to evaluate the binding properties of molecules of interest with respect to a ribosome, ribosomal subunit or a fragment thereof.

30 SPR methodologies measure the interaction between two or more macromolecules in real-time through the generation of a quantum-mechanical surface plasmon. One device, (BIAcore Biosensor RTM from Pharmacia Biosensor, Piscatawy, N.J.) provides a focused

beam of polychromatic light to the interface between a gold film (provided as a disposable biosensor "chip") and a buffer compartment that can be regulated by the user. A 100 nm thick "hydrogel" composed of carboxylated dextran that provides a matrix for the covalent immobilization of analytes of interest is attached to the gold film. When the focused light interacts with the free electron cloud of the gold film, plasmon resonance is enhanced. The resulting reflected light is spectrally depleted in wavelengths that optimally evolved the resonance. By separating the reflected polychromatic light into its component wavelengths (by means of a prism), and determining the frequencies that are depleted, the BIAcore establishes an optical interface which accurately reports the behavior of the generated surface plasmon resonance. When designed as above, the plasmon resonance (and thus the depletion spectrum) is sensitive to mass in the evanescent field (which corresponds roughly to the thickness of the hydrogel). If one component of an interacting pair is immobilized to the hydrogel, and the interacting partner is provided through the buffer compartment, the interaction between the two components can be measured in real time based on the accumulation of mass in the evanescent field and its corresponding effects of the plasmon resonance as measured by the depletion spectrum. This system permits rapid and sensitive real-time measurement of the molecular interactions without the need to label either component.

(2) *Fluorescence Polarization*. Fluorescence polarization (FP) is a measurement technique that can readily be applied to protein-protein, protein-ligand, or RNA-ligand interactions in order to derive IC_{50} s and K_d s of the association reaction between two molecules. In this technique one of the molecules of interest is conjugated with a fluorophore. This is generally the smaller molecule in the system (in this case, the compound of interest). The sample mixture, containing both the ligand-probe conjugate and the ribosome, ribosomal subunit or fragment thereof, is excited with vertically polarized light. Light is absorbed by the probe fluorophores, and re-emitted a short time later. The degree of polarization of the emitted light is measured. Polarization of the emitted light is dependent on several factors, but most importantly on viscosity of the solution and on the apparent molecular weight of the fluorophore. With proper controls, changes in the degree of polarization of the emitted light depends only on changes in the apparent molecular weight of the fluorophore, which in-turn depends on whether the probe-ligand conjugate is free in solution, or is bound to a receptor. Binding assays based on FP have a number of important advantages, including the measurement of IC_{50} s and K_d s under true homogenous equilibrium

conditions, speed of analysis and amenity to automation, and ability to screen in cloudy suspensions and colored solutions.

(3) *Protein Synthesis*. It is contemplated that, in addition to characterization by the foregoing biochemical assays, the compound of interest can also be characterized as a modulator (for example, an inhibitor of protein synthesis) of the functional activity of the ribosome or ribosomal subunit.

Furthermore, more specific protein synthesis inhibition assays can be performed by administering the compound to a whole organism, tissue, organ, organelle, cell, a cellular or subcellular extract, or a purified ribosome preparation and observing its pharmacological and inhibitory properties by determining, for example, its inhibition constant (IC_{50}) for inhibiting protein synthesis. Incorporation of 3H leucine or ^{35}S methionine, or similar experiments can be performed to investigate protein synthesis activity. A change in the amount or the rate of protein synthesis in the cell in the presence of a molecule of interest indicates that the molecule is a modulator of protein synthesis. A decrease in the rate or the amount of protein synthesis indicates that the molecule is an inhibitor of protein synthesis.

Furthermore, the compounds can be assayed for anti-proliferative or anti-infective properties on a cellular level. For example, where the target organism is a microorganism, the activity of compounds of interest can be assayed by growing the microorganisms of interest in media either containing or lacking the compound. Growth inhibition can be indicative that the molecule could be acting as a protein synthesis inhibitor. More specifically, the activity of the compounds of interest against bacterial pathogens can be demonstrated by the ability of the compound to inhibit growth of defined strains of human pathogens. For this purpose, a panel of bacterial strains can be assembled to include a variety of target pathogenic species, some containing resistance mechanisms that have been characterized. Use of such a panel of organisms permits the determination of structure-activity relationships not only in regards to potency and spectrum, but also with a view to obviating resistance mechanisms. The assays can be performed in microtiter trays according to conventional methodologies as published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS. M7-A5-Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Fifth Edition. NCCLS Document M100-S12/M7 (ISBN 1-56238-394-9)).

4. Formulation and Administration

The compounds of the invention can be useful in the prevention or treatment of a variety of human or other animal disorders, including for example, bacterial infection, fungal infections, viral infections, parasitic diseases, and cancer. It is contemplated that, once
5 identified, the active molecules of the invention can be incorporated into any suitable carrier prior to use. The dose of active molecule, mode of administration and use of suitable carrier will depend upon the intended recipient and target organism. The formulations, both for veterinary and for human medical use, of compounds according to the present invention typically include such compounds in association with a pharmaceutically acceptable carrier.

10 The carrier(s) should be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient. Pharmaceutically acceptable carriers, in this regard, are intended to include any and all solvents, dispersion media, coatings, anti-bacterial and anti-fungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media
15 and agents for pharmaceutically active substances is known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds (identified or designed according to the invention and/or known in the art) also can be incorporated into the compositions. The formulations can conveniently be presented in dosage unit form and can
20 be prepared by any of the methods well known in the art of pharmacy/microbiology. In general, some formulations are prepared by bringing the compound into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

A pharmaceutical composition of the invention should be formulated to be compatible
25 with its intended route of administration. Examples of routes of administration include oral or parenteral, for example, intravenous, intradermal, inhalation, transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine,
30 propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents

for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

Useful solutions for oral or parenteral administration can be prepared by any of the methods well known in the pharmaceutical art, described, for example, in *Remington's Pharmaceutical Sciences*, 18th ed. (Mack Publishing Company, 1990). Formulations for parenteral administration can also include glycocholate for buccal administration, methoxysalicylate for rectal administration, or citric acid for vaginal administration. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Suppositories for rectal administration also can be prepared by mixing the drug with a non-irritating excipient such as cocoa butter, other glycerides, or other compositions which are solid at room temperature and liquid at body temperatures. Formulations also can include, for example, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, and hydrogenated naphthalenes. Formulations for direct administration can include glycerol and other compositions of high viscosity. Other potentially useful parenteral carriers for these drugs include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation administration can contain as excipients, for example, lactose, or can be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or oily solutions for administration in the form of nasal drops, or as a gel to be applied intranasally. Retention enemas also can be used for rectal delivery.

Formulations of the present invention suitable for oral administration can be in the form of: discrete units such as capsules, gelatin capsules, sachets, tablets, troches, or lozenges, each containing a predetermined amount of the drug; a powder or granular composition; a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water emulsion or a water-in-oil emulsion. The drug can also be administered in the form of a bolus, electuary or paste. A tablet can be made by compressing or molding the drug optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the drug in a free-flowing form such as a powder or granules, optionally mixed by a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets can be made by molding, in a suitable machine, a mixture of the powdered drug and suitable carrier moistened with an inert liquid diluent.

Oral compositions generally include an inert diluent or an edible carrier. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients. Oral compositions prepared using a fluid carrier for use as a mouthwash include the compound in the fluid carrier and are applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose; a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). It should be stable under the conditions of manufacture and storage and should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filter sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the

case of sterile powders for the preparation of sterile injectable solutions, methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

5 Formulations suitable for intra-articular administration can be in the form of a sterile aqueous preparation of the drug that can be in microcrystalline form, for example, in the form of an aqueous microcrystalline suspension. Liposomal formulations or biodegradable polymer systems can also be used to present the drug for both intra-articular and ophthalmic administration.

10 Formulations suitable for topical administration, including eye treatment, include liquid or semi-liquid preparations such as liniments, lotions, gels, applicants, oil-in-water or water-in-oil emulsions such as creams, ointments or pastes; or solutions or suspensions such as drops. Formulations for topical administration to the skin surface can be prepared by dispersing the drug with a dermatologically acceptable carrier such as a lotion, cream,
15 ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the agent can be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions can be used to advantage. Alternatively, tissue-coating
20 solutions, such as pectin-containing formulations can be used.

 For inhalation treatments, inhalation of powder (self-propelling or spray formulations) dispensed with a spray can, a nebulizer, or an atomizer can be used. Such formulations can be in the form of a fine powder for pulmonary administration from a powder inhalation device or self-propelling powder-dispensing formulations. In the case of self-propelling
25 solution and spray formulations, the effect can be achieved either by choice of a valve having the desired spray characteristics (i.e., being capable of producing a spray having the desired particle size) or by incorporating the active ingredient as a suspended powder in controlled particle size. For administration by inhalation, the compounds also can be delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable
30 propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

 Systemic administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be

permeated are used in the formulation. Such penetrants generally are known in the art, and include, for example, for transmucosal administration, detergents and bile salts.

Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds typically are formulated
5 into ointments, salves, gels, or creams as generally known in the art.

The active compounds can be prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen,
10 polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. Liposomal suspensions can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

Oral or parenteral compositions can be formulated in dosage unit form for ease of
15 administration and uniformity of dosage. Dosage unit form refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of
20 the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals. Furthermore, administration can be by periodic injections of a bolus, or can be made more continuous by intravenous, intramuscular or intraperitoneal administration from an external reservoir (e.g., an intravenous bag).

Where adhesion to a tissue surface is desired the composition can include the drug
25 dispersed in a fibrinogen-thrombin composition or other bioadhesive. The compound then can be painted, sprayed or otherwise applied to the desired tissue surface. Alternatively, the drugs can be formulated for parenteral or oral administration to humans or other mammals, for example, in effective amounts, e.g., amounts that provide appropriate concentrations of
30 the drug to target tissue for a time sufficient to induce the desired effect.

Where the active compound is to be used as part of a transplant procedure, it can be provided to the living tissue or organ to be transplanted prior to removal of tissue or organ

from the donor. The compound can be provided to the donor host. Alternatively or, in addition, once removed from the donor, the organ or living tissue can be placed in a preservation solution containing the active compound. In all cases, the active compound can be administered directly to the desired tissue, as by injection to the tissue, or it can be provided systemically, either by oral or parenteral administration, using any of the methods and formulations described herein and/or known in the art. Where the drug comprises part of a tissue or organ preservation solution, any commercially available preservation solution can be used to advantage. For example, useful solutions known in the art include Collins solution, Wisconsin solution, Belzer solution, Eurocollins solution and lactated Ringer's solution.

The compounds of the present invention can be administered directly to a tissue locus by applying the compound to a medical device that is placed in contact with the tissue. An example of a medical device is a stent, which contains or is coated with one or more of the compounds of the present invention.

For example, an active compound can be applied to a stent at the site of vascular injury. Stents can be prepared by any of the methods well known in the pharmaceutical art. See, e.g., Fattori, R. and Piva, T., "Drug Eluting Stents in Vascular Intervention," *Lancet*, 2003, 361, 247-249; Morice, M. C., "A New Era in the Treatment of Coronary Disease?" *European Heart Journal*, 2003, 24, 209-211; and Toutouzas, K. et al., "Sirolimus-Eluting Stents: A Review of Experimental and Clinical Findings," *Z. Kardiol.*, 2002, 91(3), 49-57. The stent can be fabricated from stainless steel or another bio-compatible metal, or it can be made of a bio-compatible polymer. The active compound can be linked to the stent surface, embedded and released from polymer materials coated on the stent, or surrounded by and released through a carrier which coats or spans the stent. The stent can be used to administer single or multiple active compounds to tissues adjacent to the stent.

Active compound as identified or designed by the methods described herein can be administered to individuals to treat disorders (prophylactically or therapeutically). In conjunction with such treatment, pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) can be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician can consider applying knowledge obtained in relevant pharmacogenomics studies in determining whether to

administer a drug as well as tailoring the dosage and/or therapeutic regimen of treatment with the drug.

In therapeutic use for treating, or combating, bacterial infections in mammals, the compounds or pharmaceutical compositions thereof will be administered orally, parenterally and/or topically at a dosage to obtain and maintain a concentration, that is, an amount, or blood-level or tissue level of active component in the animal undergoing treatment which will be anti-microbially effective. The term "effective amount" is understood to mean that the compound of the invention is present in or on the recipient in an amount sufficient to elicit biological activity, for example, anti-microbial activity, anti-fungal activity, anti-viral activity, anti-parasitic activity, and/or anti-proliferative activity. Generally, an effective amount of dosage of active component will be in the range of from about 0.1 to about 100, more preferably from about 1.0 to about 50 mg/kg of body weight/day. The amount administered will also likely depend on such variables as the type and extent of disease or indication to be treated, the overall health status of the particular patient, the relative biological efficacy of the compound delivered, the formulation of the drug, the presence and types of excipients in the formulation, and the route of administration. Also, it is to be understood that the initial dosage administered can be increased beyond the above upper level in order to rapidly achieve the desired blood-level or tissue level, or the initial dosage can be smaller than the optimum and the daily dosage can be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose can also be divided into multiple doses for administration, for example, two to four times per day.

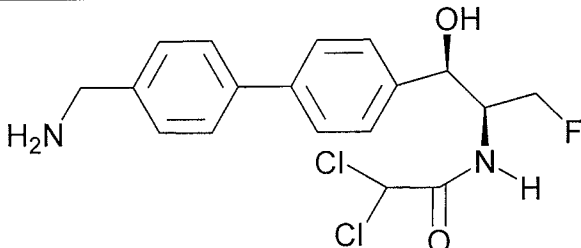
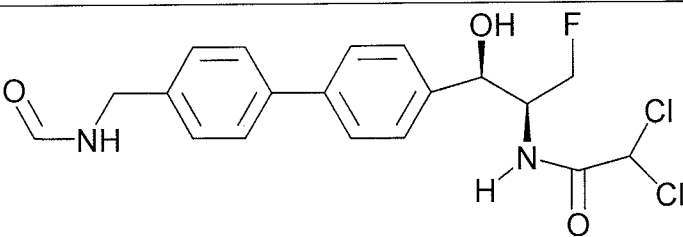
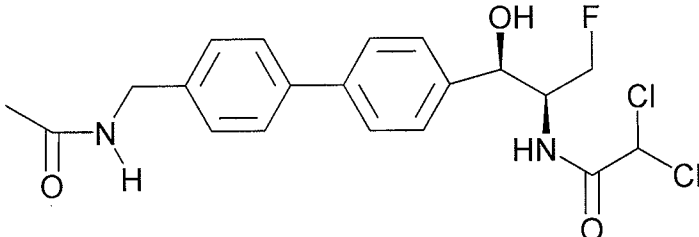
5. Examples

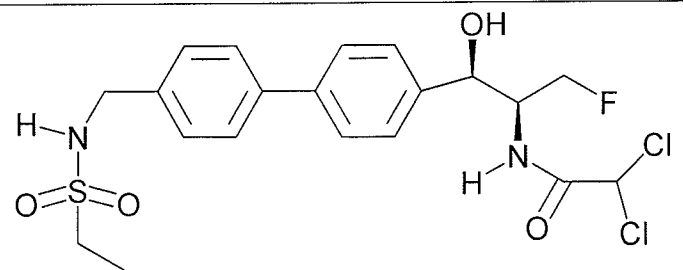
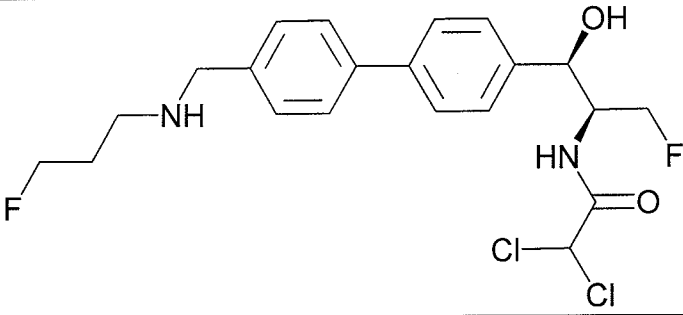
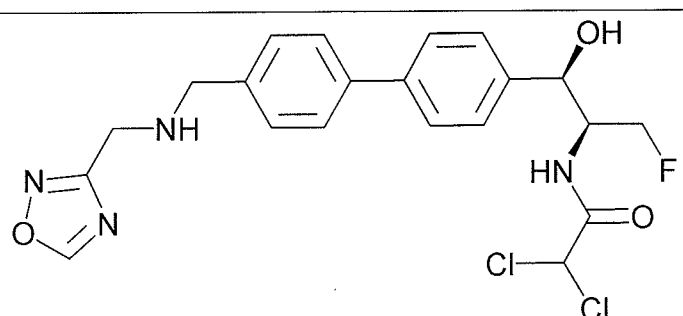
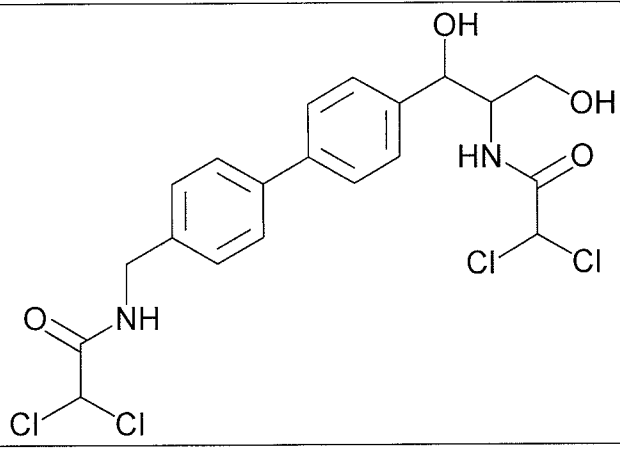
In the following examples, nuclear magnetic resonance (NMR) spectra are obtained on a Bruker Avance 300 or Avance 500 spectrometer, or in some cases a GE-Nicolet 300 spectrometer. Common reaction solvents are either high performance liquid chromatography (HPLC) grade or American Chemical Society (ACS) grade, and anhydrous as obtained from the manufacturer unless otherwise noted. "Chromatography" or "purified by silica gel" refers to flash column chromatography using silica gel (EM Merck, Silica Gel 60, 230-400 mesh) unless otherwise noted.

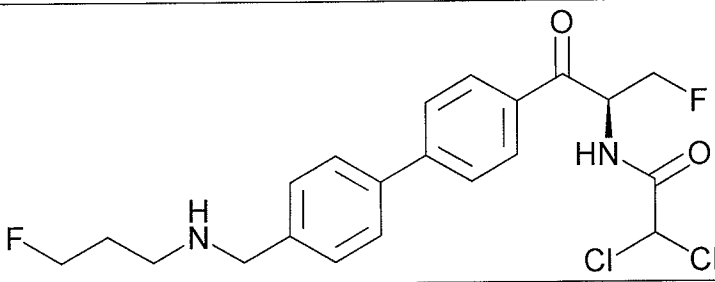
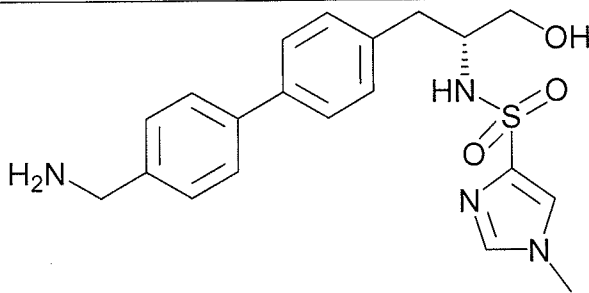
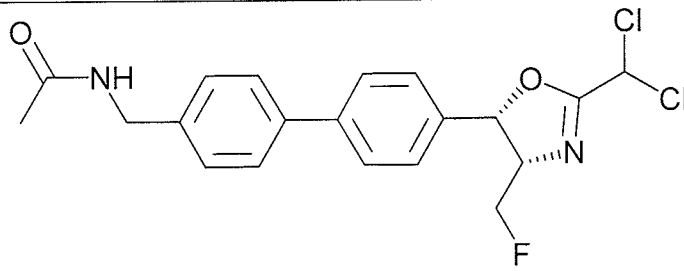
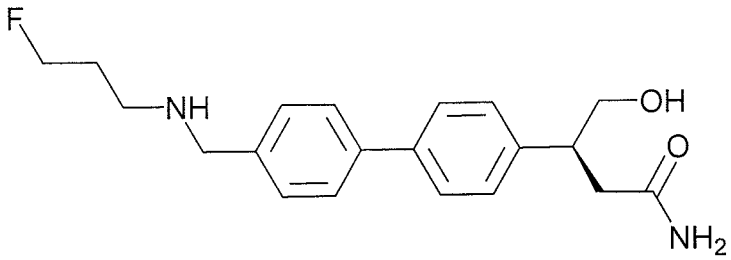
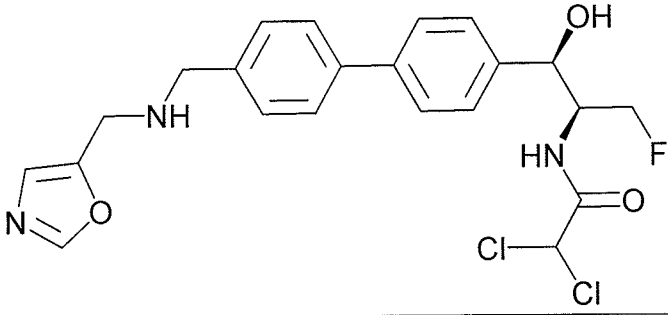
Exemplary compounds synthesized in accordance with the invention are listed in Tables 1 through 8. A bolded or dashed bond is shown to indicate a particular

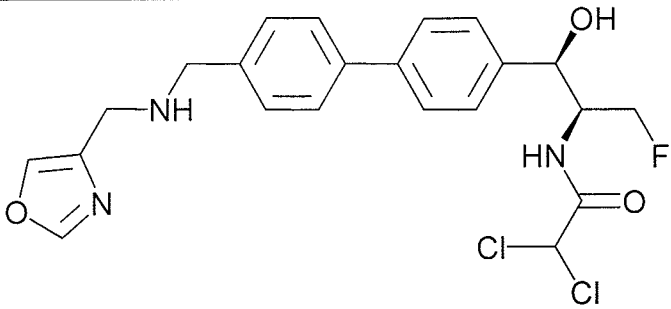
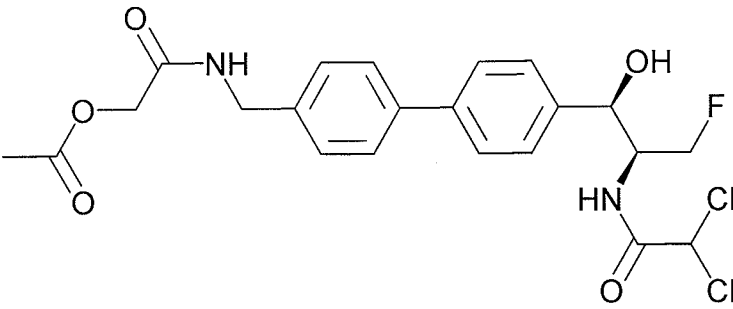
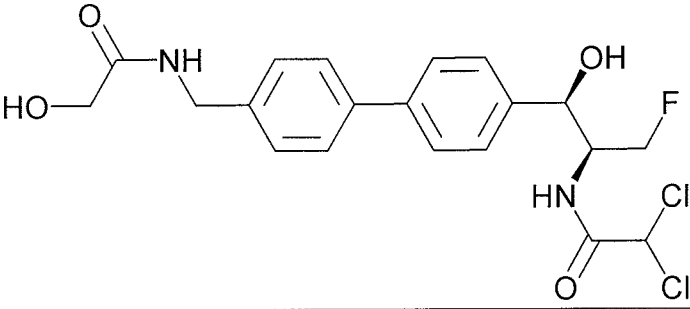
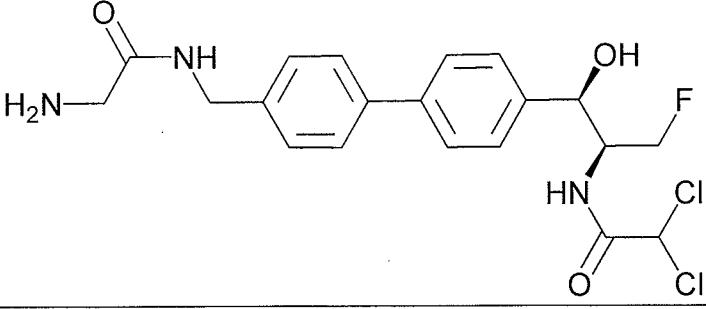
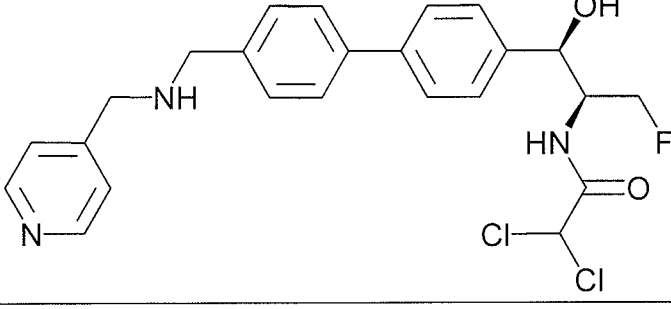
stereochemistry at a chiral center, whereas a wavy bond indicates that the substituent can be in either orientation or that the compound is a mixture thereof.

