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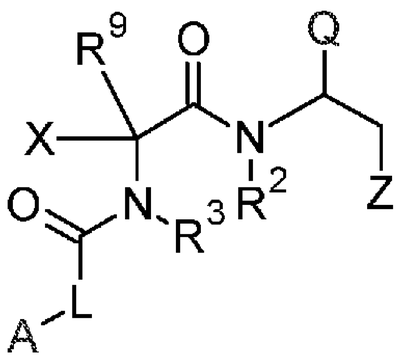
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(54) Title: SARS-COV-2 MPRO INHIBITOR COMPOUNDS



(1')

(57) Abstract: P33613WO1 93 ABSTRACT The disclosures herein relate to compounds of Formula (1'): or a salt thereof, wherein A, Q, X, Z, L, R2, R3 and R9 are defined herein, and their use in the treatment of SARS-CoV-2 and related viruses and disorders associated with SARS-CoV-2: Mpro.

SARS-COV-2 MPRO INHIBITOR COMPOUNDS

This application relates to novel compounds and their use as SARS-CoV-2 Main Protease (Mpro) inhibitors. Compounds described herein may be useful in the treatment of SARS-CoV-2 and related viruses and disorders associated with SARS-CoV-2: Mpro. The application is also directed to pharmaceutical compositions comprising these compounds and the manufacture and use of these compounds and compositions in the treatment of SARS-CoV-2 and related viruses and disorders associated with SARS-CoV-2: Mpro. The compounds and compositions may be useful in preventing death or complications arising due to chronic underlying conditions or comorbidities in patients infected with SARS-CoV-2 and related viruses.

BACKGROUND OF THE INVENTION

Coronaviruses have long existed in nature and have made zoonotic transmission to humans, generally causing mild respiratory illnesses such as the common cold upon infection. However, in the last two decades outbreaks of novel human coronavirus infections that cause severe respiratory illness have presented a major global health concern. This includes the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak in 2002-2004, the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012-2015 and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the most recently emerged strain of coronavirus, that was identified in Wuhan, China, in 2019 and is the aetiological agent responsible for the 2019-2020 viral pneumonia outbreak of coronavirus disease 2019 (COVID-19). Despite the tragic and widespread effects of these sudden occurrences and the periodic emergence of novel human coronaviruses increasing the potential for future outbreaks, we do not yet have validated antiviral treatments targeting coronavirus infections.

SARS-CoV-2 packages a large RNA genome of ~30kb, two-thirds of which encodes for the two polyproteins pp1a and pp1b (Hegyi et al. *Journal of General Virology* 83 (3): 595–99). These polyproteins are processed into 16 non-structural proteins (nsps) that are liberated from the long polypeptide chains by two viral cysteine proteases, the papain-like protease (nsp3) and the 3C-like protease (nsp5). The latter species, also referred to as the main protease (Mpro), cleaves the viral polyproteins at eleven sites to generate twelve non-structural proteins (nsp5-16). Included in these nsps are those involved in the replication and transcription machinery such as the the RNA-dependent RNA polymerase (nsp12) and helicase (nsp13). The essential role Mpro plays in viral replication has been demonstrated in mutagenesis experiments (Kim et al. *Virology* 208 (1): 1–8; Stobart et al. *Journal of Virology* 86 (9): 4801–10), which makes it an attractive target for the design of inhibitors to treat coronavirus infection.

Furthermore, there are no human proteases with similar cleavage specificity and therefore selective inhibitors of Mpro are highly likely to be non-toxic (Anand et al. 2003. *Science* 300 (5626): 1763–67).

The use of protease inhibitors for the treatment of viral diseases is well precedented (Bacon et al. *The New England Journal of Medicine* 364 (13): 1207–17) and the similarity of the SARS-CoV-2 Mpro active site to other viral proteases has driven efforts to identify clinically approved drugs that could be repurposed for the treatment of COVID-19 (Riva et al. *Nature*, 586: 113-119). Screening of a selection of 18 viral protease inhibitors designed for the treatment of human immunodeficiency virus (HIV) and Hepatitis C virus (HCV) identified the anti-HCV drug boceprevir and the pre-clinical inhibitor against feline infectious peritonitis virus (FIPV) GC376 as inhibitors of SARS-CoV-2 Mpro (Fu et al. *Nature Communications* 11 (1): 4417). While GC376 showed a more potent inhibition efficacy of recombinant protease activity (IC_{50} = 0.15 μM) than boceprevir (IC_{50} = 8 μM), GC376 has shown side effects in trials performed in cats raising potential safety concerns (Pedersen et al. *Journal of Feline Medicine and Surgery* 20 (4): 378–92). Boceprevir was also identified as an inhibitor of SARS-CoV-2 Mpro alongside telaprevir in a different study, albeit both drugs inhibited SARS-CoV-2 Mpro with IC_{50} values of >1 μM (Anson et al. 2020. doi:10.21203/rs.3.rs-26344/v1). In addition to SARS-CoV-2 Mpro, the inhibitory efficacy of boceprevir and telaprevir was also assessed at Mpro proteases from eight other coronaviruses including SARS, MERS, HKU1, HKU4, HKU5, NL63, FIPV and IBV. Within this selection boceprevir was able to inhibit all coronavirus proteases tested except NL63 and a similarly broad spectrum of activity was shown for telaprevir with inhibitory activity shown at SARS, HKU4, HKU5, NL63 and IBV. While the antiviral activity of these drugs at SARS-CoV-2 Mpro is not sufficient for clinical development, their ability to inhibit a broad range of proteases highlights the potential for the design of broad-spectrum antiviral drugs able to treat not only SARS-CoV-2 infection but also other human coronaviruses and potentially novel coronaviruses that could emerge in the future.

The sequence similarly between SARS-CoV and SARS-CoV-2 Mpro active sites was also exploited in the identification of the SARS-CoV-2 Mpro inhibitor PF-07304814, a phosphate prodrug of PF-00835231 which was originally designed for the treatment of SARS-CoV (Boras et al. *BioRxiv*, 2020.09.12.293498). PF-00835231 inhibited SARS-CoV-2 Mpro with a K_i of 0.27 nM and displayed broad inhibitory activity against ten further coronavirus strains with K_i values of 0.03-4 nM. This translated into ~1 μM activity in cell-based live virus assays. The activity of PF-00835231 in combination with remdesivir, a nucleoside RNA-dependent RNA polymerase inhibitor, was also evaluated as antiviral agents that target different aspects of the viral replication process can yield synergistic effects in combination. Indeed, PF-00835231

and remdesivir displayed either synergistic or additive effects in a cell-based antiviral assay, which suggests that the combination of Mpro inhibitors with antivirals with other modes of actions could show clinical benefit.

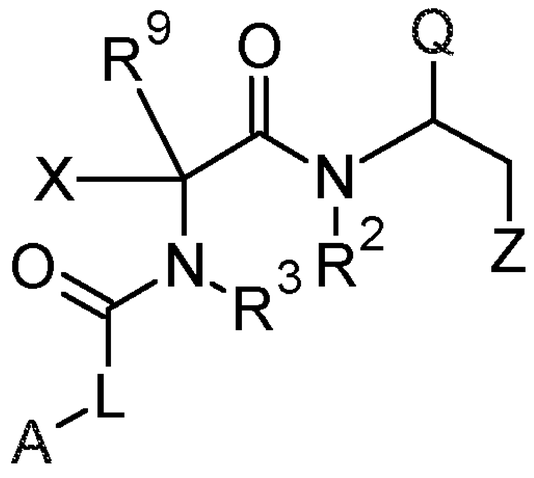
In 2020 the crystal structure of SARS-CoV-2 Mpro in complex with N3 (a Michael acceptor inhibitor) was published (Jin et al. *Nature* 582 (7811): 289–93), thereby enabling virtual screening and structure-based drug design (SBDD) for inhibitors of SARS-CoV-2 Mpro. Such SBDD efforts included the design of peptidomimetic α-ketoamides as broad-spectrum inhibitors of coronaviruses and enteroviruses with the two most promising inhibitors showing 0.71-12.27 μM IC_{50} values in recombinant inhibition assays for proteases from enteroviruses EV-A71 and CVB3 as well as coronaviruses SARS-CoV and NL63 (Zhang et al. 2020. *Journal of Medicinal Chemistry* 63 (9): 4562-4578). The activity observed in the recombinant protease assays broadly matched antiviral activity in cell-based live virus assays with IC_{50} values within 10-fold in both systems, suggesting that good activity in the protease inhibition assay is a good indicator of antiviral activity.

Currently, there are no targeted therapeutic agents for the treatment of COVID-19, and effective treatment options remain very limited. Despite much ongoing research activity and numerous clinical trials in progress, only remdesivir and favipiravir have been approved in selected countries for limited use to treat SARS-CoV-2 infection but show only modest effects (Zhou et al. *ACS Pharmacology & Translational Science* 3 (5): 813-834). There exists a need for targeted therapeutic agents for the treatment of SARS-CoV-2 infection and for the reasons outlined above SARS-CoV-2 Mpro represents an attractive drug target for SARS-CoV-2. The compounds disclosed herein are shown to be inhibitors of SARS-CoV-2 Mpro and therefore represent potential candidates for the treatment of coronavirus infection and associated disorders including but not limited to COVID-19.

THE INVENTION

The present invention provides compounds having activity as SARS-CoV-2: Mpro inhibitors.

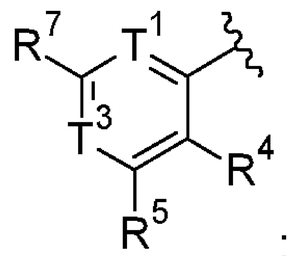
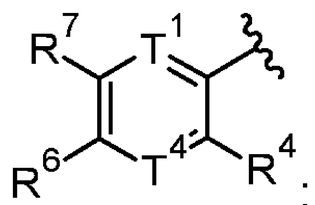
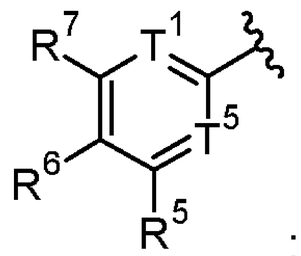
Provided is a compound of Formula (1’):

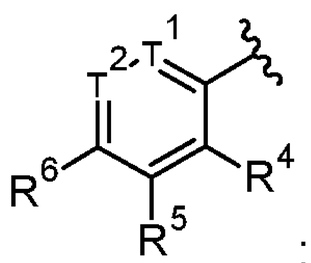
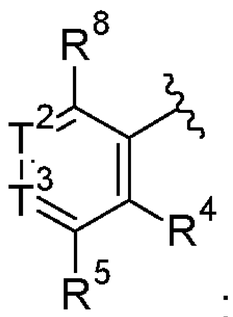
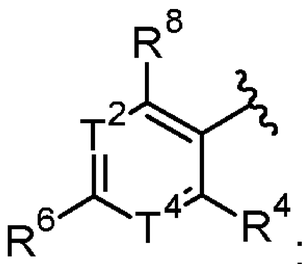


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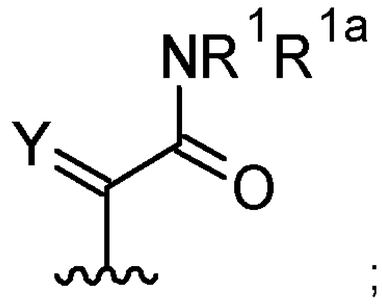
or a salt thereof, wherein;

A is selected from:


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Q is CN or a group of formula:


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X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

T^1 is CR^8 or N;

T^2 is CR^7 or N;

T^3 is CR^6 or N;

T^4 is CR^5 or N;

T^5 is CR^4 or N;

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is -$(CH_2)_pCONHR^{13}$, or Z is -$(CH_2)_pCO_2R^{13}$;

L is -CR^{11}=CR^{12}-, -CHR^{11}-CHR^{12}- or -O-CHR^{11}-;

R^1 and R^{1a} are independently H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms; or R^{11} and R^{12} are joined to form a cyclopropyl ring;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

wherein when R^1 and R^{1a} are not both H, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

Compounds of the present invention may be used as SARS-CoV-2: Mpro inhibitors. Compounds of the present invention may be used in the treatment of SARS-CoV-2 and related viruses or a disease or disorder associated with SARS-CoV-2: Mpro. Compounds of the present invention may be useful in preventing death or complications arising due to chronic underlying conditions or comorbidities in patients infected with SARS-CoV-2 and related viruses. Such chronic underlying conditions or comorbidities may include for example hypertension, obesity, chronic lung conditions (TB, asthma and cystic fibrosis), diabetes and cardiovascular conditions (coronary heart disease, congenital heart disease and heart failure). Compounds of the present invention may be used in the manufacture of medicaments. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of SARS-CoV-2 and related viruses and diseases or disorders in which SARS-CoV-2: Mpro is involved. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of chronic underlying conditions or comorbidities in patients infected with SARS-CoV-2 and related viruses.

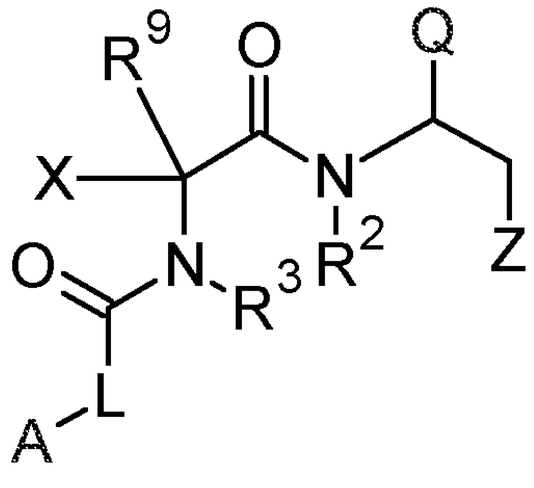
Compounds of the present invention may be for use as a single agent or in combination with one or more additional pharmaceutical agents. Compounds of the present invention may be

useful in the treatment of SARS-CoV-2 and related viruses or conditions or symptoms related thereto.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to novel compounds. The invention also relates to the use of novel compounds as inhibitors of SARS-CoV-2: Mpro. The invention further relates to the use of novel compounds in the manufacture of medicaments for use as SARS-CoV-2: Mpro inhibitors. The invention further relates to compounds, compositions and medicaments that may be useful in the treatment of SARS-CoV-2 and related viruses or conditions or symptoms related thereto.

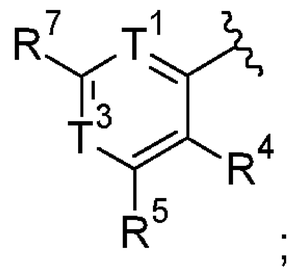
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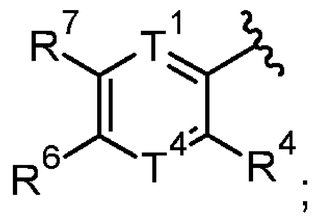


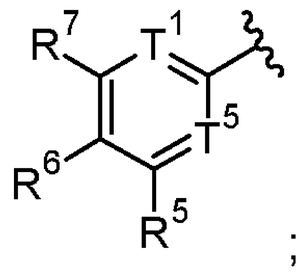
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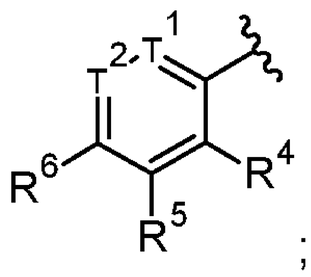
or a salt thereof, wherein;

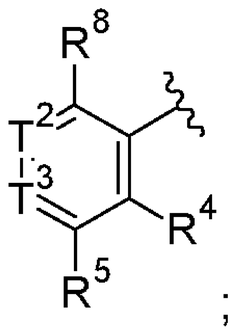
A is selected from:

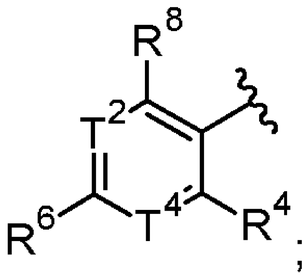

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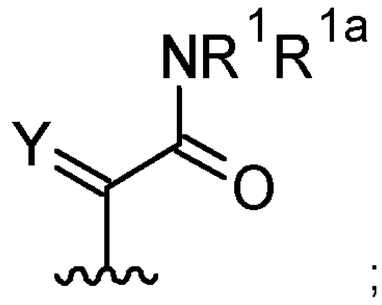

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Q is CN or a group of formula:


;

X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

T^1 is CR^8 or N;

T^2 is CR^7 or N;

T^3 is CR^6 or N;

T^4 is CR^5 or N;

T^5 is CR^4 or N;

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is $-(CH_2)_pCONHR^{13}$, or Z is $-(CH_2)_pCO_2R^{13}$;

L is $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ or $-O-CHR^{11}-$;

R^1 and R^{1a} are independently H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms; or R^{11} and R^{12} are joined to form a cyclopropyl ring;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

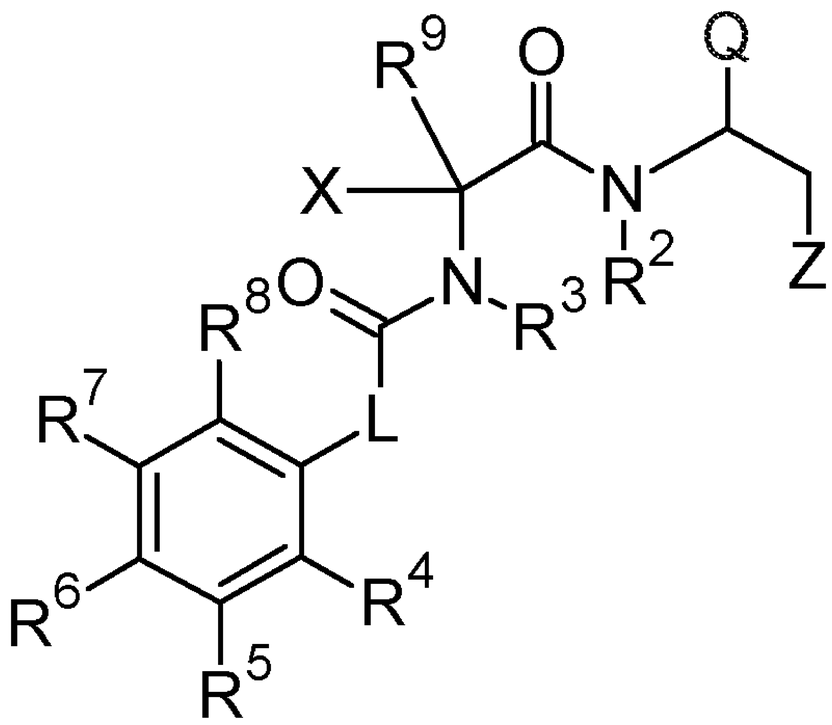
wherein when R^1 and R^{1a} are not both H, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

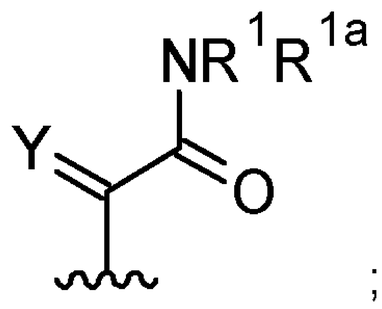
Also provided is a compound of Formula (1b):



(1b);

or a salt thereof, wherein;

Q is CN or a group of formula:



;

X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is $-(CH_2)_pCONHR^{13}$, or Z is $-(CH_2)_pCO_2R^{13}$;

L is $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ or $-O-CHR^{11}-$;

R^1 and R^{1a} are independently H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CO_2R^{14} or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

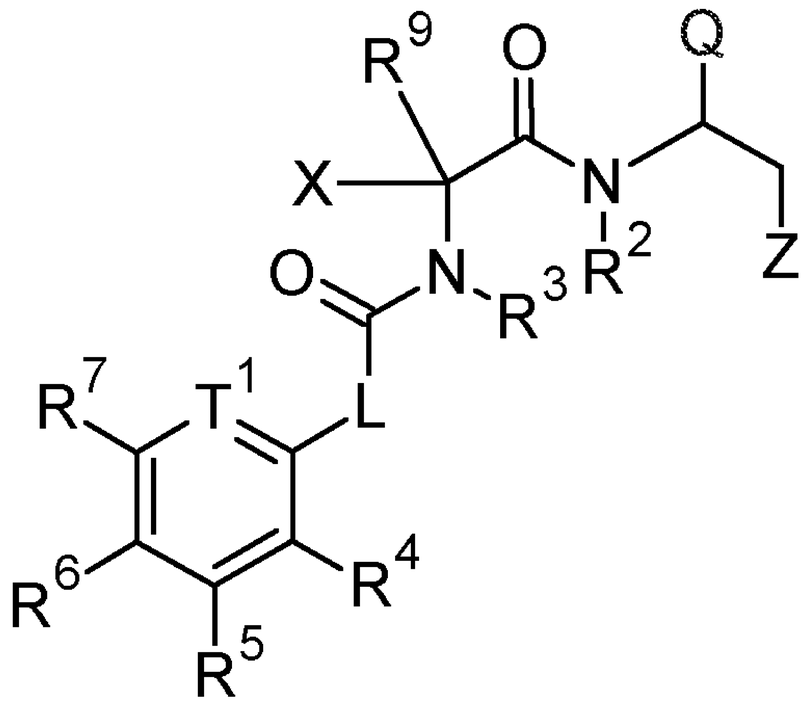
wherein when R^1 and R^{1a} are not both H, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

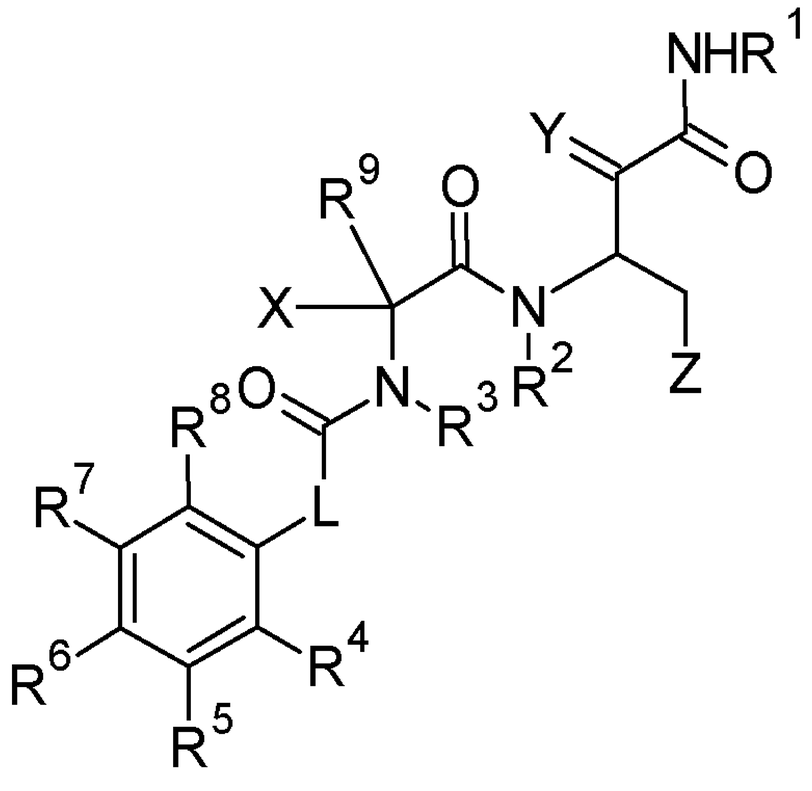
Also provided is a compound of Formula (1c):



(1c);

or a salt thereof, wherein Z, Q, X, L, T^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^9 are as defined herein.

Also provided is a compound of Formula (1):



(1);

or a salt thereof, wherein;

X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is -$(CH_2)_pCONHR^{13}$, or Z is -$(CH_2)_pCO_2R^{13}$;

L is -CR^{11}=CR^{12}-, -CHR^{11}-CHR^{12}- or -O-CHR^{11}-;

R^1 is H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CO_2R^{14} or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, -$(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

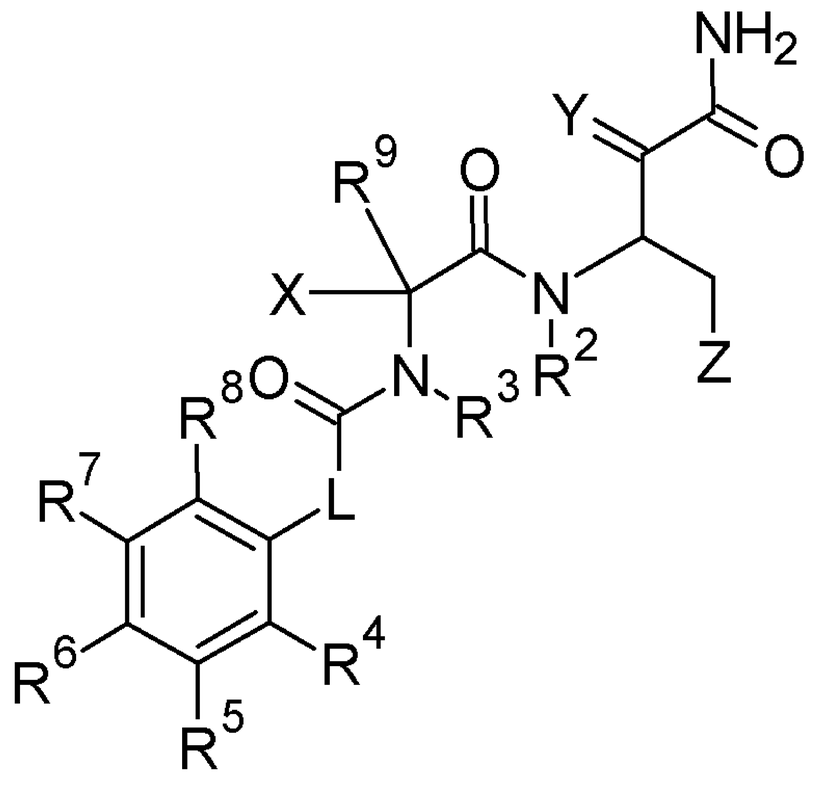
wherein when R^1 is a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, L is:

-CHR^{11}-CHR^{12}-;

-CR^{11}=CR^{12}- where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or -O-CHR^{11}- where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

Provided is a compound of Formula (1i):



(1i);

or a salt thereof, wherein;

X is a C_{1-8} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is $-(CH_2)_pCONHR^{13}$, or Z is $-(CH_2)_pCO_2R^{13}$;

L is $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ or $-O-CHR^{11}-$;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CO_2R^{14} or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

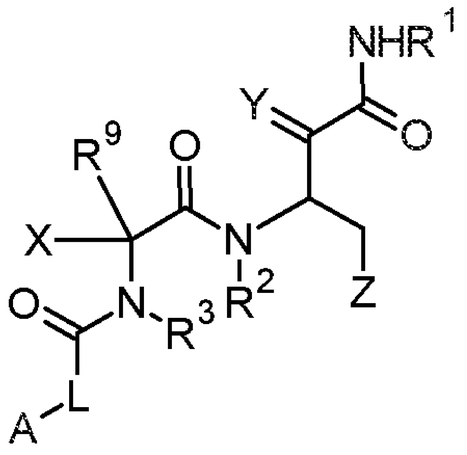
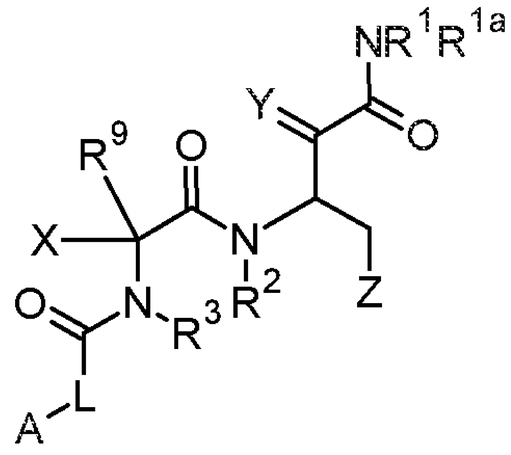
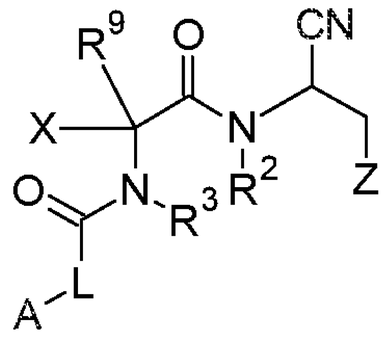
R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

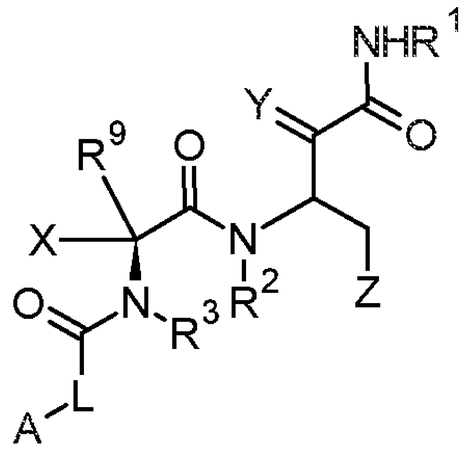
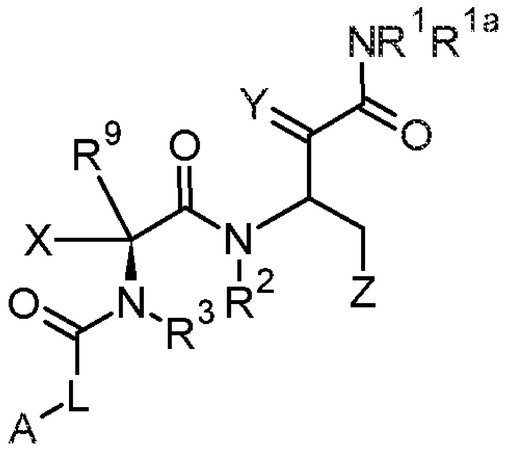
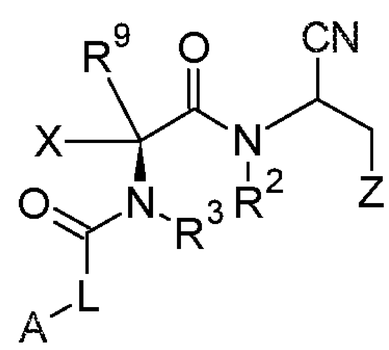
p and m are independently 0-3.

