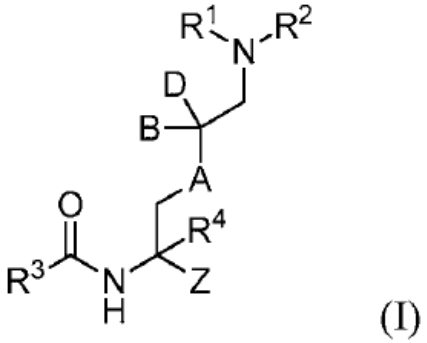
BMC Microbiol, 2009. 9: 107. New compounds for the inhibition of gingipain activity and the treatment of diseases associated with gingipain activity and *P. gingivalis* infection are needed. The present invention addresses this and other needs.

BRIEF SUMMARY

[0003a] In one aspect of the present disclosure, there is provided a compound according to Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z is halogen-substituted aryloxymethyl-carbonyl;

A is selected from the group consisting of —CH_2— and —O—;

B and D are independently selected from the group consisting of hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkox y;

R^1 is selected from the group consisting of hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5, wherein

L is selected from the group consisting of —O—, —NR—, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from the group consisting of hydrogen and C_{1-8} alkyl,

R^5 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl,

and wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, —CN, —NO_2, —N_3, —OH, R^a, R^b, —OR^a, —OR^b, —$(CH_2)_kC(O)R^c$, —$NR^d(CH_2)_uC(O)R^c$, —$O(CH_2)_uC(O)R^c$, —$(CH_2)_kCONR^dR^d$, —$(CH_2)_kNR^dC(O)R^c$, —$NR^d(CH_2)_uCONR^dR^d$, —$NR^d(CH_2)_uNR^dC(O)R^c$, —$O(CH_2)_uCONR^dR^d$, —$O(CH_2)_uNR^dC(O)R^c$, —$(CH_2)_kS(O)_2NR^dR^d$, —$(CH_2)_kNR^dS(O)_2R^c$, —$(CH_2)_kS(O)_2R^c$, —$(CH_2)_kS(O)R^c$, —$(CH_2)_kSR^d$, —$NR^d(CH_2)_uS(O)_2NR^dR^d$, —$NR^d(CH_2)_uNR^dS(O)_2R^c$, —

$NR^d(CH_2)_uS(O)_2R^c$, —$NR^d(CH_2)_uS(O)R^c$, —$NR^d(CH_2)_uSR^d$, —$O(CH_2)_uS(O)_2NR^dR^d$, —$O(CH_2)_uNR^dS(O)_2R^c$, —$O(CH_2)_uS(O)_2R^c$, —$O(CH_2)_uS(O)R^c$, and —$O(CH_2)_uSR^c$, wherein:

each R^a is independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl,

each R^b is independently selected from the group consisting of C_{3-6}cycloalkyl, C_{3-6} halocycloalkyl, C_{6-10} aryl, 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^c is independently selected from the group consisting of —OH, C_{1-8}alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, C_{6-10} aryl, (C_{6-10}aryl)-(C_{1-8} alkyl), 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^d is independently selected from the group consisting of hydrogen and C_{1-8} alkyl,

each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6, and

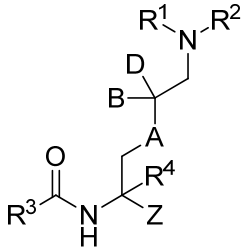
each subscript u is independently selected from 1, 2, 3, 4, 5, and 6; and

R^4 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

provided that when A is —CH_2—, and B and D are hydrogen, then R^3 is other than (2-phenyl)ethyl or substituted (2-phenyl)ethyl.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

[0003c] In a further aspect of the present disclosure, there is provided a use of a compound according to Formula Ie:



(Ie)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition associated with *P. gingivalis* infection, wherein

Z is halogen-substituted aryloxymethyl-carbonyl;

A is selected from the group consisting of -CH_2- and -O-;

B and D are independently selected from the group consisting of hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from the group consisting of hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5, wherein

L is selected from the group consisting of -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from the group consisting of hydrogen and C_{1-8} alkyl,