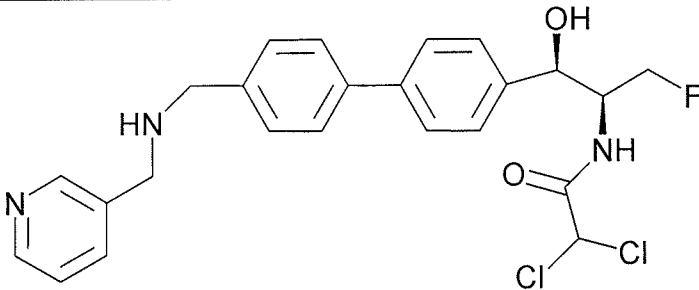
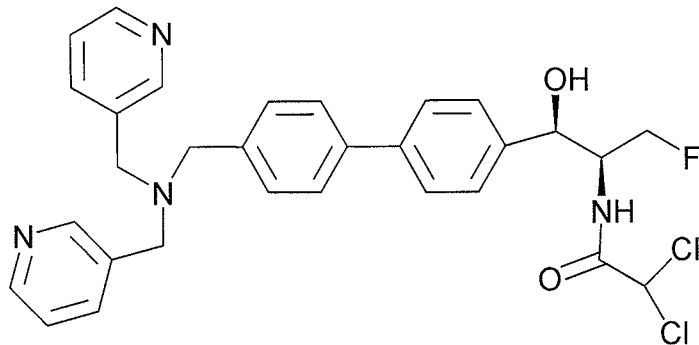
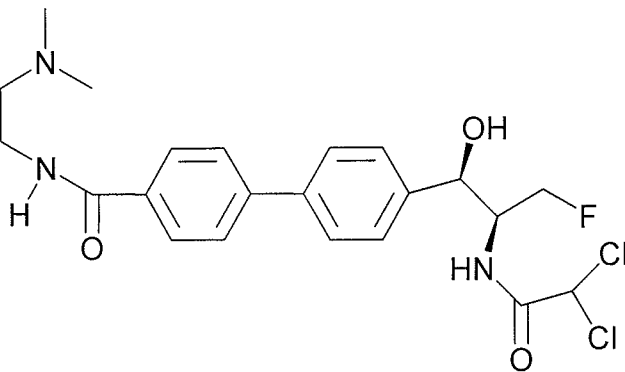
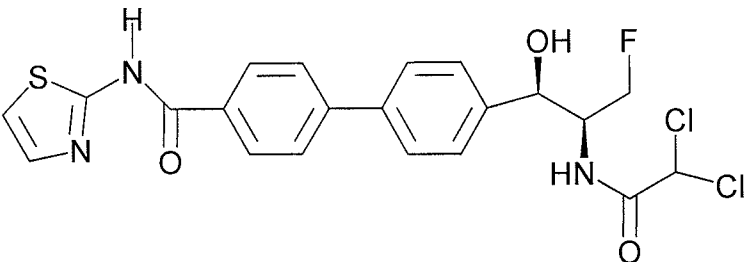
The compounds of the present invention can be prepared, formulated, and delivered as salts, esters, and prodrugs. For convenience, the compounds are generally shown without
5 indicating a particular salt, ester, or prodrug form.

Table 1	
Compound Number	Structure
1-1	 <chem>NCC1=CC=C(C=C1)-C2=CC=C(C=C2)C3(O)C(C(=O)C(Cl)(Cl)C(=O)N3CCF)</chem>
1-2	 <chem>O=CNC1=CC=C(C=C1)-C2=CC=C(C=C2)C3(O)C(C(=O)C(Cl)(Cl)C(=O)N3CCF)</chem>
1-3	 <chem>CC(=O)NC1=CC=C(C=C1)-C2=CC=C(C=C2)C3(O)C(C(=O)C(Cl)(Cl)C(=O)N3CCF)</chem>

1-4	
1-5	
1-6	
1-7	

1-8	
1-9	
1-10	
1-11	
1-12	

1-13	
1-14	
1-15	
1-16	
1-17	

1-18	
1-19	
1-20	
1-21	

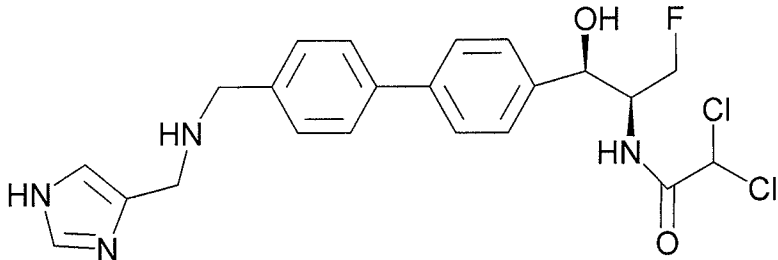
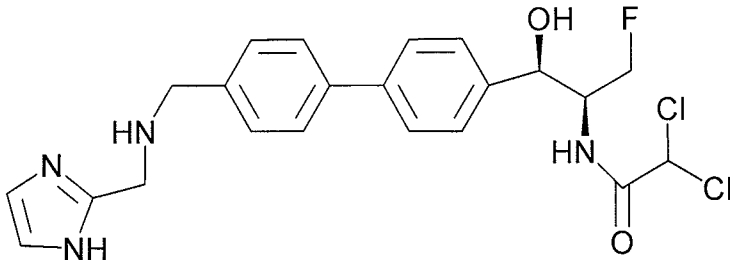
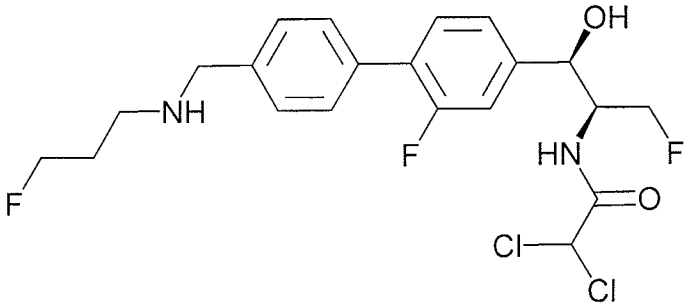
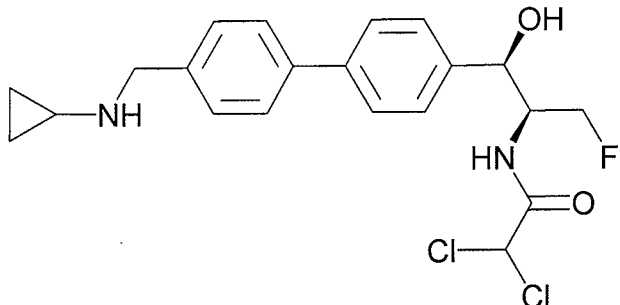
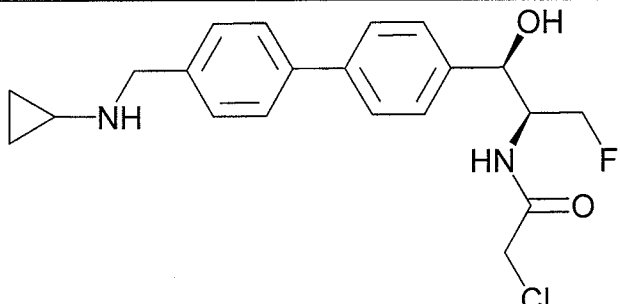
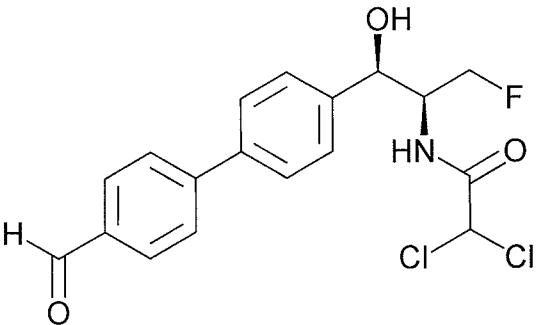
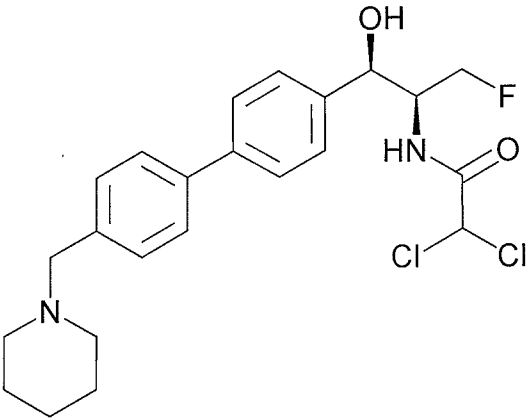
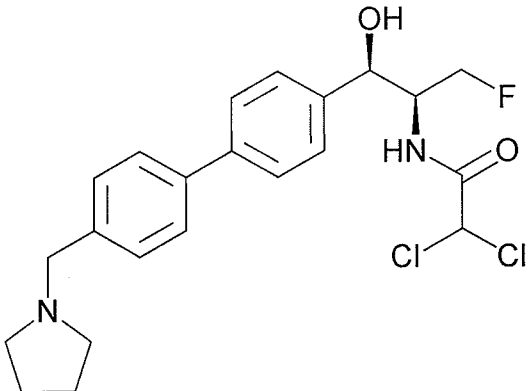
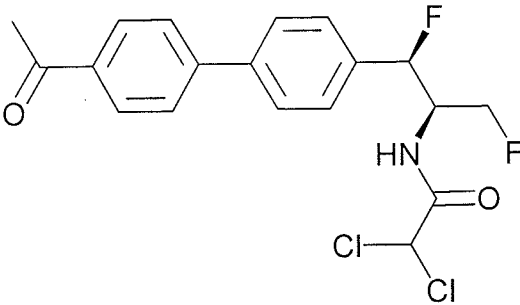
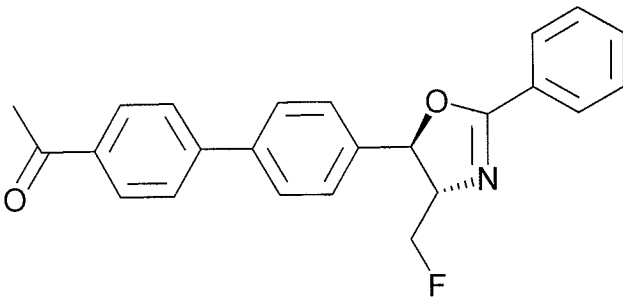
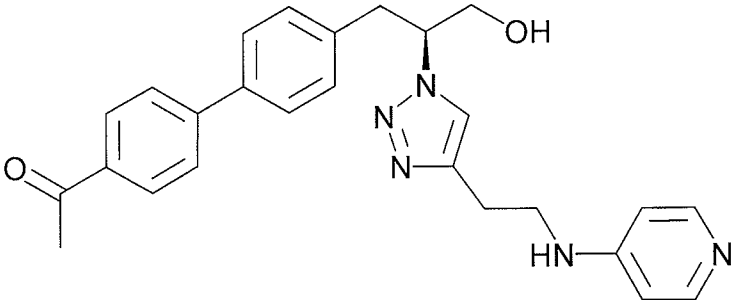
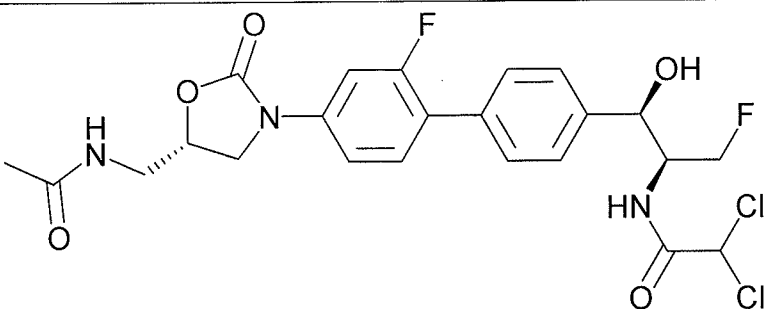
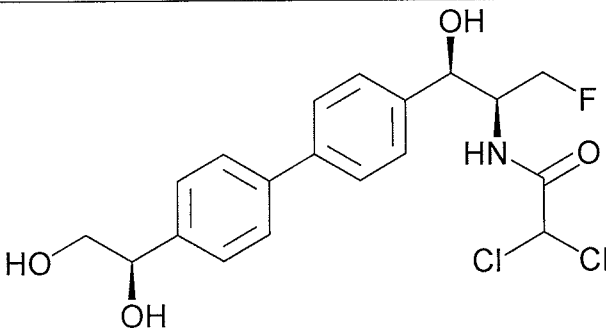
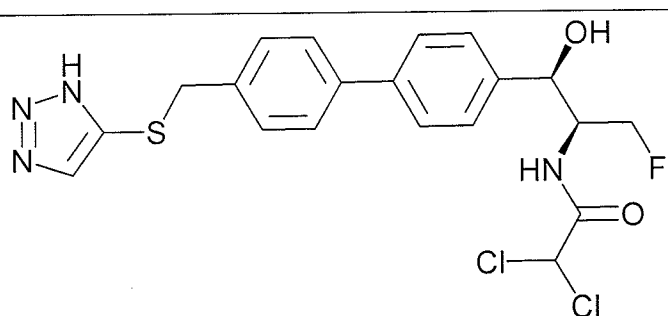
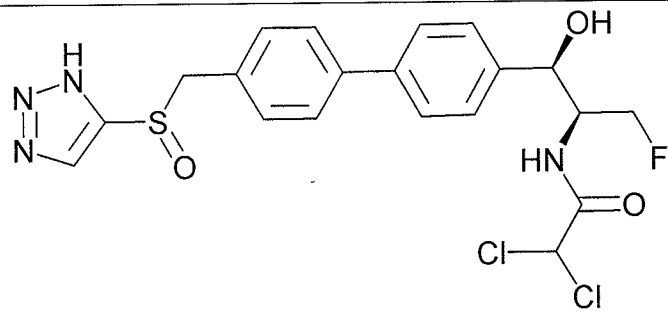
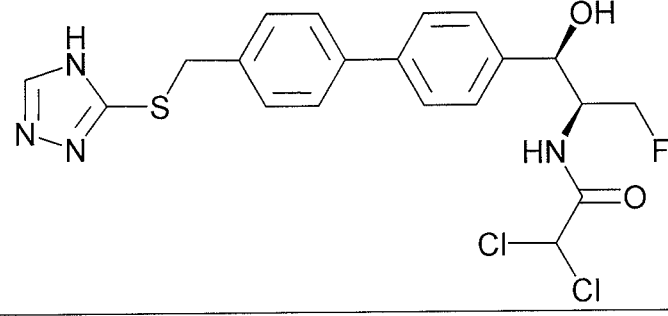
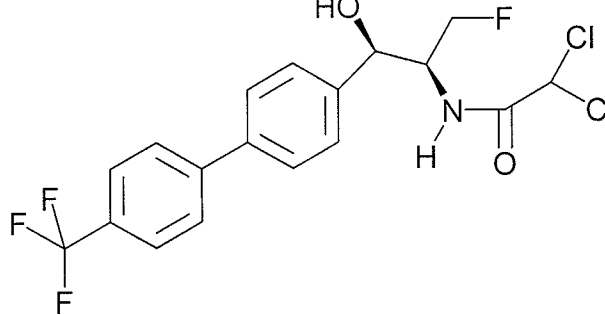
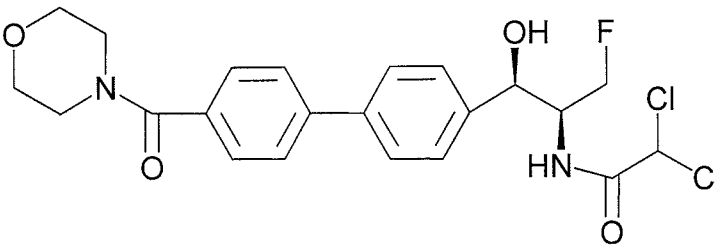
1-22	 <chem>ClC(Cl)C(=O)N[C@@H](CO)[C@H](O)c1ccc(cc1)-c2ccc(cc2)CNc3c[nH]c3</chem>
1-23	 <chem>ClC(Cl)C(=O)N[C@@H](CO)[C@H](O)c1ccc(cc1)-c2ccc(cc2)CNc3c[nH]c3</chem>
1-24	 <chem>ClC(Cl)C(=O)N[C@@H](CO)[C@H](O)c1ccc(cc1)-c2ccc(cc2)NCCF</chem>
1-25	 <chem>ClC(Cl)C(=O)N[C@@H](CO)[C@H](O)c1ccc(cc1)-c2ccc(cc2)CNc3ccccc3</chem>
1-26	 <chem>ClCC(=O)N[C@@H](CO)[C@H](O)c1ccc(cc1)-c2ccc(cc2)CNc3ccccc3</chem>

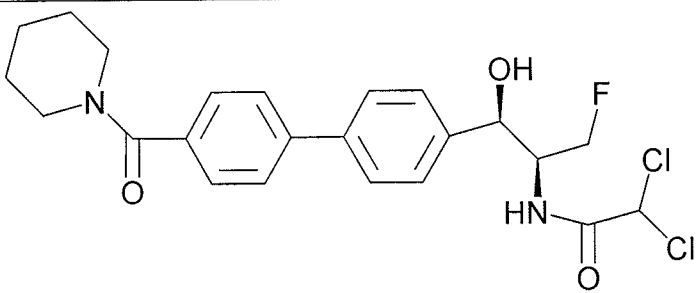
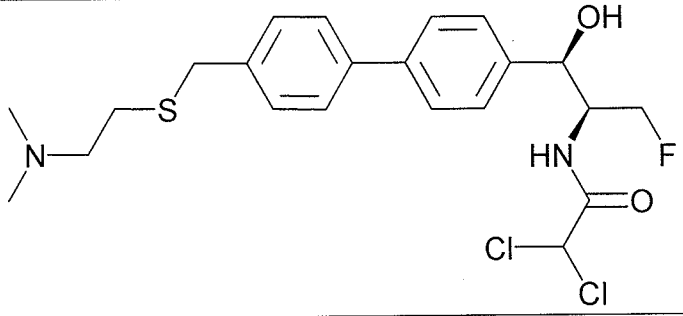
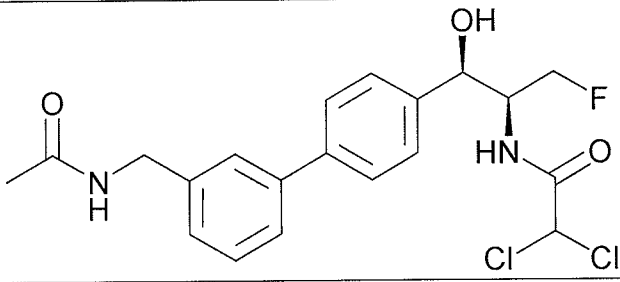
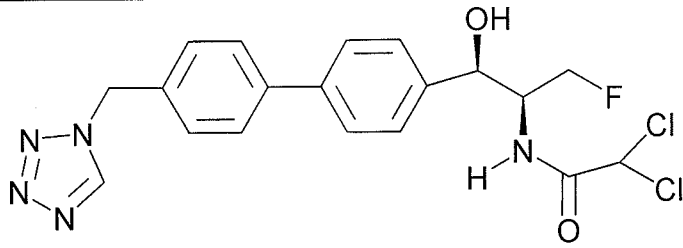
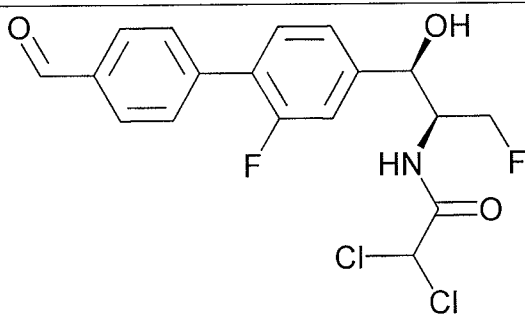
Table 2

Table 2	
Compound Number	Structure
2-1	
2-2	
2-3	

2-4	 <chem>OCC1=CC=C(C=C1)-C2=CC=C(C=C2)C(O)C(C(F)C)NC(=O)C(Cl)Cl</chem>
2-5	 <chem>C=CC1=CC=C(C=C1)-C2=CC=C(C=C2)C(O)C(C(F)C)NC(=O)C(Cl)Cl</chem>
2-6	 <chem>OCC1(O)C(C(F)C)NC(=O)C(Cl)ClC1C2=CC=C(C=C2)-C3=CC=C(C=C3)C(O)C2</chem>
2-7	 <chem>OCC1=CC=C(C=C1)-C2=CC=C(C=C2)C(O)C(CO)NC(=O)C(Cl)Cl</chem>
2-8	 <chem>CC(=O)C1=CC=C(C=C1)-C2=CC=C(C=C2)C(O)C(CO)NC(=O)C(Cl)Cl</chem>

2-9	
2-10	
2-11	
2-12	
2-13	

2-14	 <chem>C1=CN=C(N1)SCc2ccc(cc2)-c3ccc(cc3)[C@H](O)C(F)CNC(=O)C(Cl)Cl</chem>
2-15	 <chem>C1=CN=C(N1)S(=O)Cc2ccc(cc2)-c3ccc(cc3)[C@H](O)C(F)CNC(=O)C(Cl)Cl</chem>
2-16	 <chem>C1=NC=NC=N1SCc2ccc(cc2)-c3ccc(cc3)[C@H](O)C(F)CNC(=O)C(Cl)Cl</chem>
2-17	 <chem>FC(F)(F)c1ccc(cc1)-c2ccc(cc2)[C@H](O)C(F)CNC(=O)C(Cl)Cl</chem>
2-18	 <chem>C1CCN(CC1)C(=O)c2ccc(cc2)-c3ccc(cc3)[C@H](O)C(F)CNC(=O)C(Cl)Cl</chem>