Also provided are compounds of Formula (1'a), (1'ai) and (1'aii):


(1'a);

(1'ai);

(1'aii);

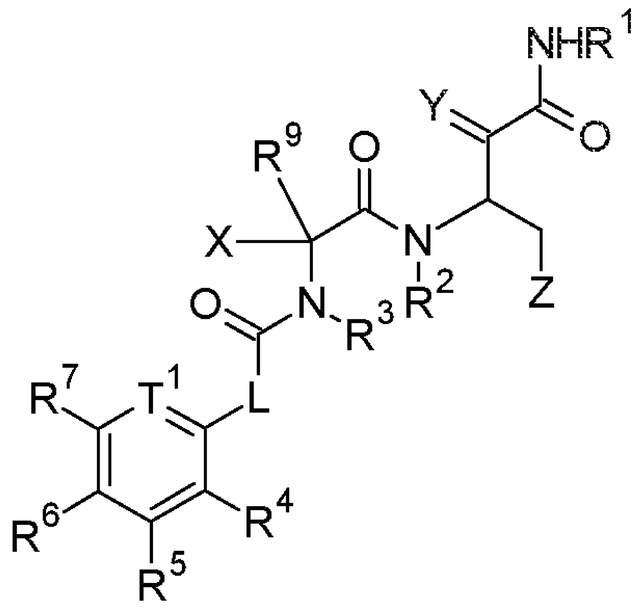
and salts thereof, wherein A, X, Z, Y, L, R^1, R^{1a}, R^2, R^3 and R^9 are as defined herein.

Also provided are compounds of Formula (1'aa), (1'aai) and (1'aaii):

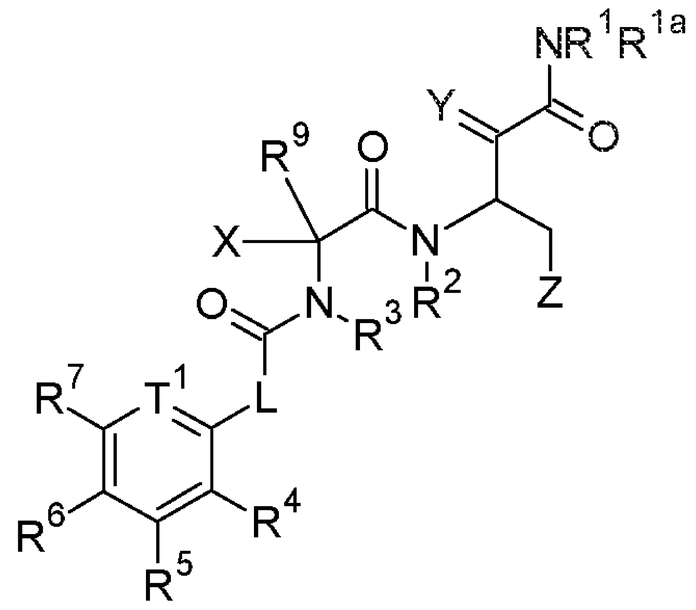

(1'aa);

(1'aai);

(1'aaii);

and salts thereof, wherein A, X, Z, Y, L, R^1, R^{1a}, R^2, R^3 and R^9 are as defined herein.

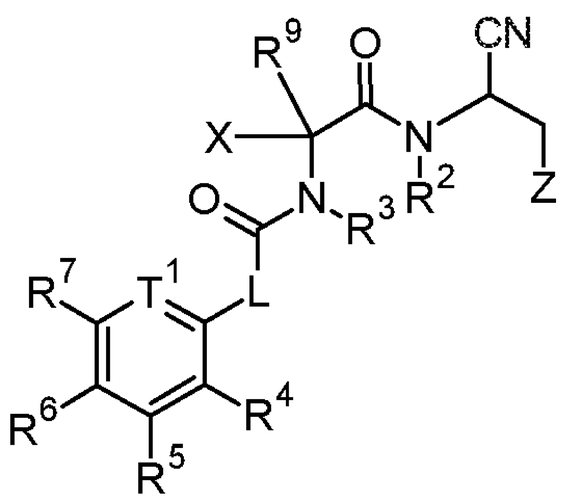
Also provided are compounds of Formula (1ca), (1cai) and (1caii):



(1ca);



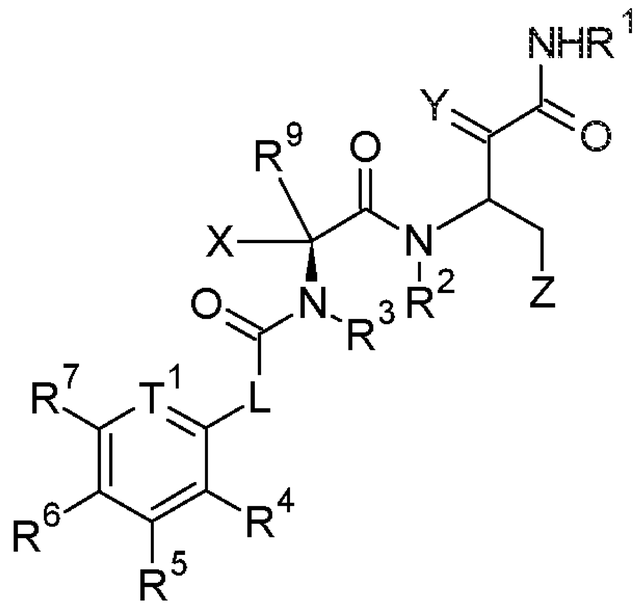
(1cai);



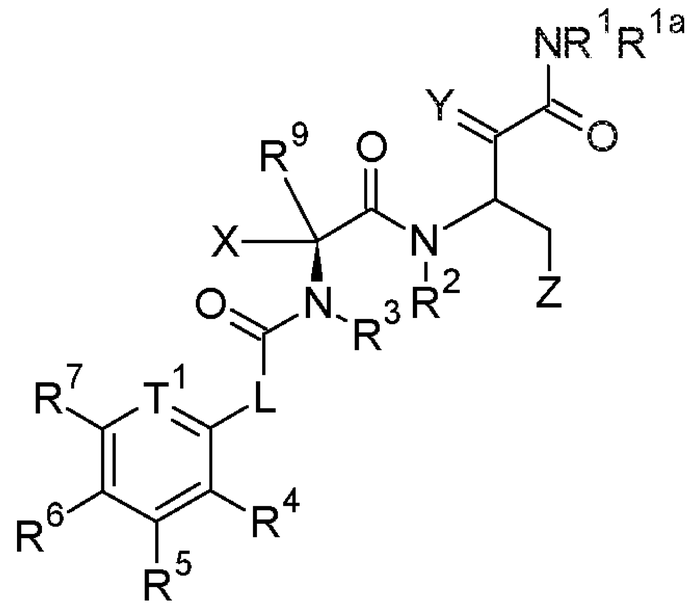
(1caii);

and salts thereof, wherein X, Z, Y, L, T^1, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7 and R^9 are as defined herein.

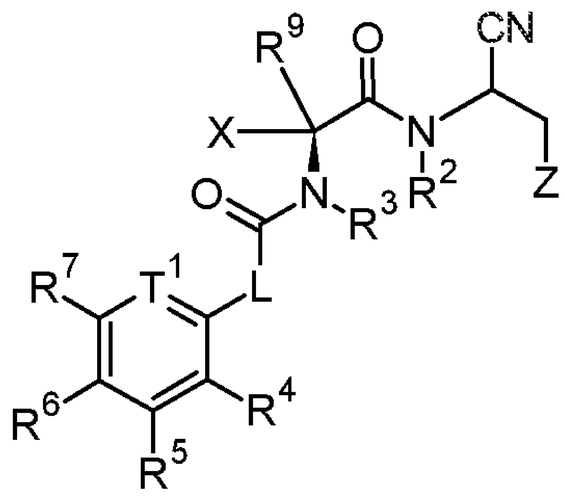
Also provided are compounds of Formula (1caa), (1caai) and (1caaii):



(1caa);



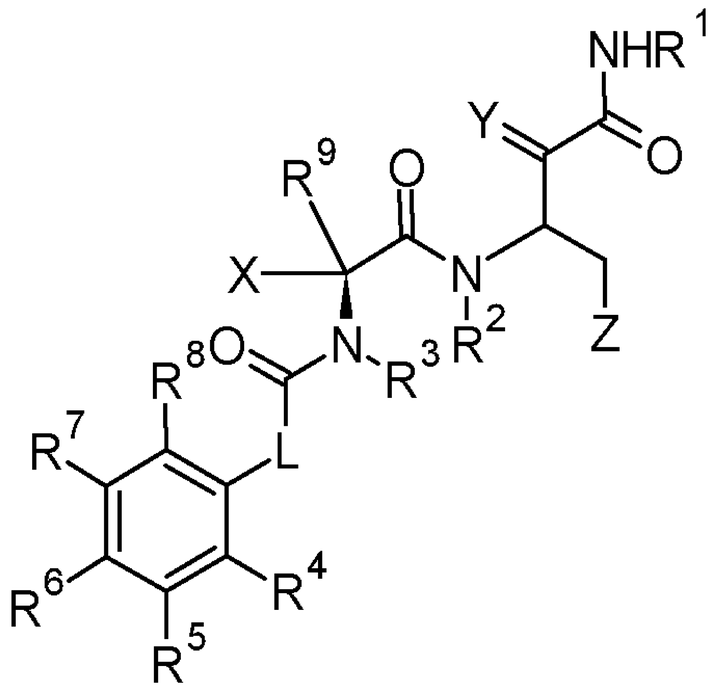
(1caai);



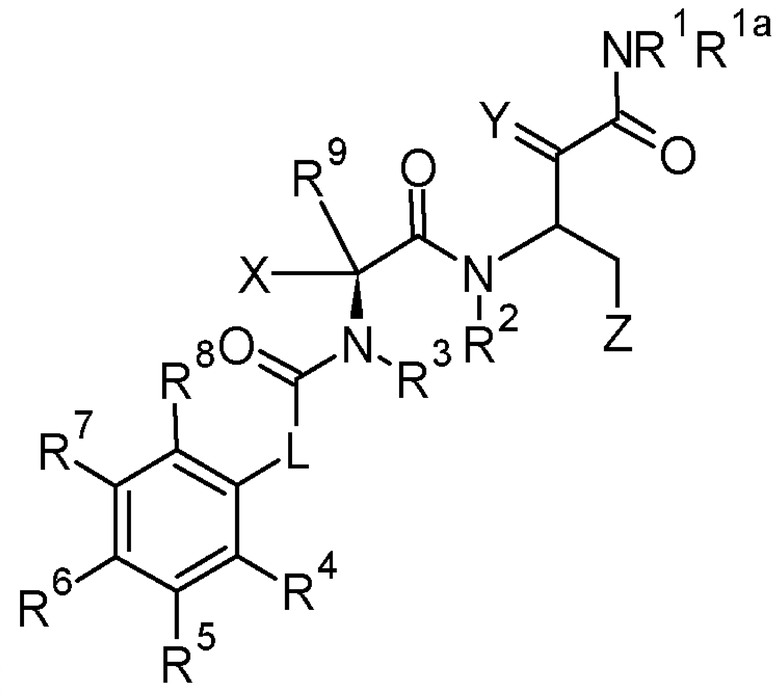
(1caaii);

and salts thereof, wherein X, Z, Y, L, T^1, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7 and R^9 are as defined herein.

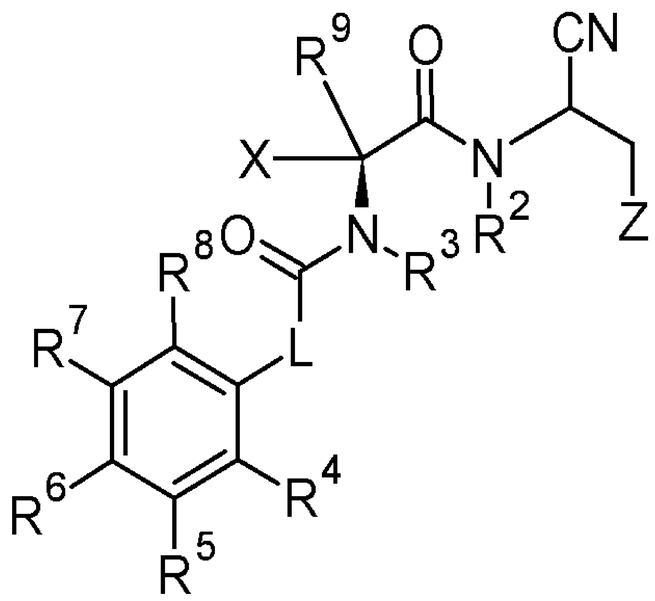
Also provided are compounds of Formula (1a), (1ai) and (1aii):



(1a);



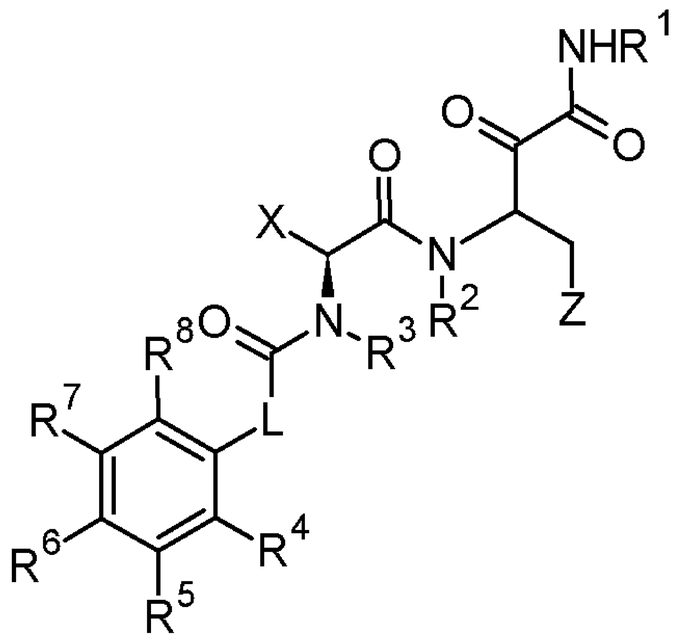
(1ai);



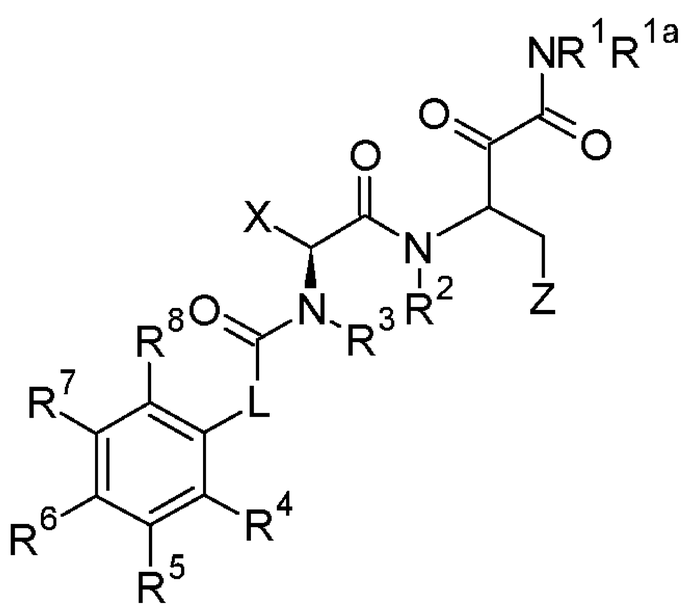
(1aii);

and salts thereof, wherein X, Z, Y, L, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are as defined herein.

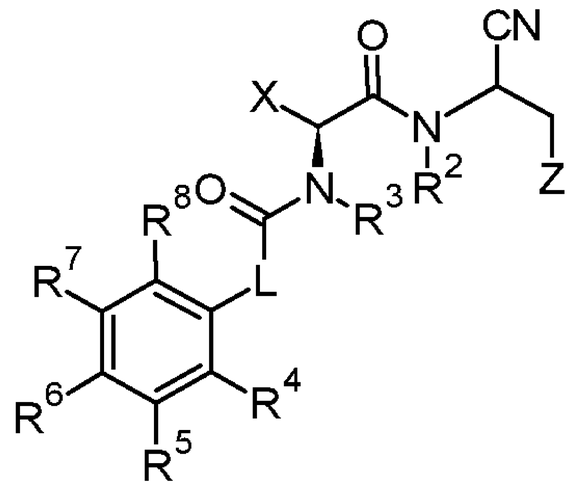
Also provided are compounds of Formula (2a), (2ai) and (2aii):



(2a);



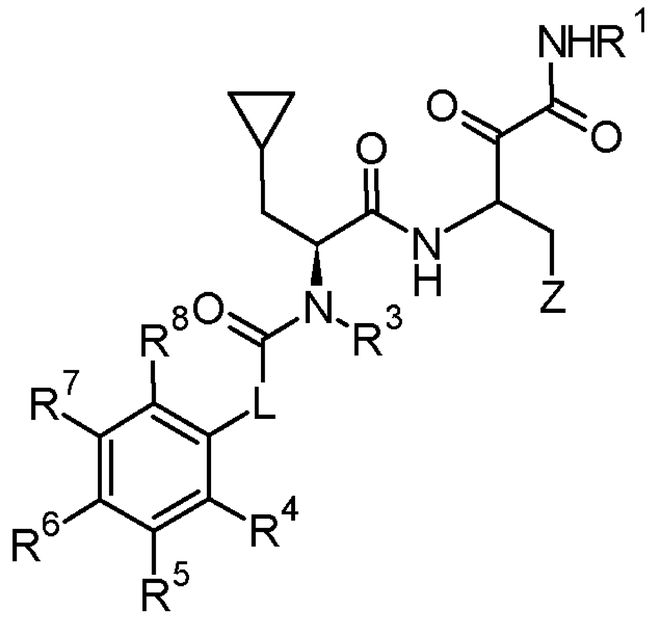
(2ai);



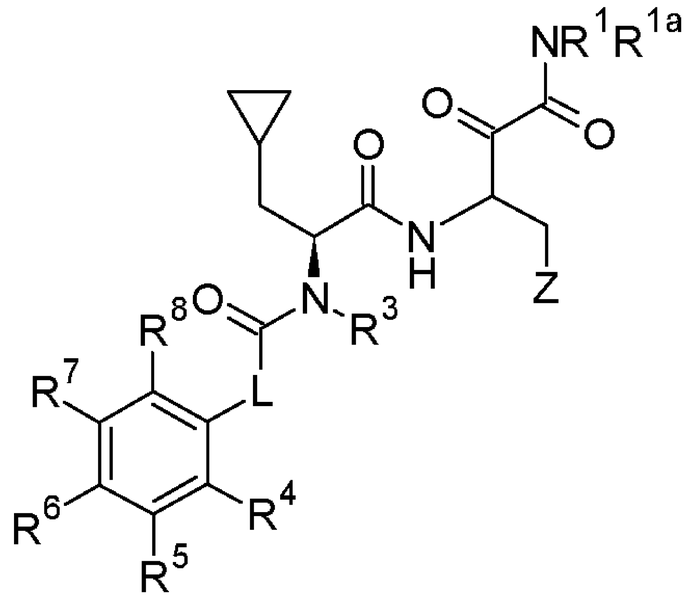
(2aii);

and salts thereof, wherein X, Z, L, R^1, R^{1a}, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

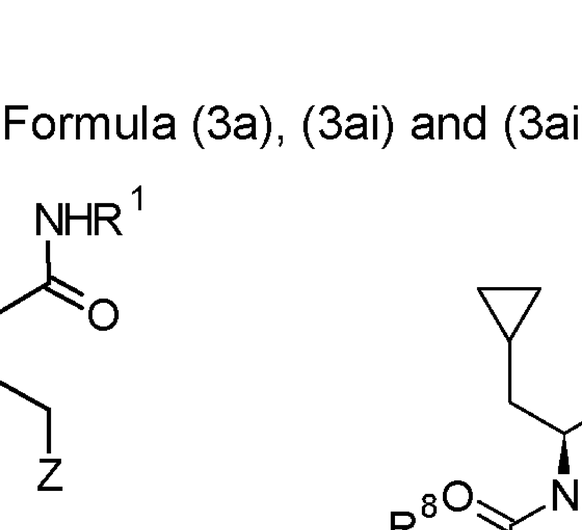
Also provided are compounds of Formula (3a), (3ai) and (3aii):



(3a);



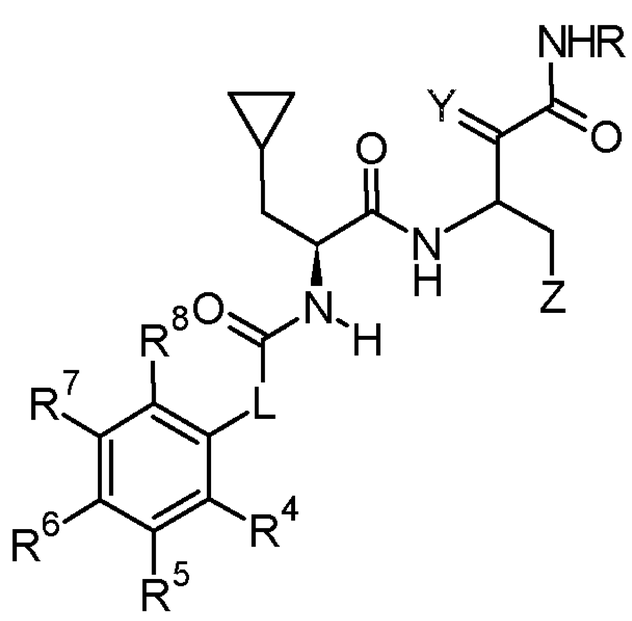
(3ai);



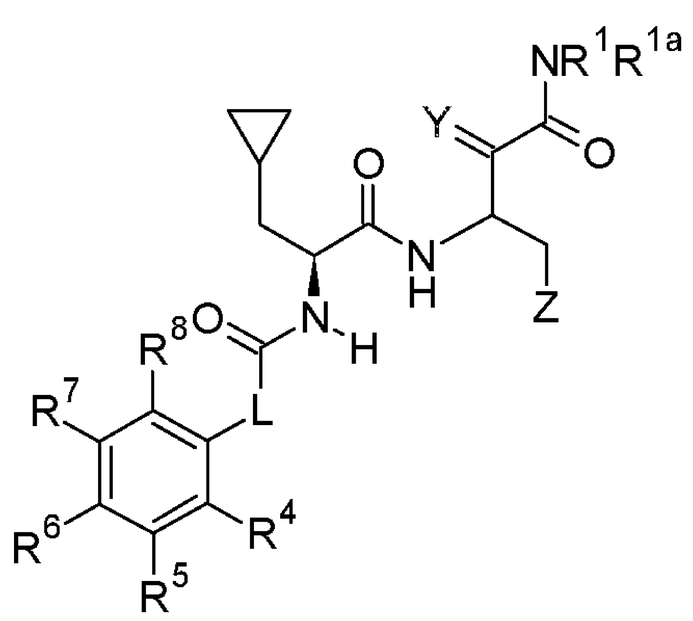
(3aii);

and salts thereof, wherein Z, L, R^1, R^{1a}, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

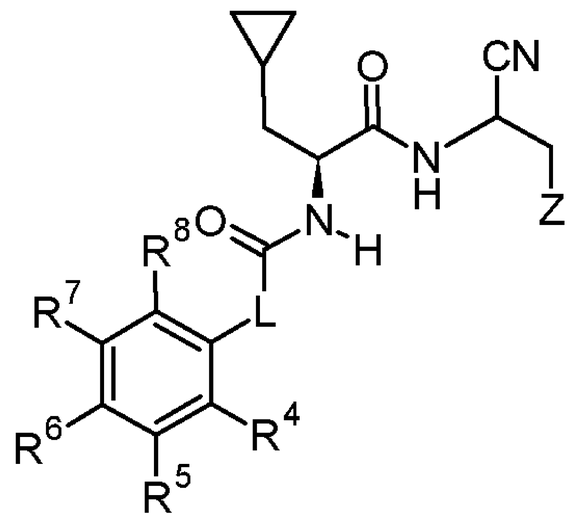
Also provided are compounds of Formula (3b), (3bi) and (3bii):



(3b);



(3bi);



(3bii);

and salts thereof, wherein

Y is O or NOH;

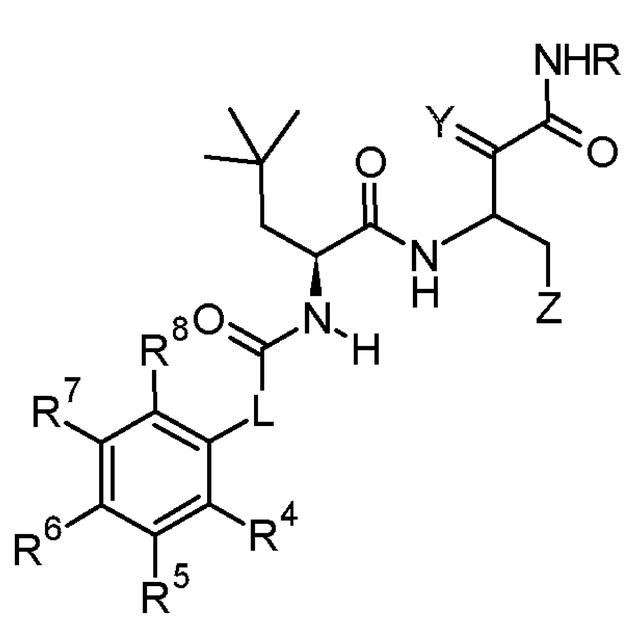
Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms;

L is -CH=CH-, $-CH_2-CH_2-$ or $-O-CH_2-$;

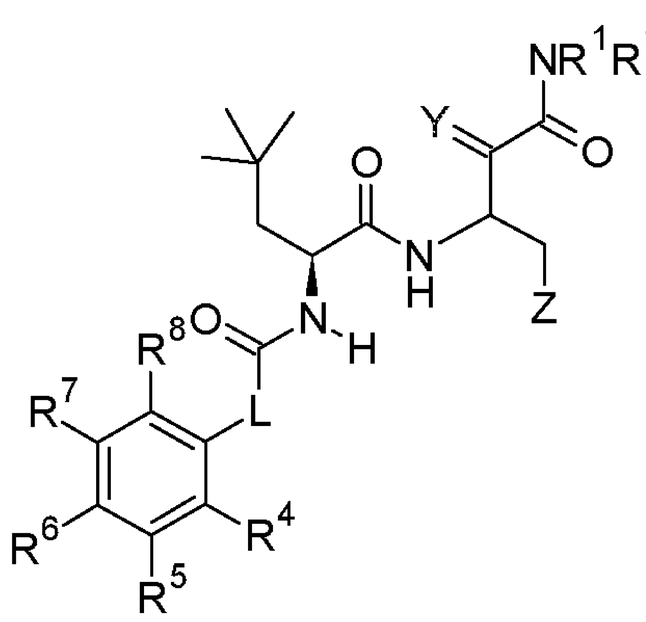
R^1 and R^{1a} are independently H or a C_{1-4} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H or halo.