R^5 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl

and wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, -CN, -NO_2, -N_3, -OH, R^a, R^b, -OR^a, -OR^b, -$(CH_2)_kC(O)R^c$, -$NR^d(CH_2)_uC(O)R^c$, -$O(CH_2)_uC(O)R^c$, -$(CH_2)_kCONR^dR^d$, -$(CH_2)_kNR^dC(O)R^c$, -$NR^d(CH_2)_uCONR^dR^d$, -$NR^d(CH_2)_uNR^dC(O)R^c$, -$O(CH_2)_uCONR^dR^d$, -$O(CH_2)_uNR^dC(O)R^c$, -$(CH_2)_kS(O)_2NR^dR^d$, -$(CH_2)_kNR^dS(O)_2R^c$, -$(CH_2)_kS(O)_2R^c$, -$(CH_2)_kS(O)R^c$, -$(CH_2)_kSR^d$, -$NR^d(CH_2)_uS(O)_2NR^dR^d$, -$NR^d(CH_2)_uNR^dS(O)_2R^c$, -$NR^d(CH_2)_uS(O)_2R^c$, -$NR^d(CH_2)_uS(O)R^c$, -$NR^d(CH_2)_uSR^d$, -$O(CH_2)_uS(O)_2NR^dR^d$, -$O(CH_2)_uNR^dS(O)_2R^c$, -$O(CH_2)_uS(O)_2R^c$, -$O(CH_2)_uS(O)R^c$, and -$O(CH_2)_uSR^c$, wherein:

each R^a is independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl,

each R^b is independently selected from the group consisting of C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{6-10} aryl, 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^c is independently selected from the group consisting of -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, C_{6-10} aryl, (C_{6-10} aryl)-(C_{1-8} alkyl), 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^d is independently selected from the group consisting of hydrogen and C_{1-8} alkyl,

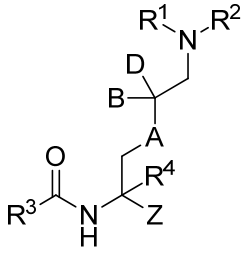
each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6, and

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6; and

R^4 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy,

provided that when A is $-CH_2-$, and B and D are hydrogen, then R^3 is other than (2-phenyl)ethyl or substituted (2-phenyl)ethyl.

[0003d] In another aspect of the present disclosure, there is provided a compound according to Formula Ie:



(Ie)

or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or condition associated with *P. gingivalis* infection, wherein

Z is halogen-substituted aryloxymethyl-carbonyl;

A is selected from the group consisting of $-CH_2-$ and -O-;

B and D are independently selected from the group consisting of hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from the group consisting of hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and $-L-R^5$, wherein

L is selected from the group consisting of -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from the group consisting of hydrogen and C_{1-8} alkyl,

R^5 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl

and wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, -CN, $-NO_2$, $-N_3$, -OH, R^a, R^b, $-OR^a$, $-OR^b$, $-(CH_2)_kC(O)R^c$, $-NR^d(CH_2)_uC(O)R^c$, $-O(CH_2)_uC(O)R^c$, $-(CH_2)_kCONR^dR^d$, $-(CH_2)_kNR^dC(O)R^c$, $-NR^d(CH_2)_uCONR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^c$, $-O(CH_2)_uCONR^dR^d$, $-O(CH_2)_uNR^dC(O)R^c$, $-(CH_2)_kS(O)_2NR^dR^d$, $-(CH_2)_kNR^dS(O)_2R^c$, $-(CH_2)_kS(O)_2R^c$, $-(CH_2)_kS(O)R^c$, $-(CH_2)_kSR^d$, $-NR^d(CH_2)_uS(O)_2NR^dR^d$, $-NR^d(CH_2)_uNR^dS(O)_2R^c$, $-NR^d(CH_2)_uS(O)_2R^c$, $-NR^d(CH_2)_uS(O)R^c$, $-NR^d(CH_2)_uSR^d$, $-O(CH_2)_uS(O)_2NR^dR^d$, $-O(CH_2)_uNR^dS(O)_2R^c$, $-O(CH_2)_uS(O)_2R^c$, $-O(CH_2)_uS(O)R^c$, and $-O(CH_2)_uSR^c$, wherein:

each R^a is independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl,

each R^b is independently selected from the group consisting of C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{6-10} aryl, 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^c is independently selected from the group consisting of -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, C_{6-10} aryl, (C_{6-10} aryl)-(C_{1-8} alkyl), 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^d is independently selected from the group consisting of hydrogen and C_{1-8} alkyl,

