

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
10 May 2012 (10.05.2012)

PCT

(10) International Publication Number
WO 2012/061552 A1

(51) International Patent Classification:

C07D 403/14 (2006.01) A61K 31/12 (2006.01)
A61K 31/4025 (2006.01)

(21) International Application Number:

PCT/US2011/059061

(22) International Filing Date:

3 November 2011 (03.11.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/410,267 4 November 2010 (04.11.2010) US
61/444,046 17 February 2011 (17.02.2011) US
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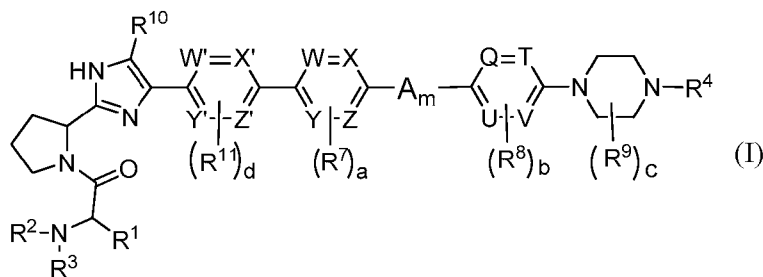
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94080 (US).(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU,
RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ,
TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,
UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD,
RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ,
DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT,
LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,
SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: NOVEL INHIBITORS OF HEPATITIS C VIRUS



(57) Abstract: The invention provides compounds of formula (I) wherein the variables are defined in the specification, or a pharmaceutically-acceptable salt thereof, that are inhibitors of replication of the hepatitis C virus. The invention also provides pharmaceutical compositions comprising such compounds, methods of using such compounds to treat hepatitis C viral infections, and processes and intermediates useful for preparing such compounds.

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NOVEL INHIBITORS OF HEPATITIS C VIRUS

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BACKGROUND OF THE INVENTION

15 Field of the Invention

The invention is directed to compounds useful as inhibitors of replication of the hepatitis C virus (HCV). The invention is also directed to pharmaceutical compositions comprising such compounds, methods of using such compounds to treat HCV infection, and processes and intermediates useful for preparing such compounds.

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State of the Art

Recent estimates place the number of people infected with the hepatitis C virus (HCV) worldwide at more than 170 million, including 3 million people in the United States. The infection rate is thought to be roughly 4 to 5 times that of the human immunodeficiency virus (HIV). While in some individuals, the natural immune response is able to overcome the virus, in the majority of cases, a chronic infection is established, leading to increased risk of developing cirrhosis of the liver and hepatocellular carcinomas. Infection with hepatitis C, therefore, presents a serious public health problem.

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Prior to mid-2011, the accepted standard of care for HCV involved the use of a pegylated interferon which is believed to act by boosting the body's immune response, together with ribavirin. Unfortunately, the course of treatment is lengthy, typically 48 weeks, often accompanied by serious adverse side effects, including depression, flu-like symptoms, fatigue, and hemolytic anemia, and ineffective in up to 50 % of patients. In

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mid-2011, two HCV protease inhibitors were approved in the United States to be used in combination with interferon and ribavirin. Although better cure rates have been reported,

the course of therapy is still lengthy and accompanied by undesirable side effects.

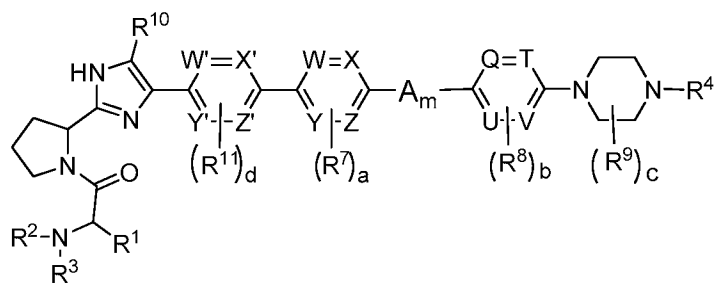
Accordingly, there remains a serious unmet need in HCV treatment.

The virus responsible for HCV infection has been identified as a positive-strand RNA virus belonging to the family *Flaviviridae*. The HCV genome encodes a polyprotein that during the viral lifecycle is cleaved into ten individual proteins, including both structural and non-structural proteins. The six non-structural proteins, denoted as NS2, NS3, NS4A, NS4B, NS5A, and NS5B have been shown to be required for RNA replication. In particular, the NS5A protein appears to play a significant role in viral replication, as well as in modulation of the physiology of the host cell. Effects of NS5A on interferon signaling, regulation of cell growth and apoptosis have also been identified. (Macdonald et al., *Journal of General Virology* (2004), 85, 2485-2502.) Compounds which inhibit the function of the NS5A protein are expected to provide a new approach to HCV therapy.

SUMMARY OF THE INVENTION

In one aspect, the invention provides novel compounds which inhibit replication of the HCV virus.

Accordingly, the invention provides a compound of formula (I):



(I)

wherein:

R¹ is selected from C₁₋₆alkyl, phenyl, C₃₋₆cycloalkyl, heteroaryl, and heterocycle; wherein C₁₋₆alkyl is optionally substituted with -OR^q, wherein R^q is hydrogen or C₁₋₃alkyl;

R² is selected from hydrogen and C₁₋₆alkyl;

R³ is selected from hydrogen, C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, -C(O)OC₃₋₆cycloalkyl, -C(O)NR^aR^b, -C(O)C₁₋₆alkyl, -C(O)C₃₋₆cycloalkyl, and -S(O)₂C₁₋₃alkyl;

wherein

R^a and R^b are independently hydrogen or C₁₋₆alkyl;

R^4 is $-C(O)R^5$ or $-S(O)_2R^6$;

R^5 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $-C(R^kR^d)NR^eR^f$, $-NR^gR^h$, heteroaryl, heterocycle, $-CH_2$ -heteroaryl, and phenyl;

wherein

5 C_{1-6} alkyl is optionally substituted with one or two substituents independently selected from $-OR^c$, $-S(O)_2C_{1-3}$ alkyl, $-NHC(O)C_{1-3}$ alkyl, and $-NHC(O)OC_{1-3}$ alkyl;

C_{1-6} alkoxy is optionally substituted with $-OR^d$;

10 C_{3-6} cycloalkyl is optionally substituted with one, two, or three substituents independently selected from C_{1-3} alkyl, NR^jR^m , $-OR^n$, and halo;

any heterocycle is optionally substituted with one, two, or three substituents independently selected from C_{1-3} alkyl, halo, $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)NHC_{1-6}$ alkyl, $-C(O)NHC_{3-6}$ cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl;

15 wherein any $-C(O)C_{1-6}$ alkyl is optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, $-OR^n$, $-NR^dR^e$, or heterocycle,

any $-C(O)C_{3-6}$ cycloalkyl is optionally substituted with one or two C_{1-3} alkyl, and

any $-C(O)NHC_{1-6}$ alkyl is optionally substituted with $-OR^n$ or

20 C_{3-6} cycloalkyl;

any heteroaryl is optionally substituted with C_{1-6} alkyl;

R^c is independently selected from hydrogen, C_{1-6} alkyl, and phenyl;

R^d is independently hydrogen or C_{1-6} alkyl;

R^e is independently hydrogen or C_{1-6} alkyl;

25 R^f is independently selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, and $-C(O)C_{1-6}$ alkyl;

R^n is independently hydrogen or C_{1-3} alkyl;

R^k is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and $-CH_2OR^n$;

30 R^g is independently hydrogen or C_{1-6} alkyl;

R^h is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl, wherein C_{1-6} alkyl is optionally substituted with $-OR^d$;

R^j is independently hydrogen or C_{1-6} alkyl;

R^m is independently selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, and $-C(O)C_{1-6}$ alkyl;

R^6 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and a heteroaryl ring;

R^7 , R^8 , and R^{11} are independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy,
5 $-C(O)OR^n$, $-CH_2NR^aR^b$, and $-CN$, wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, three, four, or five halo, and wherein C_{1-6} alkoxy is optionally substituted with $-OR^d$;

R^9 is independently selected from C_{1-6} alkyl, $-CH_2OR^n$, $-C(O)NR^nR^p$, and $C(O)OR^n$, wherein C_{1-6} alkyl is optionally substituted with $-S(O)_2C_{1-3}$ alkyl or with
10 $-SC_{1-3}$ alkyl;

R^p is independently hydrogen or C_{1-3} alkyl;

R^{10} is selected from hydrogen, halo, C_{1-6} alkyl, $-C(O)OR^c$, $-C(O)NR^aR^b$, $-CH_2NR^aR^b$, C_{3-6} cycloalkyl, and $-CN$;

W' , X' , Y' , and Z' are independently carbon or nitrogen wherein any carbon atom
15 is bonded to hydrogen or to R^{11} , provided that at least two of W' , X' , Y' , and Z' are carbon;

W , X , Y , and Z are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or to R^7 , provided that at least two of W , X , Y , and Z are carbon;

A_m is $-NHC(O)-$ or $-C(O)NH-$;

Q , T , U , and V are independently carbon or nitrogen wherein any carbon atom is
20 bonded to hydrogen or to R^8 , provided that at least two of Q , T , U , and V are carbon; and a , b , c , and d are independently 0, 1, or 2;

or a pharmaceutically-acceptable salt or stereoisomer thereof.

As used hereinafter, the phrase "compound of formula (I)" means a compound of
25 formula (I) or a pharmaceutically acceptable salt thereof; i.e., this phrase means a compound of formula (I) in free base form or in a pharmaceutically acceptable salt form unless otherwise indicated.

The invention also provides a pharmaceutical composition comprising a compound of the invention and a pharmaceutically-acceptable carrier. In addition, the
30 invention provides a pharmaceutical composition comprising a compound of the invention, a pharmaceutically-acceptable carrier and one or more other therapeutic agents useful for treating hepatitis C viral infections.

The invention also provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a therapeutically effective

amount of a compound or of a pharmaceutical composition of the invention. In addition, the invention provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a compound or a pharmaceutical composition of the invention and one or more other therapeutic agents useful for treating hepatitis C viral infections. Further, the invention provides a method of inhibiting replication of the hepatitis C virus in a mammal, the method comprising administering a compound or a pharmaceutical composition of the invention.

In separate and distinct aspects, the invention also provides synthetic processes and intermediates described herein, which are useful for preparing compounds of the invention.

The invention also provides a compound of the invention as described herein for use in medical therapy, as well as the use of a compound of the invention in the manufacture of a formulation or medicament for treating a hepatitis C viral infection in a mammal.

DETAILED DESCRIPTION OF THE INVENTION

Among other aspects, the invention provides inhibitors of HCV replication of formula (I), pharmaceutically-acceptable salts thereof, and intermediates for the preparation thereof. The following substituents and values are intended to provide representative examples of various aspects of this invention. These representative values are intended to further define such aspects and are not intended to exclude other values or limit the scope of the invention.

In a specific aspect, R^1 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, heteroaryl, and heterocycle; wherein C_{1-6} alkyl is optionally substituted with $-OR^q$; wherein R^q is hydrogen or C_{1-3} alkyl.

In another specific aspect of the invention, R^1 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, heteroaryl, and heterocycle.

In another specific aspect, R^1 is selected from C_{1-6} alkyl, phenyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with $-OR^q$; wherein R^q is hydrogen or C_{1-3} alkyl.

In another specific aspect, R^1 is selected from C_{1-6} alkyl and phenyl.

In a specific aspect, R^1 is C_{1-3} alkyl.

In another specific aspect, R^1 is isopropyl.

In a specific aspect, R^2 is hydrogen or C_{1-6} alkyl.

In other specific aspects, R^2 is hydrogen or C_{1-3} alkyl; or R^2 is hydrogen.

In a specific aspect, R^3 is selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, $-C(O)OC_{3-6}$ cycloalkyl, $-C(O)NR^aR^b$, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl, wherein R^a and R^b are independently hydrogen or C_{1-6} alkyl.

5 In another specific aspect, R^3 is selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, $-C(O)NR^aR^b$, $-C(O)C_{3-6}$ cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl, wherein R^a and R^b are independently hydrogen or C_{1-6} alkyl.

In yet other specific aspects, R^3 is selected from hydrogen, C_{1-6} alkyl, and $-C(O)OC_{1-6}$ alkyl; and R^3 is $-C(O)OC_{1-3}$ alkyl.

10 In a specific aspect, R^1 is C_{1-6} alkyl, R^2 is hydrogen, and R^3 is $-C(O)OC_{1-6}$ alkyl.

In another specific aspect, R^1 is isopropyl, R^2 is hydrogen, and R^3 is $-C(O)OCH_3$.

In yet other specific aspects, R^1 is phenyl and R^2 and R^3 are each C_{1-3} alkyl, or R^1 is phenyl and R^2 and R^3 are each ethyl; or R^1 is phenyl, R^2 is hydrogen, and R^3 is $-C(O)OC_{1-3}$ alkyl.

15 In a specific aspect, R^4 is $-C(O)R^5$ wherein R^5 is defined as in formula (I).

In another specific aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $-C(R^kR^d)NR^eR^f$, $-NR^gR^h$, heteroaryl, heterocycle, $-CH_2$ -heteroaryl, and phenyl; wherein C_{1-6} alkyl is optionally substituted with $-OR^c$ or $-S(O)_2C_{1-3}$ alkyl; C_{3-6} cycloalkyl is optionally substituted with one or two C_{1-3} alkyl, or with NR^jR^m or $-OR^n$; any heterocycle is optionally substituted with one or two substituents selected from C_{1-3} alkyl, halo, $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, and $-C(O)C_{3-6}$ cycloalkyl optionally substituted with one or two C_{1-3} alkyl; and any heteroaryl is optionally substituted with C_{1-6} alkyl, wherein R^h is selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl, and R^c , R^k , R^d , R^e , R^f , R^g , R^j , R^m , and R^n are defined as in formula (I).

25 In another specific aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $-C(R^kR^d)NR^eR^f$, $-NR^gR^h$, heteroaryl, heterocycle, and $-CH_2$ -heteroaryl, wherein any heteroaryl or heterocycle has five or six ring atoms; C_{3-6} cycloalkyl is optionally substituted with one or two C_{1-3} alkyl; any heterocycle is optionally substituted with one or two substituents selected from C_{1-3} alkyl, halo, $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, and $-C(O)C_{3-6}$ cycloalkyl optionally substituted with one or two C_{1-3} alkyl; R^k , R^d , R^e , R^g , and R^h are each independently hydrogen or C_{1-3} alkyl; and R^f is selected from hydrogen and $-C(O)C_{1-3}$ alkyl.

In another specific aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from C_{3-4} cycloalkyl, $-CH_2NR^cR^f$, $-NR^gR^h$, imidazolyl, pyrazolyl, pyrimidinyl, and pyrrolidinyl; wherein: C_{3-4} cycloalkyl is optionally substituted with one or two C_{1-3} alkyl; pyrrolidinyl is substituted with methyl and a substituent selected from $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl, and $-C(O)NHC_{1-6}$ alkyl, wherein $-C(O)C_{1-6}$ alkyl is substituted with $-NHC(O)OC_{1-3}$ alkyl, $-OR^n$, $-NR^dR^c$, or heterocycle.

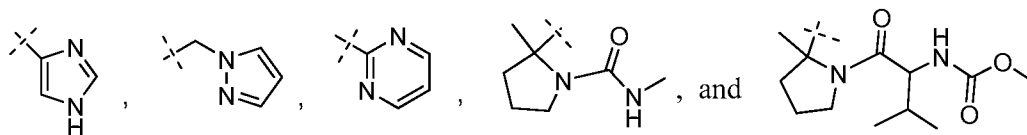
In yet another specific aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from, $-O$ -*tert*-butyl, cyclopropyl, *tert*-butyl, $-NHCH_3$, 2,2-dimethylcyclopropyl, pyrimidinyl, pyrazolyl, imidazolyl, $-CH_2$ -pyrazolyl, 1-acetylpyrrolidinyl, 2-methylpyrrolidine-1-carboxylic acid methyl ester, 1-cyclopropyl-2-methylpyrrolidine, 1-(2,2-dimethylcyclopropyl)-2-methylpyrrolidine, and [-2-methyl-1-(2-methyl-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester.

In yet another specific aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from, $-O$ -*tert*-butyl, cyclopropyl, *tert*-butyl, $-NHCH_3$, 2,2-dimethylcyclopropyl, pyrimidinyl, pyrazolyl, imidazolyl, $-CH_2$ -pyrazolyl, and 1-acetylpyrrolidinyl.

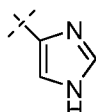
In another aspect, R^4 is $-C(O)R^5$ wherein R^5 is a five- or six-membered heteroaryl ring;

In yet another aspect R^4 is $-C(O)R^5$ wherein R^5 is cyclopropyl or 2,2-dimethylcyclopropyl.

In another aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from $-NHCH_3$, 2,2-dimethylcyclopropyl,



In another aspect, R^4 is $-C(O)R^5$ wherein R^5 is selected from $-NHCH_3$,

2,2-dimethylcyclopropyl, and 

In yet another aspect, R^4 is $-C(O)R^5$ wherein R^5 is $-NHCH_3$.

In a specific aspect, R^4 is $-S(O)_2R^6$ wherein R^6 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, and heteroaryl.

In another specific aspect, R^4 is $-S(O)_2R^6$ wherein R^6 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, and a five- or six-membered heteroaryl.

In another specific aspect, R^4 is $-S(O)_2R^6$ wherein R^6 is C_{1-6} alkyl.

In yet another specific aspect, R^4 is $-S(O)_2R^6$ wherein R^6 is methyl.

In a specific aspect, R^7 , R^8 , and R^{11} are independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)OR^n$, $-CH_2NR^aR^b$, and $-CN$, wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, or three halo and wherein C_{1-6} alkoxy is optionally substituted with $-OR^d$.

In another specific aspect, R^7 , R^8 , and R^{11} are independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)OR^n$, $-CH_2NR^aR^b$, and $-CN$, wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, or three halo

In a specific aspect, R^7 is independently selected from halo, C_{1-6} alkyl, and C_{1-6} alkoxy wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, or three halo.

In another specific aspect, R^7 is halo.

In yet another specific aspect, R^7 is chloro or fluoro.

In still another specific aspect, R^7 is selected from methyl, $-CF_3$, $-OCH_3$, $-OCF_3$, and fluoro.

In yet another specific aspect, R^7 is selected from fluoro, chloro, $-CF_3$, and $-OCF_3$.

In a specific aspect, R^9 is selected from C_{1-6} alkyl, $-CH_2OR^n$, $-C(O)NR^nR^p$, and $C(O)OR^n$, wherein C_{1-6} alkyl is optionally substituted with $-S(O)_2C_{1-3}$ alkyl or with $-SC_{1-3}$ alkyl.

In another specific aspect, R^9 is selected from C_{1-6} alkyl, $-CH_2OR^n$, $-C(O)NR^nR^p$, and $C(O)OR^n$.

In another specific aspect, R^9 is C_{1-6} alkyl or $-CH_2OR^n$.

In another specific aspect, R^9 is C_{1-6} alkyl.

In yet another specific aspect, R^9 is methyl.

In a specific aspect, R^{10} is selected from hydrogen, halo, C_{1-6} alkyl, $-C(O)OR^c$, $-C(O)NR^aR^b$, $-CH_2NR^aR^b$, C_{3-6} cycloalkyl, and $-CN$.

In a specific aspect, R^{10} is selected from hydrogen, halo, and C_{1-6} alkyl.

In other specific aspects, R^{10} is halo; or R^{10} is chloro.

In yet another specific aspect, R^{10} is hydrogen.

In a specific aspect W' , X' , Y' , and Z' are each CH.

In a specific aspect, W , X , Y , and Z are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or to R^7 , provided that at least two of W , X , Y , and Z are carbon.

In another specific aspect, W, X, Y, and Z are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or R⁷, provided that at least three of W, X, Y, and Z are carbon.

In another specific aspect, W, X, Y, and Z are each carbon and two of W, X, Y, and Z are CH and two of W, X, Y, and Z are bonded to R⁷.

In yet another specific aspect, W and Z are independently carbon bonded to R⁷ and X and Y are CH.

In a specific aspect, Q, T, U, and V are independently selected from CH and N.

In a specific aspect, Q, U, and V are each CH and T is N.

In a specific aspect, *a* is 1 or 2.

In another specific aspect, *a* is 1.

In another specific aspect *a* is 0.

In a specific aspect, *b* is 0.

In a specific aspect, *c* is 1 or 2.

In another specific aspect, *c* is 2.

In another specific aspect, *c* is 1.

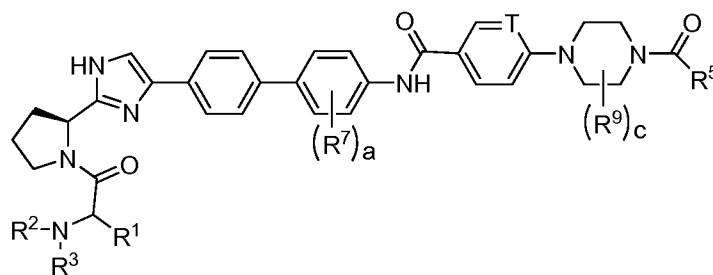
In another specific aspect, *c* is 0.

In a specific aspect, *d* is 1.

In a specific aspect, *d* is 0.

In one aspect, the invention provides compounds of formula (I) disclosed in U.S. Provisional Application No. 61/492,267, filed on June 1, 2011.

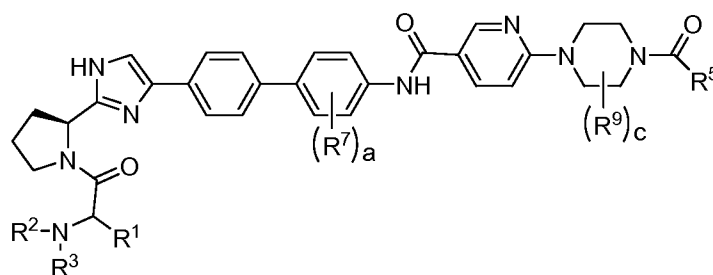
In another aspect, the invention provides compounds of formula (II):



(II)

wherein the variables of formula (II) are as defined herein.

In another aspect, the invention provides compounds of formula (III)



(III)

wherein the variables of formula (III) are as defined herein.

A particular group of compounds of formula (III) is a group wherein:

5 R^1 is selected from C_{1-6} alkyl, phenyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl is optionally substituted with $-OR^a$;

R^3 is selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, $-C(O)NR^aR^b$, $-C(O)C_{3-6}$ cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl;

10 R^5 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $-C(R^kR^d)NR^eR^f$, $-NR^gR^h$, heteroaryl, heterocycle, and $-CH_2$ -heteroaryl;

wherein:

any heteroaryl or heterocycle has 5 or 6 ring atoms;

C_{1-6} alkyl is optionally substituted with one or two substituents independently selected from $-OR^c$, $-NHC(O)C_{1-3}$ alkyl, and $-NHC(O)OC_{1-3}$ alkyl;

15 C_{1-6} alkoxy is optionally substituted with $-OR^d$;

C_{3-6} cycloalkyl is optionally substituted with one or two substituents independently selected from C_{1-3} alkyl and halo;

any heterocycle is optionally substituted with one, two, or three substituents independently selected from C_{1-3} alkyl, halo, $-C(O)OC_{1-3}$ alkyl,

20 $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)NHC_{1-6}$ alkyl, and $-C(O)NHC_{3-6}$ cycloalkyl;

wherein any $-C(O)C_{1-6}$ alkyl is optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, $-OR^n$, $-NR^dR^e$, or heterocycle,

any $-C(O)C_{3-6}$ cycloalkyl is optionally substituted with one or two C_{1-3} alkyl, and

25 any $-C(O)NHC_{1-6}$ alkyl is optionally substituted with $-OR^n$ or C_{3-6} cycloalkyl;

any heteroaryl is optionally substituted with C_{1-3} alkyl;

R^k , R^d , R^e , R^g , and R^h are each independently hydrogen or C_{1-3} alkyl;

R^f is selected from hydrogen and $-C(O)C_{1-3}alkyl$;

R^7 is selected from halo, $C_{1-3}alkyl$, and $C_{1-3}alkoxy$ wherein $C_{1-6}alkyl$ and $C_{1-6}alkoxy$ are optionally substituted with one, two, or three halo;

R^9 is $C_{1-3}alkyl$;

5 a is 1 or 2; and

c is 1 or 2; and all other variables are as defined in formula (I).

Another group of compounds of formula (III) is a group wherein:

R^5 is selected from $C_{3-4}cycloalkyl$, $-CH_2NR^eR^f$, $-NR^gR^h$, imidazolyl, pyrazolyl, pyrimidinyl, and pyrrolidinyl;

10 wherein:

$C_{3-4}cycloalkyl$ is optionally substituted with one or two $C_{1-3}alkyl$;

pyrrolidinyl is substituted with methyl and a substituent selected from $-C(O)OC_{1-3}alkyl$, $-C(O)C_{1-6}alkyl$, $-C(O)NHC_{1-6}alkyl$, wherein

$-C(O)C_{1-6}alkyl$ is substituted with $-NHC(O)OC_{1-3}alkyl$, $-OR^n$,

15 $-NR^dR^e$, or heterocycle;

wherein R^e , R^g , and R^h are each independently hydrogen or $C_{1-3}alkyl$; and

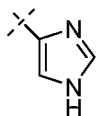
R^f is selected from hydrogen and $-C(O)C_{1-3}alkyl$.

Yet another group of compounds of formula (III) is a group wherein:

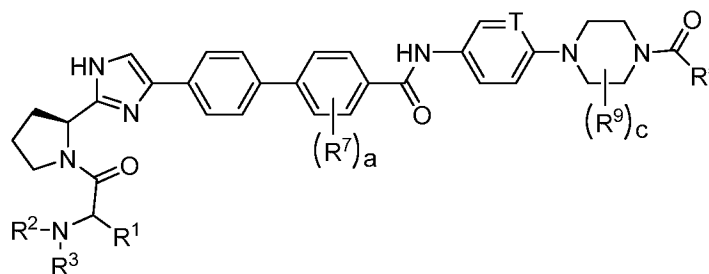
R^1 is isopropyl, R^2 is hydrogen; R^3 is $-C(O)OCH_3$;

20 R^7 is selected from fluoro, chloro, $-CF_3$, and $-OCF_3$; R^9 is methyl; and

R^5 is selected from $-NHCH_3$, 2,2-dimethylcyclopropyl, and



In another aspect, the invention additionally provides compounds of formula (IV):

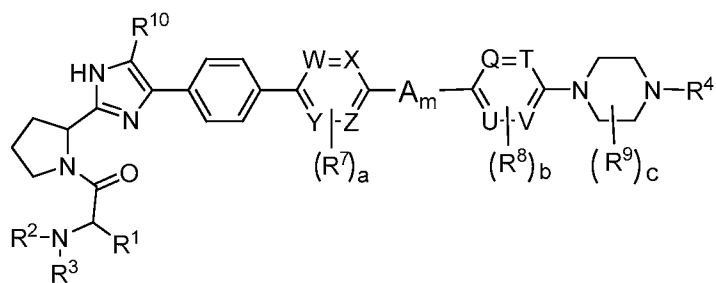


25

(IV)

wherein the variables of formula (IV) are as defined herein.

In still another aspect, the invention provides compounds of formula (V):

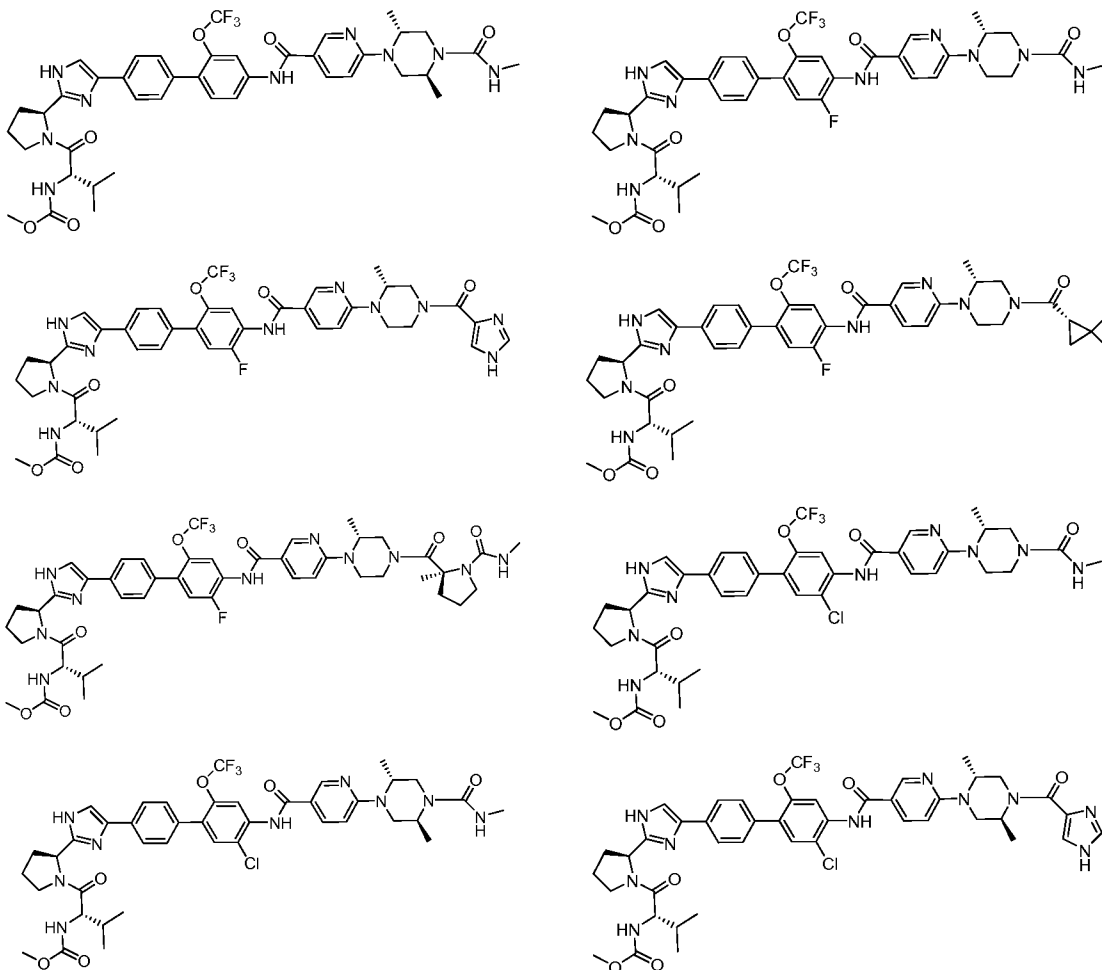


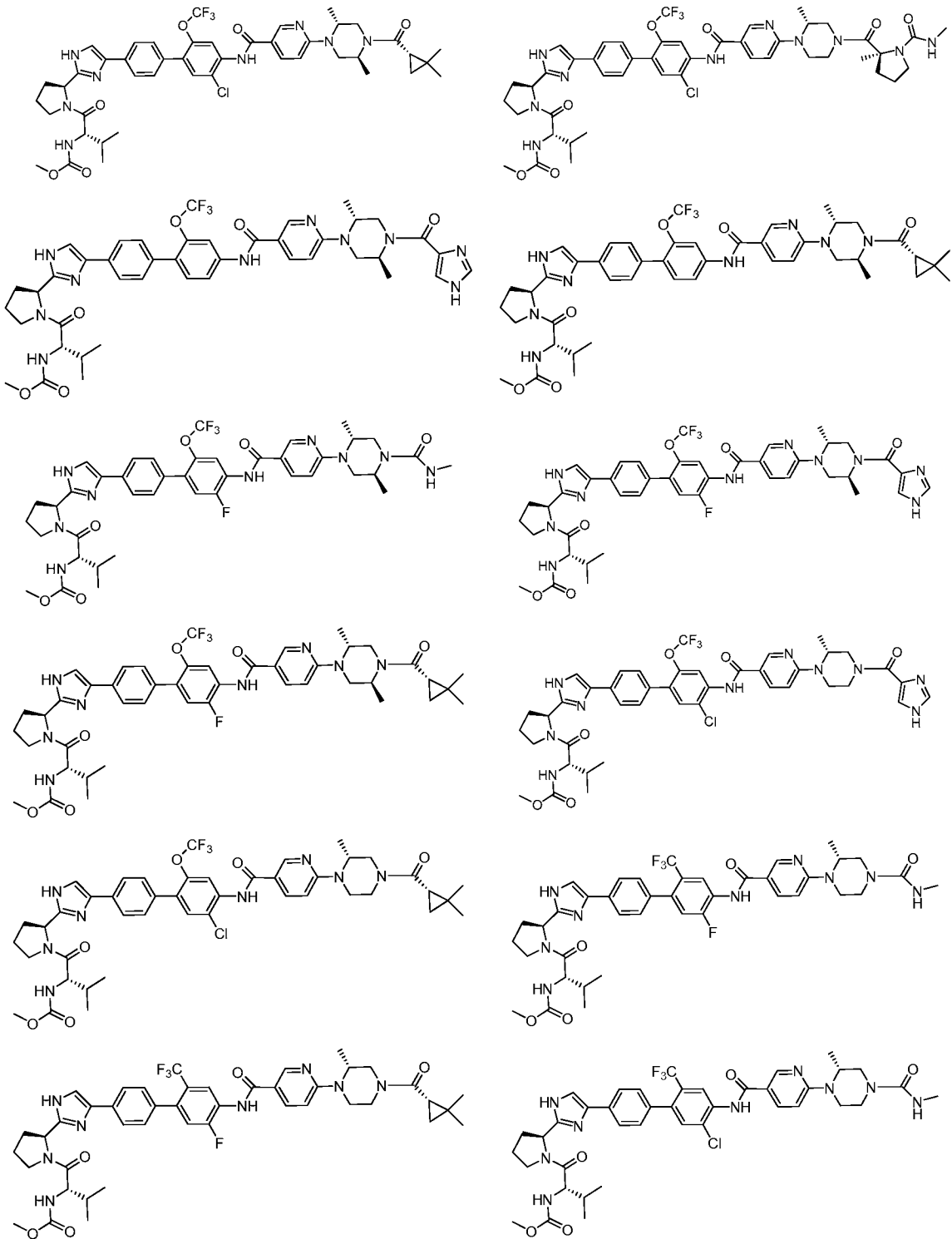
(V)

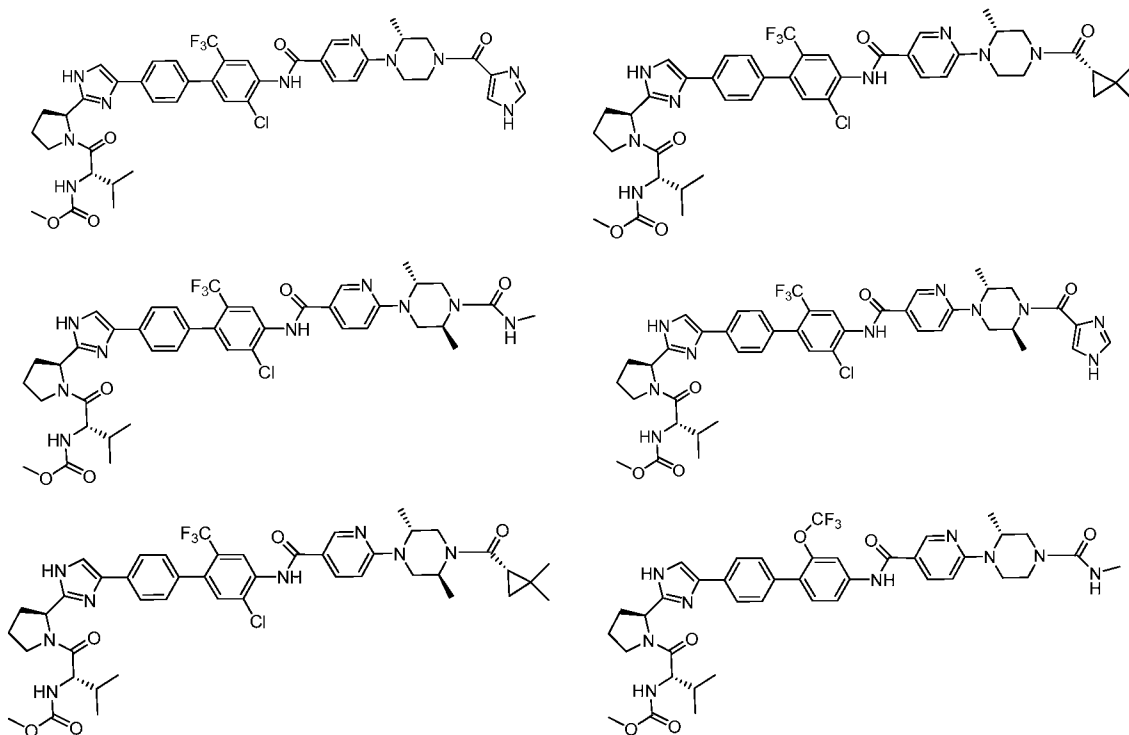
wherein the variables are as defined herein.

In one aspect, the invention provides the compounds of Examples 1-77 and
5 Tables 1-34 below.

In yet another aspect, the invention provides a compound selected from the
compounds depicted below

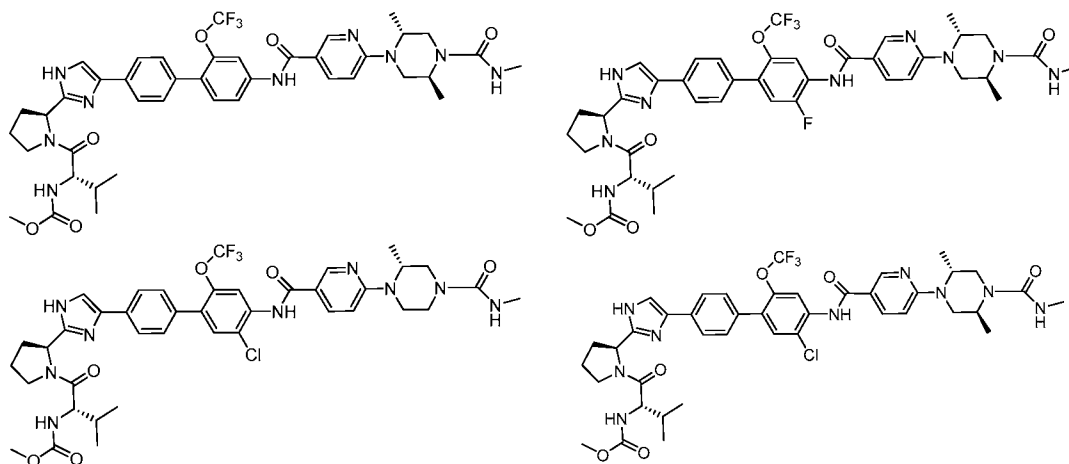






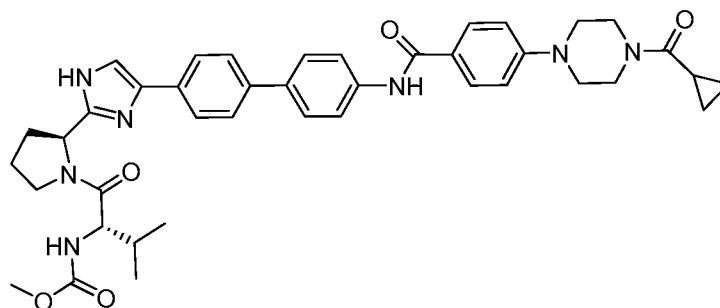
and pharmaceutically-acceptable salts thereof.

In a still further aspect, the invention provides a compound selected from the following compounds



and pharmaceutically-acceptable salts thereof.

5 The chemical naming convention used herein is illustrated for the compound of Example 1:



which is {(S)-1-[(S)-2-(4-{4'-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester according to the IUPAC conventions as implemented in AutoNom
5 software, (MDL Information Systems, GmbH, Frankfurt, Germany).

The compounds of the invention contain one or more chiral centers and therefore, such compounds (and intermediates thereof) can exist as racemic mixtures; pure stereoisomers (i.e., enantiomers or diastereomers); stereoisomer-enriched mixtures and the like. Chiral compounds shown or named herein without a defined stereochemistry at
10 a chiral center are intended to include any or all possible stereoisomer variations at the undefined stereocenter unless otherwise indicated. The depiction or naming of a particular stereoisomer means the indicated stereocenter has the designated stereochemistry with the understanding that minor amounts of other stereoisomers may also be present unless otherwise indicated, provided that the utility of the depicted or
15 named compound is not eliminated by the presence of another stereoisomer.

Compounds of formula (I) also contain several basic groups (e.g., amino groups) and therefore, such compounds can exist as the free base or in various salt forms, such a mono-protonated salt form, a di-protonated salt form, a tri-protonated salt form, or mixtures thereof. All such forms are included within the scope of this invention, unless
20 otherwise indicated.

This invention also includes isotopically-labeled compounds of formula (I), i.e., compounds of formula (I) where an atom has been replaced or enriched with an atom having the same atomic number but an atomic mass different from the atomic mass that predominates in nature. Examples of isotopes that may be incorporated into a compound
25 of formula (I) include, but are not limited to, ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³⁵S, ³⁶Cl, and ¹⁸F. Of particular interest are compounds of formula (I) enriched in tritium or carbon-14, which compounds can be used, for example, in tissue distribution studies. Also of particular interest are compounds of formula (I) enriched in deuterium especially

at a site of metabolism, which compounds are expected to have greater metabolic stability. Additionally of particular interest are compounds of formula (I) enriched in a positron emitting isotope, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , which compounds can be used, for example, in Positron Emission Tomography (PET) studies.

5

Definitions

When describing this invention including its various aspects and embodiments, the following terms have the following meanings, unless otherwise indicated.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched or combinations thereof. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms. Representative alkyl groups include, by way of example, methyl (Me), ethyl (Et), n-propyl (n-Pr) or (nPr), isopropyl (i-Pr) or (iPr), n-butyl (n-Bu) or (nBu), sec-butyl, isobutyl, tert-butyl (t-Bu) or (tBu), n-pentyl, n-hexyl, 2,2-dimethylpropyl, 2-methylbutyl, 3-methylbutyl, 2-ethylbutyl, 2,2-dimethylpentyl, 2-propylpentyl, and the like

When a specific number of carbon atoms are intended for a particular term, the number of carbon atoms is shown preceding the term. For example, the term "C₁₋₃ alkyl" means an alkyl group having from 1 to 3 carbon atoms wherein the carbon atoms are in any chemically-acceptable configuration, including linear or branched configurations..

The term "alkoxy" means the monovalent group -O-alkyl, where alkyl is defined as above. Representative alkoxy groups include, by way of example, methoxy, ethoxy, propoxy, butoxy, and the like.

The term "cycloalkyl" means a monovalent saturated carbocyclic group which may be monocyclic or multicyclic. Unless otherwise defined, such cycloalkyl groups typically contain from 3 to 10 carbon atoms. Representative cycloalkyl groups include, by way of example, cyclopropyl (cPr), cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, and the like.

The term "heterocycle", "heterocyclic", or "heterocyclic ring" means a monovalent saturated or partially unsaturated cyclic non-aromatic group, having from 3 to 10 total ring atoms, wherein the ring contains from 2 to 9 carbon ring atoms and from 1 to 4 ring heteroatoms selected from nitrogen, oxygen, and sulfur. Heterocyclic groups may be monocyclic or multicyclic (i.e., fused or bridged). Representative heterocyclic groups include, by way of example, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl,

morpholinyl, thiomorpholyl, indolin-3-yl, 2-imidazolyl, 1,2,3,4-tetrahydroisoquinolin-2-yl, quinuclidinyl, 7-azanorbornanyl, nortropanyl, and the like, where the point of attachment is at any available carbon or nitrogen ring atom. Where the context makes the point of attachment of the heterocyclic group evident, such groups may alternatively be referred to as a non-valent species, i.e. pyrrolidine, piperidine, piperazine, imidazole, etc.

The term "heteroaryl" or "heteroaryl ring" means a monovalent aromatic group having from 5 to 10 total ring atoms, wherein the ring contains from 1 to 9 carbon ring atoms and from 1 to 4 ring heteroatoms selected from nitrogen, oxygen, and sulfur. Heteroaryl groups may be monocyclic or multicyclic. Representative heteroaryl groups include, by way of example, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyridyl (or, equivalently, pyridinyl), pyrimidyl, pyridazinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, and the like, where the point of attachment is at any available carbon or nitrogen ring atom. Where the context makes the point of attachment of the heteroaryl group evident, such groups may alternatively be referred to as a non-valent species, i.e. pyrrole, isoxazole, isothiazole, pyrazole, imidazole, etc.

The term "halo" means fluoro, chloro, bromo or iodo.

The term "therapeutically effective amount" means an amount sufficient to effect treatment when administered to a patient in need of treatment.

The term "treatment" as used herein means the treatment of a disease, disorder, or medical condition in a patient (such as hepatitis C viral infection), such as a mammal (particularly a human) which includes one or more of the following:

- (a) preventing the disease, disorder, or medical condition from occurring, i.e., preventing the reoccurrence of the disease or medical condition or prophylactic treatment of a patient that is pre-disposed to the disease or medical condition;
- (b) ameliorating the disease, disorder, or medical condition, i.e., eliminating or causing regression of the disease, disorder, or medical condition in a patient, including counteracting the effects of other therapeutic agents;
- (c) suppressing the disease, disorder, or medical condition, i.e., slowing or arresting the development of the disease, disorder, or medical condition in a patient; or
- (d) alleviating the symptoms of the disease, disorder, or medical condition in a patient.

The term "pharmaceutically acceptable salt" means a salt that is acceptable for administration to a patient or a mammal, such as a human (e.g., salts having acceptable mammalian safety for a given dosage regime). Representative pharmaceutically acceptable salts include salts of acetic, ascorbic, benzenesulfonic, benzoic, 5 camphorsulfonic, citric, ethanesulfonic, edisyllic, fumaric, gentisic, gluconic, glucuronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic, nicotinic, nitric, orotic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and xinafoic acid, and the like.

10 The term "salt thereof" means a compound formed when the hydrogen of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. For example, the cation can be a protonated form of a compound of formula (I), i.e. a form where one or more amino groups have been protonated by an acid. Typically, the salt is a pharmaceutically acceptable salt, although this is not required for salts of intermediate 15 compounds that are not intended for administration to a patient.

The term "amino-protecting group" means a protecting group suitable for preventing undesired reactions at an amino nitrogen. Representative amino-protecting groups include, but are not limited to, formyl; acyl groups, for example alkanoyl groups, such as acetyl and tri-fluoroacetyl; alkoxycarbonyl groups, such as *tert* butoxycarbonyl 20 (Boc); arylmethoxycarbonyl groups, such as benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc); arylmethyl groups, such as benzyl (Bn), trityl (Tr), and 1,1-di-(4'-methoxyphenyl)methyl; silyl groups, such as trimethylsilyl (TMS), *tert*-butyldimethylsilyl (TBDMS), [2-(trimethylsilyl)ethoxy]methyl (SEM); and the like. Numerous protecting groups, and their introduction and removal, are described in T. W. 25 Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York

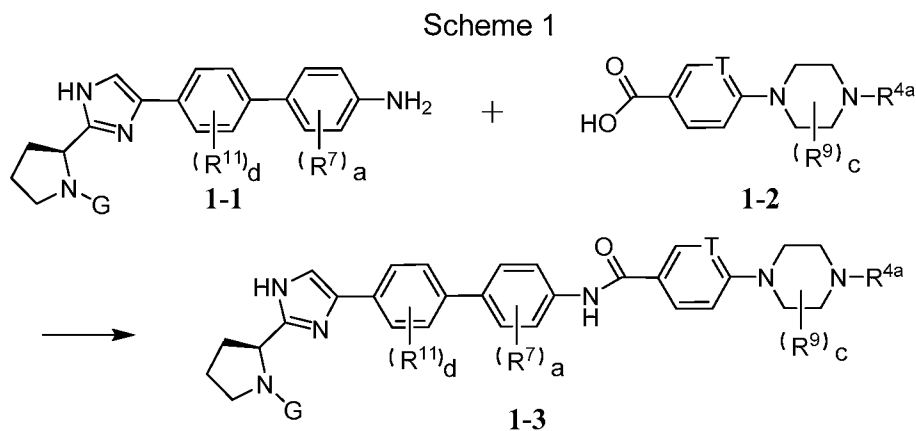
General Synthetic Procedures

Compounds of this invention, and intermediates thereof, can be prepared according to the following general methods and procedures using commercially-available 30 or routinely-prepared starting materials and reagents. The substituents and variables (e.g., R¹, R², R³, R⁴, etc.) used in the following schemes have the same meanings as those defined elsewhere herein unless otherwise indicated. Additionally, compounds having an acidic or basic atom or functional group may be used or may be produced as a salt unless

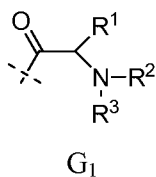
otherwise indicated (in some cases, the use of a salt in a particular reaction will require conversion of the salt to a non-salt form, e.g., a free base, using routine procedures before conducting the reaction).

Although a particular embodiment of the present invention may be shown or
 5 described in the following procedures, those skilled in the art will recognize that other
 embodiments or aspects of the present invention can also be prepared using such
 procedures or by using other methods, reagents, and starting materials known to those
 skilled in the art. In particular, it will be appreciated that compounds of the invention
 10 may be prepared by a variety of process routes in which reactants are combined in
 different orders to provide different intermediates en route to producing final products.

In one exemplary method of synthesis, compounds of formula (1-3) in which A_m
 is defined as $-NHC(O)-$ are prepared as shown in Scheme 1:



where R^{4a} is an amino-protecting group Pg or R^{4a} is R^4 as defined in formula (I), and G
 15 represents the group G_1



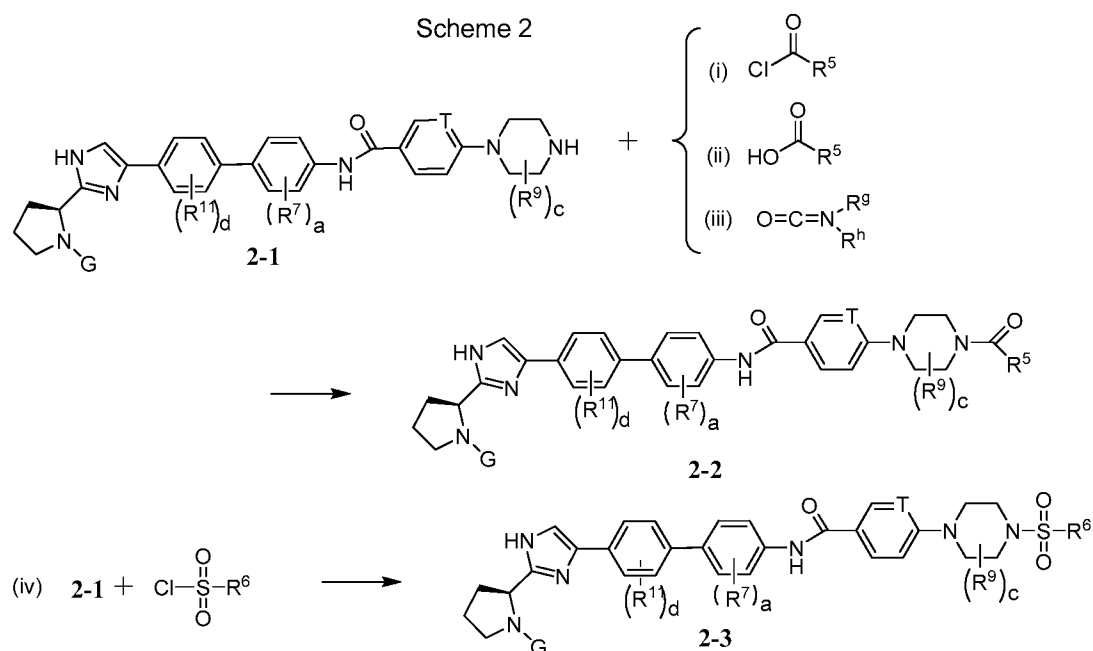
where R^1 , R^2 , and R^3 are defined as in formula (I), or as an amino-protecting group Pg.
 Aniline intermediate **1-1** is reacted with carboxylic acid **1-2** according to typical amide
 20 bond formation conditions to provide a compound of formula **1-3**. In some instances, the
 carboxylic acid **1-2** is first converted to an acid chloride and then reacted with aniline
 intermediate **1-1** to provide a compound of formula **1-3**. As shown in the examples
 below, the amide bond formation reaction may utilize coupling agents, such as *N,N,N',N'*-
 tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU), or as 1,3

dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), or benzotriazol-1-yloxytripyrrolidino-phosphonium hexafluorophosphate (PyBop), optionally combined with 1-hydroxy-7-azabenzotriazole (HOAt). Preferably, the process of Scheme 1 is used to prepare compounds of formula **1-3** in which R^7 is absent (a is 0) or R^7 is an electron rich substituent such as an unsubstituted-alkyl or unsubstituted-alkoxy, and the reaction is performed in the presence of coupling agents EDC and HOAt at a temperature of about 50 to about 60 °C. Preferably, only one of G and R^{4a} is a protecting group, or, if two protecting groups are present, groups removable under different conditions are used.

10 When the variable R^{4a} is defined as R^4 and the variable G is defined as G_1 , then the product **1-3** of the reaction of Scheme 1 is a final compound of formula (I).

Alternatively, when R^{4a} is defined as R^4 and G is defined as protecting group Pg, for example Boc, the product **1-3** of the reaction of Scheme 1 is a protected intermediate which is then deprotected, for example, by treatment with an acid, and reacted with a reagent X- G_1 , where X is a halogen leaving group, or with a carboxylic acid of formula HO- G_1 , the latter under amide bond formation conditions as described above, to provide the desired product.

In another exemplary method of synthesis, compounds of formulas **2-2** and **2-3** are prepared as shown in Scheme 2:



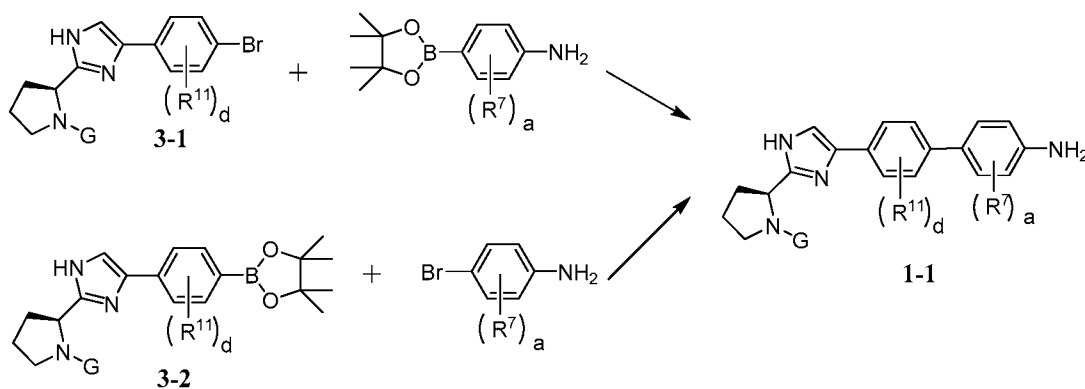
When G represents G_1 in intermediate **2-1**, then the reaction of Scheme 2, directly provides compounds of the invention. To prepare a compound of formula **2-2** where R^4 is defined as $-C(O)R^5$, intermediate **2-1** is reacted with an acid chloride (reaction (i)) or, where R^5 is defined as $-NR^gR^h$, with an isocyanate (reaction (iii)) in the presence of base.

5 Alternatively, intermediate **2-1** is reacted with a carboxylic acid (reaction (ii)) under amide bond formation conditions to prepare a compound of formula **2-2**. Similarly, to prepare a compound of formula **2-3** where R^4 is defined as $-S(O)_2R^6$, intermediate **2-1** is typically reacted with a sulfonyl chloride in the presence of base (reaction (iv)).

As described above, when G represents a protecting group a subsequent
10 deprotection step, and coupling with an intermediate $X-G_1$ or $HO-G_1$ provides the final product.

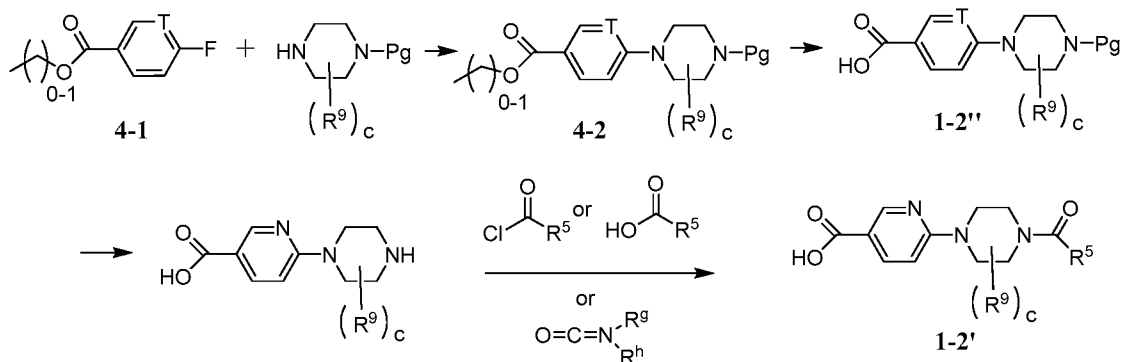
The intermediates of the above Schemes may be prepared by conventional synthetic reactions. For example, the biaryl aniline intermediate **1-1** may be prepared by the Suzuki coupling reaction in the presence of a palladium catalyst (Miyaura and Suzuki,
15 *Chem. Rev.* **1995**, 95, 2457-2483). As shown in Scheme 3 below, either coupling partner may bear the boronate moiety. Alternatively, a boronic acid reagent may be used in place of a boronate reagent, such as the pinacol boronate depicted below.

Scheme 3



20 An exemplary process for the preparation of intermediate **1-2** in which R^{4a} represents Pg (compound **1-2''**) or R^{4a} represents, for example, $-C(O)R^5$ (compound **1-2'**) is shown in Scheme 4.

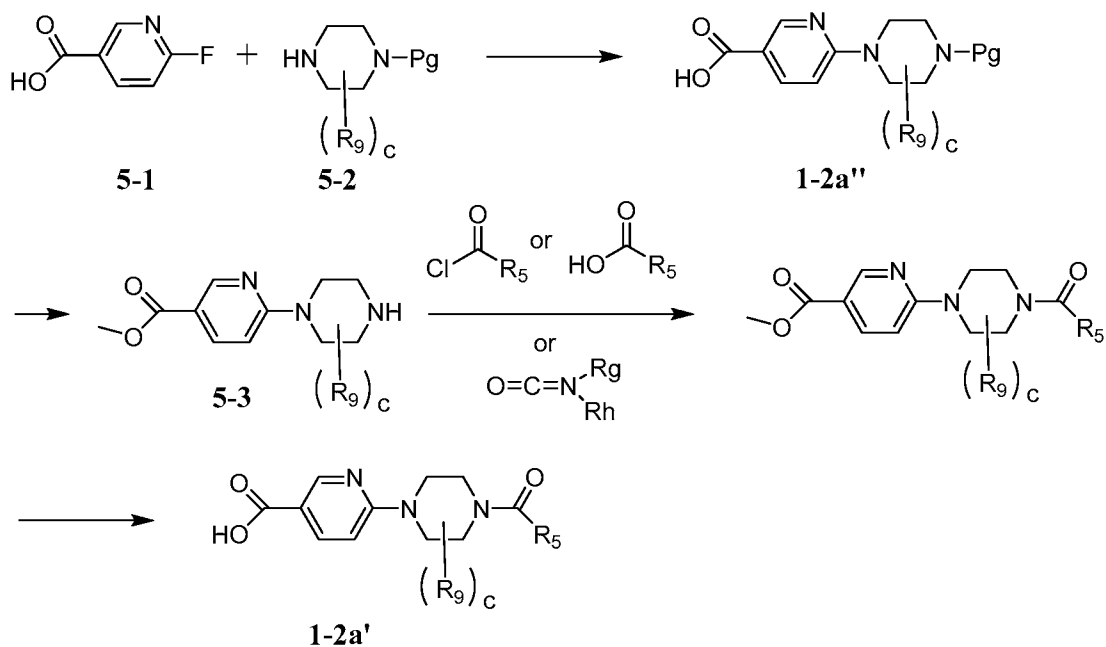
Scheme 4'



The reaction of a piperazine with a fluorobenzoic ester or fluoronicotinic ester 4-1, typically a methyl or ethyl ester, may be performed in dimethylsulfoxide in the presence of potassium carbonate at elevated temperature, typically about 100 °C to about 130 °C. The resulting intermediate 4-2 is subsequently hydrolyzed to provide protected intermediate 1-2''. To prepare intermediate 1-2', protected intermediate 1-2'', where preferably the protecting group is Boc, can be deprotected and then reacted with an acid chloride, carboxylic acid, or isocyanate as in Scheme 2 to provide intermediate 1-2'.

An alternative process for the preparation of intermediate 1-2 in which T represents nitrogen and R^{4a} represents Pg (compound 1-2a'') or R^{4a} represents -C(O)R⁵ (compound 1-2a') is shown in Scheme 5.

Scheme 5

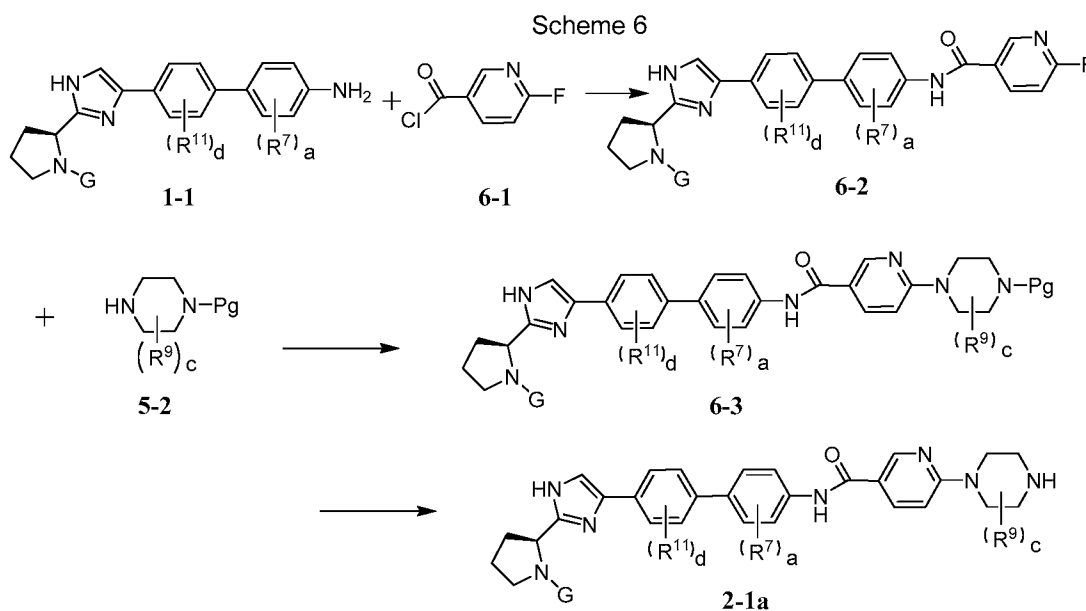


The reaction of a fluoronicotinic acid **5-1** with the protected piperazine **5-2** to provide intermediate **1-2a''** is typically performed using isopropylmagnesium chloride at a temperature below about -20 °C.