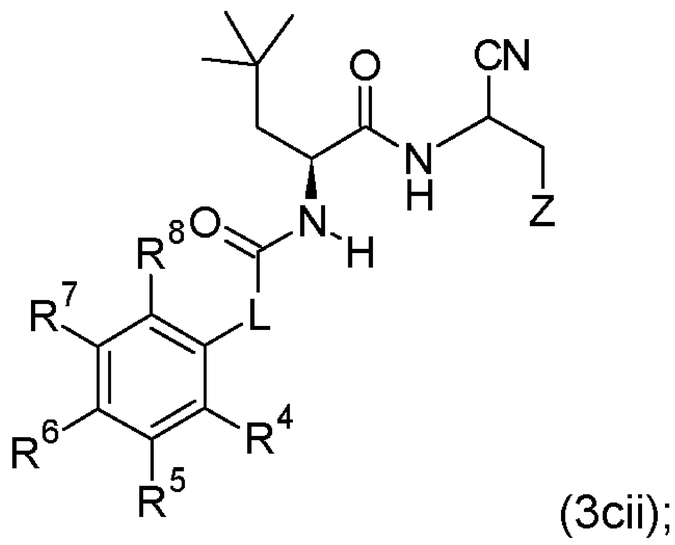
Also provided are compounds of Formula (3c), (3ci) and (3cii):



(3c);



(3ci);



(3cii);

and salts thereof, wherein

Y is O or NOH;

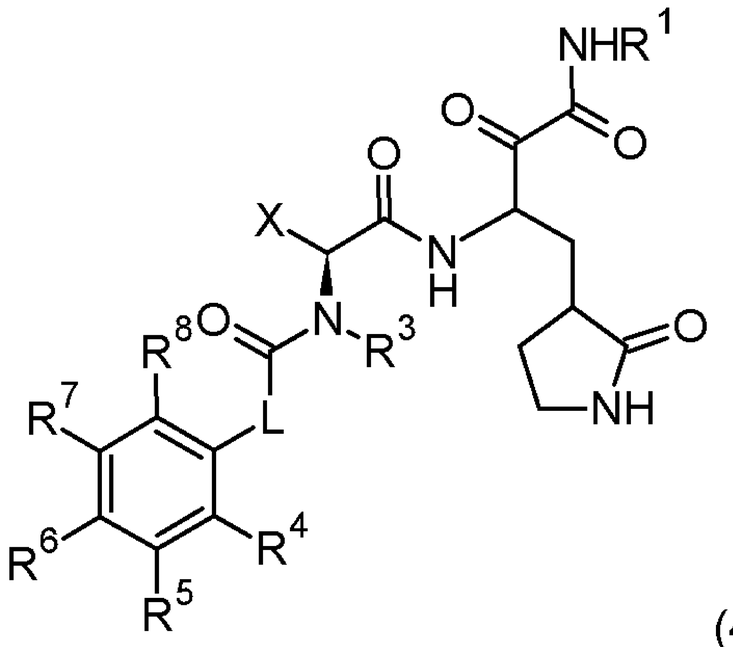
Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms;

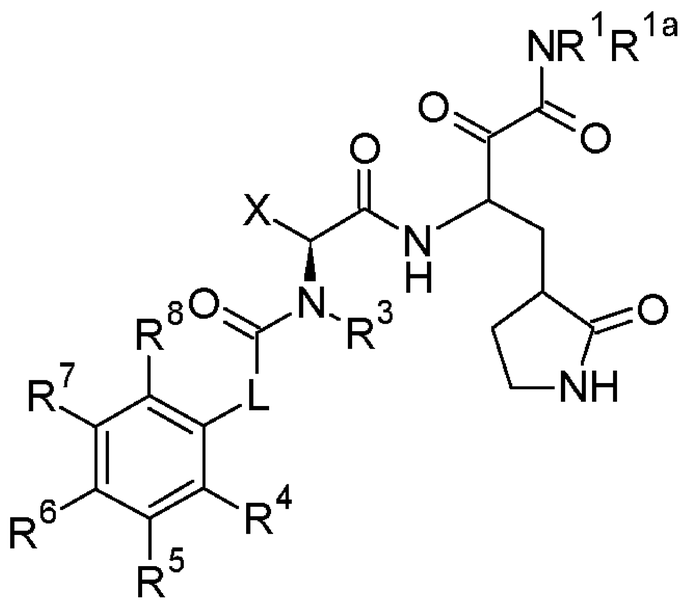
L is -CH=CH-, -CH_2-CH_2- or -O-CH_2-;

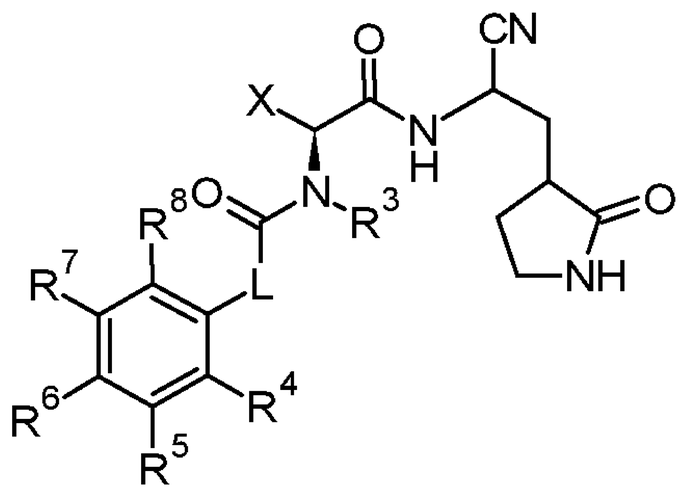
R^1 and R^{1a} are independently H or a C_{1-4} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms;

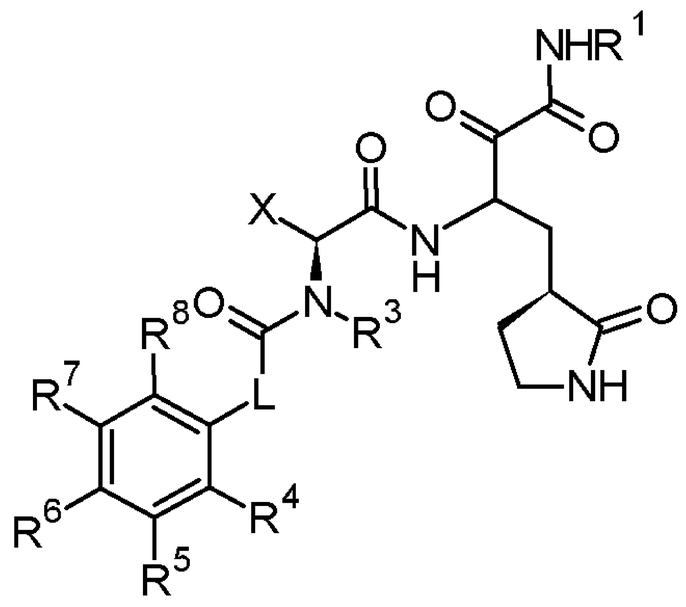
R^4, R^5, R^6, R^7 and R^8 are independently H or halo.

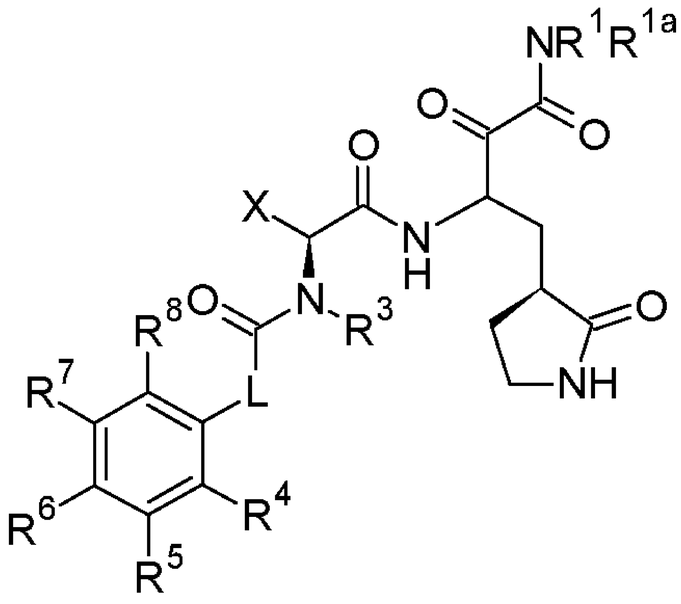
Also provided are compounds of Formula (4a), (4ai) and (4aii):

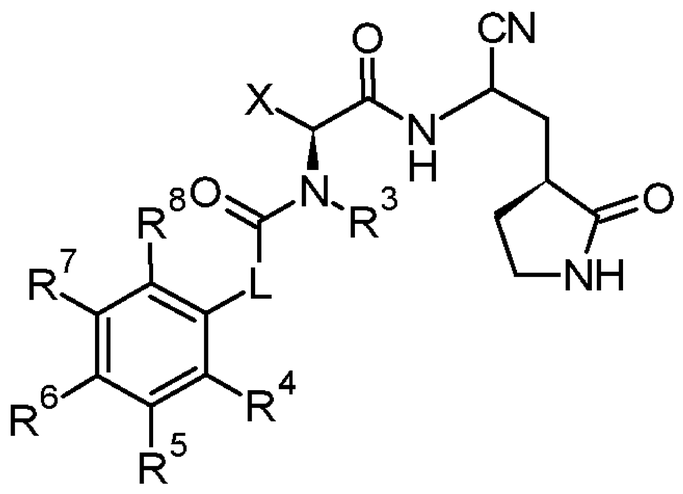

(4a);


(4ai);


(4aii);

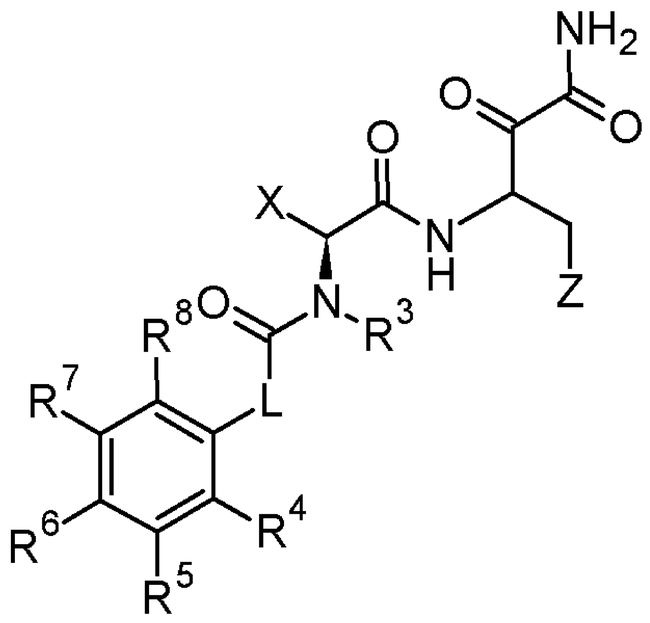

(4a');


(4ai');

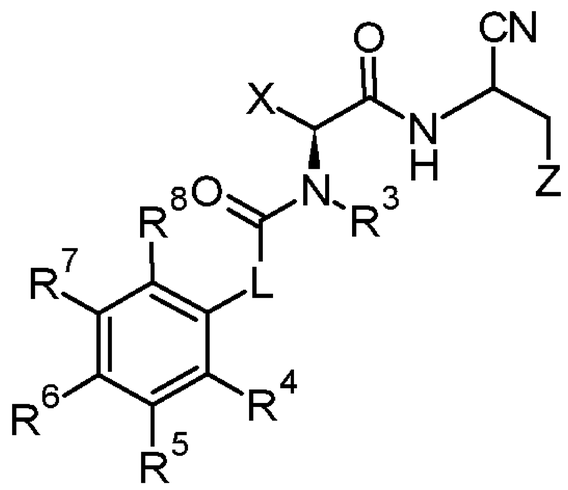

(4aii');

and salts thereof, wherein X, L, R^1, R^{1a}, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

Also provided are compounds of Formula (5a) and (5ai):



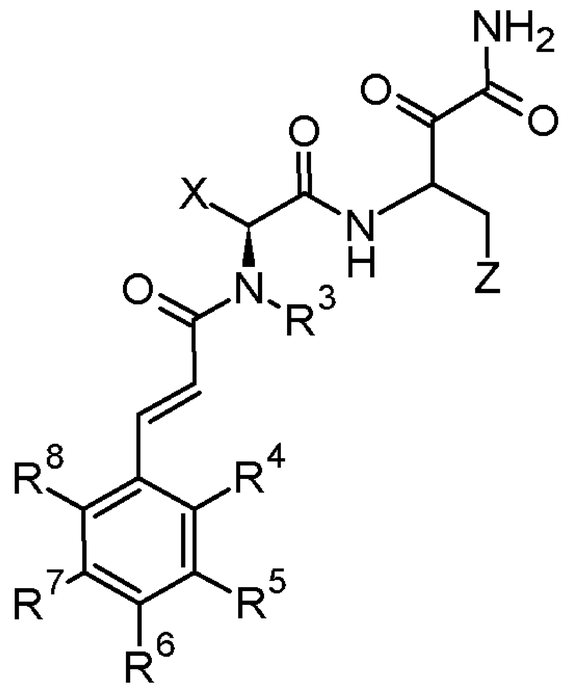
(5a);



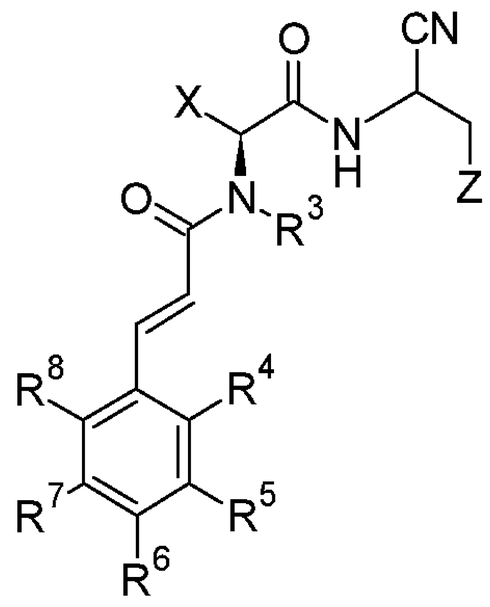
(5ai);

and salts thereof, wherein X, Z, L, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

Also provided are compounds of Formula (6a) and (6ai):



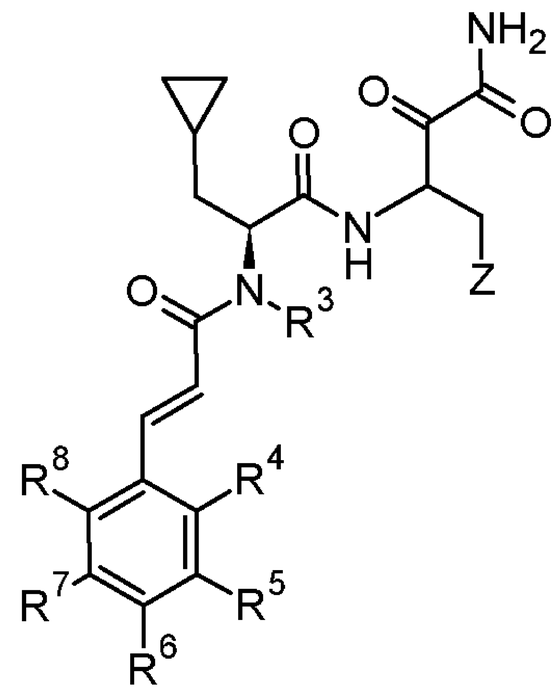
(6a);



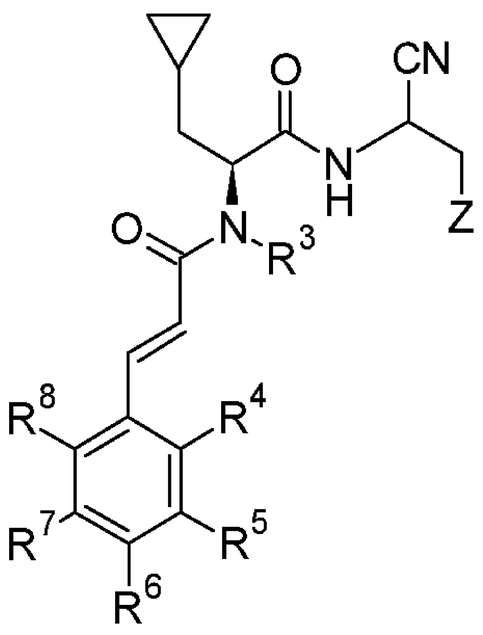
(6ai);

and salts thereof, wherein X, Z, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

Also provided are compounds of Formula (7a) and (7ai):



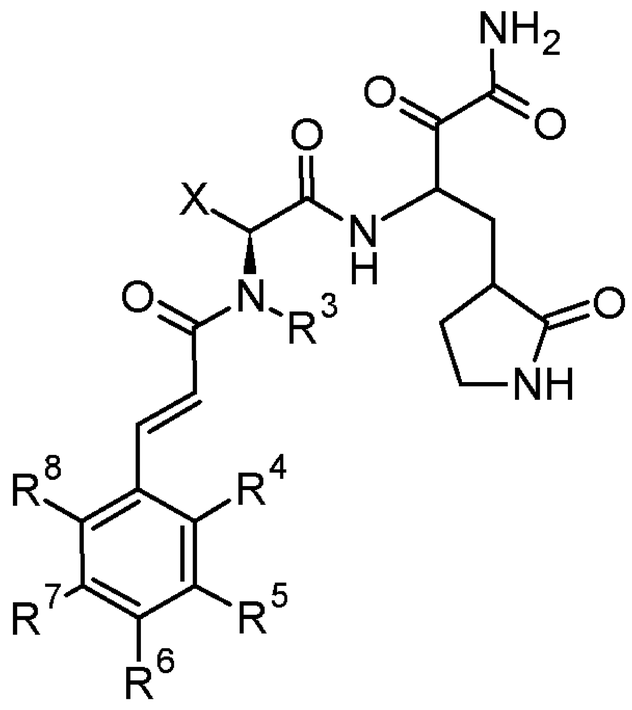
(7a);



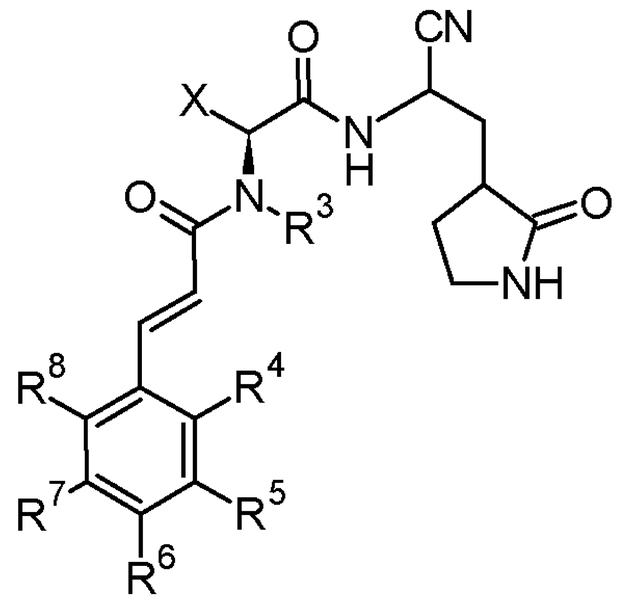
(7ai);

and salts thereof, wherein Z, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

Also provided are compounds of Formula (8a) and (8ai):



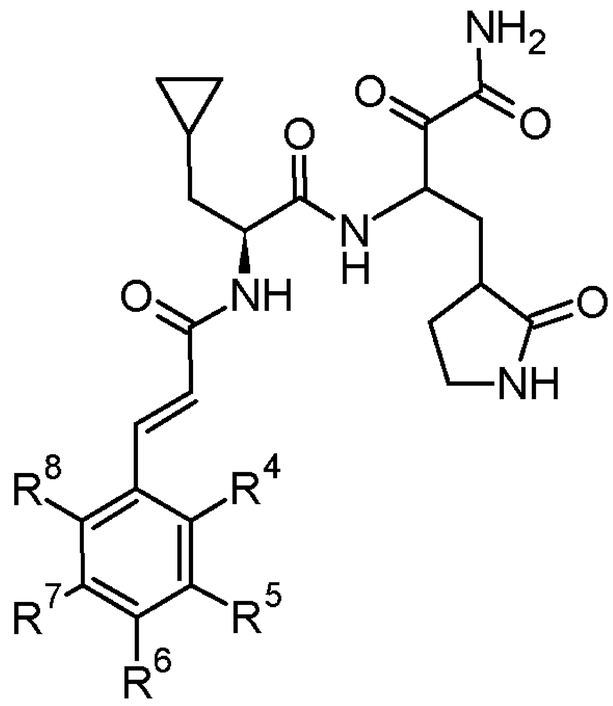
(8a);



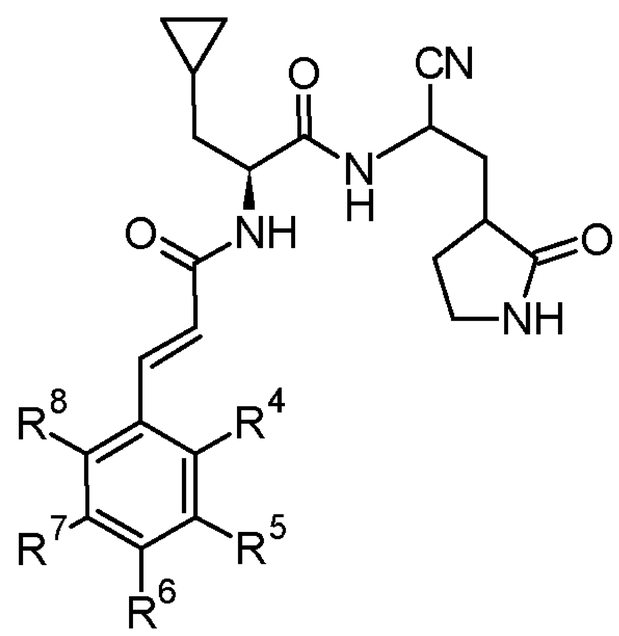
(8ai);

and salts thereof, wherein X, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

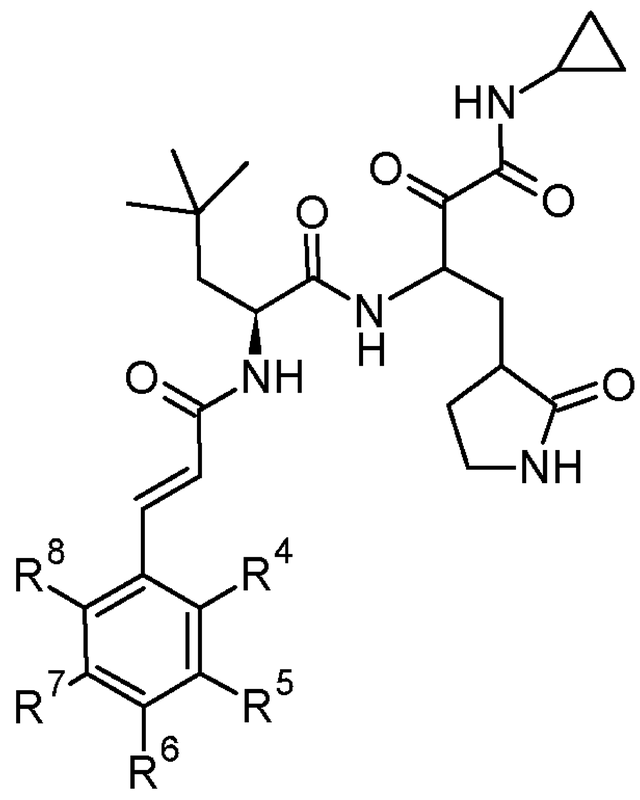
Also provided are compounds of Formula (9a), (9ai) and (9b):



(9a);



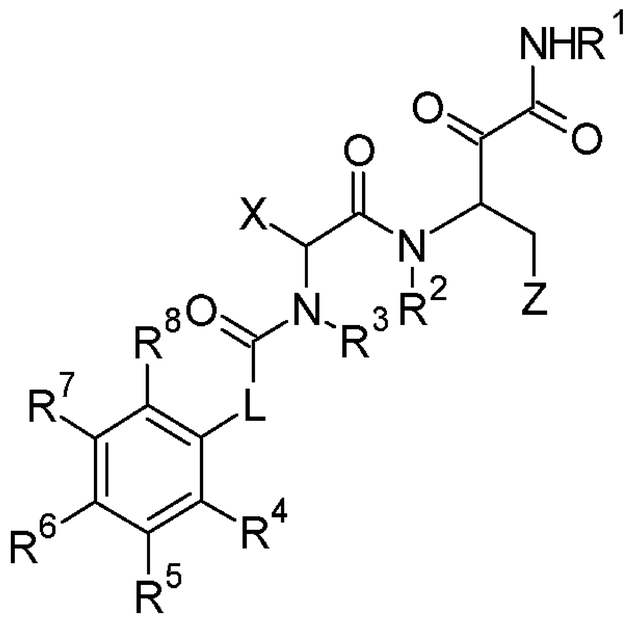
(9ai);



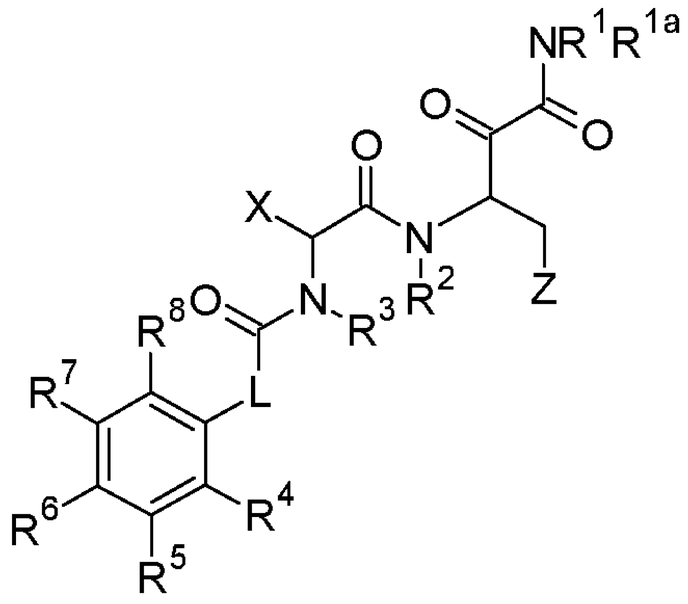
(9b);

and salts thereof, wherein R^4, R^5, R^6, R^7 and R^8 are as defined herein.

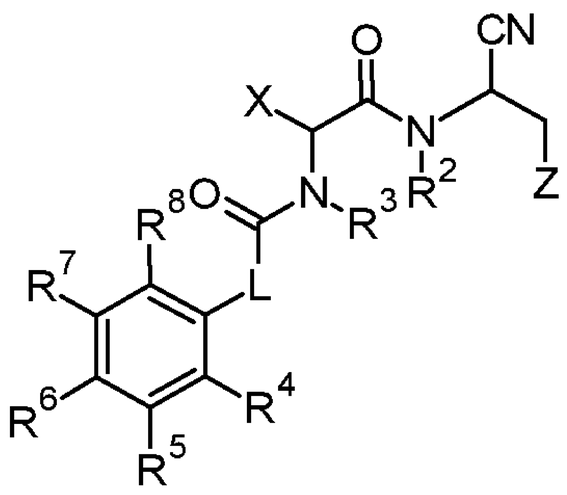
Also provided are compounds of Formula (2av) - (9bv):



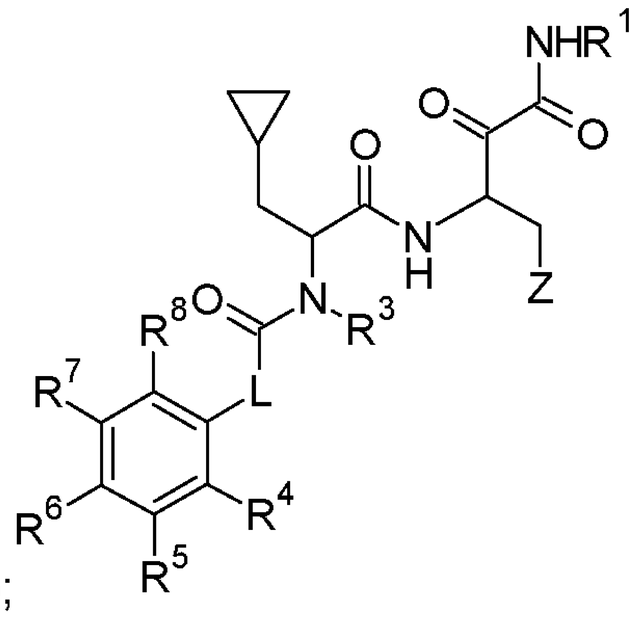
(2av);



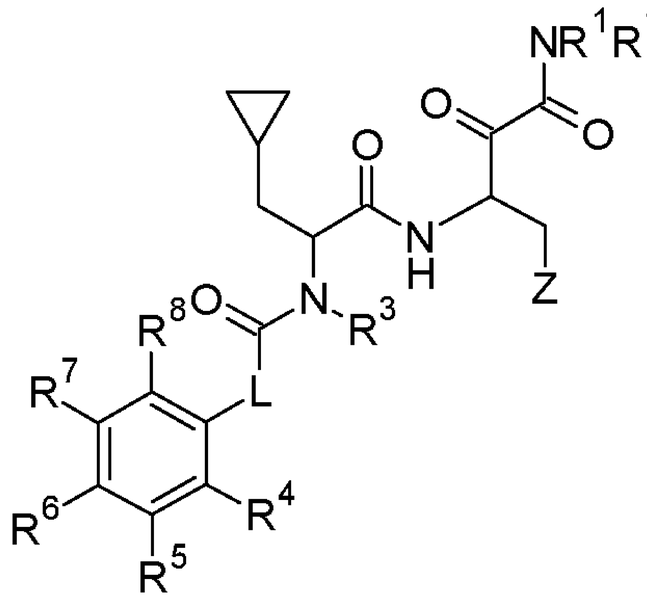
(2avi);



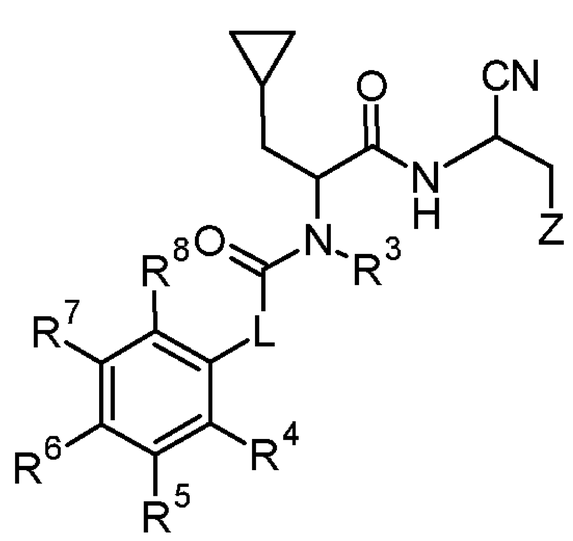
(2avii);



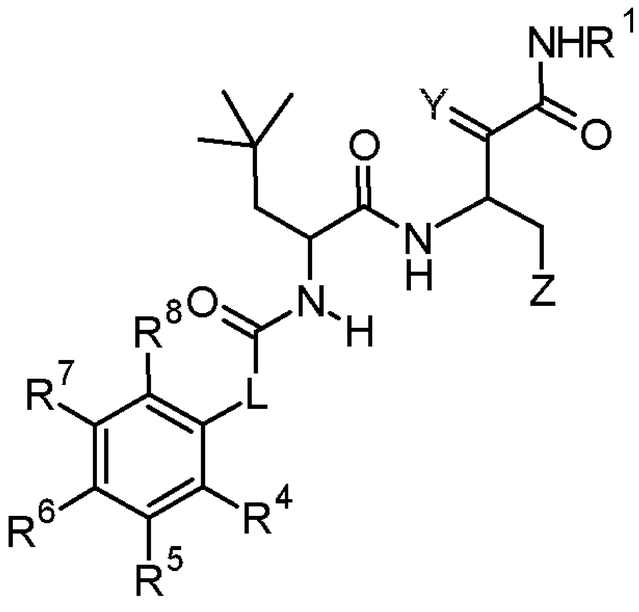
(3av);



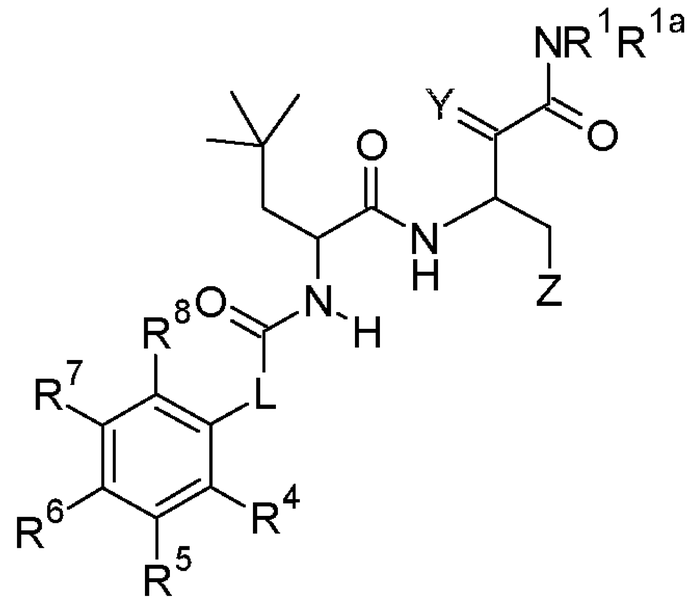
(3avi);