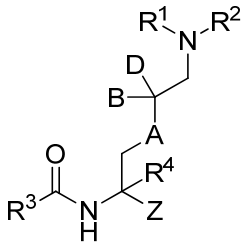
each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6, and

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6; and

R^4 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy,

provided that when A is $-CH_2-$, and B and D are hydrogen, then R^3 is other than (2-phenyl)ethyl or substituted (2-phenyl)ethyl.

[0004] The present disclosure also provides a compound according to Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z is a thiol-reactive group or a masked thiol-reactive group;

A is selected from $-CH_2-$ and -O-;

B and D are independently selected from hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, $-L-R^5$, and $-OR^6$, wherein

L is selected from -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from hydrogen and C_{1-8} alkyl,

R^5 is selected from C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl, and

$-OR^6$ and the carbonyl to which it is bonded form an amine protecting group,

and wherein R^3 is optionally substituted with one or more substituents selected from halo, -CN, $-NO_2$, $-N_3$, -OH, R^a, R^b, $-OR^a$, $-OR^b$, $-(CH_2)_kC(O)R^c$, $-NR^d(CH_2)_uC(O)R^c$, $-O(CH_2)_uC(O)R^c$, $-(CH_2)_kCONR^dR^d$, $-(CH_2)_kNR^dC(O)R^c$, $-NR^d(CH_2)_uCONR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^c$, $-O(CH_2)_uCONR^dR^d$, $-O(CH_2)_uNR^dC(O)R^c$, $-(CH_2)_kS(O)_2NR^dR^d$, $-(CH_2)_kNR^dS(O)_2R^c$, $-(CH_2)_kS(O)_2R^c$, $-(CH_2)_kS(O)R^c$, $-(CH_2)_kSR^d$, $-NR^d(CH_2)_uS(O)_2NR^dR^d$, $-NR^d(CH_2)_uNR^dS(O)_2R^c$, $-NR^d(CH_2)_uS(O)_2R^c$, $-NR^d(CH_2)_uS(O)R^c$, $-NR^d(CH_2)_uSR^d$, $-O(CH_2)_uS(O)_2NR^dR^d$, $-O(CH_2)_uNR^dS(O)_2R^c$, $-O(CH_2)_uS(O)_2R^c$, $-O(CH_2)_uS(O)R^c$, and $-O(CH_2)_uSR^c$, wherein:

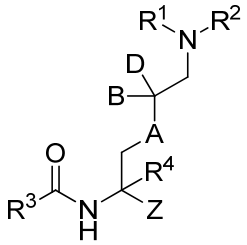
each R^a is independently selected from C_{1-4} alkyl and C_{1-4} haloalkyl,

wherein R^3 is selected from C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5,

wherein L is C_{1-4} alkylene.

[0007] The present disclosure further provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable excipient.

[0008] The present disclosure also provides a method of treating a disease or condition associated with *P. gingivalis* infection. The method includes administering to a subject an effective amount of a compound according to Formula Ie:



(Ie)

or a pharmaceutically acceptable salt thereof, wherein

Z is a thiol-reactive group or a masked thiol-reactive group;

A is selected from -CH_2- and -O-;

B and D are independently selected from hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{1-8} alkyl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, -L-R^5, and -OR^6, wherein

L is selected from -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from hydrogen and C_{1-8} alkyl,

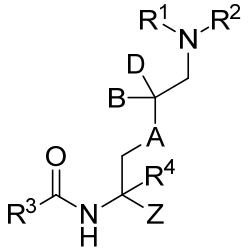
R^5 is selected from C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl, and