To prepare intermediate **1-2a'**, protected intermediate **1-2a''**, where preferably the protecting group is Boc, can be deprotected and esterified by reaction with sulfuric acid in methanol to provide an ester intermediate **5-3**, which is reacted with an acid chloride, carboxylic acid, or isocyanate as in Scheme 2 and subsequently hydrolyzed to provide intermediate **1-2a'**.

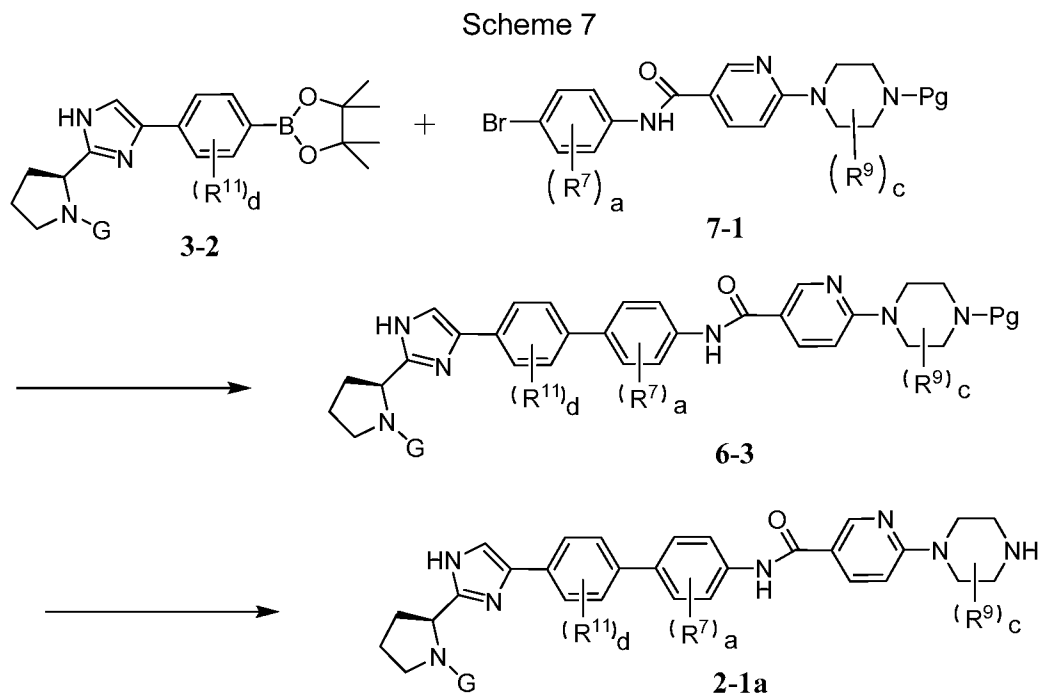
Intermediate **2-1** where G represents G₁ may be prepared by the process of Scheme 1 where the variable R^{4a} is defined as protecting group Pg. In this instance, formula **1-3** describes a protected intermediate, which is deprotected to provide intermediate **2-1**.

An alternative process for the preparation of intermediate **2-1** in which T represents nitrogen (compound **2-1a**) is shown in Scheme 6.

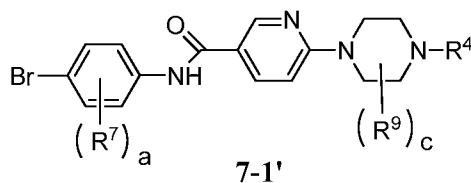


In a first step, biphenyl aniline **1-1** is reacted with a fluoropyridine carbonyl chloride **6-1** in the presence of base to provide fluoro intermediate **6-2**, which is reacted with an excess of protected piperidine **5-2** to provide protected intermediate **6-3**. The reaction typically is performed in the presence of base with heating to a temperature of about 80 °C to about 120 °C for a period of about 4 to about 48 hours. Finally, intermediate **6-3** is deprotected, for example, by treatment with hydrochloric acid in an organic solvent to provide intermediate **2-1a** as the HCl salt.

Yet another alternative process for the preparation of intermediate **2-1a** utilizes a Suzuki coupling reaction of the boronate reagent **3-2** with intermediate **7-1**, followed by a deprotection step, under conditions described above, as shown in Scheme 7.



- 5 If protected intermediate **7-1** were replaced by an intermediate **7-1'** bearing the substituent R^4

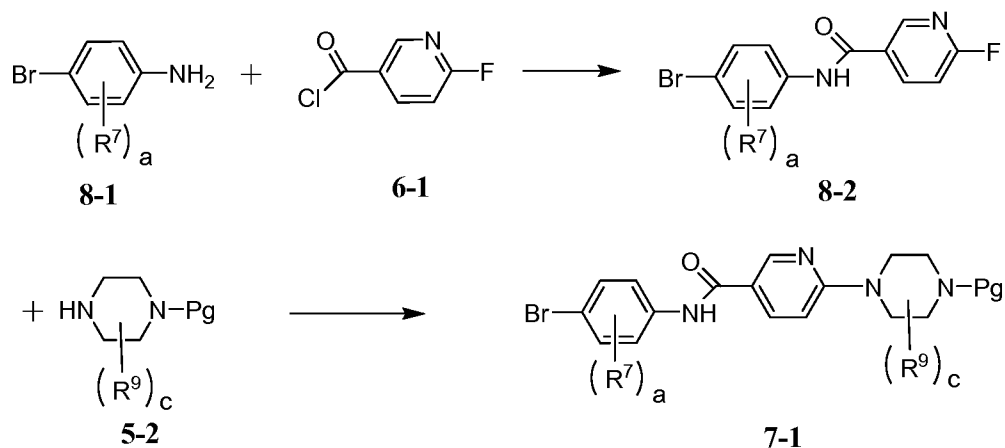


then the Suzuki coupling of the boronate **3-2** in the first step of Scheme 7 would directly provide a final compound of the invention.

- 10 In the Suzuki coupling reaction of Scheme 7, alternatively, the opposite coupling partner could bear the boronate moiety, as shown in Scheme 3.

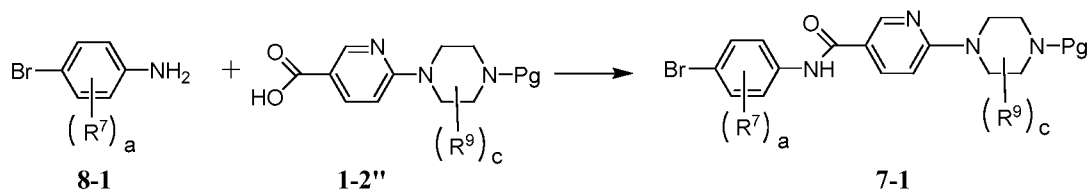
The bromo intermediate **7-1** may be prepared, for example, by amide coupling of arylamine **8-1** with a fluoropyridine carbonyl chloride **6-1**, followed by reaction with a protected piperazine **5-2** as shown in Scheme 8.

Scheme 8



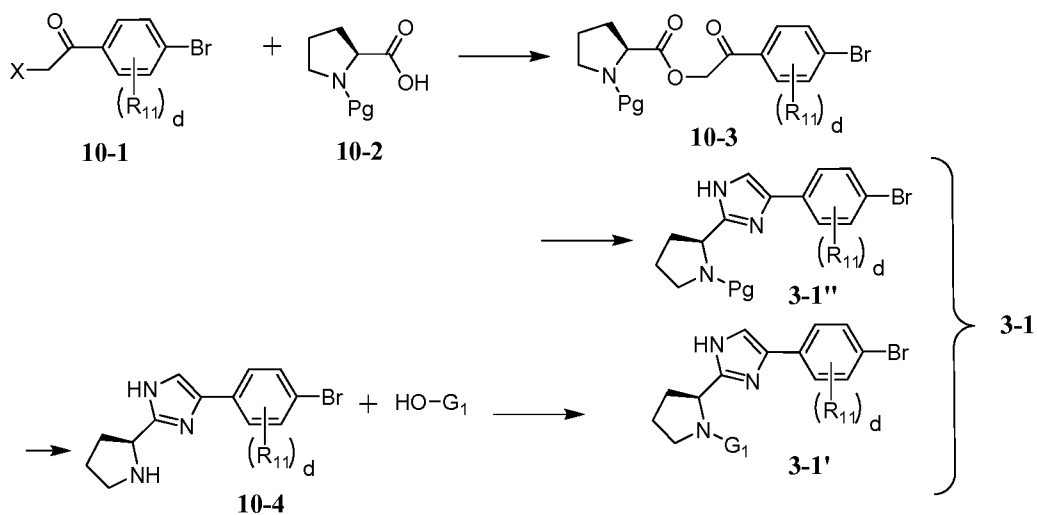
Alternatively, intermediate **7-1** may be prepared by the reaction of **8-1** with the carboxylic acid intermediate **1-2''** as given in Scheme 9.

Scheme 9



5 Intermediates **3-1** and **3-2** used in the Suzuki reaction of Scheme 3 may be prepared, for example, as shown in Schemes 10 and 11.

Scheme 10



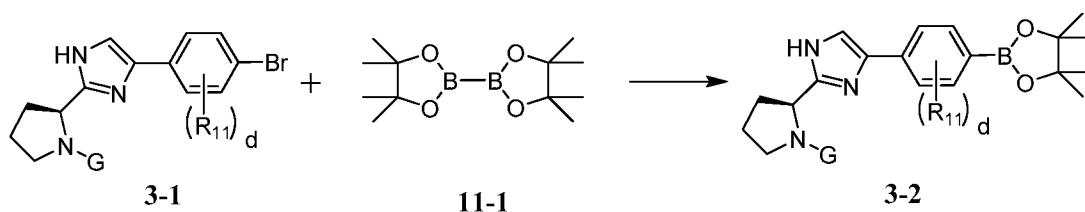
Reagent **10-1**, where X represents bromo or chloro is reacted with a protected proline carboxylic acid **10-2** to provide intermediate **10-3** which is converted to intermediate **3-1''**, where the variable G represents a protecting group, in the presence of

10

an excess of ammonium acetate. The ring closure reaction typically is performed at a temperature between about 100 °C and about 120 °C for a period of about 4 to about 24 hours. To provide compound **3-1'** where the variable G represents G₁, intermediate **3-1''** is typically deprotected to provide intermediate **10-4**, which is then coupled with a reagent HO-G₁ to provide compound **3-1'**.

Finally, to provide boronate intermediate **3-2**, intermediate **3-1** is reacted with **11-1** in the presence of a palladium catalyst as shown in Scheme 11.

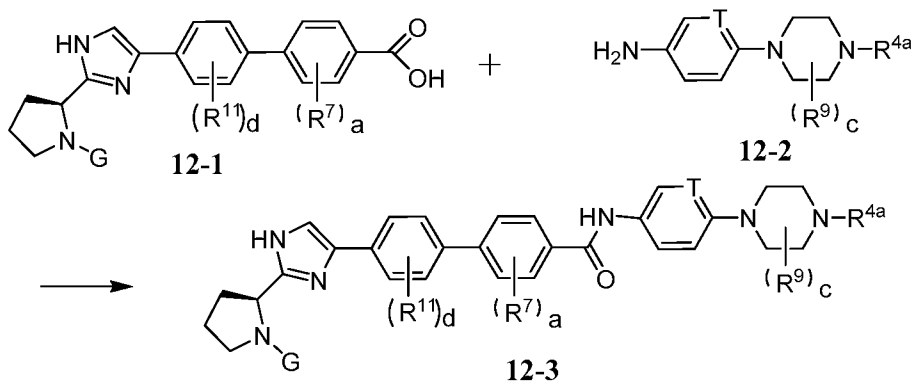
Scheme 11



For the preparation of intermediate **2-1a** in Scheme 7, boronate intermediate **3-2** may be prepared in situ according to the process of Scheme 11 and then reacted with intermediate **7-1** to provide intermediate **6-3** in a single pot process.

Compounds of Formula **12-3** in which the variable A_m is defined as -C(O)NH- are prepared by processes analogous to those described above. One exemplary process for the preparation of compounds of Formula **12-3** is shown in Scheme 12.

Scheme 12

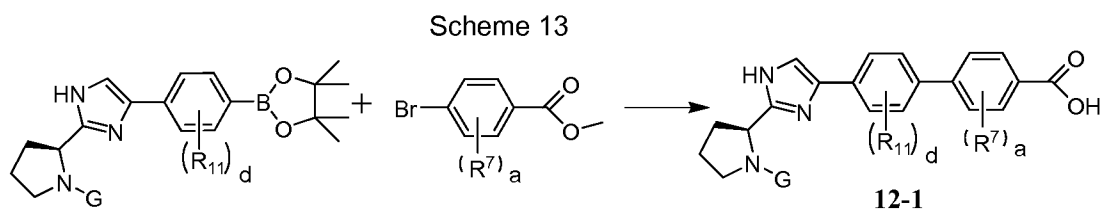


The acid **12-1** and aniline or aminopyridine **12-2** are reacted under amide bond formation conditions. As above, when the variable R^{4a} represents R⁴ and the variable G represents G₁, then the reaction of Scheme 12 directly provides final compounds of formula (I).

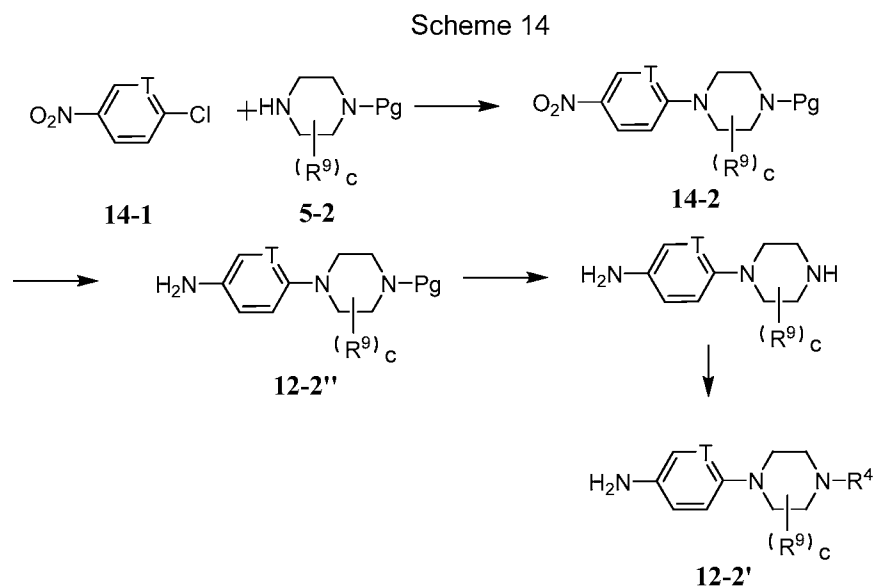
Alternatively, when R^{4a} represents R^4 and G represents protecting group Pg, for example Boc, the reaction provides a protected intermediate of formula **12-3** which is then deprotected and reacted with a reagent X-G₁, where X is a halogen leaving group, or with a carboxylic acid of formula HO—G₁, to provide the desired product.

5 In yet another alternative route, a compound of formula **12-3** in which G is defined as G₁ and R^{4a} is a protecting group Pg, provides a useful intermediate, which is deprotected and reacted, for example, with an acid chloride, carboxylic acid, or isocyanate, as in Scheme 2 to provide final compounds of formula (I).

10 The intermediates of Scheme 12 may be prepared by conventional synthetic reactions. For example, the biaryl acid intermediate **12-1** may be prepared by the Suzuki coupling reaction of Scheme 13



15 A useful process for the preparation of the aminopyridine intermediate **12-2** of Scheme 12 utilizes a nitro substituted-chloropyridine or chlorophenyl **14-1** which is reacted with a protected piperazine **5-2** to provide a protected intermediate **14-2** as shown in Scheme 14.



20 Reduction of the nitro group to the amine provides intermediate **12-2''** where R^{4a} represents a protecting group. Deprotection of compound **12-2''** and reaction, for

example, with an acid chloride, carboxylic acid, or isocyanate, as in schemes above provides intermediate **12-2'**, in which R^{4a} represents R⁴.

It will be understood by those of skill in the art, that other compounds of the invention having heterocyclic rings in place of the phenyl rings of the structures in the above schemes may be prepared by similar methods starting with appropriate starting materials. Details regarding specific reaction conditions and other procedures for preparing representative compounds of the invention or intermediates thereto are described in the examples below.

It will further be understood, this disclosure encompasses compounds of formula (I) when prepared by synthetic processes such as those described above and below or by metabolic processes including those occurring *in vivo* in human or animal body or *in vitro*.

Pharmaceutical Compositions

The compounds of the invention and pharmaceutically-acceptable salts thereof are typically used in the form of a pharmaceutical composition or formulation. Such pharmaceutical compositions may be administered to a patient by any acceptable route of administration including, but not limited to, oral, rectal, vaginal, nasal, inhaled, topical (including transdermal) and parenteral modes of administration.

Accordingly, in one of its compositions aspects, the invention is directed to a pharmaceutical composition comprising a pharmaceutically-acceptable carrier or excipient and a compound of formula (I), where, as defined above, "compound of formula (I)" means a compound of formula (I) or a pharmaceutically-acceptable salt thereof. Optionally, such pharmaceutical compositions may contain other therapeutic and/or formulating agents if desired. When discussing compositions and uses thereof, the "compound of the invention" may also be referred to herein as the "active agent". As used herein, the term "compound of the invention" is intended to include all compounds encompassed by formula (I) as well as the species embodied in formulas (II), (III), (IV), and (V), and pharmaceutically-acceptable salts thereof

The pharmaceutical compositions of the invention typically contain a therapeutically effective amount of a compound of the present invention. Those skilled in the art will recognize, however, that a pharmaceutical composition may contain more than a therapeutically effective amount, i.e., bulk compositions, or less than a therapeutically

effective amount, i.e., individual unit doses designed for multiple administration to achieve a therapeutically effective amount.

Typically, such pharmaceutical compositions will contain from about 0.1 to about 95% by weight of the active agent; preferably, from about 5 to about 70% by weight; and
5 more preferably from about 10 to about 60% by weight of the active agent.

Any conventional carrier or excipient may be used in the pharmaceutical compositions of the invention. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this
10 regard, the preparation of a suitable pharmaceutical composition for a particular mode of administration is well within the scope of those skilled in the pharmaceutical arts. Additionally, the carriers or excipients used in the pharmaceutical compositions of this invention are commercially-available. By way of further illustration, conventional formulation techniques are described in Remington: The Science and Practice of
15 Pharmacy, 20th Edition, Lippincott Williams & White, Baltimore, Maryland (2000); and H.C. Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 7th Edition, Lippincott Williams & White, Baltimore, Maryland (1999).

Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: sugars, such as lactose,
20 glucose and sucrose; starches, such as corn starch and potato starch; cellulose, such as microcrystalline cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene
25 glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical compositions.

30 Pharmaceutical compositions are typically prepared by thoroughly and intimately mixing or blending the active agent with a pharmaceutically-acceptable carrier and one or more optional ingredients. The resulting uniformly blended mixture can then be shaped or loaded into tablets, capsules, pills and the like using conventional procedures and equipment.

The pharmaceutical compositions of the invention are preferably packaged in a unit dosage form. The term "unit dosage form" refers to a physically discrete unit suitable for dosing a patient, i.e., each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect either alone or in combination with one or more additional units. For example, such unit dosage forms may be capsules, tablets, pills, and the like, or unit packages suitable for parenteral administration.

In one embodiment, the pharmaceutical compositions of the invention are suitable for oral administration. Suitable pharmaceutical compositions for oral administration may be in the form of capsules, tablets, pills, lozenges, cachets, dragees, powders, granules; or as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil liquid emulsion; or as an elixir or syrup; and the like; each containing a predetermined amount of a compound of the present invention as an active ingredient.

When intended for oral administration in a solid dosage form (i.e., as capsules, tablets, pills and the like), the pharmaceutical compositions of the invention will typically comprise the active agent and one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate. Optionally or alternatively, such solid dosage forms may also comprise: fillers or extenders, such as starches, microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and/or sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as cetyl alcohol and/or glycerol monostearate; absorbents, such as kaolin and/or bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and/or mixtures thereof; coloring agents; and buffering agents.

Release agents, wetting agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the pharmaceutical compositions of the invention. Examples of pharmaceutically-acceptable antioxidants include: water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfate, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, lecithin, propyl gallate, alpha-tocopherol, and the like; and metal-

chelating agents, such as citric acid, ethylenediamine tetraacetic acid, sorbitol, tartaric acid, phosphoric acid, and the like. Coating agents for tablets, capsules, pills and like, include those used for enteric coatings, such as cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, methacrylic acid/methacrylic acid ester copolymers, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, 5 hydroxypropyl methyl cellulose acetate succinate, and the like.

Pharmaceutical compositions of the invention may also be formulated to provide slow or controlled release of the active agent using, by way of example, hydroxypropyl methyl cellulose in varying proportions; or other polymer matrices, liposomes and/or 10 microspheres. In addition, the pharmaceutical compositions of the invention may optionally contain opacifying agents and may be formulated so that they release the active ingredient only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active agent can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients. 15

Suitable liquid dosage forms for oral administration include, by way of illustration, pharmaceutically-acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. Liquid dosage forms typically comprise the active agent and an inert diluent, such as, for example, water or other solvents, solubilizing agents and 20 emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (esp., cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Suspensions, in addition to the active ingredient, may contain suspending agents such as, for example, 25 ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

The compounds of this invention can also be administered parenterally (e.g. by intravenous, subcutaneous, intramuscular or intraperitoneal injection). For parenteral 30 administration, the active agent is typically admixed with a suitable vehicle for parenteral administration including, by way of example, sterile aqueous solutions, saline, low molecular weight alcohols such as propylene glycol, polyethylene glycol, vegetable oils, gelatin, fatty acid esters such as ethyl oleate, and the like. Parenteral formulations may also contain one or more anti-oxidants, solubilizers, stabilizers, preservatives, wetting

agents, emulsifiers, buffering agents, or dispersing agents. These formulations may be rendered sterile by use of a sterile injectable medium, a sterilizing agent, filtration, irradiation, or heat.

Alternatively, the pharmaceutical compositions of the invention are formulated for administration by inhalation. Suitable pharmaceutical compositions for administration by inhalation will typically be in the form of an aerosol or a powder. Such compositions are generally administered using well-known delivery devices, such as a metered-dose inhaler, a dry powder inhaler, a nebulizer or a similar delivery device.

When administered by inhalation using a pressurized container, the pharmaceutical compositions of the invention will typically comprise the active ingredient and a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. Additionally, the pharmaceutical composition may be in the form of a capsule or cartridge (made, for example, from gelatin) comprising a compound of the invention and a powder suitable for use in a powder inhaler. Suitable powder bases include, by way of example, lactose or starch.

The compounds of the invention can also be administered transdermally using known transdermal delivery systems and excipients. For example, the active agent can be admixed with permeation enhancers, such as propylene glycol, polyethylene glycol monolaurate, azacycloalkan-2-ones and the like, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers and buffers, may be used in such transdermal compositions if desired.

Utility

The compounds of the invention have been shown to inhibit viral replication in HCV replicon assays and therefore are expected to be useful for the treatment of hepatitis C viral infections.

In one aspect, therefore, the invention provides a method of inhibiting replication of the hepatitis C virus in a mammal (e.g., a human), the method comprising administering to the mammal a therapeutically-effective amount of a compound of the invention or of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of the invention.

The invention further provides a method of treating hepatitis C viral infections in a mammal (e.g., a human), the method comprising administering to the mammal a

therapeutically-effective amount of compound of the invention or of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier and a compound of the invention.

The compounds of the invention may inhibit viral replication by inhibiting the
5 function of the NS5A protein encoded by the HCV genome. In one aspect, therefore, the invention provides a method of inhibiting the NS5A protein of HCV in a mammal, the method comprising administering to the mammal, a compound or a composition of the invention.

When used to treat HCV infections, the compounds of the invention will typically
10 be administered orally in a single daily dose or in multiple doses per day, although other forms of administration may be used. The amount of active agent administered per dose or the total amount administered per day will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the
15 age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

Suitable doses for treating HCV infections will range from about 1 to about
2000 mg/day of active agent, including from about 5 to about 200 mg/day and from about
10 to about 130 mg per day of active agent for an average 70 kg human.

20 Combination therapy

Compounds of the invention may also be used in combination with one or more
agents which act by the same mechanism or by different mechanisms to effect treatment
of HCV. Useful classes of agents for combination therapy include, but are not limited to,
HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase
25 inhibitors, helicase inhibitors, NS4B protein inhibitors, HCV viral entry inhibitors, cyclophyllin inhibitors, toll-like receptor agonists, inhibitors of heat shock proteins, interfering RNA, antisense RNA, HCV internal ribosome entry site (IRES) inhibitors, thiazolidines, nucleoside analogs such as ribavirin and related compounds, interferons and
30 other immunomodulatory agents, inosine 5'-monophosphate dehydrogenase (IMPDH) inhibitors, and other NS5A protein inhibitors. Agents which act to inhibit HCV replication by any other mechanism may also be used in combination with the present compounds.

HCV NS3 protease inhibitors which may be used in combination therapy include, but are not limited to, telaprevir (VX-950), boceprevir (SCH-503034), TMC-435,

narlaprevir (SCH-900518), vaniprevir (MK-7009), danoprevir (ITMN-191, R-7227), BI-201335, ABT-450, BMS-650032, GS-9256, ACH-1625, ACH-2684, BMS-605339, VX-985, PHX-1766, BMS-791325, and IDX-320.

5 Examples of HCV NS5B nucleoside polymerase inhibitors include, but are not limited to, RG7128, IDX-184, PSI-7977, PSI-7851, PSI-938, INX-189 (INX-08189), RG7348, MK-0608, TMC-649128, and HCV-796, while, non-nucleoside HCV NS5B polymerase inhibitors, include but are not limited to, filibuvir (PF-8685540), tegobuvir (GS-9190), VX-222, VX-759, ANA-598 (setrobuvir), ABT-072, ABT-333, BI-207127, BMS-791325, MK-3281, IDX-37, and BMS-824393.

10 A wide variety of interferons and pegylated interferons, including alpha, beta, omega, and gamma interferons, having antiviral, antiproliferative or immunomodulatory effects, can be combined with the present compounds. Representative examples include, but are not limited to, Intron® A (interferon-alpha2b), Actimmune® (interferon-gamma-1b), Alferon N, Advaferon®, Roferon-A (interferon alpha-2a) PegIntron® (peginterferon-15 alpha 2b), Alfaferone, Pegasys® (peginterferon alpha-2a), Alfanative (interferon alpha), Zalbin™ (albinterferon alpha-2b), Infegon® (interferon alfacon-1), Omega DUROS® (omega interferon), Locteron™ (interferon alpha), PEG-rIL-29 (pegylated interferon lambda), and Rebif® (interferon beta-1a).

Nucleoside analog antiviral agents include, but are not limited to, ribavirin 20 (Copegus®, Rebetol®, Virazole®) and Viramidine (taribavirin). Interferons and ribavirin are also provided in in the form of kits which include, for example, but are not limited to, Rebetron® (interferon alpha-2b/ribavirin) and Pegetron® (Peginterferon alpha-2b/ribavirin)

Useful compounds acting by other mechanisms include, but are not limited to: 25 cyclophilin inhibitors, such as DEB-025, SCY-635, NIM-811, and cyclosporine and derivatives; toll-like receptor agonists, such as resiquimod, IMO-2125, and ANA-773, HCV viral entry inhibitors, such as civacir, thiazolides, such as nitazoxanide, and broad-spectrum viral inhibitors, such as, inosine-5'-monophosphate dehydrogenase (IMPDH) inhibitors.

30 In addition, compounds of the invention may be combined with an NS5A inhibitor, for example, BMS-790052, AZD-7295, PPI-461, PPI-1301, GS-5885, or GSK2336805.

In another aspect, therefore, the invention provides a therapeutic combination for use in the treatment of hepatitis C viral infections, the combination comprising a

compound of the invention and one or more other therapeutic agents useful for treating HCV. For example, the invention provides a combination comprising a compound of the invention and one or more agents selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated
5 interferons, and ribavirin and related nucleoside analogs. Also provided, therefore, is a pharmaceutical composition comprising a compound of the invention and one or more other therapeutic agents useful for treating HCV.

Further, in a method aspect, the invention provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a
10 compound of the invention and one or more other therapeutic agents useful for treating HCV.

In another method aspect, the invention provides a method of inhibiting replication of the hepatitis C virus in a mammal, the method comprising administering to the mammal a compound of the invention and one or more other therapeutic agents useful
15 for inhibiting replication of the hepatitis C virus.

For example, in one method aspect, the invention provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a compound of the invention, an interferon or pegylated interferon, and ribavirin.

20 In another exemplary method aspect, the invention provides a method of treating a hepatitis C viral infection in a mammal, the method comprising administering to the mammal a compound of the invention, an interferon or pegylated interferon, ribavirin, and an HCV NS3 protease inhibitor.

In still another method aspect, the invention provides a method of treating a
25 hepatitis C viral infection in a mammal, the method comprising administering to the mammal a compound of the invention, ribavirin, and an HCV NS3 protease inhibitor.

Still other combination therapies, include, for example, a compound of the invention, an HCV NS3 protease inhibitor, an HCV NS5B nucleoside polymerase inhibitor, and an HCV NS5B non-nucleoside polymerase inhibitor; and a compound of
30 the invention, an HCV NS5B nucleoside polymerase inhibitor, and an HCV NS5B non-nucleoside polymerase inhibitor.

In another method aspect, the invention provides a method of inhibiting replication of the hepatitis C virus in a mammal, using a compound of the invention in combination with other agents, as described above.

When used in combination therapy, the agents may be formulated in a single pharmaceutical composition, as disclosed above, or the agents may be provided in separate compositions that are administered simultaneously or at separate times, by the same or by different routes of administration. When administered separately, the agents
 5 are administered sufficiently close in time so as to provide a desired therapeutic effect. Such compositions can be packaged separately or may be packaged together as a kit. The two or more therapeutic agents in the kit may be administered by the same route of administration or by different routes of administration.

Finally, the compounds of the invention may also find utility as research tools, for
 10 example, for discovering new HCV NS5A protein inhibitors or explicating mechanisms of HCV replication.

Compounds of the invention have been demonstrated to be potent inhibitors of HCV replication in HCV replicon assays, as described in the following examples.

EXAMPLES

15 The following synthetic and biological examples are offered to illustrate the invention, and are not to be construed in any way as limiting the scope of the invention. In the examples below, the following abbreviations have the following meanings unless otherwise indicated. Abbreviations not defined below have their generally accepted meanings.

20	ACN	=	acetonitrile
	DCM	=	dichloromethane
	DMA	=	<i>N,N</i> -dimethylacetamide
	DMF	=	<i>N,N</i> -dimethylformamide
	DMSO	=	dimethyl sulfoxide
25	EDC	=	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
	EtOAc	=	ethyl acetate
	h	=	hour(s)
	HATU	=	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
30	HCTU	=	2-(6-chloro-1 <i>H</i> -benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate
	HOAt	=	1-hydroxy-7-azabenzotriazole
	min	=	minute(s)
35	Pd(dppf)Cl ₂	=	dichloro(1,1'-bis(diphenylphosphino)-ferrocene)dipalladium(II)
	MTBE	=	methyl <i>tert</i> -butyl ether
	RT	=	room temperature
	TFA	=	trifluoroacetic acid
40	THF	=	tetrahydrofuran

Reagents and solvents were purchased from commercial suppliers (Aldrich, Fluka, Sigma, etc.), and used without further purification. Reactions were run under nitrogen atmosphere, unless noted otherwise. Progress of reaction mixtures was monitored by thin layer chromatography (TLC), analytical high performance liquid chromatography (anal. HPLC), and mass spectrometry. Reaction mixtures were worked up as described specifically in each reaction; commonly they were purified by extraction and other purification methods such as temperature-, and solvent-dependent crystallization, and precipitation. In addition, reaction mixtures were routinely purified by preparative HPLC, typically using C18 or BDS column packings and conventional eluents. Typical preparative HPLC conditions are described below.

Characterization of reaction products was routinely carried out by mass and ¹H-NMR spectrometry. For NMR analysis, samples were dissolved in deuterated solvent (such as CD₃OD, CDCl₃, or *d*₆-DMSO), and ¹H-NMR spectra were acquired with a Varian Gemini 2000 instrument (400 MHz) under standard observation conditions. Mass spectrometric identification of compounds was performed by an electrospray ionization method (ESMS) with an Applied Biosystems (Foster City, CA) model API 150 EX instrument or an Agilent (Palo Alto, CA) model 1200 LC/MSD instrument.

General Preparative HPLC Conditions

Column: C18, 5 μm. 21.2 x 150 mm or C18, 5 μm 21 x 250 or C14 21x150
Column temperature: Room Temperature
Flow rate: 20.0 mL/min
Mobile Phases: A = Water + 0.05 % TFA
B = ACN + 0.05 % TFA,
Injection volume: (100-1500 μL)
Detector wavelength: 214 nm

Crude compounds were dissolved in 1:1 water:acetic acid at about 50 mg/mL. A 4 minute analytical scale test run was carried out using a 2.1 x 50 mm C18 column followed by a 15 or 20 minute preparative scale run using 100 μL injection with the gradient based on the % B retention of the analytical scale test run. Exact gradients were sample dependent. Samples with close running impurities were checked with a 21 x 250 mm C18 column and/or a 21 x 150 mm C14 column for best separation. Fractions containing desired product were identified by mass spectrometric analysis.

Analytical HPLC Methods A, B, C

	Column:	Zorbax Bonus-RP 3.5 μ m. 4.6 x 150 mm
	Column temperature:	35 °C
	Flow rate:	1.0 mL/min
5	Mobile Phases:	A = Water/ACN (98:2) + 0.1 % TFA B = Water/ACN (10:90) + 0.1 % TFA,
	Injection volume:	100-1500 μ L
	Detector wavelength:	254 nm (Methods A and B) 214 nm (Method C)
	Sample preparation:	Dissolve in 1:1 ACN:water

10

Gradient method A

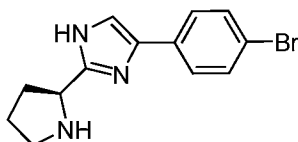
21 min total (time (min)/ % B): 0.5/10, 15/60, 16.5/80, 17/80, 18/10, 21/10.

Gradient method B

40 min total (time (min)/ % B): 0.5/15, 28/40, 30/80, 33/80, 35/15, 40/15.

15 Gradient method C

29 min total (time (min)/ % B): 0.5/10, 24/90, 25/90, 26/10, 29/10

Preparation 1: 4-(4-bromo-phenyl)-2-(S)-pyrrolidin-2-yl-1H-imidazole20 (a) 2-Bromo-1-(4-bromo-phenyl)-ethanone

Bromine (80 g, 500 mmol) was added dropwise to a solution of 1-(4-bromo-phenyl)-ethanone (100 g, 500 mmol) in dichloromethane (1500 mL) at ambient temperature. The reaction mixture was stirred for 3 h and then concentrated. The residue was washed with dichloromethane (100 mL) to give the crude title compound (120 g, 86 % yield) as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.78 (d, J =8.4 Hz, 2H), 7.57 (d, J =8.4 Hz, 2H), 4.32 (s, 2H).

25

(b) (S)-pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-phenyl)-2-oxo-ethyl] ester 1-tert-butyl ester

Diisopropylethylamine (67 g, 518 mmol) was added dropwise to a solution of the product of the previous step (120 g, 432 mmol) and (S)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (*L*-Boc proline) (102 g, 475 mmol) in acetonitrile (2 L) at room temperature. The reaction mixture was stirred overnight and concentrated to dryness. The residue was dissolved in ethyl acetate (2 L) and washed with water (2 L). The

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organic layer was dried over sodium sulfate and concentrated to give crude title compound (178 g, 100 % yield).

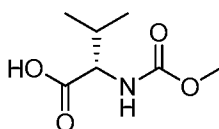
(c) (S)-2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid *tert*-butyl ester

5 A solution of the product of the previous step (178 g, 432 mmol) and ammonium acetate (500 g, 6.5 mol) in toluene (2 L) was heated at reflux overnight. The solvent was removed and the residue was dissolved in ethyl acetate (2 L) and washed with water (2 L). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography in 1:3 petroleum ether: ethyl acetate to give
10 the title compound (120 g, 71 % yield) as a yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.56 (s, 1H), 7.39 (d, *J*=8.0 Hz, 2H), 7.24 (m, 1H), 7.14 (s, 1H), 4.88 (m, 1H), 3.33 (m, 2H), 2.94 (s, 1H), 2.07 (m, 2H), 1.88 (m, 1H), 1.42 (s, 9H).

(d) 4-(4-bromo-phenyl)-2-(S)-pyrrolidin-2-yl-1H-imidazole

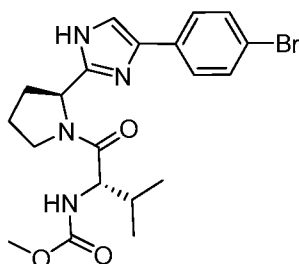
To a solution of (S)-2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-
15 carboxylic acid *tert*-butyl ester (3 g, 7.6 mmol) in methanol (3 mL) was added 4N HCl in methanol (60 mL) at 0 °C. The reaction mixture was stirred for 2 h and then concentrated to give crude hydrochloride salt of the title compound (2.51 g 100 % yield) as a yellow solid.

Preparation 2: (S)-2-Methoxycarbonylamino-3-methyl-butyric acid



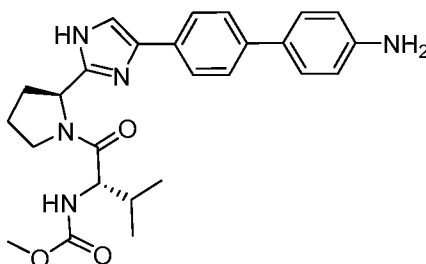
A mixture of (S)-2-amino-3-methyl-butyric acid (10 g, 85 mmol), NaOH (10.3 g, 255 mmol) in water (100 mL) was treated with methylchloridocarbonate (8 g, 85 mmol) at 0 °C. The reaction mixture was stirred for 24 h at room temperature and then 5 N aqueous HCl was added to the reaction mixture to adjust pH to 4. The mixture was
25 filtered through a pad of Celite to give the product (10 g, 67% yield) as a white solid. ¹H NMR (CH₃OD, 400 MHz) δ (ppm) 4.05(d, 1H), 3.65(s, 3H), 2.14(m, 1H), 0.95(m, 6H).

Preparation 3: ((S)-1-((S)-2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



Triethylamine (2.3 g, 11.4 mmol) was added to a solution of 4-(4-bromo-phenyl)-
 5 2-(S)-pyrrolidin-2-yl-1H-imidazole hydrochloride (2 g, 11.4 mol), (S)-2-
 methoxycarbonylamino-3-methyl-butyric acid (2.5 g, 7.6 mmol), and HATU (4.3 g, 11.4
 mmol) in dimethylformamide (50 mL) at 0 °C under nitrogen. The reaction mixture was
 stirred at room temperature overnight and treated with ethyl acetate (100 mL) and water
 (1000 mL). The organic layer was washed with water (2 x 100 mL) and brine (100 mL),
 10 dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica
 gel column chromatography in 1:1 petroleum ether:ethyl acetate to give the title
 compound (2.5 g 74 % yield) as a yellow solid. ¹H NMR (*d*₆-DMSO, 400 MHz) δ (ppm)
 7.63 (d, *J*=8.8 Hz, 2H), 7.54 (m, 1H), 7.47 (m, 2H), 7.26 (d, *J*=8.4 Hz, 1H), 5.03 (m,
 1H), 4.02 (t, *J*=8.4 Hz, 1H), 3.76 (m, 2H), 3.51 (s, 3H), 2.10 (m, 2H), 1.93 (m, 3H), 0.85
 15 (d, *J*=6.8 Hz, 3H), 0.81 (d, *J*=6.8 Hz, 3H).

Preparation 4: ((S)-1-((S)-2-[4-(4'-Amino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester

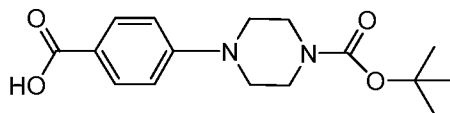


20 To a mixture of 4-(benzyloxycarbonylamino)phenylboronic acid (1.57 g, 5.79
 mmol) and ((S)-1-((S)-2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-
 carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (1.74 g, 3.86 mmol) in *N,N*-
 dimethylformamide (30 mL, 400 mmol) was added water (21.91 mL, 1216 mmol) and
 sodium bicarbonate (2.43 g, 28.96 mmol). The resulting mixture was purged with

nitrogen. Tetrakis(triphenylphosphine)palladium(0) (468 mg, 0.41 mmol) was added. The reaction mixture was purged with nitrogen and then heated at 90 °C overnight. The reaction mixture was cooled to RT, diluted with methanol (10 mL), then filtered. The filtrate was concentrated and the crude product was purified by preparative HPLC to give
5 a white solid. (1.28 g) The crude material was dissolved in methanol (40 mL) and then pumped through a continuous flow hydrogenator at 70 °C using a palladium hydroxide on carbon (20 % w/w) cartridge. The resulting solution was concentrated to ~ 10 mL, treated with Stratospheres™ PL-CO3 resin and stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated to give the title compound
10 (680 mg).

Preparation 5: ((S)-1-{(S)-2-[4-(4'-amino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

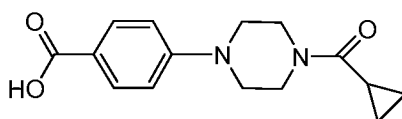
To a solution of ((S)-1-{(S)-2-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-
15 pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (9.10 g, 20.34 mmol) in dioxane:water (3:1) (200 mL), was added 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (4.9 g, 22.37 mmol), sodium carbonate (4.3 g, 40.68 mmol) and Pd(dppf)₂Cl₂ (0.83 g, 5%). The reaction mixture was warmed to reflux under nitrogen, stirred for 4 h, cooled to RT, filtered, and concentrated. The residue was extracted with
20 ethyl acetate and water, dried with sodium sulfate and concentrated. The crude product was purified by silica gel chromatography eluting with 1:1 hexane:ethyl acetate, to provide the title compound (7 g, 75% yield) as a yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.62-7.55 (m, 1H), 7.50 (d, *J*=8.0 Hz, 2 H), 7.40 (m, 3H), 7.18 (s, 1H), 6.75 (d, *J*=8.4 Hz, 2H), 5.50 (d, *J*=9.2 Hz, 1H), 5.25-5.23 (m, 1H), 4.31 (t, *J*=2.4 Hz,
25 1H), 3.83-3.80 (m, 1H), 3.67 (s, 3H), 3.59-3.53 (m, 1H), 3.05-2.95 (m, 1H), 2.40-2.30 (m, 1H), 2.19-2.11 (m, 1H), 2.08-2.03 (m, 1H), 1.98-1.93 (m, 1H), 1.07-1.01 (m, 1H), 0.85 (d, *J*=6.8 Hz, 6 H).

Preparation 6: 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid**(a) 4-(4-Ethoxycarbonyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester**

A mixture of piperazine-1-carboxylic acid *tert*-butyl ester (18.6 g, 0.1 mol), 4-fluoro-benzoic acid ethyl ester (16.8 g, 1 mol) and potassium carbonate (0.15 mol) in dimethylsulfoxide (100 mL) was stirred at 120 °C for 24 h. The reaction mixture was cooled to room temperature and poured into water (1 L). The solid precipitate was filtered, washed with water, and concentrated to dryness to provide the title compound (20 g, 60 % yield) as a white solid. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.91 (d, 2H), 6.83 (d, 2H), 4.30 (q, 2H), 3.55(m, 4H), 3.26(m, 4H), 1.46(s, 9H), 1.32(t, 3H).

(b) 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid

To a mixture of 4-(4-ethoxycarbonyl-phenyl)-piperazine-1-carboxylic acid *tert*-butyl ester (10 g, 29.9 mmol) in ethanol (200 mL) was added 1 N sodium hydroxide (100 mL). The reaction mixture was stirred at 70 °C overnight. The solvent was removed under vacuum and the residue washed twice with ethyl acetate, acidified to pH 6 with 5 N HCl, filtered, and concentrated to dryness to provide the title compound (8 g, 87 % yield) as a white solid. ¹H NMR (*d*₆-DMSO, 400 MHz) δ (ppm) 7.74 (m, 2H), 6.92 (m, 2H), 3.90 (m, 2H), 3.42(m, 2H), 3.25(m, 4H), 1.38(s, 9H).

Preparation 7: 4-(4- cyclopropanecarbonyl-piperazin-1-yl)-benzoic acid**(a) 4-piperazin-1-yl-benzoic acid**

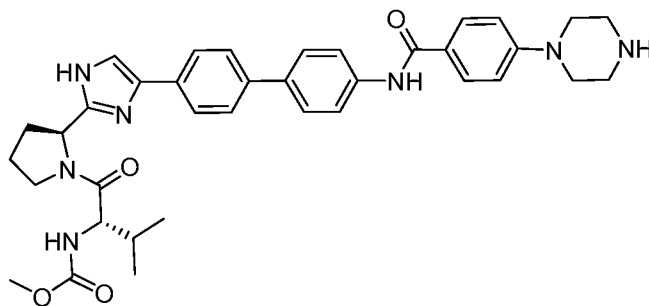
A mixture of 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid (28 g, 91 mmol) in hydrochloric acid in methanol (300 mL) was stirred at room temperature for 4 h. The resulting precipitate was collected by filtration and concentrated to dryness to provide the title compound (17 g, 61 % yield) as a white solid.

(b) 4-(4- cyclopropanecarbonyl-piperazin-1-yl)-benzoic acid

To a mixture of 4-piperazin-1-yl-benzoic acid (20 g, 71.6 mmol) and triethylamine (58 g, 573 mmol) in dichloromethane (500 mL) was added cyclopropanecarbonyl chloride dropwise at 0 °C. The reaction mixture was stirred at RT

overnight. The solvent was removed by rotary evaporation. The residue was diluted with water, treated with sodium hydroxide, and washed with ethyl acetate and dichloromethane. The aqueous phase was acidified to pH 6 with 5 N HCl. The resulting precipitate was collected by filtration and concentrated to dryness to provide the title compound (10 g, 51 % yield) as a white solid. ¹H NMR (CH₃OD, 400 MHz) δ (ppm) 7.87 (m, 2H), 6.95 (m, 2H), 3.90 (s, 2H), 3.73 (s, 2H), 3.29 (m, 4H), 1.99 (m, 1H), 0.86 (m, 4H).

Preparation 8: [(S)-2-Methyl-1-((S)-2-{4-[4'-(4-piperazin-1-yl-benzoylamino)-biphenyl-4-yl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester



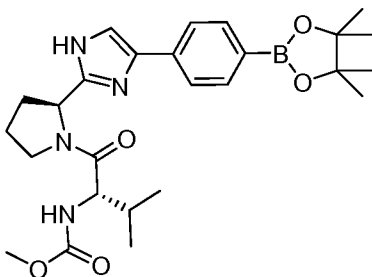
To a solution of 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid (365 mg, 1.19 mmol) in dichloromethane (18 mL, 280 mmol) and *N,N*-dimethylformamide (92.3 uL, 1.19 mmol) was added oxalyl chloride (101 uL, 1.19 mmol). The reaction mixture was stirred for 20 min at room temperature and then *N,N*-diisopropylethylamine (1.42 mL, 8.14 mmol) was added followed by ((*S*)-1-((*S*)-2-[4-(4'-amino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (500.0 mg, 1.083 mmol) and the mixture was allowed to react overnight with stirring.

A second solution of 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid (365 mg, 1.19 mmol) and oxalyl chloride (101 uL, 1.19 mmol) in dichloromethane (18 mL, 280 mmol) and *N,N*-dimethylformamide (92.3 uL, 1.19 mmol) was prepared and added to the reaction mixture which was stirred for 1 h. Methanol (10 mL) was added. The mixture was concentrated under vacuum and then dissolved in DCM (25 mL) and washed with saturated aqueous sodium bicarbonate (10 mL). The organic layer was concentrated, dissolved in 2.0 M hydrogen chloride in 1,4-dioxane (16.2 mL, 16.2 mmol) and ethanol (1.0 mL, 0.17 mmol) and stirred at room temperature overnight. The reaction mixture was dissolved in 1:1 acetic acid:water (8.0 mL), and purified by preparative HPLC using

a BDS column to provide the trifluoroacetic acid salt of the title compound. ¹H NMR (*d*₆-DMSO, 400 MHz) δ (ppm) 10.11 (s, 1H), 8.99 – 8.77 (m, 2H), 7.92 (dd, *J* = 15.0, 8.9 Hz, 4H), 7.84 (m, 4H), 7.76 (t, *J* = 9.3 Hz, 2H), 7.37 – 7.25 (m, 2H), 7.09 (d, *J* = 9.1 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.96 (d, *J* = 9.1 Hz, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.90 – 3.81 (m, 1H), 3.66 – 3.56 (m, 1H), 3.55 – 3.46 (m, 6H), 3.46 – 3.39 (m, 2H), 3.39 – 3.29 (m, 2H), 2.43 – 2.32 (m, 1H), 2.22 – 1.91 (m, 4H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H).

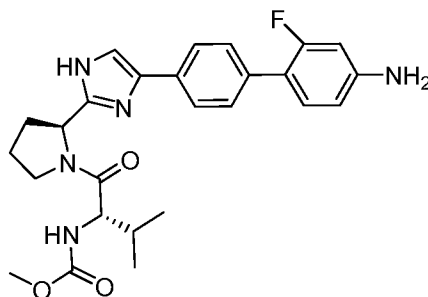
The TFA salt was dissolved in methanol (10 mL) and treated with Stratospheres™ PL-CO3 resin and stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated to provide the title compound (0.354 g).

Preparation 9: [(*S*)-2-Methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester]



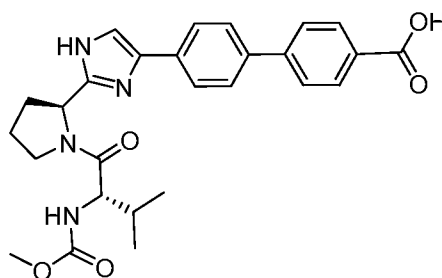
To a solution of ((*S*)-1-((*S*)-2-[4-(4-bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (50 g, 0.11 mol), 4,4,5,5,4',4',5',5'-octamethyl-[2,2']bi[[1,3,2]dioxaborolanyl] (57 g, 0.22 mol) and potassium acetate (108 g, 1.1 mol) in dioxane (1000 mL) was added Pd(dppf)Cl₂.CH₂Cl₂ (4.5 g, 5.5 mmol) under nitrogen. The reaction mixture was stirred at 85 °C overnight and then ethyl acetate (100 mL) and water (1000 mL) were added. The organic layer was washed with water (2 x 1000 mL) and brine (1000 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel column chromatography (1:1 petroleum ether:ethyl acetate) to give the title compound (22.5 g) as a yellow solid. ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.71 (m, 3H), 7.32 (m, 1H), 7.19 (m, 1H), 5.56 (m, 1H), 5.18 (m, 1H), 4.23 (m, 1H), 3.73 (m, 1H), 3.61 (s, 3H), 3.55 (m, 1H), 2.95 (m, 1H), 2.38 (s, 1H), 2.13 (m, 1H), 2.02 (m, 1H), 1.89 (m, 2H), 1.22 (s, 12H), 0.79 (d, 6H).

Preparation 10: ((*S*)-1-((*S*)-2-[4-(4'-Amino-2'-fluoro-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



5 [(*S*)-2-Methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (60 mg, 0.12 mmol) and 4-bromo-3-fluoroaniline (23 mg, 0.12 mmol) were dissolved in 1,2-dimethoxyethane (1.2 mL, 12 mmol) and water (0.44 mL, 24 mmol). The reaction mixture was purged with nitrogen. Sodium carbonate (41.6 mg, 0.39 mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (21 mg, 0.018 mmol) and the mixture was purged with nitrogen, sealed and heated at 85 °C overnight. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (5 mL), and washed with water (5 mL). The organic layer was concentrated, dissolved in 1:1 acetic acid:water (8 mL) and purified by preparative HPLC to produce the TFA salt which was passed through StratoSpheres™ PL-CO3 resin (0.36 mmol) to provide the title compound (15 mg). (*m/z*): [M+H]⁺ calcd for C₂₆H₃₀FN₅O₃ 480.23 found 480.4.

Preparation 11: 4'-{2-[(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methyl-butyl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-biphenyl-4-carboxylic acid



20

To a mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (1.05 g, 2.12 mmol) and 4-iodo-benzoic acid methyl ester (665 mg, 2.54 mmol) in *N,N*-dimethylformamide (9.0 mL, 120 mmol) at RT was added

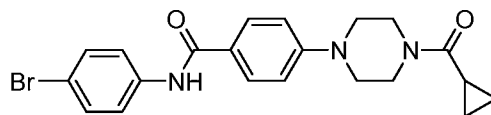
water (2.0 mL, 110 mmol) and sodium bicarbonate (711 mg, 8.46 mmol). The reaction mixture was flushed with nitrogen, and tetrakis(triphenylphosphine)palladium(0) (122 mg, 0.106 mmol) was added under nitrogen. The reaction mixture was flushed with nitrogen and then heated at 90 °C overnight under an atmosphere of nitrogen.

5 The reaction mixture was cooled to RT and partitioned between EtOAc (60.0 mL) and water (20.0 mL). The organic layer was washed with water (2 x 20.0 mL), dried over sodium sulfate, filtered and concentrated to give a black oil, which was purified by silica gel chromatography (24 g silica gel, 0-100% EtOAc:hexanes). Desired fractions were combined and concentrated to give a yellowish oil and further dried under vacuum to give
10 a yellowish foam. (956.9 mg).

The product from the previous step was combined with the corresponding product of a previous run (total 1.13 g), dissolved in methanol (10.0 mL) and water (2.1 mL) and treated with lithium hydroxide monohydrate (564.5 mg) at 60 °C for 3 h. The reaction mixture was concentrated and the residue was treated with 1:1 acetic acid:water (8.0 mL),
15 and sonicated. Additional TFA (3.0 mL) was and the reaction mixture was sonicated, resulting in a greyish solid precipitate. The reaction mixture was stirred at RT for 10 min and then filtered. The filtrate was extracted with EtOAc (20.0 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give a yellowish oil which was dissolved in 1:1 acetic acid:water (6.0 mL), and purified by reverse phase preparative
20 HPLC. Desired fractions were combined and freeze dried to give a white solid (107.6 mg). The solid from the filtration was taken up into EtOAc (60.0 mL) and washed with water (2 x 15.0 mL), aqueous saturated sodium bicarbonate (20.0 mL), and brine (15.0 mL), dried over sodium sulfate, filtered and concentrated to give the title compound as a yellowish solid (490 mg) (*m/z*): [M+H]⁺ calcd for C₂₇H₃₀N₄O₅ 491.22 found 491.6.

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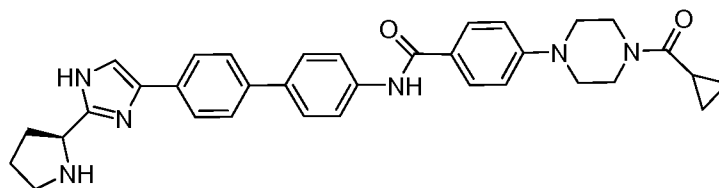
Preparation 12: *N*-(4-Bromo-phenyl)-4-(4-cyclopropanecarbonyl-piperazin-1-yl)-benzamide



A solution of 4-(4-cyclopropanecarbonyl-piperazin-1-yl)-benzoic acid (1.0 g, 3.6
30 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.70 g, 3.6 mmol) and 1-hydroxy-7-azabenzotriazole (0.50 g, 3.6 mmol) in dichloromethane (39 mL, 610 mmol) was stirred for 20 min at room temperature and then *p*-bromoaniline (0.52 g,

3.0 mmol) and *N,N*-diisopropylethylamine (2.6 mL, 15 mmol) were added and the reaction mixture was stirred for 2 days. The reaction mixture was filtered; the filtrate was dissolved in 1:1 acetic acid:water (8 mL). A precipitate formed. This material was filtered to provide the title product as the acetic acid salt (225 mg). (*m/z*): [M+H]⁺ calcd for C₂₁H₂₂BrN₃O₂ 428.09 found 428.0.

Preparation 13: 4-(4-Cyclopropanecarbonyl-piperazin-1-yl)-*N*-[4'-((*S*)-2-pyrrolidin-2-yl-1*H*-imidazol-4-yl)-biphenyl-4-yl]-benzamide

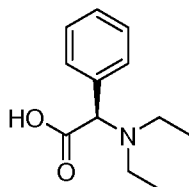


- 10 (a) (*S*)-2-(4-{4'-[4-(4-Cyclopropanecarbonyl-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester

To a mixture of (*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.40 g, 3.19 mmol) and *N*-(4-bromo-phenyl)-4-(4-cyclopropanecarbonyl-piperazin-1-yl)-benzamide (0.910 g, 2.12 mmol) in *N,N*-dimethylformamide (16.53 mL, 213.5 mmol) at RT was added sodium bicarbonate (1.338 g, 15.93 mmol). Water (12.06 mL, 669.2 mmol) was then added. Nitrogen was bubbled through the resulting mixture for 5 min and then tetrakis(triphenylphosphine)palladium(0) (0.258 g, 0.223 mmol) was added. The reaction mixture was heated at 90 °C under nitrogen overnight, cooled to RT, diluted with methanol (30.0 mL), and filtered. The filtrate was concentrated and dissolved in ethyl acetate (~3 mL) and hexanes (2 mL) was slowly added to give a precipitate of crude product. This material was filtered to provide 150 mg of the product. The filtrate was concentrated and subjected to the same precipitation conditions to provide an additional 50 mg of product. This material was combined with the first precipitation crop and was used without further purification in the next step.

- 25 (b) 4-(4-Cyclopropanecarbonyl-piperazin-1-yl)-*N*-[4'-((*S*)-2-pyrrolidin-2-yl)-1*H*-imidazol-4-yl]-biphenyl-4-yl]-benzamide

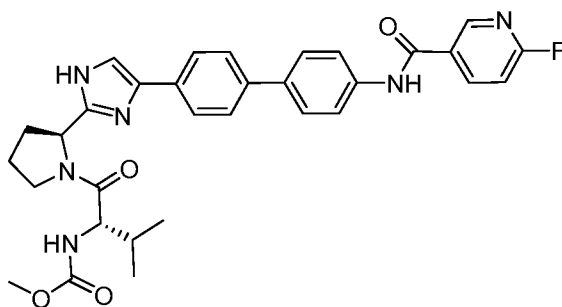
The product of the previous step (200 mg, 0.3 mmol) was dissolved in 4 M HCl in 1,4-dioxane (0.6 mL, 2 mmol). The reaction mixture was stirred for 4 h, and concentrated under vacuum to provide the title compound as the HCl salt. (176 mg). (*m/z*): [M+H]⁺ calcd for C₃₄H₃₆N₆O₂ 561.29 found 561.4.

Preparation 14: (*R*)-Diethylamino-phenyl-acetic acid

Sodium cyanoborohydride (15 g, 238 mmol) was added in portions over a few minutes to a cooled (ice/water) mixture of (*R*)-amino-phenyl-acetic acid (6.00 g, 39.7 mmol) and methanol (150 mL), and stirred for 5 min. Acetaldehyde (40 mL) was added drop-wise over 10 min. The reaction mixture was stirred at the cooled temperature for 45 min and at ambient temperature for 6.5 hr. The reaction mixture was again cooled to 0 °C. Additional acetaldehyde (60 mL) was then added drop-wise over 10 min. The reaction mixture was stirred at 0 °C for 45 min and at ambient temperature overnight.

The reaction mixture was cooled with an ice-water bath and treated with water (3 mL). Concentrated HCl was added dropwise over 45 min until the pH of the mixture was 1.5-2.0. The cooling bath was removed and stirring was continued while adding concentrated HCl to maintain the pH of the mixture ~1.5-2.0. The reaction mixture was stirred overnight, filtered, and the filtrate was concentrated under vacuum. The crude material was purified by preparative HPLC and washed with ethyl acetate to afford the title compound as a shiny white solid (5 g, 61 % yield). ¹H NMR (*d*₆-DMSO, 400 MHz) δ (ppm) 7.47 (m, 2H), 7.36 (m, 3H), 4.34 (s, 1H), 2.90 (m, 2H), 2.86 (m, 2H), 1.03 (t, 6H).

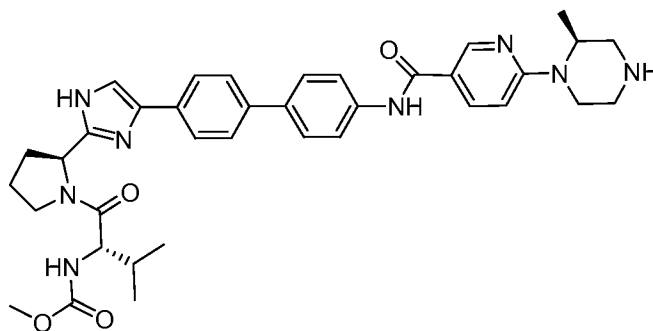
Preparation 15: {(*S*)-1-[(*S*)-2-(5-{4'-[(6-Fluoro-pyridine-3-carbonyl)-amino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



To a solution of ((*S*)-1-[(*S*)-2-[5-(4'-amino-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester (2000 mg, 4 mmol) dissolved in dichloromethane (27.8 mL) and *N,N*-dimethylacetamide (2.82 mL, 30.3 mmol) was added a solution of 2-fluoropyridine-5-carbonyl chloride (691 mg,

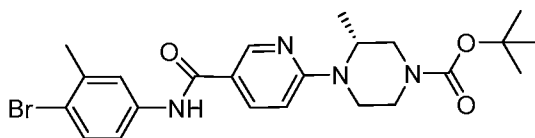
4.33 mmol) dissolved in dichloromethane (6.0 mL) and the reaction mixture mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated, dissolved in a minimal amount of dichloromethane and ethyl ether was slowly added until a white precipitate formed. The mixture was sonicated and filtered to produce the HCl salt of the
 5 desired product. The solid was dissolved in ethyl acetate (20 mL), stirred at room temperature for 30 min, and filtered to produce the HCl salt of the title product as a free flowing yellow solid (2.5 g). (*m/z*): [M+H]⁺ calcd for C₃₂H₃₃FN₆O₄ 585.26 found 585.5.