2-19	
2-20	
2-21	
2-22	
2-23	

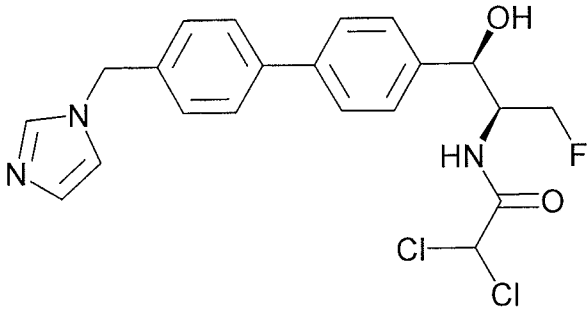
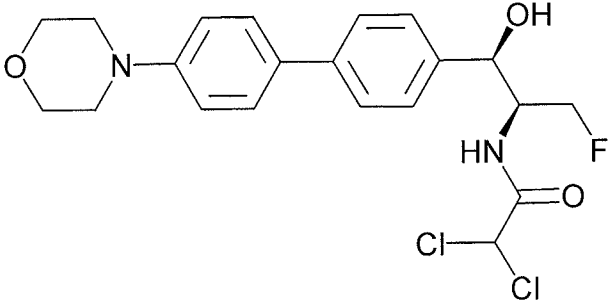
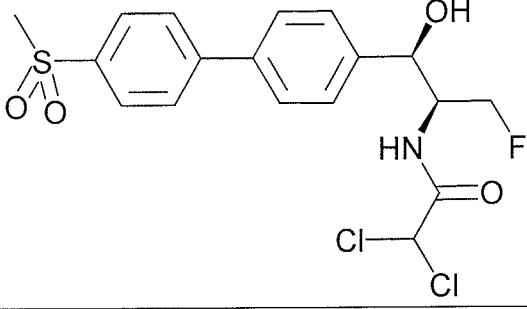
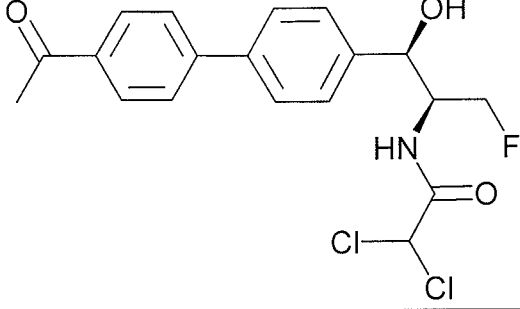
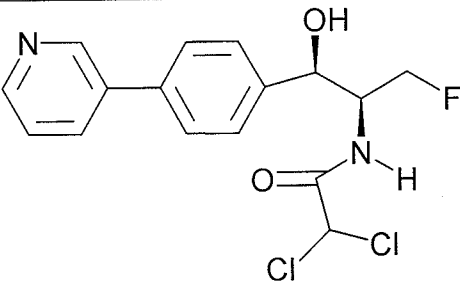
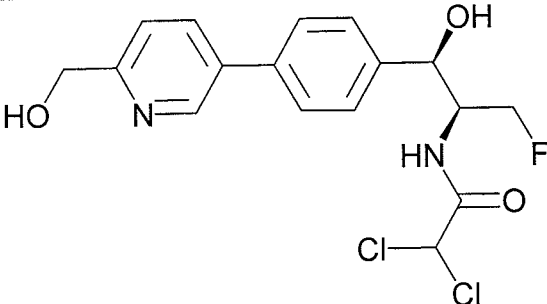
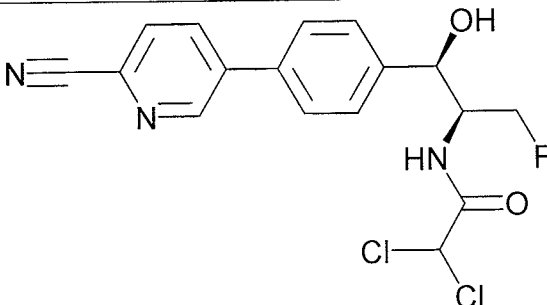
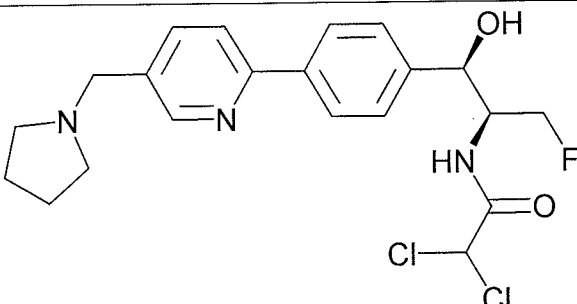
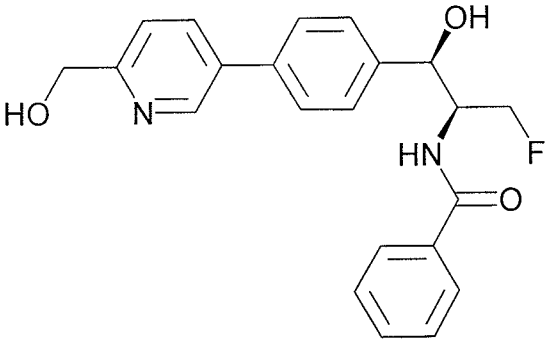
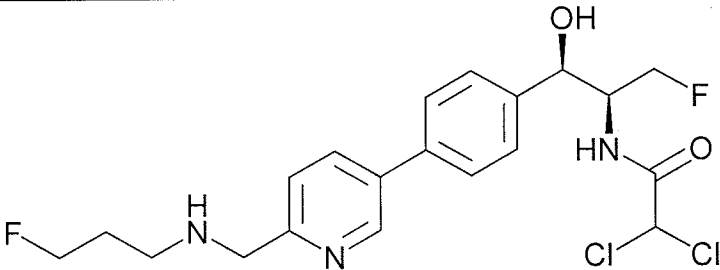
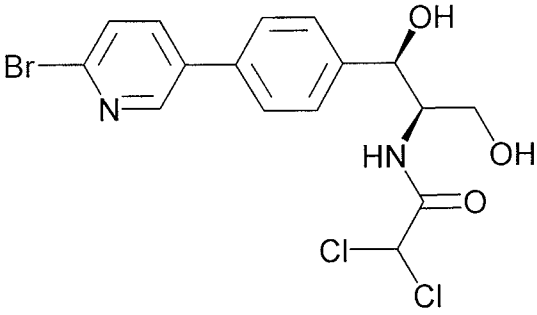
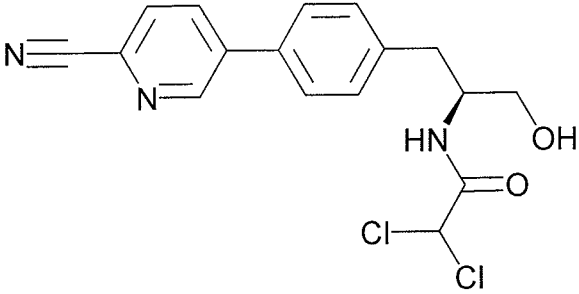
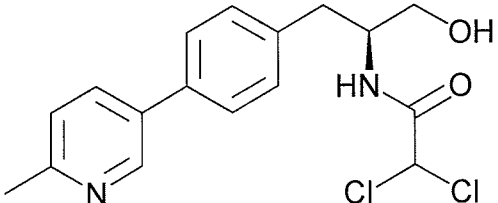
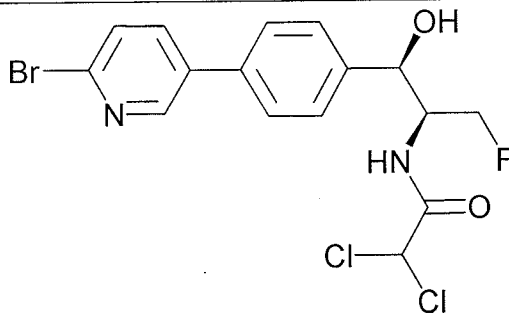
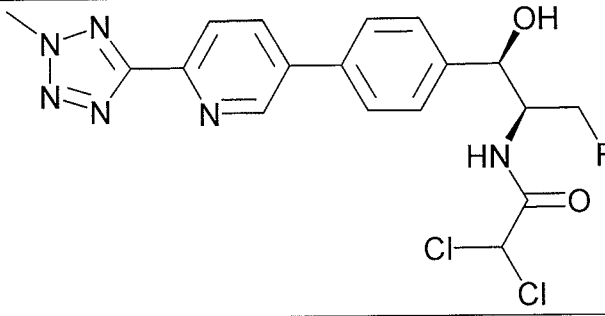
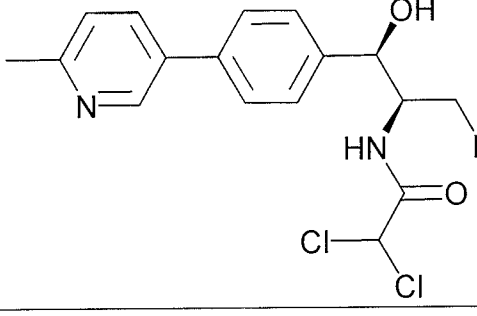
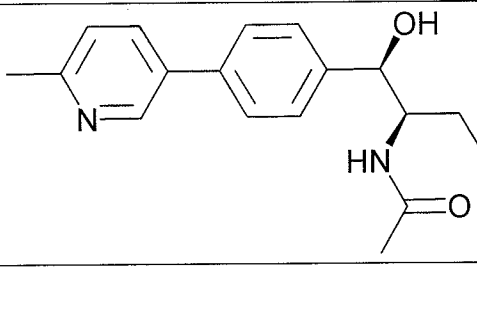
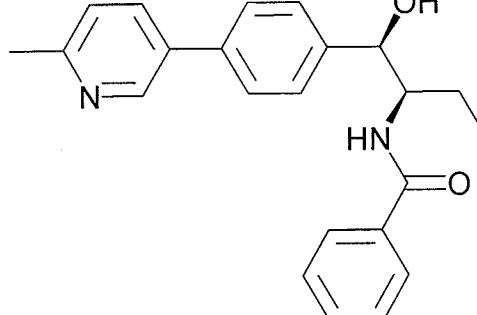
2-24	
2-25	
2-26	
2-27	

Table 3

Table 3	
Compound Number	Structure

3-1	
3-2	
3-3	
3-4	

3-5	
3-6	
3-7	
3-8	
3-9	

3-10	
3-11	
3-12	
3-13	
3-14	

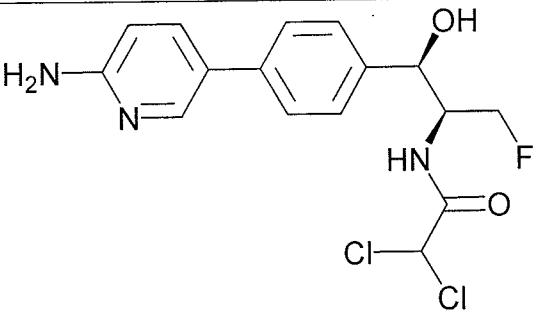
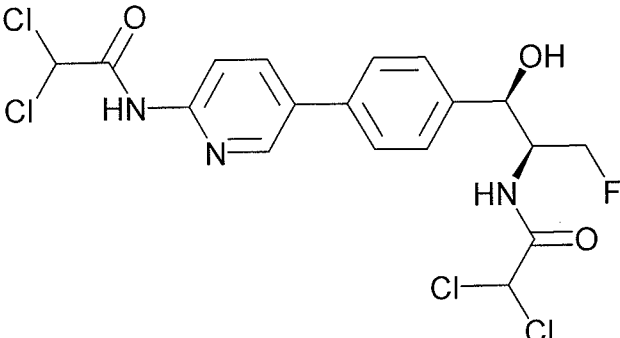
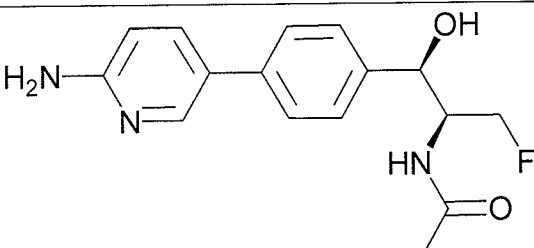
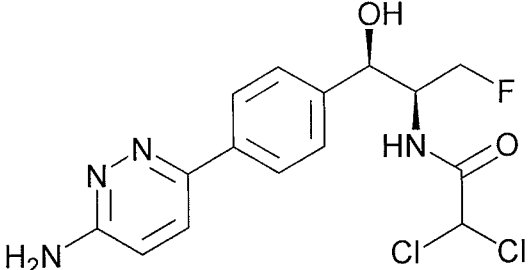
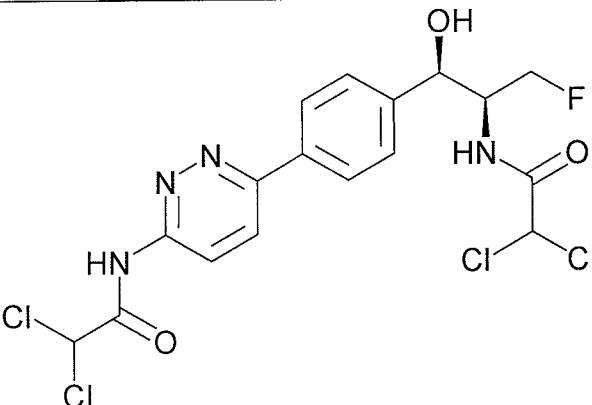
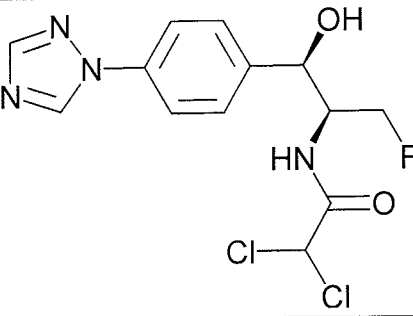
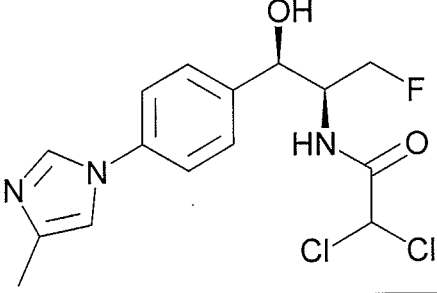
3-15	
3-16	
3-17	

Table 4

Table 4	
Compound Number	Structure

4-1	 <chem>O=Cc1ccsc1-c2ccc(cc2)[C@H](O)[C@@H](NC(=O)C(Cl)Cl)CCF</chem>
4-2	 <chem>c1ccc2c(c1)cnc2-c3ccc(cc3)[C@H](O)[C@@H](NC(=O)C(Cl)Cl)CCF</chem>
4-3	 <chem>Cn1cncn1-c2ccncc2-c3ccc(cc3)[C@H](O)[C@@H](NC(=O)C(Cl)Cl)CCF</chem>
4-4	 <chem>c1cc[nH]c1-c2ccc(cc2)[C@H](O)[C@@H](NC(=O)C(Cl)Cl)CCF</chem>

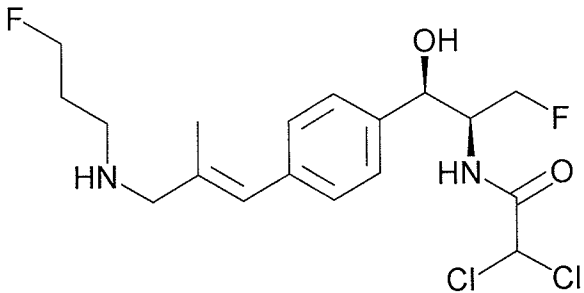
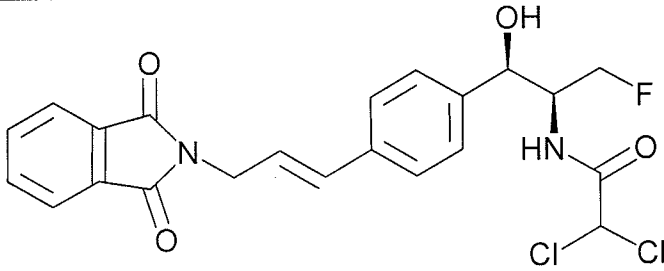
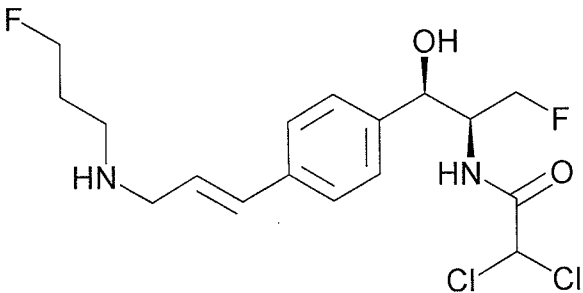
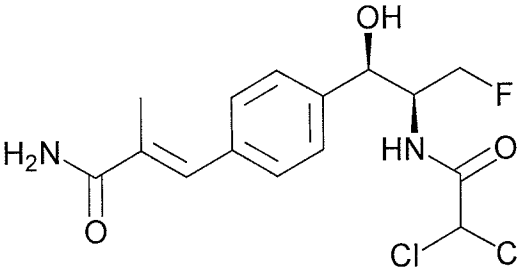
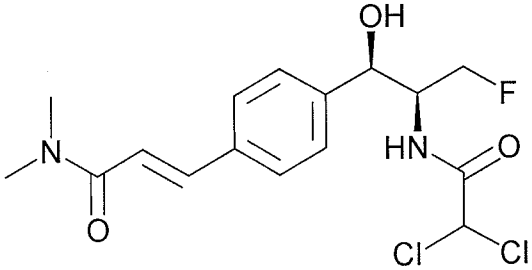
4-5	 <chem>ClC(Cl)C(=O)N[C@H](CO)c1ccc(cc1)-c2ccncc2</chem>
4-6	 <chem>ClC(Cl)C(=O)N[C@H](CO)c1ccc(cc1)-c2cc(N)ncn2</chem>
4-7	 <chem>ClC(Cl)C(=O)N[C@H](CO)c1ccc(cc1)-c2ccncc2</chem>
4-8	 <chem>ClC(Cl)C(=O)N[C@H](CO)c1ccc(cc1)-c2ccoc2</chem>
4-9	 <chem>ClC(Cl)C(=O)N[C@H](CO)c1ccc(cc1)-c2ccsc2</chem>

4-10	
4-11	
4-12	
4-13	

4-14	

Table 5

Table 5	
Compound Number	Structure
5-1	
5-2	
5-3	

5-4	
5-5	
5-6	
5-7	
5-8	

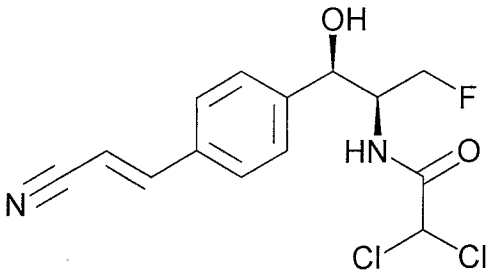
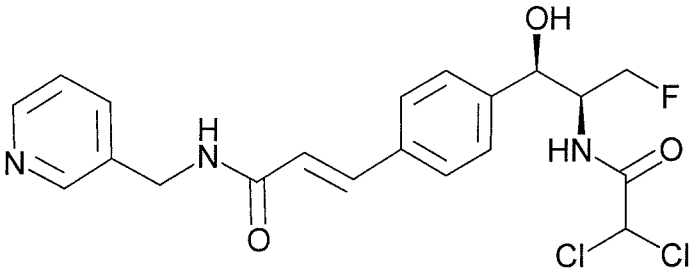
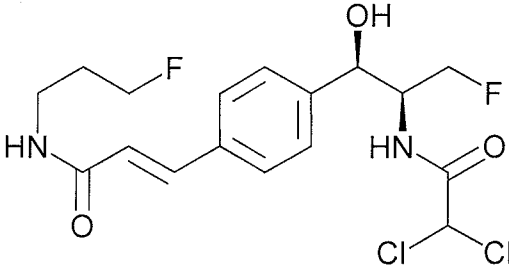
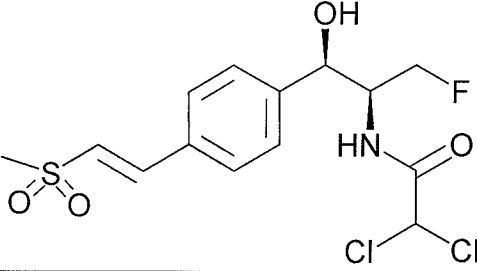
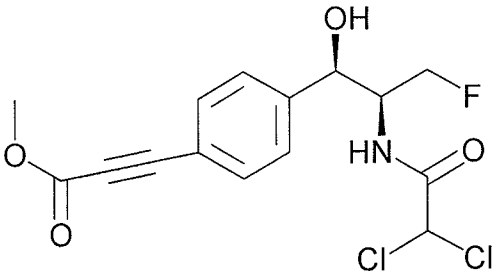
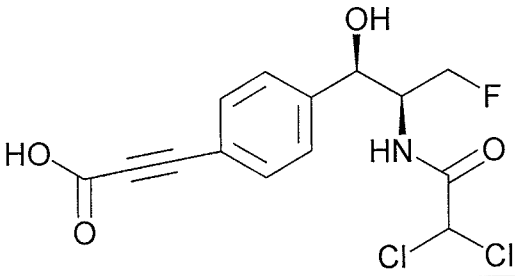
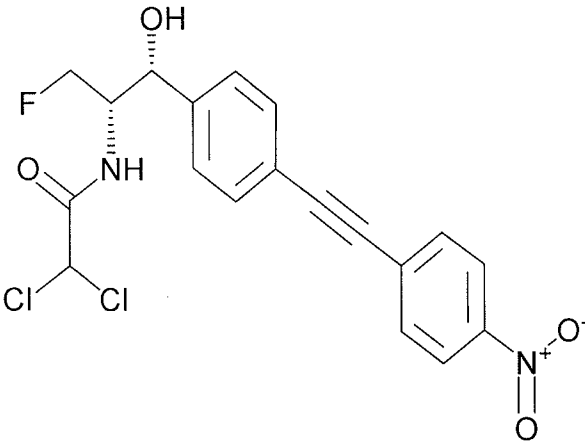
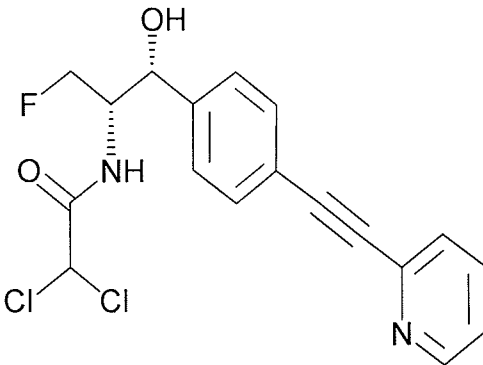
5-9	
5-10	
5-11	
5-12	

Table 6

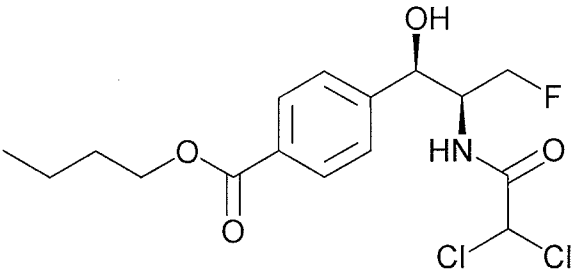
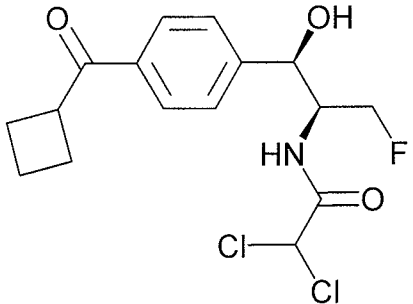
Table 6	
Compound Number	Structure