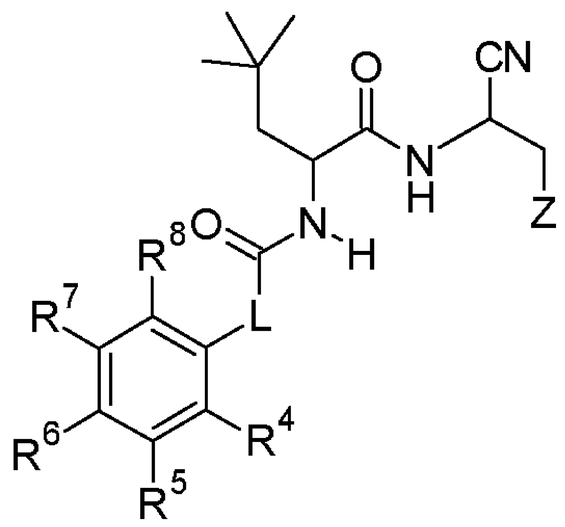
(3avii);



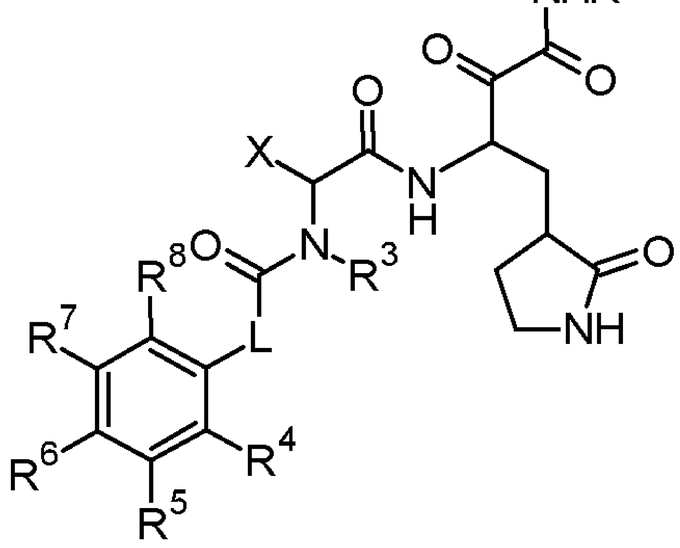
(3cv);



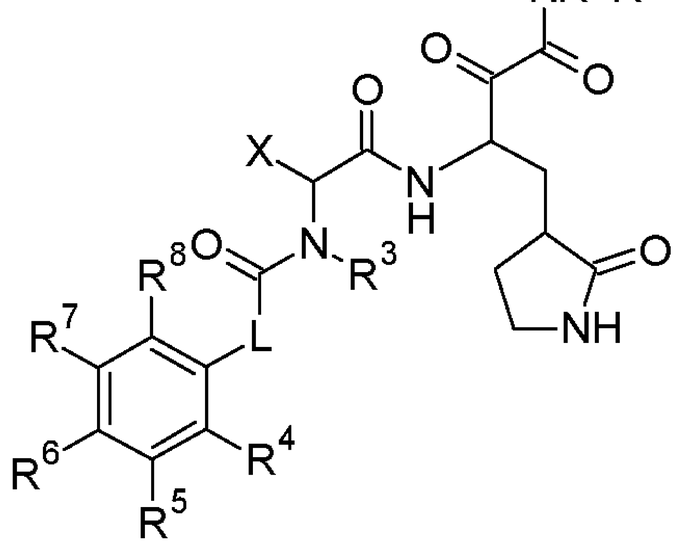
(3cvi);



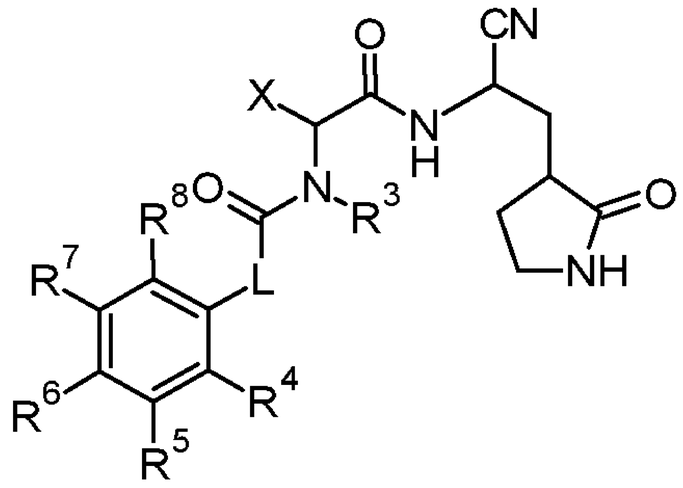
(3cvii);



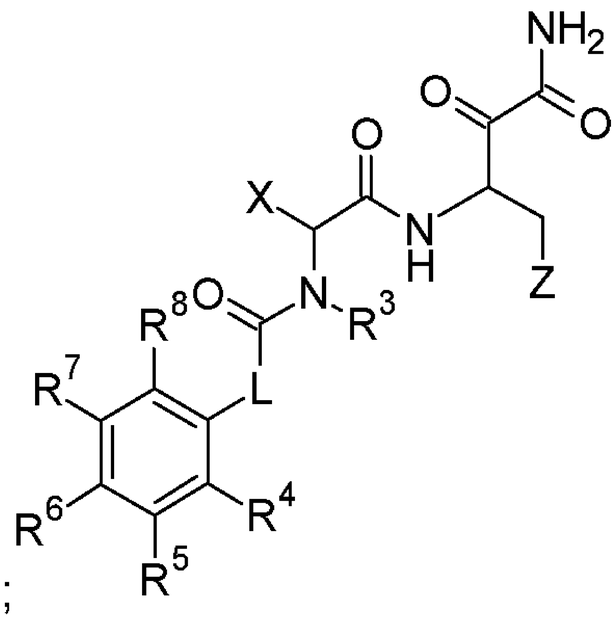
(4av);



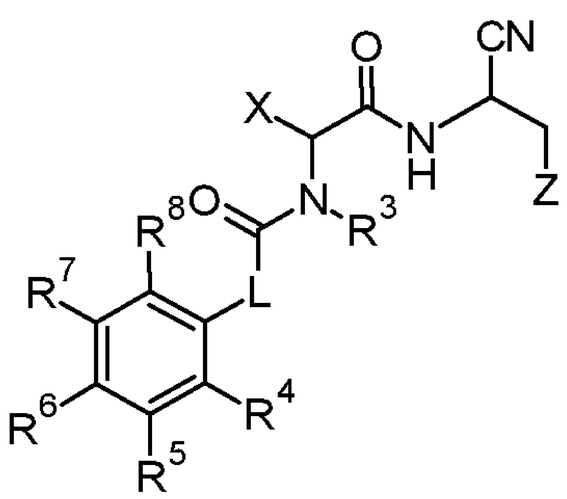
(4avi);



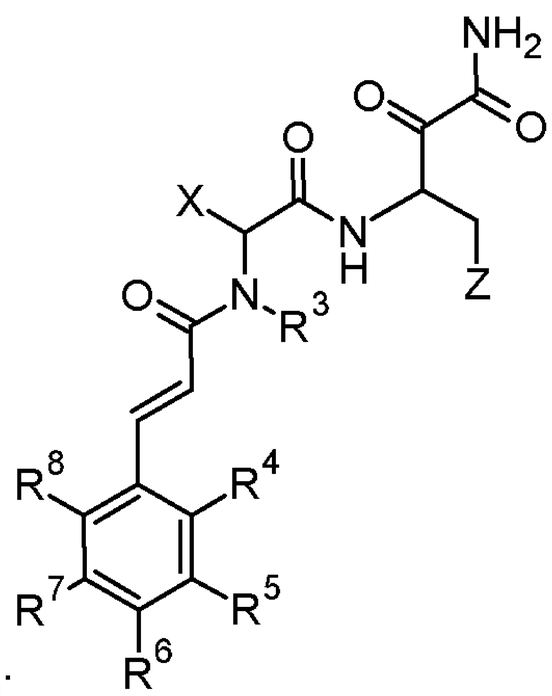
(4avii);



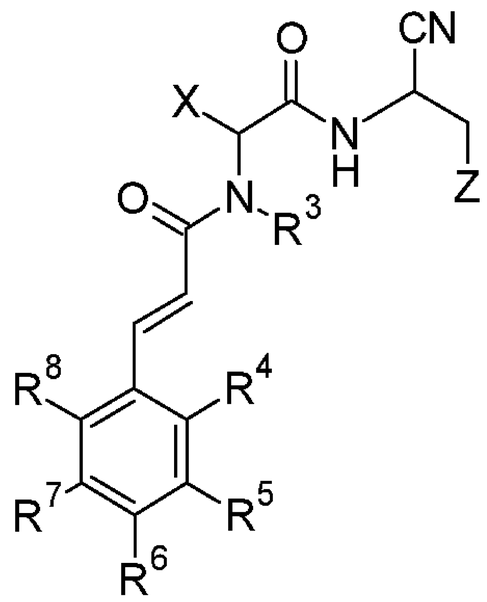
(5av);



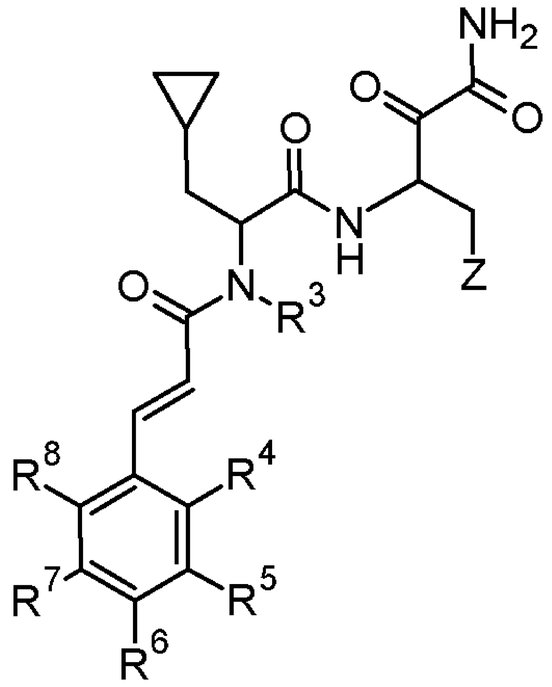
(5avi);



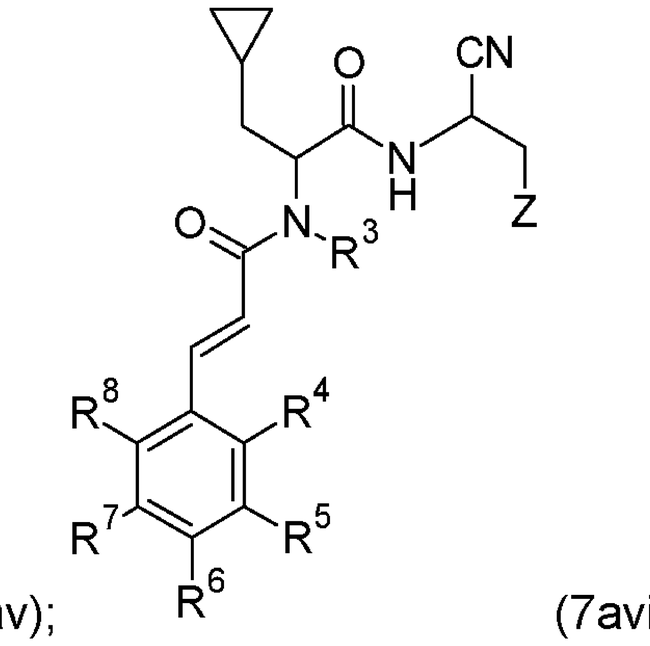
(6av);



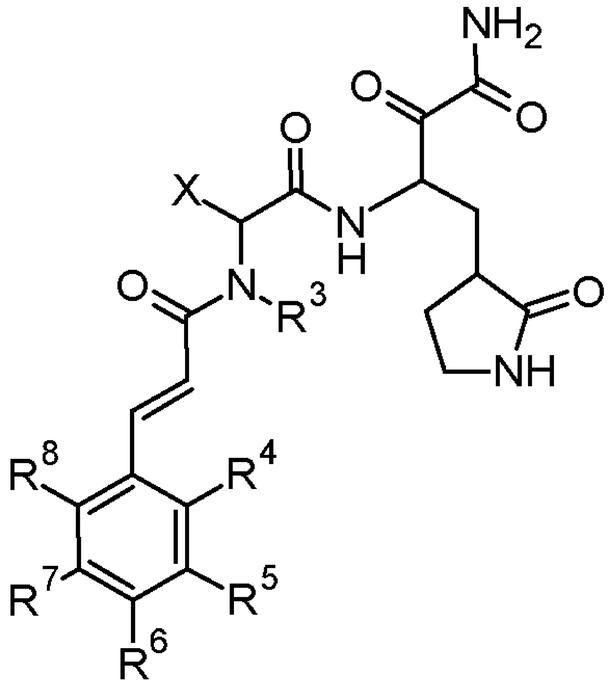
(6avi);



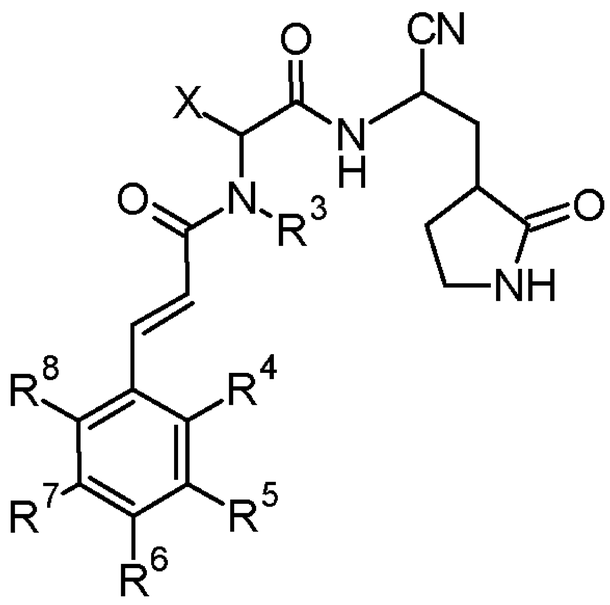
(7av);



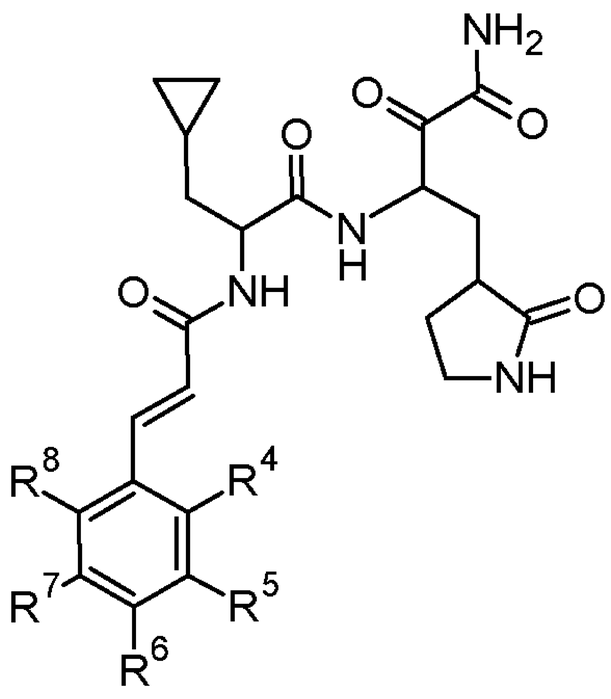
(7avi);



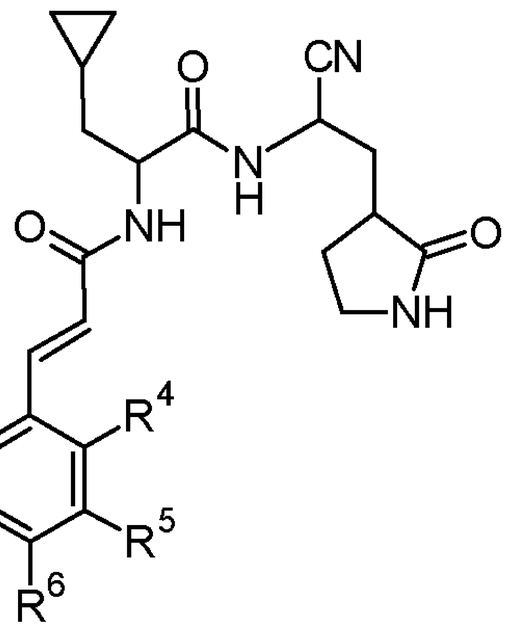
(8av);



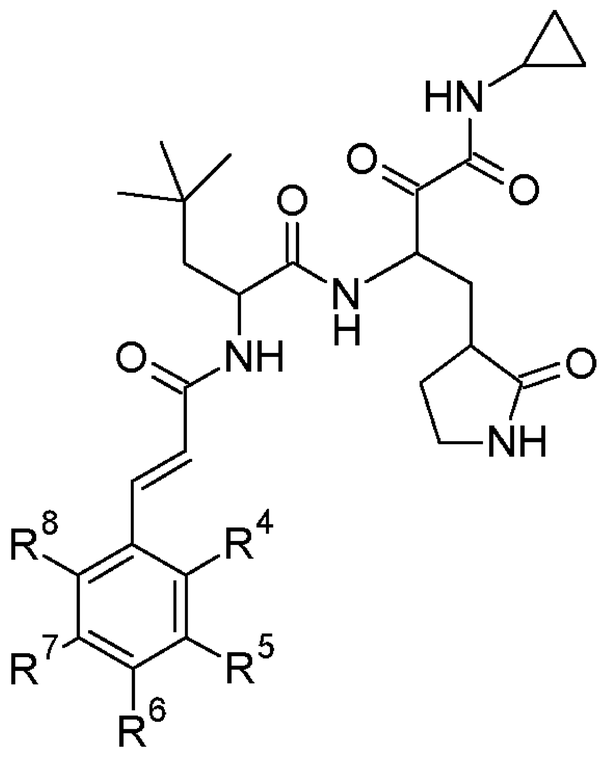
(8avi);



(9av);



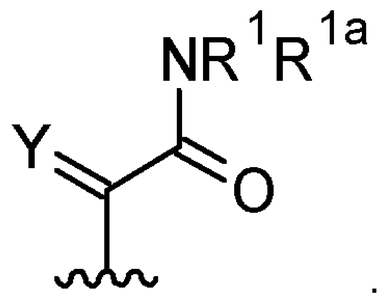
(9avi);



(9bv);

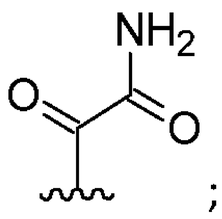
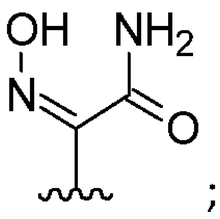
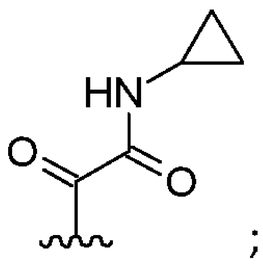
and salts thereof, wherein X, Z, Y, L, R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

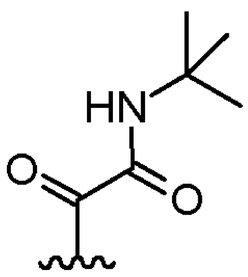
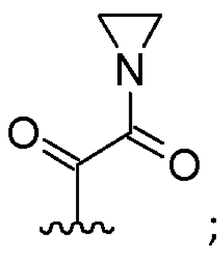
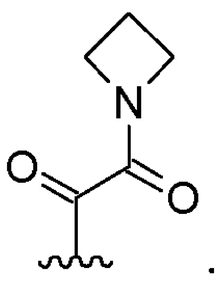
In the compounds herein, Q can be CN. Q can be a group of formula:

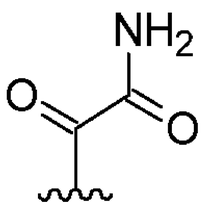
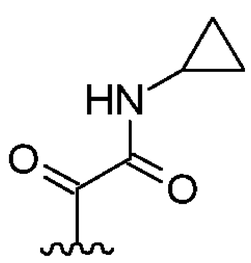


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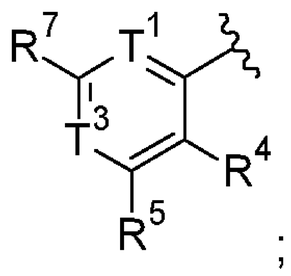
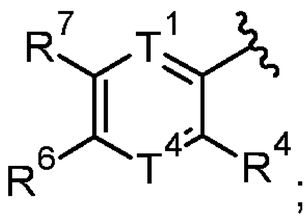
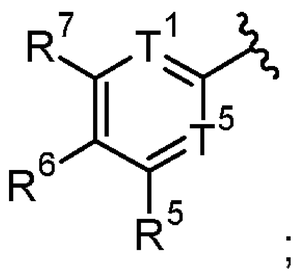
Q can be selected form the group consisting of:

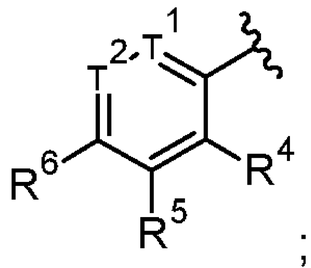
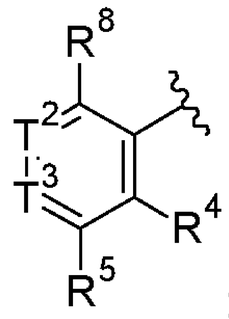
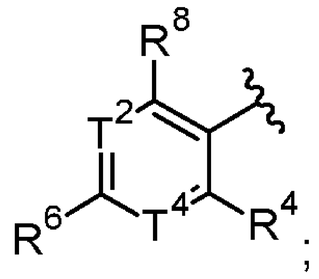
CN;  ;  ;  ;

 ;  ;  .

Q can be  . Q can be  .

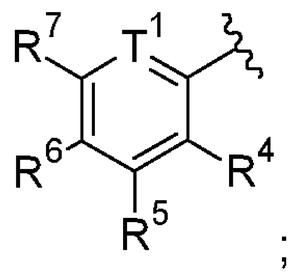
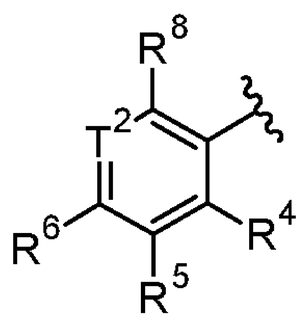
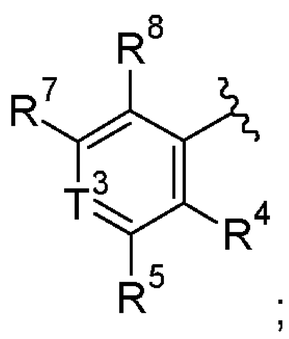
In the compounds herein, A can be selected from:

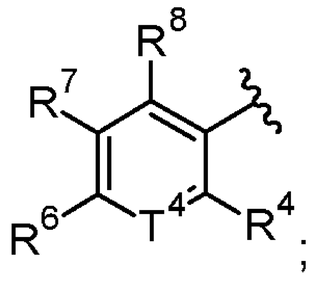
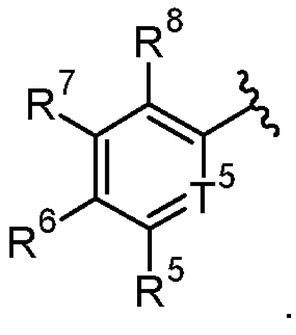
 ;  ;  ;


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;

;

wherein, T^1, T^2, T^3, T^4, T^5, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

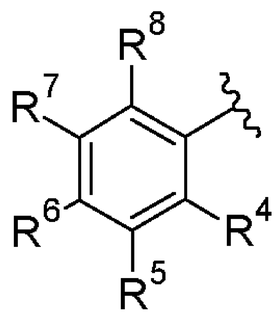
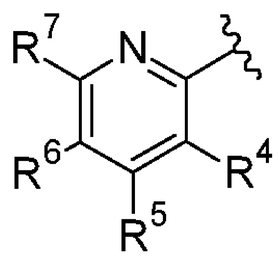
A can be selected from:


;

;

;


;

.

wherein, T^1, T^2, T^3, T^4, T^5, R^4, R^5, R^6, R^7 and R^8 are as defined herein.

A can be selected from:


;

.

In the compounds herein, T^1 can be CR^8 or N. T^1 can be CR^8. T^1 can be N.

In the compounds herein, T^2 can be CR^7 or N. T^2 can be CR^7. T^2 can be N.

In the compounds herein, T^3 can be CR^6 or N. T^3 can be CR^6. T^3 can be N.

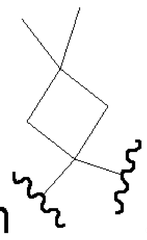
In the compounds herein, T^4 can be CR^5 or N. T^4 can be CR^5. T^4 can be N.

In the compounds herein, T^5 can be CR^4 or N. T^5 can be CR^4. T^5 can be N.

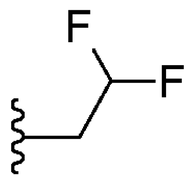
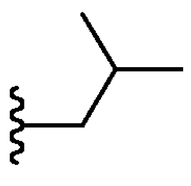
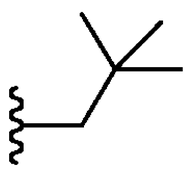
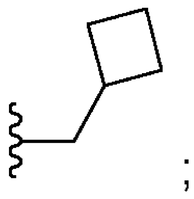
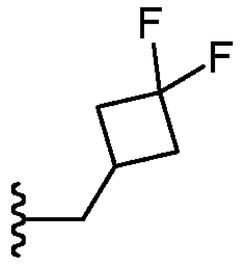
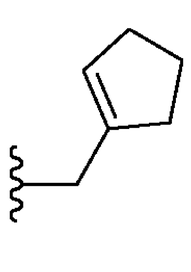
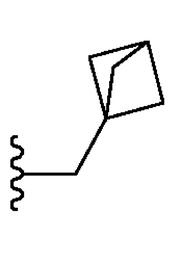
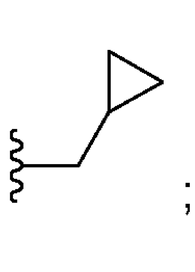
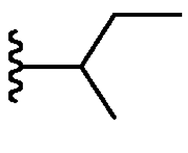
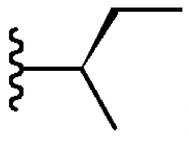
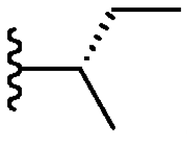
In the compounds herein, X is a $C_{1\text{-}6}$ saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a $C_{3\text{-}6}$ cycloalkyl ring which

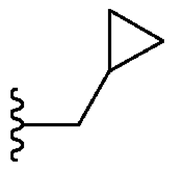
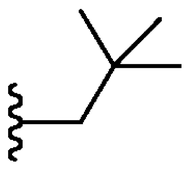
is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups. X can be a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms. X can be C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, branched C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, C_{3-6} cycloalkenyl optionally substituted with 1 to 6 fluorine atoms, -CH_2-C_{3-5} cycloalkyl optionally substituted with 1 to 6 fluorine atoms or -CH_2-C_{3-5} cycloalkenyl optionally substituted with 1 to 6 fluorine atoms. X can be C_{1-6} alkyl or branched C_{1-6} alkyl. X can be selected from the group consisting of -CH_2CHF_2, isobutyl, neopentyl, -CH_2-cyclobutyl, cyclobutylmethyl, -CH_2-cyclopropyl, cyclopropylmethyl, -CH_2-difluorocyclobutyl, -CH_2-bicyclo[1.1.1]pentanyl, -CH_2-cyclopentenyl. X can be -CH_2-cyclopropyl. X can be cyclopropylmethyl.

X can be joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups. X can be joined with R^9 to form a cyclobutyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups. X can be joined with R^9 to form a cyclobutyl ring which is optionally substituted with 1 to 3 methyl groups.

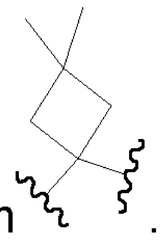
X can be joined with R^9 to form .

X can be selected from the group consisting of:

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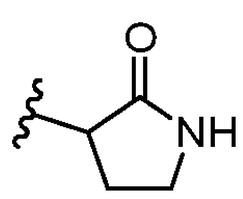
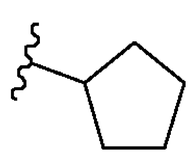
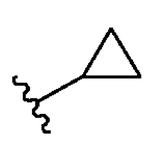
. X can be .

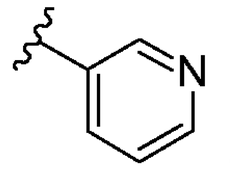
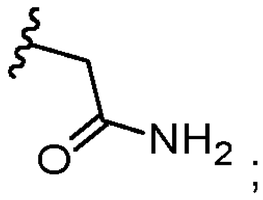
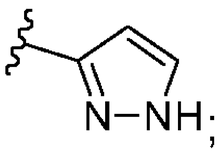
In the compounds herein, R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups. R^9 can be H. R^9 can be joined with X to form a cyclobutyl ring which is optionally substituted with 1 to 3 fluorine

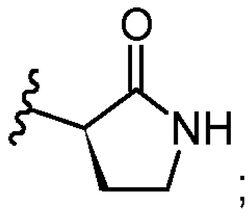
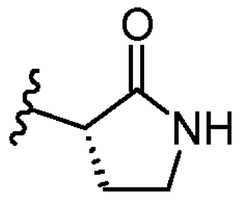
atoms or 1 to 3 C_{1-3} alkyl groups. R^9 can be joined with X to form a cyclobutyl ring which is optionally substituted with 1 to 3 methyl groups. R^9 can be joined with X to form .

In the compounds herein, Z can be a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, Z can be C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, Z can be $-(CH_2)_pCONHR^{13}$, Z can be $-(CH_2)_pCO_2R^{13}$. Z can be a pyrrolidine ring optionally substituted with oxo or 1 to 6 fluorine atoms. Z can be a pyrrolidone ring optionally substituted with 1 to 6 fluorine atoms. Z can be a 2-pyrrolidone ring optionally substituted with 1 to 6 fluorine atoms. Z can be a 2-pyrrolidone ring. Z can be selected from the group consisting of pyrrolidone, cyclopentane, cyclopropane, pyridine, $-CH_2CONH_2$ and pyrazole. Z can be pyrrolidone. Z can be 2-pyrrolidone.