-OR^6 and the carbonyl to which it is bonded form an amine protecting group,

and wherein R^3 is optionally substituted with one or more substituents selected from halo, -CN, -NO_2, -N_3, -OH, R^a, R^b, -OR^a, -OR^b, -$(CH_2)_kC(O)R^c$, -$NR^d(CH_2)_uC(O)R^c$, -$O(CH_2)_uC(O)R^c$, -$(CH_2)_kCONR^dR^d$, -$(CH_2)_kNR^dC(O)R^c$, -$NR^d(CH_2)_uCONR^dR^d$, -$NR^d(CH_2)_uNR^dC(O)R^c$, -$O(CH_2)_uCONR^dR^d$, -$O(CH_2)_uNR^dC(O)R^c$, -$(CH_2)_kS(O)_2NR^dR^d$, -$(CH_2)_kNR^dS(O)_2R^c$, -$(CH_2)_kS(O)_2R^c$, -$(CH_2)_kS(O)R^c$, -$(CH_2)_kSR^d$, -$NR^d(CH_2)_uS(O)_2NR^dR^d$, -$NR^d(CH_2)_uNR^dS(O)_2R^c$, -$NR^d(CH_2)_uS(O)_2R^c$, -$NR^d(CH_2)_uS(O)R^c$,

WHAT IS CLAIMED IS:

1. A compound according to Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein

Z is halogen-substituted aryloxymethyl-carbonyl;

A is selected from the group consisting of -CH_2- and -O-;

B and D are independently selected from the group consisting of hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from the group consisting of hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5, wherein

L is selected from the group consisting of -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from the group consisting of hydrogen and C_{1-8} alkyl,

R^5 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl,

and wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, -CN, -NO_2, -N_3, -OH, R^a, R^b, -OR^a, -OR^b, -$(CH_2)_kC(O)R^c$, -$NR^d(CH_2)_uC(O)R^c$, -$O(CH_2)_uC(O)R^c$, -$(CH_2)_kCONR^dR^d$, -$(CH_2)_kNR^dC(O)R^c$, -$NR^d(CH_2)_uCONR^dR^d$, -$NR^d(CH_2)_uNR^dC(O)R^c$, -$O(CH_2)_uCONR^dR^d$, -$O(CH_2)_uNR^dC(O)R^c$, -$(CH_2)_kS(O)_2NR^dR^d$, -$(CH_2)_kNR^dS(O)_2R^c$, -$(CH_2)_kS(O)_2R^c$, -$(CH_2)_kS(O)R^c$, -$(CH_2)_kSR^d$, -$NR^d(CH_2)_uS(O)_2NR^dR^d$, -$NR^d(CH_2)_uNR^dS(O)_2R^c$, -$NR^d(CH_2)_uS(O)_2R^c$, -$NR^d(CH_2)_uS(O)R^c$, -$NR^d(CH_2)_uSR^d$, -$O(CH_2)_uS(O)_2NR^dR^d$, -$O(CH_2)_uNR^dS(O)_2R^c$, -$O(CH_2)_uS(O)_2R^c$, -$O(CH_2)_uS(O)R^c$, and -$O(CH_2)_uSR^c$, wherein:

each R^a is independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl,

each R^b is independently selected from the group consisting of C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{6-10} aryl, 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^c is independently selected from the group consisting of -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, C_{6-10} aryl, (C_{6-10} aryl)-(C_{1-8} alkyl), 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^d is independently selected from the group consisting of hydrogen and C_{1-8} alkyl,

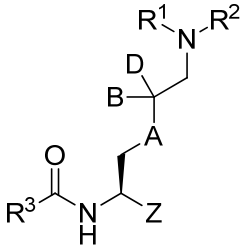
each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6, and

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6; and

R^4 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

provided that when A is -CH_2-, and B and D are hydrogen, then R^3 is other than (2-phenyl)ethyl or substituted (2-phenyl)ethyl.

2. The compound of claim 1, having a structure according to Formula Ib:



(Ib)

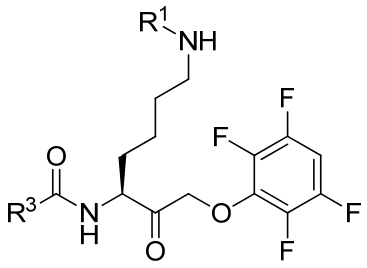
or a pharmaceutically acceptable salt thereof, wherein

B and D are independently selected from the group consisting of hydrogen, halogen, halomethyl, and halomethoxy.

3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein Z is halogen-substituted phenoxymethyl carbonyl.