**Preparation 16: ((*S*)-2-Methyl-1-((*S*)-2-[4-(4'-{6-((*S*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-
 10 carbonyl}-propyl)-carbamic acid methyl ester**



A mixture of the hydrochloride salt of ((*S*)-1-[(*S*)-2-(5-{4'-[(6-fluoro-pyridine-3-carbonyl)-amino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (600.0 mg, 0.966 mmol) and (*S*)-3-methyl-piperazine-
 15 1-carboxylic acid *tert*-butyl ester (0.290 g, 1.449 mmol) in dimethyl sulfoxide (1.5 mL) and *N,N*-diisopropylethylamine (1.01 mL, 5.80 mmol) was heated at 120 °C overnight. The reaction mixture was cooled to RT and water (5.0 mL) was added. The resulting mixture was centrifuged and filtered. To the solid was added 4.0 M hydrogen chloride in 1,4-dioxane (4.9 mL, 20 mmol) and the reaction mixture was stirred at RT for 30 min,
 20 and then concentrated. The residue was coevaporated with ethyl acetate (3 x 5.0 mL), dissolved in 1:1 acetic acid:water (8 mL), filtered, and purified by reverse phase preparative HPLC. Desired fractions were combined and freeze dried to give the title compound as the trifluoroacetic acid salt (320 mg). (*m/z*): [M+H]⁺ calcd for C₃₇H₄₄N₈O₄ 665.36 found 665.4.

Preparation 17: (*R*)-4-[5-(4-Bromo-3-methyl-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



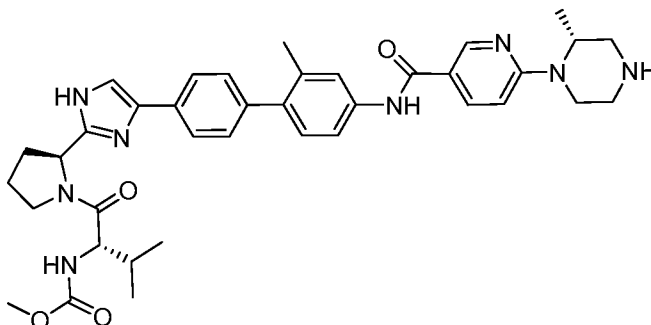
(a) *N*-(4-Bromo-3-methyl-phenyl)-6-fluoro-nicotinamide

5 To a solution of 4-bromo-3-methylaniline (200 mg, 1 mmol) dissolved in DCM (4 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (170 mg, 1.1 mmol) dissolved in DCM (1 mL). A white precipitate was observed. The reaction mixture was concentrated to produce the HCl salt of the desired product.

(b) (*R*)-4-[5-(4-Bromo-3-methyl-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

10 The white solid from the previous step was dissolved in dimethyl sulfoxide (2 mL, 30 mmol), (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (220 mg, 1.1 mmol) was added, followed by *N,N*-diisopropylethylamine (2 mL, 10 mmol). The reaction mixture was heated at 120 °C overnight, cooled to RT, and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography (0-40% ethyl acetate:hexanes) to produce the title compound as a light yellow solid (200 mg, 40 % yield). (*m/z*): [M+H]⁺ calcd for C₂₃H₂₉BrN₄O₃ 489.15 found 489.4.

20 **Preparation 18: ((*S*)-2-Methyl-1-((*S*)-2-[4-(2'-methyl-4'-{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester**



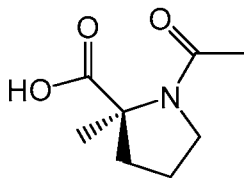
(a) (R)-4-[5-(4'-{2-[(S)-1-((S)-2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-2-methyl-biphenyl-4-ylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of [(S)-2-methyl-1-((S)-2-{4-[4-(4,4,5,5-tetramethyl-
5 [1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-
carbamic acid methyl ester (200 mg, 0.41 mmol) and (R)-4-[5-(4-bromo-3-methyl-
phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid tert-butyl ester
(200 mg, 0.4 mmol; Preparation 17) was dissolved in 1,2-dimethoxyethane (4.25 mL,
40.9 mmol) and water (0.74 mL, 40.9 mmol) and the mixture was sparged under nitrogen.
10 Sodium bicarbonate (129 mg, 1.53 mmol) was added, followed by
tetrakis(triphenylphosphine)palladium(0) (70.8 mg, 0.0613 mmol). The reaction mixture
was further sparged with nitrogen, sealed under nitrogen and heated at 90 °C overnight.
The reaction mixture was extracted with ethyl acetate (5 mL) and water (3 mL); the
organic layer was dried over sodium sulfate, filtered and concentrated to produce a brown
15 oil, which was purified by reverse phase HPLC to produce the di-TFA salt of the title
intermediate. (*m/z*): [M+H]⁺ calcd for C₄₃H₅₄N₈O₆ 779.43 found 779.5.

(b) ((S)-2-Methyl-1-[(S)-2-[4-(2'-methyl-4'-[6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-
carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl]-propyl)-
carbamic acid methyl ester

20 The TFA salt of the previous step was treated with 4 M HCl in 1,4-dioxane (3 mL,
10 mmol) and stirred at room temperature for 1 h. The reaction mixture was concentrated
and evaporated with ethyl acetate (2 x) to produce the tri-HCl salt of the title compound
as a yellow solid (180 mg, 60 % total yield). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₆N₈O₄ 679.37
found 679.7.

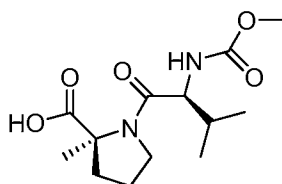
25 **Preparation 19: (S)-1-Acetyl-2-methyl-pyrrolidine-2-carboxylic acid**



To a solution of (S)-2-methyl-pyrrolidine-2-carboxylic acid (50.0 mg, 0.387
mmol) dissolved in *N,N*-dimethylacetamide (1.5 mL, 16 mmol) was added a solution of
acetyl chloride (31.9 mg, 0.406 mmol) dissolved in *N,N*-dimethylacetamide (0.5 mL), and
30 then *N,N*-diisopropylethylamine (1 mL, 6 mmol) was added and the reaction mixture

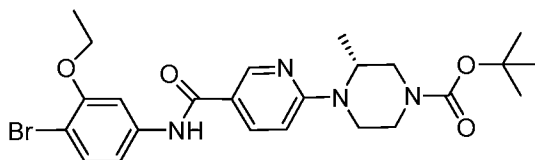
stirred at room temperature for 30 minutes. The reaction mixture was concentrated to produce the title compound as a light brown oil (30 mg, 40 % yield). (*m/z*): [M+H]⁺ calcd for C₈H₁₃NO₃ 172.10 found 172.2.

Preparation 20: (S)-1-((S)-2-Methoxycarbonylamino-3-methyl-butryl)-2-methyl-pyrrolidine-2-carboxylic acid



To a solution of (*S*)-2-methoxycarbonylamino-3-butyric acid (543 mg, 3.10 mmol) dissolved in *N,N*-dimethylacetamide (10 mL, 11 mmol) was added HATU (1413 mg, 3.72 mmol) followed by *N,N*-diisopropylethylamine (1.62 mL, 9.29 mmol). The reaction mixture stirred for 10 min and then (*S*)-2-methyl-pyrrolidine-2-carboxylic acid (400 mg, 3.10 mmol) was added. The reaction mixture was stirred at room temperature overnight, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (5 mL), filtered, and purified by preparative HPLC. Fractions with desired molecular weight were combined and lyophilized to give the title compound (604 mg 68 % yield). [M+H]⁺ calcd for C₁₃H₂₂N₂O₅ 287.15 found 287.0

Preparation 21 (R)-4-[5-(4-Bromo-3-ethoxy-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



(a) *N*-(4-Bromo-3-ethoxy-phenyl)-6-fluoro-nicotinamide

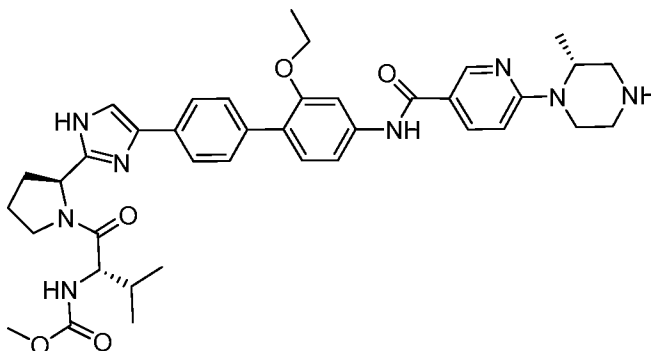
To a solution of 4-bromo-3-ethoxyaniline hydrochloride (500 mg, 2 mmol) dissolved in DCM (7 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (240 mg, 1.5 mmol) dissolved in DCM (1.2 mL). A white precipitate was observed. The reaction mixture was stirred for 1 h, and concentrated to produce the HCl salt of the title intermediate.

(*m/z*): [M+H]⁺ calcd for C₁₄H₁₂BrFN₂O₂ 339.01 found 339.0.

(b) (R)-4-[5-(4-Bromo-3-ethoxy-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

The white solid from the previous step was dissolved in DMSO (3.2 mL, 44 mmol), (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (300 mg, 1.5 mmol) was added, followed by *N,N*-diisopropylethylamine (2.6 mL, 14.8 mmol). The reaction mixture was heated at 120 °C overnight, cooled to room temperature, and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography (0-40% ethyl acetate:hexanes) to produce the title compound as a light yellow solid (324 mg, 42 % yield). (*m/z*): [M+H]⁺ calcd for C₂₄H₃₁BrN₄O₄ 519.15 found 519.5.

Preparation 22: ((*S*)-1-((*S*)-2-[4-(2'-Ethoxy-4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



(a) (R)-4-[5-(2-Ethoxy-4'-{2-[(*S*)-1-((*S*)-2-methoxycarbonylamino-3-methyl-butyl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-biphenyl-4-ylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

A mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (253 mg, 0.52 mmol) and the TFA salt of (*R*)-4-[5-(4-bromo-3-ethoxy-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (324 mg, 0.52 mmol; Preparation 21) was dissolved in 1,2-dimethoxyethane (5.32 mL, 51.2 mmol) and water (0.92 mL, 51.2 mmol) and the mixture was sparged under nitrogen. Sodium bicarbonate (161 mg, 1.92 mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (89 mg, 0.077 mmol). The reaction mixture was further sparged with nitrogen, sealed under nitrogen and heated at 90 °C overnight. The reaction mixture was extracted with ethyl acetate and water. The organic layer was

dried over sodium sulfate, filtered and concentrated to produce the title intermediate as a brown oil. (m/z): $[M+H]^+$ calcd for $C_{44}H_{56}N_8O_7$ 809.43 found 809.6.

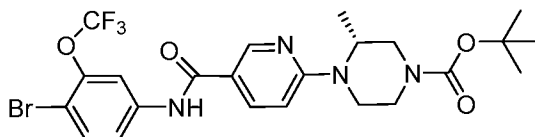
(b) ((S)-1-((S)-2-[4-(2'-Ethoxy-4'-[6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester

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The brown oil of the previous step was treated with 4 M HCl in 1,4-dioxane (3.8 mL, 15.3 mmol) and stirred at room temperature for 1 h. The reaction mixture was concentrated and evaporated with ethyl acetate (2 x) to produce a brown solid. The solid was dissolved in 1:1 acetic acid:water solution (4 mL), filtered, and purified by reverse phase HPLC to produce the tri-TFA salt of the title compound as a yellow solid.

10 (m/z): $[M+H]^+$ calcd for $C_{39}H_{48}N_8O_5$ 709.37 found 709.9.

Preparation 23-1: (R)-4-[5-(4-Bromo-3-trifluoromethoxy-phenylcarbonyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



15 (a) N-(4-Bromo-3-trifluoromethoxy-phenyl)-6-fluoro-nicotinamide

To a solution of 4-bromo-3-trifluoromethoxy-phenylamine (300 mg, 1 mmol) dissolved in DCM (5 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (190 mg, 1.2 mmol) dissolved in DCM (1 mL). A white precipitate was observed. The reaction mixture was concentrated to produce the HCl salt of the title intermediate.

20 (m/z): $[M+H]^+$ calcd for $C_{13}H_7BrF_4N_2O_2$ 378.96 found 379.0.

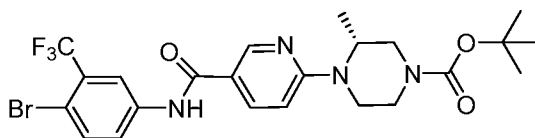
(b) (R)-4-[5-(4-Bromo-3-trifluoromethoxy-phenylcarbonyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

The white solid from the previous step was dissolved in DMSO (2 mL) and (R)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (230 mg, 1.2 mmol) was added, followed by *N,N*-diisopropylethylamine (2 mL, 10 mmol). The reaction mixture was heated at 120 °C overnight, cooled to room temperature, and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography (0-40% ethyl acetate:hexanes) to produce the title compound as a light yellow solid (200 mg, 40 % yield).

25 (m/z): $[M+H]^+$ calcd for $C_{23}H_{26}BrF_3N_4O_4$ 559.11, 561.11 found 561.0.

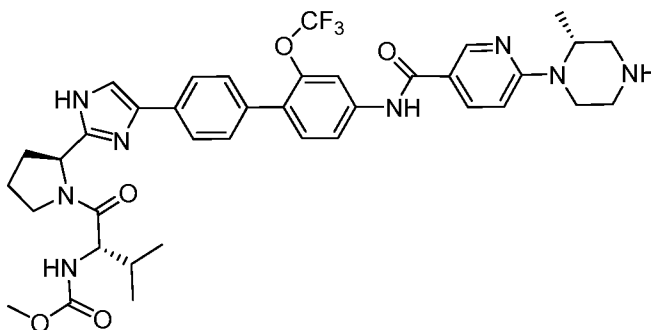
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Preparation 23-2: (*R*)-4-[5-(4-Bromo-3-trifluoromethyl-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



Following the procedure of Preparation 23-1 substituting 5-amino-2-bromobenzotrifluoride (300 mg, 1 mmol) for 4-bromo-3-trifluoromethoxy-phenylamine (300 mg, 1 mmol), the title intermediate was prepared (*m/z*): [M+H]⁺ calcd for C₂₃H₂₆BrF₃N₄O₃ 543.11, 545.11 found 545.4.

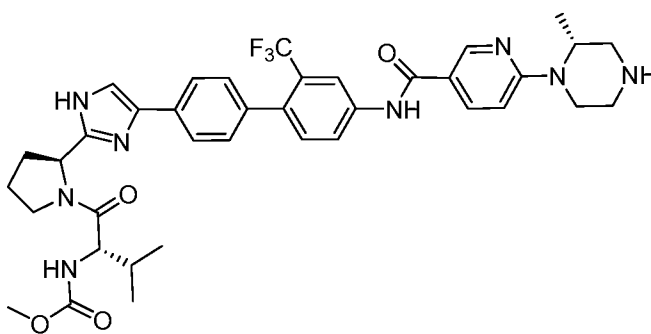
Preparation 24: ((*S*)-2-Methyl-1-((*S*)-2-[4-(4'-{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester



A mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (360 mg, 0.64 mmol) and (*R*)-4-[5-(4-bromo-3-trifluoromethoxy-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (360 mg, 0.64 mmol; Preparation 23-1) was dissolved in 1,2-dimethoxyethane (6.69 mL, 64.4 mmol) and water (1.16 mL, 64.4 mmol) and the mixture was sparged under nitrogen. Sodium bicarbonate (203 mg, 2.41 mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (112 mg, 0.097 mmol). The reaction mixture was further sparged with nitrogen, sealed under nitrogen and heated at 90 °C overnight. The reaction mixture was extracted with ethyl acetate (5 mL) and water (3 mL); the organic layer was dried over sodium sulfate, filtered and concentrated to produce a brown oil.

The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (4 mL, 20 mmol) and stirred at room temperature for 1 h. The reaction mixture was concentrated and evaporated with ethyl acetate (2 x) to produce the HCl salt of the title compound as a yellow solid which was purified by preparative HPLC to provide the tri-TFA salt of the title compound (150 mg, 21 % overall yield). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₃F₃N₈O₅ 749.33 found 749.5.

Preparation 25: ((*S*)-2-Methyl-1-((*S*)-2-[4-(4'-{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-propyl)-carbamic acid methyl ester



10

A mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (280 mg, 0.57 mmol) and (*R*)-4-[5-(4-bromo-3-trifluoromethyl-phenylcarbonyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (300 mg, 0.72 mmol; Preparation 23-2) was dissolved in 1,4-dioxane (5.8 mL, 75 mmol) and water (0.83 mL, 46 mmol). Cesium carbonate (560 mg, 1.7 mmol) was added, the reaction mixture was sparged with nitrogen and then chloro(2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*t*-butylether adduct (28 mg, 0.034 mmol) was added. The reaction mixture was sealed with nitrogen and heated at 95 °C for 3 h. The reaction mixture was extracted with ethyl acetate and water; the organic layer was dried over sodium sulfate, filtered and concentrated to produce an orange oil.

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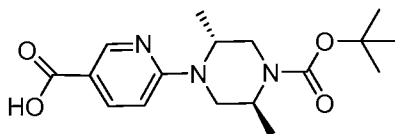
The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (4 mL, 20 mmol) and stirred at room temperature for 1 h. The reaction mixture was concentrated and evaporated with ethyl acetate (2 x) to produce the HCl salt of the title compound as a yellow solid which was purified by preparative HPLC to provide the tri-TFA salt of the

20

25

title compound (150 mg, 24 % overall yield). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₃F₃N₈O₄ 733.34 found 733.5.

Preparation 26: (2*S*,5*R*)-4-(5-Carboxy-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester



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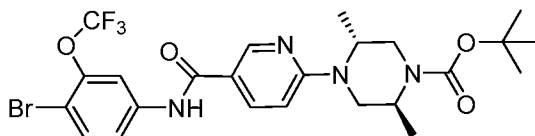
(a) (2*S*,5*R*)-4-(5-Methoxycarbonyl-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

A mixture of 6-fluoronicotinic acid methyl ester (200 mg, 1.29 mmol) and (2*S*,5*R*)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester was heated at 120 °C in DMSO (2.0 mL) with potassium carbonate (178 mg, 1.29 mmol) for 2 h. The reaction mixture was partitioned between ethyl acetate (20.0 mL) and water (5.0 mL). The organic layer was washed with water (2 x 5.0 mL), dried over sodium sulfate, filtered and concentrated to give the title intermediate as a yellowish oil.

(b) (2*S*,5*R*)-4-(5-Carboxy-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

The oil of the previous step was dissolved in methanol (10.0 mL, 247 mmol) and water (2.5 mL, 140 mmol) and treated with lithium hydroxide monohydrate (108 mg, 2.58 mmol) at 40 °C overnight. The reaction mixture was concentrated; the residue was dissolved in 1:1 acetic acid:water solution (6 mL), filtered, and purified by reverse phase HPLC. Desired fractions were combined and freeze dried to give the tri-TFA salt of the title compound as a white solid (327 mg, yield 56 %). (*m/z*): [M+H]⁺ calcd for C₁₇H₂₅N₃O₄ 336.18 found 336.5.

Preparation 27: (2*S*,5*R*)-4-[5-(4-Bromo-3-trifluoromethoxy-phenylcarbamoyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

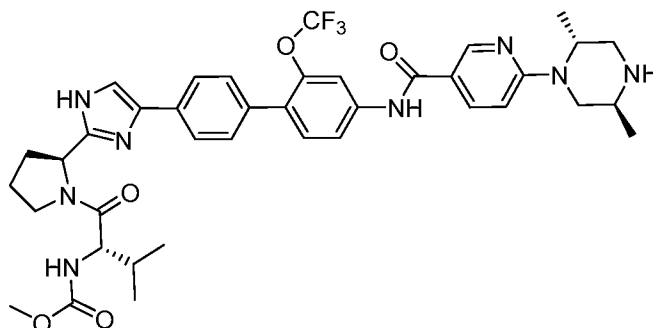


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To a solution of 4-bromo-3-trifluoromethoxy-phenylamine (190 mg, 0.74 mmol) and *N,N*-diisopropylethylamine (0.65 mL, 3.73 mmol; in *N,N*-dimethylacetamide (3 mL)

was added a solution of (2*S*,5*R*)-4-(5-carboxy-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester TFA (330 mg, 0.74 mmol; Preparation 26) and HCTU (401 mg, 0.97 mmol) in *N,N*-dimethylacetamide (3 mL). The reaction mixture was heated at 50 °C overnight. The reaction mixture was concentrated by rotary evaporation,
 5 extracted with ethyl acetate/sat. sodium carbonate, dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography (0-50% ethyl acetate:hexanes) to provide the title compound (155 mg, yield 36 %). (*m/z*): [M+H]⁺ calcd for C₂₄H₂₈BrF₃N₄O₄ 573.12, 575.12 found 575.5.

Preparation 28: ((*S*)-1-((*S*)-2-[4-(4'-{6-((2*R*,5*S*)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester

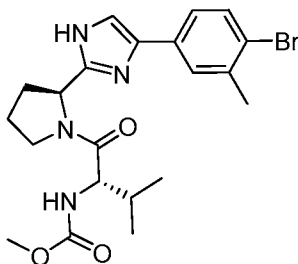


A mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-
 [1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-
 15 carbamic acid methyl ester (86 mg, 0.17 mmol) and (2*S*,5*R*)-4-[5-(4-bromo-3-trifluoromethoxy-phenylcarbonyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.2 mmol, Preparation 27) was dissolved in 1,4-dioxane (1.8 mL, 23 mmol) and water (0.25 mL, 14 mmol). Cesium carbonate (170 mg, 0.52 mmol) was added. The reaction mixture was sparged with nitrogen and then
 20 tetrakis(triphenylphosphine)palladium(0) (12.1 mg, 0.011 mmol) was added. The reaction mixture was sealed under nitrogen and heated at 95 °C overnight. The reaction mixture was extracted with ethyl acetate/water, the organic layer was dried over sodium sulfate and concentrated to produce an orange oil.

The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (2 mL,
 25 7 mmol) and stirred at room temperature for 1 h. The reaction mixture was concentrated and evaporated with ethyl acetate (2 x) to produce the HCl salt of the title compound as a yellow solid which was purified by preparative HPLC to provide the tri-TFA salt of the

title compound (150 mg, 30 % overall yield). (*m/z*): [M+H]⁺ calcd for C₃₉H₄₅F₃N₈O₅ 763.35 found 763.7.

Preparation 29-A: ((*S*)-1-((*S*)-2-[4-(4-Bromo-3-methyl-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



5

(a) 4-Bromo-*N*-methoxy-3,*N*-dimethyl-benzamide

A mixture of 4-bromo-3-methyl-benzoic acid (15 g, 0.069 mol), *O,N*-dimethyl hydroxylamine (6.5 g, 0.1 mol) HATU (38 g, 0.1 mol), and triethylamine (20 g, 0.2 mol) dissolved in DMF (50 mL) was stirred at RT for 12 h, concentrated, and purified by silica
10 gel chromatography (1:1 EtOAc: petroleum ether) to provide the title intermediate (11 g, 61 % yield) ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.52 (m, 2H), 7.32 (m, 1H), 3.50 (s, 3H), 3.29 (m, 3H), 2.38 (s, 3H).

(b) 1-(4-Bromo-3-methyl-phenyl)-ethanone

Methyl lithium (24 mL, 0.038 mol) was added to a solution of the product of the
15 previous step (9 g, 0.035 mol) in THF (20 mL) at -78 °C and the reaction mixture was stirred at RT for 12 h. The organic layer was washed with aqueous ammonium chloride (20 mL), dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography (1:5 EtOAc: petroleum ether) to provide the title intermediate (6 g, 81 % yield) ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.79 (m, 1H), 7.59 (m, 2H), 2.55 (d, *J*=2.8
20 Hz, 3H), 2.43 (d, *J*=0.4 Hz, 3H)

(c) 2-Bromo-1-(4-bromo-3-methyl-phenyl)-ethanone

Trimethyl phenylammonium tribromide (13 g, 0.036 mol) was added to a solution of 1-(4-bromo-3-methyl-phenyl)-ethanone (6.3 g, 0.030 mol) in THF (30 mL) and the reaction mixture was stirred at RT for 12 h, filtered, and concentrated to provide
25 the title intermediate (8.6 g, 100 % yield). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.82(m, 1H), 7.66 (m, 2H), 4.38 (s, 2H), 2.56 (s, 3H)

(d) (S)-Pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-3-methyl-phenyl)-2-oxo-ethyl] ester 1-tert-butyl ester

A mixture of the product of the previous step (8.6 g, 0.03 mol), (S)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (9.5 g, 0.044 mol), and potassium carbonate (12.4 g, 0.09 mol) was dissolved in ACN (50 mL) and the reaction mixture was stirred at RT for 12 h and concentrated to provide the title intermediate (13 g, 100 % yield) (*m/z*): [M+H-Boc]⁺ calcd for C₁₉H₂₄BrNO₅ 326.04 found 326.0.

(e) (S)-2-[4-(4-Bromo-3-methyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester

A mixture of the product of the previous step (13 g, 0.029 mol) and ammonium acetate (47 g, 0.61 mol) dissolved in toluene (100 mL) was stirred at 110 °C for 12 h, concentrated, and purified by silica gel chromatography (1:1 EtOAc:petroleum ether) to provide the title intermediate (8 g, 68 % yield). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.40 (m, 3H), 7.13 (m, 1H), 4.89 (m, 1H), 3.34 (m, 2H), 2.94 (m, 1H), 2.34 (s, 3H), 2.10 (m, 2H), 1.88 (m, 1H), 1.58 (m, 10H).

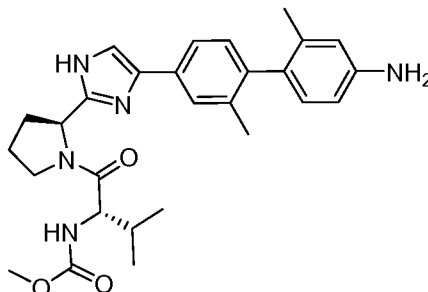
(f) 4-(4-Bromo-3-methyl-phenyl)-2-(S)-pyrrolidin-2-yl-1H-imidazole

To a solution of the product of the previous step (8 g, 0.020 mol) in methanol (3 mL) was added 4 N HCl in methanol (50 mL) at 0 °C. The reaction mixture was stirred at RT for 4 h, and concentrated to give the title intermediate (6 g, 100 % yield) as a yellow solid. (*m/z*): [M+H]⁺ calcd for C₁₄H₁₆BrN₃ 306.06 found 307.7.

(g) ((S)-1-{(S)-2-[4-(4-Bromo-3-methyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

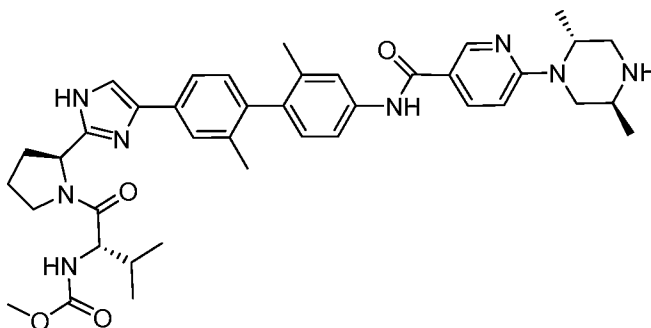
A mixture of the product of the previous step (6 g, 0.018 mol), (S)-2-methoxycarbonylamino-3-methyl-butyric acid (4.6 g, 0.026 mol), HATU (10 g, 0.026 mol), and triethylamine (5.3 g, 0.078 mol) dissolved in DCM (50 mL) was stirred at RT for 12 h, concentrated and purified by silica gel chromatography (1:1 EtOAc:petroleum ether) to provide the title intermediate (5.5 g, 69 % yield). ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 10.4 (s, 1H), 7.64 (m, 1H), 7.46 (m, 2H), 7.17 (m, 1H), 5.50 (m, 1H), 5.39 (m, 1H), 4.34 (m, 1H), 3.86 (m, 1H), 3.69 (s, 3H), 3.60 (m, 1H), 2.45-2.01 (m, 6H), 1.07 (m, 1H), 0.851 (m, 6H).

Preparation 29-B: ((S)-1-((S)-2-[4-(4'-Amino-2,2'-dimethyl-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



5 Potassium carbonate (224 mg, 1.619 mmol) was added to a mixture of ((S)-1-((S)-2-[4-(4-bromo-3-methyl-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (150 mg, 0.324 mmol) and 3-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (90.6 mg, 0.389 mmol) in toluene (0.6 mL, 6 mmol) and water (0.3 mL, 20 mmol). The reaction mixture was degassed and
 10 flushed with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (44.9 mg, 0.039 mmol) was added under nitrogen and then the reaction mixture was capped and heated at 100 °C overnight, cooled to RT and partitioned between ethyl acetate (10 mL) and water (2 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give a brownish oil, which was purified by silica gel chromatography (12 g silica gel, 0-100%
 15 EtOAc/hexanes). Desired fractions were combined and concentrated to give the title compound as a light yellowish foam (135 mg, 85 % yield). (*m/z*): [M+H]⁺ calcd for C₂₈H₃₅N₅O₃ 490.27 found 490.6.

Preparation 30: ((S)-1-((S)-2-[4-(4'-{6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-2,2'-dimethyl-biphenyl-4-yl]-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



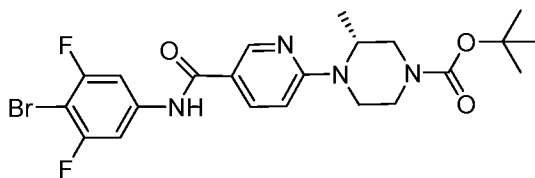
(a) (2*S*,5*R*)-4-[5-(4'-{2-[(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2,2'-dimethyl-biphenyl-4-yl)carbamoyl]-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

A mixture of (2*S*,5*R*)-4-(5-carboxy-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester TFA (80.8 mg, 0.180 mmol), EDC (34.4 mg, 0.180 mmol), and HOAt (24.5 mg, 0.180 mmol) in DMA (2.0 mL, 22 mmol) was stirred at RT for 20 min and then ((*S*)-1-[(*S*)-2-[4-(4'-amino-2,2'-dimethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester (80.0 mg, 0.163 mmol; Preparation 29-B) was added followed by *N,N*-diisopropylethylamine (0.142 mL, 0.817 mmol). The resulting mixture was heated at 50 °C overnight. The reaction mixture was partitioned between EtOAc (10 mL) and water (2 mL). The organic layer was washed with water (2 mL), dried over sodium sulfate, filtered and concentrated to give a yellowish oil. (*m/z*): [M+H]⁺ calcd for C₄₅H₅₈N₈O₆ 807.45 found 807.6.

(b) ((*S*)-1-[(*S*)-2-[4-(4'-{[6-((2*R*,5*S*)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2,2'-dimethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester

The oily residue from the previous step was treated with 4 M HCl in 1,4-dioxane (1.5 mL, 6.0 mmol) at RT for 30 min. The reaction mixture was concentrated, the residue was dissolved in 1:1 acetic acid:water solution (8 mL), filtered, and purified by reverse phase HPLC. Desired fractions were combined and freeze dried to give the tri-TFA salt of the title compound as a white solid (66 mg, yield 39 %). (*m/z*): [M+H]⁺ calcd for C₄₀H₅₀N₈O₄ 707.40 found 707.8.

Preparation 31: (*R*)-4-[5-(4-Bromo-3,5-difluoro-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



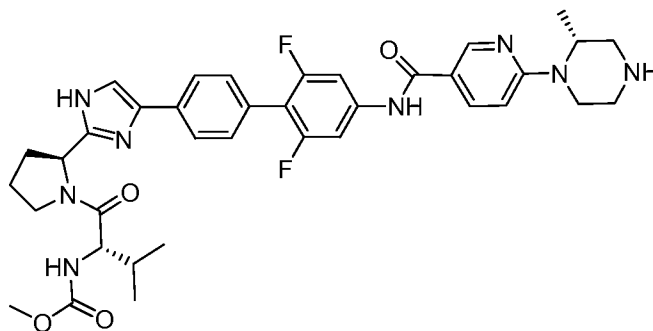
25

To a solution of 4-bromo-3,5-difluoroaniline (250 mg, 1.2 mmol) dissolved in DCM (5 mL) was added a solution of 2-fluoropyridine-5-carbonyl chloride (190 mg, 1.2 mmol) dissolved in DCM (2 mL) followed by addition of *N,N*-diisopropylethylamine (100 uL, 0.60 mmol). The reaction mixture was stirred at RT for 1 h, and concentrated to produce a clear oil.

30

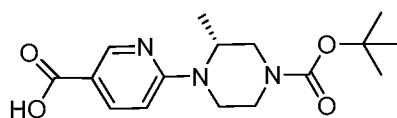
The oil from the previous step was dissolved in DMSO (2.6 mL, 36 mmol) and (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (240 mg, 1.2 mmol) and *N,N*-diisopropylethylamine (2.1 mL, 12 mmol) was added. The reaction mixture was heated at 120 °C overnight and extracted with ethyl acetate/water. The organic layer was dried
 5 over sodium sulfate, filtered, concentrated and purified by silica gel chromatography (0-40% ethyl acetate:hexanes) to produce the title product as a white solid (yield 62 %).
 (*m/z*): [M+H]⁺ calcd for C₂₂H₂₅BrF₂N₄O₃ 511.11. 513.11 found 513.4.

Preparation 32: ((*S*)-1-((*S*)-2-[4-(2',6'-Difluoro-4'-{[6-((*R*)-2-methyl-piperazin-1-yl) -pyridine-3-carbonyl]- amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester
 10



Following the procedure of Preparation 24 at the 0.4 mmol scale substituting the product of Preparation 31 for the product of Preparation 23-1, the tri-TFA salt of the title compound was prepared. (*m/z*): [M+H]⁺ calcd for C₃₇H₄₂F₂N₈O₄ 701.33 found 701.4.

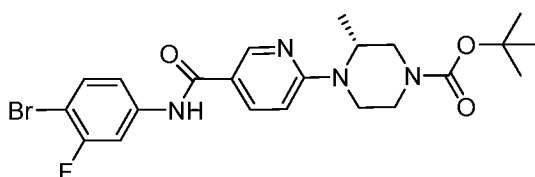
Preparation 33: (*R*)-4-(5-Carboxy-pyridin-2-yl)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester
 15



A mixture of 6-fluoronicotinic acid (150 g, 1.063 mol) and (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (234.2 g, 1.169 mol) in tetrahydrofuran (1.75
 20 L) was cooled to -40 °C and then 2 M isopropylmagnesium chloride in tetrahydrofuran (1.196 L, 2.39 mol) was added slowly maintaining the temperature less than -20 °C. The reaction mixture was slowly warmed to RT, stirred at RT for 4 h and then 1 N HCl (1.75 L) and water (1.175 L) were added. The reaction mixture was extracted with ethyl acetate (4 L). The organic phase was evaporated to provide crude solid (534 g). To the
 25 crude solid was added acetone (2 L) and water (200 mL). The resulting reaction mixture

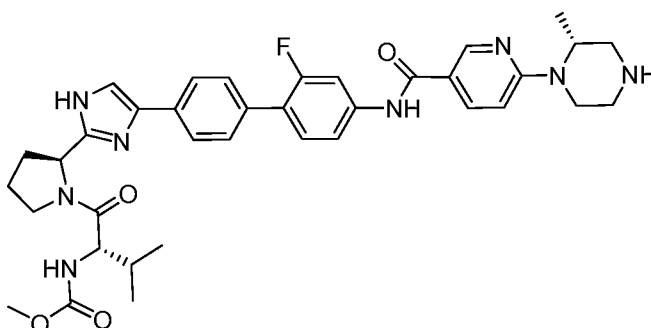
was heated to 50 °C and then water (2.8 L) was added slowly. Seed crystals from a previous run at smaller scale were added after ~ 1 L of water. The reaction mixture was cooled to 20 °C over 3 h, stirred at 20 °C overnight and filtered. The solid was washed with 2:3 acetone:water (2 x 500 mL) and dried under vacuum to provide the title compound (329 g, 96 % yield) as an off-white solid. HPLC Method A: Retention time 9.73 min.

Preparation 34: (*R*)-4-[5-(4-Bromo-3-fluoro-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



A solution of (*R*)-4-(5-carboxy-pyridin-2-yl)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (150 mg, 0.47 mmol, Preparation 33), EDC (130 mg, 0.70 mmol), and HOAt (95 mg, 0.70 mmol) dissolved in DMA (4.3 mL, 47 mmol) was stirred at RT for 30 min and then 4-bromo-3-fluoroaniline (89 mg, 0.47 mmol) was added, followed by *N,N*-diisopropylethylamine (0.2 mL, 1.2 mmol). The reaction mixture was stirred at RT overnight and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography (eluted: 0-40% EtOAc:hexanes) to provide the title compound as a light yellow oil (100 mg, 40 % yield). (*m/z*): [M+H]⁺ calcd for C₂₂H₂₆BrFN₄O₃, 493.12 found 493.2.

Preparation 35: ((*S*)-1-((*S*)-2-[4-(2'-Fluoro-4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



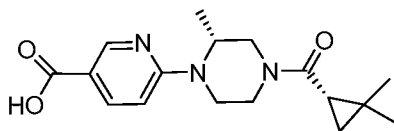
A mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (99 mg, 0.20 mmol) and (*R*)-4-[5-(4-bromo-3-fluoro-

phenylcarbamoyl]-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (100 mg, 0.2 mmol, Preparation 34) was dissolved in 1,2-dimethoxyethane (2.06 mL, 19.9 mmol) and Water (0.358 mL, 19.9 mmol) and the mixture was sparged under nitrogen. Sodium bicarbonate (62.6 mg, 0.75 mmol) was added, followed by

5 tetrakis(triphenylphosphine)palladium(0) (34.4 mg, 0.030 mmol). The reaction mixture was further sparged with nitrogen, sealed under nitrogen, and heated at 90 °C overnight. The reaction mixture was extracted with ethyl acetate (5 mL) and water (3 mL); the organic layer was dried over sodium sulfate, filtered, and concentrated to produce a brown oil.

10 The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (3 mL, 10 mmol), stirred at room temperature for 1 h, concentrated, and evaporated with ethyl acetate (2x) to produce the HCl salt of the title compound as a yellow solid, which was purified by reverse phase HPLC to yield the tri-TFA salt of the title compound (100 mg). (*m/z*): [M+H]⁺ calcd for C₃₇H₄₃FN₈O₄ 683.34 found 683.8.

15 **Preparation 36: 6-[(*R*)-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-nicotinic acid**



(a) 6-((*R*)-2-Methyl-piperazin-1-yl)-nicotinic acid methyl ester

To a mixture of (*R*)-4-(5-carboxy-pyridin-2-yl)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (50 g, 0.156 mol) and methanol (500 mL) was slowly added

20 concentrated sulfuric acid (37 mL). The reaction mixture was warmed to 64 °C, stirred at 64 °C overnight, cooled to RT and then ice water (800 mL) was added followed by 50 % aqueous sodium hydroxide (60 mL). The reaction mixture was extracted with ethyl acetate (3 x 800 mL). Combined organic layers were dried over sodium sulfate and

25 evaporated to give the title intermediate as an oil. HPLC Method A: Retention time 3.50 and 3.72 min.

(b) 6-[(*R*)-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-nicotinic acid methyl ester

To a cooled solution of the oil from the previous step in dimethylformamide (600

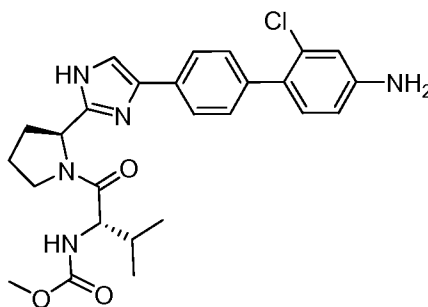
30 mL) was added (*S*)-2,2-dimethyl-cyclopropanecarboxylic acid (16.89 g, 0.148 mol) and HCTU (61.23 g 0.148 mol), followed by *N,N*-diisopropylethylamine (51.6 mL, 0.296

mol). The reaction mixture was stirred at RT overnight, diluted with ethyl acetate (1 L) and washed with 1:1 sodium carbonate:water. The aqueous phase was extracted with ethyl acetate (500 mL). Combined organic phases were washed with saturated aqueous sodium bicarbonate (500 mL) and water (1 L). The organic layer was extracted with 3 N HCl (2 x 500 mL, 300 mL) and then 50% aqueous NaOH (169 g) was added to the combined aqueous extract. After 30 min, the reaction mixture was filtered to give a solid (51.1g). To the crude solid was added acetone (300 mL), followed by water (450 mL). The reaction mixture was stirred at RT overnight and filtered to give the title intermediate (36.86 g, 71.5% y over two steps) as a slightly yellow solid. HPLC Method B: Retention time 15.05 min.

(c) 6-[(R)-4-((S)-2,2-Dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-nicotinic acid

To a mixture of the product of the previous step (35.0 g, 0.106 mol) and methanol (280 mL) was added 2 M LiOH in water (106 mL, 0.211 mol) keeping the temperature under 30 °C. The reaction mixture was stirred at RT overnight, concentrated under reduced pressure, and then ethanol (64 mL) was added, followed by 1 N HCl (230 mL). Seed crystals from a previous run at smaller scale were added after 160 mL HCl. After 1 h, the mixture was filtered to give the title compound (33.2 g, 99% yield) as a pale yellow solid. HPLC Method B: Retention time 8.27 min.

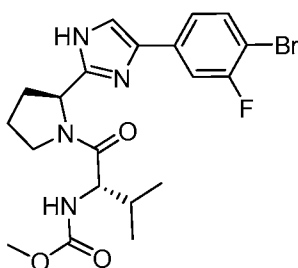
Preparation 37: ((S)-1-((S)-2-[4-(4'-Amino-2'-chloro-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



Saturated aqueous sodium carbonate (0.2 mL) was added to a mixture of [(S)-2-methyl-1-((S)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (100 mg, 0.20 mmol), 4-bromo-3-chloroaniline (46 mg, 0.22 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol), and water (0.3 mL). The reaction mixture was purged with nitrogen and then 1,4-dioxane (0.7 mL) was added.

The reaction mixture was degassed, stirred, and heated at 90 °C overnight. Water and ethyl acetate were added; the reaction mixture was concentrated; dissolved in 1:1 acetic acid:water (1 mL) and purified by preparative HPLC. Fractions were combined, adjusted to pH 8-9 with aqueous sodium bicarbonate, and extracted with DCM. Extracts were washed with water, dried with sodium sulfate, and concentrated. The concentrate was dissolved in methanol and concentrated under vacuum to provide the title compound (m/z): $[M+H]^+$ calcd for $C_{26}H_{30}ClN_5O_3$ 496.20 found 496.7.

Preparation 38-A: ((S)-1-((S)-2-[4-(4-Bromo-3-fluoro-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



10

(a) 1-(4-Bromo-3-fluoro-phenyl)-2-chloro-ethanone

Oxalyl dichloride (6.1 g, 48 mmol) was added to a solution of 4-bromo-3-fluoro-benzoic acid (7 g, 32 mmol) in DCM (80 mL) at 0 °C followed by DMF (0.2 mL) and the reaction mixture was stirred at RT for 2 h and then concentrated under vacuum to provide crude 4-bromo-3-fluoro-benzoyl chloride.

To the crude product dissolved in DCM (50 mL) was added 2 N trimethylsilyldiazomethane (48 mL, 96 mmol) at 0 °C and the reaction mixture was stirred at RT for 3 h. Acetic acid was added and the reaction mixture was diluted with DCM, washed with brine, and concentrated to provide crude 1-(4-bromo-3-fluoro-phenyl)-2-diazenyl-2-trimethylsilylanyl-ethanone (8.0 g).

To a solution of the product of the previous step (8.0 g) in THF (50 mL) was added 4 N HCl in dioxane (20 mL) at 0 °C and the reaction mixture was stirred at RT for 3 h, concentrated, and EtOAc (100 mL) was added. The solution was washed with sodium bicarbonate, dried, concentrated, and purified by silica gel chromatography (eluted with 5:1 petroleum ether:EtOAc) to give the title intermediate (6.5 g, 81 % yield). (m/z): $[M+H]^+$ calcd for $C_8H_5BrClFO$ 252.93 found 252.7. 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.72-7.76 (2H, M), 7.63-7.65 (1H, m), 4.64 (2H, s).

25

(b) (S)-Pyrrolidine-1,2-dicarboxylic acid 2-[2-(4-bromo-3-fluoro-phenyl)-2-oxo-ethyl] ester 1-tert-butyl ester

To a solution of the product of the previous step (6.1 g, 28.4 mmol) in DMF (100 mL) was added (S)-pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl ester (6.5 g, 25.8 mmol) and cesium carbonate (16.8 g, 51.6 mmol) and the reaction mixture was stirred at RT for 2 h. Ethyl acetate (500 mL) was added and the solution was washed with brine (4 x 50 mL), dried, and concentrated to give the title intermediate as a dark oil (10 g). (*m/z*): [M+H-Boc]⁺ calcd for C₁₈H₂₁BrFNO₅ 330.02 found 331.9.

10 (c) (S)-2-[4-(4-Bromo-3-fluoro-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carboxylic acid tert-butyl ester

Ammonium acetate (39.8 g, 516 mmol) was added to a solution of the product of the previous step (10 g, 25.8 mmol) in toluene (150 mL) and the reaction mixture was stirred at reflux overnight. Ethyl acetate (200 mL) was added, and the solution was washed with water (3 x 50 mL), dried, concentrated, and purified by silica gel chromatography (eluted with 4:1 petroleum ether: EtOAc) to give the title product as a yellow solid (4.2 g). (*m/z*): [M+H]⁺ calcd for C₁₈H₂₁BrFN₃O₂ 410.09 found 409.9. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 7.41-7.56 (3H, m), 7.25 (1H,s), 4.97 (1H, d), 3.43 (2H, m), 3.01 (1H,s), 2.10 (2H,m), 1.98 (2H,m). 1.42-1.51 (10H,m).

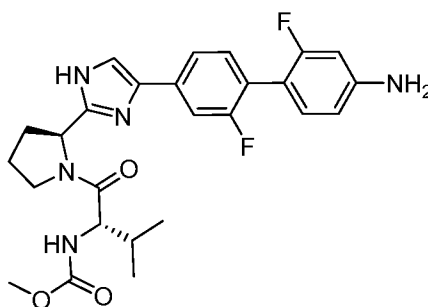
20 (d) ((S)-1-{(S)-2-[4-(4-Bromo-3-fluoro-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

To a solution of the product of the previous step (4.2 g, 10.24 mmol) in methanol was added 4 N HCl in dioxane (30 mL) and the reaction mixture was stirred at RT for 2 h and concentrated to give crude 4-(4-bromo-3-fluoro-phenyl)-2-(S)-pyrrolidin-2-yl-1H-imidazole (4.1 g)

25 To a solution of the crude product (4.1 g, 10.24 mmol) in DMF (70 mL) was added (S)-2-methoxycarbonylamino-3-methyl-butyric acid (1.97 g, 11.26 mmol), HATU (4.67 g, 12.29 mmol) and triethylamine (3.11 g, 30.72 mmol) and the reaction mixture was stirred at RT overnight. Ethyl acetate (200 mL) was added, and the solution was washed with brine (3 x 40 mL), dried, filtered, concentrated, and purified by silica gel chromatography (eluted with 2:1 petroleum ether:EtOAc) to give the title product as a yellow solid (2.6 g, 54 % yield) (*m/z*): [M+H]⁺ calcd for C₂₀H₂₄BrN₄O₃ 467.11 found 468.9. ¹H NMR (CD₃OD, 400 MHz) δ (ppm): 7.51-7.62 (m, 2 H), 7.40-7.42 (m, 2 H),

5.12-5.16 (m, 1 H), 4.22-4.20(m, 1 H), 4.05-3.95 (m, 1 H), 3.88-3.82 (m, 1 H), 3.65 (s, 3 H), 2.41-2.11 (m, 3 H), 2.05-1.99 (m, 1 H), 0.97-0.88 (m, 7 H).

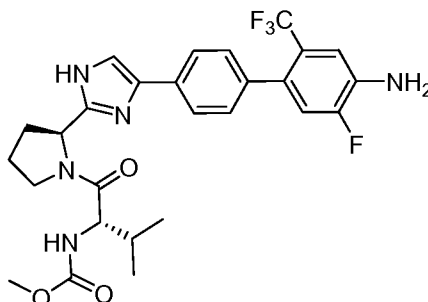
Preparation 38-B: ((S)-1-((S)-2-[4-(4'-Amino-2,2'-difluoro-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



Potassium carbonate (300 mg, 2.1 mmol) was added to a solution of ((S)-1-((S)-2-[4-(4-bromo-3-fluoro-phenyl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (200 mg, 0.4 mmol) and 3-fluoro-4-(4,4,5,5-tetramethyl-[1, 3,2]dioxaborolan-2-yl)-phenylamine (130 mg, 0.55 mmol) dissolved in 10 toluene (0.91 mL, 8.6 mmol) and water (0.38 mL, 21 mmol). The reaction mixture was sparged under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.051 mmol) was added and the reaction mixture was sparged with nitrogen and heated at 100 °C overnight. The reaction mixture was diluted in ethyl acetate and washed with water and 15 brine. The organic layer was dried over sodium sulfate, filtered and concentrated to produce a red solid. (*m/z*): [M+H]⁺ calcd for C₂₆H₂₉F₂N₅O₃ 498.20 found 498.5

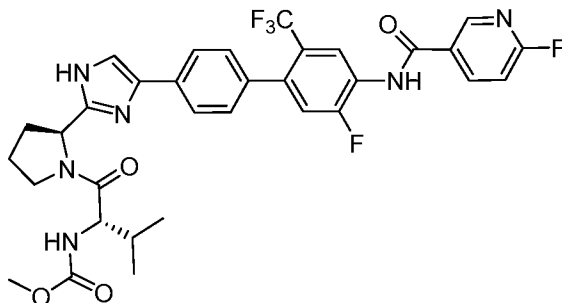
The red solid was purified by silica gel chromatography (0-100% ethyl acetate:hexanes) to produce the desired product as a yellow solid, containing triphenylphosphine oxide. A portion of the yellow solid (50 mg) was dissolved in 1:1 20 acetic acid:water (5 mL) and purified by reverse phase HPLC to produce the TFA salt of the title intermediate as a white powder (210 mg, 99.3 % purity).

Preparation 39: ((S)-1-((S)-2-[4-(4'-Amino-5'-fluoro-2'-trifluoromethyl-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



5 A mixture of 4-bromo-2-fluoro-5-(trifluoromethyl)aniline (78 mg, 0.302 mmol) and [(S)-2-methyl-1-((S)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (150 mg, 0.302 mmol) in toluene (0.6 mL, 6 mmol) and water (0.4 mL, 20 mmol) was purged with nitrogen. Potassium carbonate (208.8 g, 1.511 mmol) and tetrakis(triphenylphosphine)-
10 palladium(0) (35 mg, 0.030 mmol) were added under an atmosphere of nitrogen. The reaction mixture was capped and heated at 100 °C overnight, cooled to RT, and partitioned between ethyl acetate (5.0 mL) and water (1.5 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated to give a yellowish oil, which was purified by silica gel chromatography (12g silica gel, 0-100% EtOAc/hexanes). Desired
15 fractions were combined and concentrated to give the title intermediate as a yellowish solid (128 mg, 77 % yield). (*m/z*): [M+H]⁺ calcd for C₂₇H₂₄F₄N₅O₃ 548.22 found 548.6.

Preparation 40: ((S)-1-((S)-2-(4-{5'-Fluoro-4'-[(6-fluoro-pyridine-3-carbonyl)-amino]-2'-trifluoromethyl-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester

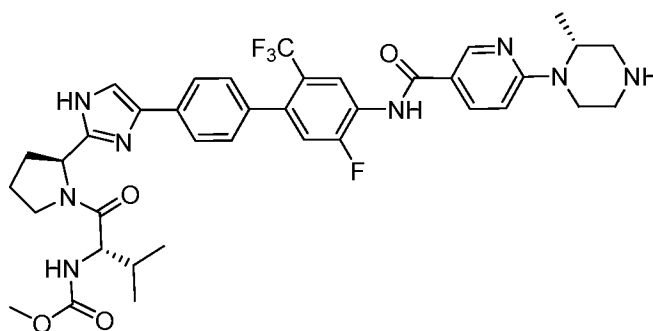


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To a solution of ((S)-1-((S)-2-[4-(4'-amino-5'-fluoro-2'-trifluoromethyl-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl

ester (128 mg, 0.234 mmol; Preparation 39) in DCM (3 mL, 47 mmol) and DMA (0.3 mL, 3 mmol) was added 2-fluoropyridine-5-carbonyl chloride (37 mg, 0.234 mmol), and the resulting solution was stirred at RT overnight. The reaction mixture was concentrated by rotary evaporation to give the monoHCl salt of the title intermediate as a brownish oil (163 mg), which was used without further purification. (*m/z*): [M+H]⁺ calcd for C₃₃H₃₁F₅N₆O₄ 671.23 found 671.7.

Preparation 41: ((*S*)-1-((*S*)-2-[4-(5'-Fluoro-4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester

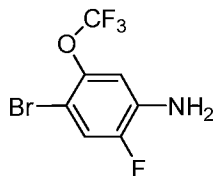


10

A solution of {(*S*)-1-[(*S*)-2-(4-{5'-fluoro-4'-[(6-fluoro-pyridine-3-carbonyl)-amino]-2'-trifluoromethyl-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester HCl (100 mg, 0.141 mmol, Preparation 40), (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (283 mg, 1.414 mmol), and *N,N*-diisopropylethylamine (246.3 μ L, 1.414 mmol) was stirred in DMSO (1.5 mL, 21 mmol) at 120 °C overnight. The reaction mixture was concentrated by rotary evaporation to provide a crude intermediate which was treated with 4.0 M HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) for 1 h, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (8 mL), filtered and purified by reverse phase HPLC. Fractions were combined and lyophilized to give the tri-TFA salt of the title intermediate (54 mg, 35 % yield). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₂F₄N₈O₄ 751.33 found 751.7.

20

Preparation 42: 4-Bromo-2-fluoro-5-trifluoromethoxy-phenylamine

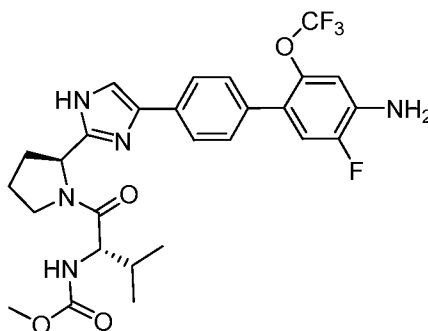


To a mixture of 2-fluoro-5-(trifluoromethoxy)aniline (1 g, 5 mmol) dissolved in DMF (2 mL) was slowly added a solution of *N*-bromosuccinimide (1.1 g, 6.2 mmol)

25

dissolved in DMF (2 mL). The reaction mixture was stirred at room temperature for 1 h, concentrated and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography (eluted 0-10% ethyl acetate:hexanes) to produce the title intermediate as a red oil (818 mg, 58 % yield). (*m/z*): [M+H]⁺ calcd for C₇H₄BrF₄NO 273.94, 275.94 found 276.1.

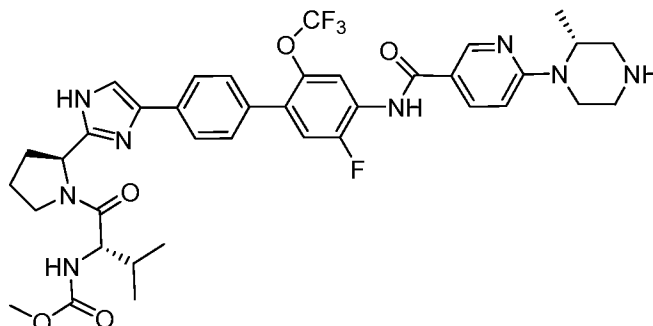
Preparation 43: ((*S*)-1-((*S*)-2-[4-(4'-Amino-5'-fluoro-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



Potassium carbonate (350 mg, 2.5 mmol) was added to a solution of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (250 mg, 0.50 mmol) and 4-bromo-2-fluoro-5-trifluoromethoxy-phenylamine (140 mg, 0.50 mmol; Preparation 42) dissolved in toluene (2 mL) and water (0.54 mL). The reaction mixture was sparged under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) was added and the reaction mixture was sparged with nitrogen and heated at 100 °C overnight. The reaction mixture was diluted in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated to produce a red solid, which was purified by silica gel chromatography (0-100% ethyl acetate:hexanes) to produce the desired product as a white solid with some triphenylphosphine oxide impurity. (*m/z*): [M+H]⁺ calcd for C₂₇H₂₉F₄N₅O₄ 564.2 found 564.4.

The solid (50 mg) was dissolved in 1:1 acetic acid:water (5 mL) and purified by reverse phase HPLC to produce the TFA salt of the title intermediate as a white solid

Preparation 44: ((*S*)-1-((*S*)-2-[4-(5'-Fluoro-4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



- 5 (a) {(S)-1-[(S)-2-(4-{5'-Fluoro-4'-[(6-fluoro-pyridine-3-carbonyl)-amino]-2'-trifluoromethoxy-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

To a solution of ((*S*)-1-((*S*)-2-[4-(4'-amino-5'-fluoro-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (50 mg, 0.09 mmol, Preparation 43) in DCM (0.6 mL, 9 mmol) was slowly added 2-fluoropyridine-5-carbonyl chloride (10 mg, 0.09 mmol;) and the reaction mixture was stirred at room temperature for 5 min and then concentrated to provide a colored solid.

- 15 (b) (*R*)-4-[5-(5-Fluoro-4'-{2-[(S)-1-((S)-2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}]-2-trifluoromethoxy-biphenyl-4-ylcarbonyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert* butyl ester

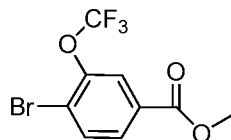
The solid from the previous step was dissolved in a mixture of dimethyl sulfoxide (0.20 mL, 2.8 mmol) and *N,N*-diisopropylethylamine (0.32 mL, 1.8 mmol) and then (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (180 mg, 0.91 mmol) was added and the reaction mixture was heated at 120 °C overnight and concentrated by rotary evaporation to produce a dark colored oil.

- 25 (c) ((S)-1-((S)-2-[4-(5'-Fluoro-4'-{[6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (2 mL, 8 mmol) and heated at 50 °C for 1 h. The reaction mixture was concentrated, and evaporated with ethyl acetate (2 x) to produce the HCl salt of the desired product as a solid, which was purified by reverse phase HPLC to produce the tri-TFA salt of the

desired product as a white solid (53 mg, 50 % yield). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₂F₄N₈O₅ 767.32 found 767.7

Preparation 45: 4-Bromo-3-trifluoromethoxy-benzoic acid methyl ester



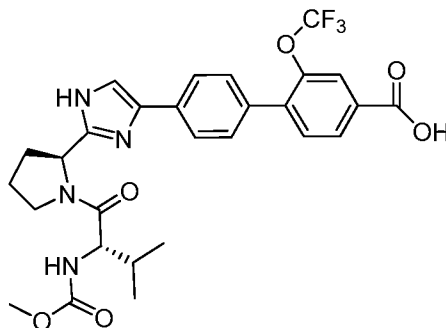
5 (a) 4-Amino-3-trifluoromethoxy-benzoic acid methyl ester

A mixture of 4-amino-3-(trifluoromethoxy)benzoic acid (5 g, 22.61 mmol), methanol (75 mL) and 4.0 M HCl in 1,4-dioxane (56.53 mL, 226.1 mmol) was stirred at RT for 2 days. The reaction mixture was concentrated and the resulting residue was evaporated with EtOAc (3 x 20 mL) and dried under vacuum to provide the HCl salt of the title intermediate (6.9 g).

10 (b) 4-Bromo-3-trifluoromethoxy-benzoic acid methyl ester

The product of the previous step (2.00 g, 7.36 mmol) was dissolved in a mixture of acetonitrile (89 mL) and water (9.2 mL) at RT. Copper(II) bromide (2.27 g, 10.2 mmol) was added followed by *tert*-butyl nitrite (1.51 mL, 12.7 mmol) dropwise. The resulting mixture was heated at 70 °C for 1 hour, cooled to RT, and treated with saturated sodium bicarbonate (30 mL). The mixture was extracted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (100 mL). Combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered, and concentrated to give a brownish oil, which was purified by silica gel chromatography, (0-30% EtOAc/hexanes).
 15
 20 Desired fractions were combined and concentrated to give the title intermediate as a light yellowish oil (1.57 g, 71 % yield) which was confirmed by NMR.

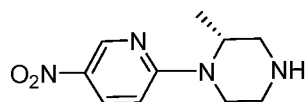
Preparation 46: 4'-{2-[(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methylbutyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-trifluoromethoxy-biphenyl-4-carboxylic acid



To a mixture of 4-Bromo-3-trifluoromethoxy-benzoic acid methyl ester (331 mg, 1.11 mmol; Preparation 45) and [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (500 mg, 1.01 mmol) in toluene (1 mL) and water (1 mL) at
5 RT was added potassium carbonate (696 mg, 5.04 mmol). The mixture was degassed and flushed with nitrogen. Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.101 mmol) was added under nitrogen and then the reaction mixture was capped and was heated at 100 °C overnight, cooled to RT and partitioned between EtOAc (20 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give a
10 brownish oil.

The oily residue from the previous step was treated with methanol (6 mL) and water (1 mL) and lithium hydroxide monohydrate (254 mg, 6.04 mmol) at 65 °C for 1 hour. The reaction mixture was concentrated and the resulting residue was treated with 1:1 acetic acid:water (20 mL), filtered, and purified by reverse phase HPLC. Desired
15 fractions were combined and freeze dried to give the TFA salt of the title intermediate as a white solid (190 mg). (*m/z*): [M+H]⁺ calcd for C₂₈H₂₉F₃N₄O₆ 575.20 found 575.5.

Preparation 47: (*R*)-2-Methyl-1-(5-nitro-pyridin-2-yl)-piperazine



(a) (*R*)-3-Methyl-4-(5-nitro-pyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester

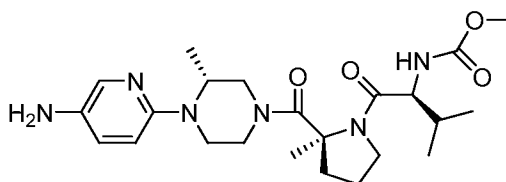
20 A mixture of 2-chloro-5-nitropyridine (1.0 g, 6.3 mmol), (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (1.4 g, 6.9 mmol) and potassium carbonate (1.308 g, 9.46 mmol) in DMSO (20 mL) was heated at 100 °C overnight. The reaction mixture was cooled to RT, and filtered through a pad of silica gel, eluted with EtOAc (150 mL). The filtrate was washed with water (2 x 20 mL) and brine (20 mL), dried over sodium sulfate,
25 filtered and concentrated to give a brownish oil which was purified by silica gel chromatography (80g silica gel, 0-60% EtOAc/hexanes). Desired fractions were combined and concentrated to give the title intermediate as a yellowish solid. (*m/z*): [M+H]⁺ calcd for C₁₅H₂₂N₄O₄ 323.16 found 323.3.