6-1	
6-2	
6-3	
6-4	

5

10

Table 7

Table 7	
Compound Number	Structure
7-1	
7-2	

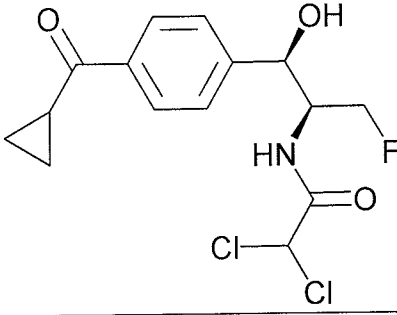
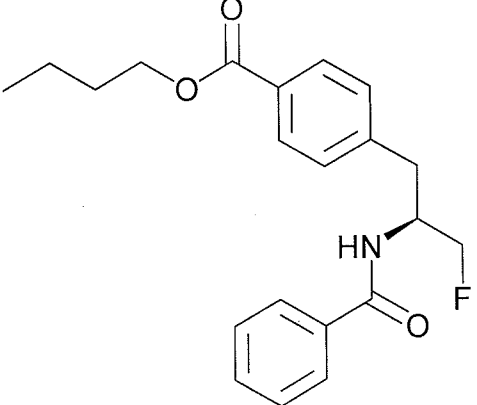
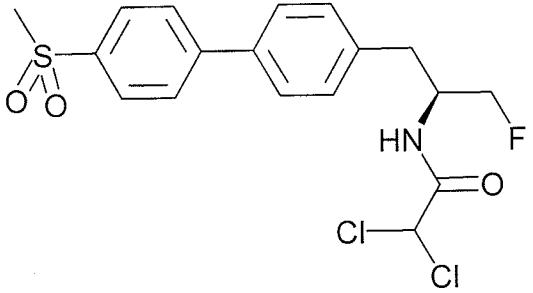
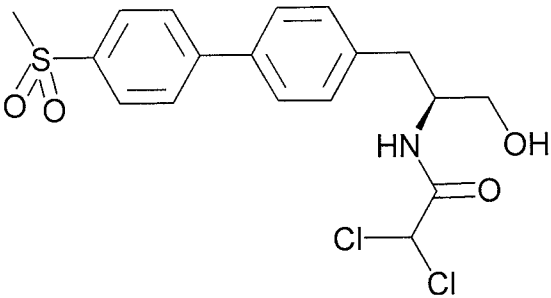
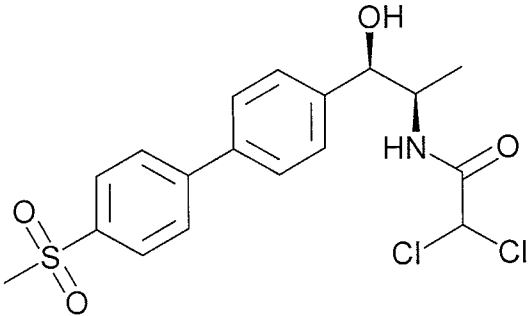
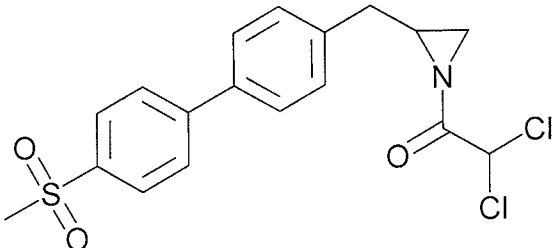
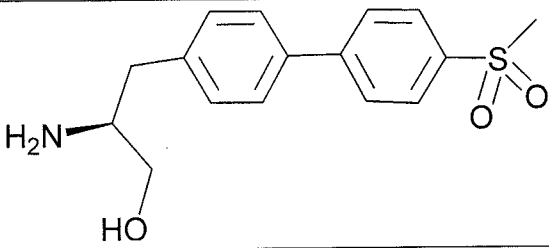
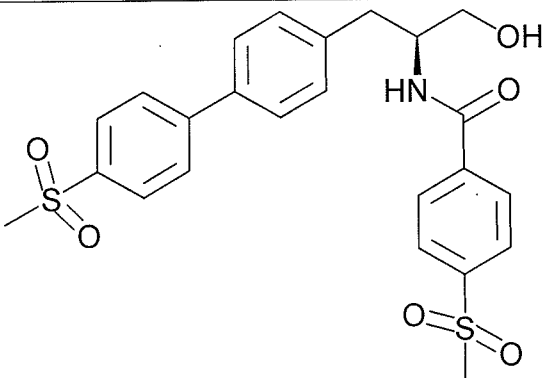
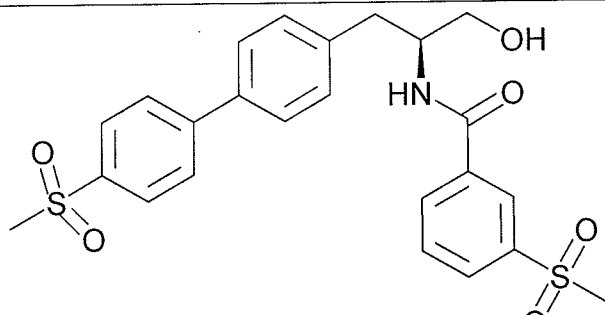
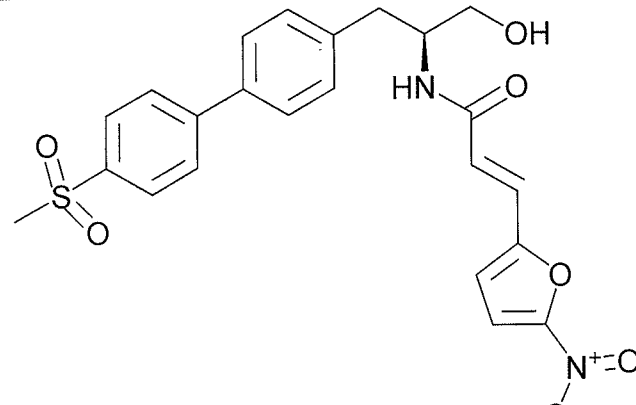
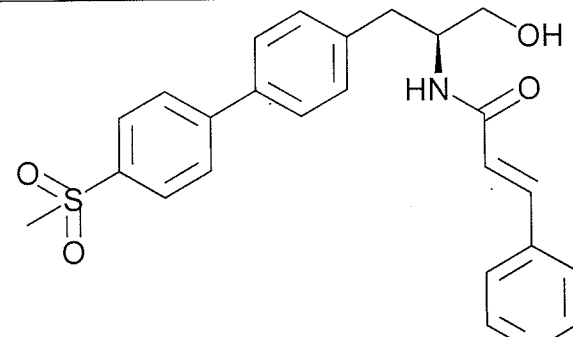
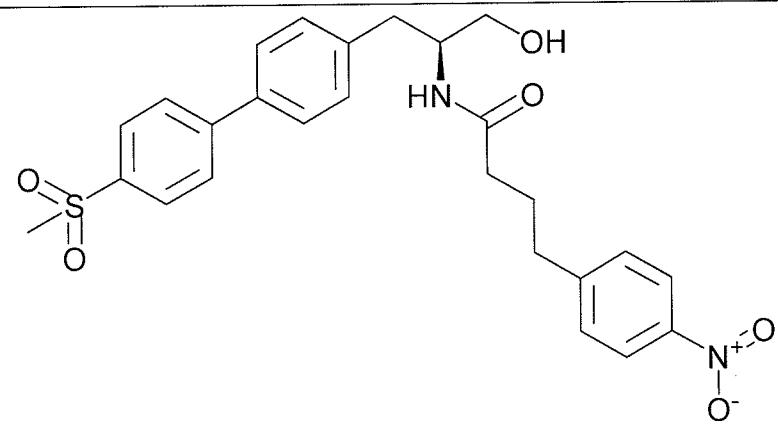
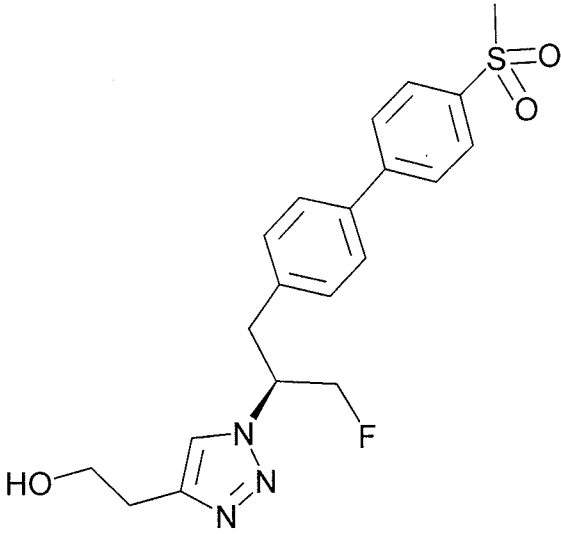
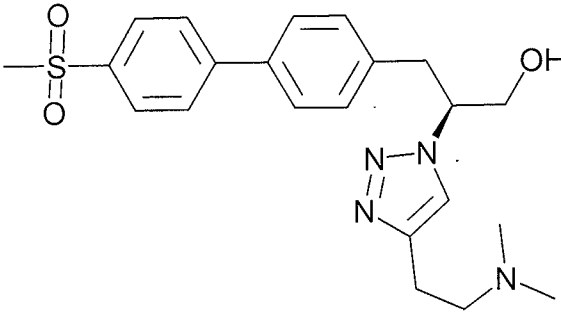
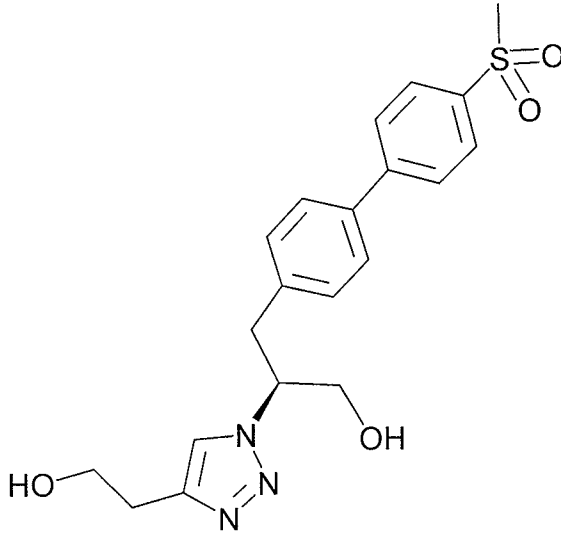
7-3	
7-4	

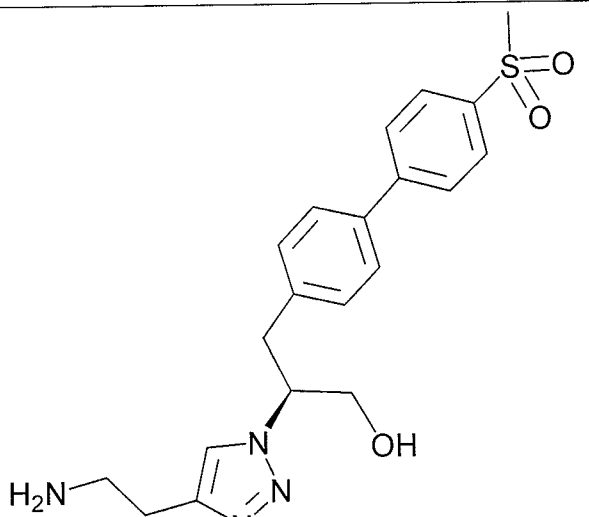
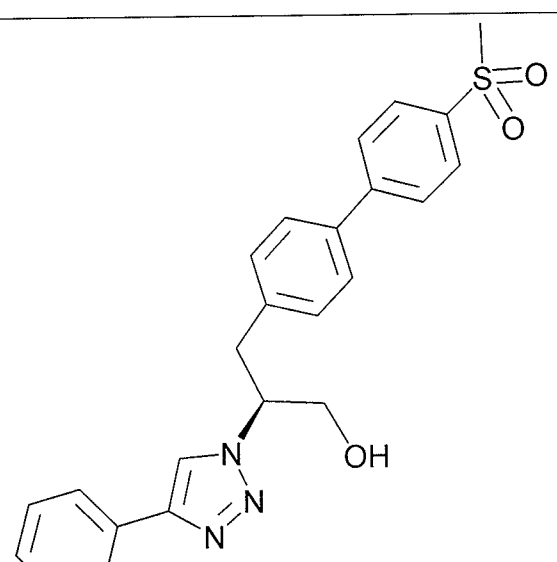
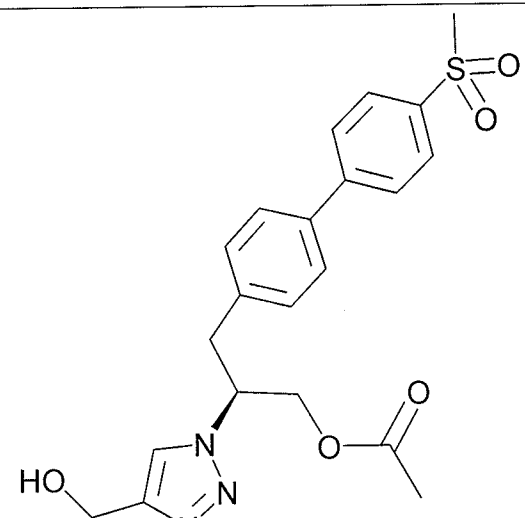
Table 8

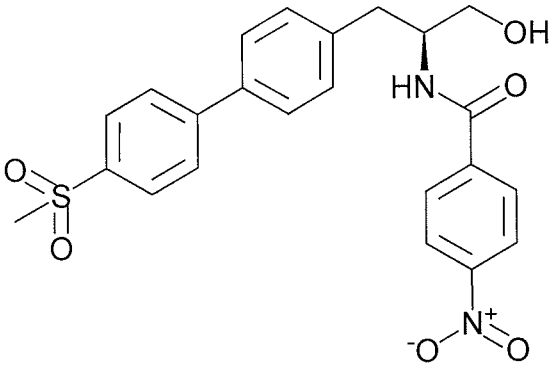
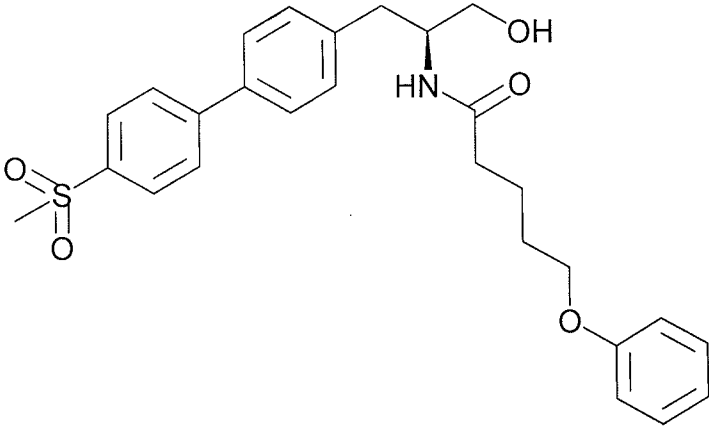
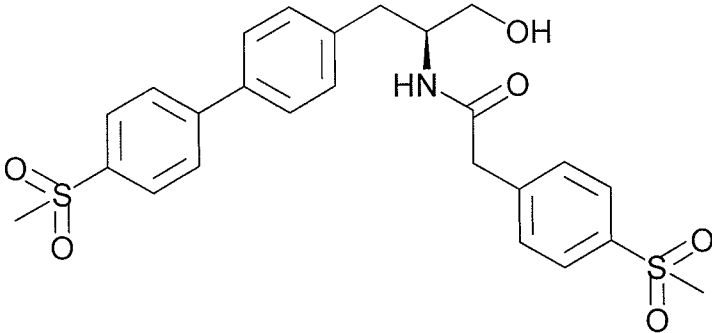
Table 8	
Compound Number	Structure
8-1	

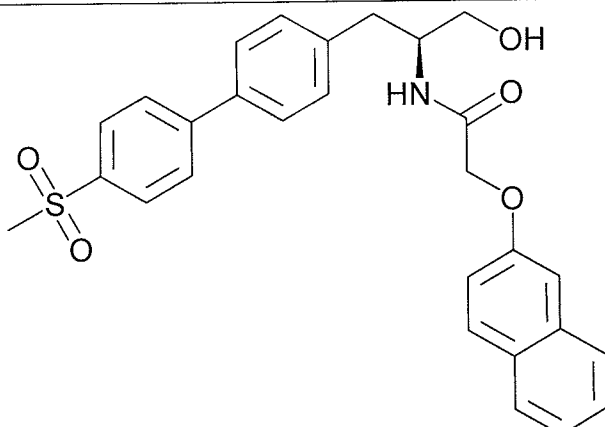
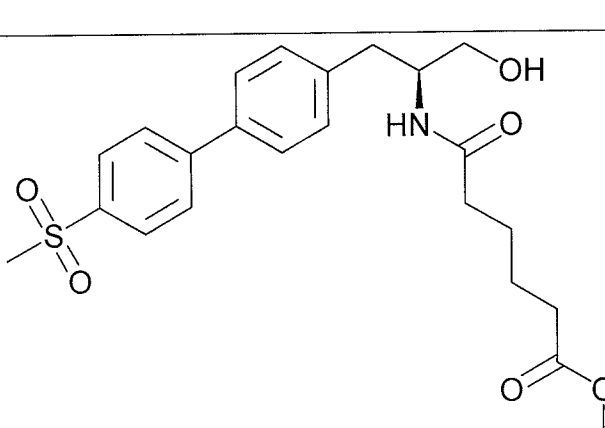
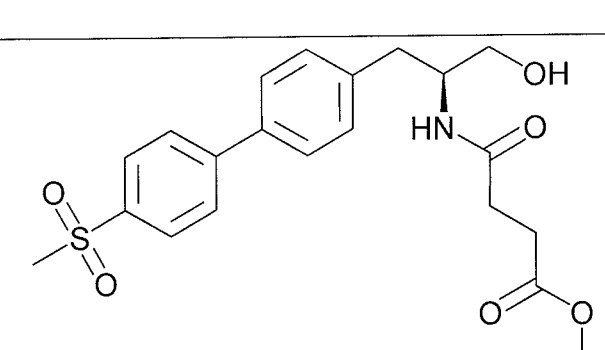
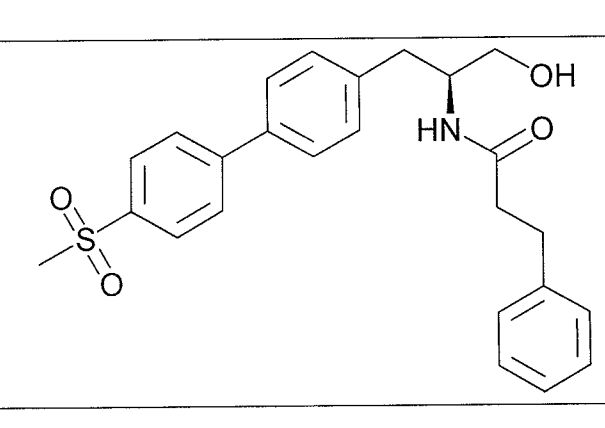
8-2	 <chem>CS(=O)c1ccc(cc1)-c2ccc(cc2)CCN[C@@H](CO)C(Cl)Cl</chem>
8-3	 <chem>CS(=O)c1ccc(cc1)-c2ccc(cc2)C[C@H](O)[C@@H](N)C(=O)C(Cl)Cl</chem>
8-4	 <chem>CS(=O)c1ccc(cc1)-c2ccc(cc2)CC1CN1C(=O)C(Cl)Cl</chem>
8-5	 <chem>CS(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](N)CO</chem>
8-6	 <chem>CS(=O)c1ccc(cc1)-c2ccc(cc2)CCN[C@@H](C(=O)c3ccc(cc3)S(=O)(=O)C)CO</chem>

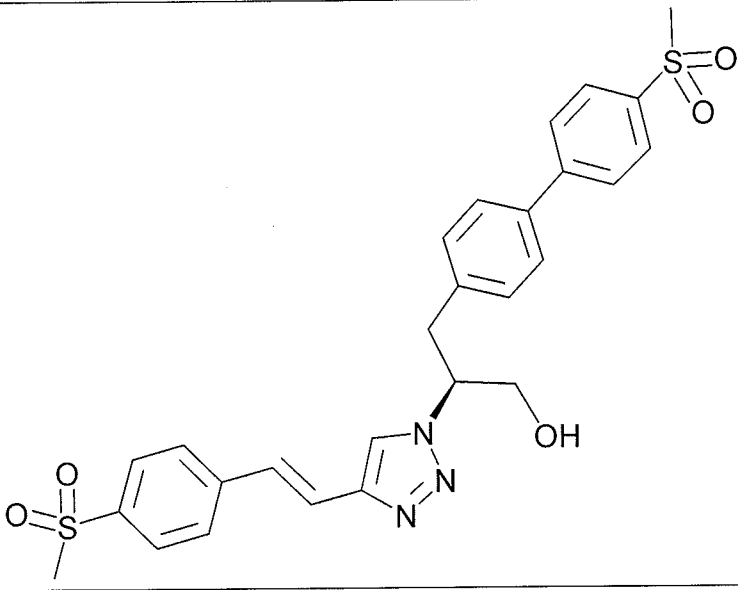
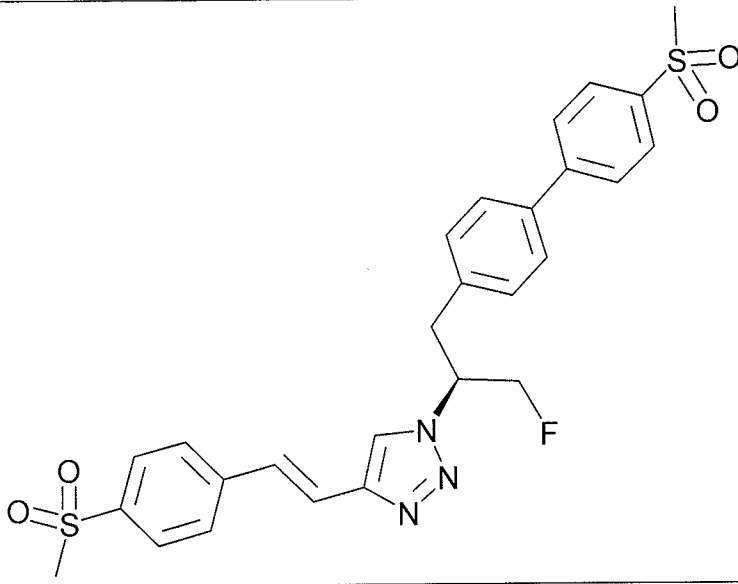
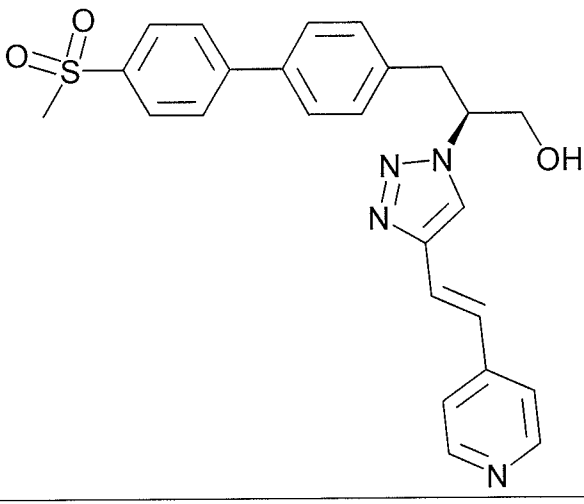
8-7	
8-8	
8-9	
8-10	