4. The compound of claim 1, wherein R^3 is selected from the group consisting of cyclohexyl, cyclopentyl, morpholino, phenyl, piperidinyl, pyridinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,4-tetrahydronaphthyl, and thiazolyl, each of which is optionally substituted with 1-3 members selected from the group consisting of methyl, methoxy, trifluoromethyl, acetyl, and -N_3.

5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, having a structure according to Formula Id:



(Id)

or a pharmaceutically acceptable salt thereof,

wherein R^3 is selected from the group consisting of $C_{6\text{-}10}$ aryl, 5-to-12 membered heteroaryl, $C_{3\text{-}8}$ cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5,

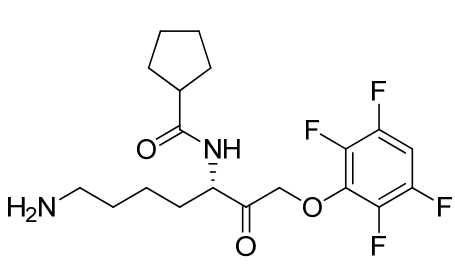
wherein L is $C_{1\text{-}4}$ alkylene.

6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein

R^3 is selected from the group consisting of cyclohexyl, cyclopentyl, morpholino, phenyl, piperidinyl, pyridinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,2,3,4-tetrahydronaphthyl, and thiazolyl,

each of which is optionally substituted with 1-3 members selected from the group consisting of methyl, methoxy, trifluoromethyl, acetyl, and -N_3.

7. The compound of claim 1, which is selected from the group consisting of:



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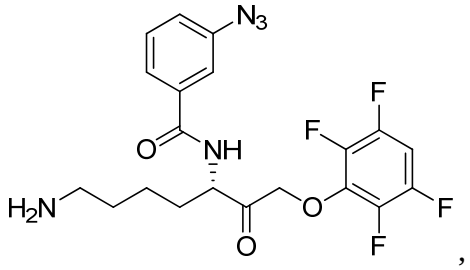

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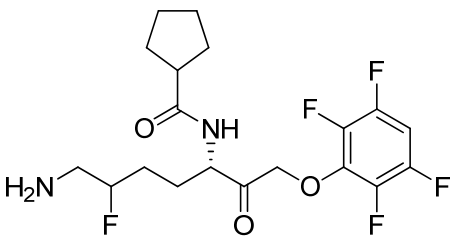
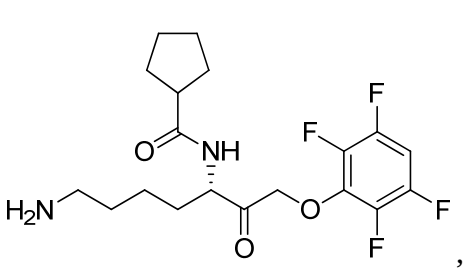


,

and pharmaceutically acceptable salts thereof.

8. The compound of claim 1, which is selected from the group consisting of: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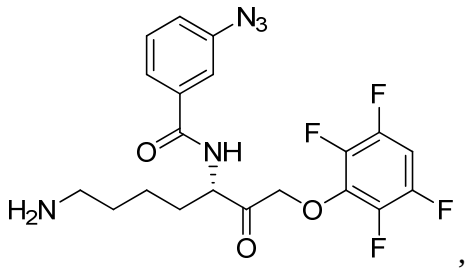
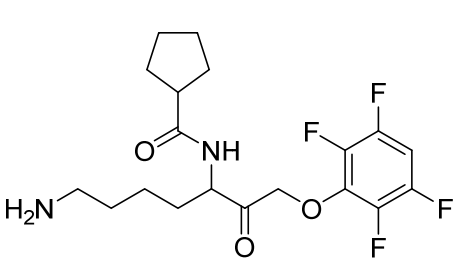

,

and pharmaceutically acceptable salts thereof.