(b) (*R*)-2-Methyl-1-(5-nitro-pyridin-2-yl)-piperazine

30 The solid from previous step was treated with 4 M HCl in 1,4-dioxane (47.3 mL) and HCl (11.6 mL) and the reaction mixture was stirred at RT for 2 h and concentrated to produce a yellow solid, which was evaporated twice with ethyl acetate to yield the diHCl

salt of the title intermediate (940 mg, 50 % yield) as a yellow solid. (m/z): $[M+H]^+$ calcd for $C_{10}H_{14}N_4O_2$ 223.11 found 223.2.

Preparation 48: ((*S*)-1-((*S*)-2-[(*R*)-4-(5-Amino-pyridin-2-yl)-3-methyl-piperazine-1-carbonyl]-2-methyl-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methylester



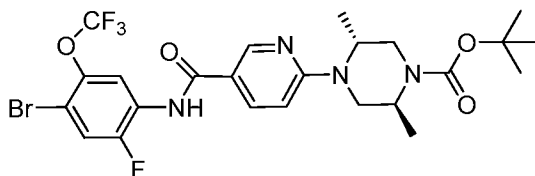
(a) ((*S*)-2-Methyl-1-((*S*)-2-methyl-2-[(*R*)-3-methyl-4-(5-nitro-pyridin-2-yl)-piperazine-1-carbonyl]-pyrrolidine-1-carbonyl]-propyl)-carbamic acid methyl ester

(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methyl-butyryl)-2-methyl-pyrrolidine-2-carboxylic acid (770 mg, 2.7 mmol) was dissolved in DMA (17 mL) and HATU (1.0 g, 2.7 mmol) was added. The reaction mixture was stirred for 20 min and then (*R*)-2-methyl-1-(5-nitro-pyridin-2-yl)-piperazine di-HCl (700 mg, 2 mmol; Preparation 47) was added followed by *N,N*-diisopropylethylamine (2.0 mL, 11 mmol) and the reaction mixture was stirred at 55 °C overnight, cooled to RT, concentrated by rotary evaporation and extracted with EtOAc/water. The organic layer was washed with water, and then brine, dried over sodium sulfate, concentrated under vacuum, and purified by silica gel chromatography (0-100% ethyl acetate:hexanes) to yield the title intermediate (970 mg) as a yellow oil. (m/z): $[M+H]^+$ calcd for $C_{23}H_{34}N_6O_6$ 491.25 found 491.7.

(b) ((*S*)-1-((*S*)-2-[(*R*)-4-(5-Amino-pyridin-2-yl)-3-methyl-piperazine-1-carbonyl]-2-methyl-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methylester

The oil from the previous step was dissolved in methanol (15 mL) and treated with 50 % wet palladium hydroxide on carbon (20 % w/w) (13 mg, 0.45 mmol) and stirred for 2 h at RT. The reaction mixture was filtered through Celite, and concentrated under vacuum to produce a dark red oil, which was purified by silica gel chromatography (0-100% ethyl acetate:hexanes for 15 min then 0-5% methanol:EtOAc for another 15 min) to yield the title intermediate (375 mg; 40 % yield) as a reddish solid. (m/z): $[M+H]^+$ calcd for $C_{23}H_{36}N_6O_4$ 461.28 found 461.6.

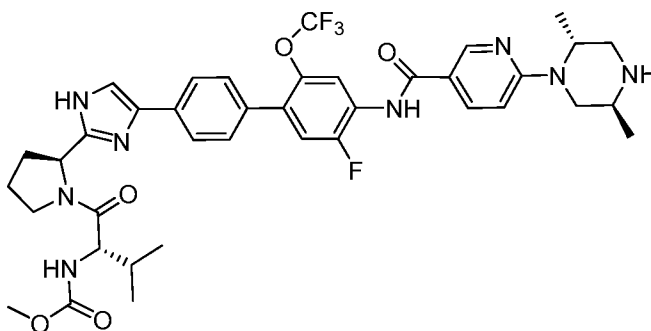
Preparation 49: (2*S*,5*R*)-4-[5-(4-Bromo-2-fluoro-5-trifluoromethoxy-phenylcarbamoyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester



5 To a solution of 4-bromo-2-fluoro-5-trifluoromethoxy-phenylamine (500 mg, 2 mmol) dissolved in DCM (1 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (290 mg, 1.8 mmol) in DCM (1 mL). A few drops of DMA were added and the reaction mixture was concentrated to form *N*-(4-bromo-2-fluoro-5-trifluoromethoxy-phenyl)-6-fluoro-nicotinamide as a purple solid.

10 The solid from the previous step was dissolved in a mixture of *N,N*-diisopropylethylamine (0.7 mL, 4 mmol) and DMSO (0.7 mL, 10 mmol) and (2*S*,5*R*)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (590 mg, 2.7 mmol) was added and the reaction mixture heated at 120 °C overnight, concentrated by rotary evaporation, dissolved in a small amount of DCM and purified by silica gel chromatography (0-40% ethyl acetate:hexanes) to produce the title intermediate (613 mg, 57 % yield) as a white solid. (*m/z*): [M+H]⁺ calcd for C₂₄H₂₇F₄N₄O₄ 591.12 found 591.4.

Preparation 50: ((*S*)-1-((*S*)-2-[4-(4'-{6-((2*R*,5*S*)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-5'-fluoro-2'-trifluoromethoxy-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



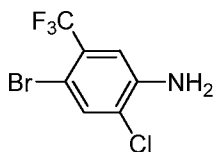
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Potassium carbonate (470 mg, 3.4 mmol) was added to a solution of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (340 mg, 0.68 mmol) and (2*S*,5*R*)-4-[5-(4-bromo-2-fluoro-5-trifluoromethoxy-phenylcarbamoyl)-

pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (400 mg, 0.68 mmol; Preparation 49) dissolved in toluene (2.5 mL) and water (0.73 mL). The reaction mixture was sparged under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (94 mg, 0.081 mmol) was added and the reaction mixture was sparged with nitrogen and heated at 100 °C for 4 h. The reaction mixture was diluted in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated to produce (2*S*,5*R*)-4-[5-(5-fluoro-4'-{2-[(*S*)-1-((*S*)-2-methoxycarbonylamino-3-methylbutyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-trifluoromethoxy-biphenyl-4-ylcarbamoyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester as a red solid.

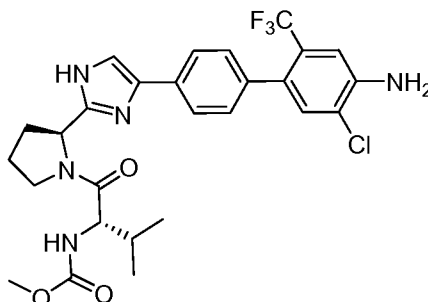
The solid from the previous step was treated with 4 M HCl in 1,4-dioxane (5 mL, 20 mmol) and stirred at 50 °C for 30 min. The reaction mixture was concentrated, dissolved in 1:1 acetic acid:water (8 mL) and purified by reverse phase HPLC. Fractions containing desired compound were combined and lyophilized to produce the tri-TFA salt of the title intermediate (490 mg, 64 % yield) as a white powder. (*m/z*): [M+H]⁺ calcd for C₃₉H₄₄F₄N₈O₅ 781.34 found 781.6.

Preparation 51: 5-Amino-2-bromo-4-chlorobenzotrifluoride



A solution of *N*-bromosuccinimide (1.0 g, 5.6 mmol) dissolved in DMF (3 mL) was slowly added to a mixture of 3-amino-4-chlorobenzotrifluoride (1 g, 5 mmol) dissolved in DMF (2 mL) and the reaction mixture was stirred at RT for 20 min, concentrated, and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate, filtered, concentrated, and purified by flash chromatography (eluted with 100% hexanes) to produce the title intermediate as a reddish colored oil (970 mg, 70 % yield). (*m/z*): [M+H]⁺ calcd for C₇H₄BrClF₃N 273.92, 275.92 found 276.2.

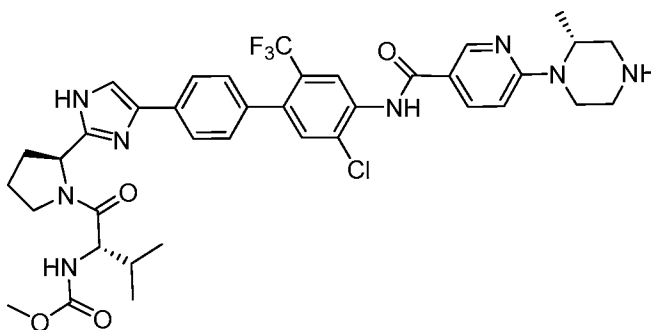
Preparation 52 ((S)-1-((S)-2-[4-(4'-Amino-5'-chloro-2'-trifluoromethyl-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



5 Potassium carbonate (280 mg, 2.0 mmol) was added to a solution of [(S)-2-methyl-1-((S)-2-{4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1H-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester (200 mg, 0.40 mmol) and 5-amino-2-bromo-4-chlorobenzotrifluoride (110 mg, 0.40 mmol; Preparation 10 51) dissolved in toluene (1.3 mL) and water (0.43 mL). The reaction mixture was sparged under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (56 mg, 0.48 mmol) was added and the reaction mixture was sparged with nitrogen and heated at 100 °C for 4 h. The reaction mixture was diluted in ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered, and concentrated to produce a red solid, which was purified by silica gel chromatography (0-100% ethyl acetate:hexanes) to produce the desired product as a yellow solid.

The solid (~30 mg) was dissolved in 1:1 acetic acid:water (5 mL) and purified by reverse phase HPLC to produce the di-TFA salt of the title intermediate (31.1 mg). (*m/z*): [M+H]⁺ calcd for C₂₇H₂₉ClF₃N₅O₃ 564.19 found 564.2.

Preparation 53: ((S)-1-((S)-2-[4-(5'-Chloro-4'-{6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-2'-trifluoromethyl-biphenyl-4-yl]-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acidmethyl ester

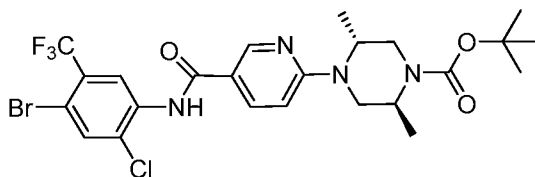


To a solution of ((*S*)-1-((*S*)-2-[4-(4'-amino-5'-chloro-2'-trifluoromethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (50 mg, 0.09 mmol; Preparation 52) dissolved in DCM (0.3 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (14 mg, 0.091 mmol) dissolved in DCM
5 (0.3 mL). The reaction mixture was stirred at RT for 5 min and concentrated to produce ((*S*)-1-((*S*)-2-(4-{5'-chloro-4'-[(6-fluoro-pyridine-3-carbonyl)-amino]-2'-trifluoromethyl-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester as a yellow solid.

The yellow solid from the previous step was dissolved in a mixture of DMSO (0.3
10 mL, 4 mmol) and *N,N*-diisopropylethylamine (0.3 mL, 2 mmol) and (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (180 mg, 0.91 mmol) was added. The reaction mixture was heated at 100 °C for 72 h, and concentrated by rotary evaporation to produce (*R*)-4-[5-(5-chloro-4'-{2-[(*S*)-1-((*S*)-2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-trifluoromethyl-biphenyl-4-yl)-carbonyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester as a dark colored oil.
15

The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (2 mL, 8 mmol) and the reaction mixture was stirred at 50 °C for 1 h, and concentrated under vacuum to produce the HCl salt of the desired product, which was dissolved in 1:1 acetic acid:water (5 mL) and purified by reverse phase HPLC. Fractions containing desired
20 product were combined and lyophilized to produce the tri-TFA salt of the title intermediate (30 mg, 30 % yield) as a white powder. (*m/z*): [M+H]⁺ calcd for C₃₈H₄₂ClF₃N₈O₄ 767.30 found 767.5.

**Preparation 54: (2*S*,5*R*)-4-[5-(4-Bromo-2-chloro-5-trifluoromethyl-phenylcarbonyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl
25 ester**

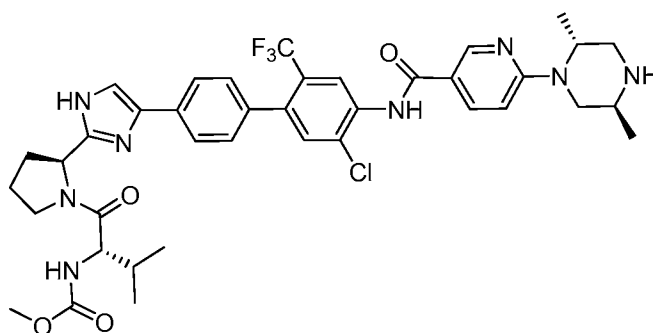


To a solution of 5-amino-2-bromo-4-chlorobenzotrifluoride (466 mg, 1.70 mmol) dissolved in DCM (1 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (270 mg, 1.70 mmol) in DCM (1 mL). A few drops of DMA were added and the

reaction mixture was concentrated to form *N*-(4-bromo-2-chloro-5-trifluoromethyl-phenyl)-6-fluoro-nicotinamide as a purple solid.

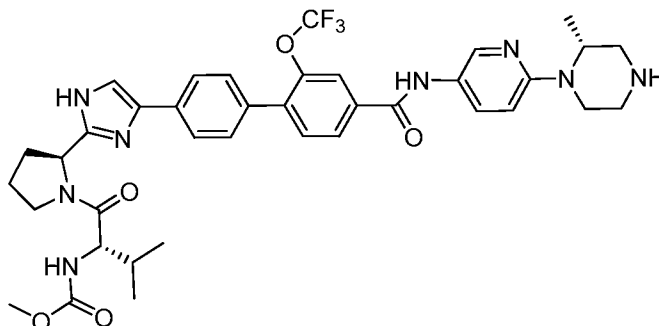
Half of the solid from the previous step was treated with *N,N*-diisopropylethylamine (0.5 mL, 3 mmol), DMSO (0.5 mL, 7 mmol) and (2*S*,5*R*)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (273 mg, 1.27 mmol) and the reaction mixture was heated at 120 °C overnight, concentrated by rotary evaporation, dissolved in a small amount of DCM and purified by silica gel chromatography (0-50% ethyl acetate:hexanes) to produce the title intermediate (288 mg, 29 % yield) as a yellow solid. (*m/z*): [M+H]⁺ calcd for C₂₄H₂₇F₄N₄O₄ 591.09, 593.09 found 593.2.

10 **Preparation 55: ((*S*)-1-{(*S*)-2-[4-5'-Chloro-(4'-{[6-((2*R*,5*S*)-2,5-dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester**



Following the procedure of Preparation 50 at the 0.24 mmol scale, substituting
 15 (2*S*,5*R*)-4-[5-(4-bromo-2-chloro-5-trifluoromethyl-phenylcarbonyl)-pyridin-2-yl]-2,5-dimethyl- piperazine-1-carboxylic acid *tert*-butyl ester(140 mg, 0.24 mmol, Preparation 54) for (2*S*,5*R*)-4-[5-(4-bromo-2-fluoro-5-trifluoromethoxy-phenylcarbonyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester (Preparation 49), the tri-TFA salt of the title intermediate (490 mg, 64 % yield) was prepared as a white powder.
 20 (*m/z*): [M+H]⁺ calcd for C₃₉H₄₄ClF₃N₈O₄ 781.31 found 781.6.

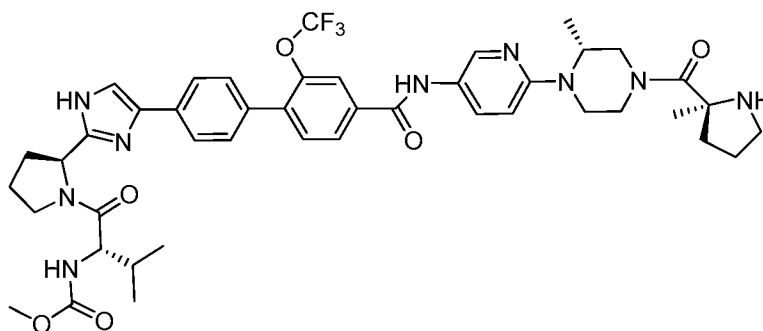
Preparation 56: *{(S)-2-Methyl-1-[(S)-2-(4-{4'-[6-((R)-2-methyl-piperazin-1-yl)-pyridin-3-ylcarbonyl]-2'-trifluoromethoxy-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester*



5 A mixture of 4'-{2-[(S)-1-((S)-2-methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-2-trifluoromethoxy-biphenyl-4-carboxylic acid TFA (600 mg, 0.9 mmol) and HATU (364 mg, 0.96 mmol) in DMA (8 mL) was stirred at RT for 15 min and then 0.5 M (R)-4-(5-amino-pyridin-2-yl)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester in DMA (1.7 mL) was added followed by *N,N*-
 10 diisopropylethylamine (0.76 mL, 4.36 mmol). The resulting mixture was heated at 55 °C overnight, washed with EtOAc (100 mL) and water (25 mL). The organic layer was washed again with water and then with brine, dried over sodium sulfate, filtered, and concentrated to yield a dark reddish oil which was purified by silica gel chromatography (40 g silica column, 0-80% hexane:EtOAc) to provide (R)-4-{5-[(4'-{2-[(S)-1-((S)-2-
 15 methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-2-trifluoromethoxy-biphenyl-4-carbonyl)-amino]-pyridin-2-yl}-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (646 mg) as a light brownish solid.

The solid product was treated with 4.0 M HCl in 1,4-dioxane (6.5 mL, 26.14 mmol) and HCl (1.6 mL) and the reaction mixture was stirred at RT for 1 h,
 20 concentrated, and evaporated with EtOAc (2 x 1 mL) to provide the tri-HCl salt of the title intermediate (693 mg) as a beige solid. (*m/z*): [M+H]⁺ calcd for C₃₈H₄₃F₃N₈O₅ 749.33 found 749.8.

Preparation 57: ((*S*)-2-Methyl-1-{{(*S*)-2-[4-(4'-{6-[(*R*)-2-methyl-4-((*S*)-2-methyl-pyrrolidine-2-carbonyl)-piperazin-1-yl]-pyridin-3-ylcarbamoyl}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester



5

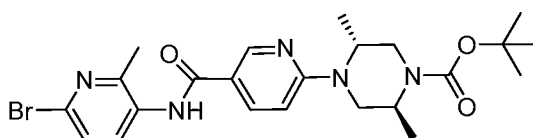
To a mixture of (*S*)-2-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (222 mg, 0.97 mmol) dissolved in DMA (6 mL) was added HATU (369 mg, 0.97 mmol) and the reaction mixture was stirred for 20 min and then {{(*S*)-2-methyl-1-[(*S*)-2-(4-{4'-[6-((*R*)-2-methyl-piperazin-1-yl)-pyridin-3-ylcarbamoyl]-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester 3 HCl (693 mg, 0.81 mmol; Preparation 56) was added followed by *N,N*-diisopropylethylamine (0.71 mL, 4.04 mmol). The reaction mixture was stirred at 55 °C overnight, concentrated by rotary evaporation, and extracted with EtOAc (80 mL) and water (20 mL). The organic layer was washed again with water and then with brine, dried over sodium sulfate, filtered, and concentrated under vacuum, and purified by silica gel chromatography (40 g silica column, 0-100% ethyl acetate:hexanes) to yield 537 mg of a light brown solid.

15

The light brown solid from the previous step was treated with 4 M HCl in 1,4-dioxane (6.1 mL, 24.23 mmol) and HCl (1.5 mL) and stirred at RT for 1 h, concentrated, and evaporated with ethyl acetate (2 x 1 mL) to produce the tri-HCl salt of the title intermediate (569 mg) as a light yellow solid. (*m/z*): [M+H]⁺ calcd for C₄₄H₅₂F₃N₉O₆ 860.40 found 860.6.

20

Preparation 58: (2*S*,5*R*)-4-[5-(6-Bromo-2-methyl-pyridin-3-ylcarbamoyl)-pyridin-2-yl]- 2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester



25

(a) (2*S*,5*R*)-4-(5-Methoxycarbonyl-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

A mixture of 6-fluoronicotinic acid methyl ester (1.0 g, 6.4 mmol), (2*S*,5*R*)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester HCl (1.6 g, 6.4 mmol), and
5 potassium carbonate (1.78 g, 12.9 mmol) were stirred in DMSO (10 mL) at 120 °C for 2 h, cooled, diluted with ethyl acetate (50 mL), washed with water (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated.

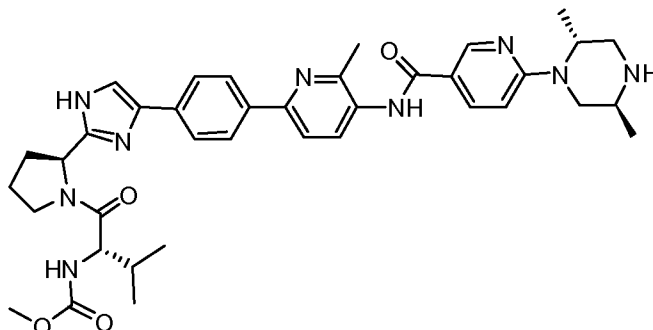
(b) (2*S*,5*R*)-4-(5-Carboxy-pyridin-2-yl)-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

10 Lithium hydroxide (618 mg, 12.9 mmol) was added to a solution of the product of the previous step in methanol (15 mL) and water (3 mL), and the resulting mixture was stirred at 40 °C for 5 h, concentrated, and acidified with 1N HCl to pH 4. The resulting mixture was extracted with ethyl acetate (2 x 50 mL). The organic layer was dried over magnesium sulfate, filtered, concentrated, dissolved in 1:1 acetic acid:water (8 mL),
15 filtered and purified by reverse phase HPLC to give the TFA salt of the title intermediate (1.55 g, 54 % yield). (*m/z*): [M+H]⁺ calcd for C₁₇H₂₅N₃O₄ 336.18 found 336.4.

(c) (2*S*,5*R*)-4-[5-(6-Bromo-2-methyl-pyridin-3-ylcarbonyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

The product of the previous step (180.2 mg, 0.40), EDC (115.3 mg, 0.60 mmol),
20 and HOAt (81.9 mg, 0.60 mmol) were stirred in DMF (2 mL) at RT for 10 min and then 6-bromo-2-methyl-pyridin-3-ylamine (75 mg, 0.40 mmol) and *N,N*-diisopropylethylamine (0.35 mL, 2.01 mmol) were added, and the reaction mixture was stirred at 50 °C overnight, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (5 mL), filtered, and purified by reverse phase HPLC. Fractions containing
25 desired product were combined and lyophilized to give the TFA salt of the title intermediate (91 mg, 37 % yield). (*m/z*): [M+H]⁺ calcd for C₂₃H₃₀BrN₅O₃ 504.15 found 504.3.

Preparation 59: [(*S*)-1-((*S*)-2-{4-[4-(5-{[6-((2*R*,5*S*)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]- amino}-6-methyl-pyridin-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



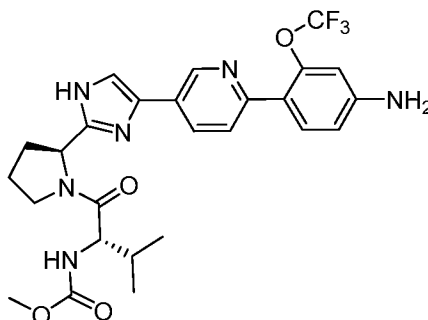
- 5 (a) (2*S*,5*R*)-4-{5-[6-(4-{2-[(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methyl-butyl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-phenyl)-2-methyl-pyridin-3-ylcarbamoyl]-pyridin-2-yl}-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

A mixture of [(*S*)-2-methyl-1-((*S*)-2-{4-[4-(4,4,5,5-tetramethyl-
[1,3,2]dioxaborolan-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-
10 carbamic acid methyl ester (73.0 mg, 0.147 mmol;), (2*S*,5*R*)-4-[5-(6-bromo-2-methyl-
pyridin-3-ylcarbamoyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-
butyl ester TFA (91.0 mg, 0.147 mmol; Preparation 58), and 2 M sodium carbonate in
water (0.29 mL, 0.588 mmol)DMF (0.9 mL, 10 mmol) was sparged with nitrogen and
then tetrakis(triphenylphosphine)palladium(0) (11.9 mg, 0.010 mmol) was added. The
15 reaction mixture was purged with nitrogen, heated at 100 °C overnight, cooled, diluted
with ethyl acetate (25 mL), washed with water (2 x 5 mL), dried over magnesium sulfate,
filtered, concentrated, dissolved in 1:1 acetic acid:water (5 ml), filtered and purified by
reverse phase HPLC. Fractions containing the desired product were combined and
lyophilized to provide the tri-TFA salt of the title intermediate (100.3 mg) (*m/z*): [M+H]⁺
20 calcd for C₄₃H₅₅N₉O₆ 794.46 found 794.6.

- (b) [(*S*)-1-((*S*)-2-{4-[4-(5-{[6-((2*R*,5*S*)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-
carbonyl]- amino}-6-methyl-pyridin-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-
carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

The product of the previous step was treated with 4 M HCl in 1,4-dioxane (1 mL,
25 4.0 mmol) for 1 h and the reaction mixture was concentrated by rotary evaporation to give
the 4-HCl salt of the title intermediate (75 mg, 61 % yield). (*m/z*): [M+H]⁺ calcd for
C₃₈H₄₇N₉O₄ 694.38 found 694.6.

Preparation 60: [(S)-1-((S)-2-{4-[6-(4-Amino-2-trifluoromethoxy-phenyl)-pyridin-3-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



5 (a) 2-Bromo-1-(6-bromo-pyridin-3-yl)-ethanone

A solution of bromine (4 g, 25 mmol) in DCM (10 mL) was added drop wise over 5 min to a cooled (0 °C) solution of 1-(6-bromo-pyridin-3-yl)-ethanone (5 g, 25 mmol) and HBr (48%, 0.2 mL). The cooling bath was removed 40 min later and stirring was continued at RT for 66 h. The solid that formed was filtered, washed with DCM and
 10 dried at room temperature to give the impure title intermediate (8.1 g) as a yellow solid.
¹H NMR (CD₃OD, 400 MHz) δ (ppm): 8.96 (m, 1H), 8.28-8.25 (m, 1H), 7.82-7.79 (m, 1H), 4.7 (s, 2H).

(b) [(S)-1-{(S)-2-[4-(6-Bromo-pyridin-3-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl]-carbamic acid methyl ester

15 Following the general procedure of Preparation 29-A, substituting the product of step a (7.6 g) for 2-bromo-1-(4-bromo-3-methyl-phenyl)-ethanone, the title intermediate was prepared (3.5 g) as a yellow foam. ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 8.73-8.68 (m, 1H), 7.93-7.9 (m, 1H), 7.45-7.43 (m, 1H), 7.25 (s, 1H), 5.52-5.49 (m, 1H), 5.24-5.21 (m, 1H), 4.34-4.29 (m, 1H), 3.87-3.81 (m, 1H), 3.69 (s, 1H), 2.36-2.31 (m, 1H), 2.29-2.20
 20 (m, 1H), 2.19-2.07 (m, 1H), 1.98-1.92 (m, 1H), 1.08-1.01 (m, 1H), 0.92-0.81 (m, 6H).

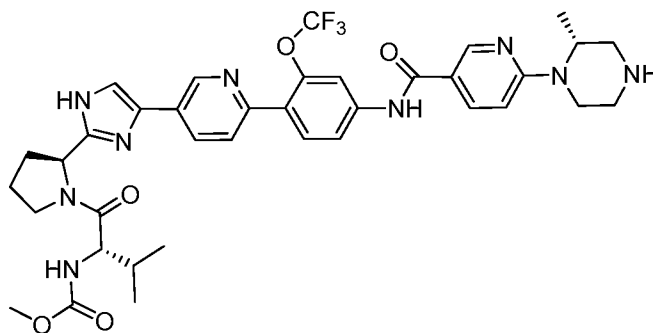
(c) [4-(5-{2-[(S)-1-((S)-2-Methoxycarbonylamino-3-methyl-butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-pyridin-2-yl)-3-trifluoromethoxy-phenyl]-carbamic acid *tert*-butyl ester

A mixture of the product of the previous step (469 mg, 1.04 mmol), [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-trifluoromethoxy-phenyl]-carbamic acid *tert*-
 25 butyl ester (420 mg, 1.04 mmol), Na₂CO₃ (331 mg, 3.12 mmol) and Pd(dppf)Cl₂ (50 mg) in dioxane (9 mL) and water (3 mL) was refluxed for 5 h. After filtration, the filtrate was concentrated under vacuum to give the crude product (700 m).

(d) [(*S*)-1-((*S*)-2-{4-[6-(4-Amino-2-trifluoromethoxy-phenyl)-pyridin-3-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

The product of the previous step (700 mg, 1.08 mmol) was dissolved in HCl/dioxane (10 mL) and the mixture was stirred at RT for 3 h. The mixture was concentrated under vacuum to give the residue, which was purified by preparative HPLC to give the title intermediate (140 mg, yield 24%). ¹H NMR (CD₃OD, 400 MHz) δ (ppm): 9.18 (s, 1H), 8.69-8.67 (m, 1H), 8.2-8.15 (m, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.02-6.98 (m, 2H), 5.26 (m, 1H), 4.23-4.21 (m, 1H), 4.09-4.05 (m, 1H), 3.9-3.88 (m, 1H), 3.65 (s, 3H), 2.64-2.5 (m, 1H), 2.38-2.0 (m, 4H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H).

10 **Preparation 61: [(*S*)-2-Methyl-1-((*S*)-2-{4-[6-(4-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2-trifluoromethoxy-phenyl)-pyridin-3-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester**

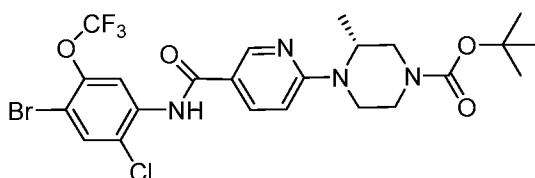


To a mixture of [(*S*)-1-((*S*)-2-{5-[6-(4-amino-2-trifluoromethoxy-phenyl)-pyridin-3-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester (140 mg, 0.26 mmol, Preparation 60) in DCM (2.56 mL) and DMA (0.25 mL) was added *N,N*-diisopropylethylamine (0.14 mL, 0.77 mmol) followed by 2-fluoropyridine-5-carbonyl chloride (40.9 mg, 0.26 mmol). The reaction mixture was stirred at RT for 1 h and concentrated.

20 The resulting residue was dissolved in DMSO (0.5 mL) and (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (128 mg, 0.64 mmol), *N,N*-diisopropylethylamine (0.11 mL, 0.64 mmol) was added and the resulting mixture was heated at 120 °C overnight. cooled to RT, and partitioned between EtOAc (10 mL) and water (2 mL). The organic layer was washed with water (2 mL), dried over sodium sulfate, filtered and concentrated to give a brownish oil, which was treated with 4 M of HCl in 1,4-dioxane (1 mL) at RT for 1 h. The reaction mixture was concentrated, dissolved in 1:1 acetic acid:water (7 mL), filtered and purified by reverse phase prep

HPLC to provide the tri-TFA salt of the title intermediate as a yellowish solid (57 mg, 20 % yield). (*m/z*): [M+H]⁺ calcd for C₃₇H₄₂F₃N₉O₅ 750.33 found 750.8.

Preparation 62: (*R*)-4-[5-(4-Bromo-2-chloro-5-trifluoromethoxy-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester



(a) 4-Bromo-2-chloro-5-trifluoromethoxy-phenylamine

To a mixture of 4-bromo-3-trifluoromethoxy-phenylamine (2.0 g, 7.8 mmol) in ACN (60 mL) was slowly added a solution of *N*-chlorosuccinimide (1.0 g, 7.8 mmol) in ACN (40 mL). The reaction mixture was heated at 60 °C overnight and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate and purified by flash chromatography (40 g column, 100% hexanes to 10% EtOAc: hexanes) to produce the desired product as an orange-ish colored oil (1.4 g, 64 % yield).

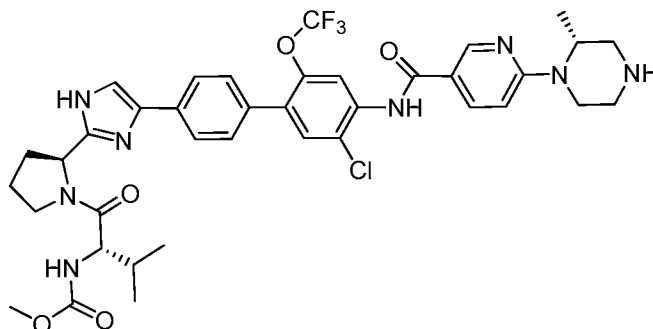
(b) *N*-(4-Bromo-2-chloro-5-trifluoromethoxy-phenyl)-6-fluoro-nicotinamide

To a solution of the product of the previous step (1.2 g, 4.1 mmol) in DCM (5 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (0.66 g, 4.1 mmol) in DCM (3 mL) and 20 drops of DMA were added. The reaction mixture was concentrated to form a yellowish solid (2 g). (*m/z*): [M+H]⁺ calcd for C₁₃H₆BrClF₄N₂O₂ 412.92, 414.92 found 413, 415.

(c) (*R*)-4-[5-(4-Bromo-2-chloro-5-trifluoromethoxy-phenylcarbamoyl)-pyridin-2-yl]-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester

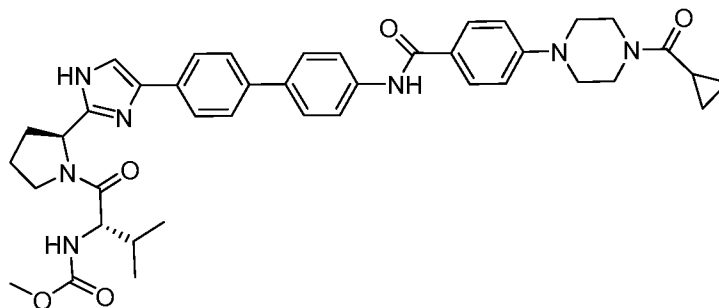
To a reaction mixture of the product of the previous step (999 mg, 2.42 mmol) in a mixture of *N,N*-diisopropylethylamine (0.84 mL, 4.83 mmol) and DMSO (0.86 mL, 12.08 mmol) was added (*R*)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (726 mg, 3.62 mmol) and the reaction mixture was heated at 120 °C overnight and extracted with ethyl acetate/water. The organic layer was dried over sodium sulfate and concentrated under vacuum. The dark oil was dissolved in a small amount of DCM and purified by silica gel chromatography (24 g column, 0-40% ethyl acetate:hexanes) to produce the title intermediate as a white solid (916 mg, 64 % yield). (*m/z*): [M+H]⁺ calcd for C₂₃H₂₅BrClF₃N₄O₄ 593.07, 595.07 found 595.4.

Preparation 63: ((S)-1-((S)-2-[4-(5'-Chloro-4'-{[6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



5 Following the procedure of Preparation 50, the product of Preparation 62 (534 mg, 0.9 mmol) was reacted to provide the tri-TFA salt of the title compound as a white powder (186 mg, ~18 % yield). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₂ClF₃N₈O₅ 783.29 found 784.3

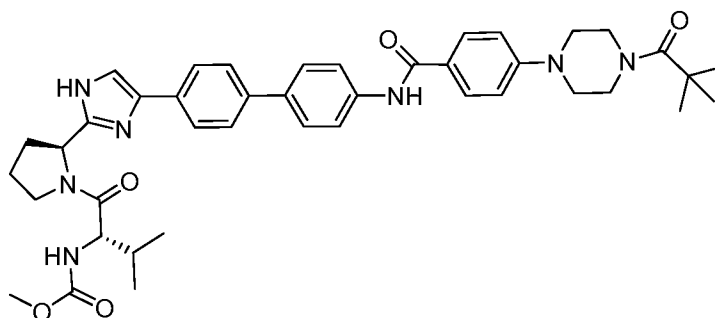
Example 1: ((S)-1-((S)-2-(4-{4'-[4-(4-Cyclopropanecarbonyl-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl};-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester



To a solution of 4-(4-cyclopropanecarbonyl-piperazin-1-yl)-benzoic acid (0.015 g, 0.055 mmol) in dichloromethane (2 mL, 30 mmol) were added *N,N*-dimethylformamide (0.004 mL, 0.055 mmol) and oxalyl chloride (0.014 mL, 0.164 mmol). The reaction mixture was stirred for 25 min and then *N,N*-diisopropylethylamine (0.048 mL, 0.273 mmol) was added, followed by ((S)-1-((S)-2-[4-(4'-amino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (0.025 g, 0.055 mmol). The reaction mixture was stirred for 90 min, dried by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (7.9 mg). (*m/z*): [M+H]⁺ calcd for C₄₁H₄₇N₇O₅ 718.36; found 718.2. ¹H NMR (*d*₆-DMSO, 400 MHz) δ

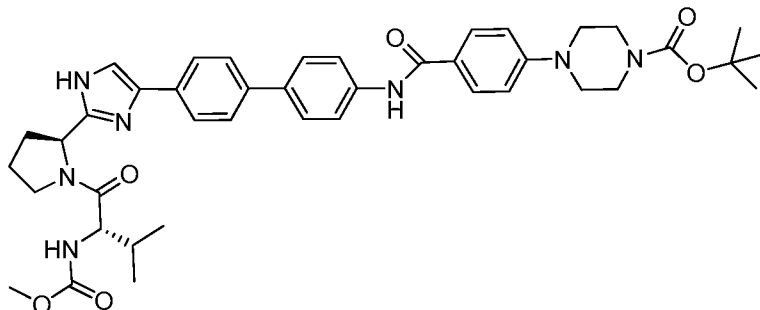
(ppm) 10.07 (s, 1H), 8.09 (s, 1H), 7.90 (dd, $J = 8.9, 2.1$ Hz, 4H), 7.83 (dd, $J = 18.2, 8.5$ Hz, 4H), 7.74 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.7$ Hz, 1H), 7.04 (d, $J = 9.1$ Hz, 2H), 5.11 (t, $J = 7.1$ Hz, 1H), 4.10 (t, $J = 7.9$ Hz, 1H), 3.96 – 3.55 (m, 9H), 3.53 (s, 3H), 3.42 – 3.22 (m, 4H), 2.45 – 2.28 (m, 1H), 2.20 – 1.92 (m, 5H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.80 – 0.69 (m, 6H).

Example 2: ((*S*)-1-((*S*)-2-[4-(4'-{4-[4-(2,2-Dimethyl-propionyl)-piperazin-1-yl]-benzoylamino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



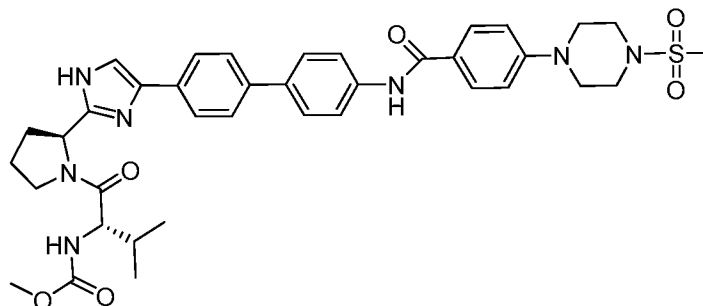
10 A reaction mixture of 4-[4-(2,2-dimethyl-propionyl)-piperazin-1-yl]-benzoic acid (10.3 mg, 0.036 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (8.17 mg, 0.043 mmol), 1-hydroxy-7-azabenzotriazole (6.77 mg, 0.050 mmol) in dichloromethane (0.3 mL, 4 mmol) was stirred to dissolution and for an additional 20 min. Then ((*S*)-1-((*S*)-2-[4-(4'-amino-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-
15 carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (8.2 mg, 0.018 mmol) and *N,N*-diisopropylethylamine (7.43 μ L, 0.0426 mmol) were added at room temperature. The reaction mixture was stirred overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the title compound as the trifluoroacetic acid salt (5.6 mg). (m/z): $[M+H]^+$ calcd for $C_{42}H_{51}N_7O_5$ 734.40 found
20 734.4.

Example 3: 4-[4-(4'-{2-[(S)-1-((S)-2-Methoxycarbonylamino-3-methylbutyryl)-pyrrolidin-2-yl]-1H-imidazol-4-yl}-biphenyl-4-ylcarbamoyl)-phenyl]-piperazine-1-carboxylic acid tert-butyl ester



5 To a solution of 4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid (24.7 mg, 0.081 mmol) in dichloromethane (0.89 mL, 14 mmol) and *N,N*-dimethylformamide (0.4 mL, 6 mmol) was added *N,N*-diisopropylethylamine (0.071 mL, 0.407 mmol) and methyl chloroformate (0.006 mL, 0.081 mmol). The reaction mixture was stirred for 15 min at room temperature, then ((*S*)-1-{(S)-2-[4-(4'-amino-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (25.0 mg, 0.054 mmol) was added and the mixture was allowed to stir overnight. The reaction mixture was concentrated and then dissolved in DCM (5 mL) and washed with saturated aqueous sodium bicarbonate (2 mL). The organic layer was concentrated. Approximately 15 mg of the crude material was concentrated, dissolved in 1:1 acetic acid: water (1.5 mL), and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (7.3 mg). (*m/z*): [M+H]⁺ calcd for C₄₂H₅₁N₇O₆ 750.39 found 750.4.

Example 4: {(S)-1-[(S)-2-(4-{4'-[4-(4-Methanesulfonyl-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

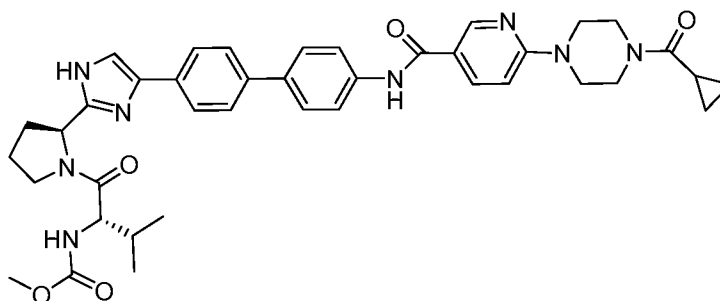


20

Methanesulfonyl chloride (1.19 mg, 0.015 mmol) was added to a solution of [(*S*)-2-methyl-1-((*S*)-2-{4-[4'-(4-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl]-1*H*-

imidazol-2-yl]-pyrrolidine-1-carbonyl]-propyl]-carbamic acid methyl ester (10.0 mg, 0.015 mmol) in dichloromethane (0.75 mL, 12 mmol), *N,N*-dimethylacetamide (0.75 mL, 8.1 mmol) and triethylamine (25 uL, 0.18 mmol). The reaction mixture was stirred for 15 min at room temperature, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL) and then purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (12.3 mg). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₅N₇O₆S 728.32 found 728.2.

Example 5: ((*S*)-1-((*S*)-2-[4-(4'-[6-(4-Cyclopropanecarbonyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



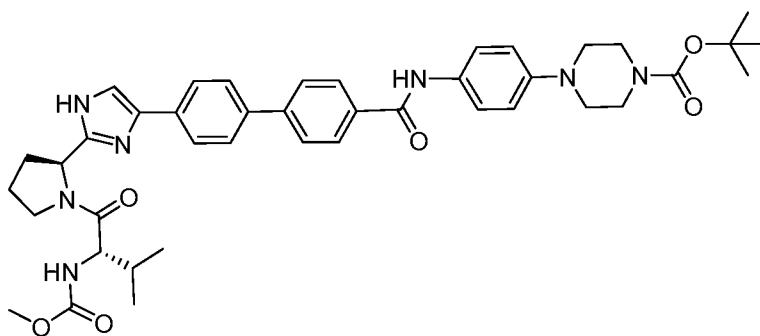
(a) {(*S*)-2-Methyl-1-[(*S*)-2-(4-{4'-[(6-piperazin-1-yl-pyridine-3-carbonyl)-amino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester

Oxalyl chloride (44.0 uL, 0.520 mmol) was added to a solution of 4-(5-carboxypyridin-2-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (70.3 mg, 0.229 mmol) in dichloromethane (6.67 mL, 104 mmol) and *N,N*-dimethylformamide (2.01 uL, 0.026 mmol). The reaction mixture was stirred at room temperature for 20 min and then *N,N*-diisopropylethylamine (0.181 mL, 1.04 mmol) was added followed by ((*S*)-1-((*S*)-2-[4-(4'-amino-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (100.0 mg, 0.217 mmol). The reaction mixture was stirred for 2 h at room temperature, then dried by rotary evaporation. The crude material was dissolved in dichloromethane (1 mL) and then washed with saturated aqueous sodium bicarbonate (1 mL). The organic layer was concentrated, dissolved in 4.0 M hydrogen chloride in 1,4-dioxane (6.7 mL, 27 mmol) and stirred for 1 h at room temperature until completely deprotected. The reaction mixture was concentrated and used directly in the next step.

(b) ((S)-1-((S)-2-[4-(4'-{[6-(4-Cyclopropanecarbonyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

Cyclopropanecarboxylic acid (26.86 mg, 0.312 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (59.81 mg, 0.312 mmol), and 1-hydroxy-7-azabenzotriazole (42.46 mg, 0.312 mmol) were dissolved in *N,N*-dimethylacetamide (3.868 mL, 41.60 mmol) and stirred for 5 min. Then half of the material from the previous step was added to the reaction mixture followed by *N,N*-diisopropylethylamine (0.269 g, 2.080 mmol). The reaction mixture was stirred overnight at room temperature, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (39.9 mg). (*m/z*): [M+H]⁺ calcd for C₄₀H₄₆N₈O₅ 719.36 found 719.2. ¹H NMR (*d*₆-DMSO, 400 MHz) δ (ppm) 10.14 (s, 1H), 8.77 (d, *J* = 2.5 Hz, 1H), 8.12 (dd, *J* = 9.7, 3.1 Hz, 2H), 7.95 – 7.78 (m, 6H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 9.3 Hz, 1H), 5.15 – 5.07 (m, 1H), 4.15 – 4.05 (m, 1H), 3.90 – 3.55 (m, 11H), 3.53 (s, 3H), 2.28 – 2.40 (m, 1H), 2.23 – 1.87 (m, 5H), 0.75 – 0.85 (m, 3H), 0.79 – 0.63 (m, 6H).

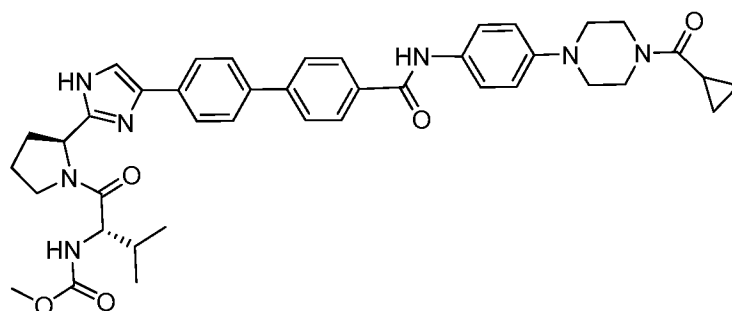
Example 6: 4-{4-[(4'-{2-[(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methyl-buteryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl]-biphenyl-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester



A mixture of 4'-{2-[(*S*)-1-((*S*)-2-methoxycarbonylamino-3-methyl-buteryl)-pyrrolidin-2-yl]-3*H*-imidazol-4-yl}-biphenyl-4-carboxylic acid (15.0 mg, 0.031 mmol) and *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (11.6 mg, 0.031 mmol) in *N,N*-dimethylformamide (0.5 mL, 6 mmol) was added to 4-(4-aminophenyl)piperazine-1-carboxylic acid *tert*-butyl ester (28.2 mg, 0.102 mmol) followed by *N,N*-diisopropylethylamine (10.6 μL, 0.061 mmol). The reaction mixture was stirred at RT overnight, concentrated, dissolved in 1:1 acetic acid: water (1.5 mL),

filtered and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (26.2 mg). (*m/z*): [M+H]⁺ calcd for C₄₂H₅₁N₇O₆ 750.39 found 750.4.

Example 7 {(S)-1-[(S)-2-(4-{4'-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-phenylcarbamoyl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



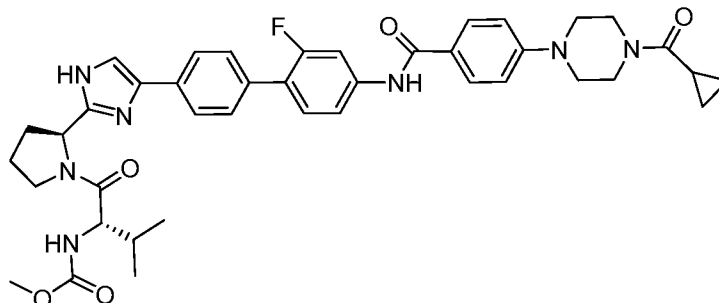
(a) [(S)-2-Methyl-1-((S)-2-{4-[4'-(4-piperazin-1-yl)-phenylcarbamoyl]-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester

To a solution of [4-{4'-[(4'-{2-[(S)-1-((S)-2-methoxycarbonylamino-3-methyl-
10 butyryl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-biphenyl-4-carbonyl)-amino]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (42.4 mg, 0.0565 mmol) in dichloromethane (0.67 mL, 10 mmol) was added trifluoroacetic acid (0.3 mL, 0.004 mmol). The reaction mixture was stirred for 1 h at room temperature, concentrated, dissolved in methanol (1 mL), passed through a Stratospheres™ PL-CO₃ resin, and the filtrate was concentrated
15 to provide the title compound. (*m/z*): [M+H]⁺ calcd for C₃₇H₄₃N₇O₄ 650.34 found 650.8.

(b) {(S)-1-[(S)-2-(4-{4'-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-phenylcarbamoyl]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester

Cyclopropanecarboxylic acid (7.30 mg, 0.085 mmol), *N*-(3-
20 dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (21.6 mg, 0.113 mmol), and 1-hydroxy-7-azabenzotriazole (15.4 mg, 0.113 mmol) were combined with dichloromethane (0.8 mL, 10 mmol), stirred to dissolution and then stirred for an additional 20 min. To the reaction mixture was added a solution of the product of the previous step in 1:1 dichloromethane: *N,N*-diisopropylethylamine (0.5 mL, 3 mmol) at
25 room temperature. The resulting reaction mixture was stirred at RT overnight, concentrated under vacuum, dissolved in 1:1 acetic acid: water (1.5 mL), filtered and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (8.2 mg). (*m/z*): [M+H]⁺ calcd for C₄₁H₄₇N₇O₅ 718.36 found 718.4.

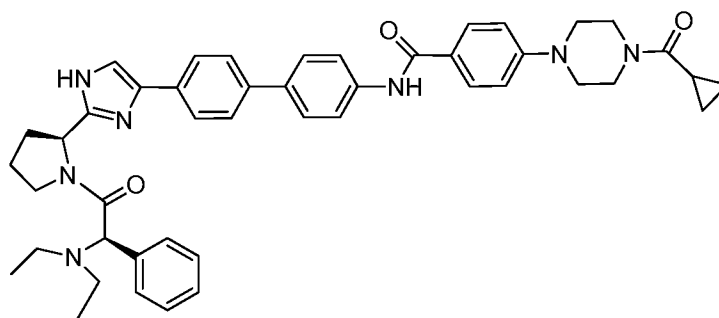
Example 8 $\{(S)\text{-}1\text{-}[(S)\text{-}2\text{-}(4\text{-}\{4'\text{-}[4\text{-}(4\text{-cyclopropanecarbonyl-piperazin-1-yl)-benzoylamino]-2'\text{-fluoro-biphenyl-4-yl}\}\text{-}1H\text{-imidazol-2-yl})\text{-pyrrolidine-1-carbonyl}]\text{-}2\text{-methyl-propyl}\}\text{-carbamic acid methyl ester}$



5

To a solution of 4-(4-cyclopropanecarbonyl-piperazin-1-yl)-benzoic acid (13 mg, 0.047 mmol) in dichloromethane (1.0 mL, 16 mmol) and one drop of *N,N*-dimethylformamide was added oxalyl chloride (0.0119 mL, 0.141 mmol). The reaction mixture was stirred for 25 min and then *N,N*-diisopropylethylamine (0.027 mL, 10 0.16 mmol) was added, followed by $\{(S)\text{-}1\text{-}\{(S)\text{-}2\text{-}[4\text{-}(4'\text{-amino-biphenyl-4-yl})\text{-}1H\text{-imidazol-2-yl})\text{-pyrrolidine-1-carbonyl}\}\text{-}2\text{-methyl-propyl}\}\text{-carbamic acid methyl ester}$ (15 mg, 0.031 mmol). The reaction mixture was stirred overnight, concentrated under vacuum, dissolved in 1:1 acetic acid:water and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (1.9 mg). (*m/z*): $[M+H]^+$ calcd for 15 $C_{41}H_{46}FN_7O_5$ 735.85; found 736.4.

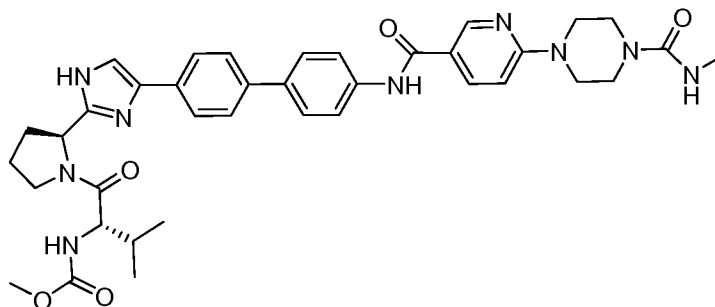
Example 9 $4\text{-}(4\text{-Cyclopropanecarbonyl-piperazin-1-yl})\text{-N}\text{-}(4'\text{-}\{2\text{-}[(S)\text{-}1\text{-}((R)\text{-}2\text{-diethylamino-2-phenyl-acetyl})\text{-pyrrolidin-2-yl}]\text{-}1H\text{-imidazol-4-yl}\}\text{-biphenyl-4-yl})\text{-benzamide}$



20 A combination of (*R*)-diethylamino-phenyl-acetic acid (6.654 mg, 0.032 mmol) *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (6.154 mg, 0.032 mmol) and 1-hydroxy-7-azabenzotriazole (4.370 mg, 0.032 mmol) in *N,N*-dimethylacetamide

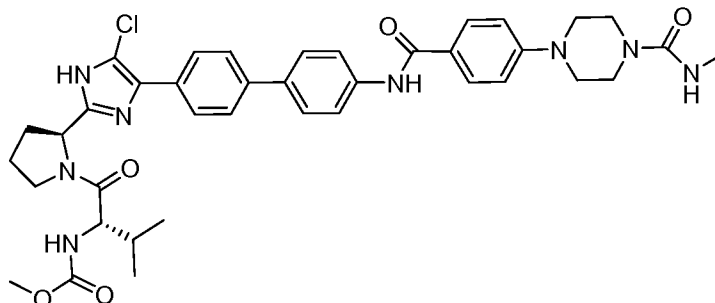
(0.498 mL, 5.350 mmol) was stirred to dissolution and then for an additional 20 min. 4-(4-Cyclopropanecarbonyl-piperazin-1-yl)-*N*-[4'-((*S*)-2-pyrrolidin-2-yl-1*H*-imidazol-4-yl)-biphenyl-4-yl]-benzamide (15 mg, 0.027 mmol) and *N,N*-diisopropylethylamine (0.023 mL, 0.134 mmol) were added to the reaction mixture which was stirred at room temperature overnight. The reaction mixture was then concentrated and dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound to provide the title compound (6.4 mg). (*m/z*): [M+H]⁺ calcd for C₄₆H₅₁N₇O₃ 750.41; found 750.4.

Example 10 ((*S*)-2-Methyl-1-((*S*)-2-[4-(4'-{[6-(4-methylcarbamoyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester



Half of the crude material from Example 5 step (a) was dissolved in *N,N*-dimethylformamide (3.22 mL, 41.6 mmol) and *N,N*-diisopropylethylamine (36.2 uL, 0.208 mmol) and then methyl isocyanate (12.36 uL, 0.208 mmol) was added. The reaction mixture was stirred overnight at room temperature, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (35.7 mg). (*m/z*): [M+H]⁺ calcd for C₃₈H₄₅N₉O₅ 708.35 found 708.2. ¹H NMR (*d*₆-DMSO, 400 MHz) δ (ppm) 10.13 (s, 1H), 8.75 (d, *J* = 2.6 Hz, 1H), 8.11 (dd, *J* = 8.5, 3.0 Hz, 2H), 7.91 - 7.79 (m, 6H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 1H), 6.95 (d, *J* = 9.1 Hz, 1H), 6.52 (br. s, 1H), 5.15 - 5.03 (m, 1H), 4.10 (t, *J* = 7.9 Hz, 1H), 3.90 - 3.75 (m, 3H), 3.66 - 3.55 (m, 4H), 3.56 - 3.50 (m, 3H), 3.42 - 3.34 (m, 3H), 2.58 (s, 3H), 1.90 - 2.25 (m, 1H), 2.18 - 1.89 (m, 4H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H).

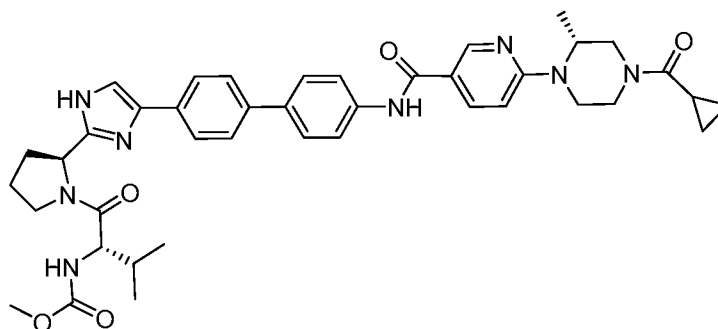
Example 11: {(S)-1-[(S)-2-(5-Chloro-4-{4'-[4-(4-methylcarbamoyl-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester



5 The TFA-salt of {(S)-2-methyl-1-[(S)-2-(4-{4'-[4-(4-methylcarbamoyl-piperazin-1-yl)-benzoylamino]-biphenyl-4-yl}-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-propyl}-carbamic acid methyl ester (22.0 mg, 0.0311 mmol) was dissolved in methanol (5 mL) and treated with Stratospheres™ PL-CO₃ resin and stirred for 15 min. The reaction mixture was filtered and the filtrate was concentrated. This crude material was dissolved

10 in *N,N*-dimethylformamide (1.5 mL, 19 mmol) and then *N*-chlorosuccinimide (6.23 mg, 0.0467 mmol) was added. The reaction mixture was heated at 50 °C and stirred overnight at 50 °C, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the trifluoroacetic acid salt of the title compound (4.5 mg). (*m/z*): [M+H]⁺ calcd for C₃₉H₄₅ClN₈O₅ 741.32 found 741.5.

15 **Example 12 ((S)-1-[(S)-2-[4-(4'-{[6-((*R*)-4-Cyclopropanecarbonyl-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl]-2-methyl-propyl)-carbamic acid methyl ester**



(a) ((S)-2-Methyl-1-((S)-2-[4-(4'-{[6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester

A mixture of the hydrochloride salt of ((S)-1-[(S)-2-(5-{4'-[(6-fluoro-pyridine-3-carbonyl)-amino]-biphenyl-4-yl}-1H-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester (728.1 mg, 1.17 mmol) [Reactant A] and (R)-3-methyl-piperazine-1-carboxylic acid *tert*-butyl ester (0.352 g, 1.76 mmol) [Reactant B] in dimethyl sulfoxide (3.7 mL) and *N,N*-diisopropylethylamine (1.23 mL, 7.03 mmol) was heated at 120 °C overnight. The reaction mixture was cooled to RT and water (5.0 mL) was added. The resulting mixture was centrifuged and filtered. The solid was combined with the product from a previous reaction in which Reactant A (237.8 mg, 0.383 mmol) was reacted with Reactant B (115.0 mg, 0.574 mmol) under the same conditions. The combined solids were dissolved in 1:1 acetic acid:water (20 mL), filtered, and split into three equal portions which were purified separately by reverse phase preparative HPLC. Desired fractions were combined and freeze dried to give a white solid. (805.5 mg total).

To the product of the previous step was added 4.0 M hydrogen chloride in 1,4-dioxane (6.0 mL, 24 mmol) and the reaction mixture was stirred at RT for 30 min, and then concentrated. The residue was coevaporated with ethyl acetate (3 x 5.0 mL) and dried under vacuum to give the tri-hydrochloride salt of the title intermediate as a light yellowish solid (655.9 mg).

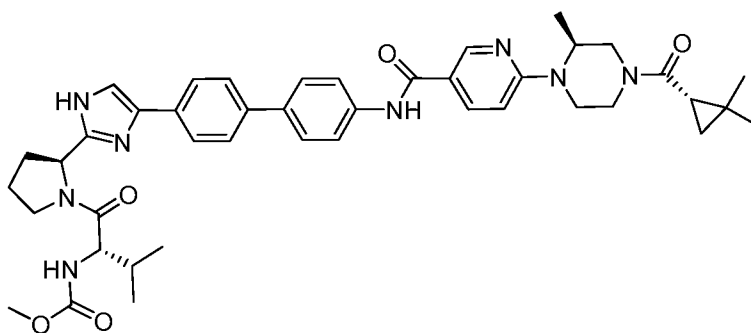
(b) ((S)-1-((S)-2-[4-(4'-{[6-((R)-4-Cyclopropanecarbonyl-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

Material from the previous step (350 mg) was dissolved in *N,N*-dimethylacetamide (2.7 mL, 29 mmol) at RT and *N,N*-diisopropylethylamine (0.52 mL, 3.0 mmol) was added followed by cyclopropanecarbonyl chloride (0.041 mL, 0.45 mmol). The reaction mixture was stirred for 10 min and additional acid chloride was added to consume all the starting material. The reaction mixture was concentrated and the residue was dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC. Desired fractions were combined and freeze dried to give a white solid.