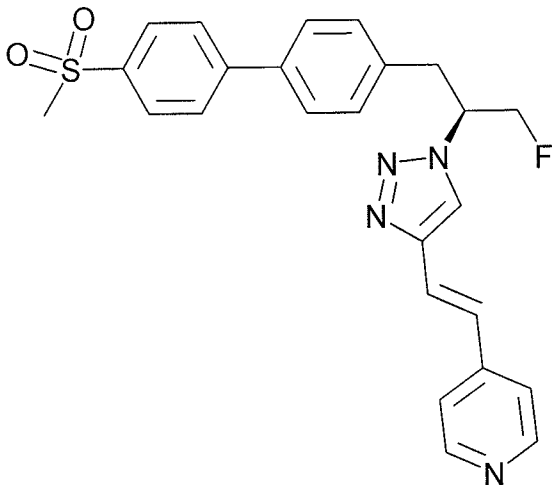
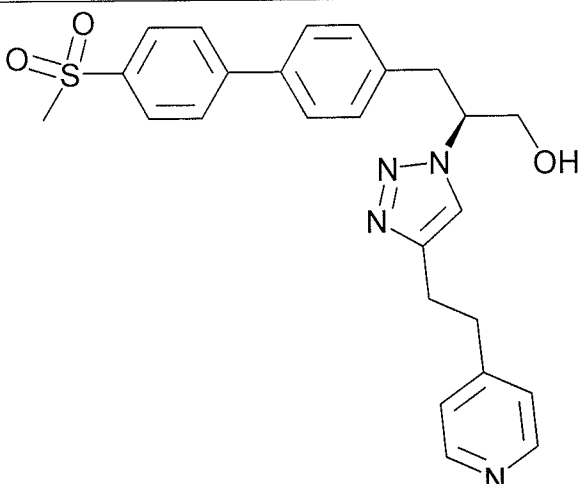
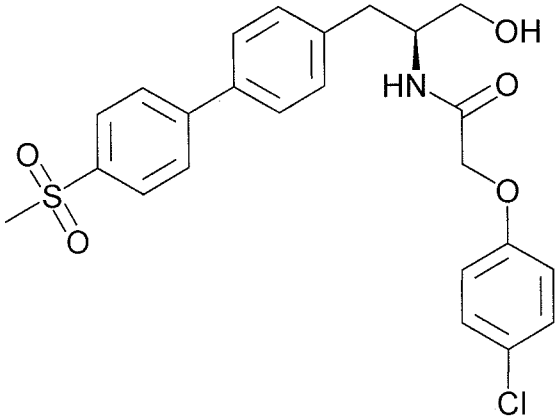
8-11	 <chem>CC(=O)S(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3CCO)CCF</chem>
8-12	 <chem>CC(=O)S(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3CCN(C)C)CCO</chem>
8-13	 <chem>CC(=O)S(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3CCO)CCO</chem>

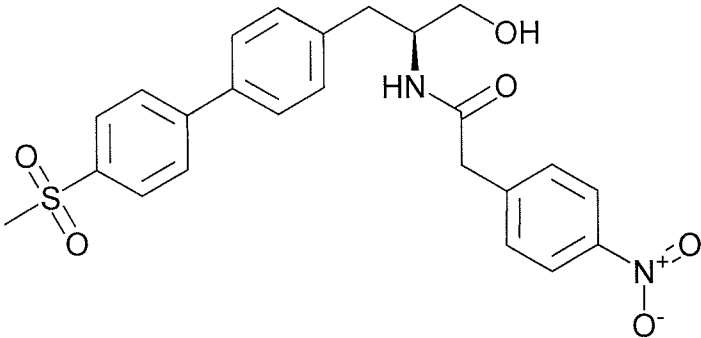
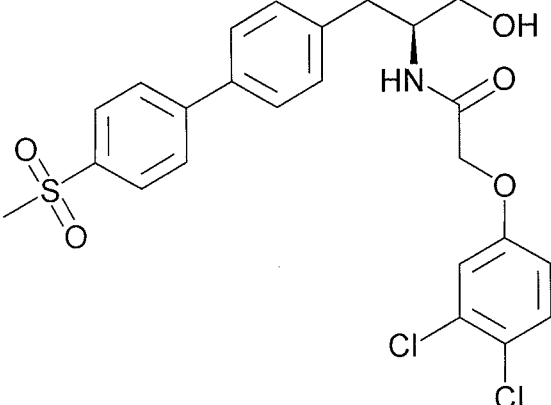
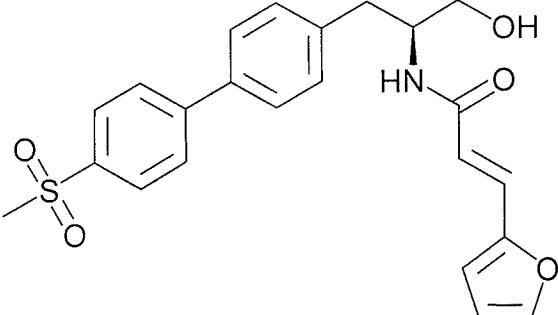
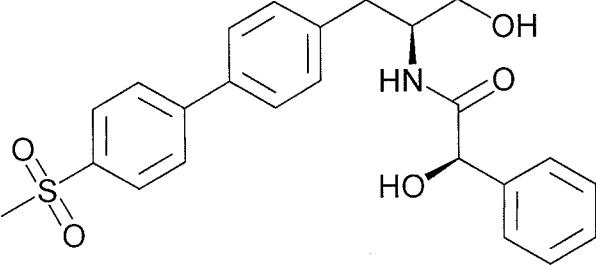
8-14	 <chem>CC(=O)S(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3)CO</chem>
8-15	 <chem>CC(=O)S(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3c4ccncc4)CO</chem>
8-16	 <chem>CC(=O)S(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3Cc4ccccc4)OC(=O)C</chem>

8-17	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)C(=O)Nc3ccc(cc3)[N+](=O)[O-]</chem>
8-18	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)C(=O)NCCCCOc3ccccc3</chem>
8-19	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)C(=O)NCCc3ccc(cc3)S(=O)(=O)C</chem>

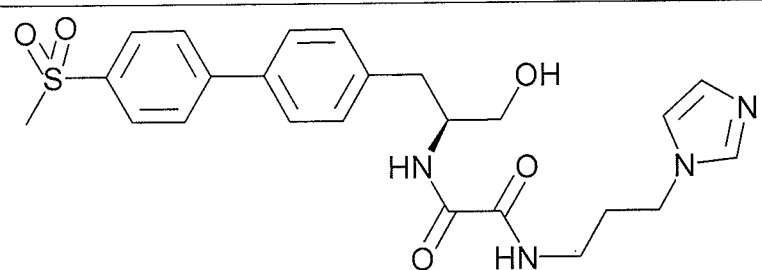
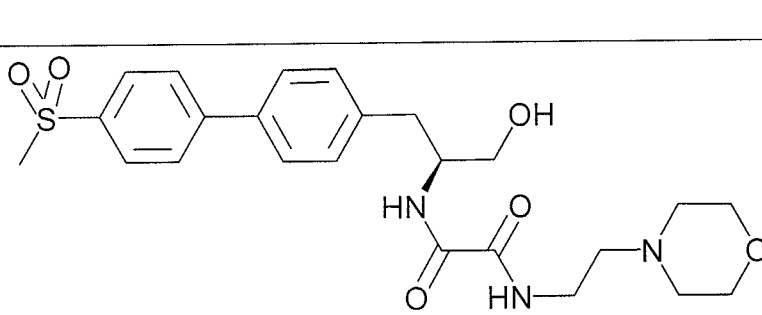
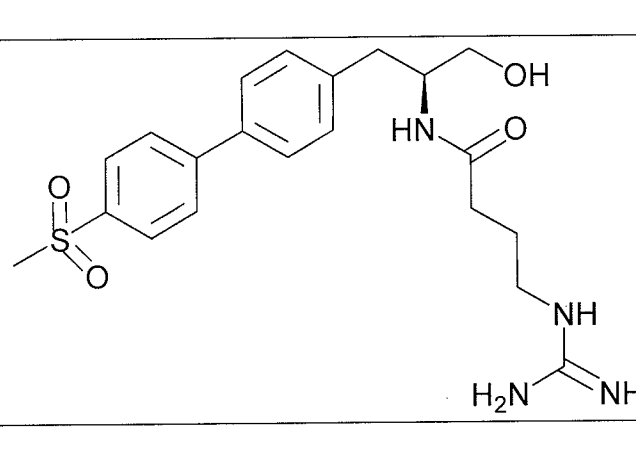
8-20	 <chem>CC(=O)N[C@H](CO)Cc1ccc(cc1)-c2ccc(cc2)S(=O)(=O)C</chem>
8-21	 <chem>CCOC(=O)CCCC(=O)N[C@H](CO)Cc1ccc(cc1)-c2ccc(cc2)S(=O)(=O)C</chem>
8-22	 <chem>CCOC(=O)CCCC(=O)N[C@H](CO)Cc1ccc(cc1)-c2ccc(cc2)S(=O)(=O)C</chem>
8-23	 <chem>CCOC(=O)N[C@H](CO)Cc1ccc(cc1)-c2ccc(cc2)S(=O)(=O)C</chem>

8-24	
8-25	
8-26	

8-27	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3)/C=C/c4ccncc4CCF</chem>
8-28	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3)CCc4ccncc4CCO</chem>
8-29	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](c3nn[nH]3)CCOCC(=O)NCCOc4ccc(Cl)cc4</chem>

8-30	
8-31	
8-32	
8-33	

8-34	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)NC(=O)CNc3ccncc3</chem>
8-35	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)NC(=O)C1CCNC1COc2ccccc2</chem>
8-36	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)NC(=O)C1CCNC1C[C@H](O)C[C@H]2O[C@H](C[C@@H](O)[C@H]2C)C</chem>
8-37	 <chem>CS(=O)(=O)c1ccc(cc1)-c2ccc(cc2)CC[C@H](O)NC(=O)C1C(=O)OC1=O</chem>

8-38	
8-39	
8-40	

The following schemes depict exemplary chemistry available for synthesizing the compounds of the invention. It will be appreciated, however, that the desired compounds can be synthesized using other alternative chemistries known in the art.

5

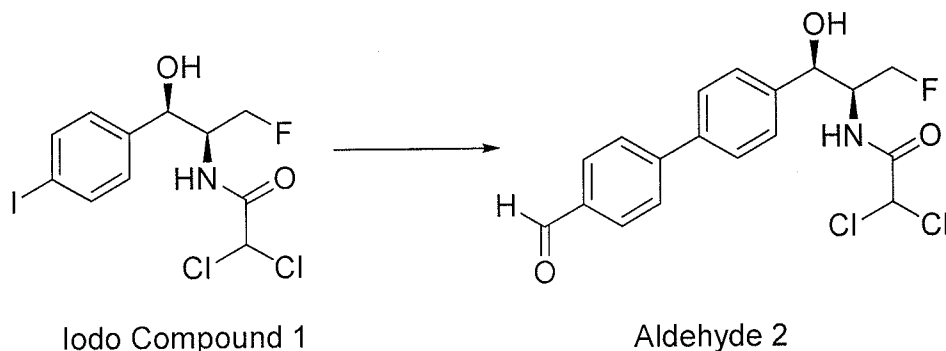
Synthetic Schemes

The compounds of the present invention can be prepared via a palladium catalyzed Suzuki coupling reaction. See, e.g., Miyaura *et al.*, *Tetrahedron Letters*, 3437 (1979), and Miyaura & Suzuki, *Chem. Comm.*, 866 (1979). Specifically, the biaryl portion of the compounds of the present invention can be made by coupling an aryl boronic acid or ester with an aryl halide, aryl tosylate, or other aryl compound with an appropriate leaving group.

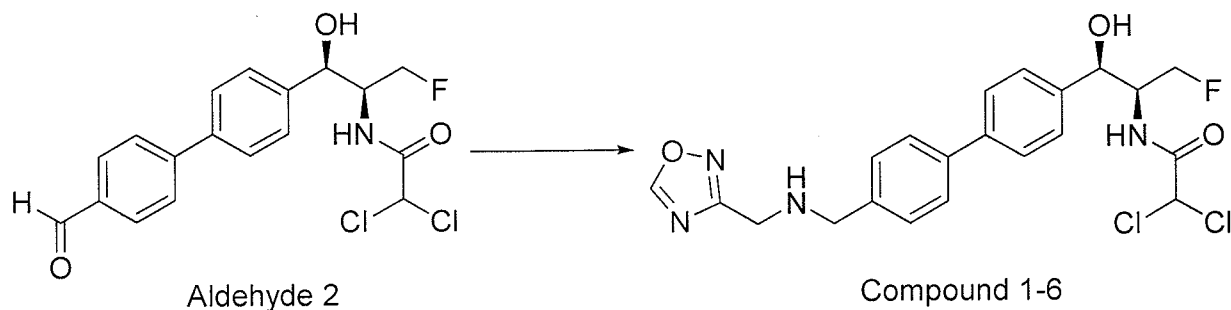
10

Example 1: Synthesis of Compound 1-6.

This example illustrates the synthesis of **Compound 1-6** via intermediate **Aldehyde 2**, this aldehyde which is prepared using a palladium catalyzed Suzuki coupling.



A solution of **Iodo Compound 1** (0.60 g, 1.5 mmol) in toluene (9 mL), ethanol (3 mL), and water (3 mL) was treated with 4-formylphenylboronic acid (0.27 g, 1.8 mmol) and potassium carbonate (0.62 g, 4.5 mmol). The solution was degassed, tetrakis(triphenylphosphine)palladium(0) (0.087 g, 0.075 mmol) was added and the solution degassed again. The reaction mixture was stirred at 60 °C for 2 h, diluted with methylene chloride (50 mL), and washed with water (15 mL). The water layer was extracted with methylene chloride (30 mL). Drying (Na_2SO_4) and evaporation to yield **Aldehyde 2** (0.52 g, 1.4 mmol, 93%) as a light brown powder: ^1H NMR (300 MHz, CDCl_3): δ 10.05 (s, 1 H), 7.95 (d, $J = 8$ Hz, 2 H), 7.74 (d, $J = 8$ Hz, 2 H), 7.64 (d, $J = 8$ Hz, 2 H), 7.50 (d, $J = 8$ Hz, 2 H), 7.08 (d, $J = 9$ Hz, 1 H), 5.87 (s, 1 H), 5.19 (broad t, $J = 4$ Hz, 1 H), 4.75-4.42 (m, 2 H), 4.41-4.30 (m, 1H), 2.70 (d, $J = 3$ Hz, 1 H).

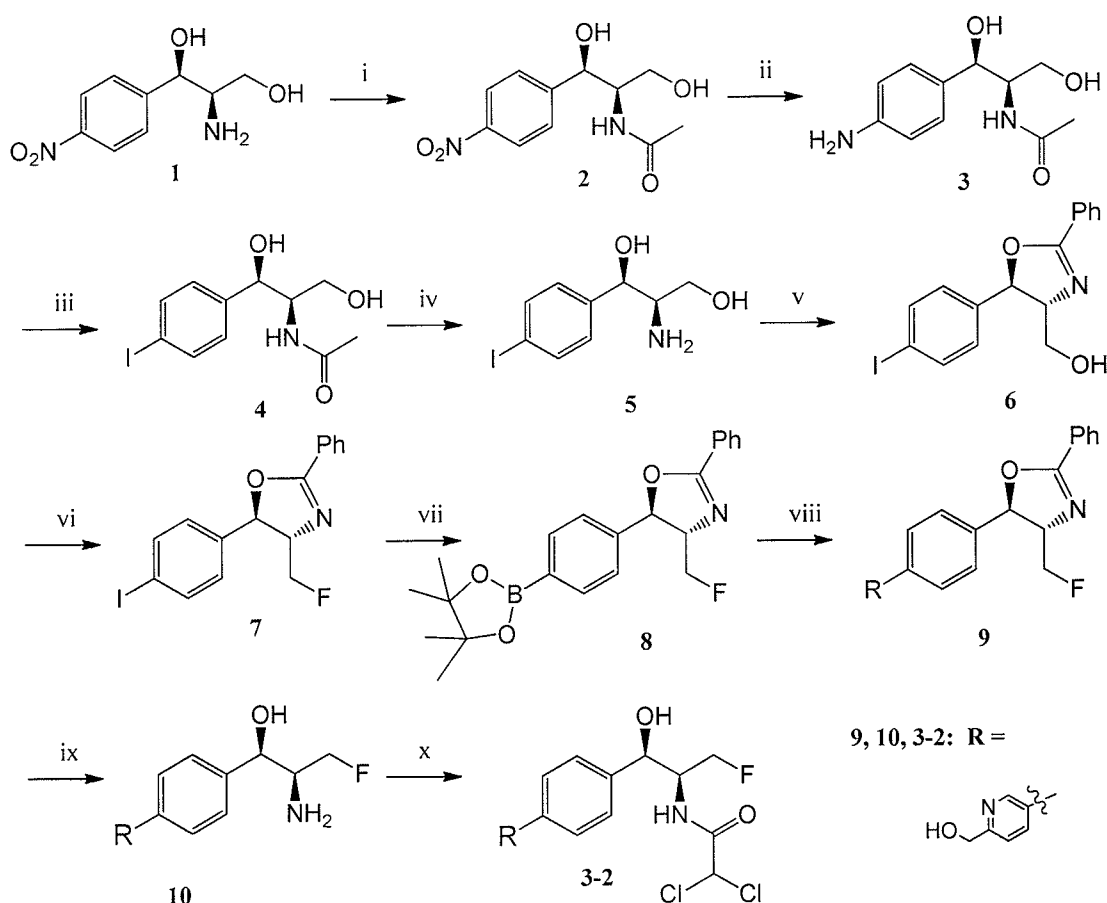


A solution of **Aldehyde 2** (0.015 g, 0.039 mmol) in methylene chloride (0.5 mL) was treated with triethylamine (0.011 mL, 0.078 mmol) and 1,2,4-oxodiazole-3-methylamine hydrochloride (0.008 g, 0.059 mmol) and stirred at 25 °C for 15 minutes. Sodium triacetoxyborohydride was added (0.025 g, 0.12 mmol), and the solution was stirred for at 25 °C for 3 h, diluted with methylene chloride (4 mL) and washed with water (1 mL). The water layer was twice extracted with methylene chloride (4 mL). Drying (Na₂SO₄) and evaporation of solvent yielded crude product, which was purified by preparatory thin-layer chromatography (SiO₂, ethyl acetate:hexane (2:1)) to afford **Compound 1-6** (0.008 g, 0.017 mmol, 44%) as a white powder: MS (ESI): 467 (M+H)⁺.

10

Example 2: Synthesis of Compounds 1-3, 3-2, and 3-7

This example illustrates the synthesis of compounds **1-3**, **3-2**, and **3-7**.



i: Acetic anhydride/NaHCO₃, H₂O/THF, 0°C-rt; ii: Pd-C/[H₂], MeOH; iii: a), NaNO₂/HCl, H₂O, 0°C; b), KI, 0 °C-rt; iv: 10% H₂SO₄, 110 °C; v: ethyl benzimidate hydrochloride/Et₃N, ClCH₂CH₂Cl, reflux; vi: DAST, CH₂Cl₂, -78°C-rt; vii: n-BuLi/ isopropyl pinacol boronate, THF, -78°C-rt; viii: R-Br/Pd(PPh₃)₄/K₂CO₃, toluene/EtOH/H₂O, 90°C; ix: AcOH/6 N HCl, 110°C; x: Cl₂CHCOCl/Et₃N, CH₂Cl₂, 0°C-rt.

N-[2-Hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]-acetamide (2): To a mixture of *D*-(-)-threo-2-amino-*p*-nitrophenyl-propane-1,3-diol (**1**) (9.85 g, 46.4 mmol), NaHCO₃ (29.2 g, 348.0 mmol), water (300 ml) and THF (100 ml) was added dropwise a solution of acetic anhydride (13.1 ml, 139.1 mmol) in THF (30 ml) at 0 °C. After addition was completed, the
5 resulted mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (300 ml x 3). The EtOAc extract was washed with brine (100 ml), dried over Na₂SO₄ and concentrated. The crude product was triturated with EtOAc (30 ml) and filtered. The solid was collected and dried to afford **2** as white powder (10.6 g, 90%).
10 ¹NMR (300 MHz, DMSO-*d*₆): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 5.82 (d, *J* = 7.5 Hz, 1H), 5.01 (m, 1H), 4.84 (t, *J* = 4.5 Hz, 1H), 3.94 (m, 1H), 3.53 (m, 1H), 3.28 (m, 1H), 1.69 (s, 3H); C₁₁H₁₄N₂O₅, LCMS (EI) *m/z*: 254 (M⁺).

N-[2-(4-Amino-phenyl)-2-hydroxy-1-hydroxymethyl-ethyl]-acetamide (3): **2** (4.07 g, 16 mmol) was dissolved in MeOH (40 ml). After purging with argon, Pd/C (10 %, 0.4 g) was
15 added and the mixture was stirred under hydrogen atmosphere for 16 h at room temperature. Filtered through a pad of celite and the filtrate was concentrated to afford **3** as light yellowish solid (3.80 g, 100%). ¹NMR (300 MHz, CD₃OD): δ 7.12 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.02 (m, 1H), 3.61 (dd, *J* = 5.4, 10.8 Hz, 1H), 3.40 (dd, *J* =
20 5.4, 10.8 Hz, 1H), 1.93 (s, 3H); C₁₁H₁₆N₂O₃, LCMS (EI) *m/z*: 225 (M⁺+H).

N-[2-Hydroxy-1-hydroxymethyl-2-(4-iodo-phenyl)-ethyl]-acetamide (4): A solution of NaNO₂ (7.47 g, 108 mmol) in water (100 ml) was added dropwise to a solution of **3** (22.4 g, 100 mmol) in 1 N HCl (200 ml) at 0 °C. After addition was completed, the mixture was
25 stirred for additional 30 min and then added slowly to a solution of KI (24.40 g, 147 mmol) in water (180 ml) at 0 °C. After addition was completed, the mixture was warmed up to room temperature and stirred overnight. The mixture was neutralized with solid KOH and extracted with EtOAc (600 ml x 3). The extract was washed with brine (500 ml), dried over Na₂SO₄ and concentrated to afford **4** as light yellowish solid (26.7 g, 81%). ¹NMR (300 MHz,
30 CD₃OD): δ 7.65 (d, *J* = 9 Hz, 2H), 7.16 (d, *J* = 9 Hz, 2H), 4.89 (d, *J* = 9 Hz, 1H), 4.04 (m, 1H), 3.68 (dd, *J* = 6.3, 10.8 Hz, 1H), 3.47 (dd, *J* = 5.4, 10.8 Hz, 1H), 2.01 (s, 3H); C₁₁H₁₄INO₃, LCMS (EI) *m/z*: 335 (M⁺).

2-Amino-1-(4-iodo-phenyl)-propane-1,3-diol (5): A solution of **4** (53.4 g, 159 mmol) in 10% H₂SO₄ (320 ml) was heated at 105 °C for 18 h. Cooled to room temperature and basified with KOH to pH = 13, extracted with EtOAc (400 ml x 6), washed with brine (50 ml), dried over Na₂SO₄ and concentrated to afford **5** as light yellowish solid (45.0 g, 96.6%). ¹NMR (300 MHz, CD₃OD): δ 7.56 (d, J = 9 Hz, 2H), 7.05 (d, J = 9 Hz, 2H), 4.45 (d, J = 8.2 Hz, 1H), 3.34 (dd, J = 4.8, 10.8 Hz, 1H), 3.21 (dd, J = 5.4, 10.8 Hz, 1H), 2.76 (m, 1H); C₉H₁₂INO₂, LCMS (EI) m/z: 294 (M⁺+H).

[5-(4-Iodo-phenyl)-2-phenyl-4,5-dihydro-oxazol-4-yl]-methanol (6): A mixture of **5** (45.0 g, 153.6 mmol), ethyl benzimidate hydrochloride (28.5 g, 153.6), triethylamine (19.8 g, 153.6 mmol) and dichloroethane (800 ml) was refluxed overnight. The mixture was then cooled to -20 °C for 4 h. The crystals were collected by filtration and washed with water, and dried to afford **6** (36.30 g, 62%). ¹NMR (300 MHz, CD₃OD): δ 8.01 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.65 (m, 1H), 7.56 (m, 2H), 7.22 (d, J = 8.4 Hz, 2H), 5.58 (d, J = 6.3 Hz, 1H), 5.12 (t, J = 5.7 Hz, 1H), 4.12 (m, 1H), 3.79 (m, 1H), 3.62 (m, 1H); C₁₆H₁₄INO₂, LCMS (EI) m/z: 379 (M⁺).