Z can be selected from the group consisting of:

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; ; ;

; .

Z can be . Z can be .

In the compounds herein p can be 0-3. p can be 0, 1, 2 or 3. p can be 0. p can be 1. p can be 2. p can be 3.

In the compounds herein, R^{13}, R^{14} and R^{15} can independently be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms.

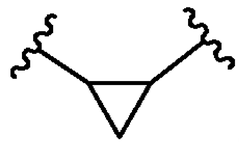
In the compounds herein R^{13} can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^{13} can be H or methyl. R^{13} can be H.

In the compounds herein R^{14} can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^{14} can be H or methyl. R^{14} can be H.

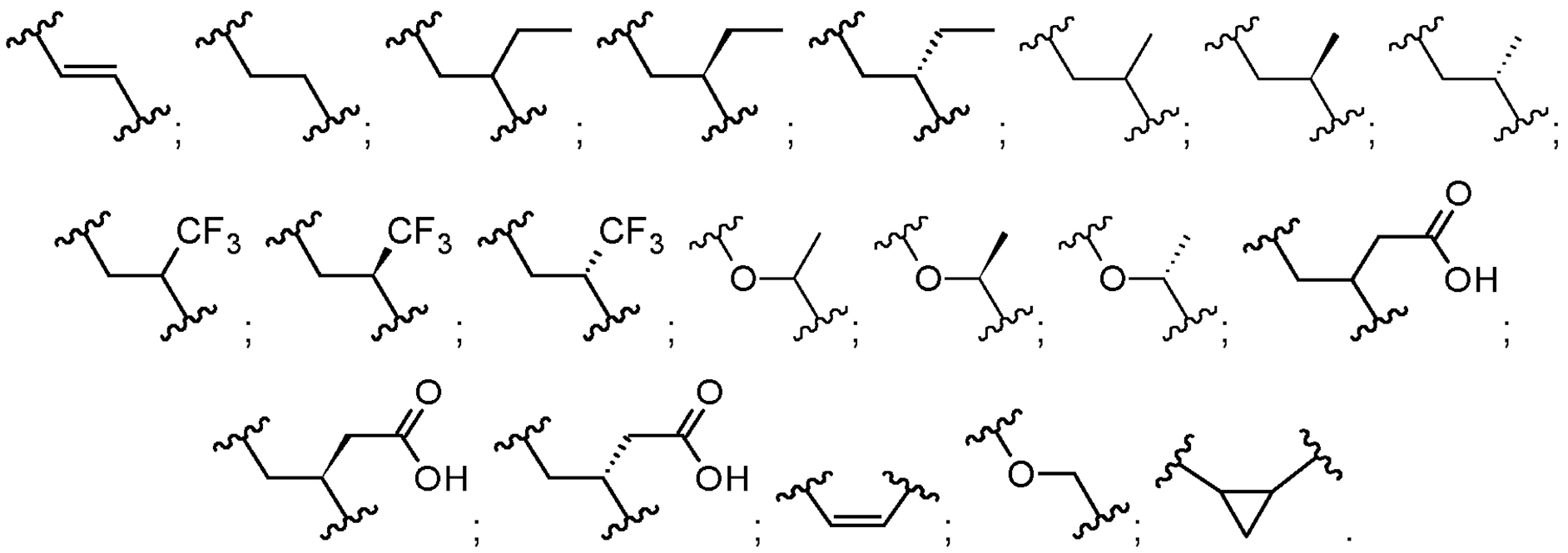
In the compounds herein R^{15} can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^{15} can be H or methyl. R^{15} can be H.

In the compounds herein, Y can be O or NOR^{16}. Y can be O. Y can be NOR^{16}. Y can be NOH.

In the compounds herein, R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^{16} can be H.

In the compounds herein, L is a linker group selected from $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ and $-O-CHR^{11}-$. L can be $-CH=CH-$, $-CH_2CH_2-$, $-CH_2-CH(CH_2CH_3)-$, $-CH_2-CH(CH_2CO_2H)-$, $-CH_2-CH(CH_3)-$, $-CH_2-CH(CF_3)-$, $-OCH_2-$, $-OCH(CH_3)-$ or . L can be $-CH=CH-$, $-CH_2CH_2-$, $-CH_2-CH(CH_2CH_3)-$, $-CH_2-CH(CH_2CO_2H)-$ or $-OCH_2-$. L can be $-CHR^{11}-CHR^{12}-$. When R^1 and R^{1a} are both H, L can be $-CR^{11}=CR^{12}-$. When R^1 and R^{1a} are not both H, L can be $-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H. When R^1 and R^{1a} are both H, L can be is $-O-CHR^{11}-$. When R^1 and R^{1a} are not both H, L can be $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

L can be selected from the group consisting of:



Unless stated otherwise L groups as defined herein can take either possible orientation with respect to their points of attachment to the remainder of the molecule. For example where L is defined as $-OCH_2-$ included are both Examples 82 and 91 and where L is defined as $-CH_2-CH(CF_3)-$ included are both Examples 86 and 88 (Table 1).

In the compounds herein R^{11} and R^{12} can be independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms; or R^{11} and R^{12} can be joined to form a cyclopropyl ring. R^{11} and R^{12} can be independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms; or R^{11} and R^{12} can be joined to form a cyclopropyl ring. R^{11} and R^{12} can independently be H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^{11} and R^{12} can independently be H, methyl, ethyl or $-CH_2CO_2H$. R^{11} can be H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^{12} can be H, methyl, ethyl or $-CH_2CO_2H$. R^{11} can be joined to R^{12} to form a cyclopropyl ring. R^{12} can be joined to R^{11} to form a cyclopropyl ring. R^{11} can be joined to R^{12} to form a cyclopropyl ring. R^{12} can be joined to R^{11} to form a cyclopropyl ring.

In the compounds herein m can be 0-3. m can be 0, 1, 2 or 3. m can be 0. m can be 1. m can be 2. m can be 3. p and m can independently be 0-3.

In the compounds herein, R^1 and R^{1a} can independently be H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom. R^1 and R^{1a} can independently be H, C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, branched C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms or $-CH_2$-C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms. R^1 and R^{1a} can independently be C_{1-6} alkyl, branched C_{1-6} alkyl, C_{3-6} cycloalkyl or $-CH_2$-C_{3-6} cycloalkyl. R^1 and R^{1a} can independently be selected from H methyl, ethyl, isopropyl, cyclopropyl, *t*-butyl, isobutyl, cyclopropylmethyl and $-CH_2$-cyclopropyl. R^1 and R^{1a} can both be H. R^1 can be joined to R^{1a} to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom. R^1 can be joined to R^{1a} to form a 3 to 6-membered saturated ring. R^1 can be joined to R^{1a} to form an aziridine ring. R^1 can be joined to R^{1a} to form an azetidine ring. R^1 can be joined to R^{1a} to form a pyrrolidine ring. R^1 can be joined to R^{1a} to form a piperidine ring.

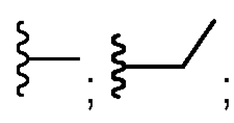
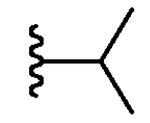
In the compounds herein, R^1 can be H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom. R^1 can be C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, branched C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms or $-CH_2$-C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms. R^1 can be C_{1-6} alkyl, branched

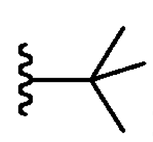
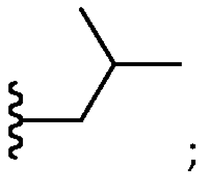
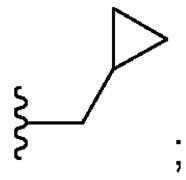
C_{1-6} alkyl, C_{3-6} cycloalkyl or -CH_2-C_{3-6} cycloalkyl. R^1 can be selected from H, methyl, ethyl, isopropyl, cyclopropyl, *t*-butyl, isobutyl, cyclopropylmethyl and -CH_2-cyclopropyl. R^1 can be H. R^1 can be cyclopropyl. R^1 can be joined to R^{1a} to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom. R^1 can be joined to R^{1a} to form a 3 to 6-membered saturated ring. R^1 can be joined to R^{1a} to form an aziridine ring. R^1 can be joined to R^{1a} to form an azetidine ring. R^1 can be joined to R^{1a} to form a pyrrolidine ring. R^1 can be joined to R^{1a} to form a piperidine ring.

In the compounds herein, R^{1a} can be H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom. R^{1a} can be C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, branched C_{1-6} alkyl optionally substituted with 1 to 6 fluorine atoms, C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms or -CH_2-C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms. R^{1a} can be C_{1-6} alkyl, branched C_{1-6} alkyl, C_{3-6} cycloalkyl or -CH_2-C_{3-6} cycloalkyl. R^{1a} can be selected from H, methyl, ethyl, isopropyl, cyclopropyl, *t*-butyl, isobutyl, cyclopropylmethyl and -CH_2-cyclopropyl. R^{1a} can be H. R^{1a} can be joined to R^1 to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom. R^{1a} can be joined to R^1 to form a 3 to 6-membered saturated ring. R^{1a} can be joined to R^1 to form an aziridine ring. R^{1a} can be joined to R^1 to form an azetidine ring. R^{1a} can be joined to R^1 to form a pyrrolidine ring. R^{1a} can be joined to R^1 to form a piperidine ring.

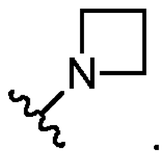
Where R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom, the optional additional heteroatom may be selected from N, O, S and oxidised forms thereof.

R^1 and R^{1a} can independently be H or selected from the group consisting of:

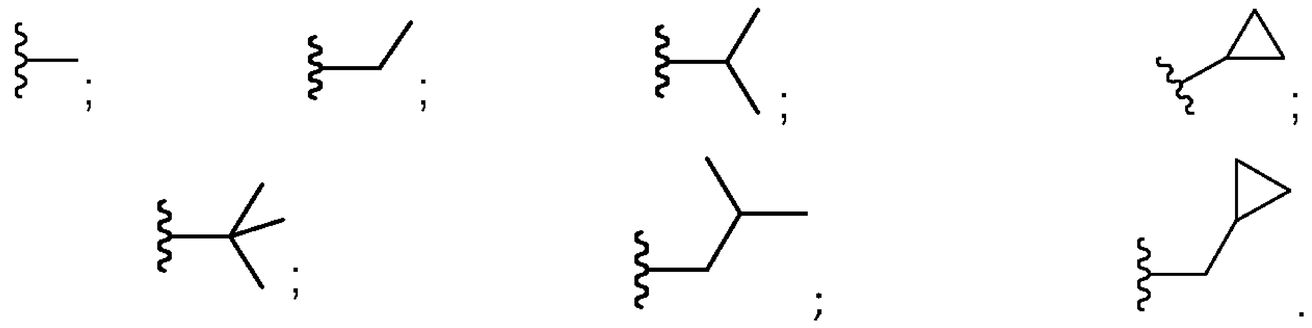
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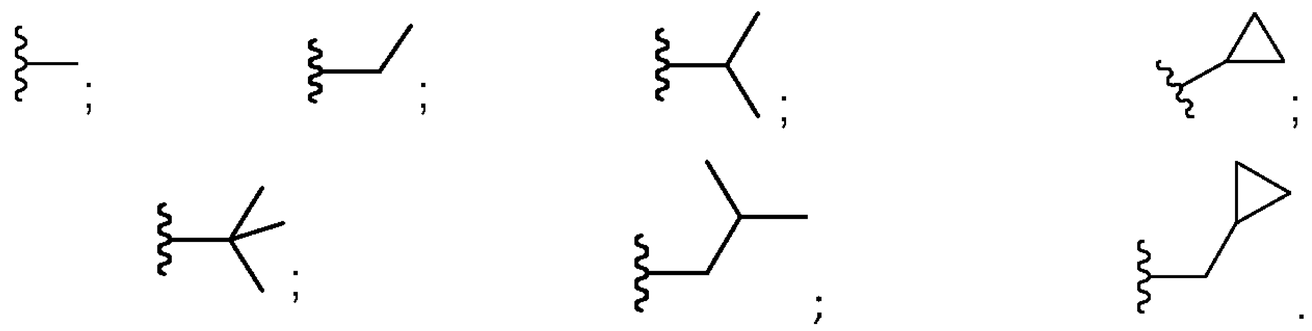
or R^1 and R^{1a} can be joined to form a ring such that the group NR^1R^{1a} is:

.

R^1 can be H or can be selected from the group consisting of:



R^{1a} can be H or can be selected from the group consisting of:



In the compounds herein R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^2 and R^3 can independently be H, methyl or CH_2CF_3. R^2 and R^3 can be H. R^1, R^2 and R^3 can be H.

In the compounds herein, R^2 can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^2 can be H. R^1 and R^2 can both be H.

In the compounds herein, R^3 can be H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^3 can be H, methyl or CH_2CF_3. R^3 can be H.

In the compounds herein, R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^4, R^5, R^6, R^7 and R^8 can be independently selected from H, halo, CO_2R^{14} or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^4, R^5, R^6, R^7, and R^8 can be independently selected from H, CN, Cl, F, CF_2H, OCH_3, OCF_3, OCF_2H, SO_2CH_3, OSO_2CH_3, $PO(CH_3)_2$, SF_5 and CO_2H. R^4, R^5, R^6, R^7, and R^8 can be independently selected from H, Cl, F, CF_2H and CO_2H. R^4, R^5, R^6, R^7 and R^8 can be independently selected from H, Cl, F and CO_2H. R^4, R^5, R^6, R^7 and R^8 can be H. R^4 can be F, R^5 can be H, R^6 can be Cl and R^7 and R^8 can be H.

R^4 can be selected from H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^4 can be selected from H, Cl, F, CF_3, CF_2H and CO_2H. R^4 can be H.

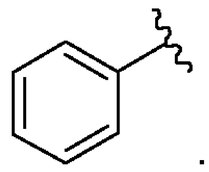
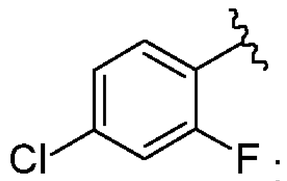
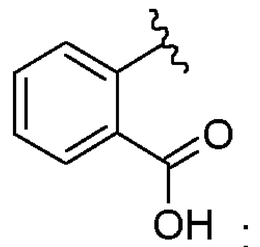
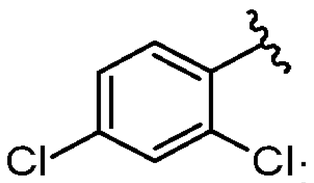
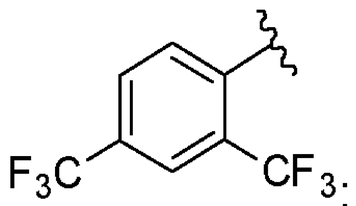
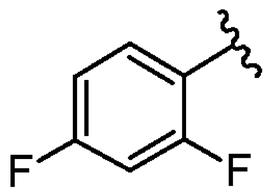
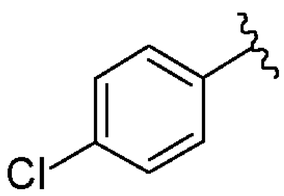
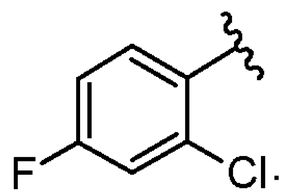
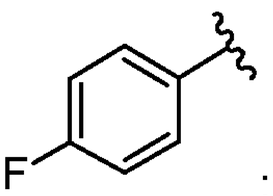
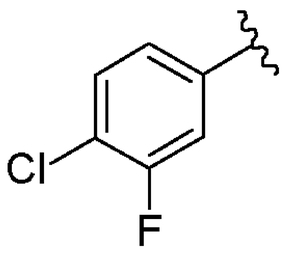
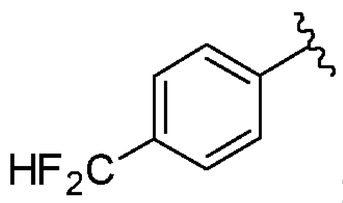
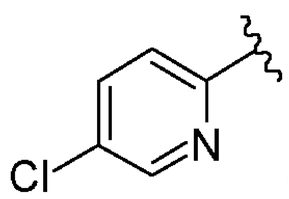
R^5 can be selected from H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^5 can be selected from H, CN, Cl, F, CF_2H, OCH_3, OCF_3, OCF_2H, SO_2CH_3, OSO_2CH_3, $PO(CH_3)_2$, SF_5 and CO_2H. R^5 can be selected from H, Cl, F, CF_3, CF_2H and CO_2H. R^5 can be H.

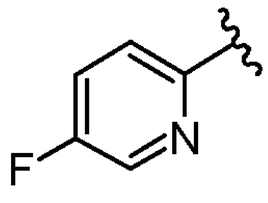
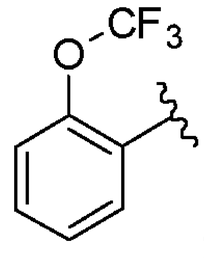
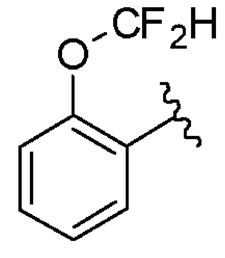
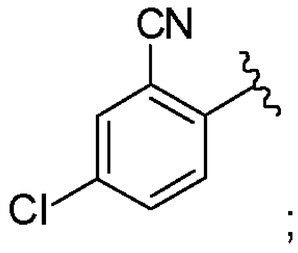
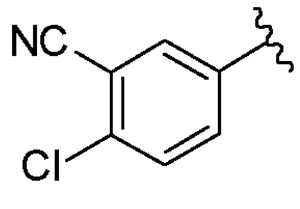
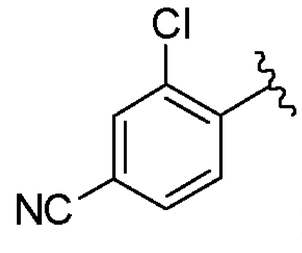
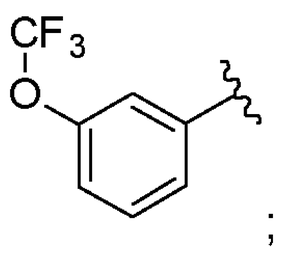
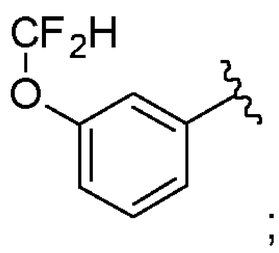
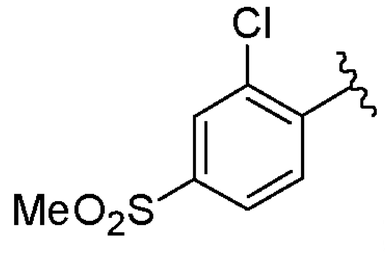
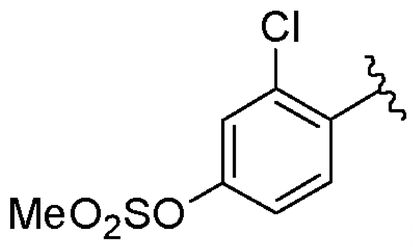
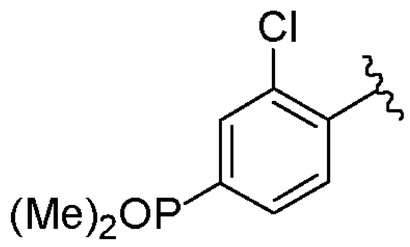
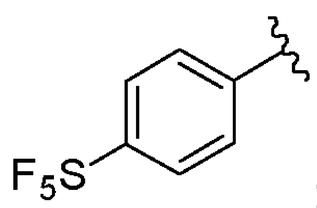
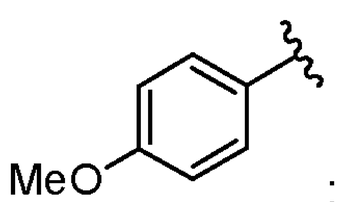
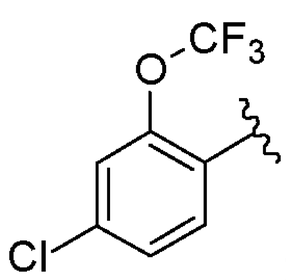
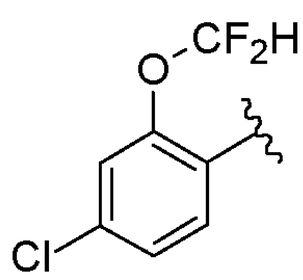
R^6 can be selected from H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^6 can be selected from H, CN, Cl, F, CF_2H, OCH_3, OCF_3, OCF_2H, SO_2CH_3, OSO_2CH_3, $PO(CH_3)_2$, SF_5 and CO_2H. R^6 can be selected from H, Cl, F, CF_3, CF_2H and CO_2H. R^6 can be H.

R^7 can be selected from H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^7 can be selected from H, CN, Cl, F, CF_2H, OCH_3, OCF_3, OCF_2H, SO_2CH_3, OSO_2CH_3, $PO(CH_3)_2$, SF_5 and CO_2H. R^7 can be selected from H, Cl, F, CF_3, CF_2H and CO_2H. R^7 can be H.

R^8 can be selected from H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms. R^8 can be selected from H, CN, Cl, F, CF_2H, OCH_3, OCF_3, OCF_2H, SO_2CH_3, OSO_2CH_3, $PO(CH_3)_2$, SF_5 and CO_2H. R^8 can be selected from H, Cl, F, CF_3, CF_2H and CO_2H. R^8 can be H.

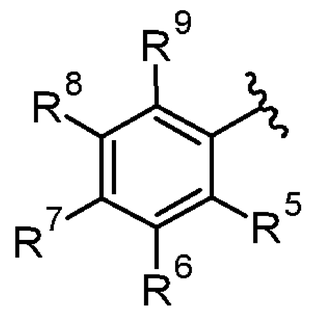
In the compounds herein, the moiety A can be selected from the group consisting of:

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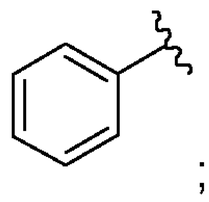
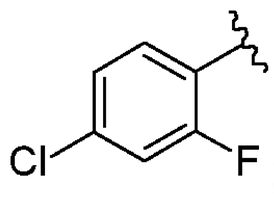
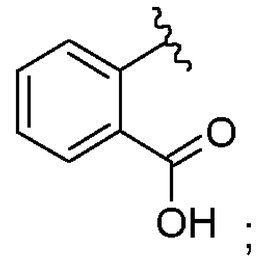
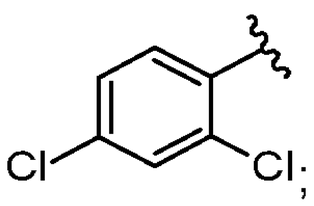
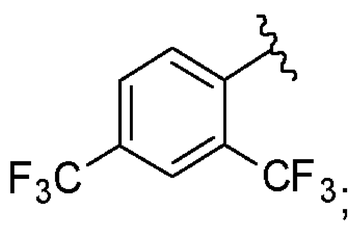
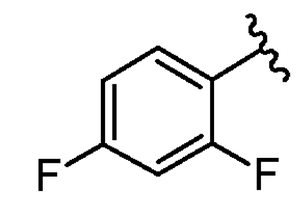

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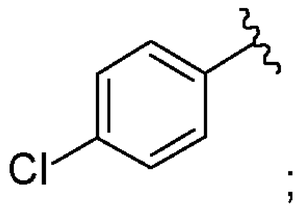
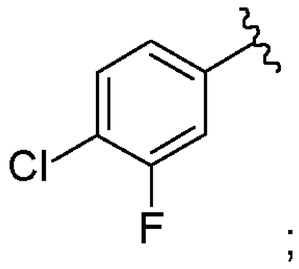
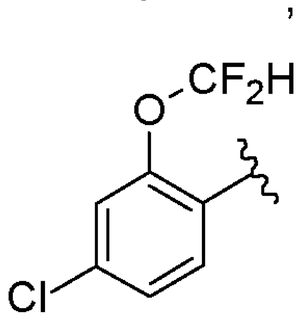
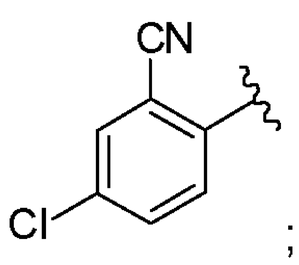
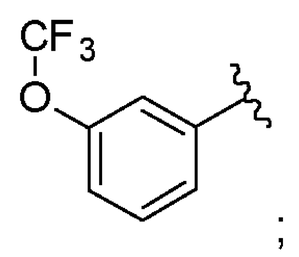
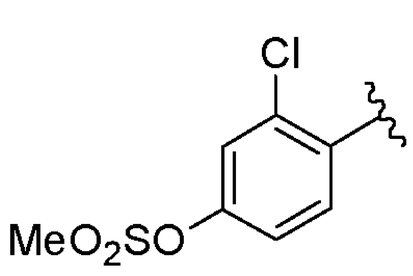
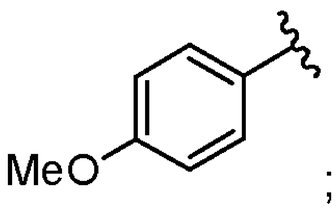
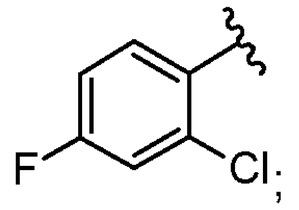
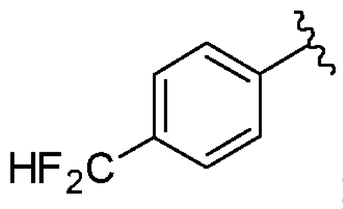
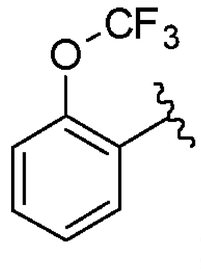
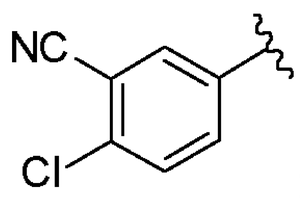
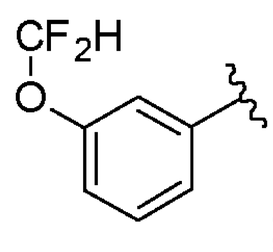
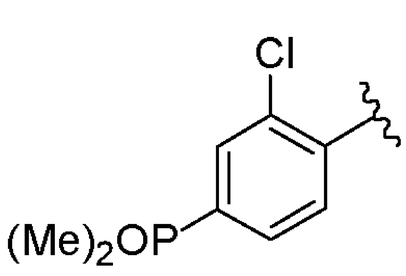
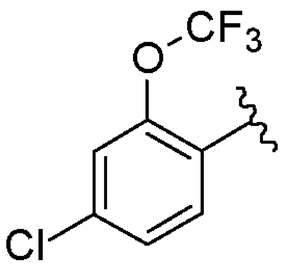
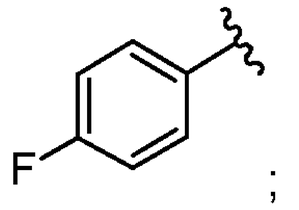
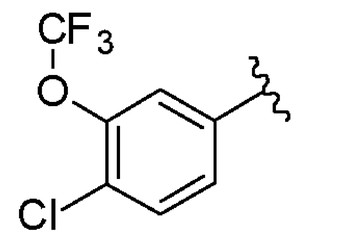
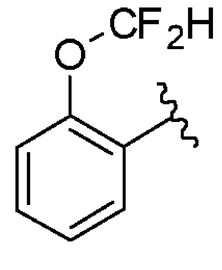
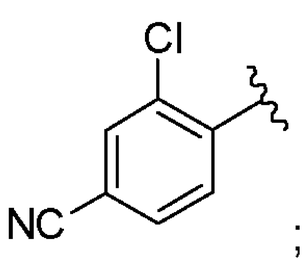
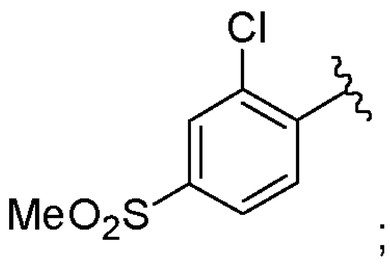
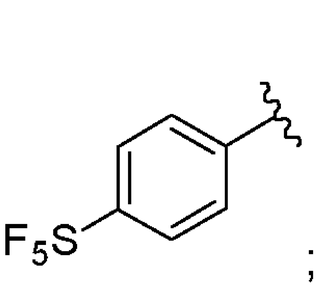
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In the compounds herein, the moiety:



can be selected from the group consisting of:


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In the compounds herein when R^1 and R^{1a} are not both H, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

For compounds where L is $-CHR^{11}-CHR^{12}-$, R^1 and R^{1a} can independently be H, a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom.

For compounds where L is $-CHR^{11}-CHR^{12}-$, R^1 and R^{1a} can both be H.

For compounds where L is -CHR^{11}-CHR^{12}-, R^1 and R^{1a} can be a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom.

For compounds where L is -CR^{11}=CR^{12}-, R^1 and R^{1a} can independently be H, a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom, provided that R^3, R^4, R^5, R^6, R^7 and R^8 are not all H.

For compounds where L is -CR^{11}=CR^{12}-, R^1 and R^{1a} can both be H.

For compounds where L is -CR^{11}=CR^{12}-, R^1 and R^{1a} can independently be a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom, provided that R^3, R^4, R^5, R^6, R^7 and R^8 are not all H.

For compounds where L is -O-CHR^{11}-, R^1 and R^{1a} can independently be H, a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom, provided that R^3 is not H, or provided that two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

For compounds where L is -O-CHR^{11}-, R^1 and R^{1a} can both be H.

For compounds where L is -O-CHR^{11}-, R^1 and R^{1a} can independently be a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} can be linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom, provided that R^3 is not H, or provided that two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

The compound can be selected from any one of Examples 1 to 93 as shown in Table 1 or a salt thereof.