9. The compound of claim 1, which is selected from the group consisting of: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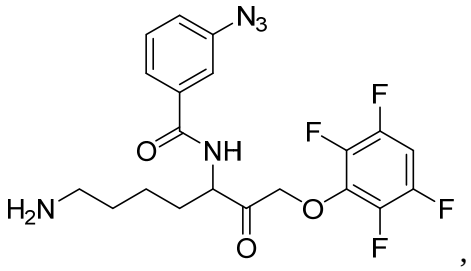
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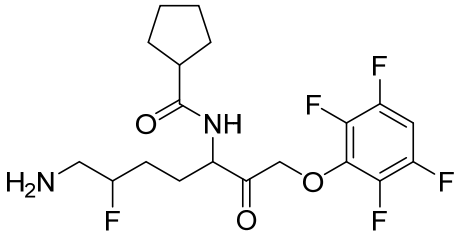
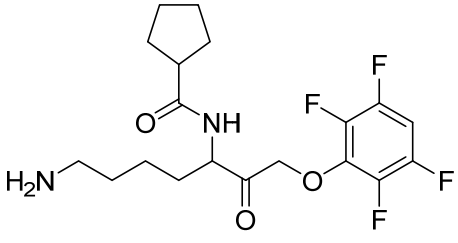

,

and pharmaceutically acceptable salts thereof.

10. The compound of claim 1, which is selected from the group consisting of: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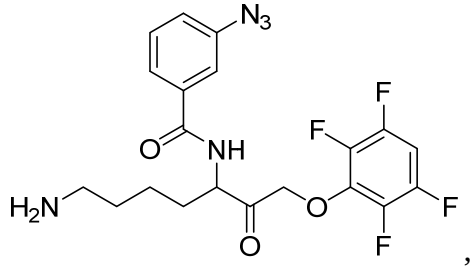
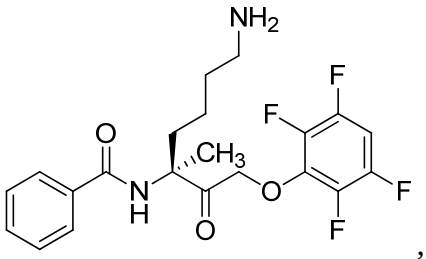

,

and pharmaceutically acceptable salts thereof.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl.

12. The compound of claim 11, which is



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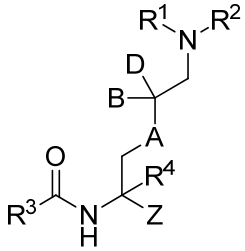
or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable excipient.

14. Use of a compound according to Formula Ie:



(Ie)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition associated with *P. gingivalis* infection, wherein

Z is halogen-substituted aryloxymethyl-carbonyl;

A is selected from the group consisting of -CH_2- and -O-;

B and D are independently selected from the group consisting of hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from the group consisting of hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5, wherein

L is selected from the group consisting of -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from the group consisting of hydrogen and C_{1-8} alkyl,

R^5 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl

and wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, -CN, $-NO_2$, $-N_3$, -OH, R^a, R^b, $-OR^a$, $-OR^b$, $-(CH_2)_kC(O)R^c$, $-NR^d(CH_2)_uC(O)R^c$, $-O(CH_2)_uC(O)R^c$, $-(CH_2)_kCONR^dR^d$, $-(CH_2)_kNR^dC(O)R^c$, $-NR^d(CH_2)_uCONR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^c$, $-O(CH_2)_uCONR^dR^d$, $-O(CH_2)_uNR^dC(O)R^c$, $-(CH_2)_kS(O)_2NR^dR^d$, $-(CH_2)_kNR^dS(O)_2R^c$, $-(CH_2)_kS(O)_2R^c$, $-(CH_2)_kS(O)R^c$, $-(CH_2)_kSR^d$, $-NR^d(CH_2)_uS(O)_2NR^dR^d$, $-NR^d(CH_2)_uNR^dS(O)_2R^c$, $-NR^d(CH_2)_uS(O)_2R^c$, $-NR^d(CH_2)_uS(O)R^c$, $-NR^d(CH_2)_uSR^d$, $-O(CH_2)_uS(O)_2NR^dR^d$, $-O(CH_2)_uNR^dS(O)_2R^c$, $-O(CH_2)_uS(O)_2R^c$, $-O(CH_2)_uS(O)R^c$, and $-O(CH_2)_uSR^c$, wherein:

each R^a is independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl,

each R^b is independently selected from the group consisting of C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{6-10} aryl, 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^c is independently selected from the group consisting of -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, C_{6-10} aryl, (C_{6-10} aryl)-(C_{1-8} alkyl), 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^d is independently selected from the group consisting of hydrogen and C_{1-8} alkyl,