4-Fluoromethyl-5-(4-iodo-phenyl)-2-phenyl-4,5-dihydro-oxazole (7): A solution of **6** (21 g, 55.40 mmol) in methylenechloride (800 ml) was cooled to -78 °C and DAST (11.62 ml, 88.67 mmol) was added dropwise. After addition, the mixture was slowly warmed up to room temperature and stirred at room temperature overnight before quenched with 10 ml of water. The mixture then washed with water (500 ml), saturated sodium bicarbonate (500 ml) and concentrated. The crude product was triturated with methylenechloride (50 ml) and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, 15% EtOAc in hexane) to afford **7** as with solid (12.5 g, 53%). ¹NMR (300 MHz, CDCl₃): δ 8.02 (d, J = 7.4 Hz, 2H), 7.72 (d, J = 7.4 Hz, 2H), 7.56 (m, 1H), 7.52 (m, 2H), 7.11 (d, J = 5.4 Hz, 2H), 5.52 (d, J = 6.9 Hz, 1H), 4.75 (ddd, J = 3.8, 9.5, 28.2 Hz, 1H), 4.60 (ddd, J = 3.8, 9.5, 28.2 Hz, 1H), 4.36 (m, 1H); C₁₆H₁₃FINO, LCMS (EI) m/z: 381 (M⁺)

4-Fluoromethyl-2-phenyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-4,5-dihydro-oxazole (8): To a solution of **7** (760 mg, 2.0 mmol) in THF (5 ml) was added n-BuLi (2 ml, 1.6 M in Hexane, 3.2 mmol) at -78 °C. After stirring for 30 min, isopropyl pinacol boronate (595 mg, 3.2 mmol) was added. Slowly warmed to room temperature and

stirred overnight. The reaction mixture was diluted with EtOAc (40 ml) and washed with water (30 ml), dried over Na₂SO₄ and concentrated. The crude product was purified by PTLC (Hexane/ EtOAc, 2:1) to afford **8** as white solid (490 mg, 64%). ¹NMR (300 MHz, CDCl₃): δ 8.04 (d, J = 7.0 Hz, 2H), 7.83 (d, J = 7.0 Hz, 2H), 7.51 (m, 1H), 7.45 (m, 2H), 7.36 (d, J = 7.8 Hz, 2H), 5.87 (d, J = 6.9 Hz, 1H), 4.76 (m, 1H), 4.61 (m, 1H), 4.35 (m, 1H), 1.34 (s, 12H); C₂₂H₂₅BFNO₃, LCMS (EI) m/z: 381 (M⁺).

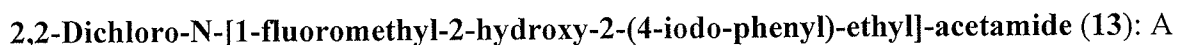
{5-[4-(4-Fluoromethyl-2-phenyl-4,5-dihydro-oxazol-5-yl)-phenyl]-pyridin-2-yl}-

methanol (9): A mixture of **8** (308 mg, 0.8 mmol), 2-hydromethyl-5-bromopyridine (150 mg, 0.8 mmol), K₂CO₃ (332 mg, 2.4 mmol), Pd(dppf)Cl₂ (34 mg, 0.04 mmol) and toluene/EtOH/H₂O (3:1:1, 10 ml) was degassed. The mixture was heated at 90 °C for 16 h under argon atmosphere. Diluted with EtOAc (50 ml), washed with H₂O (30 ml) and concentrated. The crude product was purified by PTLC (EtOAc/Hexane, 1:1) to afford **9** as white solid (180 mg, 63%). ¹NMR (300 MHz, CDCl₃): δ 8.78 (d, J = 1.8 Hz, 1H), 8.04 (d, J = 6.9 Hz, 2H), 7.87 (dd, J = 1.8, 8.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.53 (m, 1H), 7.48 (m, 4H), 7.33 (d, J = 8.1 Hz, 1H), 5.64 (d, J = 6.9 Hz, 1H), 4.82 (d, J = 4.6 Hz, 2H), 4.68 (m, 1H), 4.60 (m, 1H), 4.41 (m, 1H), 6.10 (t, J = 4.6 Hz, 1H); C₂₂H₁₉FN₂O₂, LCMS (EI) m/z: 363 (M⁺+H).

2-Amino-3-fluoro-1-[4-(6-hydroxymethyl-pyridin-3-yl)-phenyl]-propan-1-ol (10): A mixture of **9** (60 mg, 0.165 mmol), AcOH (1 ml) and 6 N HCl (1 ml) was heated at 100 °C for 16 h in a sealed tube. After basified with 6 N KOH (5 ml), the mixture was extracted with EtOAc (20 ml x 3) and dried over Na₂SO₄ and concentrated to afford **10** as light yellow solid (40 mg, 88%). ¹NMR (300 MHz, CD₃OD): δ 8.59 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 1.8, 8.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 4.63 (s, 2H), 4.60 (d, J = 6.9 Hz, 1H), 4.30 (ddd, J = 4.2, 9.5, 28.2 Hz, 1H), 4.10 (ddd, J = 4.2, 9.5, 28.2 Hz, 1H), 3.18 (m, 1H); C₁₅H₁₇FN₂O₂, LCMS (EI) m/z: 277 (M⁺+H).

2,2-Dichloro-N-{1-fluoromethyl-2-hydroxy-2-[4-(6-hydroxymethyl-pyridin-3-yl)-

phenyl]-ethyl}-acetamide (3-2): Dichloroacetic chloride (47.3 mg, 0.322 mmol) in CH₂Cl₂ (1 ml) was added slowly to a mixture of **10** (74 mg, 0.268 mmol), triethylamine (51 mg, 0.50 mmol) and DMF (10 ml) at 0 °C and the resulted mixture was stirred at room temperature for 16 h. Diluted with CH₂Cl₂ (20 ml), washed with H₂O (20 ml) and concentrated. The crude



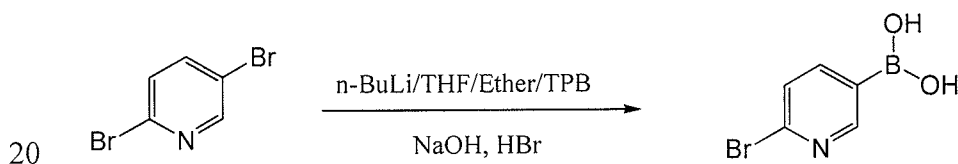
10 mixture of **7** (14.9 g, 39.2 mmol), AcOH (25 ml) and 6 N HCl (25 ml) was heated at 110 °C for 16 h in a sealed tube. After basified with 6 N KOH (150 ml), the mixture was extracted with EtOAc (300 ml x 3) and dried over Na₂SO₄ and concentrated to afford D-(-)-threo-2-amino-*p*-iodophenyl-propane-1,3-diol as a light yellow solid (12.2 g, 97%). ¹NMR (300 MHz, CDCl₃): δ 7.70 (d, J = 7.5 Hz, 4H), 7.11 (d, J = 7.5 Hz, 2H), 4.52 (d, J = 6.3 Hz, 1H),
15 4.40 (ddd, J = 5.3, 9.4, 29.2 Hz, 1H), 4.20 (ddd, J = 5.4, 9.4, 29.2 Hz, 1H), 3.07 (m, 1H).

The above product (12.2 g, 38.0 mmol) was dissolved in CH₂Cl₂ (260 ml) and Hunig's base (11.06 g, 85.7 mmol) was added. The resulted mixture was cool to 0 °C and a solution of dichloroacetic chloride (6.32 g, 43.0 mmol) in CH₂Cl₂ (40 ml) was added dropwise. After addition was completed, the mixture was stirred at room temperature for 3 h. Washed with H₂O (200 ml) and concentrated. The crude product was purified by flash chromatography (EtOAc/Hexane, 2:1) to afford **13** as white solid (11.3 g, 53%). ¹NMR (300 MHz, CDCl₃): δ 7.70 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.98 (d, J = 8.4 Hz, 1H), 5.86 (s, 1H), 5.08 (t, J = 3.6 Hz, 1H), 4.63 (ddd, J = 3.6, 9.3, 31.8 Hz, 1H), 4.40 (ddd, J = 4.2, 9.3, 29.4 Hz, 1H), 4.27 (m, 1H); C₁₁H₁₁Cl₂FNO₂, LCMS (EI) m/z: 404 (M⁺).

N-{2-[4'-(Acetylamino-methyl)-biphenyl-4-yl]-1-fluoromethyl-2-hydroxy-ethyl}-2,2-dichloro-acetamide (1-3) A mixture of **13** (300 mg, 0.74 mmol), 4-

acetylaminomethylphenylboronic acid (172 mg, 0.89 mmol), K_2CO_3 (306 mg, 2.22 mmol), tetrakis(triphenylphosphine)palladium (0) (41 mg, 0.037 mmol) and toluene/EtOH/ H_2O (3:1:1, 10 ml) was degassed. The mixture was heated at 90 °C for 3 h under argon atmosphere. Diluted with EtOAc (30 ml), washed with H_2O (20 ml) and concentrated. The crude product was purified by PTLC (EtOAc/Hexane/MeOH, 1:2:0.3) to afford **1-3** as solid (250 mg, 79%). 1NMR (300 MHz, $CDCl_3$): δ 7.58 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.28 (s, 1H), 4.97 (d, J = 3.9 Hz, 1H), 4.62 (ddd, J = 5.3, 9.3, 31.8 Hz, 1H), 4.40 (ddd, J = 4.2, 9.3, 29.4 Hz, 1H), 4.30 (m, 1H);

N-{2-[4-(6-Bromo-pyridin-3-yl)-phenyl]-1-fluoromethyl-2-hydroxy-ethyl}-2,2-dichloro-acetamide (3-7) A mixture of **13** (205 mg, 0.50 mmol), 2-bromo-pyridinyl-5-boronic acid (101 mg, 0.50 mmol), K_2CO_3 (208 mg, 1.50 mmol), $Pd(dppf)Cl_2$ (28 mg, 0.025 mmol) and DMF/ H_2O (3:1, 6 ml) was degassed. The mixture was heated at 80 °C for 3 h under argon atmosphere. Diluted with EtOAc (30 ml), washed with H_2O (20 ml) and concentrated. The crude product was purified by PTLC (EtOAc/Hexane/MeOH, 1:2:0.3) to afford **3-7** as a solid (80 mg, 37%). 1NMR (300 MHz, $CDCl_3$): δ 8.52 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 2.4, 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 1H), 5.87 (s, 1H), 5.20 (d, J = 3.6 Hz, 1H), 4.68 (ddd, J = 6.3, 9.3, 32.4 Hz, 1H), 4.54 (ddd, J = 4.5, 9.3, 29.4 Hz, 1H), 4.31 (m, 1H);

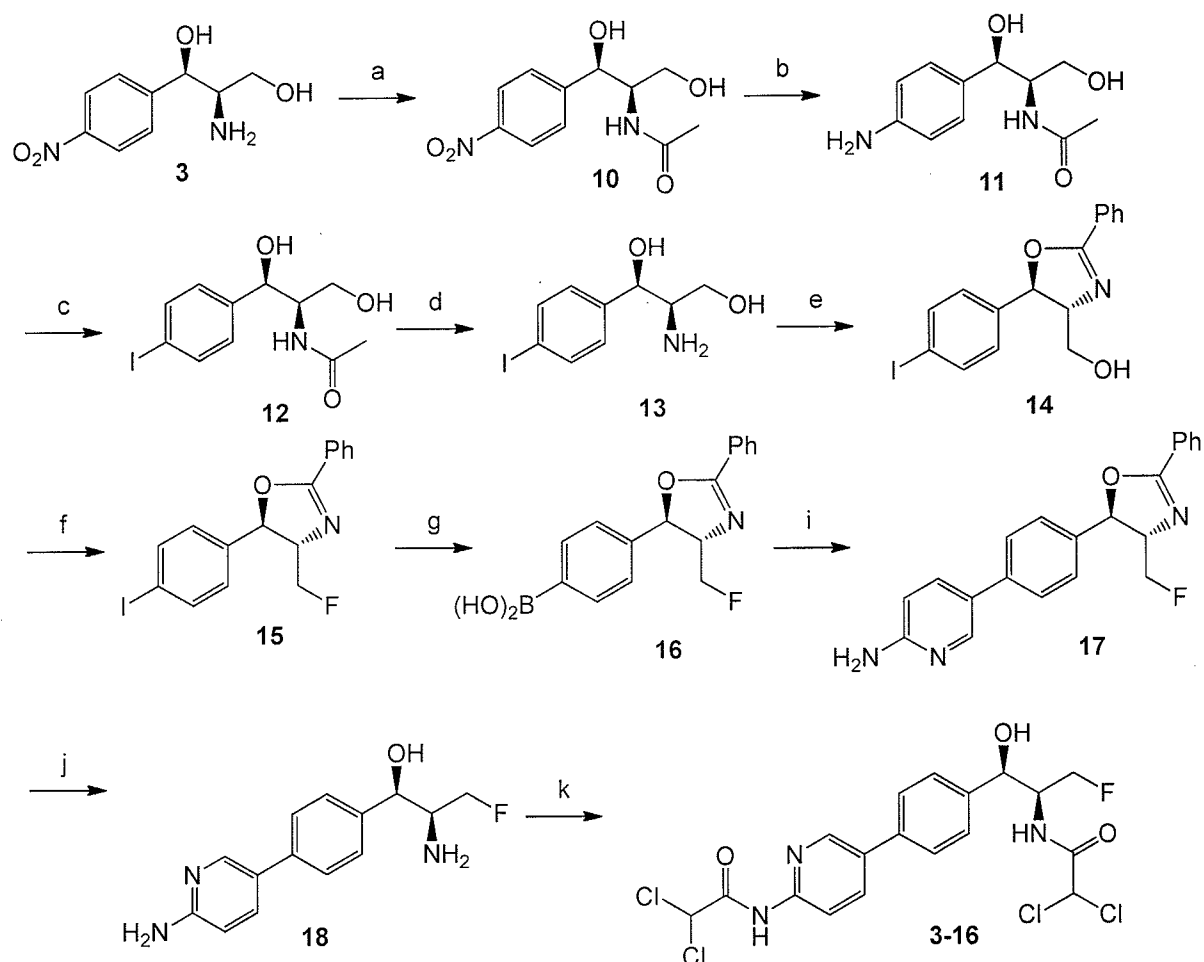


To a solution of 2,5-dibromopyridine (2.37 g, 10 mmol) in 90 mL of Ether/THF (8:1) was added 7.5 mL of $n-BuLi$ (1.6 M in hexane) at -78°C dropwise. After addition, the mixture was stirred for 2h at -78°C. Triisopropylborate (4.49g, 24 mmol) was added. The resulted mixture was stirred for 2h at -78°C, then allowed to warm to rt and quenched with 10 mL of water. The reaction mixture was stirred overnight. The organic solvent was evaporated and the remaining aqueous layer was taken to pH 10 with 5% of $NaOH$ and washed with ether (30 mL x 3). The aqueous layer was then carefully acidified to pH 4 with 48% of HBr to give the desired boronic acid (1.46 g, 72%). 1NMR (300 MHz, $DMSO-d_3$): δ 8.68 (dd, J = 2.1, 0.7 Hz, 1H), 8.53 (br.s, 2H), 8.05 (dd, J = 2.1, 7.8 Hz, 1H), 7.67 (dd, J = 7.8, 0.7 Hz, 1H).

30

Example 3: Synthesis of Compound 3-16

This example illustrates the synthesis of compound **3-16**.



^a Reagents and conditions: (a) Acetic anhydride/ NaHCO_3 , $\text{H}_2\text{O}/\text{THF}$, 0°C -rt; (b) $\text{Pd-C}/[\text{H}_2]$, MeOH ; (c) (1) NaNO_2/HCl , H_2O , 0°C ; (2) KI , 0°C -rt; (d): 10% H_2SO_4 , 110°C ; (e) ethyl benzimidate hydrochloride/ Et_3N , $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux; (f) DAST , CH_2Cl_2 , -78°C -rt; (g) $n\text{-BuLi}$ /triisopropylboron, THF , -78°C -rt, then HCl ; (i) $\text{R-Br}/\text{Pd}(\text{PPh}_3)_4/\text{K}_2\text{CO}_3$, toluene/ $\text{EtOH}/\text{H}_2\text{O}$, 90°C ; (j) $\text{AcOH}/6\text{ N HCl}$, 110°C ; (k) $\text{Cl}_2\text{CHCOCl}/\text{Et}_3\text{N}$, CH_2Cl_2 , 0°C -rt.

5

N-[2-Hydroxy-1-hydroxymethyl-2-(4-nitro-phenyl)-ethyl]-acetamide (10). To a mixture of *D*-(-)-threo-2-amino-*p*-nitrophenyl-propane-1,3-diol (**3**) (9.85 g, 46.4 mmol, 1.0 eq.), NaHCO_3 (29.2 g, 348.0 mmol, 7.5 eq.), H_2O (300 mL) and THF (100 mL) was added dropwise a solution of acetic anhydride (13.1 mL, 139.1 mmol) in THF (30 mL) at 0°C .

10 After addition was completed, the resulted mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc (300 mL x 3). The EtOAc extract was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The crude product was triturated with EtOAc (30 mL) and filtered. The solid was collected and dried to afford

10 as white powder (10.6 g, 90%). ¹NMR (300 MHz, DMSO-*d*₆): δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 5.82 (d, *J* = 7.5 Hz, 1H), 5.01 (m, 1H), 4.84 (t, *J* = 4.5 Hz, 1H), 3.94 (m, 1H), 3.53 (m, 1H), 3.28 (m, 1H), 1.69 (s, 3H); C₁₁H₁₄N₂O₅, LCMS (EI) *m/z*: 254 (M⁺).

- 5 ***N*-[2-(4-Amino-phenyl)-2-hydroxy-1-hydroxymethyl-ethyl]-acetamide (11)**. A solution of **10** (4.07 g, 16 mmol) in MeOH (40 mL) was purged with Argon, Pd/C (10 %, 0.4 g) was added. The resulted mixture was stirred under hydrogen atmosphere for 16 h at room temperature. Filtered through a pad of celite and the filtrate was concentrated to afford **11** as light yellowish solid (3.80 g, 100%). ¹NMR (300 MHz, CD₃OD): δ 7.12 (d, *J* = 8.4 Hz, 2H),
10 6.70 (d, *J* = 8.4 Hz, 2H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.02 (m, 1H), 3.61 (dd, *J* = 5.4, 10.8 Hz, 1H), 3.40 (dd, *J* = 5.4, 10.8 Hz, 1H), 1.93 (s, 3H); C₁₁H₁₆N₂O₃, LCMS (EI) *m/z*: 225 (M + H)⁺.

- N*-[2-Hydroxy-1-hydroxymethyl-2-(4-iodo-phenyl)-ethyl]-acetamide (12)**. A solution of
15 NaNO₂ (7.47 g, 108 mmol, 1.08 eq.) in water (100 mL) was added dropwise to a solution of **11** (22.4 g, 100 mmol, 1.0 eq.) in 1 N HCl (200 mL) at 0 °C. After addition was completed, the mixture was stirred for additional 30 min and then added slowly to a solution of KI (24.40 g, 147 mmol, 1.47 eq.) in water (180 mL) at 0 °C. After addition was completed, the mixture was warmed up to room temperature and stirred overnight. The reaction mixture was
20 neutralized with solid KOH and extracted with EtOAc (600 mL x 3). The extract was washed with brine (500 mL), dried over Na₂SO₄ and concentrated to afford **12** as light yellowish solid (26.7 g, 81%). ¹NMR (300 MHz, CD₃OD): δ 7.65 (d, *J* = 9.0 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 4.89 (d, *J* = 9.0 Hz, 1H), 4.04 (m, 1H), 3.68 (dd, *J* = 6.3, 10.8 Hz, 1H), 3.47 (dd, *J* = 5.4, 10.8 Hz, 1H), 2.01 (s, 3H); C₁₁H₁₄INO₃, LCMS (EI) *m/z*: 335 (M⁺).

25

- 2-Amino-1-(4-iodo-phenyl)-propane-1,3-diol (13)**. A solution of **12** (53.4 g, 159 mmol) in 10% H₂SO₄ (320 mL) was heated at 105 °C for 18 h. After cooled to room temperature the reaction mixture was basified with KOH to pH = 13, extracted with EtOAc (400 mL x 6), washed with brine (50 mL), dried over Na₂SO₄ and concentrated to afford **13** as light
30 yellowish solid (45.0 g, 96.6%). ¹NMR (300 MHz, CD₃OD): δ 7.56 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 4.45 (d, *J* = 8.2 Hz, 1H), 3.34 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.21 (dd, *J* = 5.4, 10.8 Hz, 1H), 2.76 (m, 1H); C₉H₁₂INO₂, LCMS (EI) *m/z*: 294 (M + H)⁺.

[5-(4-Iodo-phenyl)-2-phenyl-4,5-dihydro-oxazol-4-yl]-methanol (14). A mixture of **13** (45.0 g, 153.6 mmol, 1.0 eq.), ethyl benzimidate hydrochloride (28.5 g, 153.6 mmol, 1.0 eq.), triethylamine (19.8 g, 153.6 mmol, 1.0 eq) and dichloroethane (800 mL) was refluxed for 16 h. The mixture was then cooled to -20 °C for 4 h. The crystals were collected by filtration and washed thoroughly with water, and dried under vacuum to afford **14** (36.30 g, 62%). ¹NMR (300 MHz, CD₃OD): δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.65 (m, 1H), 7.56 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 5.58 (d, *J* = 6.3 Hz, 1H), 5.12 (t, *J* = 5.7 Hz, 1H), 4.12 (m, 1H), 3.79 (m, 1H), 3.62 (m, 1H); C₁₆H₁₄INO₂, LCMS (EI) *m/z*: 379 (M⁺).

4-Fluoromethyl-5-(4-iodo-phenyl)-2-phenyl-4,5-dihydro-oxazole (15). A of **14** (21.0 g, 55.40 mmol, 1.0 eq.) in CH₂Cl₂ (800 mL) was cooled to -78 °C and DAST (11.62 mL, 88.67 mmol, 1.6 eq.) was added dropwise. After addition, the mixture was slowly warmed up to room temperature and stirred at room temperature overnight before quenched with H₂O (10 mL). The mixture then washed with H₂O (500 mL), saturated NaHCO₃ (500 mL) and concentrated. The crude product was triturated with CH₂Cl₂ (50 mL) and filtered. The filtrate was concentrated and purified by flash chromatography (15% EtOAc in hexane) to afford **15** as white solid (12.5 g, 53%). ¹NMR (300 MHz, CDCl₃): δ 8.02 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 7.4 Hz, 2H), 7.56 (m, 1H), 7.52 (m, 2H), 7.11 (d, *J* = 5.4 Hz, 2H), 5.52 (d, *J* = 6.9 Hz, 1H), 4.75 (ddd, *J* = 3.8, 9.5, 28.2 Hz, 1H), 4.60 (ddd, *J* = 3.8, 9.5, 28.2 Hz, 1H), 4.36 (m, 1H); LCMS (EI) *m/z*: 381 (M + H)⁺, C₁₆H₁₄FINO.

4-Fluoromethyl-2-phenyl-5-[(4-dihydroxyboronyl)-phenyl]-4,5-dihydro-oxazole (16). To a solution of **15** (9.3 g, 24.47 mmol, 1 eq.) in THF (110 mL) was added *n*-BuLi (18.4 mL, 1.6 M in Hexane, 29.4 mmol, 1.2 eq.) dropwise at -78 °C. After stirring for 30 min, triisopropoxylboron (11.0 g, 58.73 mmol, 2.4 eq.) was added. Slowly warmed to room temperature and stirred overnight. The reaction mixture was concentrated and dissolved in MeOH (50 mL). 2 N NaOH was added to adjust pH to 11, concentrated to a volume of 50 mL and 6 N of HCl was added to adjust pH to 2, extracted with EtOAc (100 mL x 5), dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (EtOAc in Hexane, line-gradient 5%-100%) to afford **16a** as brown solid (4.2 g, 57%). ¹NMR (300 MHz, CD₃OD): δ 8.04 (d, *J* = 7.0 Hz, 2H), 7.83 (d, *J* = 7.0 Hz, 2H), 7.51 (m, 1H), 7.45 (m, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 6.02 (d, *J* = 6.9 Hz, 1H), 4.76 (m, 1H), 4.61 (m, 1H), 4.35 (m, 1H); LCMS (EI) *m/z*: 299.0 (M + H)⁺, C₁₆H₁₆BFNO₃.