The compound can be selected from the group consisting of:

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-2-cinnamamido-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

benzyl ((2*S*)-1-((4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-(hydroxyimino)-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

N-(*tert*-butyl)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopropyl-2-oxobutanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopentyl-2-oxobutanamide;

3-((*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

(2*S*)-*N*-(1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylbutanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylbutanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylpentanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylpentanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide

(2*S*)-*N*-(4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-4-methylpentanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-*N*-ethyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-3-cyclopropyl-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-*N*-cyclopropyl-2-oxo-4-((S)-2-oxopyrrolidin-3-yl)butanamide;

(2*S*)-*N*-(4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-*N*-(4-(ethylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

3-((*S*)-3-cyclopropyl-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)propanamido)-*N*-ethyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

N-cyclopropyl-3-((*S*)-3-cyclopropyl-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

(2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-*N*-(4-(ethylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-*N*-cyclopropyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

benzyl ((2*S*)-3-cyclopropyl-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-1-oxopropan-2-yl)carbamate;

N-cyclopropyl-3-((*S*)-3-cyclopropyl-2-(3-(2,4-dichlorophenyl)propanamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclobutylpropanamido)-*N*-cyclopropyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

(3*S*)-*N*-((2*S*)-3-cyclopropyl-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-1-oxopropan-2-yl)-3-phenylpentanamide;

(3*R*)-*N*-((2*S*)-3-cyclopropyl-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-1-oxopropan-2-yl)-3-phenylpentanamide;

(2*S*)-*N*-(4-(azetidin-1-yl)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-difluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chlorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(2-chloro-4-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-fluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-3-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(5-chloropyridin-2-yl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(5-fluoropyridin-2-yl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-(difluoromethyl)phenyl)acrylamido)-4,4-dimethylpentanamide;

(1*R*,2*R*)-*N*-((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-2-phenylcyclopropane-1-carboxamide;

(1*S*,2*S*)-*N*-((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-2-phenylcyclopropane-1-carboxamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2,4-difluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2,4-difluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2,4-dichlorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2,4-dichlorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(4-chloro-2-fluorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-3-(4-chloro-2-fluorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(4-chlorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-3-(4-chlorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(4-fluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(4-fluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(azetidin-1-yl)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-(2-(trifluoromethoxy)phenyl)pentanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-(2-(trifluoromethoxy)phenyl)pentanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2-(difluoromethoxy)phenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2-(difluoromethoxy)phenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-2-cyanophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-3-cyanophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(2-chloro-4-cyanophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-(3-(trifluoromethoxy)phenyl)butanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-(3-(trifluoromethoxy)phenyl)butanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(3-(difluoromethoxy)phenyl)butanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(3-(difluoromethoxy)phenyl)butanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-3-(2-chloro-4-(methylsulfonyl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(2-chloro-4-(methylsulfonyl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

3-chloro-4-((3*R*)-1-(((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-1-oxopentan-3-yl)phenyl methanesulfonate;

3-chloro-4-((3*S*)-1-(((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-1-oxopentan-3-yl)phenyl methanesulfonate;

(2*S*)-2-((*R*)-3-(2-chloro-4-(dimethylphosphoryl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(2-chloro-4-(dimethylphosphoryl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*E*)-3-(4-(pentafluoro-l6-sulfaneyl)phenyl)acrylamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(4-methoxyphenyl)pentanamido)-4,4-dimethylpentanamide;

(2S)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(4-methoxyphenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-2-(trifluoromethoxy)phenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-2-(difluoromethoxy)phenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-2-cyanophenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(2-chloro-4-cyanophenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-3-(trifluoromethoxy)phenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-(3-(2,4-dichlorophenyl)propanamido)-4,4-dimethylpentanamide;

2,4-dichlorobenzyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

4-chloro-2-fluorobenzyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

(*S*)-1-(4-chloro-2-fluorophenyl)ethyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

(*R*)-1-(4-chloro-2-fluorophenyl)ethyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2,4-difluorophenyl)-4,4,4-trifluorobutanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2,4-difluorophenyl)-4,4,4-trifluorobutanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-2-benzyl-3,3,3-trifluoropropanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-2-benzyl-3,3,3-trifluoropropanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(1*S*,2*S*)-2-(4-chlorophenyl)-*N*-((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)cyclopropane-1-carboxamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(2-(2,4-dichlorophenoxy)acetamido)-4,4-dimethylpentanamide;

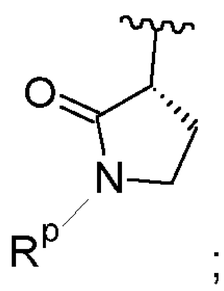
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-2-(2,4-dichlorophenoxy)propanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-2-(2,4-dichlorophenoxy)propanamido)-4,4-dimethylpentanamide;
or a salt thereof.

The compounds of the invention may be presented in the form of a prodrug. By "prodrug" is meant for example any compound that is converted *in vivo* into a biologically active compound of the invention. For example, some prodrugs are esters or phosphate esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). During metabolism, the ester group (-C(=O)OR) or phosphate ester group ($P(=O)(OH)_2$-OR) is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of a hydroxyl group present in the parent compound with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required. Other functionality present in the active compound, for example an amide group or amino group, can be used to form a prodrug. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in ADEPT, GDEPT, LIDEPT, etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

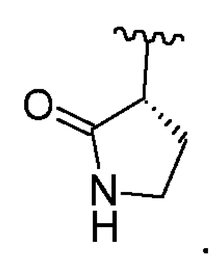
Accordingly, provided is a prodrug of a compound as defined herein wherein the compound contains a functional group which is convertible under physiological conditions to form a hydroxyl group, amide group or amino group. Suitable prodrugs may for example include compounds where group Z is functionalised with a group which is cleaved *in vivo* to release the active compound.

For example, in prodrugs of the compounds, Z may be a group:



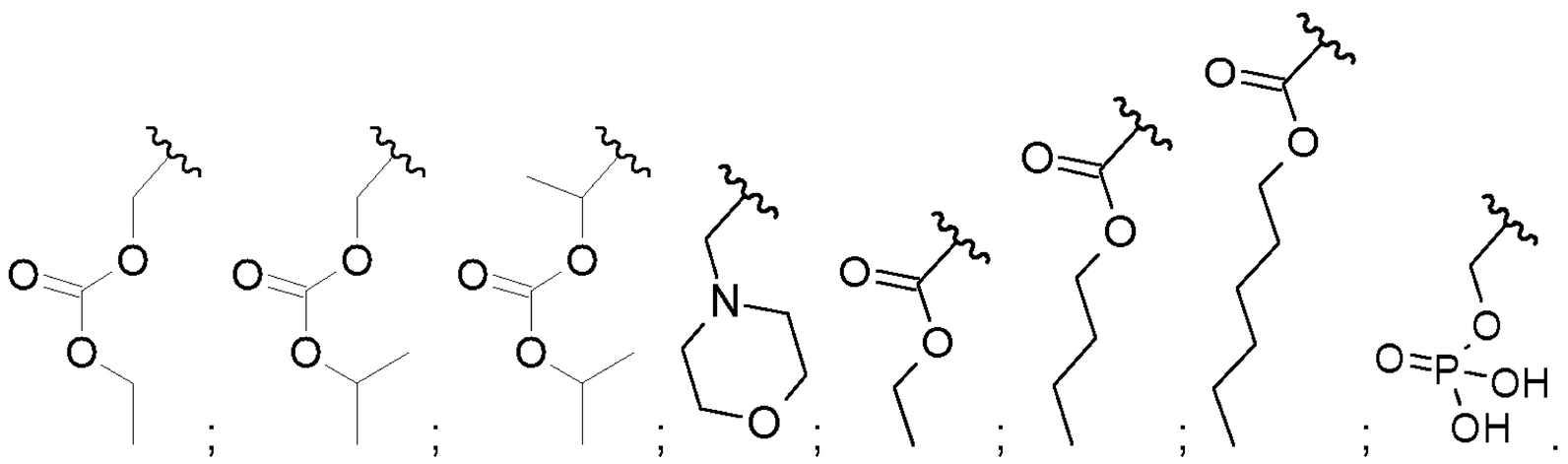
;

wherein R^P is any group which may be cleaved *in vivo* to afford a compound where Z is:

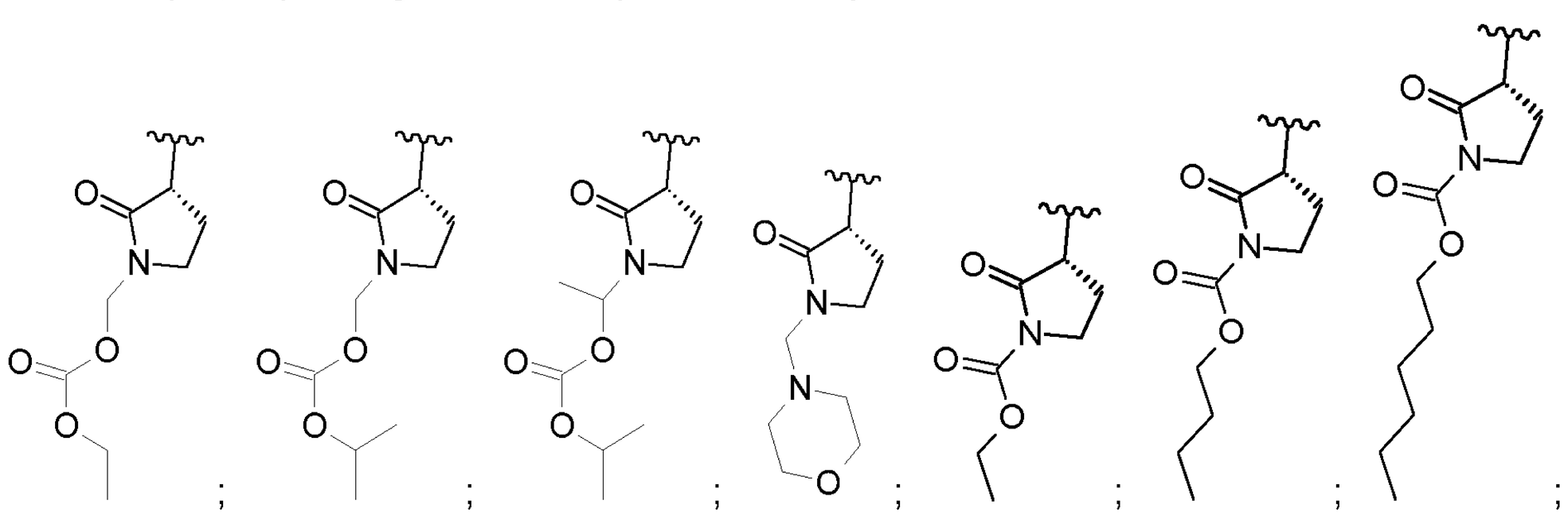


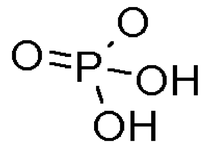
.

R^P can be selected from:



For example, in prodrugs of the compounds, Z may be selected from:





Further embodiments include the use of a compound of the invention or a salt thereof or a pharmaceutical composition comprising a compound of the invention as a SARS-CoV-2: Mpro inhibitor. Compounds of the present invention may be used as SARS-CoV-2: Mpro inhibitors. Compounds of the present invention may be used in the treatment of SARS-CoV-2 or a disease or disorder associated with SARS-CoV-2: Mpro. Compounds of the present invention may be useful in preventing death or complications arising due to chronic underlying conditions or comorbidities in patients infected with SARS-CoV-2. Such chronic underlying conditions or comorbidities may include for example hypertension, obesity, chronic lung conditions (TB, asthma and cystic fibrosis), diabetes and cardiovascular conditions (coronary heart disease, congenital heart disease and heart failure). Compounds of the present invention may be used in the manufacture of medicaments. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of SARS-CoV-2 and diseases or disorders in which SARS-CoV-2: Mpro is involved. The compounds or medicaments may be for use in treating, preventing, ameliorating, controlling or reducing the risk of chronic underlying conditions or comorbidities in patients infected with SARS-CoV-2.

Compounds of the present invention may be for use as a single agent or in combination with one or more additional pharmaceutical agents. Compounds of the present invention may be useful in the treatment of SARS-CoV-2 or conditions or symptoms related thereto.

As provided herein, compounds or salts thereof described herein and compositions described herein may be administered with an agent to treat any of the diseases and disorders disclosed herein.

DEFINITIONS

In this application, the following definitions apply, unless indicated otherwise.

The term “SARS-CoV-2: Mpro inhibitor” as used herein refers to any compound which binds to and modulates the function of SARS-CoV-2: Mpro.

The term “treatment”, in relation to the uses of any of the compounds described herein, including those of Formula (1b) is used to describe any form of intervention where a compound is administered to a subject suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term “treatment” covers both preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

The term “effective therapeutic amount” (for example in relation to methods of treatment of a disease or condition) refers to an amount of the compound which is effective to produce a desired therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

Terms such as “bicyclic”, “hydrocarbon”, “heterocyclic”, “carbocyclic”, “alkyl”, “cycloalkyl” and “halo” are all used in their conventional sense (e.g. as defined in the IUPAC Gold Book), unless indicated otherwise. “optionally substituted” as applied to any group means that the said group may if desired be substituted with one or more substituents, which may be the same or different.

To the extent that any of the compounds described have chiral centres, the present invention extends to all optical isomers of such compounds, whether in the form of racemates or

resolved enantiomers. The invention described herein relates to all crystal forms, solvates and hydrates of any of the disclosed compounds however so prepared. To the extent that any of the compounds disclosed herein have acid or basic centres such as carboxylates or amino groups, then all salt forms of said compounds are included herein. In the case of pharmaceutical uses, the salt should be seen as being a pharmaceutically acceptable salt.

Salts or pharmaceutically acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Examples of pharmaceutically acceptable salts include acid addition salts derived from mineral acids and organic acids, and salts derived from metals such as sodium, magnesium, potassium and calcium.

Examples of acid addition salts include acid addition salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, aryl sulfonic acids (e.g. benzenesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic and *p*-toluenesulfonic), ascorbic (e.g. L-ascorbic), L-aspartic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic (e.g. D-gluconic), glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α-oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and (±)-DL-lactic), lactobionic, maleic, malic (e.g. (-)-L-malic), malonic, (±)-DL-mandelic, metaphosphoric, methanesulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, tartaric (e.g.(+)-L-tartaric), thiocyanic, undecylenic and valeric acids.

Also encompassed are any solvates of the compounds and their salts. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols

(such as ethanol, isopropanol and butanol) and dimethylsulfoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray crystallography.

The solvates can be stoichiometric or non-stoichiometric solvates. Particular solvates may be hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn *et al*, Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

The term “pharmaceutical composition” in the context of this invention means a composition comprising an active agent and comprising additionally one or more pharmaceutically acceptable carriers. The composition may further contain ingredients selected from, for example, diluents, adjuvants, excipients, vehicles, preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispersing agents, depending on the nature of the mode of administration and dosage forms. The compositions may take the form, for example, of tablets, dragees, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets, lozenges, emulsions, solutions, cachets, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

The compounds of the invention may contain one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (D), and ^{3}H (T). Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and ^{16}O and ^{18}O. In an analogous manner, a reference to a particular functional group also includes within its scope isotopic variations, unless the context indicates otherwise. For example, a reference to an alkyl group such as an ethyl group or an alkoxy group such as a methoxy group also covers variations in which one or more of the hydrogen atoms in the group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group) or a methoxy group in which all three hydrogen atoms are in the deuterium isotopic form (a trideuteromethoxy group). The isotopes may be radioactive or non-radioactive.

Therapeutic dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with the smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The magnitude of an effective dose of a compound will, of course, vary with the nature of the severity of the condition to be treated and with the particular compound and its route of administration. The selection of appropriate dosages is within the ability of one of ordinary skill in this art, without undue burden. In general, the daily dose range may be from about 10 µg to about 30 mg per kg body weight of a human and non-human animal, preferably from about 50 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 50 µg to about 10 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 30 mg per kg of body weight of a human and non-human animal, for example from about 100 µg to about 10 mg per kg of body weight of a human and non-human animal and most preferably from about 100 µg to about 1 mg per kg of body weight of a human and non-human animal.

PHARMACEUTICAL FORMULATIONS

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

Accordingly, in some embodiments of the invention, there is provided a pharmaceutical composition comprising at least one compound of the invention together with at least one pharmaceutically acceptable excipient.

The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents such as fillers or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers,

taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

The term “pharmaceutically acceptable” as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be “acceptable” in the sense of being compatible with the other ingredients of the formulation.

Pharmaceutical compositions containing compounds of the invention can be formulated in accordance with known techniques, see for example, Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA. The pharmaceutical compositions can be in any form suitable for oral, parenteral, intravenous, intramuscular, intrathecal, subcutaneous, topical, intranasal, intrabronchial, sublingual, buccal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration.

Pharmaceutical dosage forms suitable for oral administration include tablets (coated or uncoated), capsules (hard or soft shell), caplets, pills, lozenges, syrups, solutions, powders, granules, elixirs and suspensions, sublingual tablets, wafers or patches such as buccal patches.

The composition may be a tablet composition or a capsule composition. Tablet compositions can contain a unit dosage of active compound together with an inert diluent or carrier such as a sugar or sugar alcohol, eg; lactose, sucrose, sorbitol or mannitol; and/or a non-sugar derived diluent such as sodium carbonate, calcium phosphate, calcium carbonate, or a cellulose or derivative thereof such as microcrystalline cellulose (MCC), methyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, and starches such as corn starch. Tablets may also contain such standard ingredients as binding and granulating agents such as polyvinylpyrrolidone, disintegrants (e.g. swellable crosslinked polymers such as crosslinked carboxymethylcellulose), lubricating agents (e.g. stearates), preservatives (e.g. parabens), antioxidants (e.g. BHT), buffering agents (for example phosphate or citrate buffers), and effervescent agents such as citrate/bicarbonate mixtures. Such excipients are well known and do not need to be discussed in detail here.

Tablets may be designed to release the drug either upon contact with stomach fluids (immediate release tablets) or to release in a controlled manner (controlled release tablets) over a prolonged period of time or with a specific region of the GI tract.

The pharmaceutical compositions typically comprise from approximately 1% (w/w) to approximately 95%, preferably% (w/w) active ingredient and from 99% (w/w) to 5% (w/w) of a pharmaceutically acceptable excipient (for example as defined above) or combination of such excipients. Preferably, the compositions comprise from approximately 20% (w/w) to approximately 90% (w/w) active ingredient and from 80% (w/w) to 10% of a pharmaceutically excipient or combination of excipients. The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, pre-filled syringes, dragées, powders, tablets or capsules.

Tablets and capsules may contain, for example, 0-20% disintegrants, 0-5% lubricants, 0-5% flow aids and/or 0-99% (w/w) fillers/ or bulking agents (depending on drug dose). They may also contain 0-10% (w/w) polymer binders, 0-5% (w/w) antioxidants, 0-5% (w/w) pigments. Slow release tablets would in addition typically contain 0-99% (w/w) release-controlling (e.g. delaying) polymers (depending on dose). The film coats of the tablet or capsule typically contain 0-10% (w/w) polymers, 0-3% (w/w) pigments, and/or 0-2% (w/w) plasticizers.

The composition may be a parenteral composition. Parenteral formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

The pharmaceutical formulations may be presented to a patient in “patient packs” containing an entire course of treatment in a single package, usually a blister pack.

The compounds of the invention will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges, particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams

(for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).

For oral compositions, a unit dosage form may contain from 1 milligram to 2 grams, more typically 10 milligrams to 1 gram, for example 50 milligrams to 1 gram, e.g. 100 milligrams to 1 gram, of active compound.

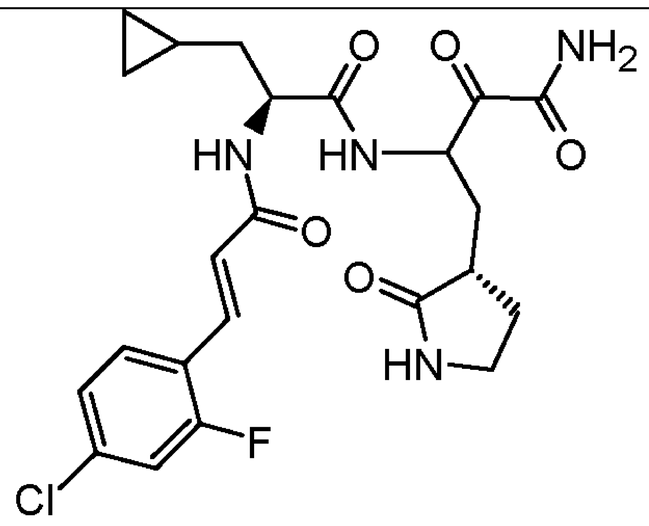
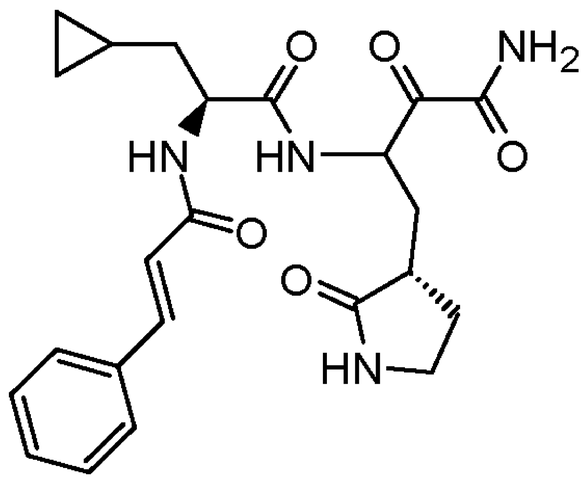
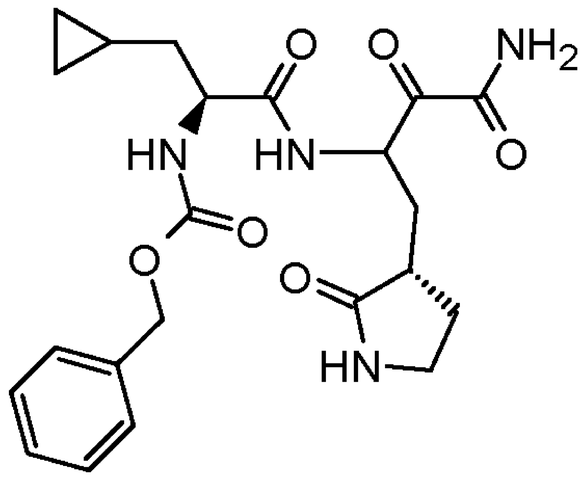
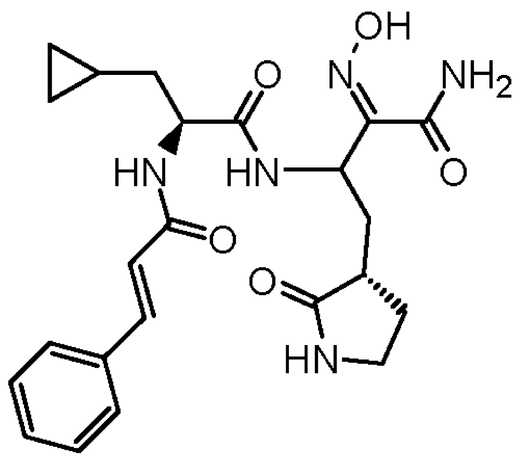
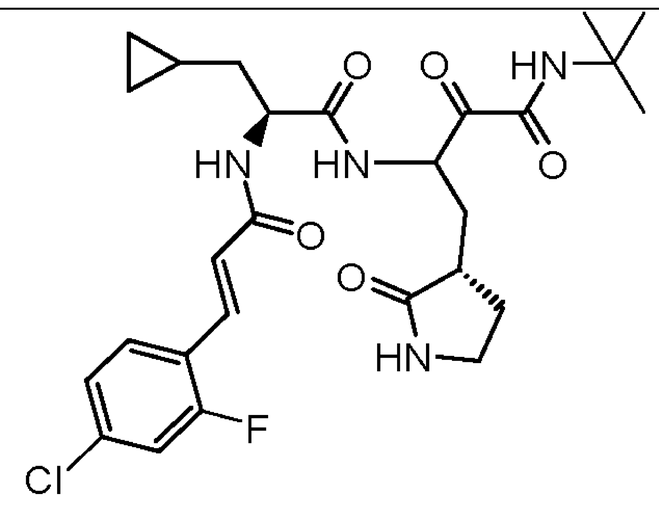
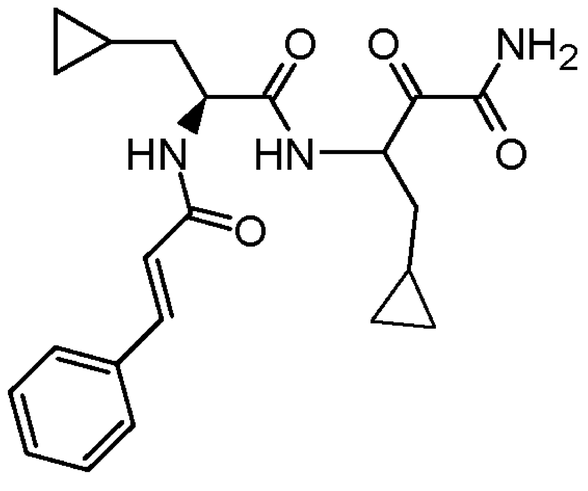
The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