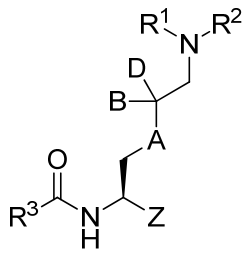
each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6, and

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6; and

R^4 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy,

provided that when A is $-CH_2-$, and B and D are hydrogen, then R^3 is other than (2-phenyl)ethyl or substituted (2-phenyl)ethyl.

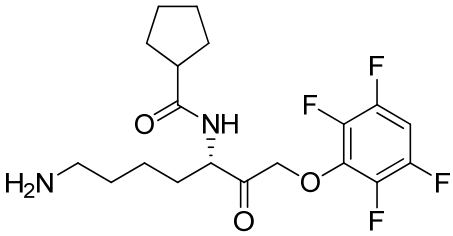
15. The use of claim 14, wherein the compound of Formula Ie has the structure:



,

wherein B and D are independently selected from the group consisting of hydrogen, halogen, halomethyl, and halomethoxy.

16. The use of claim 14, wherein the compound is selected from the group consisting of: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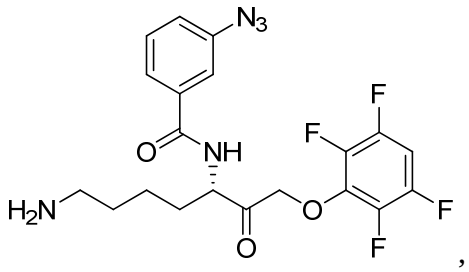
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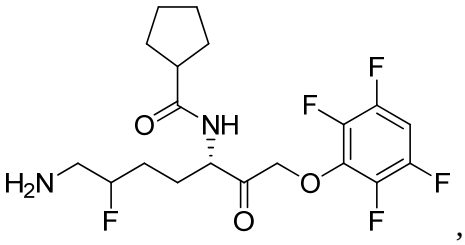
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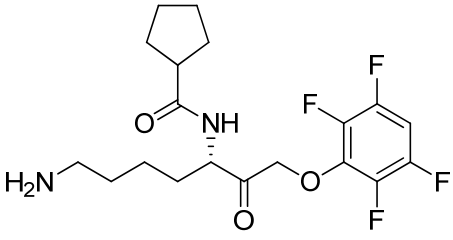
and pharmaceutically acceptable salts thereof.

17. The use of claim 14, wherein the compound is selected from the group consisting of: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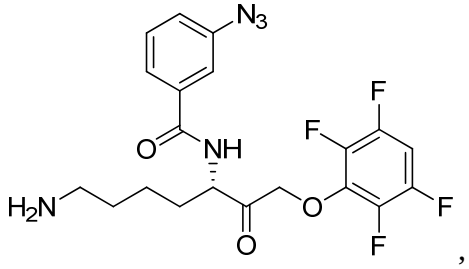
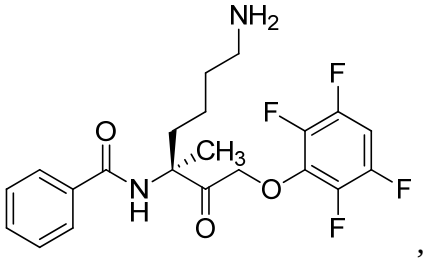

,

and pharmaceutically acceptable salts thereof.

18. The use of claim 14, wherein the compound is


,

or a pharmaceutically acceptable salt thereof.

19. The use of claim 14, wherein the disease or condition is selected from a brain disorder, periodontal disease, diabetes, a cardiovascular disease, arthritis, elevated risk of preterm birth, pneumonia, cancer, a kidney disease, a liver disease, a retinal disorder, and glaucoma.