5-[4-(4-Fluoromethyl-2-phenyl-4,5-dihydro-oxazol-5-yl)-phenyl]-pyridin-2-ylamine (17).

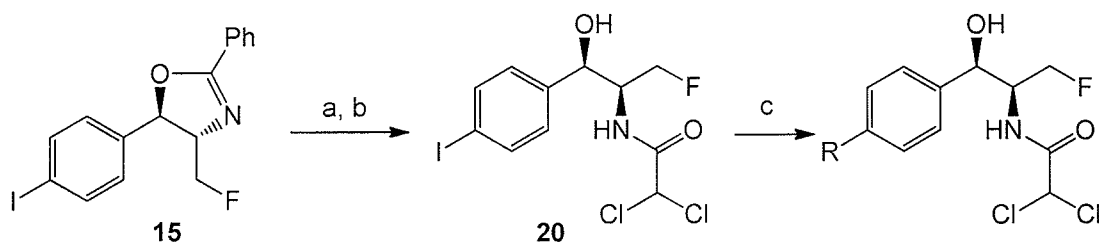
A mixture of **16** (1.0 eq.), arylbromide (1.3 eq.), K₂CO₃ (3.0 eq.), tetrakis(triphenylphosphine)palladium (0) (0.05 eq.) and toluene/EtOH/H₂O (3:1:1, 5 mL) was degassed three times under a steady stream of Argon. The mixture was then heated at 90 °C for 3 to 16 h under argon atmosphere. After TLC and LCMS analysis showing the reaction was completed, the reaction mixture was then diluted with EtOAc (20 mL), washed with H₂O (20 mL) and concentrated. The crude product was purified by PTLC (EtOAc/Hexane/MeOH, 1:2:0.3). Yield: 87%; brown solid. ¹NMR (300 MHz, CDCl₃): δ 8.32 (d, *J* = 2.1 Hz, 1H), 8.04 (d, *J* = 6.9 Hz, 2H), 7.68 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.56 (m, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.43 (m, 4H), 6.58 (d, *J* = 8.4 Hz, 1H), 5.60 (d, *J* = 6.9 Hz, 1H), 4.78 (ddd, *J* = 3.8, 9.5, 28.2 Hz, 1H), 4.62 (ddd, *J* = 3.8, 9.5, 28.2 Hz, 1H), 4.52 (bs, 2H), 4.46 (m, 1H); LCMS (EI) *m/z*: 348 (M + H)⁺, C₂₁H₁₉FN₃O.

2,2-Dichloro-N-(2-{4-[6-(2,2-dichloro-acetyl-amino)-pyridin-3-yl]-phenyl}-1-

fluoromethyl-2-hydroxy-ethyl)-acetamide (3-16). A mixture of oxazoline **17** (0.25 mmol, 1.0 eq.), AcOH (2 mL) and 6 N HCl (2 mL) was heated at 100-110 °C for 16 h in a sealed tube. After basified with 6 N KOH to pH = 13, the mixture was extracted with EtOAc (40 mL x 3). The combined extract was dried over Na₂SO₄ and concentrated to afford corresponding amine **18**. A solution of dichloroacetic chloride (1.0 eq.) in CH₂Cl₂ (1 mL) was added slowly to a mixture of amine **18** (1 eq.), triethylamine (2.0 eq.) and CH₂Cl₂ (5 mL) at 0 °C. The resulting mixture was warmed up to room temperature and stirred for 16 h, washed with H₂O (5 mL) and concentrated. The crude product was purified by PTLC (EtOAc/Hexane/MeOH, 1:3:0.3) to afford **3-16** as white solid (Yield: 23% from **17**). ¹NMR (300 MHz, CD₃OD): δ 8.60 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 2.4, 8.7 Hz, 1H), 8.06 (dd, *J* = 2.4, 8.7, 1H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 6.51 (s, 1H), 6.28 (s, 1H), 5.00 (d, *J* = 3.6 Hz, 1H), 4.65 (ddd, *J* = 4.2, 9.5, 28.2 Hz, 1H), 4.41 (ddd, *J* = 4.2, 9.5, 28.2 Hz, 1H), 4.32 (m, 1H); LCMS (EI) *m/z*: 484.9 (M + H)⁺, C₁₈H₁₇Cl₄FN₃O₃.

Example 4: Synthesis of compounds 4-3 and 3-11

This example illustrates the synthesis of compounds **4-3** and **3-11**.



^a Reagents and conditions: (a) AcOH/6 N HCl, 110°C; (b) Cl₂CHCOCl/Et₃N, CH₂Cl₂, 0°C-rt. (c) R-B(OR')₂/ Pd(dppf)Cl₂/K₂CO₃, toluene/EtOH/H₂O, 90°C;

- 5 **2,2-Dichloro-N-[1-fluoromethyl-2-hydroxy-2-(4-iodo-phenyl)-ethyl]-acetamide (20).** A mixture of oxazoline **15** (12.2 g, 38.0 mmol, 1.0 eq.), AcOH (40 mL) and 6 N HCl (40 mL) was heated at 100-110 °C for 16 h in a sealed tube. After basified with 6 N KOH to pH = 13, the mixture was extracted with EtOAc (100 mL x 3). The combined extract was dried over Na₂SO₄ and concentrated to afford corresponding amine. A solution of dichloroacetic chloride (1.0 eq.) in CH₂Cl₂ (10 mL) was added slowly to a mixture of the above obtained, triethylamine (2.0 eq.) and CH₂Cl₂ (100 mL) at 0 °C. The resulted mixture was warmed up to room temperature and stirred for 16 h, washed with H₂O (100 mL) and concentrated. The crude product was purified by flash chromatography (0%-50% EtOAc in Hexane, linear gradient) to afford **20** as white solid (11.3 g, 53%);. ¹NMR (300 MHz, CDCl₃): δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.86 (s, 1H), 5.08 (t, *J* = 3.6 Hz, 1H), 4.63 (ddd, *J* = 3.6, 9.3, 31.8 Hz, 1H), 4.40 (ddd, *J* = 4.2, 9.3, 29.4 Hz, 1H), 4.27 (m, 1H); LCMS (EI) *m/z*: 404 (M⁺), C₁₁H₁₂Cl₂FNO₂.
- 10
- 15

General procedure for synthesis of dichloroacetamides 4-3 and 3-11. A mixture of **20** (1 eq.), aryl pinacolate boronate (1.3 eq.), K₂CO₃ (3 equiv), Pd(dppf)Cl₂ (0.05 equiv) and toluene/EtOH/H₂O (3:1:1, 5 mL) was degassed three times under a steady stream of Argon. The mixture was heated at 90 °C for 5h under argon atmosphere. After TLC and LCMS analysis showing the reaction was completed. The reaction mixture was diluted with EtOAc

20

(30 mL), washed with H₂O (20 mL) and concentrated. The crude product was purified by column chromatography (0 – 6% MeOH/CH₂Cl₂ gradient elution) to afford **4-3** and **3-11**.

2,2-Dichloro-N-(1-fluoromethyl-2-hydroxy-2-{4-[6-(1-methyl-1H-tetrazol-5-yl)-pyridin-

5 **3-yl]-phenyl}-ethyl)-acetamide (4-3).** Yield: 29%; pale-yellow solids. ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.07 (d, *J* = 1.7 Hz, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.30 (dd, *J* = 2.3, 8.3 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 6.53 (s, 1H), 6.02 (d, *J* = 4.3 Hz, 1H), 4.94 (d, *J* = 3.0 Hz, 1H), 4.65 (ddd, *J* = 5.5, 9.1, 46.8 Hz, 1H), 4.47 (s, 3H), 4.37 (m, 1H), 4.24 (m, 1H); LCMS (EI) *m/z*: 439 (M + H)⁺, C₁₈H₁₈Cl₂FN₆O₂.

10

2,2-Dichloro-N-(1-fluoromethyl-2-hydroxy-2-{4-[6-(2-methyl-2H-tetrazol-5-yl)-pyridin-

3-yl]-phenyl}-ethyl)-acetamide (3-11). Yield: 30%; pale-yellow solids. ¹H NMR (300 MHz, CDCl₃) δ 8.91 (d, *J* = 1.5 Hz, 1H), 8.06 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H, NH), 7.62 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 1H), 5.95 (s, 1H),
15 5.10 (d, *J* = 3.5 Hz, 1H), 4.63 (ddd, *J* = 6.4, 9.2, 46.2 Hz, 1H), 4.48 (ddd, *J* = 4.4, 9.2, 36.7 Hz, 1H), 4.36 (m, 1H), 3.35 (s, 1H), 3.41 (s, 3H); LCMS (EI) *m/z*: 439 (M + H)⁺, C₁₈H₁₈Cl₂FN₆O₂.

20 **INCORPORATION BY REFERENCE**

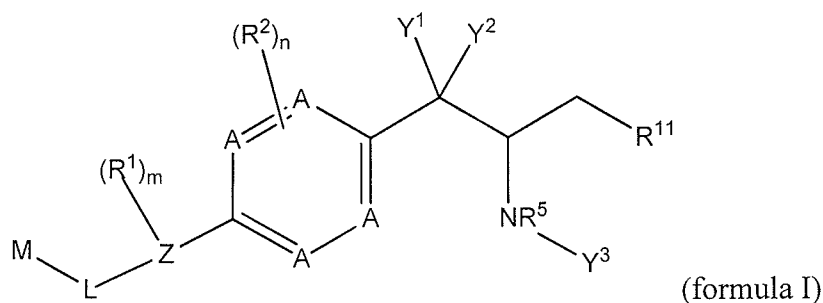
The entire disclosure of each of the patent documents, including certificates of correction, patent application documents, scientific articles, governmental reports, websites, and other references referred to herein is incorporated by reference in its entirety for all purposes.

25 **EQUIVALENTS**

The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing
30 description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

each A is individually selected from CH, CR^2 , nitrogen, and nitrogen oxide;

Y^1 and Y^2 are independently selected from: a) H, b) F, c) Cl, d) Br, e) I, f) $-CF_3$, g) $-OR^7$, h) $-CN$, i) $-NO_2$, j) $-NR^5R^5$, k) $-C(O)R^5$, l) $-C(O)OR^5$, m) $-OC(O)R^5$, n) $-C(O)NR^5R^5$, o) $-NR^5C(O)R^5$, p) $-OC(O)NR^5R^5$, q) $-NR^5C(O)OR^5$, r) $-NR^5C(O)NR^5R^5$, s) $-C(S)R^5$, t) $-C(S)OR^5$, u) $-OC(S)R^5$, v) $-C(S)NR^5R^5$, w) $-NR^5C(S)R^5$, x) $-OC(S)NR^5R^5$, y) $-NR^5C(S)OR^5$, z) $-NR^5C(S)NR^5R^5$, aa) $-NR^5C(NR^5)NR^5R^5$, bb) $-S(O)_pR^5$, and cc) R^5 ;

alternatively, Y^1 and Y^2 taken together form a) $=O$, b) $=S$, c) $=NR^5$, d) $=NOR^5$, or e) $=N-NR^5R^5$;

Y^3 is selected from: a) H, b) $S(O)_pR^7$, c) C_{1-6} alkyl, d) C_{2-6} alkenyl, e) C_{2-6} alkynyl, f) $C(O)-C_{1-6}$ alkyl, g) $C(O)-C_{2-6}$ alkenyl, h) $C(O)-C_{2-6}$ alkynyl, i) C_{3-14} saturated, unsaturated, or aromatic carbocycle, j) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, k) $C(O)-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, l) $C(O)-3-14$ membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, m) $C(O)C(O)-NR^5R^5$, and n) $C(O)C(O)-OR^5$,

wherein any of c) – l) optionally is substituted with one or more R^5 , R^{12} , R^{13} or R^{18} , and

any of the carbon atom of c) – h) optionally is replaced with NR^5 , oxygen, or sulfur;

alternatively, Y^3 and R^5 taken together form a 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur optionally substituted with one or more R^7 ;

alternatively, R^5 and R^{11} taken together form a 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur optionally substituted with one or more R^7 ;

Z is selected from a) bond, b) C_{3-14} saturated, unsaturated, or aromatic carbocycle, c) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, d) C_{1-6} alkyl, e) C_{2-6} alkenyl, and f) C_{2-6} alkynyl,

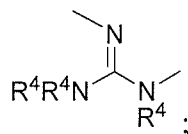
wherein any of b) – f) optionally is substituted with one or more R^5 groups;

M-L is selected from:

- a) M-X, b) $M-L^1$, c) $M-L^1-X$, d) $M-X-L^2$, e) $M-L^1-X-L^2$, f) $M-X-L^1-X-L^2$,
g) $M-L^1-X-L^2-X$, h) M-X-X-, i) $M-L^1-X-X-$, j) $M-X-X-L^2$, and
k) $M-L^1-X-X-L^2$, wherein

X, at each occurrence, independently is selected from:

- a) -O-, b) $-NR^4-$, c) $-N(O)-$, d) $-N(OR^4)-$, e) $-S(O)_p-$, f) $-SO_2NR^4-$,
g) $-NR^4SO_2-$, h) $-NR^4-N=$, i) $=N-NR^4-$, j) $-O-N=$, k) $=N-O-$,
l) $-N=$, m) $=N-$, n) $-NR^4-NR^4-$, o) $-NR^4C(O)O-$, p) $-OC(O)NR^4-$,
q) $-NR^4C(O)NR^4-$, r) $-NR^4C(NR^4)NR^4-$, s) $-C(O)-$, t) $-NR^4C(O)-$,
u) $-C(O)NR^4-$, v) $-OC(O)-$, w) $-C(O)O-$, and
x)



L^1 is selected from:

- a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups; and

L^2 is selected from:

- a) C_{1-6} alkyl, b) C_{2-6} alkenyl, and c) C_{2-6} alkynyl,

wherein any of a) – c) optionally is substituted with one or more R^5 groups;

alternatively, L in M-L is a bond;

M is selected from:

- a) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, b) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, c) C₁₋₆ alkyl, d) C₂₋₆ alkenyl, e) C₂₋₆ alkynyl, f) -NH₂, g) -CN, h) H, i) F, j) Cl, k) Br, l) I, m) OH, n) C(O)H, o) C(O)R⁶, p) S(O)_pR⁶, and q) NO₂,

wherein any of a) - e) optionally is substituted with one or more R⁵ groups;

R¹, at each occurrence, independently is selected from:

- a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷, j) -C(O)R⁷, k) -C(O)OR⁷, l) -OC(O)R⁷, m) -C(O)NR⁷R⁷, n) -NR⁷C(O)R⁷, o) -OC(O)NR⁷R⁷, p) -NR⁷C(O)OR⁷, q) -NR⁷C(O)NR⁷R⁷, r) -C(S)R⁷, s) -C(S)OR⁷, t) -OC(S)R⁷, u) -C(S)NR⁷R⁷, v) -NR⁷C(S)R⁷, w) -OC(S)NR⁷R⁷, x) -NR⁷C(S)OR⁷, y) -NR⁷C(S)NR⁷R⁷, z) -NR⁷C(NR⁷)NR⁷R⁷, aa) -S(O)_pR⁷, bb) -SO₂NR⁷R⁷, and cc) R⁷;

R², at each occurrence, independently is selected from:

- a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷, j) -C(O)R⁷, k) -C(O)OR⁷, l) -OC(O)R⁷, m) -C(O)NR⁷R⁷, n) -NR⁷C(O)R⁷, o) -OC(O)NR⁷R⁷, p) -NR⁷C(O)OR⁷, q) -NR⁷C(O)NR⁷R⁷, r) -C(S)R⁷, s) -C(S)OR⁷, t) -OC(S)R⁷, u) -C(S)NR⁷R⁷, v) -NR⁷C(S)R⁷, w) -OC(S)NR⁷R⁷, x) -NR⁷C(S)OR⁷, y) -NR⁷C(S)NR⁷R⁷, z) -NR⁷C(NR⁷)NR⁷R⁷, aa) -S(O)_pR⁷, bb) -SO₂NR⁷R⁷, and cc) R⁷;

R⁴, at each occurrence, independently is selected from:

- a) H, b) F, c) Cl, d) Br, e) I, f) =O, g) =S, h) =NR⁵, i) =NOR⁵, j) =N-NR⁵R⁵, k) -CF₃, l) -OR⁵, m) -CN, n) -NO₂, o) -NR⁵R⁵, p) -C(O)R⁵, q) -C(O)OR⁵, r) -OC(O)R⁵, s) -C(O)NR⁵R⁵, t) -NR⁵C(O)R⁵, u) -OC(O)NR⁵R⁵, v) -NR⁵C(O)OR⁵, w) -NR⁵C(O)NR⁵R⁵, x) -C(S)R⁵, y) -C(S)OR⁵, z) -OC(S)R⁵, aa) -C(S)NR⁵R⁵, bb) -NR⁵C(S)R⁵, cc) -OC(S)NR⁵R⁵, dd) -NR⁵C(S)OR⁵, ee) -NR⁵C(S)NR⁵R⁵, ff) -NR⁵C(NR⁵)NR⁵R⁵, gg) -S(O)_pR⁵, hh) R⁵, and ii) C₁₋₆ alkyl optionally substituted with R⁷;

R⁵, at each occurrence, independently is selected from:

- a) H, b) C₁₋₆ alkyl, c) C₂₋₆ alkenyl, d) C₂₋₆ alkynyl, e) -C(O)-C₁₋₆ alkyl, f) -C(O)-C₂₋₆ alkenyl, g) -C(O)-C₂₋₆ alkynyl, h) -C(O)O-C₁₋₆ alkyl,

i) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkenyl, j) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkynyl, k) F, l) Cl, m) Br, n) I, o) OH, p) $\text{C}(\text{O})\text{H}$, q) $\text{C}(\text{O})\text{R}^7$, r) NR^7R^7 , s) $\text{NR}^7\text{C}(\text{O})\text{R}^7$, t) $\text{C}(\text{O})\text{NR}^7\text{R}^7$, u) $\text{S}(\text{O})_p\text{R}^6$, v) CN, w) C_{3-14} saturated, unsaturated, or aromatic carbocycle, x) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, y) $-\text{O}-\text{C}_{1-6}$ alkyl, z) $-\text{O}-\text{C}_{2-6}$ alkenyl, aa) $-\text{O}-\text{C}_{2-6}$ alkynyl, bb) $\text{NR}^7\text{C}(=\text{NR}^7)\text{NR}^7\text{R}^7$, and cc) NO_2 ,

wherein any of b) – j) and x) – aa) optionally is substituted with one or more R^6 groups;

R^6 , at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) $-\text{CF}_3$, f) $-\text{OH}$, g) $-\text{OC}_{1-6}$ alkyl, h) $-\text{SH}$, i) $-\text{SC}_{1-6}$ alkyl, j) $-\text{CN}$, k) $-\text{NO}_2$, l) $-\text{NH}_2$, m) $-\text{NHC}_{1-6}$ alkyl, n) $-\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, o) $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl, p) $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl, q) $-\text{C}(\text{O})\text{NH}_2$, r) $-\text{C}(\text{O})\text{NHC}_{1-6}$ alkyl, s) $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, t) $-\text{NHC}(\text{O})\text{C}_{1-6}$ alkyl, u) $-\text{S}(\text{O})_p\text{R}^7$, v) NHR^7 , w) NR^7R^7 , x) C_{3-14} saturated, unsaturated, or aromatic carbocycle, y) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, and z) OR^8 ,

wherein any of x) – y) optionally is substituted with one or more R^8 ;

R^7 , at each occurrence, independently is selected from:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, g) $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl, h) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkenyl, i) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkynyl, j) $-\text{C}(\text{O})-\text{C}_{3-14}$ saturated, unsaturated, or aromatic carbocycle, k) $-\text{C}(\text{O})-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl, m) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkenyl, n) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkynyl, o) $-\text{C}(\text{O})\text{O}-\text{C}_{3-14}$ saturated, unsaturated, or aromatic carbocycle, and

p) $-C(O)O$ -3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^8 groups;

R^8 , at each occurrence, is independently selected from:

a) F, b) Cl, c) Br, d) I, e) $=O$, f) $=S$, g) $=NR^9$, h) $=NOR^9$, i) $=N-NR^9R^9$, j) $-CF_3$, k) $-OR^9$, l) $-CN$, m) $-NO_2$, n) $-NR^9R^9$, o) $-C(O)R^9$, p) $-C(O)OR^9$, q) $-OC(O)R^9$, r) $-C(O)NR^9R^9$, s) $-NR^9C(O)R^9$, t) $-OC(O)NR^9R^9$, u) $-NR^9C(O)OR^9$, v) $-NR^9C(O)NR^9R^9$, w) $-C(S)R^9$, x) $-C(S)OR^9$, y) $-OC(S)R^9$, z) $-C(S)NR^9R^9$, aa) $-NR^9C(S)R^9$, bb) $-OC(S)NR^9R^9$, cc) $-NR^9C(S)OR^9$, dd) $-NR^9C(S)NR^9R^9$, ee) $-NR^9C(NR^9)NR^9R^9$, ff) $-S(O)_pR^9$, gg) $-SO_2NR^9R^9$, and hh) R^9 ;

R^9 , at each occurrence, independently is selected from:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, g) $-C(O)-C_{1-6}$ alkyl, h) $-C(O)-C_{2-6}$ alkenyl, i) $-C(O)-C_{2-6}$ alkynyl, j) $-C(O)-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, k) $-C(O)-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) $-C(O)O-C_{1-6}$ alkyl, m) $-C(O)O-C_{2-6}$ alkenyl, n) $-C(O)O-C_{2-6}$ alkynyl, o) $-C(O)O-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, and p) $-C(O)O-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more moieties selected from:

a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OH$, g) $-OC_{1-6}$ alkyl, h) $-SH$, i) $-SC_{1-6}$ alkyl, j) $-CN$, k) $-NO_2$, l) $-NH_2$, m) $-NHC_{1-6}$ alkyl, n) $-N(C_{1-6} \text{ alkyl})_2$, o) $-C(O)C_{1-6}$ alkyl,

p) $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl, q) $-\text{C}(\text{O})\text{NH}_2$, r) $-\text{C}(\text{O})\text{NHC}_{1-6}$ alkyl, s) $-\text{C}(\text{O})\text{N}(\text{C}_{1-6}$ alkyl) $_2$, t) $-\text{NHC}(\text{O})\text{C}_{1-6}$ alkyl, u) $-\text{SO}_2\text{NH}_2$, v) $-\text{SO}_2\text{NHC}_{1-6}$ alkyl, w) $-\text{SO}_2\text{N}(\text{C}_{1-6}$ alkyl) $_2$, and
 x) $-\text{S}(\text{O})_p\text{C}_{1-6}$ alkyl;

R^{11} is selected from a) $-\text{OH}$, b) F, c) H, d) $\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl, and e) $\text{OC}(\text{O})-\text{C}_{1-6}$ alkyl;

R^{12} and R^{13} are independently selected from a) H, b) C_{1-4} alkyl, c) F, d) Cl, e) Br, f) I, g) CF_3 , h) NH_2 , i) CN, and j) N_3 ;

R^{18} is selected from a) H and b) F;

alternatively, R^{18} is absent and R^{12} and R^{13} together form

a) $=\text{O}$,

b) C_{3-14} saturated, unsaturated, or aromatic carbocycle, or

c) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of a) – b) optionally is substituted with one or more moieties selected from:

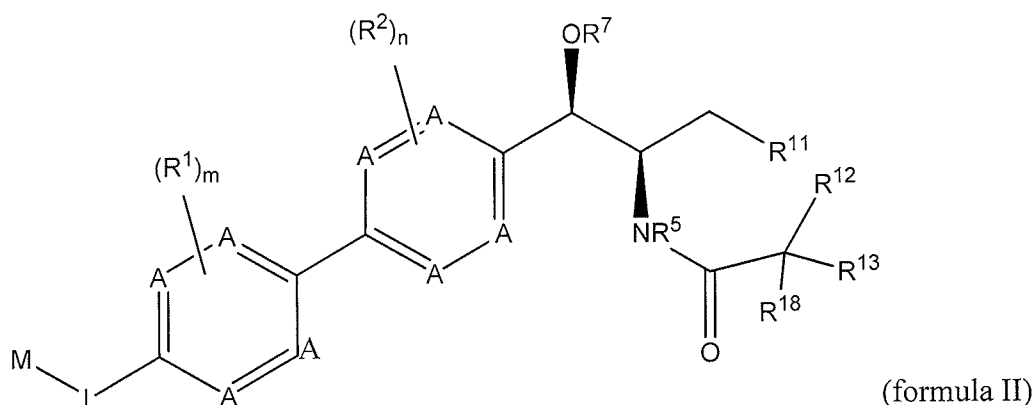
a) F, b) Cl, c) Br, d) I, e) $-\text{CF}_3$, f) $-\text{OH}$, g) $-\text{OC}_{1-6}$ alkyl, h) $-\text{SH}$, i) $-\text{SC}_{1-6}$ alkyl, j) $-\text{CN}$, k) $-\text{NO}_2$, l) $-\text{NH}_2$, m) $-\text{NHC}_{1-6}$ alkyl, n) $-\text{N}(\text{C}_{1-6}$ alkyl) $_2$, o) $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl, p) $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl, q) $-\text{C}(\text{O})\text{NH}_2$, r) $-\text{C}(\text{O})\text{NHC}_{1-6}$ alkyl, s) $-\text{C}(\text{O})\text{N}(\text{C}_{1-6}$ alkyl) $_2$, t) $-\text{NHC}(\text{O})\text{C}_{1-6}$ alkyl, u) $-\text{SO}_2\text{NH}_2$, v) $-\text{SO}_2\text{NHC}_{1-6}$ alkyl, w) $-\text{SO}_2\text{N}(\text{C}_{1-6}$ alkyl) $_2$, and
 x) $-\text{S}(\text{O})_p\text{C}_{1-6}$ alkyl;

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

p, at each occurrence, independently is 0, 1, or 2.