The white solid was dissolved in ethanol (15.0 mL) at RT and 4.0 M hydrogen chloride in 1,4-dioxane (6.0 mL) was added. The reaction mixture was stirred for 10 min, and concentrated. The residue was dissolved in 1:1 acetic acid:water (8 mL), filtered, and purified by reverse phase preparative HPLC. Desired fractions were combined and freeze

dried to give the trifluoroacetic acid salt of the title compound as a white solid (194.6 mg) (m/z): $[M+H]^+$ calcd for $C_{41}H_{48}N_8O_5$ 733.38 found 733.5. 1H NMR (CD_3OD , 400 MHz) δ (ppm): 8.65 (s, 1H), 8.08-8.10 (dd, 1H, $J=10$, 4), 7.67-7.77 (m, 7H), 7.60-7.62 (m, 2H), 6.86-6.88 (d, 1H, $J=8$), 5.13-5.17 (t, 1H, $J=15.2$), 4.52-4.56 & 4.64-4.68 (m, total 1H), 3.99-4.37 (m, 5H), 3.74-3.80 (m, 1H), 3.56 (s, 3H), 2.96-3.00 & 3.13-3.23 & 3.38-3.60 (m, total 3H), 2.45-2.52 (m, 1H), 1.91-2.20 (m, 4H), 1.09-1.18 (m, 4H), 0.76-0.90 (m, 10H).

Example 13 [(*S*)-1-((*S*)-2-{4-[4'-({6-[(*S*)-4-((*S*)-2,2-Dimethyl-cyclopropane-carbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



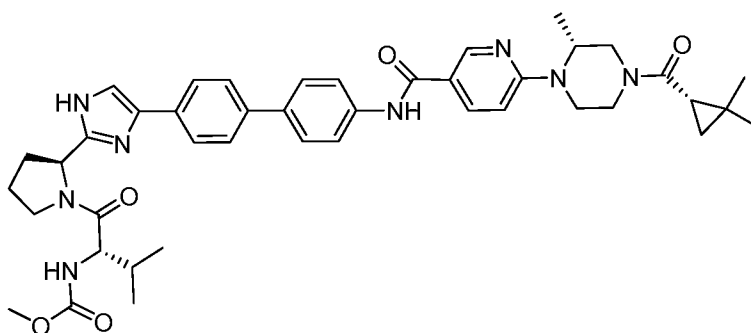
To a mixture of the TFA salt of ((*S*)-2-methyl-1-{{(*S*)-2-[4-(4'-{6-((*S*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester (320.0 mg, 0.318 mmol, Preparation 16) and (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid (39.9 mg, 0.350 mmol) in *N,N*-dimethylformamide (30.0 mL, 387.4 mmol) at RT was added *N,N,N',N'*-tetramethyl-*O*-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (0.133 g, 0.350 mmol) followed by *N,N*-diisopropylethylamine (0.277 mL, 1.589 mmol).

The reaction mixture was diluted with water (40.0 mL) and extracted with ethyl acetate (2 x 20.0 mL). Combined organic layers were washed with water (20.0 mL) and brine (20.0 mL), dried over sodium sulfate, filtered and concentrated to give a yellowish oil. The residue was dissolved in 1:1 acetic acid:water (8 mL), filtered and purified by reverse phase preparative HPLC. Desired fractions were combined and freeze dried.. Material was repurified by reverse phase preparative HPLC.. Desired fractions were combined and freeze dried to give the trifluoroacetic acid salt of the title compound as a white solid. (205.1 mg). (m/z): $[M+H]^+$ calcd for $C_{43}H_{52}N_8O_5$ 761.42 found 761.7. 1H NMR (CD_3OD , 400 MHz) δ (ppm): 8.65 (s, 1H), 8.12-8.15 (m, 1H), 7.67-7.77 (m,

7H), 7.6-7.62 (m, 2H), 6.94-6.96 (d, 1H, J=8), 5.13-5.17 (t, 1H, J=16), 4.56-4.65 (m, 1H), 4.33-4.36 (m, 1H), 3.99-4.25 (m, 4H), 3.75-3.81 (m, 1H), 3.56 (s, 3H), 3.4-3.53 (m, 1H), 3.24-3.3 (m, 1H), 2.95-3.11 (m, 1H), 2.45-2.52 (m, 1H), 1.93-2.21 (m, 4H), 1.65-1.71 (m, 1H), 1.16-1.24 (m, 4H), 1.00-1.09 (m, 4H), 0.79-0.93 (m, 8H), 0.68-0.71 (m, 1H).

5

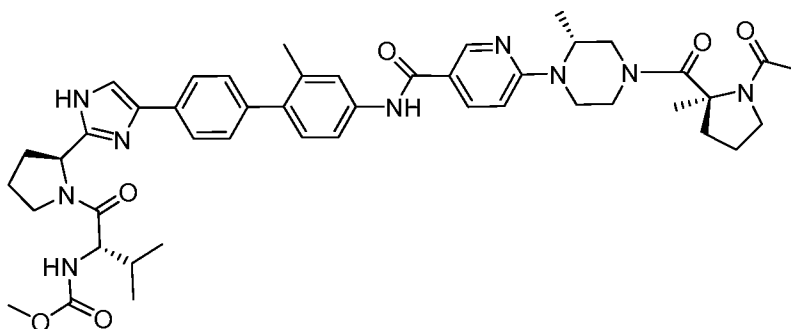
Example 14 [(*S*)-1-((*S*)-2-{4-[4'-({6-[(*R*)-4-((*S*)-2,2-Dimethyl-cyclopropane-carbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl]-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



10

To a mixture of the hydrochloride salt of ((*S*)-2-methyl-1-((*S*)-2-[4-(4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-propyl)-carbamic acid methyl ester (60.0 mg, 0.0775 mmol) and (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid (10.6 mg, 0.093 mmol) in *N,N*-
 15 dimethylformamide (1.5 mL, 19 mmol) at RT was added *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (35.4 mg, 0.093 mmol) and *N,N*-diisopropylethylamine (54.0 uL, 0.310 mmol). The reaction mixture was stirred at RT overnight, and then concentrated. The residue was redissolved in 1:1 acetic acid:water (6 mL), filtered and purified by reverse phase preparative HPLC. Desired fractions were
 20 combined and freeze dried to give a white solid 34.1 mg. (*m/z*): [M+H]⁺ calcd for C₄₃H₅₂N₈O₅ 761.42 found 761.7. ¹H NMR (CD₃OD, 400 MHz) δ (ppm): 8.76 (s, 1H), 8.18-8.20 (m, 1H), 7.76-7.86 (m, 7H), 7.68-7.7 (m, 2H), 6.95-6.99 (m, 1H), 5.22-5.26 (t, 1H, J=16), 4.59-4.73 (m, 1H), 4.03-4.38 (m, 5H), 3.82-3.89 (m, 1H), 3.69-3.74 (m, 1H), 3.65 (s, 3H), 3.12-3.2 & 3.3-3.5 (m, total 2H), 2.53-2.6 (m, 1H), 2.0-2.3 (m, 4H), 1.75-
 25 1.78 & 1.82-1.85 (m, total 1H), 1.25 (s, 3H), 1.12 (s, 3H), 1.07-1.1 & 1.14-1.17 (m, total 1H), 0.96 (s, 3H), 0.88-0.96 & 1.21-1.27 (m, total 6H), 0.76-0.8 (m, 1H).

Example 15 [(*S*)-1-((*S*)-2-{5-[4'-({6-[(*R*)-4-((*S*)-1-Acetyl-2-methyl-pyrrolidine-2-carbonyl) 2-methyl-piperazin-1-yl]-pyridine-3-carbonyl]-amino)-2'-methyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



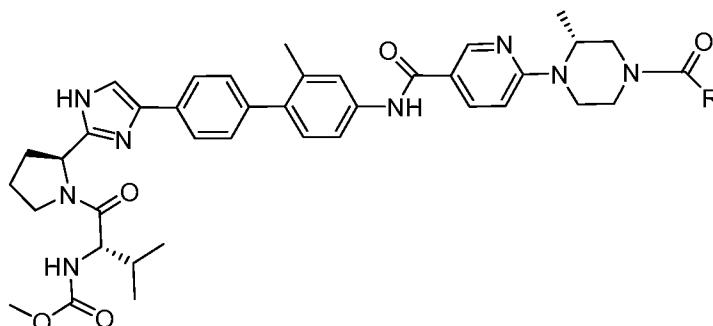
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
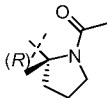
To a solution of [((*S*)-2-methyl-1-{(*S*)-2-[5-(2'-methyl-4'-{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-propyl)-carbamic acid methyl ester tri-HCl (15 mg, 0.019 mmol; Preparation 18) and *N,N*-diisopropylethylamine (33.1 μ L, 0.190 mmol) dissolved in DMA (0.6 mL, 7 mmol) was added (*S*)-1-acetyl-2-methyl-pyrrolidine-2-carboxylic acid (3.2 mg, 0.019 mmol, Preparation 19) and HATU (11 mg, 0.028 mmol). The reaction mixture was stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (4 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (9.1 mg). (*m/z*): [M+H]⁺ calcd for C₄₆H₅₇N₉O₆ 832.44 found 832.4.

15

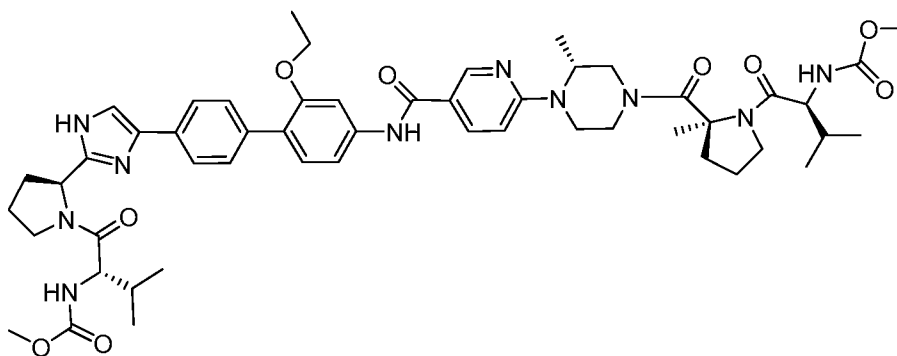
Examples 16-20

Following the procedure of Example 15, the intermediate of Preparation 19 (20 mg, 0.02 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
16		0.5 M (S)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (38 uL, 0.019 mmol) HATU (11 mg, 0.028)	2 TFA salt (11.4 mg) (m/z): [M+H] ⁺ calcd for C ₄₄ H ₅₄ N ₈ O ₅ 775.42 found 775.4
17		cyclopropanecarbonyl chloride (1.7 uL, 0.019 mmol)	2 TFA salt (16.3 mg) (m/z): [M+H] ⁺ calcd for C ₄₂ H ₅₀ N ₈ O ₅ 747.39 found 747.4
18	NHCH ₃	1 M methyl isocyanate in toluene (19 uL, 0.019 mmol)	2 TFA salt (14.8 mg) (m/z): [M+H] ⁺ calcd for C ₄₀ H ₄₉ N ₉ O ₅ 736.39 found 736.4
19		imidazol-4-carboxylic acid (2.1 mg, 0.019 mmol), EDC (5.5 mg, 0.028 mmol), and HOAt (3.9 mg, 0.028 mmol)	3 TFA salt (7.6 mg) (m/z): [M+H] ⁺ calcd for C ₄₂ H ₄₈ N ₁₀ O ₅ 773.38 found 773.4
20		(R)-1-acetyl-2-methyl-pyrrolidine-2-carboxylic acid (3.2 mg, 0.019 mmol) HATU (11 mg, 0.028 mmol).	2 TFA salt (12.1 mg) (m/z): [M+H] ⁺ calcd for C ₄₆ H ₅₇ N ₉ O ₆ 832.44 found 832.4

Example 21 [(S)-1-((S)-2-[4-(2'-Ethoxy-4'-{6-[(R)-4-((S)-1-((S)-2-methoxycarbonylamino-3-methyl-butyl)-2-methyl-pyrrolidine-2-carbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl)-amino]-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

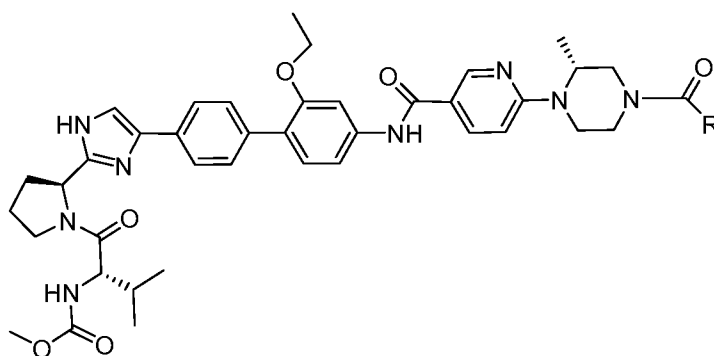


The tri-TFA salt of (S)-1-((S)-2-[4-(2'-ethoxy-4'-{6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (30 mg, 0.03 mmol; Preparation 22) was dissolved in DMA (1.0 mL, 11 mmol) and *N,N*-diisopropylethylamine (0.015 mL, 0.086 mmol) was added followed by a solution containing 0.5 M (S)-1-((S)-2-methoxycarbonylamino-3-methyl-butyl)-2-methyl-pyrrolidine-2-carboxylic acid in

DMA (68.5 uL, 0.034 mmol) and HATU (13.0 mg, 0.034 mmol). The reaction mixture was stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (13.5 mg). (*m/z*): [M+H]⁺ calcd for C₅₂H₆₈N₁₀O₉ 977.52 found 977.6.

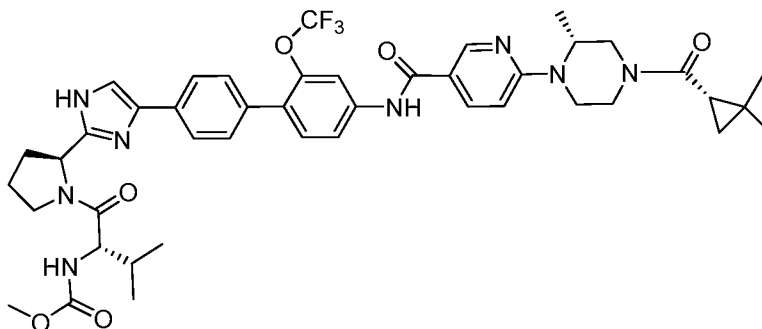
5 Examples 22-24

Following the procedure of Example 21, the intermediate of Preparation 22 (30 mg, 0.03 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
22		0.5 M (<i>S</i>)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (69.5 uL, 0.034 mmol), HATU (13 mg, 0.034)	2 TFA salt (23.8 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₅ H ₅₆ N ₈ O ₆ 805.43 found 805.4
23	NHCH ₃	1 M methyl isocyanate in toluene(34.2 μL, 0.034 mmol)	2 TFA salt (26.2 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₁ H ₅₁ N ₉ O ₆ 766.40 found 766.4
24		imidazol-4-carboxylic acid (3.84 mg, 0.034 mmol), HATU (13 mg, 0.034)	3 TFA salt (24 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₅₀ N ₁₀ O ₆ 803.39 found 803.4

Example 25 [(*S*)-1-((*S*)-2-{5-[4'-({6-[(*R*)-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-2'-trifluoromethoxy-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



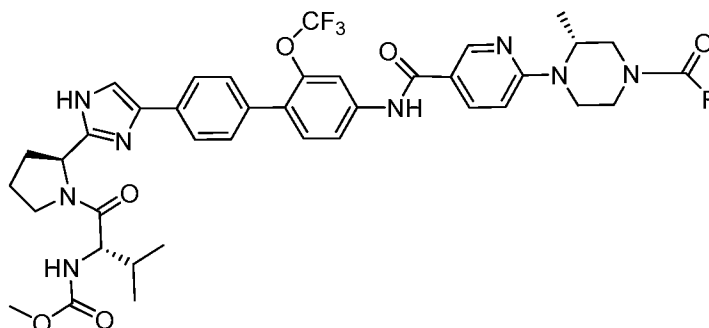
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

To a solution of ((*S*)-2-methyl-1-{{(*S*)-2-[4-(4'-{{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-2'-trifluoromethoxy-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-propyl)-carbamic acid methyl ester 3[C₂HF₃O₂] (15 mg, 0.014 mmol; Preparation 24) and *N,N*-diisopropylethylamine (24 uL, 0.14 mmol) dissolved in DMA (0.5 mL, 5 mmol) was added 0.5 M (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (28 uL, 0.014 mmol) and HATU (7.8 mg, 0.021 mmol). The reaction mixture was stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (11.4 mg). (*m/z*): [M+H]⁺ calcd for C₄₄H₅₁F₃N₈O₆ 845.39 found 845.4.

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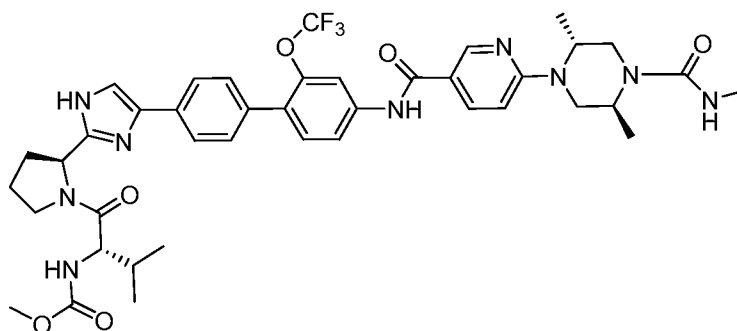
Examples 26-28

Following the procedure of Example 25, the intermediate of Preparation 24 (15 mg, 0.014 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
26	NHCH ₃	1 M methyl isocyanate in toluene (14 uL, 0.014 mmol)	2 TFA salt (11.7 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₀ H ₄₆ F ₃ N ₉ O ₆ 806.35 found 806.4
27		imidazol-4-carboxylic acid (1.5 mg, 0.014 mmol), EDC (4.0 mg, 0.021 mmol), and HOAt (2.8 mg, 0.021 mmol)	3 TFA salt (14.2 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₂ H ₄₅ F ₃ N ₁₀ O ₆ 843.35 found 843.2
28		cyclopropanecarbonyl chloride (1.2 uL, 0.014 mmol)	2 TFA salt (8.8 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₂ H ₄₇ F ₃ N ₈ O ₆ 817.36 found 817.2

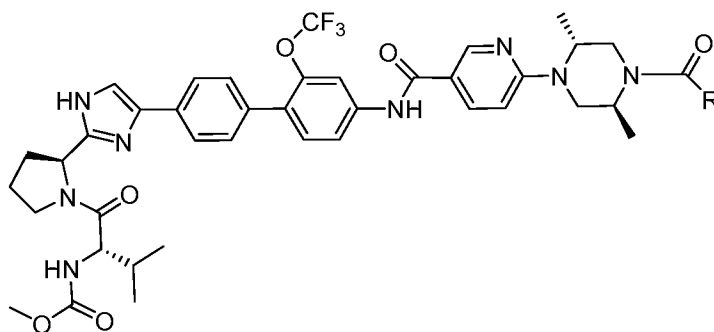
Example 29 ((*S*)-1-((*S*)-2-[4-(4'-{[6-((2*R*,5*S*)-2,5-Dimethyl-4-methylcarbamoyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester



To a solution of ((*S*)-1-((*S*)-2-[4-(4'-{[6-((2*R*,5*S*)-2,5-dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester tri-TFA (11.4 mg, 0.011 mmol; Preparation 28) and *N,N*-diisopropylethylamine (18 uL, 0.11 mmol) dissolved in DMA (0.4 mL, 4 mmol) was added 1.0 M methyl isocyanate in toluene (10 uL, 0.01 mmol). The reaction mixture was stirred at RT overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (7.1 mg). (*m/z*): [M+H]⁺ calcd for C₄₁H₄₈F₃N₉O₆ 820.37 found 820.5.

Examples 30-33

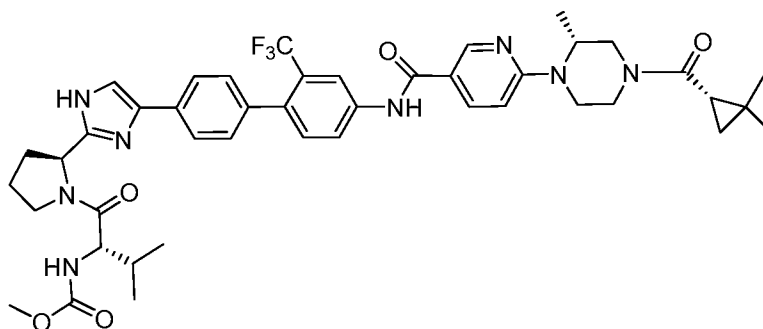
Following the procedure of Example 29, the intermediate of Preparation 28 (11.4 mg, 0.011 mmol) was reacted with the appropriate reagents to provide the following compounds:



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Ex. No.	R	Reagent	Product
30		cyclopropanecarbonyl chloride (0.94 uL, 0.01 mmol)	2 TFA salt (9.7 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₄₉ F ₃ N ₈ O ₆ 831.37 found 831.2
31		0.5 M (<i>S</i>)-2-methyl-pyrrolidine-1,2-dicarboxylic acid 1-methyl ester in DMA (20.6 uL, 0.0103 mmol) HATU (5.9 mg, 0.0215 mmol).	2 TFA salt (2.9 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₇ H ₅₆ F ₃ N ₉ O ₈ 932.42 found 932.4
32		imidazol-4-carboxylic acid (2.1 mg, 0.019 mmol), EDC (3 mg, 0.015 mmol), and HOAt (2.1 mg, 0.015 mmol)	3 TFA salt (12.2 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₄₇ F ₃ N ₁₀ O ₆ 857.36 found 857.2
33		0.5 M (<i>S</i>)-(+)-2,2-dimethyl-cyclopropane carboxylic acid in DMA (21 uL, 0.010 mmol) HATU (5.9 mg, 0.015)	2 TFA salt (8.2 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₅ H ₅₃ F ₃ N ₈ O ₅ 859.40 found 859.4

Example 34 [(*S*)-1-((*S*)-2-{5-[4'-({6-[(*R*)-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-2'-trifluoromethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



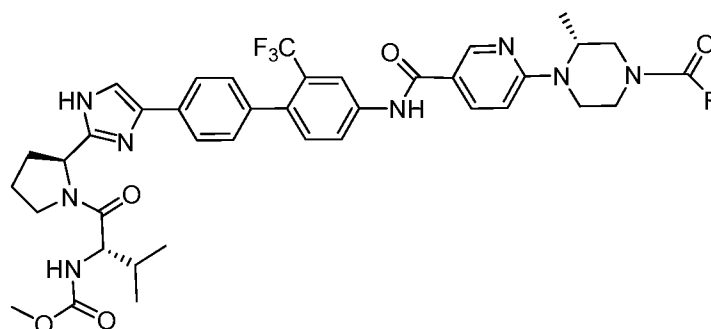
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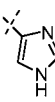
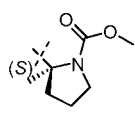
To a solution of ((*S*)-2-methyl-1-((*S*)-2-[4-(4'-{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-2'-trifluoromethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-propyl)-carbamic acid methyl ester tri-TFA (17 mg, 0.016 mmol; Preparation 25) and *N,N*-diisopropylethylamine (27.5 uL, 0.158 mmol) dissolved in DMA (0.5 mL, 6 mmol) was added 0.5 M (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (32 uL, 0.016 mmol) and HATU (9 mg, 0.024 mmol). The reaction mixture was stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (8.3 mg). (*m/z*): [M+H]⁺ calcd for C₄₄H₅₁F₃N₈O₅ 829.39 found 829.4.

15

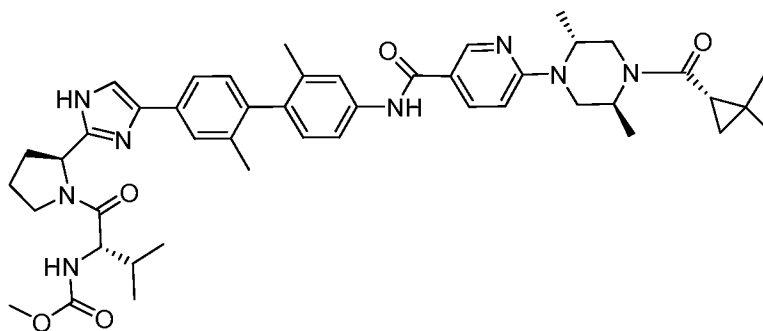
Examples 35-38

Following the procedure of Example 34, the intermediate of Preparation 25 (17 mg, 0.016 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
35		cyclopropanecarbonyl chloride (1.4 uL, 0.016 mmol)	2 TFA salt (14.1 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₂ H ₄₇ F ₃ N ₈ O ₅ 801.36 found 801.2
36	NHCH ₃	1.0 M methyl isocyanate in toluene(16 uL, 0.016 mmol)	2 TFA salt (12.3 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₀ H ₄₆ F ₃ N ₉ O ₅ 790.36 found 790.2
37		imidazol-4-carboxylic acid (2 mg, 0.02 mmol), EDC (4.5 mg, 0.024 mmol), and HOAt (3.2 mg, 0.024 mmol)	3 TFA salt (14.4 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₂ H ₄₅ F ₃ N ₁₀ O ₅ 827.36 found 827.2
38		0.5 M (<i>S</i>)-2-methyl-pyrrolidine- 1,2-dicarboxylic acid 1-methyl ester in DMA (31.6 uL, 0.016 mmol) HATU (9 mg, 0.024 mmol).	2 TFA salt (6.8 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₆ H ₅₄ F ₃ N ₉ O ₇ 902.41 found 902.4

Example 39 [(*S*)-1-((*S*)-2-{4-[4'-({6-[(*2R,5S*)-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2,5-dimethyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-2,2'-dimethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]- carbamic acid methyl ester



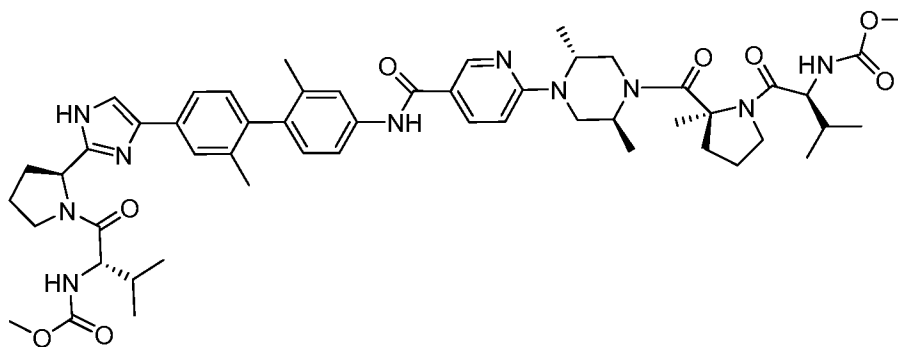
To a mixture of (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid (2.39 mg, 0.021 mmol) and ((*S*)-1-((*S*)-2-[4-(4'-{[6-((*2R,5S*)-2,5-dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-2,2'-dimethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester tri-TFA (20 mg, 0.019 mmol, Preparation 30) in DMF (0.5 mL, 6 mmol) at RT was added HATU (7.98 mg, 0.021 mmol) followed by *N,N*-diisopropylethylamine (16.60 uL, 0.095 mmol). The reaction mixture was stirred at RT overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL), filtered, and purified by preparative HPLC to provide the di-TFA

salt of the title compound (15 mg).

(*m/z*): [M+H]⁺ calcd for C₄₆H₅₈N₈O₅ 803.45 found 803.4.

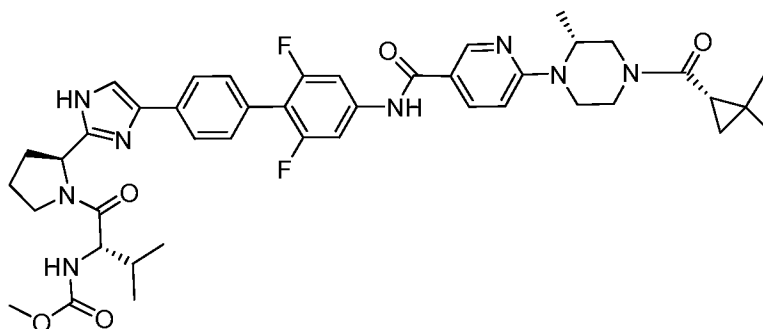
Example 40

Following the procedure of Example 39, the intermediate of Preparation 30
 5 (20 mg, 0.019 mmol) was reacted with (*S*)-1-((*S*)-2-methoxycarbonylamino-3-methyl-
 butyryl)-2-methyl-pyrrolidine-2-carboxylic acid (6 mg, 0.021 mmol) to provide the di-
 TFA salt of the following compound (6 mg) (*m/z*): [M+H]⁺ calcd for C₅₃H₇₀N₁₀O₈ 975.45
 found 975.6.



10

Example 41 [(*S*)-1-((*S*)-2-{5-[4'-({6-[(*R*)-4-((*S*)-2,2-Dimethyl-
 cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-2',6'-
 difluoro-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-
 carbamic acid methyl ester



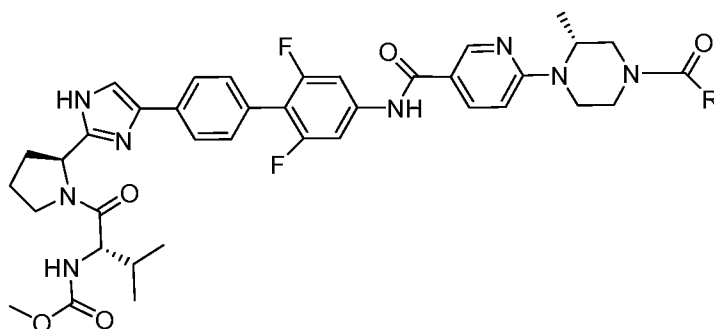
15

To a solution of ((*S*)-1-((*S*)-2-[4-(2',6'-difluoro-4'-{[6-((*R*)-2-methyl-piperazin-1-
 yl)-pyridine-3-carbonyl]-amino}-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-
 carbonyl)-2-methyl-propyl)-carbamic acid methyl ester tri-TFA (20 mg, 0.02 mmol;
 Preparation 32) and *N,N*-diisopropylethylamine (33.4 uL, 0.192 mmol) dissolved in DMA
 20 (0.6 mL, 7 mmol) was added 0.5 M (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid in
 DMA (38 uL, 0.019 mmol) and HATU (11 mg, 0.029 mmol). The reaction mixture was

stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (10.1 mg). (*m/z*): [M+H]⁺ calcd for C₄₃H₅₀F₂N₈O₅ 797.39 found 797.4.

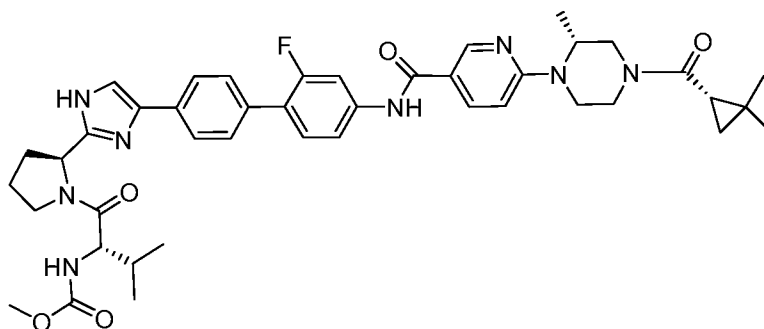
Examples 42-44

- 5 Following the procedure of Example 41, the intermediate of Preparation 32 (20 mg, 0.02 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
42		cyclopropanecarbonyl chloride (1.7 uL, 0.019 mmol)	2 TFA salt (7.2 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₁ H ₄₄ F ₂ N ₈ O ₅ 769.36 found 769.2
43	NHCH ₃	1 M methyl isocyanate in toluene (19 uL, 0.19 mmol)	2 TFA salt (4.1 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₃₉ H ₄₅ F ₂ N ₉ O ₅ 758.35 found 758.4
44		imidazol-4-carboxylic acid (2.1 mg, 0.019 mmol), EDC (5.5 mg, 0.029 mmol), and HOAt (3.9 mg, 0.029 mmol)	3 TFA salt (5.1 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₁ H ₄₄ F ₂ N ₁₀ O ₅ 795.35 found 795.2

Example 45 [(S)-1-((S)-2-{5-[4'-({6-[(R)-4-((S)-2,2-Dimethyl-cyclopropanecarbonyl)- 2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-2'-fluoro-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



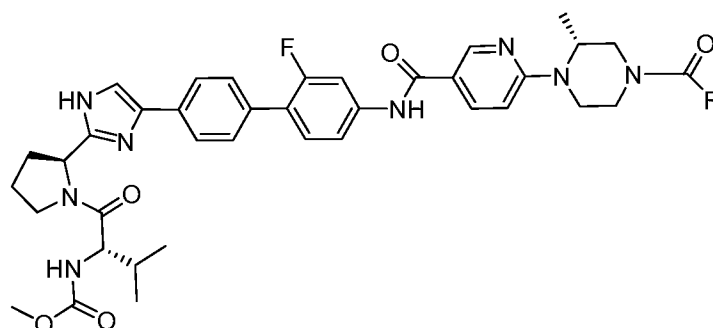
5



To a solution of ((S)-1-((S)-2-[4-(2'-fluoro-4'-{[6-((R)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester 3[C₂HF₃O₂] (15 mg, 0.015 mmol; Preparation 35) and *N,N*-diisopropylethylamine (25.5 uL, 0.146 mmol) dissolved in DMA (0.5 mL, 5 mmol) was added 0.5 M (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (29 uL, 0.015 mmol) and HATU (8.3 mg, 0.022 mmol). The reaction mixture was stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (9.5 mg). (*m/z*): [M+H]⁺ calcd for C₄₃H₅₁FN₈O₅ 779.40 found 779.4.

15

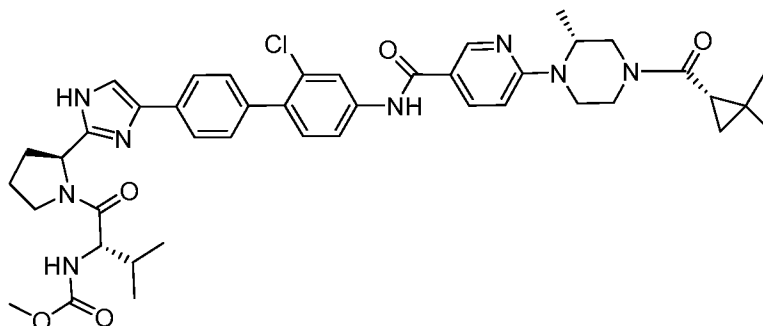
Examples 46-48

Following the procedure of Example 45, the intermediate of Preparation 35 (15 mg, 0.015 mmol) was reacted with the appropriate reagents to provide the following compounds:



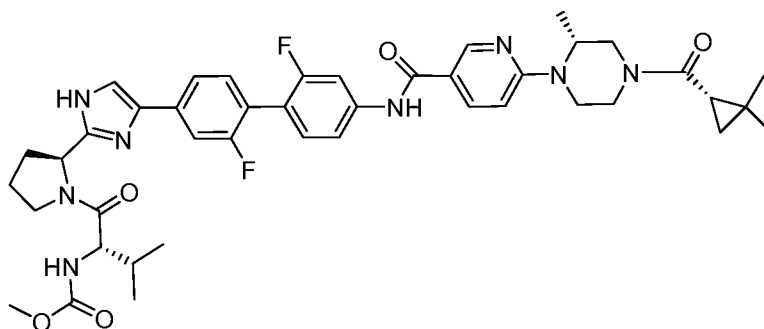
Ex. No.	R	Reagent	Product
46		cyclopropanecarbonyl chloride (1.3 uL, 0.015 mmol)	2 TFA salt (12 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₁ H ₄₇ FN ₈ O ₅ 751.37 found 751.2
47	NHCH ₃	1 M methyl isocyanate in toluene (15 uL, 0.15 mmol)	2 TFA salt (10.9 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₃₉ H ₄₆ FN ₉ O ₅ 740.36 found 740.4
48		imidazol-4-carboxylic acid (1.6 mg, 0.015 mmol), EDC (4.2 mg, 0.022 mmol), and HOAt (3.0 mg, 0.022 mmol)	3 TFA salt (10.7 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₁ H ₄₅ FN ₁₀ O ₅ 777.36 found 777.2

Example 49 [(*S*)-1-((*S*)-2-{4-[2'-Chloro-4'-({6-[(*R*)-4-((*S*)-2,2-dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



A mixture of 6-[(*R*)-4-((*S*)-2,2-dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-nicotinic acid (4.54 mg, 0.014 mmol; Preparation 36), HCTU (8.0 mg, 0.019 mmol), *N,N*-diisopropylethylamine (0.013 mL, 0.072 mmol), and DMA (0.2 mL, 2 mmol) was stirred for 30 min at 50 °C and then ((*S*)-1-((*S*)-2-[4-(4'-amino-2'-chloro-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (7.1 mg, 0.014 mmol; Preparation 37) was added. The reaction mixture was stirred overnight and then HCTU (8 mg) was added and the reaction mixture was heated to 55 °C. After 5 h, the reaction mixture was cooled to RT, ethyl acetate and water were added. The organic layer was concentrated under vacuum and purified by preparative HPLC to provide the di-TFA salt of the title compound (1.3 mg). (*m/z*): [M+H]⁺ calcd for C₄₃H₅₁ClN₈O₅ 795.37 found 795.4.

Example 50 [(*S*)-1-((*S*)-2-{4-[4'-({6-[(*R*)-4-((*S*)-2,2-dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-2,2'-difluoro-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



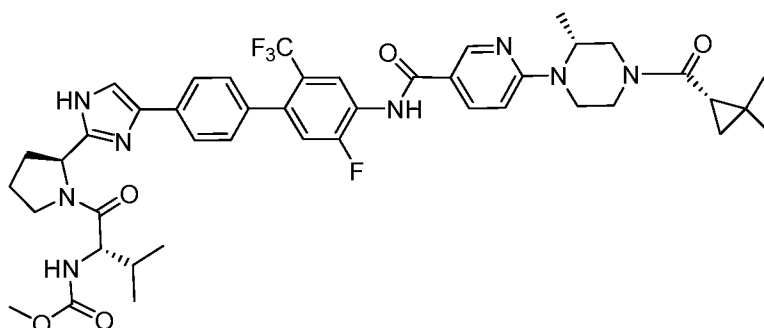
5

To a solution of 6-[(*R*)-4-((*S*)-2,2-dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-nicotinic acid (6.4 mg, 0.020 mmol; Preparation 36) was added EDC (5.8 mg, 0.030 mmol) and HOAt (4.2 mg, 0.030 mmol) in DMA (0.5 mL, 5 mmol). The reaction mixture was stirred at RT for 30 min and then ((*S*)-1-((*S*)-2-[4-(4'-amino-2,2'-difluoro-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester (10 mg, 0.02 mmol; Preparation 38-B) and *N,N*-diisopropylethylamine (18 μ L, 0.10 mmol) were added and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by reverse phase HPLC to provide the di-TFA salt of the title compound (6.8 mg). (*m/z*): [M+H]⁺ calcd for C₄₃H₅₀F₂N₈O₅ 797.39 found 797.4.

15

Example 51 [(*S*)-1-((*S*)-2-{4-[4'-({6-[(*R*)-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-5'-fluoro-2'-trifluoromethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester

20



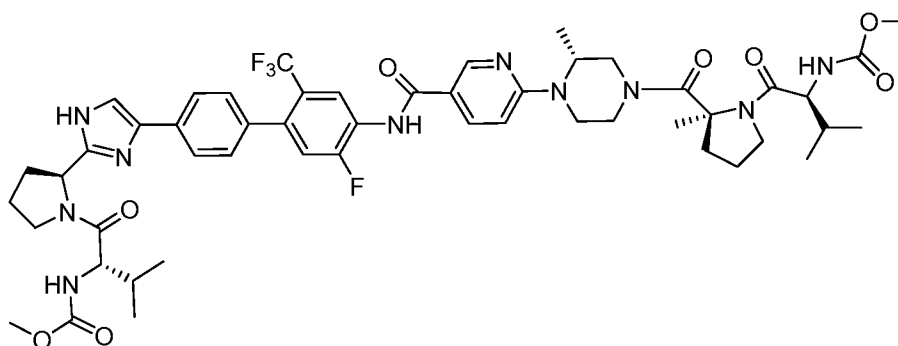
A mixture of (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid (2.09 mg, 0.018 mmol) and HATU (8.35 mg, 0.022 mmol) was stirred in DMA (1.0 mL, 11 mmol) for 10 min. and then ((*S*)-1-{(*S*)-2-[4-(5'-fluoro-4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethyl-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester tri-TFA (20.0 mg, 0.018 mmol, Preparation 41) and *N,N*-diisopropylethylamine (15.94 μ L, 0.091 mmol) were added. The reaction mixture was stirred at RT overnight, concentrated by rotary evaporation, dissolved in 1:1 acetic acid:water (1.5 mL), filtered, and purified by preparative HPLC to provide the di-TFA salt of the title compound (4.8 mg). (*m/z*):

10 $[M+H]^+$ calcd for $C_{44}H_{50}F_4N_8O_5$, 847.38 found 847.4.

Example 52

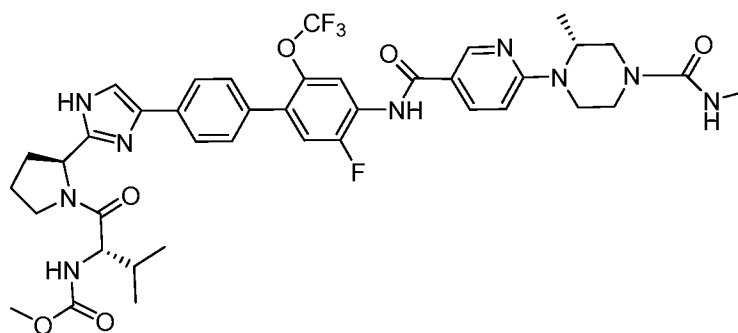
Following the procedure of Example 51, the intermediate of Preparation 41 (20 mg, 0.019 mmol) was reacted with (*S*)-1-((*S*)-2-methoxycarbonylamino-3-methyl-butyl)-2-methyl-pyrrolidine-2-carboxylic acid (5.24 mg, 0.018 mmol) to provide the

15 di-TFA salt of the following compound (2.8 mg) (*m/z*): $[M+H]^+$ calcd for $C_{51}H_{62}F_4N_{10}O_8$, 1019.47 found 1019.4.



Example 53 ((*S*)-1-{(*S*)-2-[4-(5'-Fluoro-4'-{[6-((*R*)-2-methyl-4-methylcarbamoyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

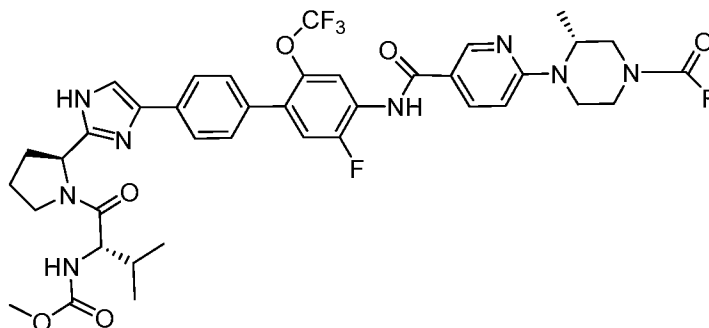
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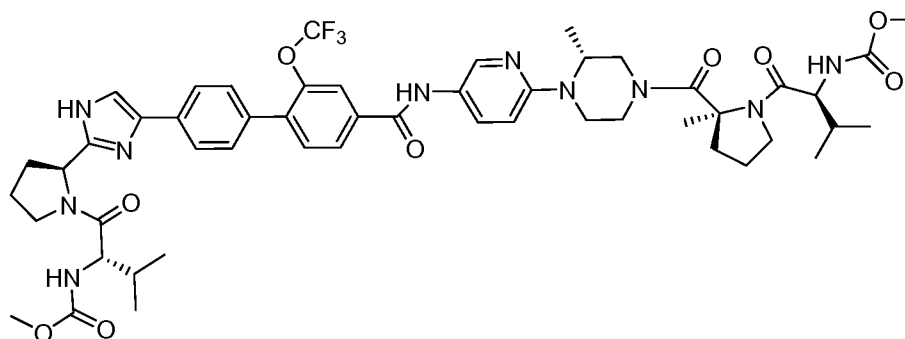
To a solution of 1.0 M methyl isocyanate in toluene (11.4 uL, 0.011 mmol) dissolved in DMA (0.5 mL), was added ((*S*)-1-((*S*)-2-[4-(5'-fluoro-4'-[[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester tri-TFA (12.7 mg, 0.011 mmol; Preparation 44) and *N,N*-diisopropylethylamine (19.9 uL, 0.114 mmol) and the reaction mixture was stirred at room temperature overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by preparative HPLC to provide the di-TFA salt of the title compound (7.7 mg). (*m/z*): [M+H]⁺ calcd for C₄₀H₄₈F₄N₉O₆ 824.34 found 824.4.

10 Examples 54-55

Following the procedure of Example 53, the intermediate of Preparation 44 (12.7 mg, 0.011 mmol) was reacted with the appropriate reagents to provide the following compounds:

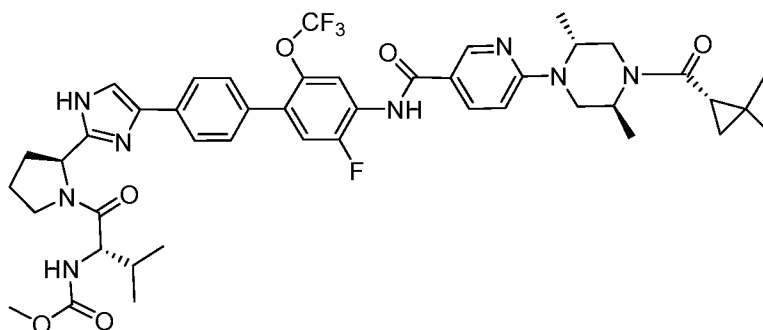


Ex. No.	R	Reagent	Product
54		0.5 M (<i>S</i>)-(+)-2,2-dimethyl-cyclopropane carboxylic acid in DMA (22.9 uL, 0.011 mmol) HATU (6.5 mg, 0.017)	2 TFA salt (11.8 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₄ H ₅₀ F ₄ N ₈ O ₆ 863.38 found 863.4
55		(<i>S</i>)-1-((<i>S</i>)-2-methoxycarbonyl-amino-3-methyl-butyl)-2-methyl-pyrrolidine-2-carboxylic acid (3.27 mg, 0.011 mmol) HATU (6.5 mg, 0.017)	2 TFA salt (6.7 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₅₁ H ₆₂ F ₄ N ₁₀ O ₉ 1,035.46 found 1035.4

Example 56

To a mixture of 4'-{2-[(*S*)-1-((*S*)-2-methoxycarbonylamino-3-methyl-butyl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-trifluoromethoxy-biphenyl-4-carboxylic acid TFA
 5 (23.0 mg, 0.033 mmol; Preparation 46) and ((*S*)-1-{(*S*)-2-[(*R*)-4-(5-amino-pyridin-2-yl)-3-methyl-piperazine-1-carbonyl]-2-methyl-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (15.4 mg, 0.033 mmol; Preparation 48) in DMF (0.5 mL) at RT was added HATU (14.0 mg, 0.037 mmol) and *N,N*-diisopropylethylamine (29.1 μ L, 0.167 mmol). The resulting mixture was stirred at RT for 2 h, and then partitioned
 10 between EtOAc (10 mL) and water (2 mL). The organic layer was washed with water (2 mL), dried over sodium sulfate, filtered and concentrated to give a brownish oil. The residue was dissolved in 1:1 acetic acid:water (1.5 mL), filtered and purified by reverse phase HPLC. Desired fractions were combined and freeze dried to give the di-TFA salt of the title compound (9.1 mg, 22 % yield) as a light pinkish solid. (*m/z*): [M+H]⁺ calcd for
 15 C₅₁H₆₃F₃N₁₀O₉ 1,017.47 found 1017.9.

Example 57 [(*S*)-1-((*S*)-2-{4-[4'-{(6-[(*2R*),5*S*]-4-((*S*)-2,2-Dimethyl-cyclopropanecarbonyl)-2,5-dimethyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-5'-fluoro-2'-trifluoromethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



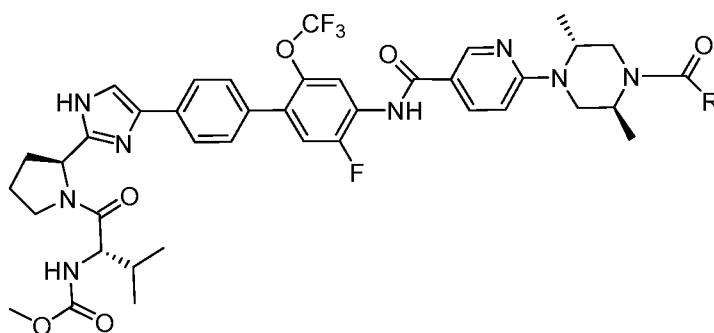
20

To a solution of ((*S*)-1-{(*S*)-2-[4-(4'-{[6-((*2R*),5*S*)-2,5-dimethyl-piperazin-1-yl]-pyridine-3-carbonyl]-amino)-5'-fluoro-2'-trifluoromethoxy-biphenyl-4-yl]-1*H*-imidazol-

2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester 3-TFA(15 mg, 0.013 mmol; Preparation 50) and N,N-diisopropylethylamine (23 uL, 0.13 mmol) dissolved in DMA (0.5 mL, 5 mmol;) was added 0.5 M (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (27 μ L, 0.013 mmol) and HATU (7.6 mg, 0.020 mmol). The
 5 reaction mixture was stirred at 50 °C for 2 h, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by reverse phase HPLC to provide the title compound (9.1 mg) as the di-TFA salt. (*m/z*): [M+H]⁺ calcd for C₄₅H₅₂F₄N₈O₆ 877.39 found 878.0.

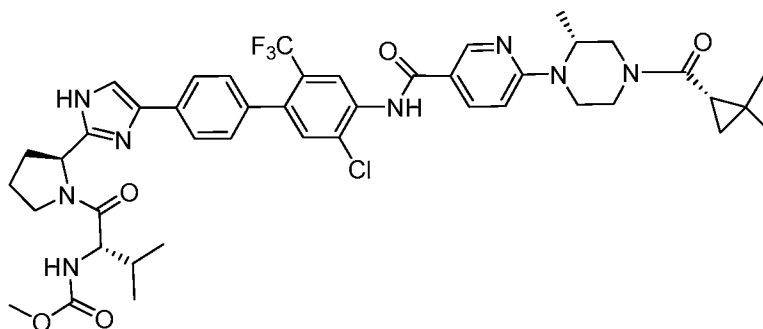
Examples 58-60

Following the procedure of Example 57, the intermediate of Preparation 50
 10 (15 mg, 0.013 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
58	NHCH ₃	1 M methyl isocyanate in toluene (13 uL, 0.013 mmol)	2 TFA salt (4.5 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₁ H ₄₇ F ₄ N ₉ O ₆ 838.36 found 839.0
59		imidazol-4-carboxylic acid (1.5 mg, 0.013 mmol), HATU (7.6 mg, 0.020mmol)	3 TFA salt (6.6 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₄₆ F ₄ N ₁₀ O ₆ 875.35 found 876.0
60		4-pyrazolecarboxylic acid (1.5 mg, 0.013 mmol) HATU (7.6 mg, 0.020mmol)	3 TFA salt (6.7 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₄₆ F ₄ N ₁₀ O ₆ 875.35 found 876.0

Example 61 [(*S*)-1-((*S*)-2-[4-[5'-Chloro-4'-({6-[(*R*)-4-((*S*)-2,2-dimethylcyclopropanecarbonyl)-2-methyl-piperazin-1-yl]-pyridine-3-carbonyl]-amino)-2'-trifluoromethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester



5

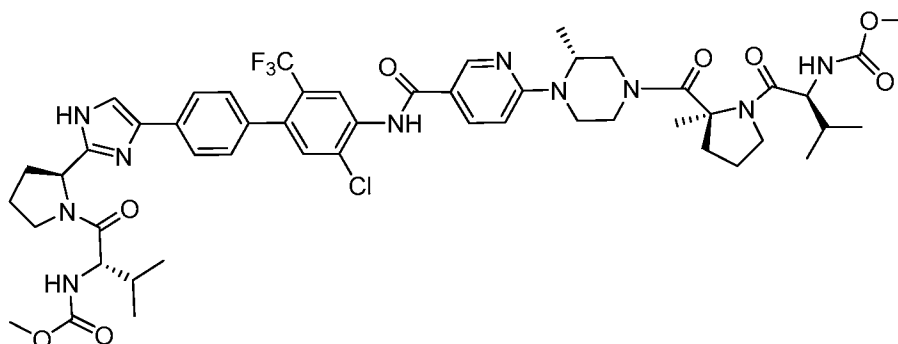
To a solution of 0.5 M (*S*)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (28.9 μ L, 0.015 mmol); and HATU (8.25 mg, 0.022 mmol) dissolved in DMA (0.5 mL), was added ((*S*)-1-((*S*)-2-[4-(5'-Chloro-4'-{6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino)-2'-trifluoromethyl-biphenyl-4-yl]-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-2-methyl-propyl)-carbamic acid methyl ester 3 TFA (16 mg, 0.014 mmol; Preparation 53) and *N,N*-diisopropylethylamine (25.2 μ L, 0.15 mmol) and the reaction mixture was stirred at RT overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by reverse phase HPLC to provide the title compound (8.6 mg) as the di-TFA salt. (*m/z*): [M+H]⁺ calcd for C₄₄H₅₀ClF₃N₈O₅ 863.35 found 863.4.

15

Example 62

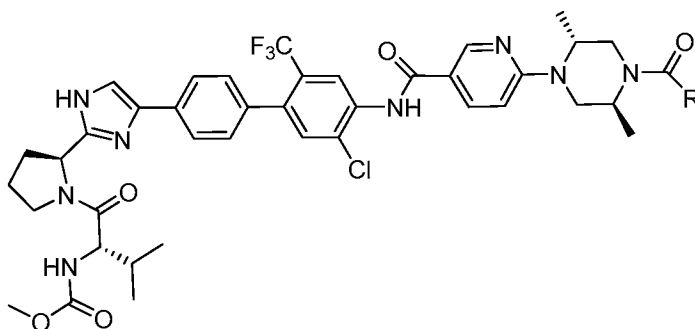
Following the procedure of Example 61 the intermediate of Preparation 53 (16 mg, 0.014 mmol) was reacted with (*S*)-1-((*S*)-2-methoxycarbonylamino-3-methylbutyryl)-2-methyl-pyrrolidine-2-carboxylic acid (4.14 mg, 0.015 mmol) to provide the di-TFA salt of the following compound (6.5 mg) (*m/z*): [M+H]⁺ calcd for C₅₁H₆₂ClF₃N₁₀O₈ 1,035.44 found 1035.4.

20



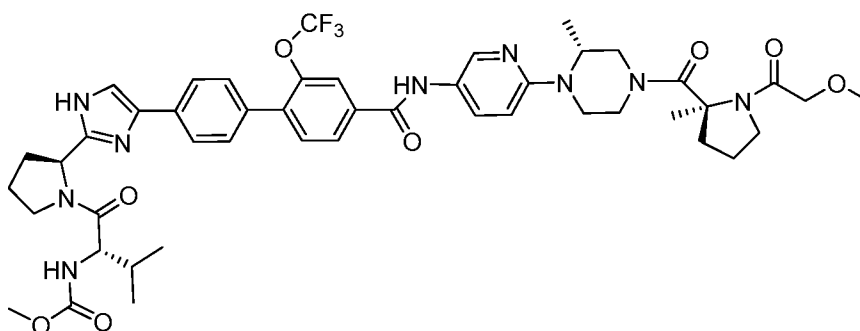
Example 63-65

Following the procedure of Example 57, substituting the intermediate of Preparation 55 (15 mg, 0.013 mmol) for the intermediate of Preparation 50 (15 mg, 0.013 mmol), the following compounds were prepared



5

Ex. No.	R	Reagent	Product
63		0.5 M (S)-(+)-2,2-dimethylcyclopropane carboxylic acid in DMA (27 μ L, 0.013 mmol) HATU (7.6 mg, 0.02)	2 TFA salt (14.6 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₅ H ₅₂ ClF ₃ N ₈ O ₅ 877.37 found 878.0
64	NHCH ₃	1 M methyl isocyanate in toluene (13 μ L, 0.013 mmol)	2 TFA salt (15.3 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₄₆ ClF ₃ N ₁₀ O ₅ 875.33 found 876.0
65		imidazol-4-carboxylic acid (1.5 mg, 0.013 mmol), HATU (7.6 mg, 0.020mmol)	3 TFA salt (15.3 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₃ H ₄₆ ClF ₃ N ₁₀ O ₅ 875.33 found 876.0

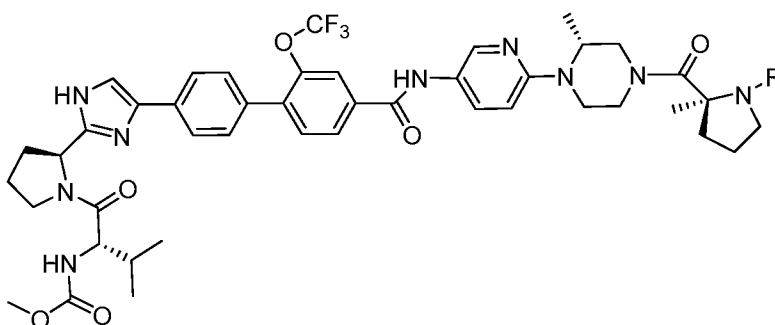
Example 66:

Methoxyacetic acid (1.14 μL , 0.014 mmol) was dissolved in DMA (1 mL) and HATU (5.65 mg, 0.015 mmol) was added. The reaction mixture was stirred at RT for 15 min and then ((*S*)-2-methyl-1-((*S*)-2-[4-(4'-{6-[(*R*)-2-methyl-4-((*S*)-2-methyl-pyrrolidine-2-carbonyl)-piperazin-1-yl]-pyridin-3-ylcarbonyl}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl)-propyl)-carbamic acid methyl ester 3 HCl (12.0 mg, 0.012 mmol; Preparation 57) was added followed by *N,N*-diisopropylethylamine (10.8 μL , 0.062 mmol) and the reaction mixture was stirred at 55 $^{\circ}\text{C}$ overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by reverse phase HPLC to provide the di-TFA salt of the title compound (8.3 mg) (*m/z*):

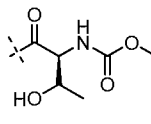
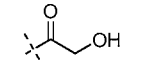
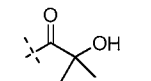
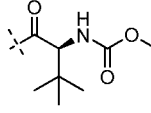
10 $[\text{M}+\text{H}]^{+}$ calcd for $\text{C}_{47}\text{H}_{56}\text{F}_3\text{N}_9\text{O}_8$ 932.42 found 932.4.

Examples 67-70

Following the procedure of Example 66, the intermediate of Preparation 57 (12.0 mg, 0.012 mmol) was reacted with the appropriate reagents to provide the following compounds:

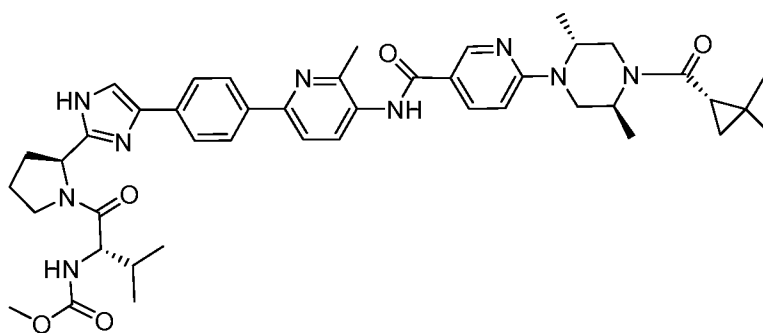


15

Ex. No.	R	Reagent	Product
67		(2 <i>S</i> ,3 <i>S</i>)-3-hydroxy-2-methoxycarbonylamino-butyrac acid (2.63 mg, 0.015 mmol) HATU (5.65 mg, 0.015 mmol)*	2 TFA salt (1.7 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₅₀ H ₆₁ F ₃ N ₁₀ O ₁₀ 1,019.45 found 1019.4
68		glycolic acid (1.13 mg, 0.015 mmol) HATU (5.65 mg, 0.015 mmol)	2 TFA salt (1.5 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₆ H ₅₄ F ₃ N ₉ O ₈ 918.41 found 918.4
69		2-hydroxy-2-methyl-propionic acid (1.55 mg, 0.015 mmol) HATU (5.65 mg, 0.015 mmol)	2 TFA salt (0.6 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₄₈ H ₅₈ F ₃ N ₉ O ₈ 946.44 found 946.4
70		(<i>S</i>)-2-Methoxycarbonylamino-3,3-dimethyl-butyrac acid (2.81 mg, 0.015 mmol) HATU (5.65 mg, 0.015 mmol)*	2 TFA salt (1 mg) (<i>m/z</i>): [M+H] ⁺ calcd for C ₅₂ H ₆₅ F ₃ N ₁₀ O ₉ 1,031.49 found 1031.4

* Prior to isolation and purification, another equivalent of the corresponding acid, along with HOAt (2.53 mg, 0.019 mmol) and EDC (3.56 mg, 0.019 mmol), previously stirred at RT for 15 min, were added to the reaction mixture which was stirred at 60 °C overnight

5 **Example 71** *{(S)-1-[(S)-2-(4-{4-[5-({6-[(2*R*,5*S*)-4-((S)-2,2-Dimethyl-cyclopropanecarbonyl)-2,5-dimethyl-piperazin-1-yl]-pyridine-3-carbonyl}-amino)-6-methyl-pyridin-2-yl]-phenyl)-1*H*-imidazol-2-yl)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic acid methyl ester*

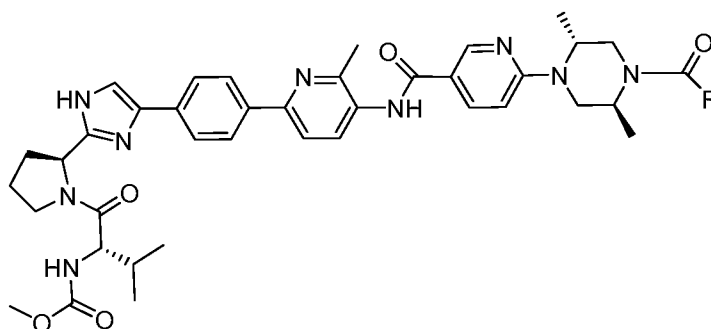


- 10 A mixture of (*s*)-(+)-2,2-dimethylcyclopropane carboxylic acid (2.13 mg, 0.019 mmol), and HATU (8.52 mg, 0.022 mmol) was stirred in DMA (1 mL) for 10 min and then [(*S*)-1-((*S*)-2-{4-[4-(5-{{6-((2*R*,5*S*)-2,5-dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-6-methyl-pyridin-2-yl)-phenyl]-1*H*-imidazol-2-yl}-pyrrolidine-1-carbonyl)-2-methyl-propyl]-carbamic acid methyl ester 4 HCl (15 mg, 0.018 mmol;
- 15 Preparation 59) and *N,N*-diisopropylethylamine (16.3 μL, 0.093 mmol) were added. The reaction mixture was stirred at RT overnight, concentrated by rotary evaporation,

dissolved in 1:1 acetic acid:water (1.5 mL) and purified by reverse phase HPLC to provide the tri-TFA salt of the title compound (11 mg). m/z : $[M+H]^+$ calcd for $C_{44}H_{55}N_9O_5$ 790.43 found 790.4.