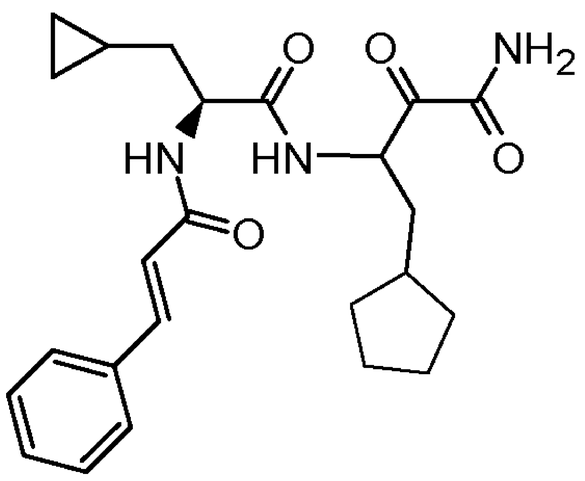
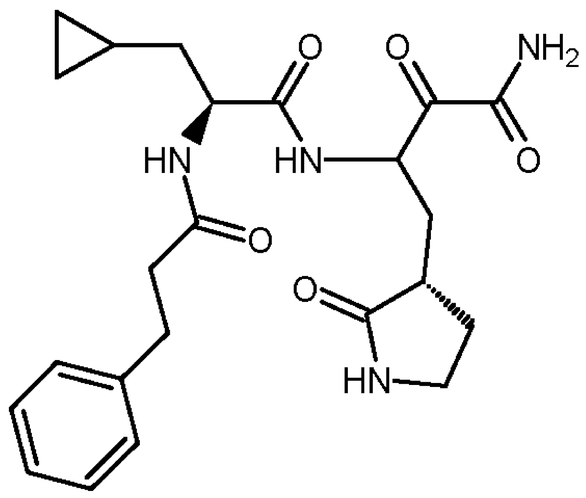
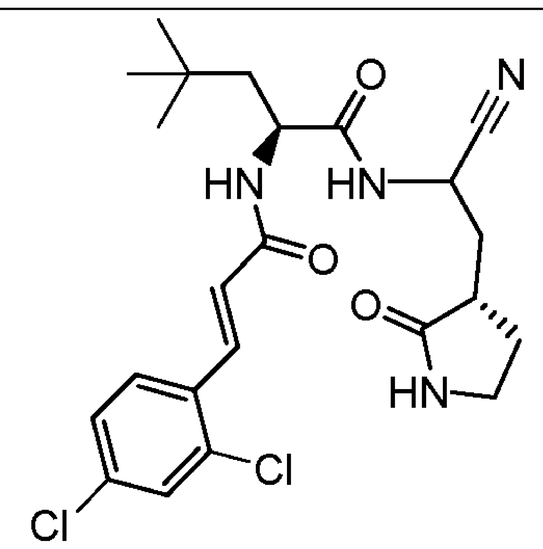
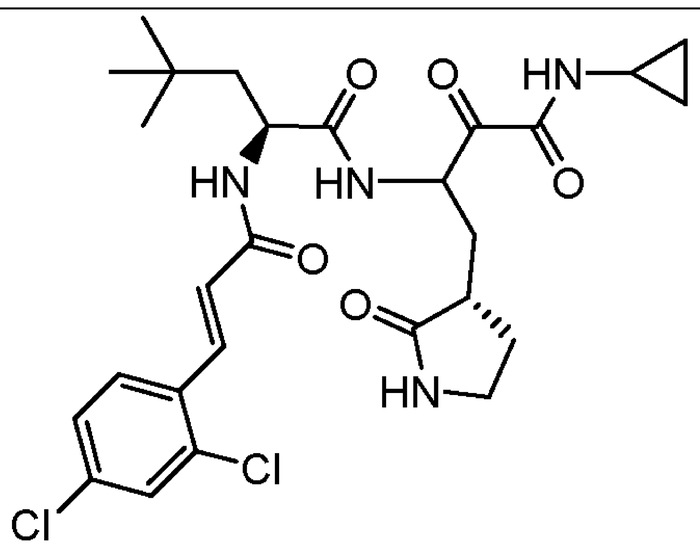
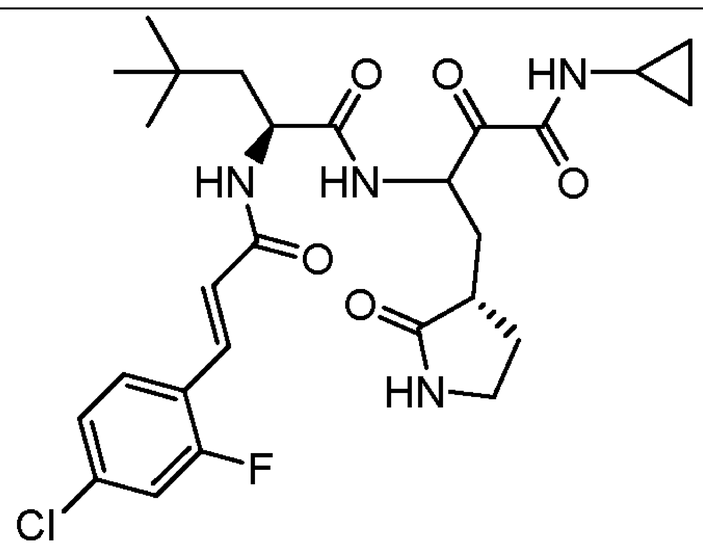
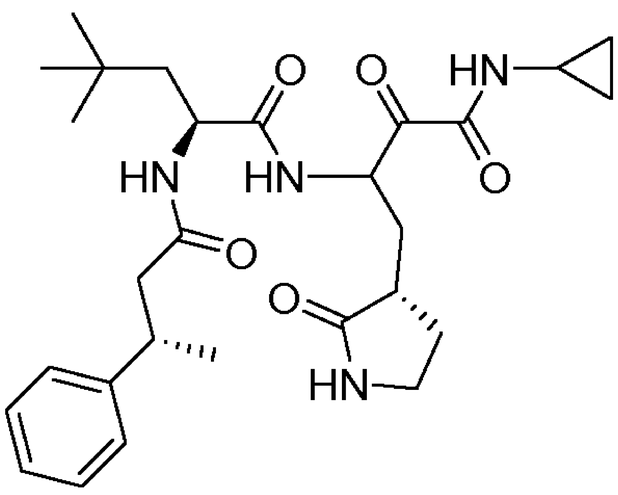
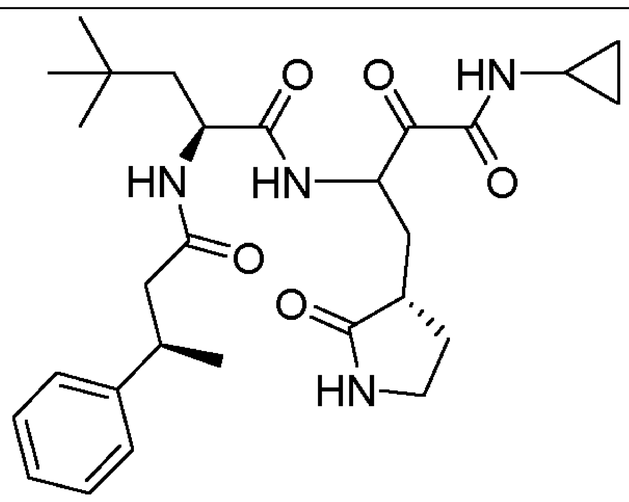
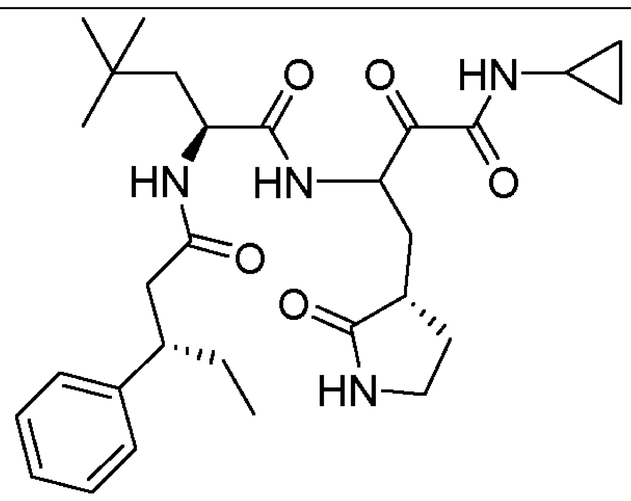
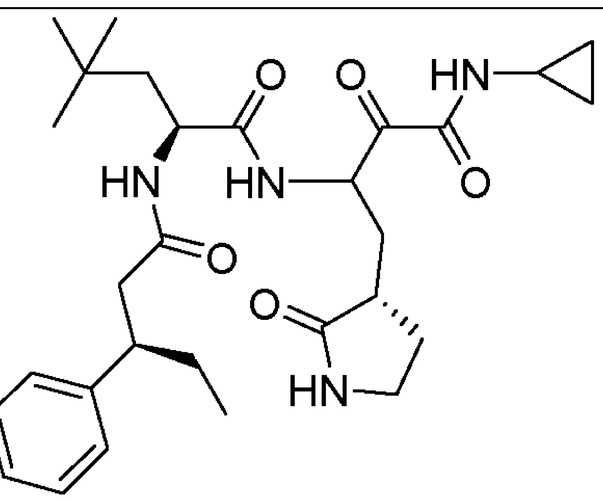
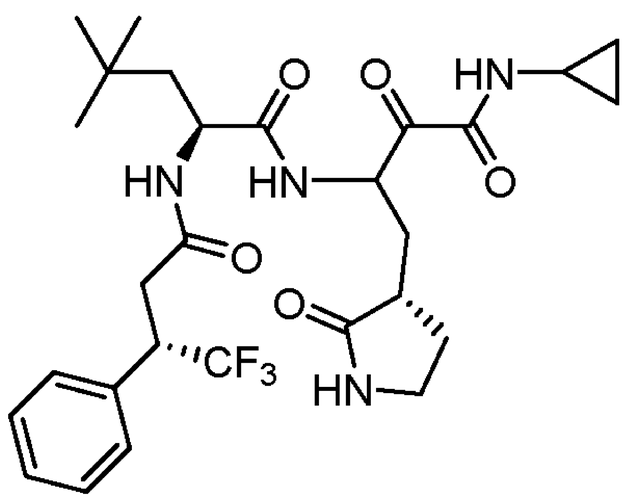
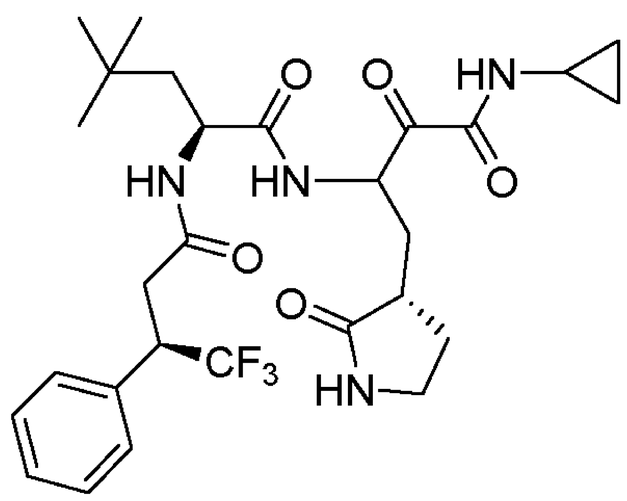
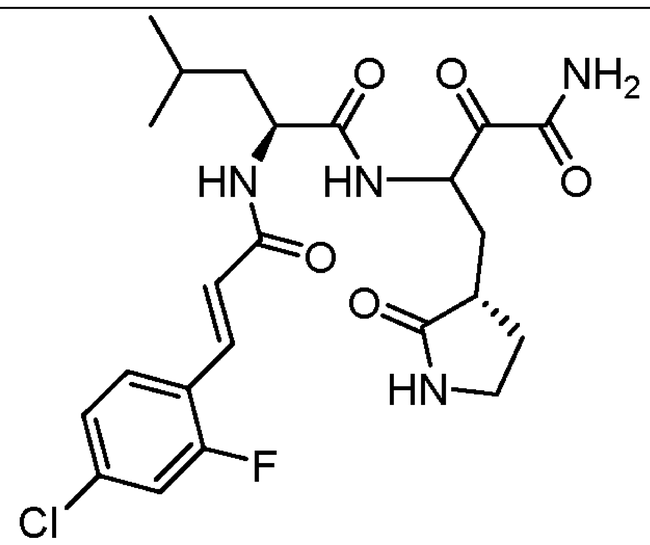
The compounds may be administered alongside other agents, for example other agents used in treating subjects with SARS-CoV-2. The compounds may be co-administered with HIV drugs which are known to block cypP450 mediated metabolism, such as ritonavir or a combination of lopinavir/ritonavir.

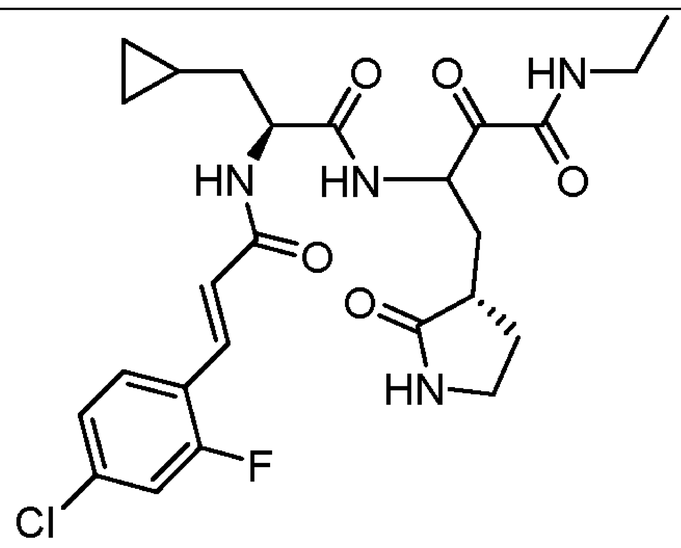
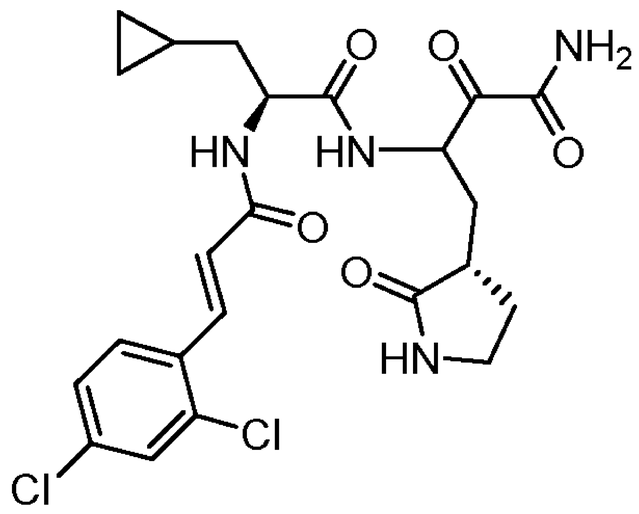
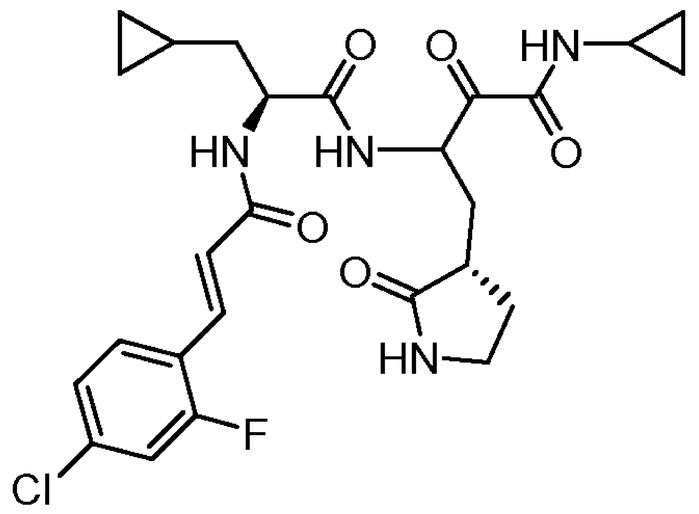
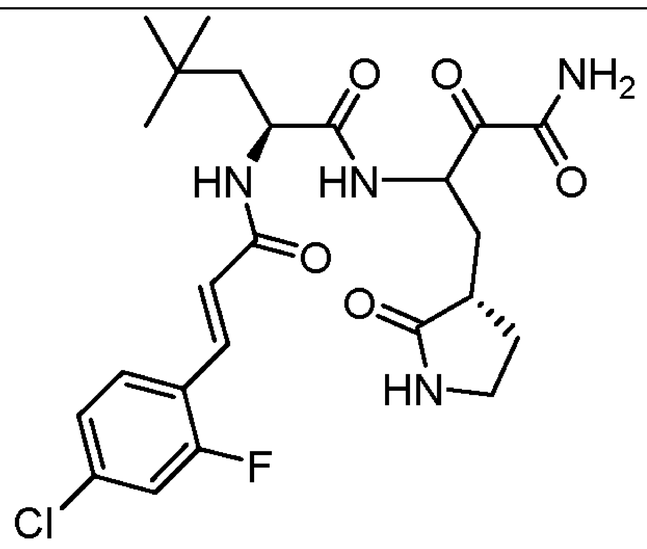
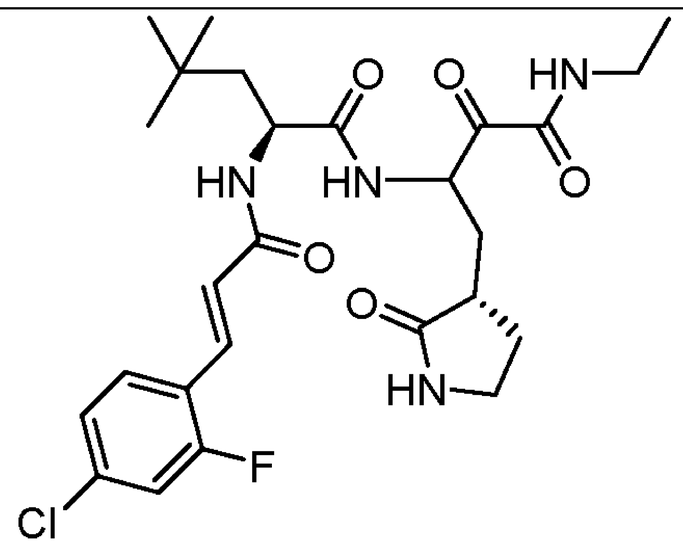
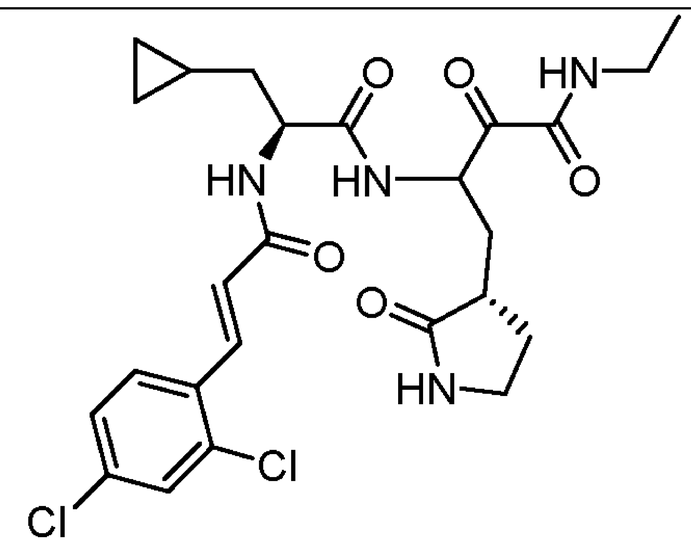
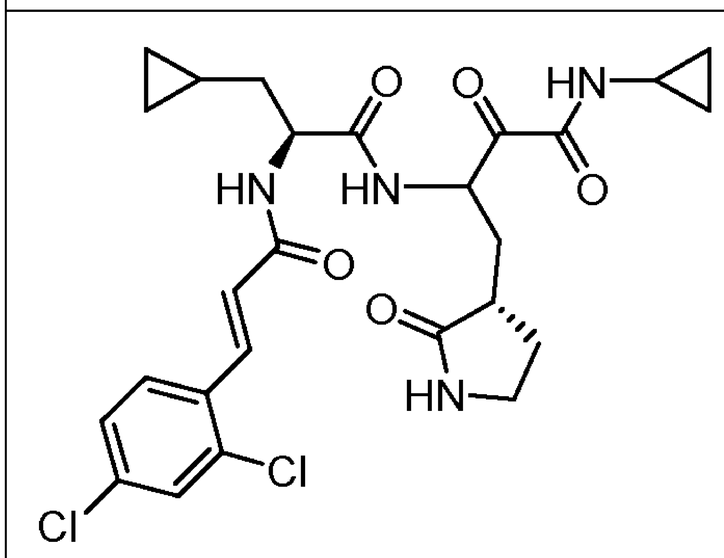
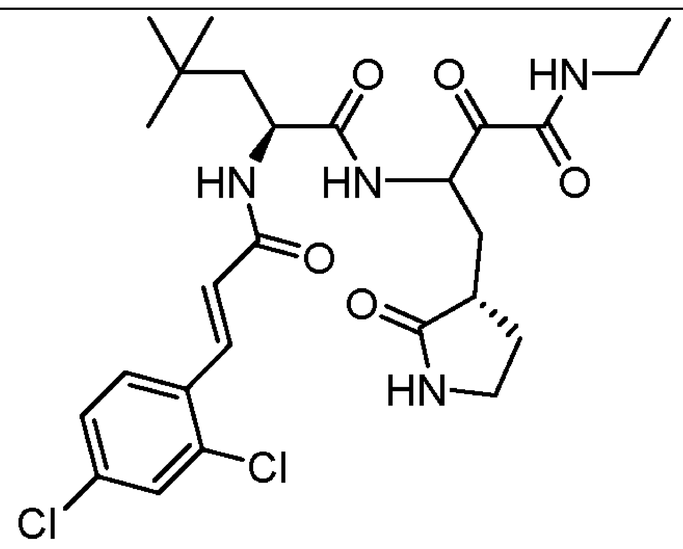
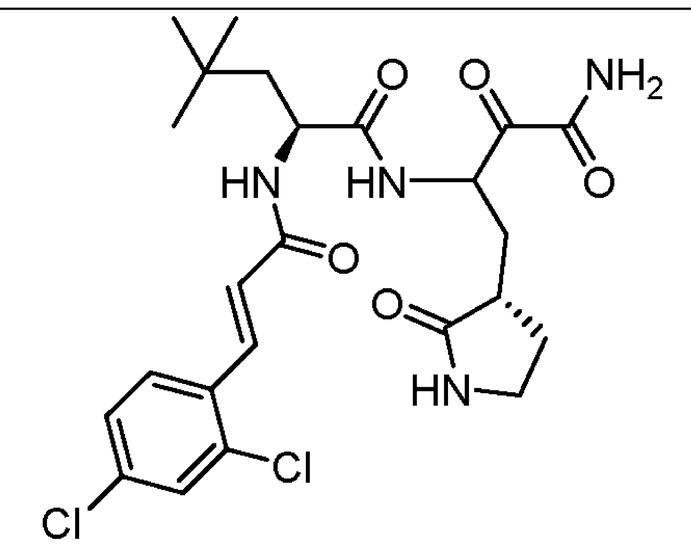
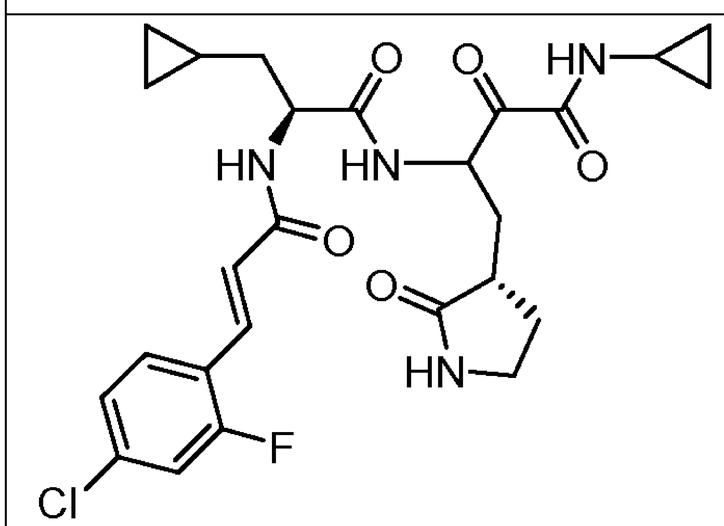
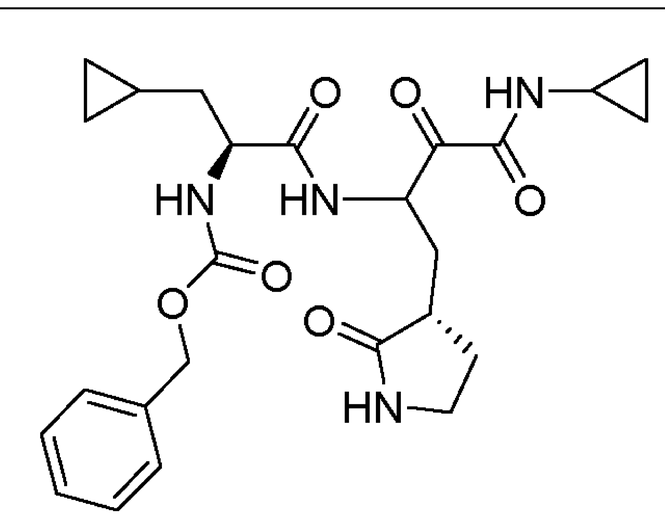
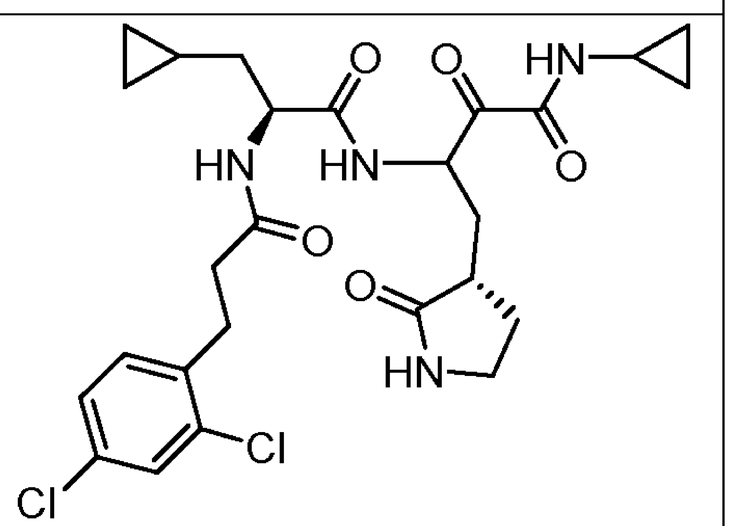
EXAMPLES

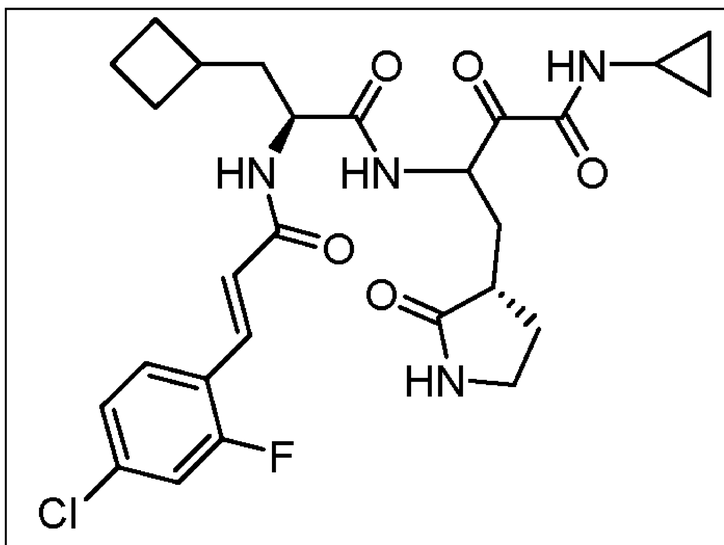
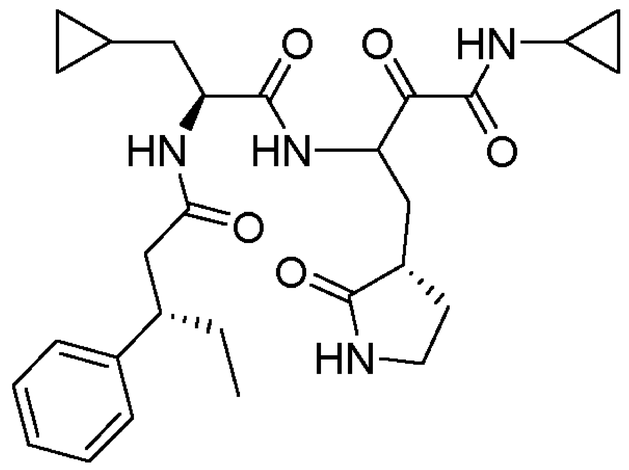
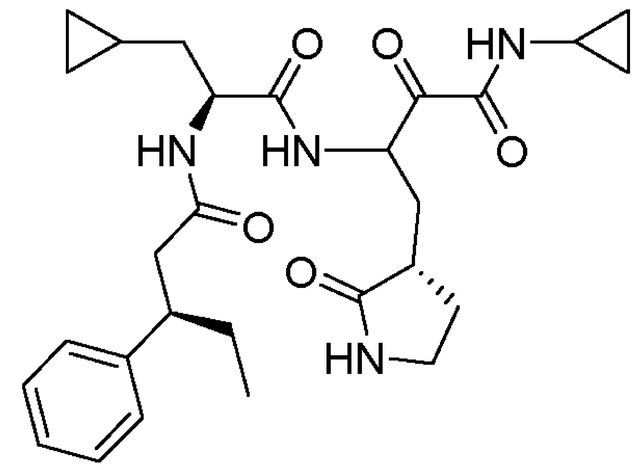
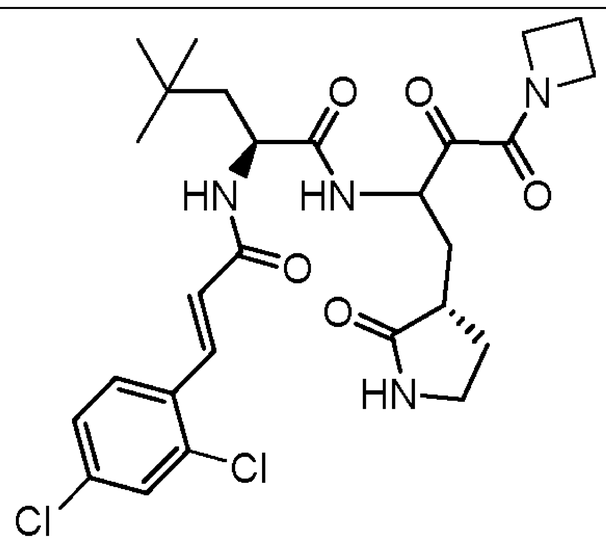
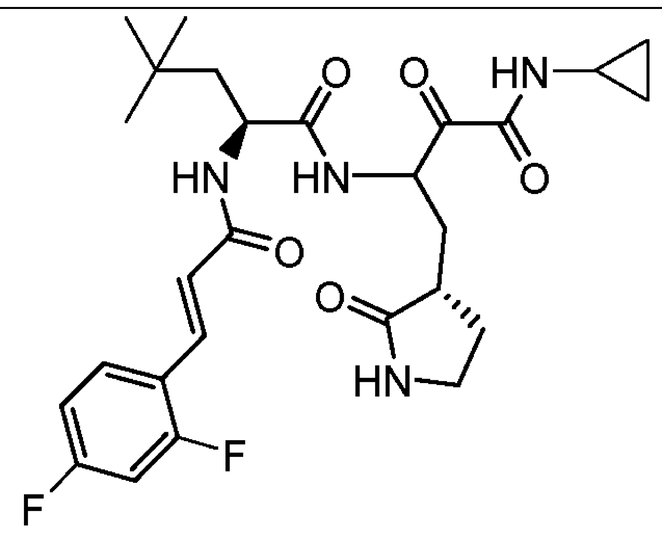
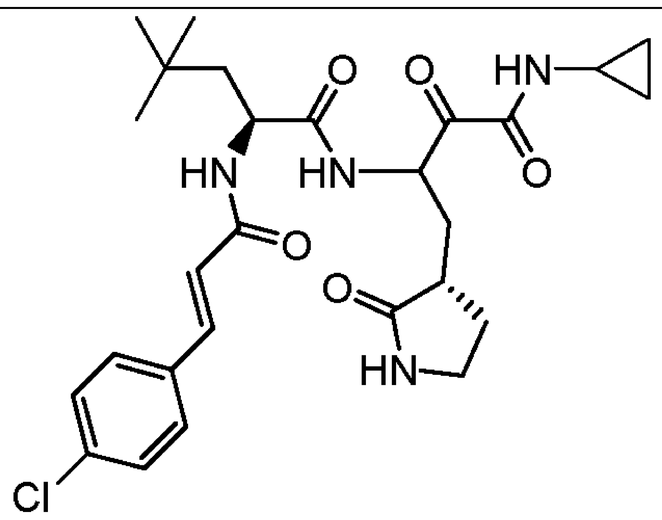
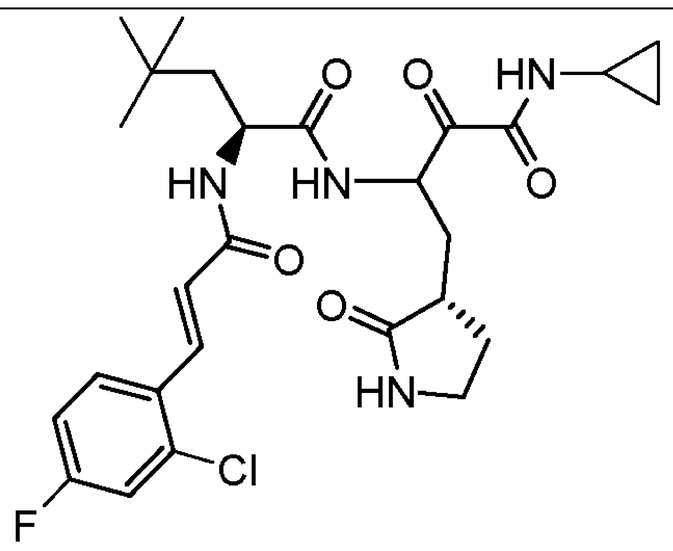
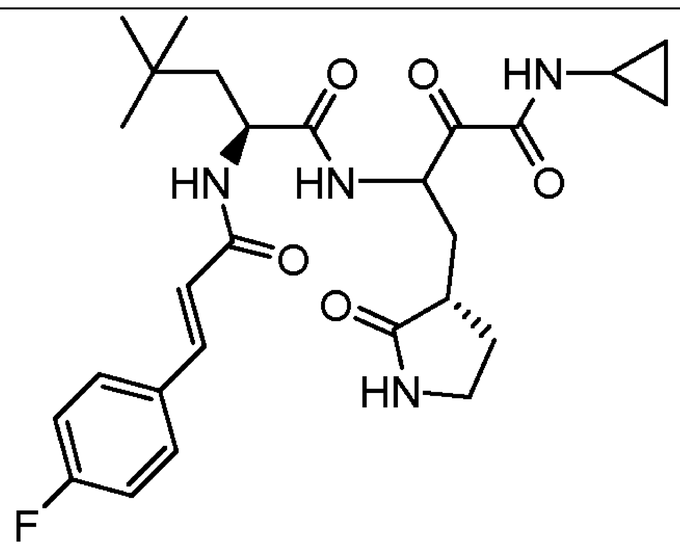
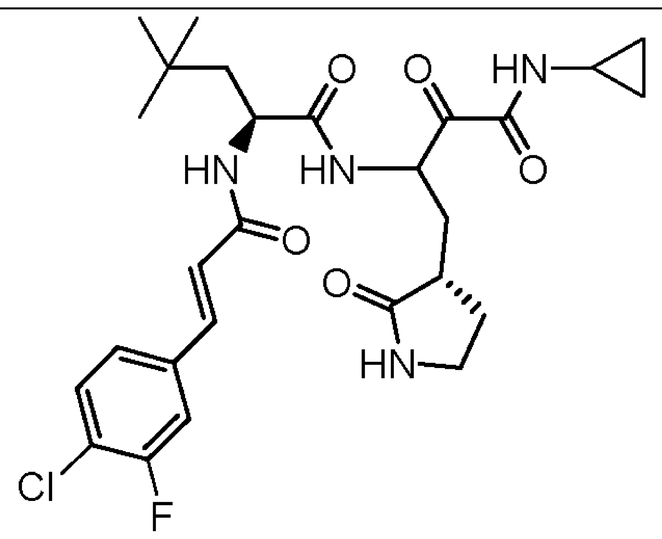
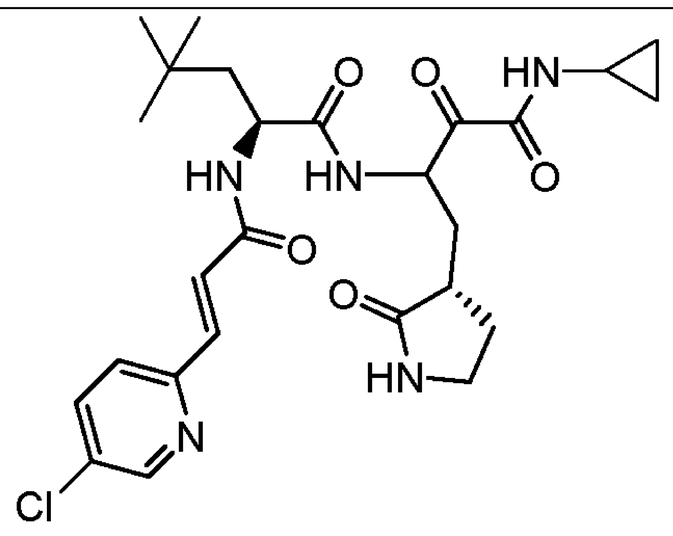
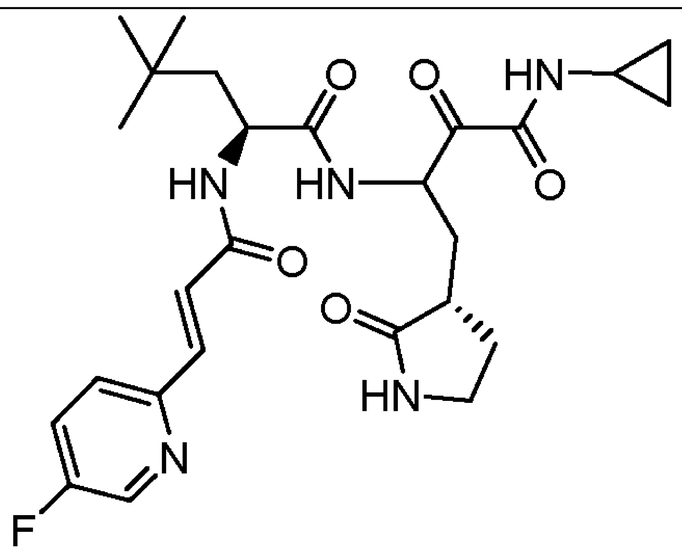
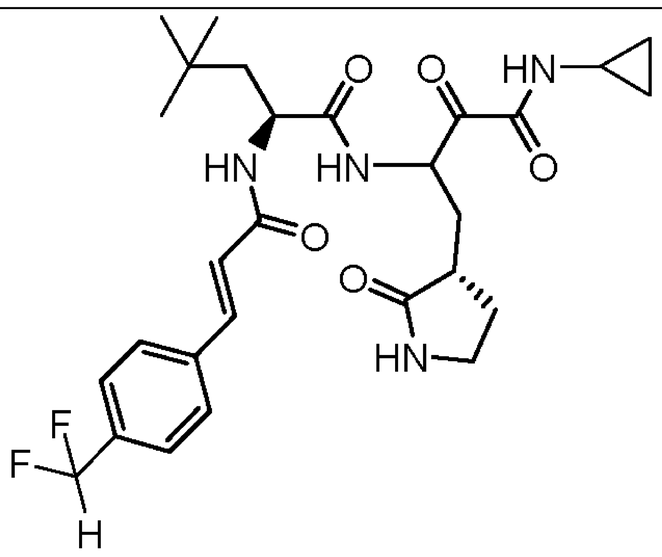
The invention will now be illustrated, but not limited, by reference to the following examples shown in Table 1.