2. The compound according to claim 1 having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof, wherein:

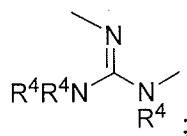
each A is individually selected from CH, CR², nitrogen, or nitrogen oxide;

M-L is selected from:

- a) M-X, b) M-L¹, c) M-L¹-X, d) M-X-L², e) M-L¹-X-L², f) M-X-L¹-X-L²,
 g) M-L¹-X-L²-X, h) M-X-X-, i) M-L¹-X-X-, j) M-X-X-L², and
 k) M-L¹-X-X-L², wherein

X, at each occurrence, independently is selected from:

- a) -O-, b) -NR⁴-, c) -N(O)-, d) -N(OR⁴)-, e) -S(O)_p-, f) -SO₂NR⁴-,
 g) -NR⁴SO₂-, h) -NR⁴-N=, i) =N-NR⁴-, j) -O-N=, k) =N-O-,
 l) -N=, m) =N-, n) -NR⁴-NR⁴-, o) -NR⁴C(O)O-, p) -OC(O)NR⁴-,
 q) -NR⁴C(O)NR⁴-, r) -NR⁴C(NR⁴)NR⁴-, and
 s)



L¹ is selected from:

- a) C₁₋₆ alkyl, b) C₂₋₆ alkenyl, and c) C₂₋₆ alkynyl,
 wherein any of a) – c) optionally is substituted with one or
 more R⁵ groups; and

L² is selected from:

- a) C₁₋₆ alkyl, b) C₂₋₆ alkenyl, and c) C₂₋₆ alkynyl,
 wherein any of a) – c) optionally is substituted with one or
 more R⁵ groups;

alternatively, L in M-L is a bond;

M is selected from:

a) C₃₋₁₄ saturated, unsaturated, or aromatic carbocycle, b) 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, c) C₁₋₆ alkyl, d) C₂₋₆ alkenyl, e) C₂₋₆ alkynyl, f) -NH₂, and g) -CN, wherein any of a) - e) optionally is substituted with one or more R⁵ groups;

R¹, at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷, j) -C(O)R⁷, k) -C(O)OR⁷, l) -OC(O)R⁷, m) -C(O)NR⁷R⁷, n) -NR⁷C(O)R⁷, o) -OC(O)NR⁷R⁷, p) -NR⁷C(O)OR⁷, q) -NR⁷C(O)NR⁷R⁷, r) -C(S)R⁷, s) -C(S)OR⁷, t) -OC(S)R⁷, u) -C(S)NR⁷R⁷, v) -NR⁷C(S)R⁷, w) -OC(S)NR⁷R⁷, x) -NR⁷C(S)OR⁷, y) -NR⁷C(S)NR⁷R⁷, z) -NR⁷C(NR⁷)NR⁷R⁷, aa) -S(O)_pR⁷, bb) -SO₂NR⁷R⁷, and cc) R⁷;

R², at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) -CF₃, f) -OR⁷, g) -CN, h) -NO₂, i) -NR⁷R⁷, j) -C(O)R⁷, k) -C(O)OR⁷, l) -OC(O)R⁷, m) -C(O)NR⁷R⁷, n) -NR⁷C(O)R⁷, o) -OC(O)NR⁷R⁷, p) -NR⁷C(O)OR⁷, q) -NR⁷C(O)NR⁷R⁷, r) -C(S)R⁷, s) -C(S)OR⁷, t) -OC(S)R⁷, u) -C(S)NR⁷R⁷, v) -NR⁷C(S)R⁷, w) -OC(S)NR⁷R⁷, x) -NR⁷C(S)OR⁷, y) -NR⁷C(S)NR⁷R⁷, z) -NR⁷C(NR⁷)NR⁷R⁷, aa) -S(O)_pR⁷, bb) -SO₂NR⁷R⁷, and cc) R⁷;

R⁴, at each occurrence, independently is selected from:

a) H, b) F, c) Cl, d) Br, e) I, f) =O, g) =S, h) =NR⁵, i) =NOR⁵, j) =N-NR⁵R⁵, k) -CF₃, l) -OR⁵, m) -CN, n) -NO₂, o) -NR⁵R⁵, p) -C(O)R⁵, q) -C(O)OR⁵, r) -OC(O)R⁵, s) -C(O)NR⁵R⁵, t) -NR⁵C(O)R⁵, u) -OC(O)NR⁵R⁵, v) -NR⁵C(O)OR⁵, w) -NR⁵C(O)NR⁵R⁵, x) -C(S)R⁵, y) -C(S)OR⁵, z) -OC(S)R⁵, aa) -C(S)NR⁵R⁵, bb) -NR⁵C(S)R⁵, cc) -OC(S)NR⁵R⁵, dd) -NR⁵C(S)OR⁵, ee) -NR⁵C(S)NR⁵R⁵, ff) -NR⁵C(NR⁵)NR⁵R⁵, gg) -S(O)_pR⁵, and hh) R⁵;

R⁵, at each occurrence, independently is selected from:

a) H, b) C₁₋₆ alkyl, c) C₂₋₆ alkenyl, d) C₂₋₆ alkynyl, e) -C(O)-C₁₋₆ alkyl, f) -C(O)-C₂₋₆ alkenyl, g) -C(O)-C₂₋₆ alkynyl, h) -C(O)O-C₁₋₆ alkyl,

i) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkenyl, and j) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkynyl,

wherein any of b) – j) optionally is substituted with one or more R^6 groups;

R^6 , at each occurrence, independently is selected from:

a) F, b) Cl, c) Br, d) I, e) $-\text{CF}_3$, f) $-\text{OH}$, g) $-\text{OC}_{1-6}$ alkyl, h) $-\text{SH}$,
 i) $-\text{SC}_{1-6}$ alkyl, j) $-\text{CN}$, k) $-\text{NO}_2$, l) $-\text{NH}_2$, m) $-\text{NHC}_{1-6}$ alkyl,
 n) $-\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, o) $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl, p) $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl, q) $-\text{C}(\text{O})\text{NH}_2$, r) $-\text{C}(\text{O})\text{NHC}_{1-6}$ alkyl, s) $-\text{C}(\text{O})\text{N}(\text{C}_{1-6} \text{ alkyl})_2$, t) $-\text{NHC}(\text{O})\text{C}_{1-6}$ alkyl, and u) $-\text{S}(\text{O})_p\text{C}_{1-6}$ alkyl;

R^7 , at each occurrence, independently is selected from:

a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,
 g) $-\text{C}(\text{O})\text{C}_{1-6}$ alkyl, h) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkenyl, i) $-\text{C}(\text{O})-\text{C}_{2-6}$ alkynyl,
 j) $-\text{C}(\text{O})-\text{C}_{3-14}$ saturated, unsaturated, or aromatic carbocycle,
 k) $-\text{C}(\text{O})-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ alkyl, m) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkenyl, n) $-\text{C}(\text{O})\text{O}-\text{C}_{2-6}$ alkynyl, o) $-\text{C}(\text{O})\text{O}-\text{C}_{3-14}$ saturated, unsaturated, or aromatic carbocycle, and p) $-\text{C}(\text{O})\text{O}-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more R^8 groups;

R^8 , at each occurrence, is independently selected from:

a) F, b) Cl, c) Br, d) I, e) $=\text{O}$, f) $=\text{S}$, g) $=\text{NR}^9$, h) $=\text{NOR}^9$, i) $=\text{N}-\text{NR}^9\text{R}^9$,
 j) $-\text{CF}_3$, k) $-\text{OR}^9$, l) $-\text{CN}$, m) $-\text{NO}_2$, n) $-\text{NR}^9\text{R}^9$, o) $-\text{C}(\text{O})\text{R}^9$, p) $-\text{C}(\text{O})\text{OR}^9$,
 q) $-\text{OC}(\text{O})\text{R}^9$, r) $-\text{C}(\text{O})\text{NR}^9\text{R}^9$, s) $-\text{NR}^9\text{C}(\text{O})\text{R}^9$, t) $-\text{OC}(\text{O})\text{NR}^9\text{R}^9$,
 u) $-\text{NR}^9\text{C}(\text{O})\text{OR}^9$, v) $-\text{NR}^9\text{C}(\text{O})\text{NR}^9\text{R}^9$, w) $-\text{C}(\text{S})\text{R}^9$, x) $-\text{C}(\text{S})\text{OR}^9$,
 y) $-\text{OC}(\text{S})\text{R}^9$, z) $-\text{C}(\text{S})\text{NR}^9\text{R}^9$, aa) $-\text{NR}^9\text{C}(\text{S})\text{R}^9$, bb) $-\text{OC}(\text{S})\text{NR}^9\text{R}^9$,
 cc) $-\text{NR}^9\text{C}(\text{S})\text{OR}^9$, dd) $-\text{NR}^9\text{C}(\text{S})\text{NR}^9\text{R}^9$, ee) $-\text{NR}^9\text{C}(\text{NR}^9)\text{NR}^9\text{R}^9$,

ff) $-S(O)_pR^9$, gg) $-SO_2NR^9R^9$, and hh) R^9 ;

R^9 , at each occurrence, independently is selected from:

- a) H, b) C_{1-6} alkyl, c) C_{2-6} alkenyl, d) C_{2-6} alkynyl, e) C_{3-14} saturated, unsaturated, or aromatic carbocycle, f) 3-14 membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,
- g) $-C(O)-C_{1-6}$ alkyl, h) $-C(O)-C_{2-6}$ alkenyl, i) $-C(O)-C_{2-6}$ alkynyl,
- j) $-C(O)-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle,
- k) $-C(O)-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur, l) $-C(O)O-C_{1-6}$ alkyl,
- m) $-C(O)O-C_{2-6}$ alkenyl, n) $-C(O)O-C_{2-6}$ alkynyl, o) $-C(O)O-C_{3-14}$ saturated, unsaturated, or aromatic carbocycle, and
- p) $-C(O)O-3-14$ membered saturated, unsaturated, or aromatic heterocycle comprising one or more heteroatoms selected from nitrogen, oxygen, and sulfur,

wherein any of b) – p) optionally is substituted with one or more moieties selected from:

- a) F, b) Cl, c) Br, d) I, e) $-CF_3$, f) $-OH$, g) $-OC_{1-6}$ alkyl,
- h) $-SH$, i) $-SC_{1-6}$ alkyl, j) $-CN$, k) $-NO_2$, l) $-NH_2$,
- m) $-NHC_{1-6}$ alkyl, n) $-N(C_{1-6} \text{ alkyl})_2$, o) $-C(O)C_{1-6}$ alkyl,
- p) $-C(O)OC_{1-6}$ alkyl, q) $-C(O)NH_2$, r) $-C(O)NHC_{1-6}$ alkyl, s) $-C(O)N(C_{1-6} \text{ alkyl})_2$, t) $-NHC(O)C_{1-6}$ alkyl, u) $-SO_2NH_2$, v) $-SO_2NHC_{1-6}$ alkyl, w) $-SO_2N(C_{1-6} \text{ alkyl})_2$, and
- x) $-S(O)_pC_{1-6}$ alkyl;

R^{11} is selected from a) $-OH$, and b) F;

R^{12} and R^{13} are independently selected from a) H, b) C_{1-4} alkyl, c) F, d) Cl, e) Br, f) I, g) CF_3 , h) NH_2 , i) CN , and j) N_3 ;

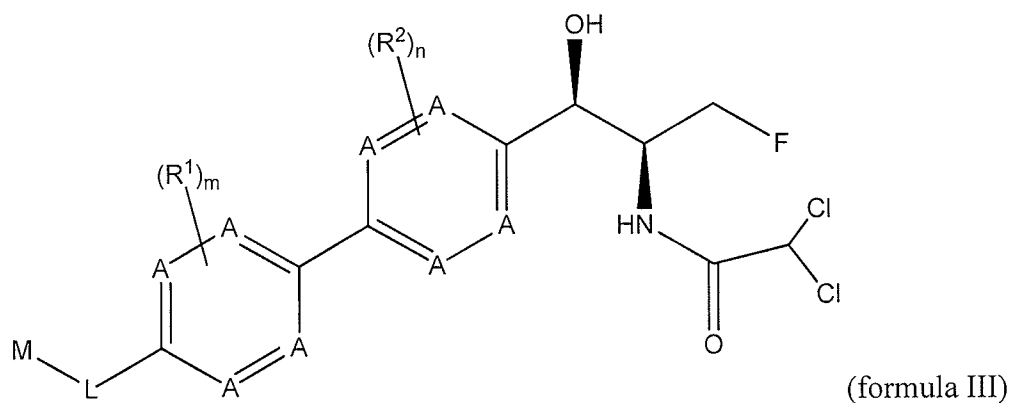
R^{18} is selected from a) H, and b) F,

m is 0, 1, 2, 3, or 4;

n is 0, 1, 2, 3, or 4; and

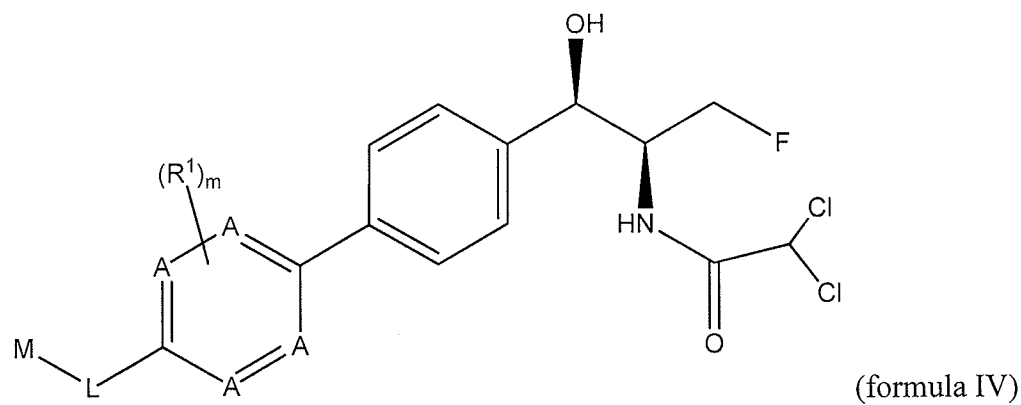
p, at each occurrence, independently is 0, 1, or 2.

3. The compound according to any one of claims 1-2 having the formula:



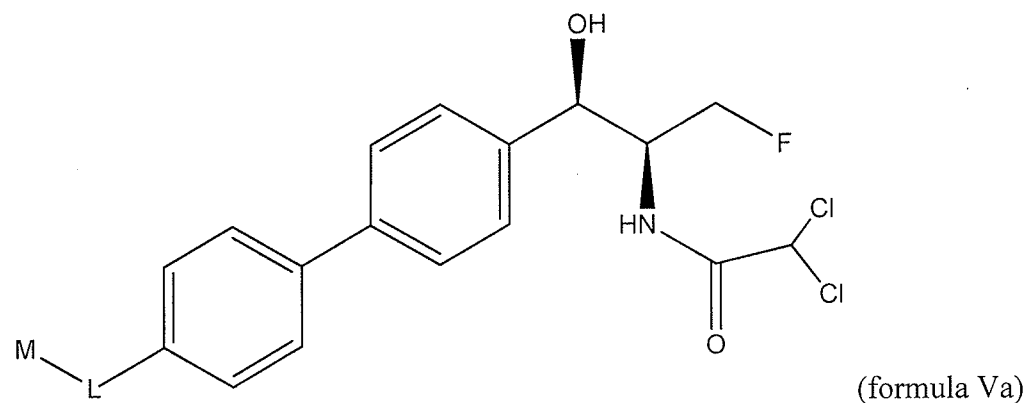
or a pharmaceutically acceptable salt, ester or prodrug thereof.

4. The compound according to any one of claims 1-3 having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof.

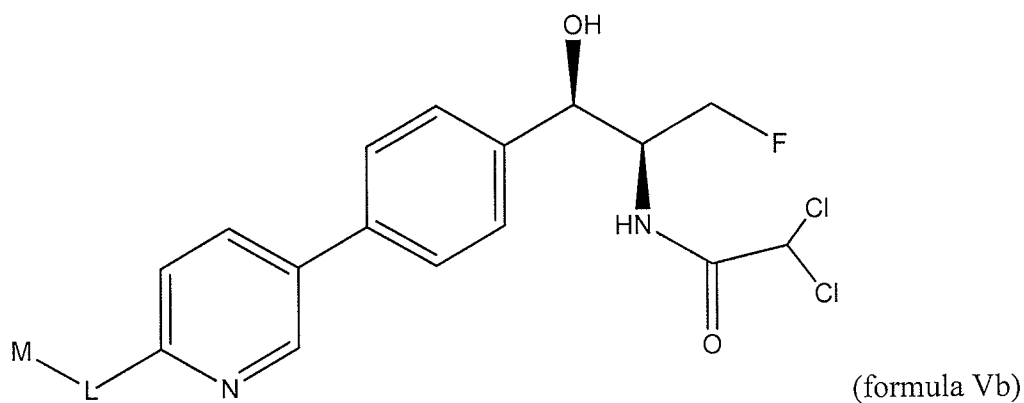
5. The compound according to any one of claims 1-4 having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof.

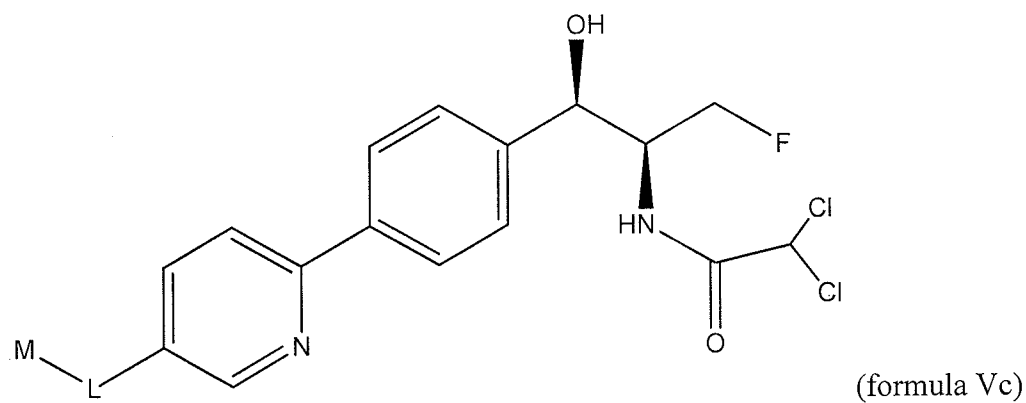
6. The compound according to any one of claims 1-4 having the formula:

- 98 -



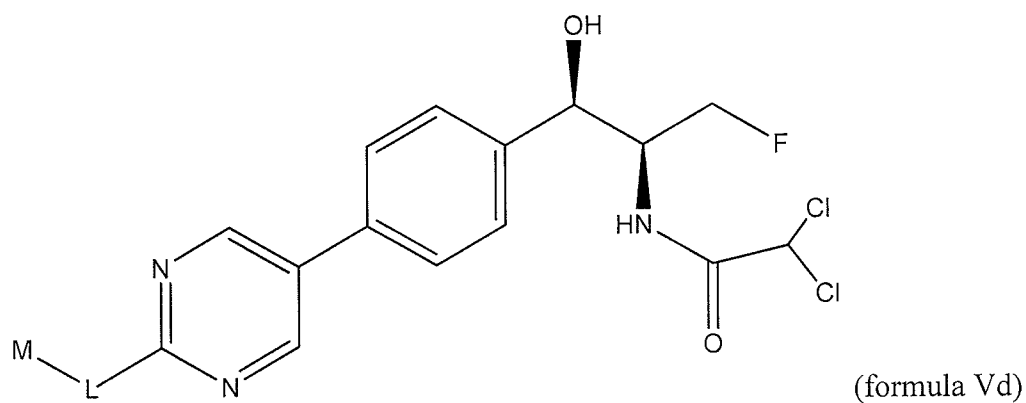
or a pharmaceutically acceptable salt, ester or prodrug thereof.

7 The compound according to any one of claims 1-4 having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof.

8 The compound according to any one of claims 1-4 having the formula:



or a pharmaceutically acceptable salt, ester or prodrug thereof.

9. The compound according to claim 1, wherein Z is a 3-14 membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur.
10. The compound according to claim 9, wherein Z is a 6-membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur.
11. The compound according to claim 9, wherein Z is a 5-membered saturated, unsaturated, or aromatic heterocycle containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur.
12. The compound according to any one of claims 1-11, wherein L in M-L is a bond.
13. A compound having a structure corresponding to any one of the compounds listed in Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, or Table 8; or a pharmaceutically acceptable salt, ester, or prodrug thereof.
14. A pharmaceutical composition comprising a pharmaceutically acceptable amount of a compound according to any one of claims 1-13 and a pharmaceutically acceptable carrier.
15. Use of one or more compounds according to any one of claims 1-13 in the manufacture of a medicament for the treatment of a disorder or disease selected from microbial infection, fungal infection, parasitic disease, proliferative disease, viral infection, inflammatory disease, and gastrointestinal motility disorder in a mammal.
16. Use of one or more compounds according to any one of claims 1-13 in the manufacture of medicament for the treatment of a disorder, wherein the disorder is selected from:
 - a skin infection, nosocomial pneumonia, post-viral pneumonia, an abdominal infection, a urinary tract infection, bacteremia, septicemia, endocarditis, an atrio-

ventricular shunt infection, a vascular access infection, meningitis, surgical prophylaxis, a peritoneal infection, a bone infection, a joint infection, a methicillin-resistant *Staphylococcus aureus* infection, a vancomycin-resistant *Enterococci* infection, a linezolid-resistant organism infection, and tuberculosis.

17. The use according to any one of claims 15-16, wherein the compound is administered orally, parenterally, or topically.
18. A method of synthesizing a compound or a pharmaceutically acceptable salt, ester, or prodrug thereof according to any one of claims 1-13.
19. A medical device containing one or more compounds or a pharmaceutically acceptable salt thereof according to any one of claims 1-13.
20. The medical device according to claim 19, wherein the device is a stent.