20. The use of claim 19, wherein the disease or condition is a brain disorder.

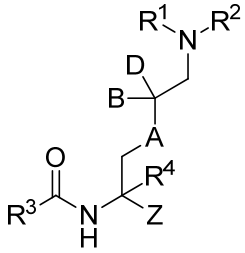
21. The use of claim 20, wherein the brain disorder is selected from the group consisting of Alzheimer's disease, Down's syndrome, epilepsy, autism, Parkinson's disease, essential tremor, fronto-temporal dementia, progressive supranuclear palsy, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis, mild cognitive impairment, age associated memory impairment, chronic traumatic encephalopathy, stroke, Lewy Body disease, multiple system atrophy, schizophrenia, and depression.

22. The use of claim 21, wherein the brain disorder is Alzheimer's disease.

23. The use of claim 14, wherein the compound is to be administered to a subject for at least one month.

24. The use of claim 14, wherein in the treatment, the compound is to be administered to a human subject, a canine subject, or a feline subject.

25. A compound according to Formula Ie:



(Ie)

or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or condition associated with *P. gingivalis* infection, wherein

Z is halogen-substituted aryloxymethyl-carbonyl;

A is selected from the group consisting of -CH_2- and -O-;

B and D are independently selected from the group consisting of hydrogen, halogen, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^1 is selected from the group consisting of hydrogen and an amine protecting group;

R^2 is hydrogen; and

R^3 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, 5-to-12 membered saturated heterocyclyl, and -L-R^5, wherein

L is selected from the group consisting of -O-, -NR-, C_{1-4} alkylene, and 2- to 4-membered heteroalkylene, wherein R is selected from the group consisting of hydrogen and C_{1-8} alkyl,

R^5 is selected from the group consisting of C_{6-10} aryl, 5-to-12 membered heteroaryl, C_{3-8} cycloalkyl, and 5-to-12 membered saturated heterocyclyl

and wherein R^3 is optionally substituted with one or more substituents selected from the group consisting of halo, -CN, $-NO_2$, $-N_3$, -OH, R^a, R^b, $-OR^a$, $-OR^b$, $-(CH_2)_kC(O)R^c$, $-NR^d(CH_2)_uC(O)R^c$, $-O(CH_2)_uC(O)R^c$, $-(CH_2)_kCONR^dR^d$, $-(CH_2)_kNR^dC(O)R^c$, $-NR^d(CH_2)_uCONR^dR^d$, $-NR^d(CH_2)_uNR^dC(O)R^c$, $-O(CH_2)_uCONR^dR^d$, $-O(CH_2)_uNR^dC(O)R^c$, $-(CH_2)_kS(O)_2NR^dR^d$, $-(CH_2)_kNR^dS(O)_2R^c$, $-(CH_2)_kS(O)_2R^c$, $-(CH_2)_kS(O)R^c$, $-(CH_2)_kSR^d$, $-NR^d(CH_2)_uS(O)_2NR^dR^d$, $-NR^d(CH_2)_uNR^dS(O)_2R^c$, $-NR^d(CH_2)_uS(O)_2R^c$, $-NR^d(CH_2)_uS(O)R^c$, $-NR^d(CH_2)_uSR^d$, $-O(CH_2)_uS(O)_2NR^dR^d$, $-O(CH_2)_uNR^dS(O)_2R^c$, $-O(CH_2)_uS(O)_2R^c$, $-O(CH_2)_uS(O)R^c$, and $-O(CH_2)_uSR^c$, wherein:

each R^a is independently selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl,

each R^b is independently selected from the group consisting of C_{3-6} cycloalkyl, C_{3-6} halocycloalkyl, C_{6-10} aryl, 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^c is independently selected from the group consisting of -OH, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{3-8} cycloalkyl, C_{3-8} halocycloalkyl, C_{6-10} aryl, (C_{6-10} aryl)-(C_{1-8} alkyl), 5-to-12 membered heteroaryl, and 5-to-12 membered saturated heterocyclyl,

each R^d is independently selected from the group consisting of hydrogen and C_{1-8} alkyl,

each subscript k is independently selected from 0, 1, 2, 3, 4, 5, and 6, and

each subscript u is independently selected from 1, 2, 3, 4, 5, and 6; and

R^4 is selected from the group consisting of hydrogen, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy,

provided that when A is $-CH_2-$, and B and D are hydrogen, then R^3 is other than (2-phenyl)ethyl or substituted (2-phenyl)ethyl.