Examples 72-75

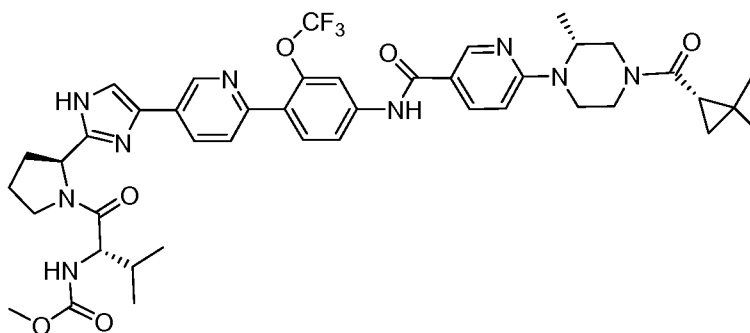
- 5 Following the procedure of Example S, the intermediate of Preparation 59 (15.0 mg, 0.018 mmol) was reacted with the appropriate reagents to provide the following compounds:



Ex. No.	R	Reagent	Product
72		(S)-1-((S)-2-methoxycarbonyl-amino-3-methyl-butyl)-2-methyl-pyrrolidine-2-carboxylic acid (5.35 mg, 0.019 mmol) HATU (8.52 mg, 0.022 mmol)	3 TFA salt (1.7 mg) (m/z): $[M+H]^+$ calcd for $C_{51}H_{67}N_{11}O_8$ 962.52 found 962.4
73		cyclopropanecarbonyl chloride (1.95 mg, 0.019 mmol)	3 TFA salt (6.5 mg) (m/z): $[M+H]^+$ calcd for $C_{42}H_{51}N_9O_5$ 762.40 found 762.4
74	NHCH ₃	methylaminoformyl chloride (1.75 mg, 0.019 mmol)	3 TFA salt (4 mg) (m/z): $[M+H]^+$ calcd for $C_{40}H_{50}N_{10}O_5$ 751.40 found 751.4
75		imidazol-4-carboxylic acid (2.09 mg, 0.019 mmol), EDC (5.37 mg, 0.028 mmol)	3 TFA salt (5.4 mg) (m/z): $[M+H]^+$ calcd for $C_{42}H_{49}N_{11}O_5$ 788.39 found 788.4

Example 76 $\{(S)\text{-}1\text{-}[(S)\text{-}2\text{-}(4\text{-}\{6\text{-}[4\text{-}\{(R)\text{-}4\text{-}((S)\text{-}2,2\text{-Dimethyl-cyclopropanecarbonyl})\text{-}2\text{-methyl-piperazin-1-yl}\}\text{-pyridine-3-carbonyl}\}\text{-amino})\text{-trifluoromethoxyphenyl}\}\text{-pyridin-3-yl}\}\text{-}1H\text{-imidazol-2-yl}\}\text{-pyrrolidine-1-carbonyl}\}\text{-}2\text{-methyl-propyl}\}\text{-carbamic acid methyl ester}$

5



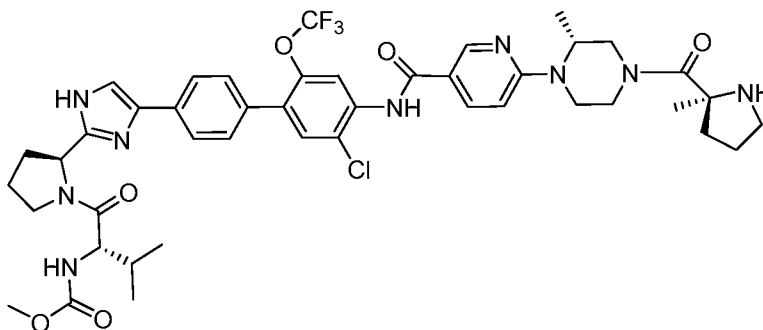
To a mixture of $[(S)\text{-}2\text{-methyl-}1\text{-}((S)\text{-}2\text{-}\{4\text{-}[6\text{-}(4\text{-}\{6\text{-}((R)\text{-}2\text{-methyl-piperazin-1-yl})\text{-pyridine-3-carbonyl}\}\text{-amino})\text{-}2\text{-trifluoromethoxy-phenyl})\text{-pyridin-3-yl}\}\text{-}1H\text{-imidazol-2-yl}\}\text{-pyrrolidine-1-carbonyl}\}\text{-propyl}\}\text{-carbamic acid methyl ester 3-TFA}$ (14.25 mg, 0.013 mmol; Preparation 61) and $(S)\text{-}(+)\text{-}2,2\text{-dimethylcyclopropane carboxylic acid}$ (2.2 mg, 0.020 mmol) and HATU (7.4 mg, 0.020 mmol) in DMF (0.5 mL) at RT was added N,N -diisopropylethylamine (11.37 μL , 0.065 mmol). The reaction mixture was stirred at RT overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL), and purified by reverse phase HPLC to provide the tri-TFA salt of the title compound (10.8 mg). m/z : $[M+H]^+$ calcd for $C_{43}H_{50}F_3N_9O_6$ 846.38 found 847.0.

15

Example 77:

(a) $[(S)\text{-}1\text{-}((S)\text{-}2\text{-}\{4\text{-}[5\text{-}Cl\text{-}2\text{-trifluoromethoxy-}4\text{-}\{(6\text{-}[(R)\text{-}2\text{-methyl-}4\text{-}((S)\text{-}2\text{-methyl-pyrrolidine-2-carbonyl})\text{-piperazin-1-yl}\}\text{-pyridine-3-carbonyl}\}\text{-amino})\text{-biphenyl-4-yl}\}\text{-}1H\text{-imidazol-2-yl}\}\text{-pyrrolidine-1-carbonyl}\}\text{-}2\text{-methyl-propyl}\}\text{-carbamic acid methyl ester}$

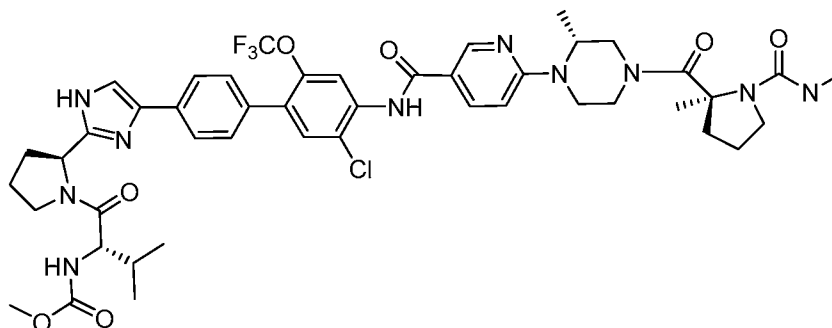
20



A mixture of (*S*)-2-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (23.2 mg, 0.10 mmol) and HATU (38.5 mg, 0.10 mmol) in DMA (1 mL) was stirred at RT for 20 min and then ((*S*)-1-{(*S*)-2-[4-(5'-chloro-4'-{[6-((*R*)-2-methyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester 3TFA (95.0 mg, 0.084 mmol; Preparation 62) was added followed by *N,N*-diisopropylethylamine (0.074 mL, 0.42 mmol) and the reaction mixture was stirred at 55 °C overnight. The reaction mixture was diluted in ethyl acetate and washed with water followed by brine. The organic layer was dried over sodium sulfate, filtered and concentrated to produce a yellow oil.

The oil from the previous step was treated with 4 M HCl in 1,4-dioxane (0.63 mL, 2.53 mmol) and HCl (0.16 mL) and the reaction mixture was stirred at RT for 1 h, concentrated, and evaporated with EtOAc (2x) to produce the tri-HCl salt of the title intermediate as a light yellow solid (87.3 mg).

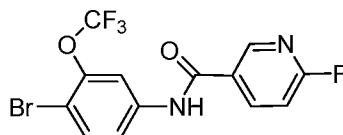
(b)



To the product of the previous step (22 mg, 0.022 mmol) dissolved in DMA was added 0.5 M methylaminoformyl chloride in DMA (52.6 μ L, 0.026 mmol), followed by *N,N*-diisopropylethylamine (0.016 mL, 0.089 mmol) and the reaction mixture was stirred at RT overnight, concentrated, dissolved in 1:1 acetic acid:water (1.5 mL) and purified by reverse phase HPLC to provide the di-TFA salt of the title compound (14.4 mg). m/z : $[M+H]^+$ calcd for $C_{46}H_{54}ClF_3N_{10}O_7$ 951.38 found 951.6.

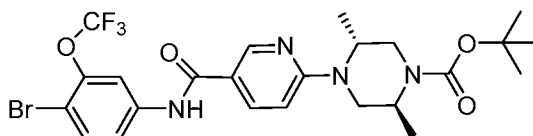
Example 78: Alternative synthesis of ((*S*)-1-((*S*)-2-[4-(4'-{[6-((*2R,5S*)-2,5-Dimethyl-4-methylcarbamoyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

- 5 (a) N-(4-Bromo-3-trifluoromethoxy-phenyl)-6-fluoro-nicotinamide



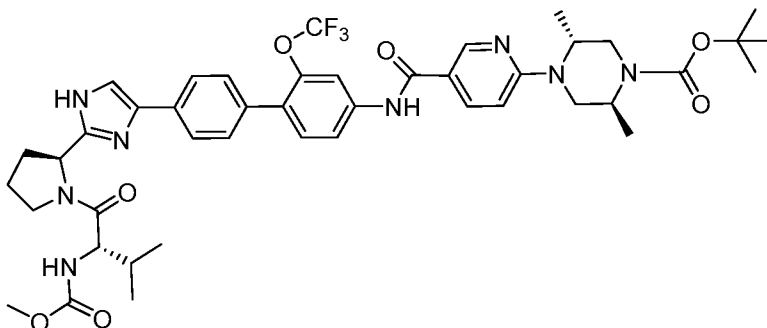
To a solution of 4-bromo-3-trifluoromethoxy-phenylamine (3.15 g, 12.3 mmol) and triethylamine (3.43 mL, 24.6 mmol) in DCM (25 mL) was slowly added a solution of 2-fluoropyridine-5-carbonyl chloride (2.36 g, 14.8 mmol) in DCM (10 mL). After 2 h
 10 at RT, MTBE (90 mL) was added and the reaction mixture was washed with water, brine, and saturated sodium carbonate, dried, and evaporated to give a solid (5.4 g). Ethanol (43 mL) was added to the solid and then water (43 mL) was slowly added. The reaction mixture was stirred for 1.5 h, filtered, and washed with 1:4 ethanol:water (2 x 25 mL) to give the title intermediate as a white solid (3.87 g). HPLC method C: Retention time =
 15 21.3 min.

- (b) (2*S*,5*R*)-4-[5-(4-Bromo-3-trifluoromethoxy-phenylcarbamoyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester



The product of the previous step (3.86 g, 10.2 mmol) (2*S*,5*R*)-2,5-dimethyl-
 20 piperazine-1-carboxylic acid *tert*-butyl ester (2.62 g, 12.2 mmol) and *N,N*-diisopropylethylamine (5.32 mL, 30.5) was dissolved in DMSO (12 mL). The reaction mixture heated at 120 °C for 3 h, diluted with EtOAc (100 mL), washed with water, and saturated NH₄Cl, water, and brine. The reaction mixture was evaporated to about 40% volume and 3 M HCl in cyclopentyl methyl ether (4.24 mL, 12.7 mmol) was added
 25 slowly. Seeds from a previous run at smaller scale were added and the reaction mixture was stirred for 2 days and filtered to provide the HCl salt of the title intermediate (5.15 g, 83 % yield). HPLC method C: Retention time = 21.1 min

(c) (2*S*,5*R*)-4-[5-(4'-{2-[(*S*)-1-((*S*)-2-Methoxycarbonylamino-3-methyl-butyl)-pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-trifluoromethoxy-biphenyl-4-ylcarbamoyl)-pyridin-2-yl]-2,5-dimethyl-piperazine-1-carboxylic acid *tert*-butyl ester

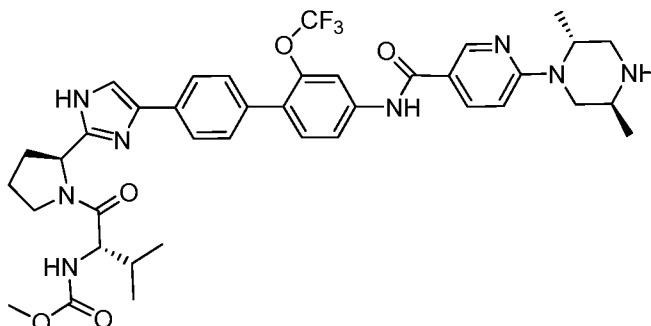


5 To a solution of ((*S*)-1-{(*S*)-2-[4-(4-bromo-phenyl)-1*H*-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester (3.05 g, 6.8 mmol); bis(pinacolato)diboron (1.81 g, 7.1 mmol) and potassium acetate (1.00 g, 10.2 mmol) was added nitrogen sparged toluene (15 mL). The resulting mixture was sparged with nitrogen and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride
10 dichloromethane (Pd catalyst) (0.17 g, 0.204 mmol) was added. The reaction mixture was stirred at 90 °C overnight.

The reaction mixture was cooled to RT and to this mixture was added nitrogen sparged water (7.6 mL), potassium carbonate (5.16 g, 37.3 mmol). The reaction mixture was stirred at 95°C overnight.

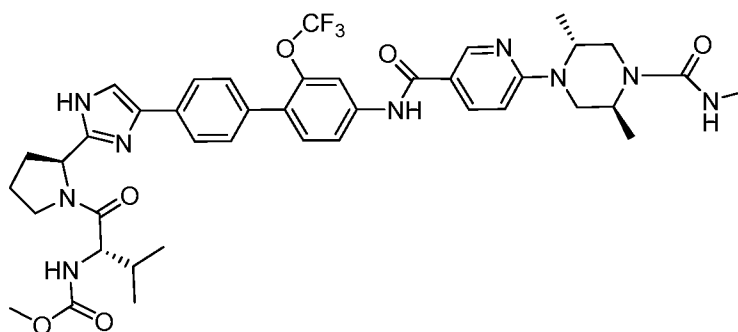
15 Another portion of the Pd catalyst used above (0.08 g, 0.10 mmol) was added to the reaction mixture. After 5 h, the reaction mixture was cooled to RT, diluted with EtOAc (150 mL), washed with water (150 mL) and brine (100 mL), dried over sodium sulfate, and evaporated to give a black residue (6.7 g), which was purified by silica gel chromatography (eluted with 50-100 % EtOAc/hexane) to provide the title intermediate
20 (5.3 g, 90 % yield). HPLC method C: Retention time = 14.7 min.

(d) ((S)-1-((S)-2-[4-(4'-{[6-((2R,5S)-2,5-Dimethyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester



5 Acetyl chloride (2.57 mL, 36.2 mmol) was added to ethanol (18 mL) and stirred at RT for 1 h. To the resulting HCl solution was added a solution of the product of the previous step (3.90 g, 4.5 mmol) in ethanol (18 mL). The reaction mixture was warmed to 35 °C and stirred overnight. Acetyl chloride (1.28 mL, 18.1 mmol) was added to ethanol (7.8 mL) and stirred for 30 min. The resulting HCl solution was added to the reaction
 10 mixture at 35 °C. The temperature was raised to 40 °C. The mixture was concentrated to dryness chased by dichloromethane to provide the crude tri-HCl salt of the title intermediate (5.4 g) which was used directly in the next step. HPLC method C: Retention time = 10.1 min.

(e) ((S)-1-((S)-2-[4-(4'-{[6-((2R,5S)-2,5-Dimethyl-4-methylcarbamoyl-piperazin-1-yl)-pyridine-3-carbonyl]-amino}-2'-trifluoromethoxy-biphenyl-4-yl)-1H-imidazol-2-yl]-pyrrolidine-1-carbonyl}-2-methyl-propyl)-carbamic acid methyl ester

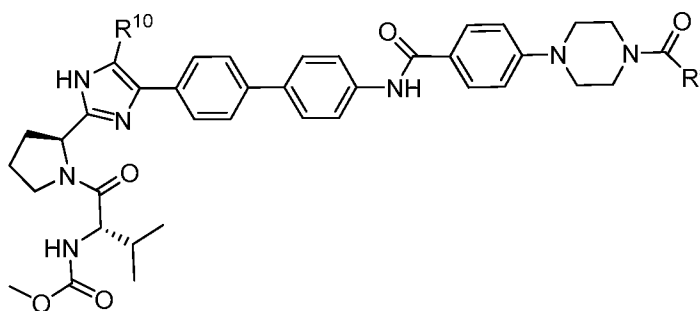


To a solution of the product of the previous step (5.4 g crude, ca. 3.96 mmol) and *N,N*-diisopropylethylamine (6.89 mL, 39.6 mmol) in DCM (52 mL) was slowly added 1
 20 M methylaminoformyl chloride in DMA (4.3 mL). The reaction mixture stirred at room temperature for 1 h, and then water (50 mL) was added. The organic layer was washed with saturated NH₄Cl and then brine, dried over Na₂SO₄ and evaporated to give 5.2 g

crude product, which was purified by silica gel chromatography (133 g silica, 2 to 8 % methanol/DCM for 15 min then 8 % methanol/DCM for 40 min) to provide the title compound (2.4 g, 74 % yield). HPLC method C: Retention time 11.2 min.

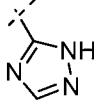

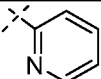

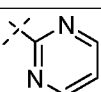
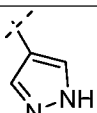

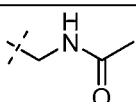
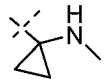
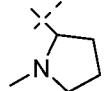
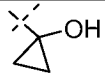
- 5 Using similar synthetic methods, the compounds of Tables 1-34 were prepared where a blank in any column denotes hydrogen and further when more than one variable is listed in a single column, (e.g. Table 5) any variable not specified is hydrogen:

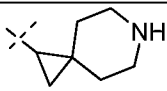

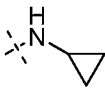
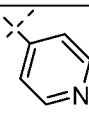
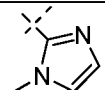
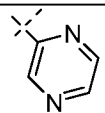
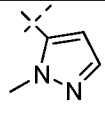
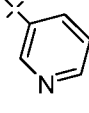
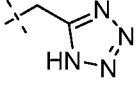
Table 1

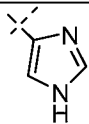
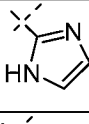
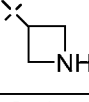
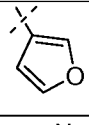
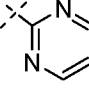
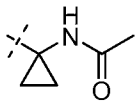
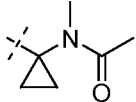
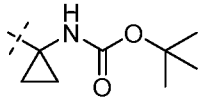
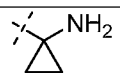


10

Ex. No.	R ⁵	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
1-1	OCH ₃		C ₃₉ H ₄₅ N ₇ O ₆	708.34	708.2
1-2	OCH ₂ phenyl		C ₄₅ H ₄₉ N ₇ O ₆	784.37	784.2
1-3	CH ₃		C ₃₈ H ₄₅ N ₇ O ₄	664.35	664.2
1-4	CH ₂ OCH ₃		C ₄₀ H ₄₇ N ₇ O ₆	722.36	722.4
1-5	CH((S)-iPr)NHC(O)OCH ₃		C ₄₄ H ₅₄ N ₈ O ₇	807.41	807.4
1-6	CH((S)-iPr)N(Et) ₂		C ₄₆ H ₆₀ N ₈ O ₅	805.47	805.4
1-7	CH((R)-phenyl)NH-C(O)OCH ₃		C ₄₇ H ₅₂ N ₈ O ₇	841.4	841.4
1-8	CH((R)-phenyl)N(Et) ₂		C ₄₉ H ₅₈ N ₈ O ₅	839.45	839.4
1-9	CH ₂ N(CH ₃)C(O)OtBu		C ₄₅ H ₅₆ N ₈ O ₇	821.43	821.4
1-10	CH ₂ NHC(O)OtBu		C ₄₄ H ₅₄ N ₈ O ₇	807.41	807.0
1-11	CH ₂ N(CH ₃) ₂		C ₄₁ H ₅₀ N ₈ O ₅	735.39	735.4
1-12	CH ₂ NH ₂		C ₃₉ H ₄₆ N ₈ O ₅	707.36	707.2
1-13	CH ₂ NHCH ₃		C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.4
1-14	CH ₂ OH		C ₃₉ H ₄₅ N ₇ O ₆	708.34	708.2
1-15	NHCH ₃		C ₃₉ H ₄₆ N ₈ O ₅	707.36	707.4
1-16	N(CH ₃) ₂		C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.2

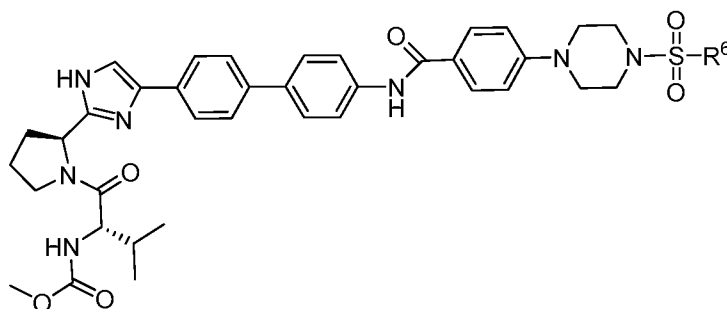
Ex. No.	R ⁵	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
1-17			C ₄₀ H ₄₄ N ₁₀ O ₅	745.35	745.4
1-18			C ₄₂ H ₄₅ N ₇ O ₆	744.34	744.2
1-19			C ₄₃ H ₄₆ N ₈ O ₅	755.36	755.4
1-20			C ₄₂ H ₄₅ N ₇ O ₆	744.34	744.2
1-21			C ₄₂ H ₄₅ N ₉ O ₅	756.35	756.4
1-22			C ₄₁ H ₄₅ N ₉ O ₅	744.35	744.2
1-23			C ₄₁ H ₄₄ N ₈ O ₆	745.34	745.2
1-24	NH ₂		C ₃₈ H ₄₄ N ₈ O ₅	693.34	693.4
1-25	cPr	Cl	C ₄₁ H ₄₆ ClN ₇ O ₅	752.33	752.2
1-26			C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.2
1-27	CH((S)iPr)NHC(O)OtBu		C ₄₇ H ₆₀ N ₈ O ₇	849.46	849.4
1-28	CH((S)iPr)NH ₂		C ₄₂ H ₅₂ N ₈ O ₅	749.41	749.4
1-29	CH ₃		C ₃₉ H ₄₅ N ₇ O ₅	692.35	692.2
1-30			C ₄₂ H ₅₀ N ₈ O ₅	747.39	747.4
1-31	CH((S)OH)iPr		C ₄₂ H ₅₁ N ₇ O ₆	750.39	750.2
1-32			C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4
1-33	C(CH ₃) ₂ NHCH ₃		C ₄₂ H ₅₂ N ₈ O ₅	749.41	749.4
1-34			C ₄₁ H ₄₇ N ₇ O ₆	734.36	734.2

Ex. No.	R ⁵	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
1-35	CH ₂ iPr		C ₄₂ H ₄₉ N ₇ O ₅	732.38	732.4
1-36			C ₄₅ H ₅₄ N ₈ O ₅	787.42	787.4
1-37	CH((R)OH)iPr		C ₄₂ H ₅₁ N ₇ O ₆	750.39	750.4
1-38	NHiPr		C ₄₁ H ₅₀ N ₈ O ₅	735.39	735.4
1-39	O-iPr		C ₄₁ H ₄₉ N ₇ O ₆	736.37	736.2
1-40			C ₄₂ H ₅₀ N ₈ O ₅	747.39	747.4
1-41	OCH ₂ CH ₃		C ₄₀ H ₄₇ N ₇ O ₆	722.36	722.2
1-42	NHCH ₂ CH ₃		C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.4
1-43	NHCH ₂ -iPr		C ₄₂ H ₅₂ N ₈ O ₅	749.41	749.4
1-44	cPr	CH ₃	C ₄₂ H ₄₉ N ₇ O ₅	732.38	732.7
1-45	NHCH ₃	CH ₃	C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.6
1-46			C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.4
1-47	NH-tBu		C ₄₂ H ₅₂ N ₈ O ₅	749.41	749.4
1-48			C ₄₃ H ₄₆ N ₈ O ₅	755.36	755.2
1-49	iPr		C ₄₁ H ₄₉ N ₇ O ₅	720.38	720.2
1-50			C ₄₂ H ₄₇ N ₉ O ₅	758.37	758.2
1-51			C ₄₂ H ₄₅ N ₉ O ₅	756.35	756.2
1-52			C ₄₂ H ₄₇ N ₉ O ₅	758.37	758.2
1-53			C ₄₃ H ₄₆ N ₈ O ₅	755.36	755.2
1-54			C ₄₀ H ₄₅ N ₁₁ O ₅	760.36	760.2

Ex. No.	R ⁵	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
1-55	CH((S)CH ₂ OH)NH ₂		C ₄₀ H ₄₈ N ₈ O ₆	737.37	737.4
1-56			C ₄₁ H ₄₅ N ₉ O ₅	744.35	744.2
1-57			C ₄₁ H ₄₅ N ₉ O ₅	744.35	744.2
1-58			C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.2
1-59	CH((S)CH ₂ OH)NHC(O)OtBu		C ₄₅ H ₅₆ N ₈ O ₈	837.42	837.4
1-60		Cl	C ₄₂ H ₄₄ ClN ₇ O ₆	778.30	778.2
1-61		Cl	C ₄₂ H ₄₄ ClN ₉ O ₅	790.32	790.4
1-62	CH((R)cPr)NH ₂		C ₄₂ H ₅₀ N ₈ O ₅	747.39	747.4
1-63			C ₄₃ H ₅₀ N ₈ O ₆	775.39	775.4
1-64	CH((R)cPr)NHC(O)CH ₃		C ₄₄ H ₅₂ N ₈ O ₆	789.40	789.4
1-65			C ₄₄ H ₅₂ N ₈ O ₆	789.40	789.4
1-66	CH ₂ N(CH ₃)C(O)CH ₃		C ₄₂ H ₅₀ N ₈ O ₆	763.39	763.4
1-67			C ₄₆ H ₅₆ N ₈ O ₇	833.43	833.4
1-68			C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.4
1-69	CH ₂ NHC(O)CH ₃	Cl	C ₄₁ H ₄₇ ClN ₈ O ₆	783.33	783.2
1-70	<i>t</i> Bu	Cl	C ₄₂ H ₅₀ ClN ₇ O ₅	768.36	768.2
1-71	CH((R)CH ₃)NH ₂		C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.2
1-72	CH((R)CH ₂ OH)NHCH ₃		C ₄₁ H ₅₀ N ₈ O ₆	751.39	751.2
1-73	CH((R)Pr)NHC(O)CH ₃		C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
1-74	CH((S)CH ₃)NHC(O)OtBu		C ₄₅ H ₅₆ N ₈ O ₇	821.43	821.4

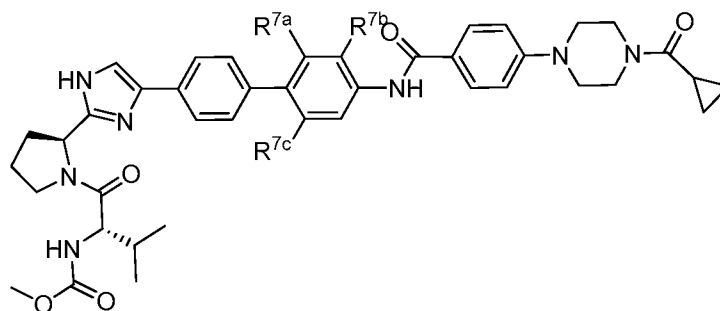
Ex. No.	R ⁵	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
1-75	CH((S)CH ₃)N(CH ₃)C(O)OtBu		C ₄₆ H ₅₈ N ₈ O ₇	835.44	835.4
1-76	CH((S)iPr)NHC(O)CH ₃		C ₄₅ H ₅₆ N ₈ O ₆	805.43	805.4
1-77	CH((S)CH ₃)NHCH ₃		C ₄₁ H ₅₀ N ₈ O ₅	735.39	735.4
1-78	CH((S)CH ₃)NH ₂		C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.2
1-79	CH((R)CH ₃)N(CH ₃)C(O)OtBu		C ₄₅ H ₅₆ N ₈ O ₇	821.43	821.4

Table 2



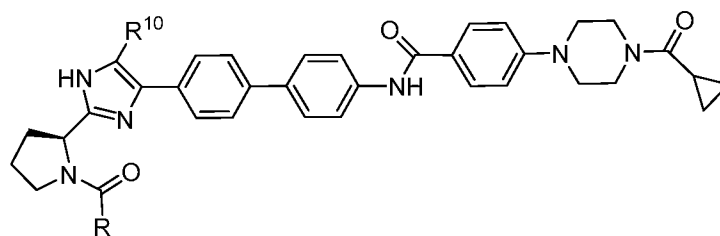
Ex. No.	R ⁶	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
2-1		C ₄₀ H ₄₅ N ₉ O ₆ S	780.32	780.4
2-2	NH ₂	C ₃₇ H ₄₄ N ₈ O ₆ S	729.31	729.2
2-3	cyclopropyl	C ₄₀ H ₄₇ N ₇ O ₆ S	754.33	754.2
2-4	phenyl	C ₄₃ H ₄₇ N ₇ O ₆ S	790.33	790.2

Table 3



Ex. No.	R ^{7a}	R ^{7b}	R ^{7c}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
3-1	F			C ₄₁ H ₄₆ FN ₇ O ₅	736.35	736.4
3-2	OCH ₃			C ₄₂ H ₄₉ N ₇ O ₆	748.37	748.4
3-3	F		F	C ₄₁ H ₄₅ F ₂ N ₇ O ₅	754.35	754.2
3-4	Cl			C ₄₁ H ₄₆ ClN ₇ O ₅	752.33	752.4
3-5	Cl		Cl	C ₄₁ H ₄₅ Cl ₂ N ₇ O ₅	786.29	786.2
3-6		F		C ₄₁ H ₄₆ FN ₇ O ₅	736.35	736.4
3-7		Cl		C ₄₁ H ₄₆ ClN ₇ O ₅	752.33	752.2

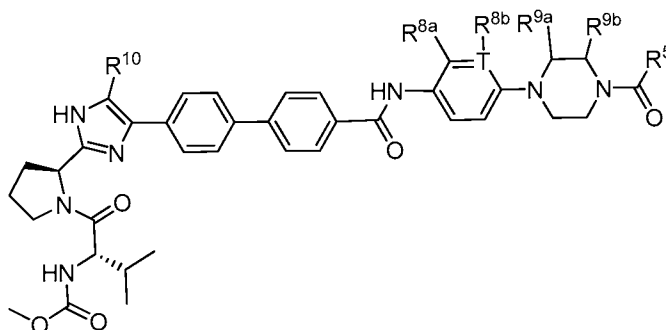
Table 4



5

Ex. No.	R	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
4-1	CH((S)-iPr)NHSO ₂ CH ₃		C ₄₀ H ₄₇ N ₇ O ₅ S	738.34	738.2
4-2	CH((S)-iPr)NHC(O)NHCH ₃		C ₄₁ H ₄₈ N ₈ O ₄	717.38	717.2
4-3	CH((S)-iPr)N(C ₂ H ₅) ₂		C ₄₃ H ₅₃ N ₇ O ₃	716.42	716.4
4-4	CH((S)-iPr)NHC(O)OtBu		C ₄₄ H ₅₃ N ₇ O ₅	760.41	760.4
4-5	CH((R)phenyl)NHC(O)OCH ₃		C ₄₄ H ₄₅ N ₇ O ₅	752.35	752.2
4-6	CH((S)-iPr)NHC(O)cPr		C ₄₃ H ₄₉ N ₇ O ₄	728.38	728.4
4-7	CH((S)-iPr)NH ₂		C ₃₉ H ₄₅ N ₇ O ₃	660.36	660.2
4-8	CH((R)phenyl)N(C ₂ H ₅) ₂	Cl	C ₄₆ H ₅₀ ClN ₇ O ₃	784.37	785.2

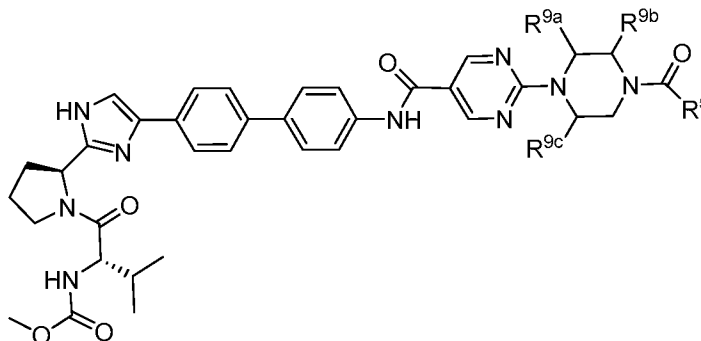
Table 5



Ex No.	R ⁵	R ¹⁰	T	R ^{8a} , R ^{8b} , R ^{9a} , R ^{9d*}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
5-1	OtBu		CH		C ₄₂ H ₅₁ N ₇ O ₆	750.39	750.4
5-2	cPr	Br	CH		C ₄₁ H ₄₆ BrN ₇ O ₅	796.27	796.2
5-3	OtBu	Br	CH		C ₄₂ H ₅₀ BrN ₇ O ₆	828.30	828.5
5-4	CH ₂ iPr	Br	CH		C ₄₂ H ₅₀ BrN ₇ O ₅	812.31	812.2
5-5	CH ₃		CH		C ₃₉ H ₄₅ N ₇ O ₅	692.35	692.4
5-6	OtBu		N		C ₄₁ H ₅₀ N ₈ O ₆	751.39	751.4
5-7	OtBu		CH	R ^{9a} =(S)CH ₃	C ₄₃ H ₅₃ N ₇ O ₆	764.41	764.4
5-8	OtBu		CH	R ^{9a} =(R)CH ₃	C ₄₃ H ₅₃ N ₇ O ₆	764.41	764.4
5-9	cPr		C	R ^{8b} =F	C ₄₁ H ₄₆ FN ₇ O ₅	736.35	736.4
5-10	OtBu		CH	R ^{9b} =(S)iPr	C ₄₅ H ₅₇ N ₇ O ₆	792.44	792.4
5-11	cPr		C	R ^{8b} =OMe	C ₄₂ H ₄₉ N ₇ O ₆	748.37	748.4
5-12	cPr		CH	R ^{9a} =(R)CH ₃	C ₄₂ H ₄₉ N ₇ O ₅	732.38	732.4
5-13	cPr		CH	R ^{9a} =(S)CH ₃	C ₄₂ H ₄₉ N ₇ O ₅	732.38	732.4
5-14	cPr		C	R ^{8b} =Me	C ₄₂ H ₄₉ N ₇ O ₅	732.38	732.4
5-15	cPr		C	R ^{8b} =Cl	C ₄₁ H ₄₆ ClN ₇ O ₅	752.33	752.2
5-16	cPr		CH	R ^{9b} =(S)iPr	C ₄₄ H ₅₃ N ₇ O ₅	760.41	760.4
5-17	cPr		CH	R ^{8a} =Me	C ₄₂ H ₄₉ N ₇ O ₅	732.38	732.4
5-18	OtBu		C	R ^{8b} =COOH	C ₄₃ H ₅₁ N ₇ O ₈	794.38	794.2
5-19	cPr		CH	R ^{8a} =Cl	C ₄₁ H ₄₆ ClN ₇ O ₅	752.33	752.2
5-20	OtBu		C	R ^{8b} =COOMe	C ₄₄ H ₅₃ N ₇ O ₈	808.40	808.2
5-21	cPr	H	C	R ^{8b} =CH ₂ NH ₂	C ₄₂ H ₅₀ N ₈ O ₅	747.39	747.4

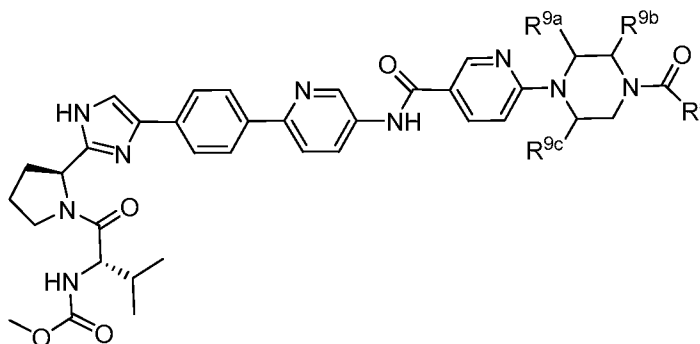
* R^{8a}, R^{9a}, R^{9b}, R¹⁰ are each H where not specified

Table 6



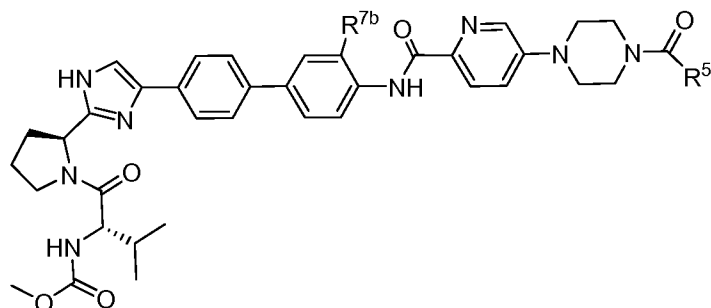
Ex No.	R ⁵	R ^{9a}	R ^{9b}	R ^{9c}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
6-1	OMe				C ₃₇ H ₄₃ N ₉ O ₆	710.33	710.2
6-2	cPr				C ₃₉ H ₄₅ N ₉ O ₅	720.35	720.2
6-3	NHCH ₃				C ₃₇ H ₄₄ N ₁₀ O ₅	709.35	710.4
6-4	OtBu	(S)CH ₃		(R)CH ₃	C ₄₂ H ₅₃ N ₉ O ₆	780.41	780.4
6-5	OtBu	(R)CH ₃			C ₄₁ H ₅₁ N ₉ O ₆	766.40	766.4
6-6	OtBu				C ₄₀ H ₄₉ N ₉ O ₆	752.38	752.4
6-7	OtBu		(S)CH ₃		C ₄₁ H ₅₁ N ₉ O ₆	766.40	766.4
6-8	OtBu		(R)CH ₃		C ₄₁ H ₅₁ N ₉ O ₆	766.40	766.4
6-9	OtBu	(S)CH ₃			C ₄₁ H ₅₁ N ₉ O ₆	766.40	766.4

Table 7



Ex No.	R ⁵	R ^{9a}	R ^{9b}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
7-1	OtBu	(R)CH ₃		C ₄₁ H ₅₁ N ₉ O ₆	766.4	766.2
7-2	OtBu			C ₄₀ H ₄₉ N ₉ O ₆	752.38	752.2
7-3	OtBu		(R)CH ₃	C ₄₁ H ₅₁ N ₉ O ₆	766.40	766.4
7-4	cPr			C ₃₉ H ₄₅ N ₉ O ₅	720.35	720.2
7-5	Me			C ₃₇ H ₄₃ N ₉ O ₅	694.34	694.2
7-6	NHCH ₃			C ₃₇ H ₄₄ N ₁₀ O ₅	709.35	709.2
7-7	Me		(R)CH ₃	C ₃₈ H ₄₅ N ₉ O ₅	708.35	708.2
7-8	cPr		(R)CH ₃	C ₄₀ H ₄₇ N ₉ O ₅	734.37	734.2
7-9	NHCH ₃		(R)CH ₃	C ₃₈ H ₄₆ N ₁₀ O ₅	723.37	723.4
7-10	cPr	(R)CH ₃		C ₄₀ H ₄₇ N ₉ O ₅	734.37	734.2
7-11	NHCH ₃	(R)CH ₃		C ₃₈ H ₄₆ N ₁₀ O ₅	723.37	723.4

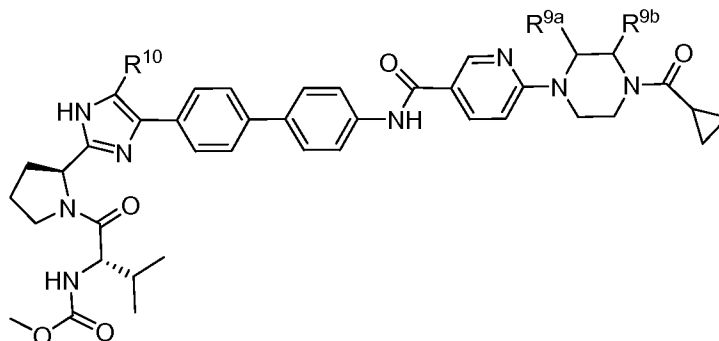
Table 8



Ex No.	R ⁵	R ^{7b}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
8-1	cPr		C ₄₀ H ₄₆ N ₈ O ₅	719.36	719.2
8-2	Me		C ₃₈ H ₄₄ N ₈ O ₅	693.34	693.2
8-3	NHSO ₂ CH ₃		C ₃₉ H ₄₈ N ₈ O ₆ S	757.34	757.2
8-4	OtBu	OCH ₃	C ₄₂ H ₅₂ N ₈ O ₇	781.40	781.4
8-5	cPr	OCH ₃	C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.2

5

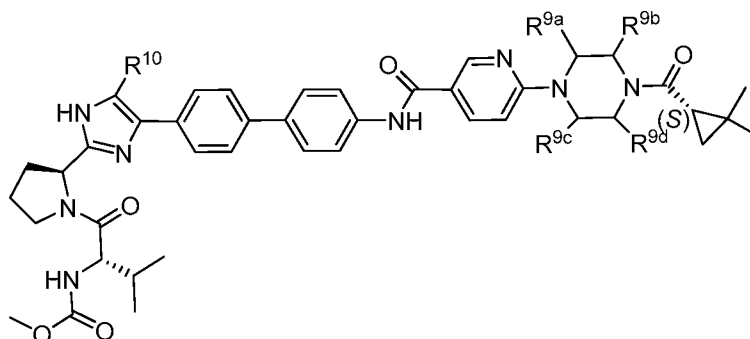
Table 9



Ex No.	R ^{9a}	R ^{9b}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
9-1				C ₄₀ H ₄₆ N ₈ O ₅	719.36	719.2
9-2	(S)CH ₃			C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.2
9-3	(R)CH ₃			C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.4
9-4		(R)CH ₃		C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.4
9-5		(S)CH ₃		C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.4
9-6	(R)CH ₂ OH			C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.4
9-7	(S)CH ₂ OH			C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.4

Ex No.	R ^{9a}	R ^{9b}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
9-8		(S)CH ₂ OH		C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.4
9-9		(R)CH ₂ OH		C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.4
9-10		(R)CH ₂ OCH ₃		C ₄₂ H ₅₀ N ₈ O ₆	763.39	763.4
9-11			Cl	C ₄₀ H ₄₅ ClN ₈ O ₅	753.32	753.2
9-12		(S)C(O)NH ₂		C ₄₁ H ₄₇ N ₉ O ₆	762.37	762.4
9-13		(R)C(O)NH ₂		C ₄₁ H ₄₇ N ₉ O ₆	762.37	762.4
9-14		(S)C(O)N(CH ₃) ₂		C ₄₃ H ₅₁ N ₉ O ₆	790.40	790.4
9-15		(R)C(O)N(CH ₃) ₂		C ₄₃ H ₅₁ N ₉ O ₆	790.40	790.4

Table 10



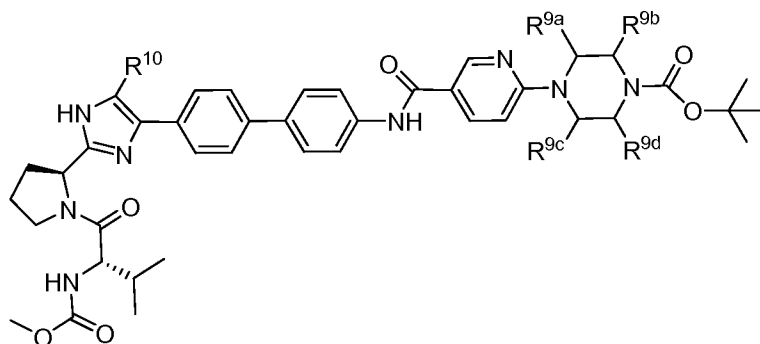
Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
10-1						C ₄₂ H ₅₀ N ₈ O ₅	747.39	747.4
10-2		(R)CH ₃				C ₄₃ H ₅₂ N ₈ O ₅	761.41	762.0
10-3		(S)CH ₃				C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4
10-4		(S)CH ₂ OH				C ₄₃ H ₅₂ N ₈ O ₆	777.4	789.2
10-5		(R)CH ₂ OH				C ₄₃ H ₅₂ N ₈ O ₆	777.4	799.4
10-6		(R)CH ₂ OCH ₃				C ₄₄ H ₅₄ N ₈ O ₆	791.42	792.4
10-7		(R)CH ₃			Cl	C ₄₃ H ₅₁ ClN ₈ O ₅	795.37	795.4
10-8		(S)C(O)N(CH ₃) ₂				C ₄₅ H ₅₅ N ₉ O ₆	818.43	818.4
10-9		(R)C(O)N(CH ₃) ₂				C ₄₅ H ₅₅ N ₉ O ₆	818.43	818.4
10-10		(S)CH ₃	(R)CH ₃			C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
10-11		(S)CH ₃		(R)CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
10-12		(S)CH ₃			Cl	C ₄₃ H ₅₁ ClN ₈ O ₅	795.37	795.4

Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
10-13	(R)CH ₂ OH					C ₄₃ H ₅₂ N ₈ O ₆	777.40	777.3
10-14	(S)CH ₂ OH					C ₄₃ H ₅₂ N ₈ O ₆	777.40	777.4
10-15		(S)CH ₂ OCH ₃				C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
10-16		(R)CH ₂ OH			Cl	C ₄₃ H ₅₁ ClN ₈ O ₆	811.36	811.2
10-17		(S)CH ₂ OH			Cl	C ₄₃ H ₅₁ ClN ₈ O ₆	811.36	811.2
10-18		(R)CH ₃			Et	C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.4
10-19		(S)C ₂ H ₅				C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
10-20		(R)CH ₃	(S)CH ₃			C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
10-21	(S)CH ₃		(R)CH ₃			C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
10-22		(a)				C ₄₉ H ₆₁ N ₉ O ₆	872.47	872.4
10-23	(R)C ₂ H ₅					C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
10-24		(b)				C ₅₁ H ₅₉ N ₉ O ₇	910.45	910.4
10-25		(R)CH ₂ SCH ₃				C ₄₄ H ₅₄ N ₈ O ₅ S	807.39	807.2
10-26	(S)C ₂ H ₅					C ₄₄ H ₅₄ N ₈ O ₅	775.42	776.2
10-27		(R)CH ₂ S(O) ₂ CH ₃				C ₄₄ H ₅₄ N ₈ O ₇ S	839.38	839.4
10-28		(S)C(O)NH ₂				C ₄₃ H ₅₁ N ₉ O ₆	790.40	790.4

(a) (R)CH₂NH(S)C(O)(1,1-di-methylcyclopropyl)

(b) (R)CH₂NHC(O)OCH₂phenyl

Table 11

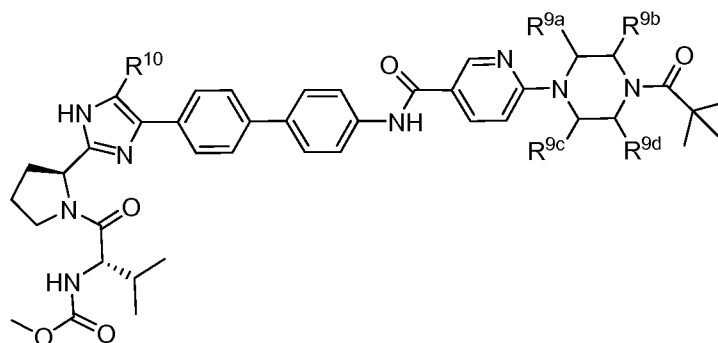


Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
11-1					C ₄₁ H ₅₀ N ₈ O ₆	751.39	751.4
11-2	CH ₃				C ₄₂ H ₅₂ N ₈ O ₇	781.40	781.2
11-3	(S)CH ₃				C ₄₂ H ₅₂ N ₈ O ₆	765.40	765.4
11-4	(R)CH ₃				C ₄₂ H ₅₂ N ₈ O ₆	765.40	765.4
11-5		(R)CH ₃			C ₄₂ H ₅₂ N ₈ O ₆	765.40	765.2
11-6		(S)CH ₃			C ₄₂ H ₅₂ N ₈ O ₆	765.40	765.4
11-7	(S)CH ₂ OH				C ₄₂ H ₅₂ N ₈ O ₇	781.40	781.7
11-8		(S)CH ₂ OH			C ₄₂ H ₅₂ N ₈ O ₇	781.40	781.4
11-9		(R)CH ₂ OH			C ₄₂ H ₅₂ N ₈ O ₇	781.40	781.4
11-10		(R)CH ₂ OCH ₃			C ₄₃ H ₅₄ N ₈ O ₇	795.41	795.4
11-11*		(S)CH ₂ OH			C ₄₂ H ₅₁ ClN ₈ O ₇	815.36	815.6
11-12*		(R)CH ₂ OH			C ₄₂ H ₅₁ ClN ₈ O ₇	815.36	815.7
11-13	(S)CONH ₂				C ₄₂ H ₅₁ N ₉ O ₇	794.39	795.4
11-14		(S)CONH ₂			C ₄₂ H ₅₁ N ₉ O ₇	794.39	794.4
11-15		(R)CONH ₂			C ₄₂ H ₅₁ N ₉ O ₇	794.39	794.2
11-16	(R)COOH				C ₄₂ H ₅₀ N ₈ O ₈	795.38	795.4
11-17	(S)COOH				C ₄₂ H ₅₀ N ₈ O ₈	795.38	795.4
11-18		(R)COOH			C ₄₂ H ₅₀ N ₈ O ₈	795.38	795.4
11-19		(R)CH ₂ CH ₃			C ₄₃ H ₅₄ N ₈ O ₆	779.42	779.4
11-20		(S)CH ₂ CH ₃			C ₄₃ H ₅₄ N ₈ O ₆	779.42	779.4
11-21		COOCH ₃			C ₄₃ H ₅₂ N ₈ O ₈	809.39	809.2
11-22		(R)COOCH ₃			C ₄₃ H ₅₂ N ₈ O ₈	809.39	809.4
11-23		(S)COOCH ₃			C ₄₃ H ₅₂ N ₈ O ₈	809.39	809.4
11-24		(S)CH(CH ₃) ₂			C ₄₄ H ₅₆ N ₈ O ₆	793.43	793.4
11-25		(R)CH(CH ₃) ₂			C ₄₄ H ₅₆ N ₈ O ₆	793.43	793.4

Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
11-26		(S)CON(CH ₃) ₂			C ₄₄ H ₅₅ N ₉ O ₇	822.42	822.4
11-27		(R)CON(CH ₃) ₂			C ₄₄ H ₅₅ N ₉ O ₇	822.42	822.4
11-28	(S)CH ₃			(R)CH ₃	C ₄₃ H ₅₄ N ₈ O ₆	779.42	780.0
11-29	(R)CH ₃			(S)CH ₃	C ₄₃ H ₅₄ N ₈ O ₆	779.42	780.4
11-30	(R)CH ₃			(R)CH ₃	C ₄₃ H ₅₄ N ₈ O ₆	779.42	779.4
11-31		(S)CH ₃		(R)CH ₃	C ₄₃ H ₅₄ N ₈ O ₆	779.42	779.4
11-32	(S)CH ₃		(R)CH ₃		C ₄₃ H ₅₄ N ₈ O ₆	779.42	779.4
11-33	(S)C(O)NH ₂				C ₄₂ H ₅₁ N ₉ O ₇	794.39	795.4
11-34		(R)C(O)NH ₂			C ₄₂ H ₅₁ N ₉ O ₇	794.39	794.2
11-35		(S)C(O)NH ₂			C ₄₂ H ₅₁ N ₉ O ₇	794.39	794.4

* R¹⁰ is Cl; all other R¹⁰ are hydrogen

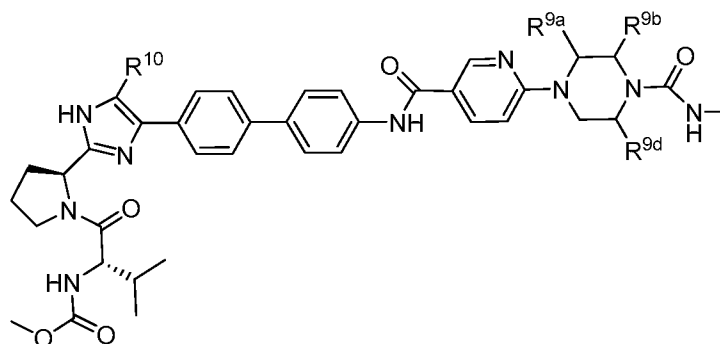
Table 12



5

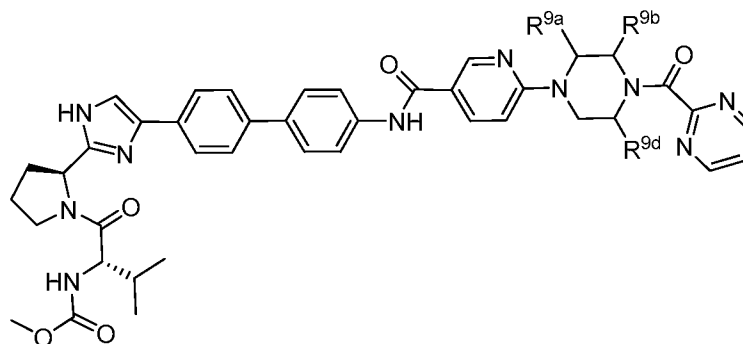
Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
12-1			(R)CH ₃			C ₄₂ H ₅₂ N ₈ O ₅	749.41	750.4
12-2			(S)CH ₃			C ₄₂ H ₅₂ N ₈ O ₅	749.41	749.4
12-3			(R)CH ₂ OH			C ₄₂ H ₅₂ N ₈ O ₆	765.40	766.4
12-4		(S)CH ₃		(R)CH ₃		C ₄₃ H ₅₄ N ₈ O ₅	763.42	763.4

Table 13



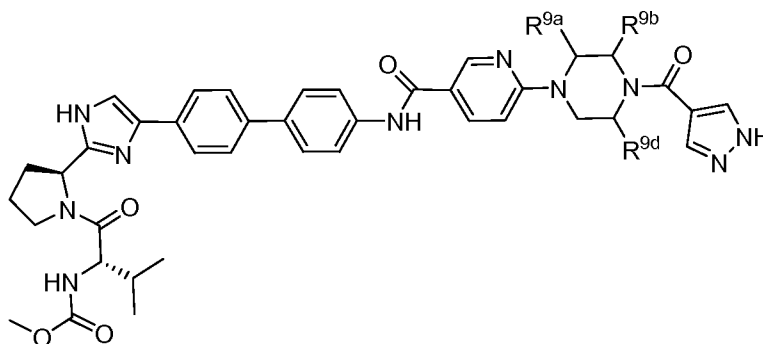
Ex No.	R ^{9a}	R ^{9b}	R ^{9d}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
13-1					C ₃₈ H ₄₅ N ₉ O ₅	708.35	708.2
13-2				CH ₃	C ₃₉ H ₄₇ N ₉ O ₅	722.37	722.2
13-3				Cl	C ₃₈ H ₄₄ ClN ₉ O ₅	742.32	742.2
13-4	(S)CH ₃				C ₃₉ H ₄₇ N ₉ O ₅	722.37	722.2
13-5	(R)CH ₃				C ₃₉ H ₄₇ N ₉ O ₅	722.37	722.4
13-6	(R)CH ₃			Cl	C ₃₉ H ₄₆ ClN ₉ O ₆	772.33	772.2
13-7		(R)CH ₃			C ₃₉ H ₄₇ N ₉ O ₅	722.37	722.4
13-8		(R)CH ₃		Cl	C ₃₉ H ₄₆ ClN ₉ O ₅	756.33	756.2
13-9		(S)CH ₃			C ₃₉ H ₄₇ N ₉ O ₅	722.37	722.2
13-10		(S)CH ₃		Cl	C ₃₉ H ₄₆ ClN ₉ O ₅	756.33	756.2
13-11	(R)CH ₂ OH				C ₃₉ H ₄₇ N ₉ O ₆	738.37	738.4
13-12	(S)CH ₂ OH				C ₃₉ H ₄₇ N ₉ O ₆	738.37	738.2
13-13		(S)CH ₂ OH			C ₃₉ H ₄₇ N ₉ O ₆	738.37	738.4
13-14		(R)CH ₂ OH			C ₃₉ H ₄₇ N ₉ O ₆	738.37	738.2
13-15		(S)CH ₂ OCH ₃			C ₄₀ H ₄₉ N ₉ O ₆	752.38	752.4
13-16		(S)CH ₃	(R)CH ₃		C ₄₀ H ₄₉ N ₉ O ₅	736.39	736.4

Table 14



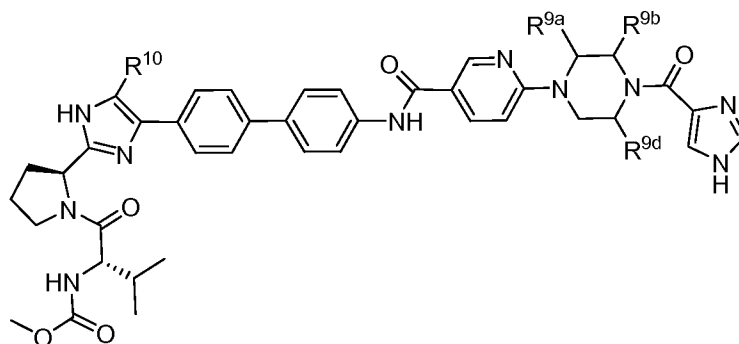
Ex No.	R ^{9a}	R ^{9b}	R ^{9d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
14-1				C ₄₁ H ₄₄ N ₁₀ O ₅	757.35	757.4
14-2	(S)CH ₃			C ₄₂ H ₄₆ N ₁₀ O ₅	771.37	771.4
14-3	(R)CH ₃			C ₄₂ H ₄₆ N ₁₀ O ₅	771.37	771.4
14-4		(R)CH ₃		C ₄₂ H ₄₆ N ₁₀ O ₅	771.37	771.4
14-5		(S)CH ₃		C ₄₂ H ₄₆ N ₁₀ O ₅	771.37	771.4
14-6	(R)CH ₂ OH			C ₄₂ H ₄₆ N ₁₀ O ₆	787.36	787.4
14-7	(S)CH ₂ OH			C ₄₂ H ₄₆ N ₁₀ O ₆	787.36	787.4
14-8		(S)CH ₂ OH		C ₄₂ H ₄₆ N ₁₀ O ₆	787.36	788.2
14-9		(R)CH ₂ OH		C ₄₂ H ₄₆ N ₁₀ O ₆	787.36	787.4
14-10		(S)CH ₂ OCH ₃		C ₄₃ H ₄₈ N ₁₀ O ₆	801.38	801.4
14-11		(S)CH ₃	(R)CH ₃	C ₄₃ H ₄₈ N ₁₀ O ₅	785.38	785.4

Table 15



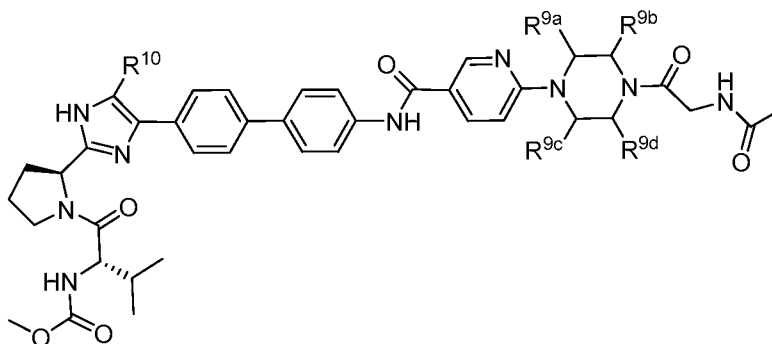
Ex No.	R ^{9a}	R ^{9b}	R ^{9d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
15-1				C ₄₀ H ₄₄ N ₁₀ O ₅	745.35	745.4
15-2	(S)CH ₃			C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.2
15-3	(R)CH ₃			C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
15-4		(R)CH ₃		C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
15-5		(S)CH ₃		C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.2
15-6	(R)CH ₂ OH			C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.4
15-7	(S)CH ₂ OH			C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.2
15-8		(S)CH ₂ OH		C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.2
15-9		(R)CH ₂ OH		C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.2
15-10		(S)CH ₂ OCH ₃		C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.4
15-11		(S)CH ₃	(R)CH ₃	C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	773.4

Table 16



Ex No.	R ^{9a}	R ^{9b}	R ^{9d}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
16-1					C ₄₀ H ₄₄ N ₁₀ O ₅	745.35	745.4
16-2	(S)CH ₃				C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
16-3	(R)CH ₃				C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.2
16-4		(R)CH ₃			C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
16-5		(R)CH ₃		Cl	C ₄₁ H ₄₅ ClN ₁₀ O ₅	793.33	793.4
16-6		(S)CH ₃			C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
16-7		(S)CH ₃		Cl	C ₄₁ H ₄₅ ClN ₁₀ O ₅	793.33	793.2
16-8	(R)CH ₂ OH				C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.4
16-9	(S)CH ₂ OH				C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.4
16-10		(S)CH ₂ OH			C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.4
16-11		(R)CH ₂ OH			C ₄₁ H ₄₆ N ₁₀ O ₆	775.36	775.4
16-12		(S)CH ₂ OCH ₃			C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.4
16-13		(S)CH ₃	(R)CH ₃		C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	773.4

Table 17



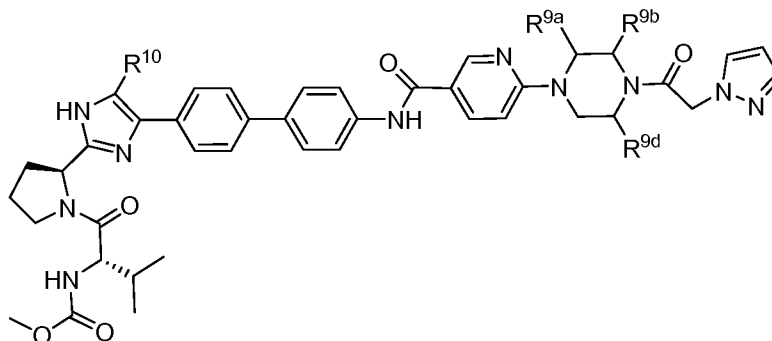
Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
17-1					C ₄₀ H ₄₇ N ₉ O ₆	750.37	750.3
17-2 ^(b)					C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.4
17-3	(S)CH ₃				C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.2
17-4 ^(a)	(S)CH ₃				C ₄₁ H ₄₈ ClN ₉ O ₆	798.34	798.2
17-5	(R)CH ₃				C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.2
17-6		(R)CH ₃			C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.8
17-7 ^(a)		(R)CH ₃			C ₄₁ H ₄₈ ClN ₉ O ₆	798.34	798.2
17-8		(S)CH ₃			C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.4
17-9 ^(a)		(S)CH ₃			C ₄₁ H ₄₈ ClN ₉ O ₆	798.34	798.2
17-10	(R)CH ₂ OH				C ₄₁ H ₄₉ N ₉ O ₇	780.38	780.4
17-11	(S)CH ₂ OH				C ₄₁ H ₄₉ N ₉ O ₇	780.38	780.4
17-12		(S)CH ₂ OH			C ₄₁ H ₄₉ N ₉ O ₇	780.38	780.4
17-13		(R)CH ₂ OH			C ₄₁ H ₄₉ N ₉ O ₇	780.38	780.4
17-14		(S)CH ₃	(R)CH ₃		C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.2
17-15		(S)CH ₂ OCH ₃			C ₄₂ H ₅₁ N ₉ O ₇	794.39	795.4
17-16		(S)CH ₃		(R)CH ₃	C ₄₂ H ₅₁ N ₉ O ₆	778.4	778.4
17-17		(S)C(O)NH ₂			C ₄₁ H ₄₈ N ₁₀ O ₇	793.37	793.2
17-18		(R)C(O)NH ₂			C ₄₁ H ₄₈ N ₁₀ O ₇	793.37	793.4
17-19		(S)CON(CH ₃) ₂			C ₄₃ H ₅₂ N ₁₀ O ₇	821.4	821.4
17-20		(R)CON(CH ₃) ₂			C ₄₃ H ₅₂ N ₁₀ O ₇	821.4	821.4

(a) R¹⁰ is Cl

5

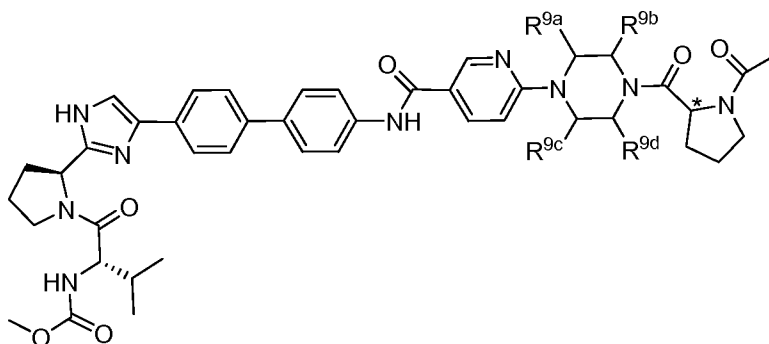
(b) R¹⁰ is CH₃

Table 18



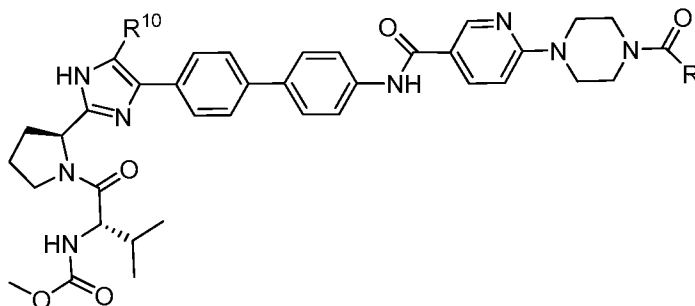
Ex No.	R ^{9a}	R ^{9b}	R ^{9d}	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
18-1					C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
18-2	(S)CH ₃				C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	774
18-3	(R)CH ₃				C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	773.4
18-4		(R)CH ₃			C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	774.4
18-5		(R)CH ₃		Cl	C ₄₂ H ₄₇ ClN ₁₀ O ₅	807.34	807.2
18-6		(S)CH ₃			C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	773.4
18-7		(S)CH ₃		Cl	C ₄₂ H ₄₇ ClN ₁₀ O ₅	807.34	807.4
18-8	(R)CH ₂ OH				C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.4
18-9	(S)CH ₂ OH				C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.4
18-10		(S)CH ₂ OH			C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.4
18-11		(S)CH ₂ OH		Cl	C ₄₂ H ₄₇ ClN ₁₀ O ₆	823.34	823.2
18-12		(R)CH ₂ OH			C ₄₂ H ₄₈ N ₁₀ O ₆	789.38	789.4
18-13		(R)CH ₂ OH		Cl	C ₄₂ H ₄₇ ClN ₁₀ O ₆	823.34	823.2
18-14		(R)CH ₂ OCH ₃			C ₄₃ H ₅₀ N ₁₀ O ₆	803.39	803.4
18-15		(S)CH ₂ OCH ₃			C ₄₃ H ₅₀ N ₁₀ O ₆	803.39	803.4
18-16		(S)CH ₃	(R)CH ₃		C ₄₃ H ₅₀ N ₁₀ O ₅	787.40	787.4
18-17		(S)CON(CH ₃) ₂			C ₄₄ H ₅₁ N ₁₁ O ₆	830.40	830.4
18-18		(R)CON(CH ₃) ₂			C ₄₄ H ₅₁ N ₁₁ O ₆	830.40	830.4

Table 19



Ex No.	R ^{9a}	R ^{9b}	R ^{9c}	R ^{9d}	*	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
19-1					(R)	C ₄₃ H ₅₁ N ₉ O ₆	790.4	790.4
19-2					(S)	C ₄₃ H ₅₁ N ₉ O ₆	790.4	790.4
19-3	(R)CH ₃				(R)	C ₄₄ H ₅₃ N ₉ O ₆	804.41	804.4
19-4		(R)CH ₃			(R)	C ₄₄ H ₅₃ N ₉ O ₆	804.41	804.4
19-5		(S)CH ₃			(R)	C ₄₄ H ₅₃ N ₉ O ₆	804.41	804.4
19-6		(S)CH ₂ OH			(R)	C ₄₄ H ₅₃ N ₉ O ₇	820.41	820.4
19-7		(R)CH ₂ OH			(R)	C ₄₄ H ₅₃ N ₉ O ₇	820.41	820.4
19-8		(R)CH ₃	(R)CH ₃		(R)	C ₄₅ H ₅₅ N ₉ O ₆	818.43	818.4
19-9		(S)CH ₃		(R)CH ₃	(R)	C ₄₅ H ₅₅ N ₉ O ₆	818.43	818.4

Table 20



Ex No.	R	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
20-1			C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.2
20-2			C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.6
20-3	CH ₂ SO ₂ CH ₃	CH ₃	C ₄₀ H ₄₈ N ₈ O ₇ S	785.34	785.2
20-4			C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
20-5	C(CH ₃) ₂ OH		C ₄₀ H ₄₈ N ₈ O ₆	737.37	737.2
20-6	CH(CH ₂ OH)NHC(O)CH ₃		C ₄₁ H ₄₉ N ₉ O ₇	780.38	780.2
20-7	CH((R) <i>i</i> Pr)NHC(O)CH ₃		C ₄₃ H ₅₃ N ₉ O ₆	792.41	792.4
20-8	CH((S)CH ₃)NHC(O)CH ₃		C ₄₁ H ₄₉ N ₉ O ₆	764.38	764.2
20-9	N <i>Hi</i> Pr		C ₄₀ H ₄₉ N ₉ O ₅	736.39	736.4
20-10			C ₄₃ H ₄₈ N ₁₀ O ₅	785.38	785.4
20-11			C ₄₅ H ₄₆ N ₁₀ O ₅	807.37	807.4
20-12			C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
20-13			C ₄₂ H ₄₄ ClN ₉ O ₅	790.32	790.2
20-14			C ₄₂ H ₄₄ FN ₉ O ₅	774.35	774.3

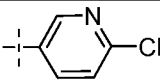
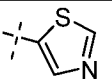
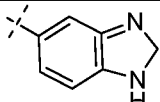
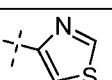
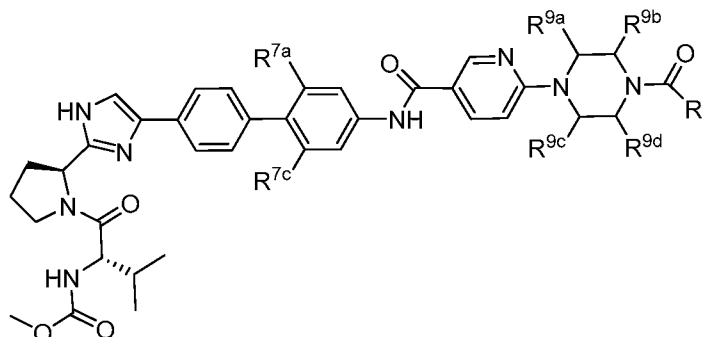
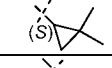


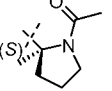
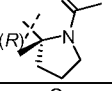
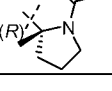
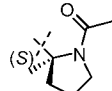



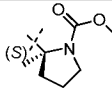



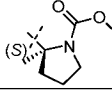






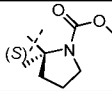


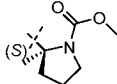




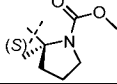

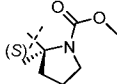


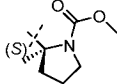







Ex No.	R	R ¹⁰	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
20-15			C ₄₂ H ₄₄ ClN ₉ O ₅	790.32	790.2
20-16			C ₄₀ H ₄₃ N ₉ O ₅ S	762.31	762.2
20-17			C ₄₄ H ₄₆ N ₁₀ O ₅	795.37	795.4
20-18			C ₄₀ H ₄₃ N ₉ O ₅ S	762.31	762.2
20-19	phenyl		C ₄₃ H ₄₆ N ₈ O ₅	755.36	755.4
20-20	CH ₂ SO ₂ CH ₃		C ₃₉ H ₄₆ N ₈ O ₇ S	771.32	771.2





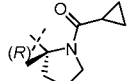
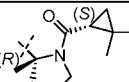
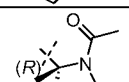
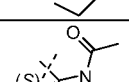
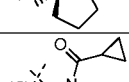
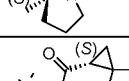
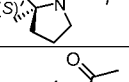
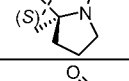
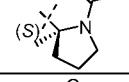
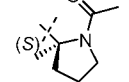
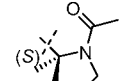
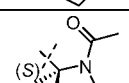
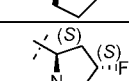
Table 21

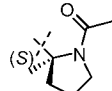
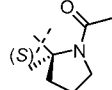


Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9c} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
21-1	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃	OtBu	C ₄₃ H ₅₄ N ₈ O ₆	779.42	779.4
21-2	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
21-3	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₂ H ₅₀ N ₈ O ₅	747.39	747.4
21-4	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₉ N ₉ O ₅	736.39	736.4
21-5	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	773.4
21-6	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₇ N ₉ O ₆	832.44	832.4
21-7	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₇ N ₉ O ₆	832.44	832.4
21-8		R ^{9b} =(S)CH ₃ , R ^{9c} =(R)CH ₃		C ₄₆ H ₅₇ N ₉ O ₆	832.44	832.4

Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9c} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
21-9		R ^{9b} =(S)CH ₃ , R ^{9c} =(R)CH ₃		C ₄₆ H ₅₇ N ₉ O ₆	832.44	832.4
21-10	R ^{7a} =CH ₃ , R ^{7c} =CH ₃	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₁ H ₅₁ N ₉ O ₅	750.40	750.4
21-11	R ^{7a} =CH ₃ , R ^{7c} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.4
21-12	R ^{7a} =CH ₃ , R ^{7c} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₃ H ₅₀ N ₁₀ O ₅	787.40	787.4
21-13	R ^{7a} =CH ₃ , R ^{7c} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4
21-14	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₇ N ₉ O ₇	848.44	848.4
21-15	R ^{7a} =CH ₃	R ^{9b} =(S)CH ₃ , R ^{9d} =(R)CH ₃		C ₄₃ H ₅₀ N ₁₀ O ₅	787.40	787.2
21-16	R ^{7a} =CH ₃	R ^{9b} =(S)CH ₃ , R ^{9d} =(R)CH ₃	NHCH ₃	C ₄₁ H ₅₁ N ₉ O ₅	750.40	750.4
21-17	R ^{7a} =CH ₃	R ^{9b} =(S)CH ₃ , R ^{9d} =(R)CH ₃		C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.4
21-18	R ^{7a} =CH ₃	R ^{9b} =(S)CH ₃ , R ^{9d} =(R)CH ₃		C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4
21-19	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₇ H ₅₉ N ₉ O ₇	862.45	862.4
21-20	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.4
21-21	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4
21-22	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃	NHCH ₃	C ₄₁ H ₅₁ N ₉ O ₅	750.40	750.4
21-23	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₃ H ₅₀ N ₁₀ O ₅	787.40	787.4
21-24	R ^{7a} =CF ₃	R ^{9a} =(R)CH ₃		C ₄₂ H ₄₇ F ₃ N ₈ O ₅	801.36	801.2
21-25	R ^{7a} =CF ₃	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₅	829.39	829.4
21-26	R ^{7a} =CF ₃	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₆ F ₃ N ₉ O ₅	790.36	790.2
21-27	R ^{7a} =CF ₃	R ^{9a} =(R)CH ₃		C ₄₂ H ₄₅ F ₃ N ₁₀ O ₅	827.35	827.4
21-28	R ^{7a} =CF ₃	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₄ F ₃ N ₉ O ₇	902.41	902.4
21-29	R ^{7a} =CN	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₆ N ₁₀ O ₅	747.37	747.4
21-30	R ^{7a} =CN	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₁ N ₉ O ₅	786.40	786.4
21-31	R ^{7a} =CN	R ^{9a} =(R)CH ₃		C ₄₂ H ₄₅ N ₁₁ O ₅	784.36	784.4

Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9c} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
21-32	R ^{7a} =CN	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₄ N ₁₀ O ₇	859.42	859.4
21-33	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₂ SO ₂ CH ₃		C ₄₅ H ₅₆ N ₈ O ₇ S	853.40	853.4
21-34	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4
21-35	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₆ F ₃ N ₉ O ₆	806.35	806.4
21-36	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃		C ₄₂ H ₄₅ F ₃ N ₁₀ O ₆	843.35	843.2
21-37	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃		C ₄₂ H ₄₇ F ₃ N ₈ O ₆	817.36	817.2
21-38	R ^{7a} =OCH ₃	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₇ N ₉ O ₈	864.43	864.4
21-39	R ^{7a} =OCH ₃	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₉ N ₉ O ₆	752.38	752.4
21-40	R ^{7a} =OCH ₃	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
21-41	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₄ F ₃ N ₉ O ₈	918.41	918.4
21-42	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃		C ₄₃ H ₄₈ F ₃ N ₉ O ₇	860.36	860.4
21-43	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₃ H ₄₉ F ₃ N ₈ O ₆	831.37	831.2
21-44	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₇ H ₅₆ F ₃ N ₉ O ₈	932.42	932.4
21-45	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₃ H ₄₇ F ₃ N ₁₀ O ₆	857.36	857.2
21-46	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₅ H ₅₃ F ₃ N ₈ O ₆	859.40	859.4
21-47	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃ , R ^{9d} =(S)CH ₃	NHCH ₃	C ₄₁ H ₄₈ F ₃ N ₉ O ₆	820.37	820.5
21-48	R ^{7a} =OCF ₃	R ^{9b} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₃ H ₄₉ F ₃ N ₈ O ₆	831.37	831.4
21-49	R ^{7a} =OCF ₃	R ^{9b} =(R)CH ₃ , R ^{9d} =(S)CH ₃	NHCH ₃	C ₄₁ H ₄₈ F ₃ N ₉ O ₆	820.37	820.4
21-50	R ^{7a} =OCF ₃	R ^{9b} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₃ H ₄₇ F ₃ N ₁₀ O ₆	857.36	857.4
21-51	R ^{7a} =OCF ₃	R ^{9b} =(R)CH ₃ , R ^{9d} =(S)CH ₃		C ₄₅ H ₅₃ F ₃ N ₈ O ₆	859.40	860.2
21-52	R ^{7a} =F	R ^{9a} =(R)CH ₃		C ₄₁ H ₄₇ FN ₈ O ₅	751.37	751.2
21-53	R ^{7a} =F	R ^{9a} =(R)CH ₃	NHCH ₃	C ₃₉ H ₄₆ FN ₉ O ₅	740.36	740.4
21-54	R ^{7a} =F	R ^{9a} =(R)CH ₃		C ₄₁ H ₄₅ FN ₁₀ O ₅	777.36	777.2

Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9c} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
21-55	R ^{7a} =F	R ^{9a} =(R)CH ₃		C ₄₃ H ₅₁ FN ₈ O ₅	779.40	779.4
21-56	R ^{7a} =F, R ^{7c} =F	R ^{9a} =(R)CH ₃		C ₄₁ H ₄₆ F ₂ N ₈ O ₅	769.36	769.2
21-57	R ^{7a} =F, R ^{7c} =F	R ^{9a} =(R)CH ₃		C ₄₃ H ₅₀ F ₂ N ₈ O ₅	797.39	797.4
21-58	R ^{7a} =F, R ^{7c} =F	R ^{9a} =(R)CH ₃	NHCH ₃	C ₃₉ H ₄₅ F ₂ N ₉ O ₅	758.35	758.4
21-59	R ^{7a} =F, R ^{7c} =F	R ^{9a} =(R)CH ₃		C ₄₁ H ₄₄ F ₂ N ₁₀ O ₅	795.35	795.2
21-60				C ₄₅ H ₅₃ N ₉ O ₆	816.41	816.4
21-61				C ₄₇ H ₅₇ N ₉ O ₆	844.44	844.4
21-62				C ₄₄ H ₅₃ N ₉ O ₆	804.41	804.4
21-63				C ₄₄ H ₅₃ N ₉ O ₆	804.41	804.2
21-64				C ₄₆ H ₅₅ N ₉ O ₆	830.43	830.4
21-65				C ₄₈ H ₅₉ N ₉ O ₆	858.46	858.4
21-66		R ^{9a} =(S)CH ₃		C ₄₅ H ₅₅ N ₉ O ₆	818.43	818.4
21-67		R ^{9b} =(S)CH ₂ OCH ₃		C ₄₆ H ₅₇ N ₉ O ₇	848.44	848.4
21-68		R ^{9b} =(R)CH ₂ OH		C ₄₅ H ₅₅ N ₉ O ₇	834.42	834.4
21-69		R ^{9b} =(S)CH ₂ OH		C ₄₅ H ₅₅ N ₉ O ₇	834.42	834.4
21-70		R ^{9a} =(R)CH ₃		C ₄₅ H ₅₅ N ₉ O ₆	818.43	818.4
21-71				C ₄₃ H ₅₀ FN ₉ O ₆	808.39	808.4
21-72		R ^{9a} =(R)CH ₃		C ₄₅ H ₅₅ N ₉ O ₇	834.42	834.4

Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9c} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
21-73		R ^{9a} =(R)CH ₂ CH ₃		C ₄₆ H ₅₇ N ₉ O ₆	832.44	832.4
21-74		R ^{9a} =(S)CH ₂ CH ₃		C ₄₆ H ₅₇ N ₉ O ₆	832.44	832.4
21-75		R ^{9a} =(R)CH ₃	(b)	C ₅₀ H ₆₄ N ₁₀ O ₈	933.49	933.4
21-76		R ^{9a} =(R)CH ₃	(a)	C ₅₀ H ₆₄ N ₁₀ O ₈	933.49	933.4
21-77	R ^{7a} =OCH ₃	R ^{9a} =(R)CH ₃	(a)	C ₅₁ H ₆₆ N ₁₀ O ₉	963.50	963.4

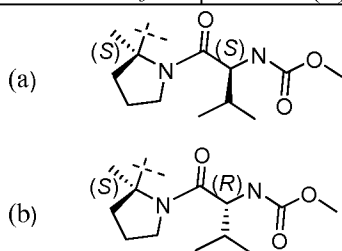
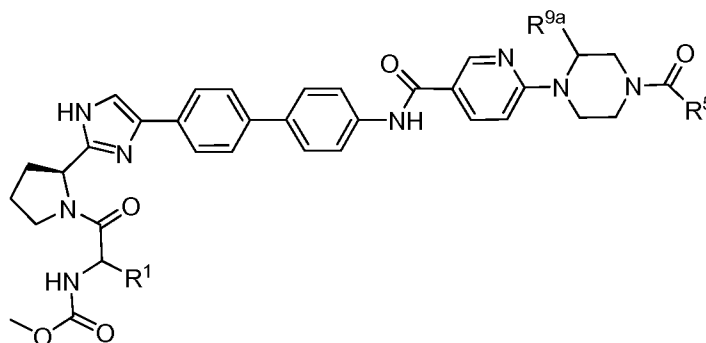









Table 22



5

Ex No.	R ¹	R ^{9a}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
22-1	(S)CH ₃			C ₃₈ H ₄₂ N ₈ O ₅	691.33	691.2
22-2	(S)CH ₂ OH			C ₃₈ H ₄₂ N ₈ O ₆	707.32	707.7
22-3	(S)C(CH ₃) ₂ OH			C ₄₀ H ₄₆ N ₈ O ₆	735.35	735.2
22-4	(R)phenyl			C ₄₃ H ₄₄ N ₈ O ₅	753.34	753.2
22-5	(S) CH ₂ ((S)CH ₃)OCH ₃			C ₄₀ H ₄₆ N ₈ O ₆	735.35	735.2
22-6	(S)CH ₃	(R)CH ₃		C ₄₁ H ₄₈ N ₈ O ₅	733.38	733.4
22-7	(S)CH ₂ OH	(R)CH ₃		C ₄₁ H ₄₈ N ₈ O ₆	749.37	749.4






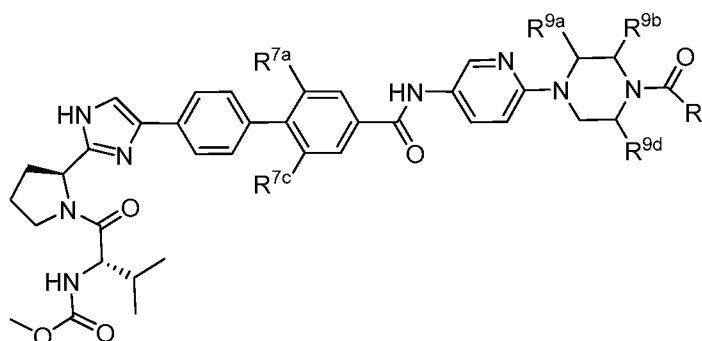








Ex No.	R ¹	R ^{9a}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
22-8	(R)phenyl	(R)CH ₃		C ₄₆ H ₅₀ N ₈ O ₅	795.39	795.4
22-9	(S) CH ₂ ((S)CH ₃)OCH ₃	(R)CH ₃		C ₄₃ H ₅₂ N ₈ O ₆	777.40	777.4
22-10	(S) C(CH ₃) ₃	(R)CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
22-11	(S)cPr	(R)CH ₃		C ₄₃ H ₅₀ N ₈ O ₅	759.39	759.4
22-12	(R)CH(CH ₃) ₂	(R)CH ₃		C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4

Table 23



Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
23-1		R ^{9a} =(R)CH ₃		C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.7
23-2		R ^{9a} =(R)CH ₃		C ₄₄ H ₅₆ N ₈ O ₆	793.43	793.4
23-3		R ^{9a} =(R)CH ₃		C ₄₁ H ₄₆ N ₁₀ O ₅	759.37	759.4
23-4		R ^{9a} =(R)CH ₃		C ₄₅ H ₅₅ N ₉ O ₇	834.42	834.4
23-5		R ^{9a} =(R)CH ₃	NHCH ₃	C ₃₉ H ₄₇ N ₉ O ₅	722.37	722.4
23-6		R ^{9a} =(R)CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
23-7		R ^{9a} =(R)CH ₃ R ^{9d} =(S)CH ₃		C ₄₂ H ₄₈ N ₁₀ O ₅	773.38	773.4
23-8		R ^{9a} =(R)CH ₃ R ^{9d} =(S)CH ₃	(a)	C ₅₁ H ₆₆ N ₁₀ O ₈	947.51	947.6
23-9		R ^{9a} =(R)CH ₃ R ^{9d} =(S)CH ₃	NHCH ₃	C ₄₀ H ₄₉ N ₉ O ₅	736.39	736.4
23-10		R ^{9a} =(R)CH ₃	(a)	C ₅₀ H ₆₄ N ₁₀ O ₈	933.49	933.4

Ex No.	R ^{7a} , R ^{7c}	R ^{9a} , R ^{9b} , R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
23-11	R ^{7a} =OCH ₃	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
23-12	R ^{7a} =CH ₃	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₉ N ₉ O ₅	736.39	736.4
23-13	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.8
23-14	R ^{7a} =OCF ₃	R ^{9a} =(R)CH ₃	(a)	C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1017.47	1017.9

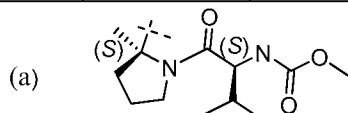
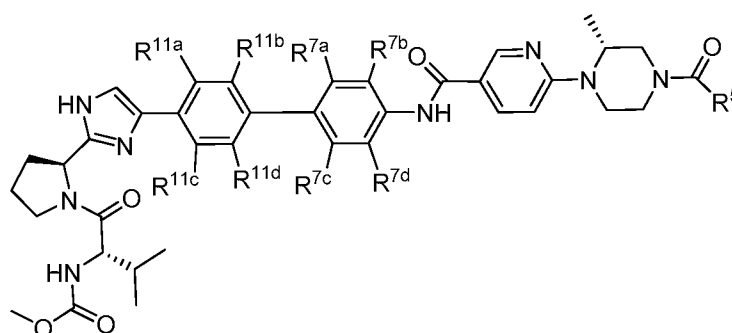
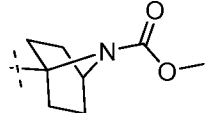
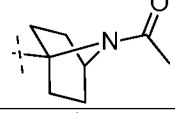
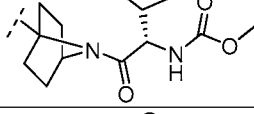
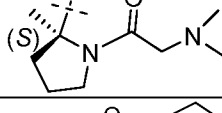
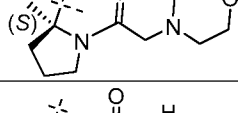
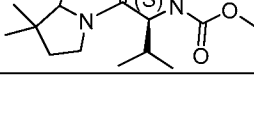

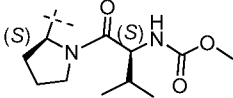

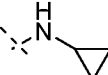
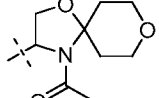
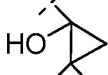
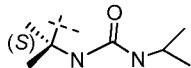
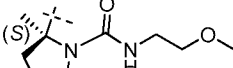
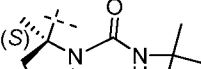
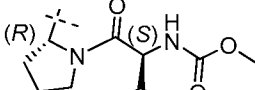
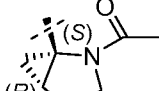
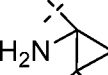


Table 24



5

Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
24-1				C ₄₆ H ₅₅ N ₉ O ₇	846.42	846.4
24-2				C ₄₆ H ₅₅ N ₉ O ₆	830.43	830.4
24-3				C ₅₁ H ₆₄ N ₁₀ O ₈	945.49	945.4
24-4				C ₄₇ H ₆₀ N ₁₀ O ₆	861.47	861.4
24-5				C ₄₉ H ₆₂ N ₁₀ O ₇	903.48	903.4
24-6				C ₅₁ H ₆₆ N ₁₀ O ₈	947.51	945.4

Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
24-7				C ₄₃ H ₅₂ N ₈ O ₅	761.41	761.4
24-8				C ₄₉ H ₆₂ N ₁₀ O ₈	919.48	919.6
24-9				C ₄₃ H ₅₃ N ₉ O ₅	776.42	776.4
24-10			CH ₂ t-Bu	C ₄₃ H ₅₄ N ₈ O ₅	763.42	763.4
24-11				C ₄₁ H ₄₉ N ₉ O ₅	748.39	748.4
24-12			NHC(CH ₃) ₂ CH ₂ OH	C ₄₂ H ₅₃ N ₉ O ₆	780.41	780.4
24-13				C ₄₇ H ₅₇ N ₉ O ₈	876.43	876.4
24-14				C ₄₃ H ₅₂ N ₈ O ₆	777.4	777.4
24-15		R ^{7a} =OiPr	NHCH ₃	C ₄₂ H ₅₃ N ₉ O ₆	780.41	780.4
24-16				C ₄₇ H ₆₀ N ₁₀ O ₆	861.47	861.6
24-17				C ₄₇ H ₆₀ N ₁₀ O ₇	877.47	877.4
24-18				C ₄₈ H ₆₂ N ₁₀ O ₆	875.49	875.6
24-19				C ₄₉ H ₆₂ N ₁₀ O ₈	919.48	919.4
24-20	R ^{11b} =CH ₃			C ₄₆ H ₅₅ N ₉ O ₆	830.43	830.7
24-21				C ₄₃ H ₅₃ N ₉ O ₅	776.42	776.4
24-22		R ^{7a} =OCHF ₂	NHCH ₃	C ₄₀ H ₄₇ F ₂ N ₉ O ₆	788.36	788.4
24-23	R ^{11b} =OCF ₃		NHCH ₃	C ₄₀ H ₄₆ F ₃ N ₉ O ₆	806.35	806.4


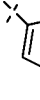


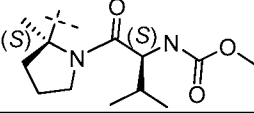
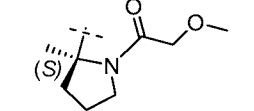
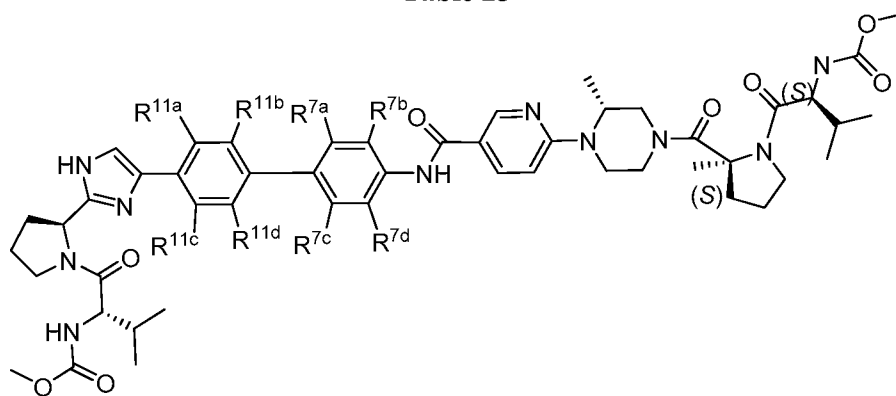
Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
24-24		R ^{7a} =CH ₃ R ^{7d} =F	NHCH ₃	C ₄₀ H ₄₈ FN ₉ O ₅	754.38	754.8
24-25		R ^{7a} =OCH ₃ R ^{7d} =Cl		C ₄₂ H ₄₉ ClN ₈ O ₆	797.35	798.0
24-26		R ^{7b} =OH	NHCH ₃	C ₃₉ H ₄₇ N ₉ O ₆	738.37	738.8
24-27		R ^{7b} =CH ₂ CH ₃		C ₄₃ H ₅₀ N ₁₀ O ₅	787.4	787.8
24-28		R ^{7b} =CH ₂ CH ₃	NHCH ₃	C ₄₁ H ₅₁ N ₉ O ₅	750.4	750.8
24-29		R ^{7a} =Cl R ^{7b} =F		C ₄₁ H ₄₄ ClFN ₁₀ O ₅	811.32	811.6
24-30		R ^{7a} =Cl R ^{7b} =F	NHCH ₃	C ₃₉ H ₄₅ ClFN ₉ O ₅	774.32	774.8
24-31		R ^{7a} =Cl R ^{7b} =F		C ₄₃ H ₅₀ ClFN ₈ O ₅	813.36	813.6
24-32		R ^{7a} =Cl R ^{7b} =F		C ₅₀ H ₆₂ ClFN ₁₀ O ₈	985.44	985.6
24-33		R ^{7a} =OCH ₃ R ^{7c} =OCH ₃		C ₄₈ H ₆₁ N ₉ O ₉	908.46	907.8

Table 25

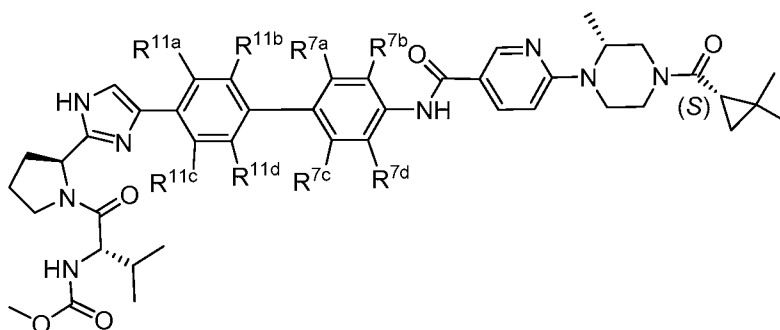


Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
25-1		R ^{7a} =CF ₃	C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
25-2		R ^{7a} =CN	C ₅₁ H ₆₃ N ₁₁ O ₈	958.49	958.4

Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
25-3	R ^{11b} =CH ₃		C ₅₁ H ₆₆ N ₁₀ O ₈	947.51	947.8
25-4		R ^{7a} =CH ₃	C ₅₁ H ₆₆ N ₁₀ O ₈	947.51	947.4
25-5		R ^{7a} =O(CH ₂) ₂ OCH ₃	C ₅₃ H ₇₀ N ₁₀ O ₁₀	1,007.53	1007.4
25-6		R ^{7a} =OiPr	C ₅₃ H ₇₀ N ₁₀ O ₉	991.53	991.6
25-7	R ^{11b} =F		C ₅₀ H ₆₃ FN ₁₀ O ₈	951.48	951.4
25-8	R ^{11b} =CF ₃		C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
25-9		R ^{7b} =F R ^{7d} =F	C ₅₀ H ₆₂ F ₂ N ₁₀ O ₈	969.47	969.4
25-10	R ^{11b} =OCH ₃		C ₅₁ H ₆₆ N ₁₀ O ₉	963.5	963.4
25-11	R ^{11b} =F	R ^{7a} =F	C ₅₀ H ₆₂ F ₂ N ₁₀ O ₈	969.47	969.6
25-12		R ^{7a} =CH ₃ R ^{7c} =CH ₃	C ₅₂ H ₆₈ N ₁₀ O ₈	961.52	961.6
25-13		R ^{7a} =Cl	C ₅₀ H ₆₃ ClN ₁₀ O ₈	967.45	967.4
25-14		R ^{7a} =F R ^{7c} =F	C ₅₀ H ₆₂ F ₂ N ₁₀ O ₈	969.47	969.4
25-15	R ^{11b} =OCF ₃		C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1,017.47	1017.4
25-16	R ^{11a} =CH ₃	R ^{7c} =F	C ₅₁ H ₆₅ FN ₁₀ O ₈	965.5	965.4
25-17	R ^{11b} =CF ₃	R ^{7a} =F	C ₅₁ H ₆₂ F ₄ N ₁₀ O ₈	1,019.47	1019.4
25-18		R ^{7b} =OCH ₃	C ₅₁ H ₆₆ N ₁₀ O ₉	963.5	963.4
25-19		R ^{7b} =CF ₃	C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
25-20	R ^{11a} =CH ₃		C ₅₁ H ₆₆ N ₁₀ O ₈	947.51	947.6
25-21		R ^{7b} =F	C ₅₀ H ₆₃ FN ₁₀ O ₈	951.48	951.4
25-22		R ^{7b} =Cl	C ₅₀ H ₆₃ ClN ₁₀ O ₈	967.45	967.6
25-23	R ^{11b} =OCHF ₂		C ₅₁ H ₆₄ F ₂ N ₁₀ O ₉	999.48	999.6
25-24		R ^{7a} =CF ₃ R ^{7b} =F	C ₅₁ H ₆₂ F ₄ N ₁₀ O ₈	1,019.47	1019.4

Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
25-25		R ^{7a} =OCF ₃ R ^{7b} =F	C ₅₁ H ₆₂ F ₄ N ₁₀ O ₉	1,035.46	1035.4
25-26	R ^{11b} =CH ₃	R ^{7a} =F	C ₅₁ H ₆₅ FN ₁₀ O ₈	965.5	965.4
25-27	R ^{11a} =CF ₃		C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
25-28	R ^{11a} =F		C ₅₀ H ₆₃ FN ₁₀ O ₈	951.48	951.4
25-29	R ^{11a} =OCF ₃		C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1,017.47	1017.4
25-30		R ^{7b} =CN	C ₅₁ H ₆₃ N ₁₁ O ₈	958.49	958.4
25-31		R ^{7a} =Cl R ^{7d} =OCH ₃	C ₅₁ H ₆₅ ClN ₁₀ O ₉	997.46	997.6
25-32	R ^{11b} =CH ₃	R ^{7a} =F R ^{7c} =F	C ₅₁ H ₆₄ F ₂ N ₁₀ O ₈	983.49	983.4
25-33		R ^{7a} =F R ^{7d} =F	C ₅₀ H ₆₂ F ₂ N ₁₀ O ₈	969.47	969.6
25-34		R ^{7a} =Cl R ^{7d} =F	C ₅₀ H ₆₂ ClFN ₁₀ O ₈	985.44	985.4
25-35		R ^{7a} =CH ₃ R ^{7d} =F	C ₅₁ H ₆₅ FN ₁₀ O ₈	965.5	965.6
25-36		R ^{7a} =OCH ₃ R ^{7d} =Cl	C ₅₁ H ₆₅ ClN ₁₀ O ₉	997.46	998.2
25-37		R ^{7b} =OH	C ₅₀ H ₆₄ N ₁₀ O ₉	949.49	950.2
25-38		R ^{7a} =OCH ₃ R ^{7c} =OCH ₃	C ₅₂ H ₆₈ N ₁₀ O ₁₀	993.51	994.2
25-39		R ^{7a} =F R ^{7b} =F	C ₅₀ H ₆₂ F ₂ N ₁₀ O ₈	969.47	969.4
25-40		R ^{7a} =F R ^{7d} =Cl	C ₅₀ H ₆₂ ClFN ₁₀ O ₈	985.44	985.4
25-41		R ^{7b} =CH ₂ CH ₃	C ₅₂ H ₆₈ N ₁₀ O ₈	961.52	961.6

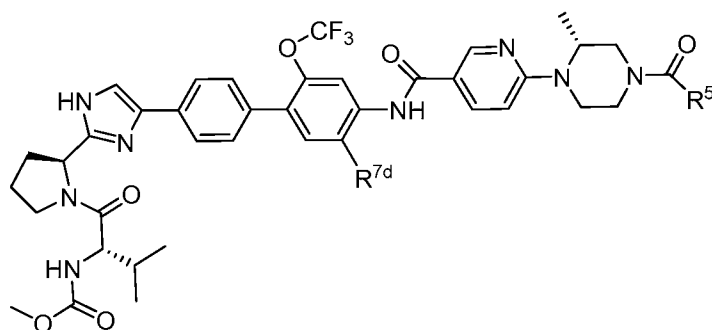
Table 26



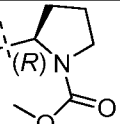

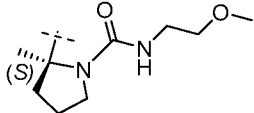
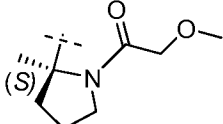
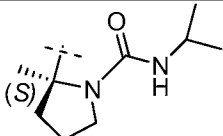
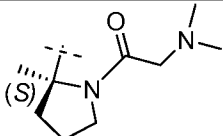
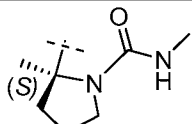
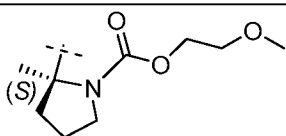
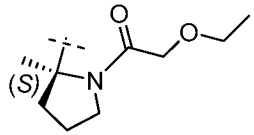
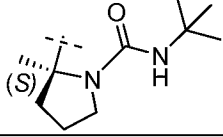
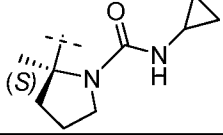

Ex. No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
26-1	R ^{11b} =CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
26-2		R ^{7a} =O(CH ₂) ₂ OCH ₃	C ₄₆ H ₅₈ N ₈ O ₇	835.44	835.4
26-3		R ^{7a} =OiPr	C ₄₆ H ₅₈ N ₈ O ₆	819.45	819.4
26-4	R ^{11b} =F		C ₄₃ H ₅₁ FN ₈ O ₅	779.4	779.4
26-5		R ^{7b} =F R ^{7d} =F	C ₄₃ H ₅₀ F ₂ N ₈ O ₅	797.39	797.4
26-6	R ^{11b} =OCH ₃		C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
26-7	R ^{11b} =CF ₃	R ^{7a} =F	C ₄₄ H ₅₀ F ₄ N ₈ O ₅	847.38	847.4
26-8	R ^{11b} =CF ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₅	829.39	829.6
26-9	R ^{11a} =CH ₃	R ^{7c} =F	C ₄₄ H ₅₃ FN ₈ O ₅	793.41	793.4
26-10	R ^{11b} =OCF ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.0
26-11		R ^{7b} =OCH ₃	C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
26-12		R ^{7b} =CF ₃	C ₄₄ H ₅₁ F ₃ N ₈ O ₅	829.39	829.4
26-13	R ^{11a} =CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
26-14		R ^{7b} =F	C ₄₃ H ₅₁ FN ₈ O ₅	779.4	779.4
26-15		R ^{7b} =Cl	C ₄₃ H ₅₁ ClN ₈ O ₅	795.37	795.4
26-16		R ^{7ab} =OCHF ₂	C ₄₄ H ₅₂ F ₂ N ₈ O ₆	827.4	827.4
26-17	R ^{11a} =CF ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₅	829.39	829.4

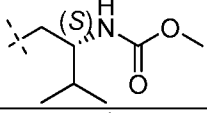
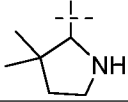
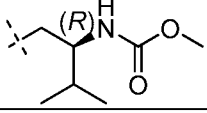
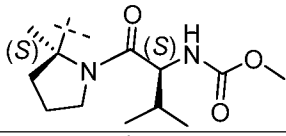
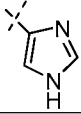

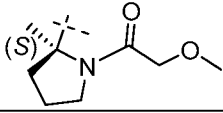
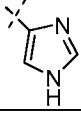
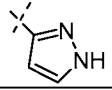
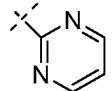
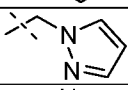
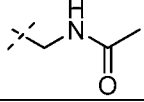
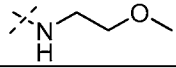
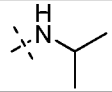
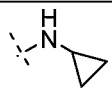
Ex. No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
26-18	R ^{11a} =OCF ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4
26-19	R ^{11a} =F		C ₄₃ H ₅₁ FN ₈ O ₅	779.4	779.4
26-20		R ^{7a} =CF ₃ R ^{7b} =F	C ₄₄ H ₅₀ F ₄ N ₈ O ₅	847.38	847.4
26-21		R ^{7a} =OCF ₃ R ^{7b} =F	C ₄₄ H ₅₀ F ₄ N ₈ O ₆	863.38	863.4
26-22		R ^{7b} =CN	C ₄₄ H ₅₁ N ₉ O ₅	786.4	786.4
26-23		R ^{7a} =Cl R ^{7d} =OCH ₃	C ₄₄ H ₅₃ ClN ₈ O ₆	825.38	825.4
26-24	R ^{11b} =CH ₃	R ^{7a} =F	C ₄₄ H ₅₃ FN ₈ O ₅	793.41	793.0
26-25	R ^{11b} =CH ₃	R ^{7a} =F R ^{7c} =F	C ₄₄ H ₅₂ F ₂ N ₈ O ₅	811.4	811.4
26-26		R ^{7a} =F R ^{7d} =F	C ₄₃ H ₅₀ F ₂ N ₈ O ₅	797.39	797.4
26-27		R ^{7a} =Cl R ^{7d} =F	C ₄₃ H ₅₀ ClFN ₈ O ₅	813.36	813.4
26-28		R ^{7a} =F R ^{7b} =F	C ₄₃ H ₅₀ F ₂ N ₈ O ₅	797.39	797.4
26-29		R ^{7a} =F R ^{7d} =Cl	C ₄₃ H ₅₀ ClFN ₈ O ₅	813.36	813.4
26-30		R ^{7a} =CH ₃ R ^{7d} =F	C ₄₄ H ₅₃ FN ₈ O ₅	793.41	793.8
26-31		R ^{7a} =OCH ₃ R ^{7d} =Cl	C ₄₄ H ₅₃ ClN ₈ O ₆	825.38	826.0
26-32		R ^{7b} =OH	C ₄₃ H ₅₂ N ₈ O ₆	777.4	778.0
26-33		R ^{7a} =OCH ₃ R ^{7c} =OCH ₃	C ₄₅ H ₅₆ N ₈ O ₇	821.43	822.0
26-34		R ^{7b} =CH ₂ CH ₃	C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.8

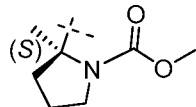
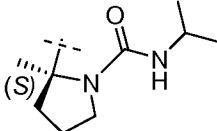
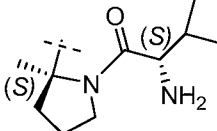
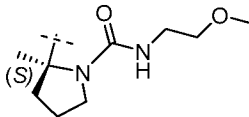
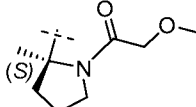
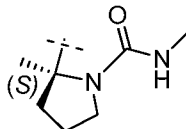
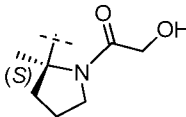
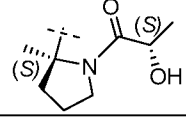
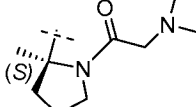
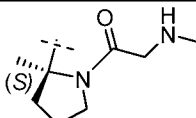
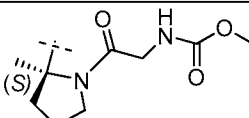
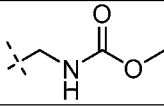
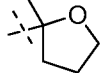
Table 27

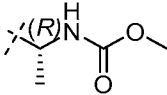
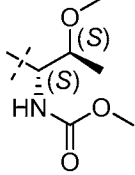
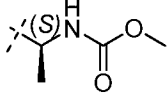
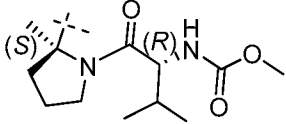
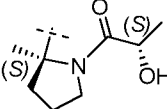
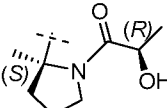
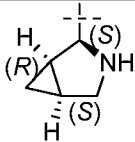
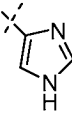

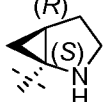


Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
27-1			C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1,017.47	1017.4
27-2		NH(CH ₂) ₂ OCH ₃	C ₄₂ H ₅₀ F ₃ N ₉ O ₇	850.38	850.4
27-3			C ₄₃ H ₅₂ F ₃ N ₉ O ₆	848.40	848.4
27-4			C ₄₂ H ₅₀ F ₃ N ₉ O ₆	834.38	834.4
27-5		t-Bu	C ₄₃ H ₅₁ F ₃ N ₈ O ₆	833.39	833.4
27-6			C ₄₂ H ₄₈ F ₃ N ₉ O ₆	832.37	832.4
27-7			C ₄₃ H ₄₇ F ₃ N ₁₀ O ₆	857.36	857.4
27-8	F		C ₄₉ H ₅₉ F ₄ N ₉ O ₈	978.44	977.6
27-9	F		C ₄₄ H ₅₁ F ₄ N ₉ O ₆	878.39	877.8
27-10			C ₄₄ H ₅₀ F ₃ N ₉ O ₆	858.38	857.6
27-11			C ₄₃ H ₄₇ F ₃ N ₁₀ O ₆	857.36	856.6

Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
27-12			C ₄₅ H ₅₂ F ₃ N ₉ O ₈	904.39	903.6
27-13		O(CH ₂) ₂ OCH ₃	C ₄₂ H ₄₉ F ₃ N ₈ O ₈	851.36	850.6
27-14			C ₄₃ H ₄₉ F ₃ N ₈ O ₆	831.37	830.6
27-15			C ₄₈ H ₅₉ F ₃ N ₁₀ O ₈	961.45	961.6
27-16			C ₄₇ H ₅₆ F ₃ N ₉ O ₈	932.42	932.6
27-17			C ₄₈ H ₅₉ F ₃ N ₁₀ O ₇	945.45	945.6
27-18			C ₄₈ H ₅₉ F ₃ N ₁₀ O ₇	945.45	945.6
27-19			C ₄₆ H ₅₅ F ₃ N ₁₀ O ₇	917.42	917.6
27-20			C ₄₈ H ₅₈ F ₃ N ₉ O ₉	962.43	962.6
27-21			C ₄₈ H ₅₈ F ₃ N ₉ O ₈	946.44	946.6
27-22			C ₄₉ H ₆₁ F ₃ N ₁₀ O ₇	959.47	959.6
27-23			C ₄₈ H ₅₇ F ₃ N ₁₀ O ₇	943.44	943.6
27-24			C ₄₄ H ₅₀ F ₃ N ₉ O ₆	858.38	858.6

Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
27-25			C ₄₆ H ₅₆ F ₃ N ₉ O ₈	920.42	920.6
27-26			C ₄₅ H ₅₄ F ₃ N ₉ O ₆	874.42	874.6
27-27			C ₄₆ H ₅₆ F ₃ N ₉ O ₈	920.42	920.6
27-28	OCH ₃		C ₅₂ H ₆₅ F ₃ N ₁₀ O ₁₀	1,047.48	1046.6
27-29	OCH ₃		C ₄₃ H ₄₇ F ₃ N ₁₀ O ₇	873.36	872.6
27-30	OCH ₃		C ₄₅ H ₅₃ F ₃ N ₈ O ₇	875.4	874.6
27-31	OCH ₃		C ₄₈ H ₅₈ F ₃ N ₉ O ₉	962.43	961.6
27-32	OCH ₃	NHCH ₃	C ₄₁ H ₄₈ F ₃ N ₉ O ₇	836.36	835.8
27-33	F		C ₄₂ H ₄₄ F ₄ N ₁₀ O ₆	861.34	862.0
27-34	F		C ₄₂ H ₄₄ F ₄ N ₁₀ O ₆	861.34	862.0
27-35	F		C ₄₃ H ₄₄ F ₄ N ₁₀ O ₆	873.34	874.0
27-36	F		C ₄₃ H ₄₆ F ₄ N ₁₀ O ₆	875.35	876.0
27-37	F		C ₄₂ H ₄₇ F ₄ N ₉ O ₇	866.35	867.0
27-38	F		C ₄₂ H ₄₉ F ₄ N ₉ O ₇	868.37	869.0
27-39	F		C ₄₂ H ₄₉ F ₄ N ₉ O ₆	852.37	853.0
27-40	F		C ₄₂ H ₄₇ F ₄ N ₉ O ₆	850.36	851.0
27-41	F	O(CH ₂) ₂ OCH ₃	C ₄₂ H ₄₈ F ₄ N ₈ O ₈	869.35	870.0

Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
27-42	F		C ₄₆ H ₅₃ F ₄ N ₉ O ₈	936.40	937.0
27-43	F		C ₄₈ H ₅₈ F ₄ N ₁₀ O ₇	963.44	964.2
27-44	F		C ₄₉ H ₆₀ F ₄ N ₁₀ O ₇	977.46	978.2
27-45	F		C ₄₈ H ₅₈ F ₄ N ₁₀ O ₈	979.44	980.0
27-46	F		C ₄₇ H ₅₅ F ₄ N ₉ O ₈	950.41	951.0
27-47	F		C ₄₆ H ₅₄ F ₄ N ₁₀ O ₇	935.41	937.0
27-48	F		C ₄₆ H ₅₃ F ₄ N ₉ O ₈	936.4	936.0
27-49	F		C ₄₇ H ₅₅ F ₄ N ₉ O ₈	950.41	951.0
27-50	F		C ₄₈ H ₅₈ F ₄ N ₁₀ O ₇	963.44	964.0
27-51			C ₄₇ H ₅₇ F ₃ N ₁₀ O ₇	931.44	932.0
27-52			C ₄₈ H ₅₇ F ₃ N ₁₀ O ₉	975.43	976.0
27-53			C ₄₂ H ₄₈ F ₃ N ₉ O ₈	864.36	865.0
27-54			C ₄₄ H ₅₁ F ₃ N ₈ O ₇	861.38	862.0

Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
27-55			C ₄₃ H ₅₀ F ₃ N ₉ O ₈	878.37	879.0
27-56			C ₄₅ H ₅₄ F ₃ N ₉ O ₉	922.4	923.0
27-57			C ₄₃ H ₅₀ F ₃ N ₉ O ₈	878.37	879.0
27-58			C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1,017.47	1018.2
27-59			C ₄₇ H ₅₆ F ₃ N ₉ O ₈	932.42	933.0
27-60			C ₄₇ H ₅₆ F ₃ N ₉ O ₈	932.42	933.0
27-61		CH ₂ N(CH ₃) ₂	C ₄₂ H ₅₀ F ₃ N ₉ O ₆	834.38	834.8
27-62			C ₄₄ H ₅₀ F ₃ N ₉ O ₆	858.38	858.8
27-63		CH ₂ Oi-Pr	C ₄₃ H ₅₁ F ₃ N ₈ O ₇	849.38	849.8
27-64		CH(CH ₃)OCH ₃	C ₄₂ H ₄₉ F ₃ N ₈ O ₇	835.37	835.8
27-65		NH(CH ₂) ₃ OCH ₃	C ₄₃ H ₅₂ F ₃ N ₉ O ₇	864.39	864.8
27-66	Cl		C ₄₂ H ₄₄ ClF ₃ N ₁₀ O ₆	877.31	877.6
27-67	Cl	NH(CH ₂) ₃ OCH ₃	C ₄₂ H ₄₉ ClF ₃ N ₉ O ₇	884.34	884.6
27-68	Cl	NHCH ₃	C ₄₀ H ₄₅ ClF ₃ N ₉ O ₆	840.31	840.6
27-69	Cl		C ₄₄ H ₅₀ ClF ₃ N ₈ O ₆	879.35	879.6
27-70	Cl		C ₄₄ H ₄₉ ClF ₃ N ₉ O ₆	892.35	892.6

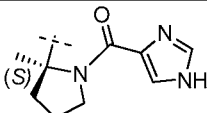
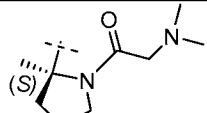
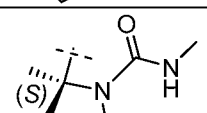
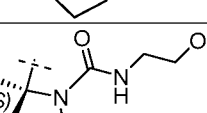
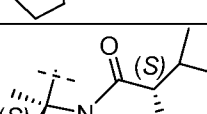
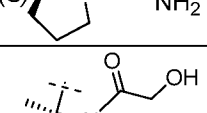
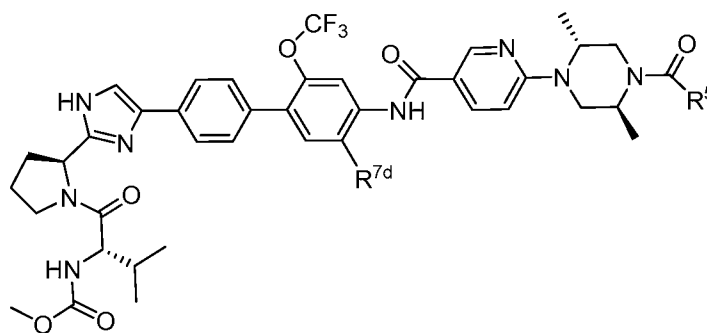
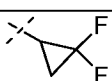
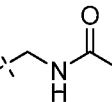
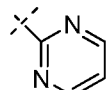
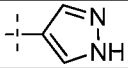

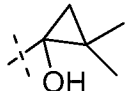
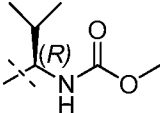



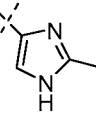

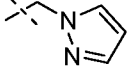
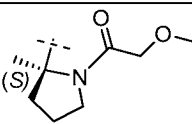
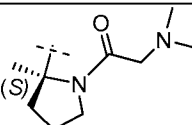
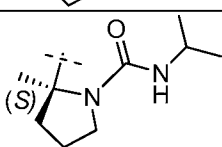
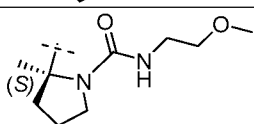
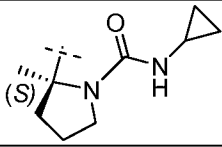
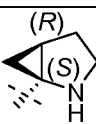
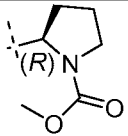
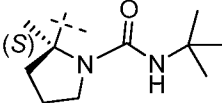
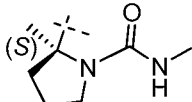
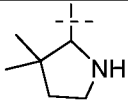
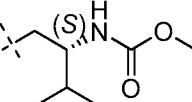
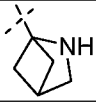
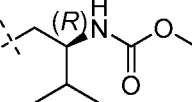
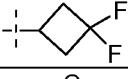
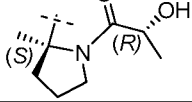
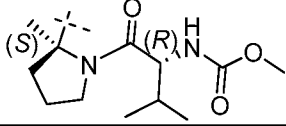
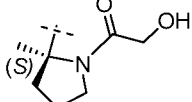
Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
27-71	Cl		C ₄₈ H ₅₃ ClF ₃ N ₁₁ O ₇	988.38	989.6
27-72	Cl		C ₄₈ H ₅₈ ClF ₃ N ₁₀ O ₇	979.41	979.6
27-73	Cl		C ₄₆ H ₅₄ ClF ₃ N ₁₀ O ₇	951.38	951.6
27-74	Cl		C ₄₈ H ₅₈ ClF ₃ N ₁₀ O ₈	995.41	995.6
27-75	Cl		C ₄₉ H ₆₀ ClF ₃ N ₁₀ O ₇	993.43	993.5
27-76	Cl		C ₄₆ H ₅₃ ClF ₃ N ₉ O ₈	952.37	952.9

Table 28



Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
28-1			C ₄₃ H ₄₇ F ₅ N ₈ O ₆	867.35	867.4
28-2			C ₄₃ H ₅₀ F ₃ N ₉ O ₇	862.38	862.4
28-3			C ₄₄ H ₄₇ F ₃ N ₁₀ O ₆	869.36	869.4

Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
28-4			C ₄₃ H ₄₇ F ₃ N ₁₀ O ₆	857.36	857.4
28-5		C(CH ₃) ₂ OH	C ₄₃ H ₅₁ F ₃ N ₈ O ₇	849.38	849.4
28-6			C ₄₃ H ₄₉ F ₃ N ₈ O ₇	847.37	847.4
28-7			C ₄₅ H ₅₃ F ₃ N ₈ O ₇	875.4	875.4
28-8			C ₄₆ H ₅₆ F ₃ N ₉ O ₈	920.42	920.4
28-9			C ₄₄ H ₅₄ F ₃ N ₉ O ₆	862.42	862.4
28-10			C ₄₃ H ₅₂ F ₃ N ₉ O ₆	848.4	848.4
28-11		NH(CH ₂) ₂ OCH ₃	C ₄₃ H ₅₂ F ₃ N ₉ O ₇	864.39	864.4
28-12			C ₄₃ H ₅₀ F ₃ N ₉ O ₆	846.38	846.4
28-13			C ₄₄ H ₄₉ F ₃ N ₁₀ O ₆	871.38	871.4
28-14			C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4
28-15			C ₄₄ H ₄₉ F ₃ N ₁₀ O ₆	871.38	871.4
28-16			C ₄₈ H ₅₈ F ₃ N ₉ O ₈	946.44	946.4
28-17			C ₄₉ H ₆₁ F ₃ N ₁₀ O ₇	959.47	959.4
28-18			C ₄₉ H ₆₁ F ₃ N ₁₀ O ₇	959.47	959.4
28-19			C ₄₉ H ₆₁ F ₃ N ₁₀ O ₈	975.46	975.4

Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
28-20			C ₄₉ H ₅₉ F ₃ N ₁₀ O ₇	957.45	957.4
28-21		O(CH ₂) ₂ OCH ₃	C ₄₃ H ₅₁ F ₃ N ₈ O ₈	865.38	865.4
28-22			C ₄₅ H ₅₂ F ₃ N ₉ O ₆	872.40	872.4
28-23		tBu	C ₄₄ H ₅₃ F ₃ N ₈ O ₆	847.40	848.4
28-24			C ₄₆ H ₅₄ F ₃ N ₉ O ₈	918.41	918.6
28-25			C ₅₀ H ₆₃ F ₃ N ₁₀ O ₇	973.48	973.6
28-26			C ₄₇ H ₅₇ F ₃ N ₁₀ O ₇	931.44	931.6
28-27			C ₄₆ H ₅₆ F ₃ N ₉ O ₆	888.43	888.6
28-28			C ₄₇ H ₅₈ F ₃ N ₉ O ₈	934.44	934.6
28-29			C ₄₅ H ₅₂ F ₃ N ₉ O ₆	872.40	872.6
28-30			C ₄₇ H ₅₈ F ₃ N ₉ O ₈	934.44	934.6
28-31			C ₄₄ H ₄₉ F ₅ N ₈ O ₆	881.37	882.0
28-32			C ₄₈ H ₅₈ F ₃ N ₉ O ₈	946.44	947.0
28-33			C ₅₂ H ₆₅ F ₃ N ₁₀ O ₉	1,031.49	1032.2
28-34			C ₄₇ H ₅₆ F ₃ N ₉ O ₈	932.42	933.0


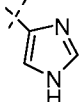
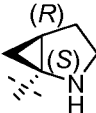
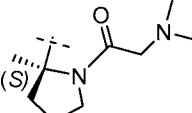
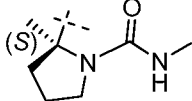
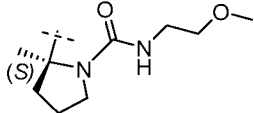
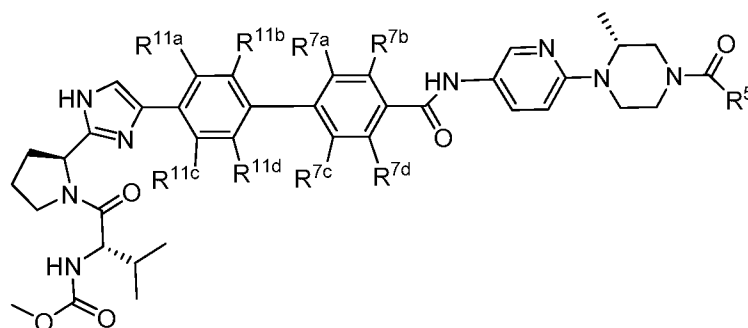
Ex No.	R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
28-35		CH ₂ N(CH ₃) ₂	C ₄₃ H ₅₂ F ₃ N ₉ O ₆	848.4	848.8
28-36	Cl	NHCH ₃	C ₄₁ H ₄₇ ClF ₃ N ₉ O ₆	854.33	854.6
28-37	Cl	NH(CH ₂) ₂ OCH ₃	C ₄₃ H ₅₁ ClF ₃ N ₉ O ₇	898.36	898.6
28-38	Cl		C ₄₅ H ₅₂ ClF ₃ N ₈ O ₆	893.37	893.6
28-39	Cl		C ₄₃ H ₄₆ ClF ₃ N ₁₀ O ₆	891.32	891.6
28-40	Cl		C ₄₅ H ₅₁ ClF ₃ N ₉ O ₆	906.36	906.6
28-41	Cl		C ₄₉ H ₆₀ ClF ₃ N ₁₀ O ₇	993.43	993.4
28-42	Cl		C ₄₇ H ₅₆ ClF ₃ N ₁₀ O ₇	965.4	965.4
28-43	Cl		C ₄₉ H ₆₀ ClF ₃ N ₁₀ O ₈	1,009.42	1009.5

Table 29



Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
29-1		R ^{7a} =CF ₃		C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
29-2		R ^{7a} =CF ₃		C ₄₂ H ₄₇ F ₃ N ₈ O ₅	801.36	801.4
29-3		R ^{7a} =CF ₃	NHCH ₃	C ₄₀ H ₄₆ F ₃ N ₉ O ₅	790.36	790.2
29-4		R ^{7a} =CF ₃		C ₄₂ H ₄₅ F ₃ N ₁₀ O ₅	827.35	827.2
29-5		R ^{7a} =CF ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₅	829.39	829.4
29-6		R ^{7a} =CH ₃		C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
29-7		R ^{7a} =OCH ₂ CHF ₂		C ₅₂ H ₆₆ F ₂ N ₁₀ O ₉	1,013.50	1013.6
29-8	R ^{11b} =CH ₃			C ₄₄ H ₅₄ N ₈ O ₅	775.42	775.4
29-9		R ^{7a} =OCH ₂ cPr		C ₄₅ H ₅₂ N ₁₀ O ₆	829.41	829.4
29-10		R ^{7a} =OCH ₂ cPr		C ₅₄ H ₇₀ N ₁₀ O ₉	1,003.53	1004.0
29-11		R ^{7a} =OCH ₃		C ₅₁ H ₆₆ N ₁₀ O ₉	963.5	963.6
29-12		R ^{7a} =O(CH ₂) ₂ OCH ₃		C ₄₆ H ₅₈ N ₈ O ₇	835.44	835.4
29-13		R ^{7a} =Oi-Pr	NHCH ₃	C ₄₂ H ₅₃ N ₉ O ₆	780.41	780.4
29-14	R ^{11d} =CH ₃	R ^{7a} =OCF ₃		C ₄₅ H ₅₃ F ₃ N ₈ O ₆	859.4	859.4

Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
29-15		R ^{7a} =OCH ₂ t-Bu		C ₅₅ H ₇₄ N ₁₀ O ₉	1,019.56	1019.6
29-16		R ^{7a} =OcPr		C ₄₆ H ₅₆ N ₈ O ₆	817.43	817.4
29-17		R ^{7a} =OCF ₃		C ₄₉ H ₆₀ F ₃ N ₉ O ₈	960.45	960.4
29-18		R ^{7a} =OCF ₃		C ₄₈ H ₅₉ F ₃ N ₁₀ O ₇	945.45	945.4
29-19		R ^{7a} =OCF ₃		C ₄₆ H ₅₄ F ₃ N ₉ O ₇	902.41	902.4
29-2-		R ^{7a} =OCF ₃		C ₄₆ H ₅₄ F ₃ N ₉ O ₈	918.41	918.4
29-21		R ^{7a} =OCF ₃		C ₄₈ H ₅₆ F ₃ N ₉ O ₇	928.43	928.4
29-22	R ^{11b} =CF ₃			C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
29-23	R ^{11b} =OCH ₃			C ₄₄ H ₅₄ N ₈ O ₆	791.42	791.4
29-24	R ^{11b} =F			C ₄₃ H ₅₁ FN ₈ O ₅	779.4	779.4
29-25		R ^{7a} =OCH ₃ R ^{7c} =OCH ₃		C ₅₂ H ₆₈ N ₁₀ O ₁₀	993.51	993.4
29-26	R ^{11b} =OCF ₃			C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4
29-27	R ^{11a} =CH ₃			C ₅₁ H ₆₆ N ₁₀ O ₈	947.51	947.6
29-28		R ^{7a} =OCHF ₂		C ₅₁ H ₆₄ F ₂ N ₁₀ O ₉	999.48	999.4
29-29		R ^{7a} =OCF ₃		C ₄₈ H ₅₇ F ₃ N ₁₀ O ₇	943.44	943.4

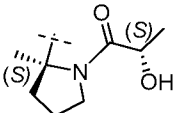
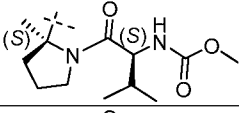
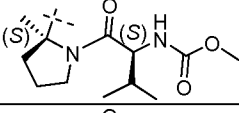
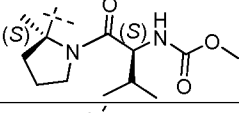
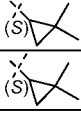
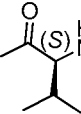
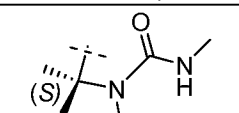

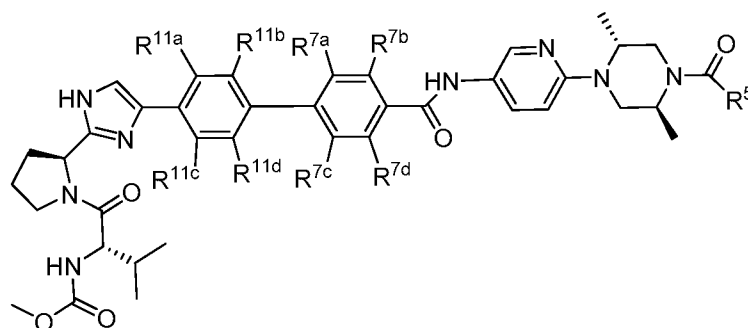
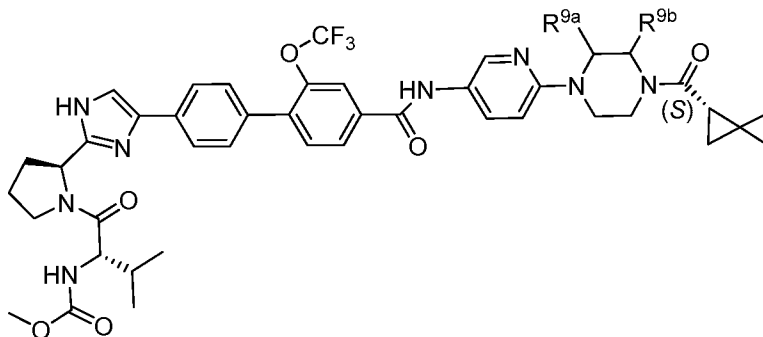
Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
29-30		R ^{7a} =OCF ₃		C ₄₇ H ₅₆ F ₃ N ₉ O ₈	932.42	932.4
29-31		R ^{7a} =OCF ₃		C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1,017.47	1017.4
29-32	R ^{11a} =OCF ₃			C ₅₁ H ₆₃ F ₃ N ₁₀ O ₉	1,017.47	1017.4
29-33	R ^{11a} =CF ₃			C ₅₁ H ₆₃ F ₃ N ₁₀ O ₈	1,001.48	1001.4
29-34	R ^{11d} =CH ₃	R ^{7a} =CH ₃		C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.4
29-35	R ^{11a} =OCH ₃			C ₄₄ H ₅₄ N ₈ O ₆	791.42	792.0
29-36		R ^{7b} =F		C ₅₀ H ₆₃ FN ₁₀ O ₈	951.48	952.2
29-37	R ^{11a} =Cl			C ₄₅ H ₅₅ ClN ₁₀ O ₆	867.4	867.0

Table 30



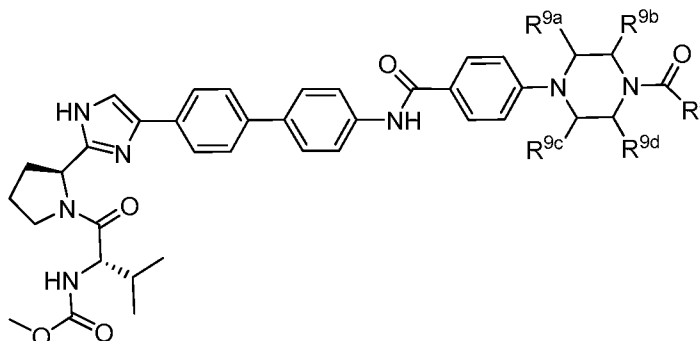
Ex No.	R ^{11a} R ^{11b} R ^{11c} R ^{11d}	R ^{7a} R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
30-1			CH((R)OH)CH ₂ OH	C ₄₁ H ₅₀ N ₈ O ₇	767.38	767.6
30-2	R ^{11b} =CH ₃			C ₄₅ H ₅₆ N ₈ O ₅	789.44	789.4
30-3		R ^{7a} =OCH ₂ CHF ₂		C ₄₄ H ₅₀ F ₂ N ₁₀ O ₆	853.39	853.4
30-4		R ^{7a} =OCH ₂ CHF ₂		C ₄₆ H ₅₆ F ₂ N ₈ O ₆	855.43	855.4
30-5	R ^{11b} =CH ₃			C ₅₂ H ₆₈ N ₁₀ O ₈	961.52	961.6
30-6		R ^{7a} =OCH ₃		C ₄₅ H ₅₆ N ₈ O ₆	805.43	805.4
30-7		R ^{7a} =CF ₃		C ₄₅ H ₅₃ F ₃ N ₈ O ₅	843.41	843.4
30-8		R ^{7a} =OCH ₂ CH ₃		C ₅₃ H ₇₀ N ₁₀ O ₉	991.53	991.4
30-9		R ^{7a} =OCF ₃		C ₄₅ H ₅₃ F ₃ N ₈ O ₆	859.4	859.4

Table 31




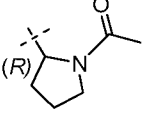
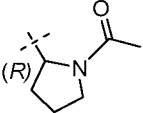

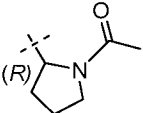
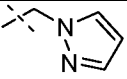

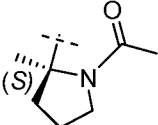



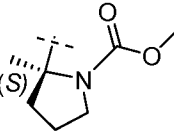

Ex No.	R ^{9a}	R ^{9b}	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
31-1		(R)CH ₃	C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4
31-2		(S)CH ₃	C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4
31-3	(S)CH ₃		C ₄₄ H ₅₁ F ₃ N ₈ O ₆	845.39	845.4

Table 32



5

Ex No.	R ^{9a} R ^{9b} R ^{9c} R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
32-1	R ^{9b} =(S)CH ₂ OCH ₃		C ₄₅ H ₅₅ N ₇ O ₆	790.42	790.4
32-2	R ^{9b} =(R)CH ₃	CH ₂ NHC(O)CH ₃	C ₄₂ H ₅₀ N ₈ O ₆	763.39	763.4
32-3	R ^{9b} =(R)CH ₃		C ₄₃ H ₄₉ N ₉ O ₅	772.39	772.4
32-4	R ^{9b} =(R)CH ₃		C ₄₄ H ₅₃ N ₇ O ₅	760.41	760.4
32-5	R ^{9b} =(S)CH ₃	CH ₂ NHC(O)CH ₃	C ₄₂ H ₄₇ N ₉ O ₅	758.37	758.4
32-6	R ^{9b} =(S)CH ₃		C ₄₄ H ₅₃ N ₇ O ₅	760.41	760.4

Ex No.	R ^{9a} R ^{9b} R ^{9c} R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
32-7	R ^{9a} =(R)CH ₃	tBu	C ₄₃ H ₅₃ N ₇ O ₅	748.41	748.4
32-8	R ^{9a} =(R)CH ₃	NHCH ₃	C ₄₀ H ₄₈ N ₈ O ₅	721.38	721.2
32-9	R ^{9a} =(R)CH ₃		C ₄₄ H ₅₃ N ₇ O ₅	760.41	760.4
32-10	R ^{9a} =(R)CH ₃		C ₄₅ H ₅₄ N ₈ O ₆	803.42	803.4
32-11	R ^{9a} =(S)CH ₃		C ₄₅ H ₅₄ N ₈ O ₆	803.42	803.4
32-12	R ^{9a} =(S)CH ₃		C ₄₄ H ₅₃ N ₇ O ₅	760.41	760.4
32-13	R ^{9b} =(S)CH ₂ OCH ₃		C ₄₆ H ₅₆ N ₈ O ₇	833.43	833.4
32-14	R ^{9b} =(R)CH ₂ OCH ₃		C ₄₄ H ₅₁ N ₉ O ₆	802.4	802.4
32-15	R ^{9b} =(R)CH ₂ OCH ₃	CH ₂ NHC(O)CH ₃	C ₄₃ H ₅₂ N ₈ O ₇	793.4	793.4
32-16	R ^{9a} =(S)CH ₃ R ^{9c} =(R)CH ₃		C ₄₃ H ₅₁ N ₇ O ₅	746.4	746.4
32-17	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₆ N ₈ O ₆	817.43	817.4
32-18	R ^{9b} =(S)CH ₂ OH		C ₄₄ H ₅₃ N ₇ O ₆	776.41	776.2
32-19	R ^{9b} =(S)CH ₃ R ^{9d} =(R)CH ₃		C ₄₃ H ₅₁ N ₇ O ₅	746.4	746.4
32-20	R ^{9b} =(S)CH ₃ R ^{9c} =(R)CH ₃		C ₄₅ H ₅₅ N ₇ O ₅	774.43	774.4
32-21	R ^{9a} =(R)CH ₃		C ₄₆ H ₅₆ N ₈ O ₇	833.43	833.4
32-22	R ^{9b} =(R)CH ₃ R ^{9c} =(S)CH ₃		C ₄₅ H ₅₅ N ₇ O ₅	774.43	774.4

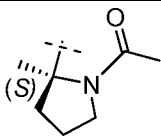
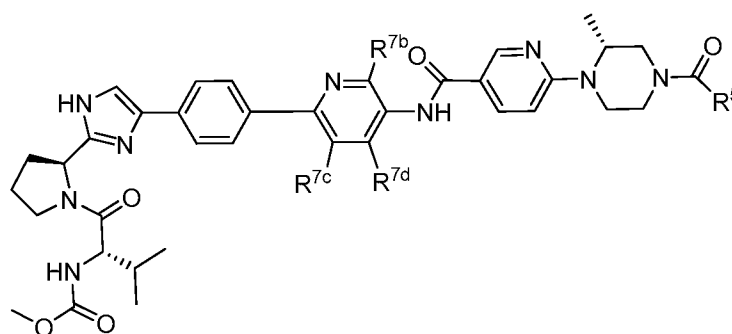
Ex No.	R ^{9a} R ^{9b} R ^{9c} R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
32-23	R ^{9b} =(R)CH ₃ R ^{9c} =(S)CH ₃		C ₄₇ H ₅₈ N ₈ O ₆	831.45	831.4

Table 33



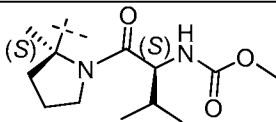


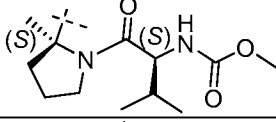
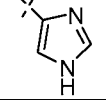
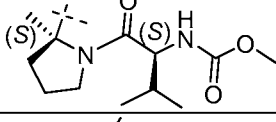
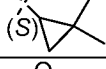
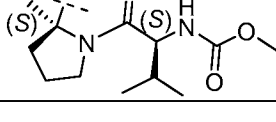
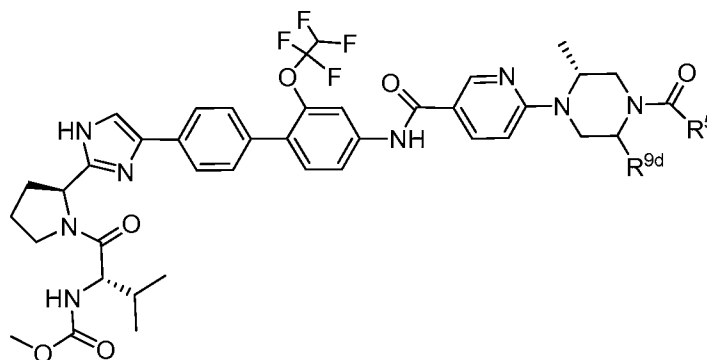
Ex No.	R ^{7b} R ^{7c} R ^{7d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
33-1	R ^{7c} =CH ₃		C ₅₀ H ₆₅ N ₁₁ O ₈	948.5	948.4
33-2	R ^{7c} =CH ₃		C ₄₃ H ₅₃ N ₉ O ₅	776.42	776.4
33-3	R ^{7c} =CF ₃		C ₄₃ H ₅₀ F ₃ N ₉ O ₅	830.39	830.4
33-4	R ^{7c} =CF ₃		C ₅₀ H ₆₂ F ₃ N ₁₁ O ₈	1,002.47	1002.4
33-5	R ^{7c} =CF ₃		C ₄₁ H ₄₄ F ₃ N ₁₁ O ₅	828.35	828.4
33-6	R ^{7b} =OCH ₃		C ₅₀ H ₆₅ N ₁₁ O ₉	964.5	964.6
33-7			C ₄₂ H ₅₁ N ₉ O ₅	762.40	762.9
33-8			C ₄₉ H ₆₃ N ₁₁ O ₈	934.49	934.1

Table 34



Ex No.	R ^{9d}	R ⁵	Formula	Calc [M+H] ⁺	Found [M+H] ⁺
34-1	(S)CH ₃		C ₄₄ H ₄₈ F ₄ N ₁₀ O ₆	889.37	889.6
34-2	(S)CH ₃		C ₄₆ H ₅₄ F ₄ N ₈ O ₆	891.41	891.6
34-3	(S)CH ₃	NHCH ₃	C ₄₂ H ₄₉ F ₄ N ₉ O ₆	852.37	852.6
34-4			C ₄₅ H ₅₂ F ₄ N ₈ O ₆	877.39	877.6
34-5			C ₄₃ H ₄₆ F ₄ N ₁₀ O ₆	875.35	875.4
34-6		NHCH ₃	C ₄₁ H ₄₇ F ₄ N ₉ O ₆	838.36	838.4

5 Biological Assays

The hepatitis C virus has been classified into six major different genotypes on the basis of nucleotide sequence, and further divided into subtypes within genotypes. Compounds of the invention demonstrated inhibition of HCV replication in one or more of the following HCV replicon assays.

10

Assay 1: HCV Genotype 1b Replicon Assay

The HCV genotype 1b replicon cell line was obtained from Apath LLC (Brooklyn, NY) (APC144; Huh7 cell background). This subgenomic replicon contains the N-terminus of the HCV core protein fused to the neomycin-resistance selectable marker.

The EMCV IRES lies downstream and drives expression of humanized Renilla luciferase fused to the non-structural proteins NS3-NS5B. This cell line was used to determine compound potency using the luciferase activity readout as a measurement of compound inhibition of replicon levels.

5 Cells were grown at 37°C in a 5% CO₂ humidified incubator in DMEM (Invitrogen) with 10% FBS (HyClone), 1x NEAA (Invitrogen), 1x Pen-Strep (Invitrogen), and 500µg/mL G418 (Invitrogen). On day 1 of the assay, cells were plated at 10,000 cells/well in white 96-well tissue culture plates (Costar) in 200µL media lacking G418. Four hours later, once the cells have adhered, the media was removed and
10 replaced with media (no G418) containing dose-responses of test compounds. Compounds were initially diluted in DMSO and then diluted another 200 x in media to bring the final DMSO concentration down to 0.5%. The cells were incubated with test compounds for 48 hours. At the end of the incubation period, media and compound were removed from the plates and the luciferase activity was determined using Promega
15 Renilla-Glo reagents.

To analyze the data, the luciferase activity was plotted vs. the compound concentration, and EC₅₀ values were determined from a 4-parameter robust fit model with the GraphPad Prism software package (GraphPad Software, Inc., San Diego, CA). Results are expressed as the negative decadic logarithm of the EC₅₀ value, pEC₅₀.

20 Test compounds having a higher pEC₅₀ value in this assay show greater inhibition of HCV genotype 1b replication. Compounds of the invention tested in this assay typically exhibited pEC₅₀ values between about 7 and about 12.

Assay 2: HCV Genotype 1a Replicon Assay

The HCV genotype 1a replicon cell line was obtained from Apath LLC (APC89; Huh7.5 cell background). This subgenomic replicon contains the N-terminus of the HCV core protein fused to the neomycin-resistance selectable marker. The EMCV IRES lies downstream and drives expression of the non-structural proteins NS3-NS5B. Compound potencies were determined using the NS3-specific protease activity in lysates as a measurement of compound inhibition of replicon levels.

30 Cells were grown at 37°C in a 5% CO₂ humidified incubator in DMEM (Invitrogen) with 10% FBS (HyClone), 1x NEAA (Invitrogen), 1x Pen-Strep (Invitrogen), and 850µg/mL G418 (Invitrogen). On day 1 of the assay, cells were plated at 15,000 cells/well in black 96-well tissue culture plates (Costar) in 200µL media lacking

G418. Four hours later, once the cells had adhered, the media was removed and replaced with media (no G418) containing dose-responses of test compounds. Compounds were initially diluted in DMSO and then diluted another 200x in media to bring the final DMSO concentration down to 0.5%. The cells were incubated with test compounds for 48
5 or 72 hours. At the end of the incubation period, media and compound were removed from the plates.

To determine the NS3-specific protease activity in lysates, the cells were lysed at room temperature in 50 μ L/well of 50mM Hepes pH 7.5, 150mM NaCl, 15% Glycerol, 0.15% Triton X-100, 10mM DTT for 20 minutes with shaking. 50 μ L of an NS3/4a
10 protease-specific FRET substrate (Anaspec RET S1 Cat#22991) was then added to the wells at a final concentration of 15 μ M. The plates were incubated at 37°C for 20 minutes, which corresponds to a timepoint at which the protease activity is still in the linear phase. Protease activity was determined by measuring fluorescence (Excitation: 340 nm; Emission: 509nm).

15 To analyze the data, the fluorescence was plotted vs. the compound concentration, and EC50 values were determined from a 4-parameter robust fit model using GraphPad Prism software. Compounds of the invention tested in this assay typically exhibited pEC₅₀ values between about 7 and about 11.5.

Assay 3: Replicon Assays Against Resistant Mutants

20 To create replicon cells with resistant mutations of interest, the mutation was first introduced into the parental plasmid by site-directed mutagenesis. Mutations in genotype 1b included L31V, Y93H, and the L31V/Y93H double mutant. Mutations in genotype 1a included Q30R and L31V. The replicon plasmid was then linearized and *in vitro* transcribed to RNA. The RNA was used to stably transfect Huh7 cells by
25 electroporation, and new cell lines were selected with 500 μ g/mL G418. Potencies of test compounds against these mutant cell lines were determined as previously described above for the HCV Genotype 1b and 1a replicon assays.

Potencies of test compounds against additional mutations of interest were determined using transient transfection assays. These mutants included and genotype 1a
30 Y93C, Y93H, M28T, Q30E, Q30K. The mutation was first introduced into the parental plasmid by site-directed mutagenesis. The replicon plasmid was then linearized and *in vitro* transcribed to RNA. The RNA was used to transiently transfect Huh-LUNET cells (obtained from ReBLikon GmbH, Schriesheim, Germany) by electroporation, and the

potencies of test compounds against the mutants were determined as previously described.

Assay 4: Colony Formation Assay

Colony formation assays were used to assess overall genetic barrier of resistance of test compounds. Replicon cells were plated in tissue culture flasks and treated with various concentrations of test compound(s) (or DMSO control) in the presence of G418 (500-850 $\mu\text{g}/\text{mL}$) for 3-4 weeks. The media was replaced with fresh media containing compound and G418 twice per week. Cells were split as necessary. During this time, many cells died, and resistant colonies emerged. The colonies were then fixed and stained with crystal violet/methanol. The combination of a compound of the invention and danoprevir (an NS3 protease inhibitor) was able to significantly suppress the emergence of resistant mutants to a greater degree than either single compound alone.

Assay 5: Replicon Assays of Combinations of Agents

Combinations of a compound of the invention and another therapeutic agent were tested as described for the HCV genotype 1b and 1a replicon assays. Cells were incubated with various combinations (in a checkerboard matrix) of test compounds for 48 hours. Potencies of either compound alone were determined as described above, and MacSynergy II software was used to determine if the combination of test compounds exhibited synergy vs additivity vs antagonism. The combination of a compound of the invention and danoprevir (an NS3 protease inhibitor) showed an additive antiviral effect. Similarly, the combination of a compound of the invention and interferon alpha2b showed an additive antiviral effect.

Assay Results

All of the compounds of Examples 1 to 77 and Tables 1 to 33 were tested in one or more of the assays described above. For example, the following results were obtained in the HCV genotype 1b and 1a replicon assays where A represents a pEC_{50} value between 7 and 8 (EC_{50} between 100 nM and 10 nM), B represents pEC_{50} between 8 and 9 (EC_{50} between 1 and 10 nM), C represents pEC_{50} between and 9 and about 10, (EC_{50} between 1 nM and 0.1 nM), and D represents $\text{pEC}_{50} > 10$ ($\text{EC}_{50} < 0.1$ nM).

Example No.	Genotype 1b	Genotype 1a
1	D	B
2	D	B*
3	D	B*
4	D	A*
5	D	B
6	D	A*
7	D	B*
8	D	B
9	D	C*
10	D	C*
11	D	C*
12	D	C
13	D	D
14	D	D
15	D	D
16	D	D
17	D	C
18	D	C
19	D	C
20		B
21	D	D
22	D	D
23		C
24		C
25	D	D
26	D	D
27	D	D
28	D	C
29	D	D
30	D	D
31	D	D
32	D	D

Example No.	Genotype 1b	Genotype 1a
33	D	D
34	D	D
35	D	C
36	D	C
37	D	C
38	D	D
39	D	D
40	D	C
41	D	D
42	D	C
43	D	C
44	D	C
45	D	D
46	D	C
47	D	C
48	D	C
49	D	D
50	D	D
51	D	D
52	D	D
53	D	D
54	D	D
55	D	D
56	D	C
57	D	D
58	D	D
59	D	D
60	D	D
61	D	D
62	D	D
63	D	D
64	D	D

Example No.	Genotype 1b	Genotype 1a
65	D	D
66	D	D
67		C
68	D	C
69	D	C
70		C
71	D	C
72	C	B
73		B
74		B
75		B
76		C
77	D	D
27-1		D
27-2		C
27-3		C
27-4		C
27-5	D	D
27-6		C
27-7	D	D
27-8		D
27-9		B
27-10	D	D
27-11		C
27-12	D	D
27-13		C
27-14		D
27-15	D	D
27-16	D	D
27-17	D	D
27-18	D	D
27-19		D
27-20	D	D
27-21	D	D

Example No.	Genotype 1b	Genotype 1a
27-22	D	D
27-23	D	D
27-24		C
27-25		B
27-26		C
27-27		B
27-28	D	D
27-29		C
27-30		D
27-31	D	D
27-32		C
27-33	D	D
27-34	D	D
27-35		C
27-36	D	D
27-37	D	D
27-38	D	D
27-39		C
27-40		C
27-41		C
27-42	D	D
27-43	D	D
27-44	D	D
27-45	D	D
27-46	D	D
27-47	D	D
27-48	D	D
27-49		D
27-50	D	D
27-51		C
27-52	D	D
27-53		C
27-54		C
27-55		D

Example No.	Genotype 1b	Genotype 1a
27-56		C
27-57		B
27-58		D
27-59		D
27-60		D
27-61		C
27-62		C
27-63		C
27-64		D
27-65		C
27-66		D
27-67	D	C
27-68	D	D
27-69	D	D
27-70		C
27-71		D
27-72	D	D
27-73	D	D
27-74		D
27-75		D
27-76		D
28-1	D	D
28-2	D	D
28-3		C
28-4		D
28-5	D	D
28-6		C
28-7		D
28-8	D	D
28-9		C
28-10		C
28-11		C

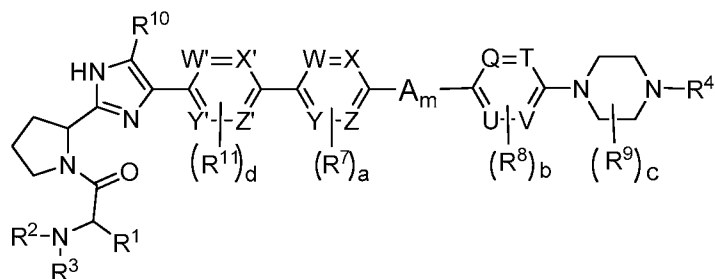
Example No.	Genotype 1b	Genotype 1a
28-12		C
28-13		D
28-14	D	D
28-15	D	D
28-16	D	D
28-17	D	D
28-18	D	D
28-19	D	D
28-20	D	D
28-21		C
28-22	D	D
28-23	D	D
28-24	D	D
28-25	D	D
28-26	D	D
27-27		B
28-28		B
28-29	D	D
28-30		B
28-31		C
28-32		D
28-32		D
28-34		D
28-35		C
28-36	D	D
28-37		D
28-38	D	D
28-39	D	D
28-40	D	D
28-41		D
28-42		D
28-43		D

*Compounds incubated for 48 hours; all other Genotype 1a results for 72 hour incubation

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto. Additionally, all publications, patents, and patent documents cited hereinabove are incorporated by reference herein in full, as though individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

- 5 wherein:

R^1 is selected from C_{1-6} alkyl, phenyl, C_{3-6} cycloalkyl, heteroaryl, and heterocycle; wherein C_{1-6} alkyl is optionally substituted with $-OR^q$, wherein R^q is hydrogen or C_{1-3} alkyl;

R^2 is selected from hydrogen and C_{1-6} alkyl;

- 10 R^3 is selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, $-C(O)OC_{3-6}$ cycloalkyl, $-C(O)NR^aR^b$, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl;

wherein

R^a and R^b are independently hydrogen or C_{1-6} alkyl;

R^4 is $-C(O)R^5$ or $-S(O)_2R^6$;

- 15 R^5 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $-C(R^kR^d)NR^eR^f$, $-NR^gR^h$, heteroaryl, heterocycle, $-CH_2$ -heteroaryl, and phenyl;

wherein

C_{1-6} alkyl is optionally substituted with one or two substituents independently selected from $-OR^c$, $-S(O)_2C_{1-3}$ alkyl, $-NHC(O)C_{1-3}$ alkyl, and $-NHC(O)OC_{1-3}$ alkyl;

20

C_{1-6} alkoxy is optionally substituted with $-OR^d$;

C_{3-6} cycloalkyl is optionally substituted with one, two, or three substituents independently selected from C_{1-3} alkyl, NR^iR^m , $-OR^n$, and halo;

any heterocycle is optionally substituted with one, two, or three

25

substituents independently selected from C_{1-3} alkyl, halo, $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)C_{3-6}$ cycloalkyl, $-C(O)NHC_{1-6}$ alkyl, $-C(O)NHC_{3-6}$ cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl;

wherein any $-C(O)C_{1-6}$ alkyl is optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, $-OR^n$, $-NR^dR^e$, or heterocycle,

- any $-C(O)C_{3-6}$ cycloalkyl is optionally substituted with one or two C_{1-3} alkyl, and
- any $-C(O)NHC_{1-6}$ alkyl is optionally substituted with $-OR^n$ or C_{3-6} cycloalkyl;
- 5 any heteroaryl is optionally substituted with C_{1-6} alkyl or halo;
 R^c is independently selected from hydrogen, C_{1-6} alkyl, and phenyl;
 R^d is independently hydrogen or C_{1-6} alkyl;
 R^e is independently hydrogen or C_{1-6} alkyl;
 R^f is independently selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl,
- 10 and $-C(O)C_{1-6}$ alkyl;
 R^n is independently hydrogen or C_{1-3} alkyl;
 R^k is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and $-CH_2OR^n$;
 R^g is independently hydrogen or C_{1-6} alkyl;
- 15 R^h is independently selected from hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, and $-S(O)_2C_{1-3}$ alkyl, wherein C_{1-6} alkyl is optionally substituted with $-OR^d$;
 R^j is independently hydrogen or C_{1-6} alkyl;
 R^m is independently selected from hydrogen, C_{1-6} alkyl, $-C(O)OC_{1-6}$ alkyl, and $-C(O)C_{1-6}$ alkyl;
- 20 R^6 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl, and a heteroaryl ring;
 R^7 , R^8 , and R^{11} are independently selected from halo, C_{1-6} alkyl, C_{1-6} alkoxy, $-C(O)OR^n$, $-CH_2NR^aR^b$, and $-CN$, wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, three, four, or five halo, and wherein C_{1-6} alkoxy is optionally substituted with $-OR^d$;
- 25 R^9 is independently selected from C_{1-6} alkyl, $-CH_2OR^n$, $-C(O)NR^nR^p$, and $C(O)OR^n$, wherein C_{1-6} alkyl is optionally substituted with $-S(O)_2C_{1-3}$ alkyl or with $-SC_{1-3}$ alkyl;
 R^p is independently hydrogen or C_{1-3} alkyl;
 R^{10} is selected from hydrogen, halo, C_{1-6} alkyl, $-C(O)OR^c$, $-C(O)NR^aR^b$,
- 30 $-CH_2NR^aR^b$, C_{3-6} cycloalkyl, and $-CN$;
 W' , X' , Y' , and Z' are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or to R^{11} , provided that at least two of W' , X' , Y' , and Z' are carbon;

W, X, Y, and Z are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or to R⁷, provided that at least two of W, X, Y, and Z are carbon;

A_m is -NHC(O)- or -C(O)NH-;

Q, T, U, and V are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or to R⁸, provided that at least two of Q, T, U, and V are carbon; and

a, b, c, and d are independently 0, 1, or 2;

or a pharmaceutically-acceptable salt or stereoisomer thereof.

2. The compound of Claim 1 wherein:

10 R⁵ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, -C(R^kR^d)NR^eR^f, -NR^gR^h, heteroaryl, heterocycle, -CH₂-heteroaryl, and phenyl;

wherein

C₁₋₆alkyl is optionally substituted with -OR^c or -S(O)₂C₁₋₃alkyl;

15 C₃₋₆cycloalkyl is optionally substituted with one or two C₁₋₃alkyl, or with NR^jR^m or -ORⁿ;

any heterocycle is optionally substituted with one or two substituents selected from C₁₋₃alkyl, halo, -C(O)OC₁₋₃alkyl, -C(O)C₁₋₆alkyl optionally substituted with -NHC(O)OC₁₋₃alkyl, and -C(O)C₃₋₆cycloalkyl optionally substituted with one or two C₁₋₃alkyl;

20 any heteroaryl is optionally substituted with C₁₋₆alkyl;

R^h is selected from hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, and -S(O)₂C₁₋₃alkyl;

R⁶ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, and a heteroaryl ring; and

25 R⁷, R⁸, and R¹¹ are independently selected from halo, C₁₋₆alkyl, C₁₋₆alkoxy, -C(O)ORⁿ, -CH₂NR^aR^b, and -CN, wherein C₁₋₆alkyl and C₁₋₆alkoxy are optionally substituted with one, two, or three halo.

3. The compound of Claim 2 wherein:

30 R¹ is selected from C₁₋₆alkyl, phenyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl is optionally substituted with -OR^q;

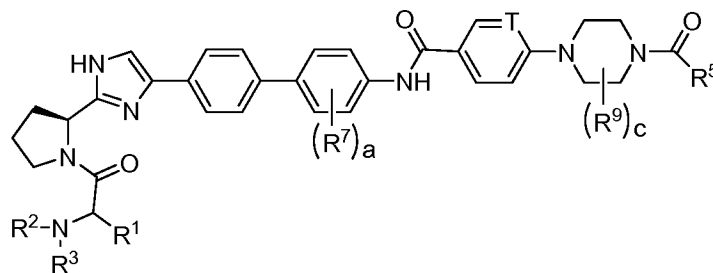
R³ is selected from hydrogen, C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, -C(O)NR^aR^b, -C(O)C₃₋₆cycloalkyl, and -S(O)₂C₁₋₃alkyl;

R¹⁰ is selected from hydrogen, halo, and C₁₋₆alkyl;

W', X', Y', and Z' are each CH; and

W, X, Y, and Z are independently carbon or nitrogen wherein any carbon atom is bonded to hydrogen or to R⁷, provided that at least three of W, X, Y, and Z are carbon.

4. The compound of Claim 3 wherein the compound is a compound of
5 formula (II):



(II)

wherein

- R⁵ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, -C(R^kR^d)NR^eR^f, -NR^gR^h,
10 heteroaryl, heterocycle, and -CH₂-heteroaryl;

wherein

any heteroaryl or heterocycle has five or six ring atoms;

C₃₋₆cycloalkyl is optionally substituted with one or two C₁₋₃alkyl;

- any heterocycle is optionally substituted with one or two substituents
15 selected from C₁₋₃alkyl, halo, -C(O)OC₁₋₃alkyl, -C(O)C₁₋₆alkyl optionally
substituted with -NHC(O)OC₁₋₃alkyl, and -C(O)C₃₋₆cycloalkyl optionally
substituted with one or two C₁₋₃alkyl;

R^k, R^d, R^e, R^g, and R^h are each independently hydrogen or C₁₋₃alkyl;

R^f is selected from hydrogen and -C(O)C₁₋₃alkyl;

- 20 R⁷ is selected from halo, C₁₋₆alkyl, and C₁₋₆alkoxy wherein C₁₋₆alkyl and
C₁₋₆alkoxy are optionally substituted with one, two, or three halo;

R⁹ is C₁₋₃alkyl or -CH₂ORⁿ; and

T is CH or N.

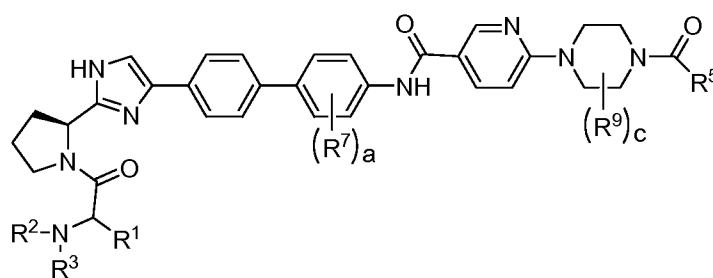
- 25 5. The compound of Claim 4 wherein T is N.

6. The compound of Claim 4 wherein R¹ is isopropyl; R² is hydrogen; and R³
is -C(O)OCH₃.

7. The compound of Claim 4 wherein R⁵ is selected from, -O-*tert*-butyl, cyclopropyl, *tert*-butyl, -NHCH₃, 2,2-dimethylcyclopropyl, pyrimidinyl, pyrazolyl, imidazolyl, -CH₂-pyrazolyl, 1-acetylpyrrolidinyl, 2-methylpyrrolidine-1-carboxylic acid methyl ester, 1-cyclopropyl-2-methylpyrrolidine, 1-(2,2-dimethylcyclopropyl)-2-

5 methylpyrrolidine, and [-2-methyl-1-(2-methyl-pyrrolidine-1-carbonyl)-propyl]-carbamic acid methyl ester.

8. The compound of Claim 1 wherein the compound of formula (I) is a compound of formula (III):



10

(III)

wherein

R¹ is selected from C₁₋₆alkyl, phenyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl is optionally substituted with -OR^q;

15 R³ is selected from hydrogen, C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, -C(O)NR^aR^b, -C(O)C₃₋₆cycloalkyl, and -S(O)₂C₁₋₃alkyl;

R⁵ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, -C(R^kR^d)NR^eR^f, -NR^gR^h, heteroaryl, heterocycle, and -CH₂-heteroaryl;

wherein:

20 any heteroaryl or heterocycle has 5 or 6 ring atoms;

C₁₋₆alkyl is optionally substituted with one or two substituents independently selected from -OR^c, -NHC(O)C₁₋₃alkyl, and -NHC(O)OC₁₋₃alkyl;

C₁₋₆alkoxy is optionally substituted with -OR^d;

25 C₃₋₆cycloalkyl is optionally substituted with one or two substituents independently selected from C₁₋₃alkyl and halo;

any heterocycle is optionally substituted with one, two, or three substituents independently selected from C₁₋₃alkyl, halo, -C(O)OC₁₋₃alkyl, -C(O)C₁₋₆alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)NHC₁₋₆alkyl, and -C(O)NHC₃₋₆cycloalkyl;

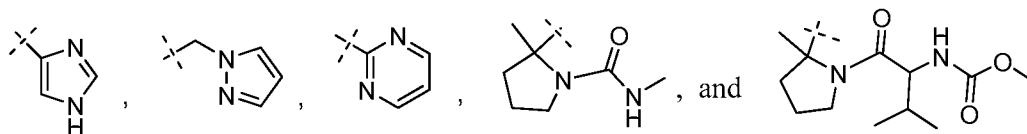
- wherein any $-C(O)C_{1-6}$ alkyl is optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, $-OR^n$, $-NR^dR^e$, or heterocycle,
 any $-C(O)C_{3-6}$ cycloalkyl is optionally substituted with one or two C_{1-3} alkyl, and
 5 any $-C(O)NHC_{1-6}$ alkyl is optionally substituted with $-OR^n$ or C_{3-6} cycloalkyl;
 any heteroaryl is optionally substituted with C_{1-3} alkyl;
 R^k , R^d , R^e , R^g , and R^h are each independently hydrogen or C_{1-3} alkyl;
 R^f is selected from hydrogen and $-C(O)C_{1-3}$ alkyl;
 10 R^7 is selected from halo, C_{1-3} alkyl, and C_{1-3} alkoxy wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, or three halo; and
 R^9 is C_{1-3} alkyl;
 a is 1 or 2; and
 c is 1 or 2.

15

9. The compound of Claim 8 wherein R^5 is selected from C_{3-4} cycloalkyl, $-CH_2NR^eR^f$, $-NR^gR^h$, imidazolyl, pyrazolyl, pyrimidinyl, and pyrrolidinyl;
 wherein:

- C_{3-4} cycloalkyl is optionally substituted with one or two C_{1-3} alkyl;
 20 pyrrolidinyl is substituted with methyl and a substituent selected from $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl, and $-C(O)NHC_{1-6}$ alkyl, wherein
 $-C(O)C_{1-6}$ alkyl is substituted with $-NHC(O)OC_{1-3}$ alkyl, $-OR^n$, $-NR^dR^e$, or heterocycle.

- 25 10. The compound of Claim 8, wherein R^5 is selected from $-NHCH_3$, 2,2-dimethylcyclopropyl,



- 30 11. The compound of Claim 8 wherein R^1 is C_{1-6} alkyl, R^2 is hydrogen; and R^3 is $-C(O)OC_{1-6}$ alkyl.

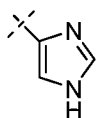
12. The compound of Claim 8 wherein R⁷ is selected from fluoro, chloro, -CF₃, and -OCF₃; and R⁹ is methyl.

13. The compound of Claim 8 wherein:

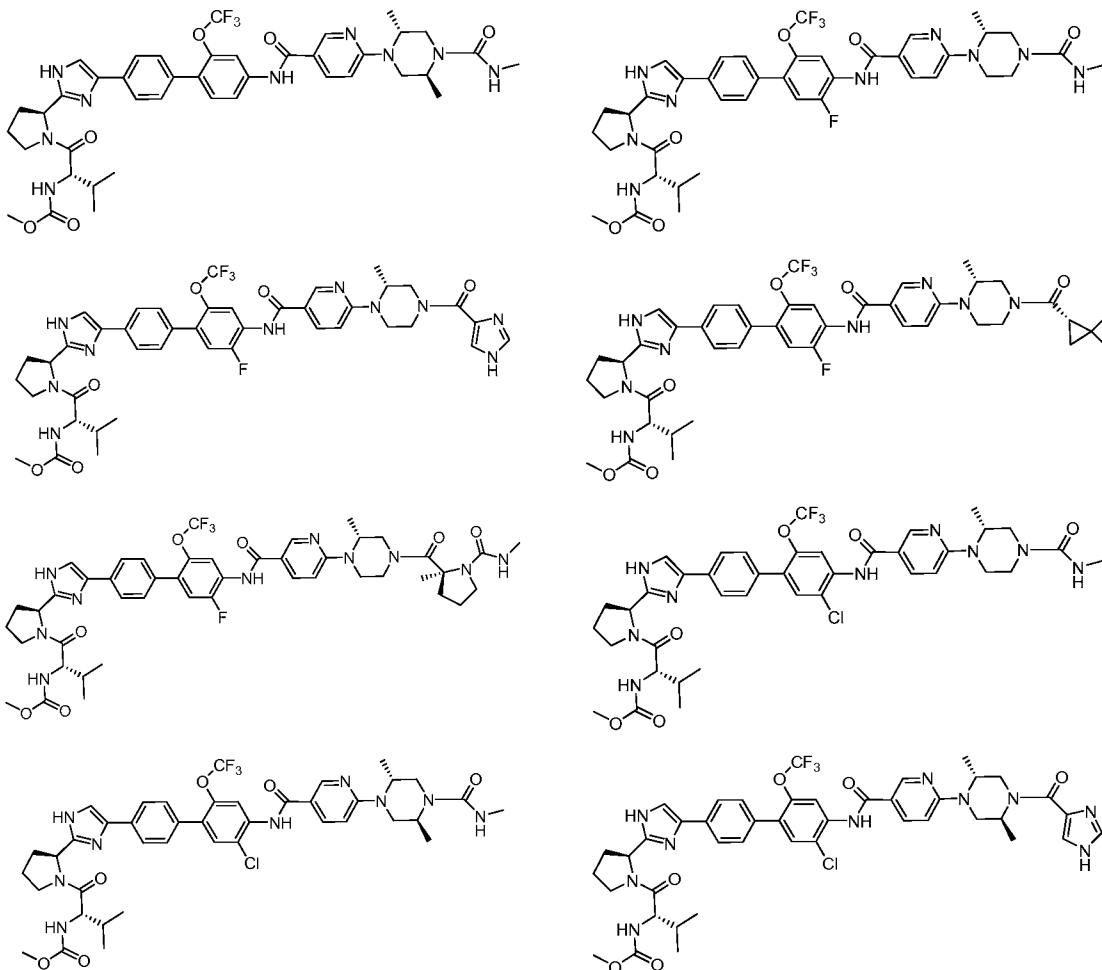
5 R¹ is isopropyl, R² is hydrogen; and R³ is -C(O)OCH₃;

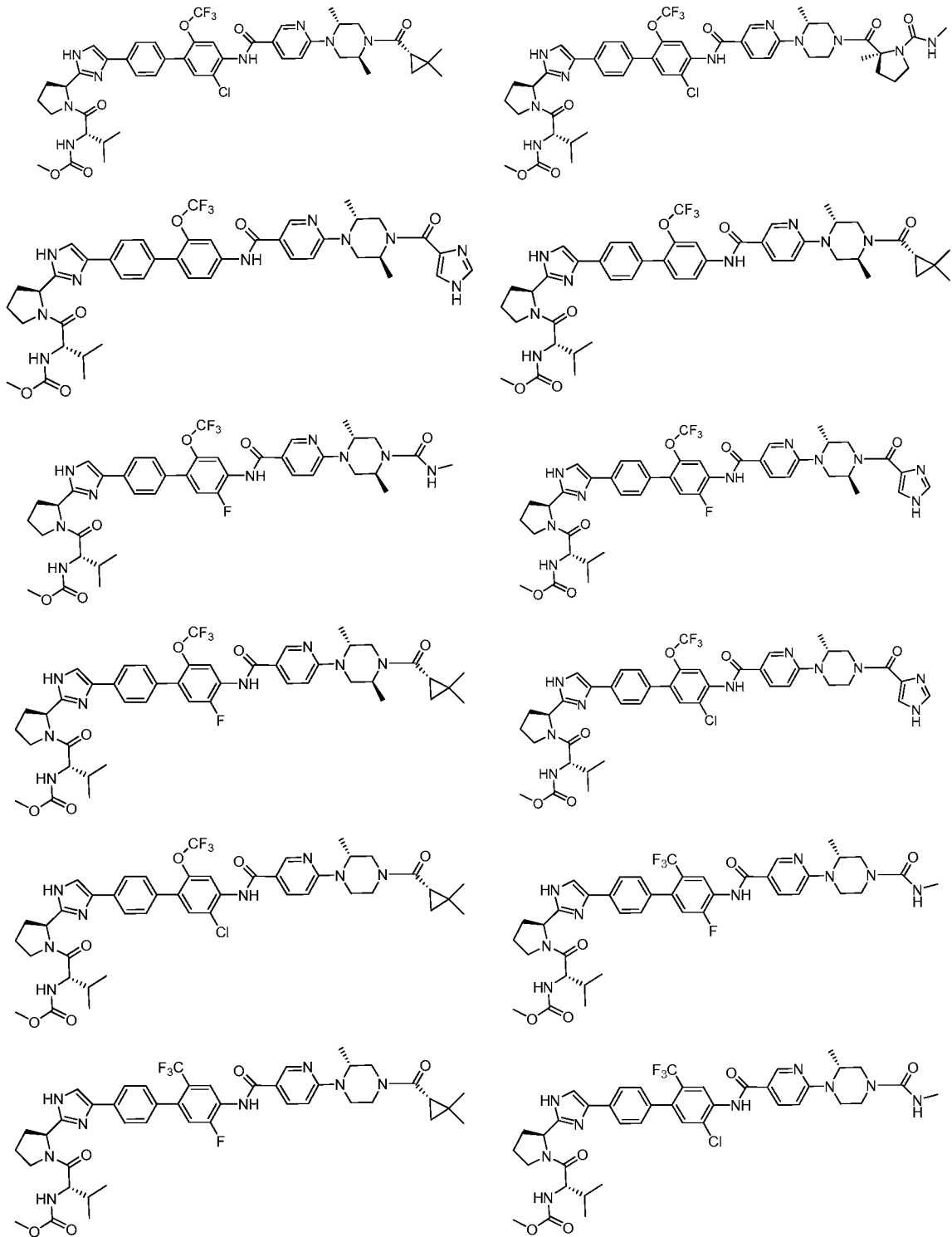
R⁷ is selected from fluoro, chloro, -CF₃, and -OCF₃; and R⁹ is methyl; and

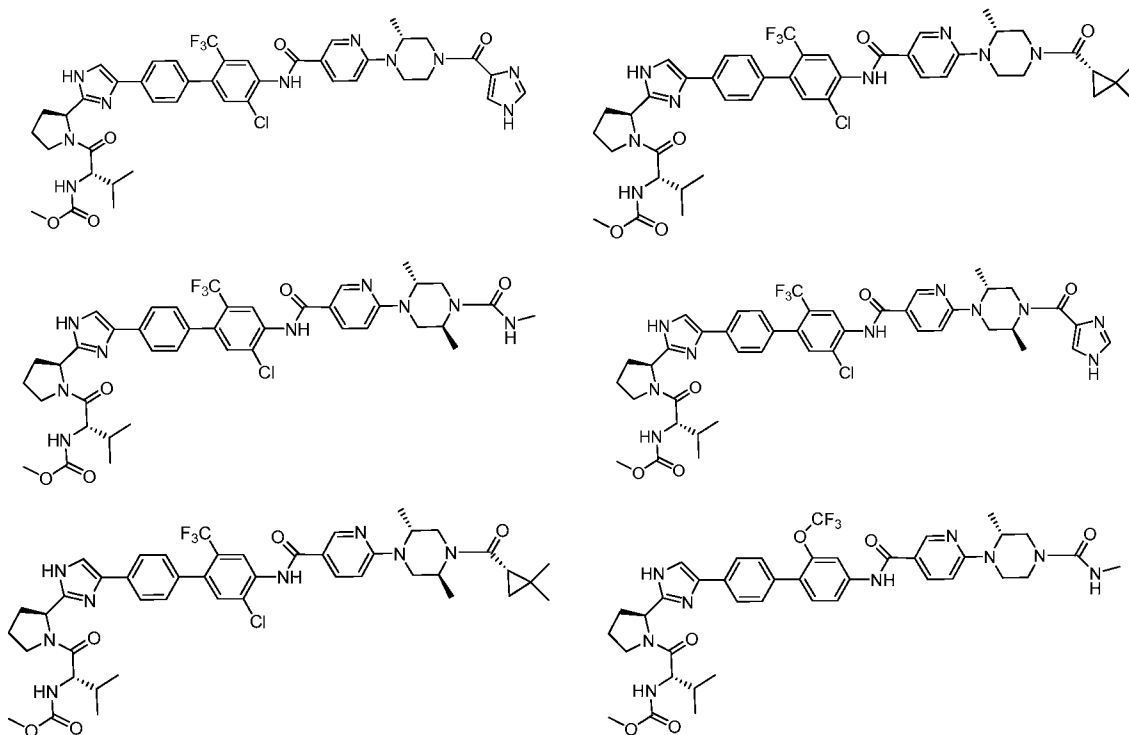
R⁵ is selected from -NHCH₃, 2,2-dimethylcyclopropyl, and



10 14. The compound of Claim 8 wherein the compound is selected from:

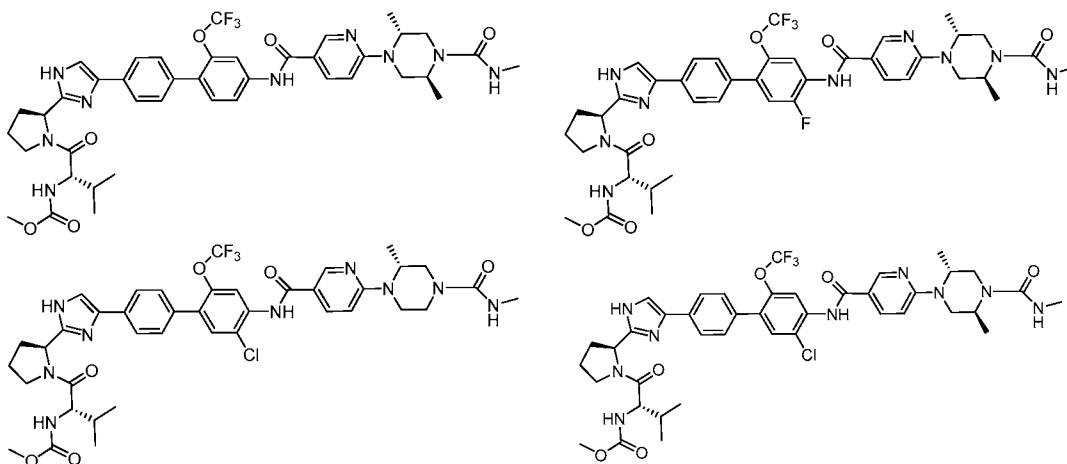






and pharmaceutically-acceptable salts thereof.

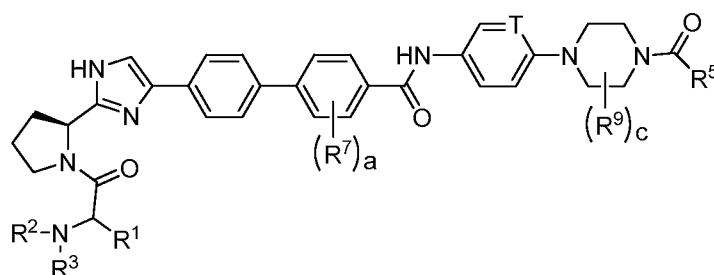
15. The compound of Claim 8 wherein the compound is selected from:



and pharmaceutically-acceptable salts thereof.

5

16. The compound of Claim 1 wherein the compound of formula (I) is a compound of formula (IV):



(IV)

wherein:

R¹ is selected from C₁₋₆alkyl, phenyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl is
 5 optionally substituted with -OR^q;

R³ is selected from hydrogen, C₁₋₆alkyl, -C(O)OC₁₋₆alkyl, -C(O)NR^aR^b,
 -C(O)C₃₋₆cycloalkyl, and -S(O)₂C₁₋₃alkyl;

R⁵ is selected from C₁₋₆alkyl, C₃₋₆cycloalkyl, C₁₋₆alkoxy, -C(R^kR^d)NR^eR^f, -NR^gR^h,
 heteroaryl, heterocycle, and -CH₂-heteroaryl;

10 wherein:

any heteroaryl or heterocycle has 5 or 6 ring atoms;

C₁₋₆alkyl is optionally substituted with one or two substituents
 independently selected from -OR^c, -NHC(O)C₁₋₃alkyl, and -NHC(O)OC₁₋₃alkyl;

C₁₋₆alkoxy is optionally substituted with -OR^d;

15 C₃₋₆cycloalkyl is optionally substituted with one or two substituents
 independently selected from C₁₋₃alkyl and halo;

any heterocycle is optionally substituted with one, two, or three
 substituents independently selected from C₁₋₃alkyl, halo, -C(O)OC₁₋₃alkyl,
 -C(O)C₁₋₆alkyl, -C(O)C₃₋₆cycloalkyl, -C(O)NHC₁₋₆alkyl, and

20 -C(O)NHC₃₋₆cycloalkyl;

wherein any -C(O)C₁₋₆alkyl is optionally substituted with
 -NHC(O)OC₁₋₃alkyl, -ORⁿ, -NR^dR^e, or heterocycle,

any -C(O)C₃₋₆cycloalkyl is optionally substituted with one or two
 C₁₋₃alkyl, and

25 any -C(O)NHC₁₋₆alkyl is optionally substituted with -ORⁿ or
 C₃₋₆cycloalkyl;

any heteroaryl is optionally substituted with C₁₋₃alkyl;

R^k, R^d, R^e, R^g, and R^h are each independently hydrogen or C₁₋₃alkyl;

R^f is selected from hydrogen and -C(O)C₁₋₃alkyl; and

R^7 is selected from halo, C_{1-3} alkyl, and C_{1-3} alkoxy wherein C_{1-6} alkyl and C_{1-6} alkoxy are optionally substituted with one, two, or three halo; and

R^9 is C_{1-3} alkyl or $-CH_2OR^n$.

5 17. The compound of Claim 16 wherein

R^5 is selected from C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} alkoxy, $-C(R^kR^d)NR^eR^f$, $-NR^gR^h$, heteroaryl, heterocycle, and $-CH_2$ -heteroaryl;

wherein

any heteroaryl or heterocycle has five or six ring atoms;

10 C_{3-6} cycloalkyl is optionally substituted with one or two C_{1-3} alkyl;

any heterocycle is optionally substituted with one or two substituents selected from C_{1-3} alkyl, halo, $-C(O)OC_{1-3}$ alkyl, $-C(O)C_{1-6}$ alkyl optionally substituted with $-NHC(O)OC_{1-3}$ alkyl, and $-C(O)C_{3-6}$ cycloalkyl optionally substituted with one or two C_{1-3} alkyl;

15 R^k , R^d , R^e , R^g , and R^h are each independently hydrogen or C_{1-3} alkyl; and R^f is selected from hydrogen and $-C(O)C_{1-3}$ alkyl.

18. A pharmaceutical composition comprising a compound of any one of Claims 1 to 17 and a pharmaceutically-acceptable carrier.

20

19. The pharmaceutical composition of Claim 18 further comprising one or more other therapeutic agents useful for treating hepatitis C viral infections.

20. The pharmaceutical composition of Claim 19 wherein the one or more
25 other therapeutic agents is selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, and ribavirin and related nucleoside analogs.

21. A compound of any one of Claims 1 to 17 for use in therapy.

30

22. A compound of any one of Claims 1 to 17 for use in the treatment of a hepatitis C viral infection in a mammal.

23. A compound of any one of Claims 1 to 17 for use in the treatment of a hepatitis C viral infection in a mammal together with one or more other therapeutic agents.

5 24. The compound of Claim 23 wherein the one or more other therapeutic agents is selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, and ribavirin and related nucleoside analogs.

10 25. A compound of any one of Claims 1 to 17 for use in inhibiting replication of the hepatitis C virus in a mammal.

 26. The compound of Claim 25 for use in combination with one or more other therapeutic agents selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside
15 and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, and ribavirin and related nucleoside analogs.

 27. A method of treating hepatitis C viral infection in a mammal, the method comprising administering to the mammal a pharmaceutical composition comprising a
20 compound of any one of Claims 1 to 17 and a pharmaceutically-acceptable carrier.

 28. The method of Claim 27 wherein the method further comprises administering to the mammal one or more other therapeutic agents useful for treating hepatitis C viral infections.

25 29. The method of Claim 28 wherein the one or more other therapeutic agents is selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, and ribavirin and related nucleoside analogs.

30 30. A method of inhibiting replication of the hepatitis C virus in a mammal, the method comprising administering to the mammal a pharmaceutical composition comprising a compound of any one of Claims 1 to 17 and a pharmaceutically-acceptable carrier.

31. The method of Claim 30 wherein the method further comprises administering to the mammal one or more other therapeutic agents useful for inhibiting replication of the hepatitis C virus in a mammal.

5

32. The method of Claim 31 wherein the one or more other therapeutic agents is selected from HCV NS3 protease inhibitors, HCV NS5B nucleoside and non-nucleoside polymerase inhibitors, interferons and pegylated interferons, and ribavirin and related nucleoside analogs.

10

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/059061

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D403/14 A61K31/4025 A61P31/12
 ADD.
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
 EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/094977 A1 (ARROW THERAPEUTICS LTD [GB]; CARTER MALCOLM CLIVE [GB]; MATHEWS NEIL []) 26 August 2010 (2010-08-26) page 77; examples 40-45 -----	1-32
A	WO 2008/021927 A2 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; BELEMA MAKONEN [US];) 21 February 2008 (2008-02-21) claim 1 -----	1-32

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search 10 January 2012	Date of mailing of the international search report 26/01/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Baston, Eckhard

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/059061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010094977 A1	26-08-2010	AR 075587 A1	20-04-2011
		TW 201036968 A	16-10-2010
		US 2010215618 A1	26-08-2010
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