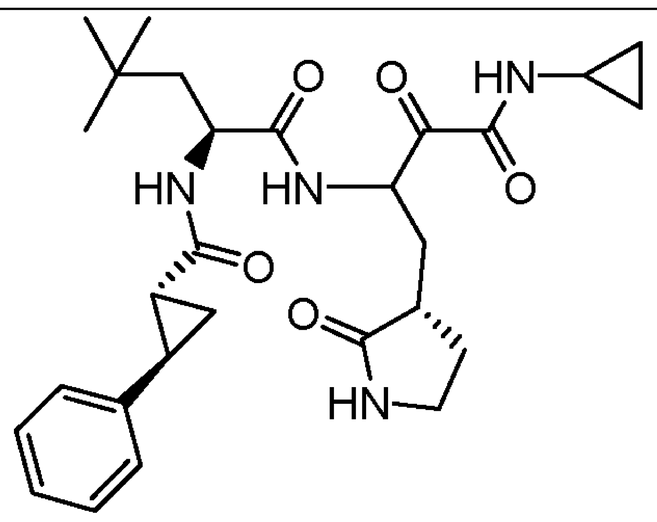
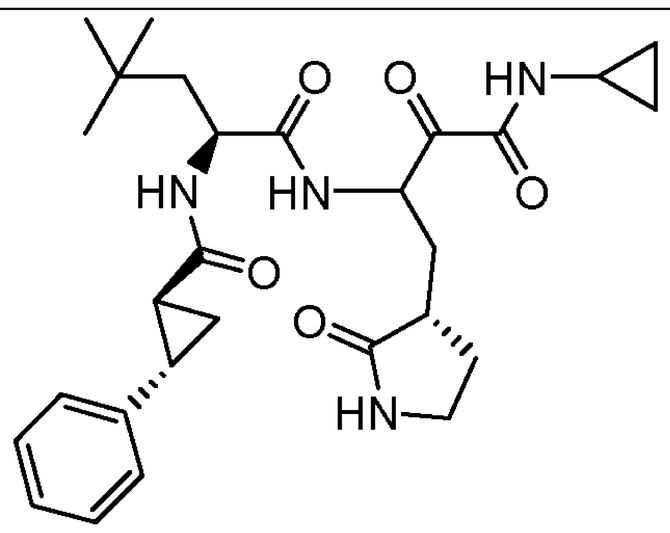
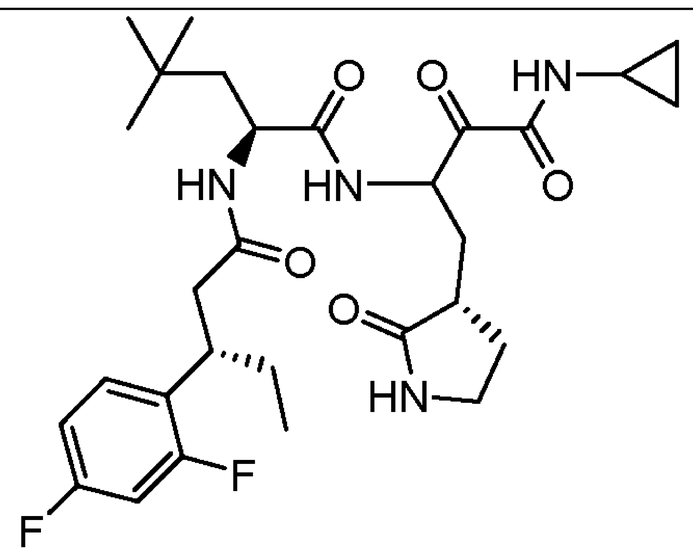
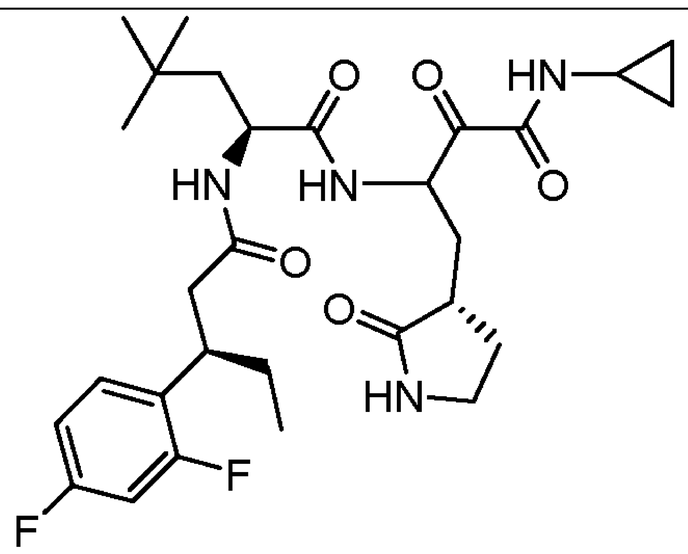
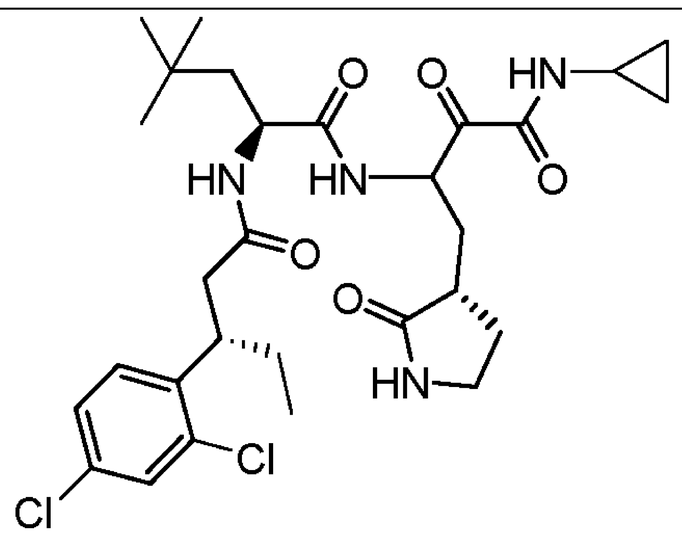
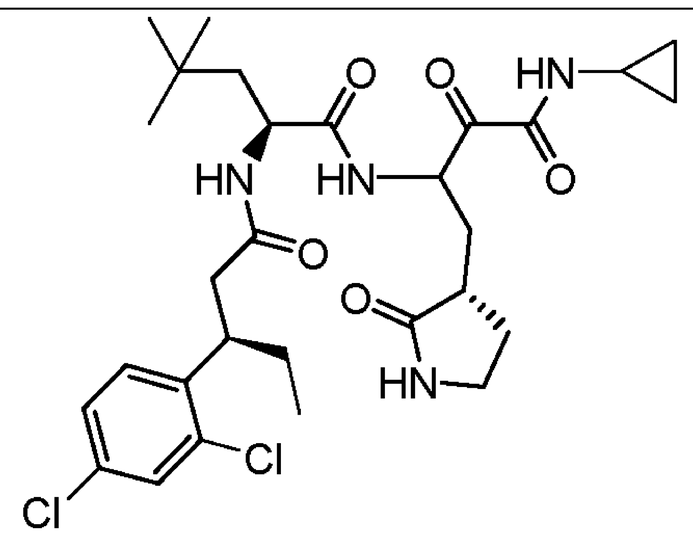
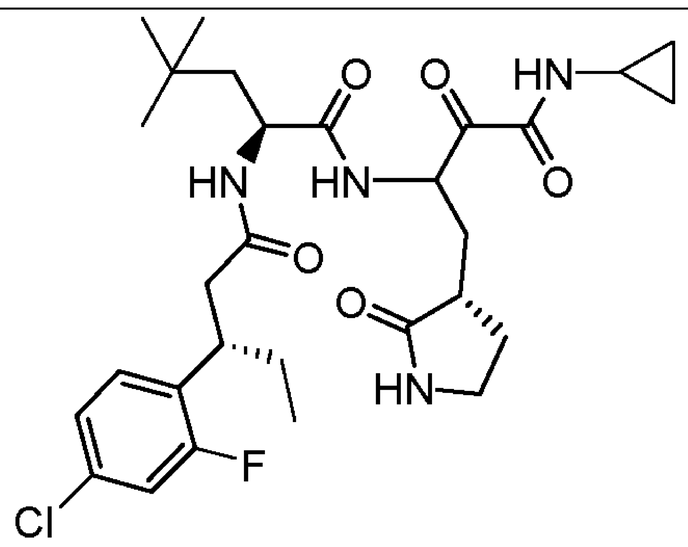
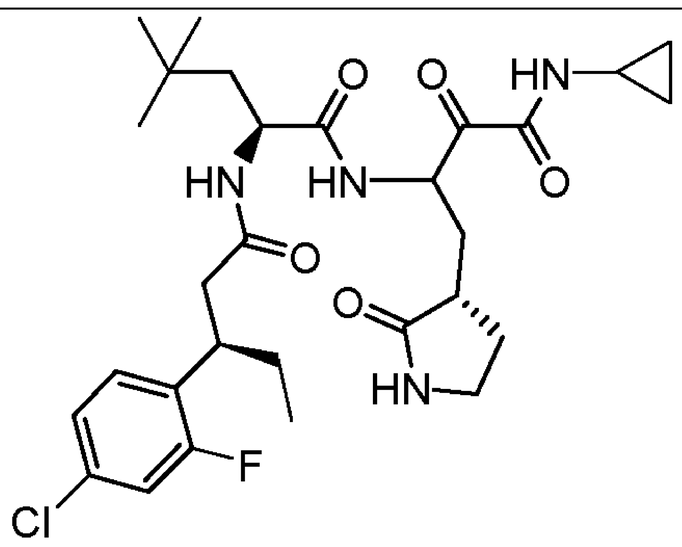
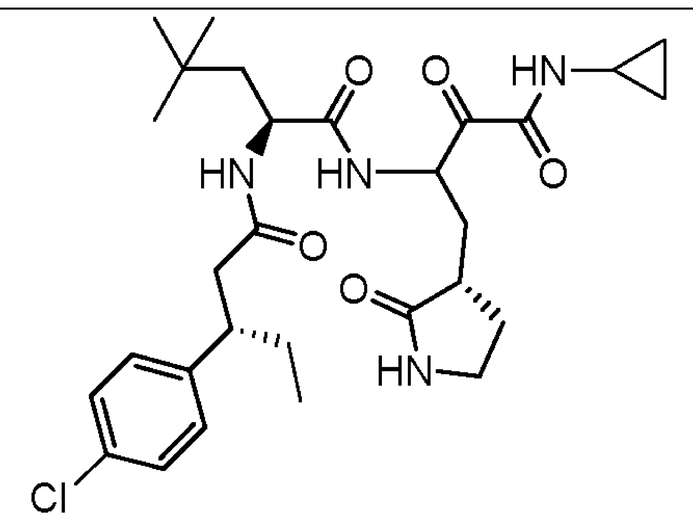
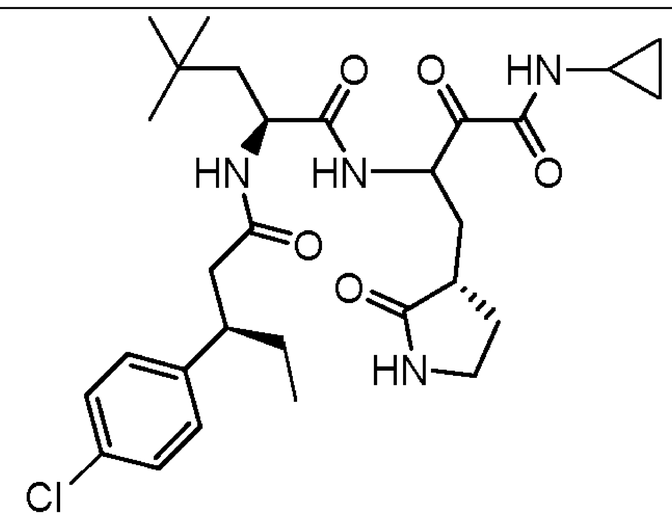
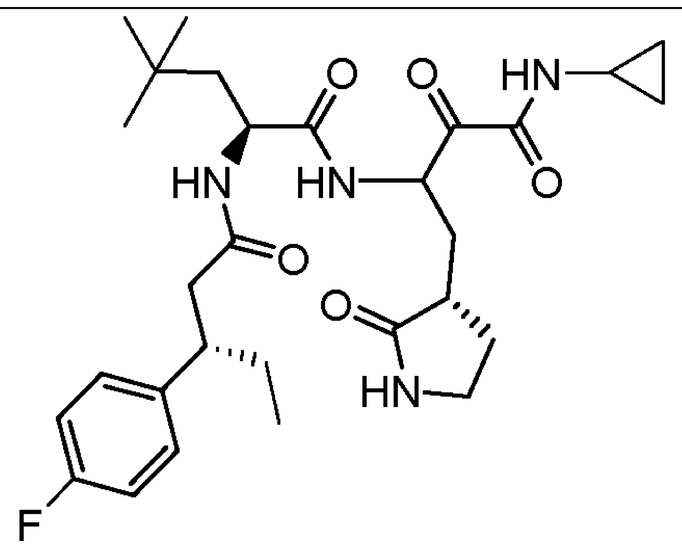
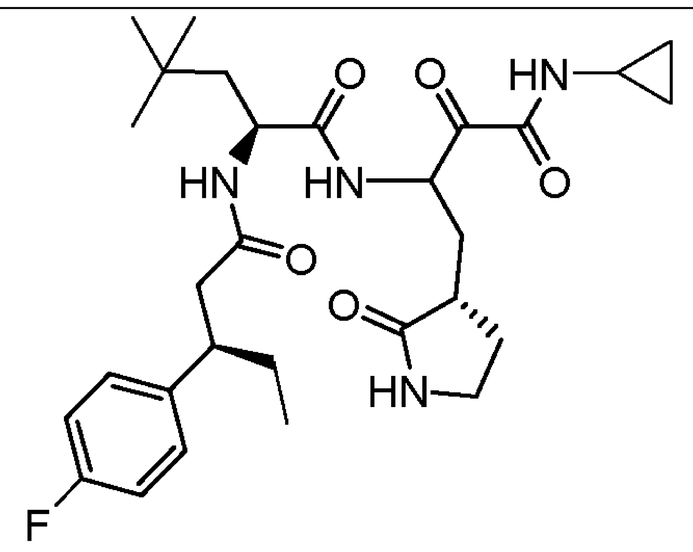
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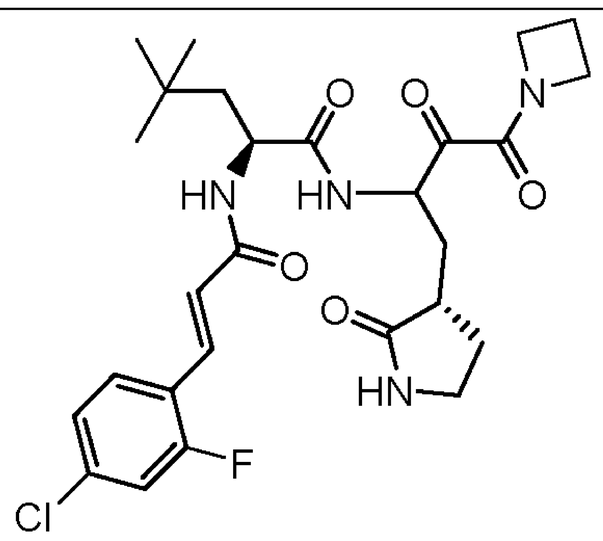
 Example 1	 Example 2	 Example 3
 Example 4	 Example 5	 Example 6

 Example 7	 Example 8	 Example 9
 Example 10	 Example 11	 Example 12
 Example 13	 Example 14	 Example 15
 Example 16	 Example 17	 Example 18

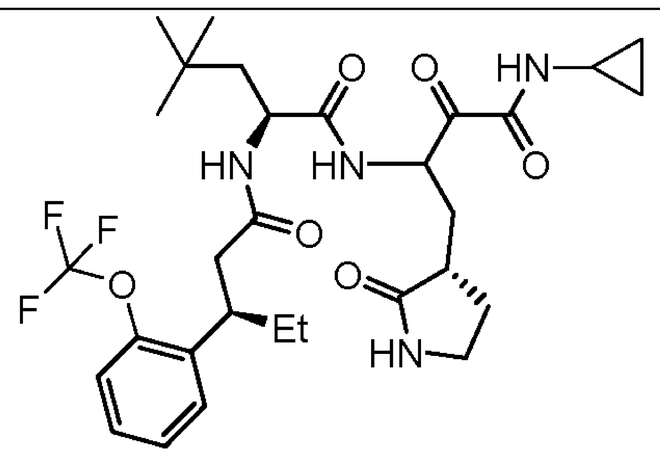
		
Example 19	Example 20	Example 21
		
Example 22	Example 23	Example 24
		
Example 25	Example 26	Example 27
		
Example 28	Example 29	Example 30

 Example 31	 Example 32	 Example 33
 Example 34	 Example 35	 Example 36
 Example 37	 Example 38	 Example 39
 Example 40	 Example 41	 Example 42

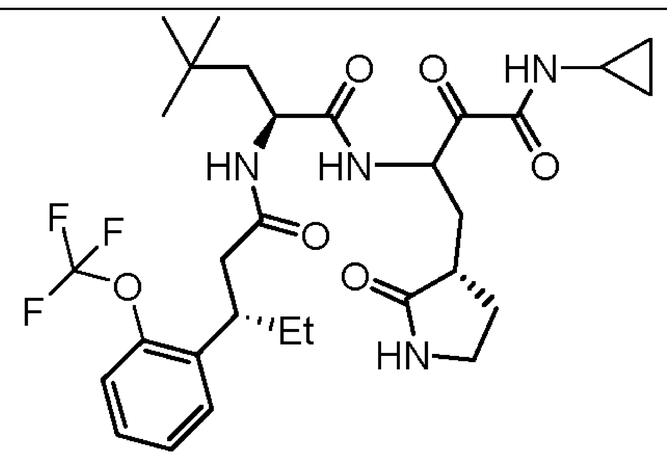
 Example 43	 Example 44	 Example 45
 Example 46	 Example 47	 Example 48
 Example 49	 Example 50	 Example 51
 Example 52	 Example 53	 Example 54



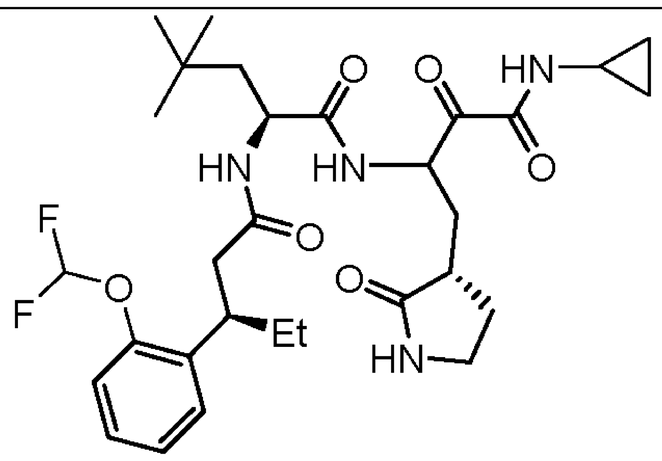
Example 55



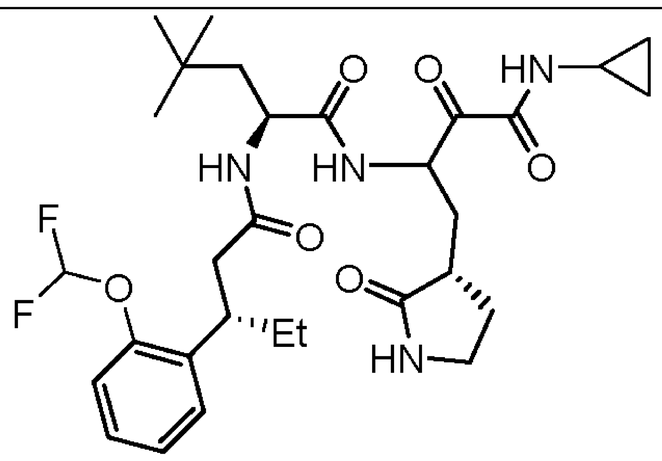
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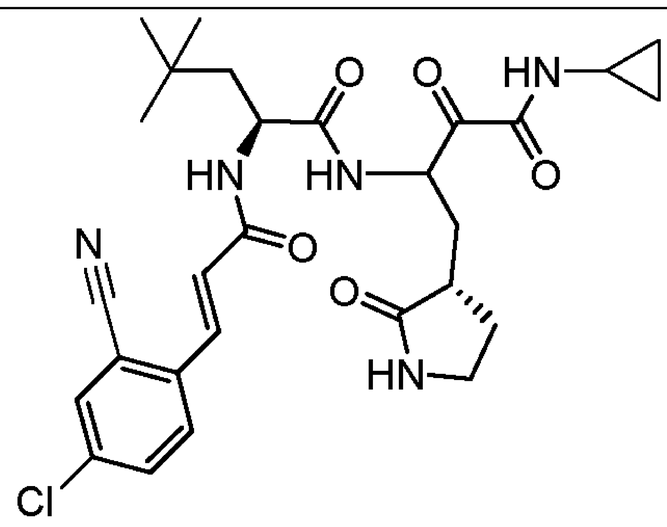
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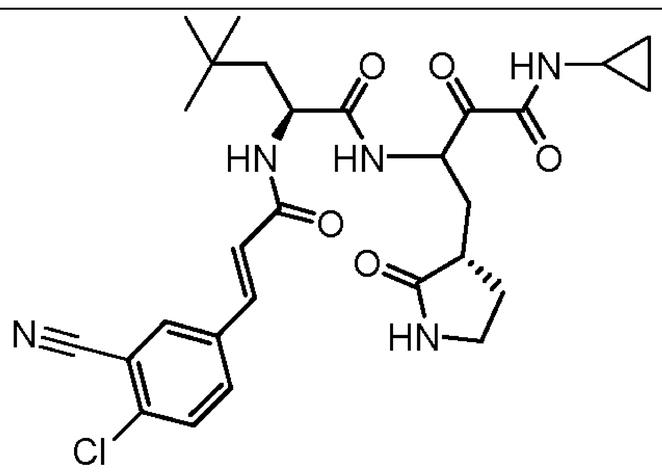
Example 58



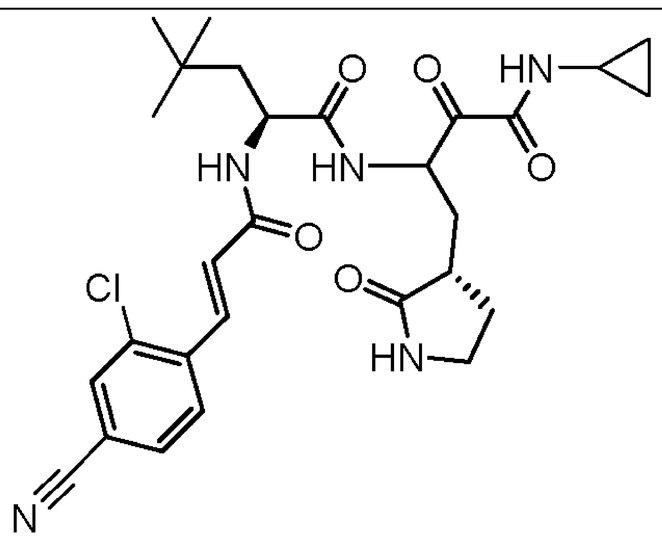
Example 59



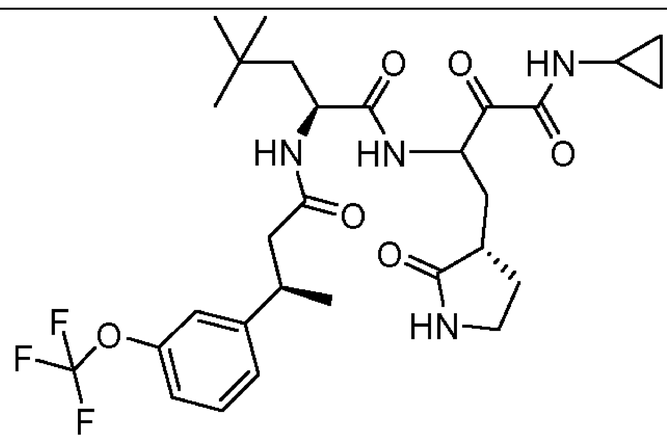
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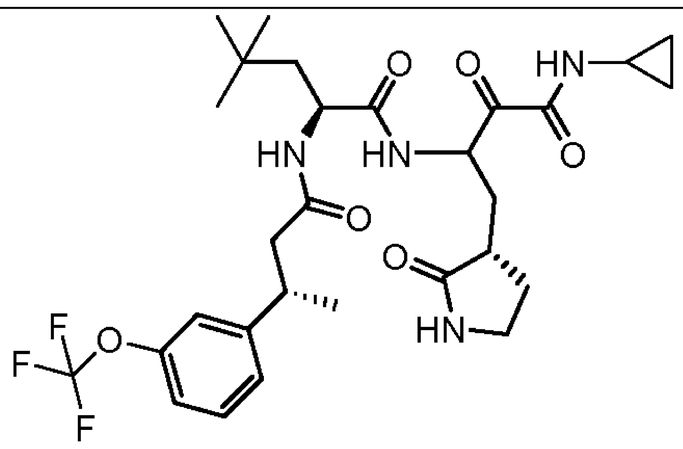
Example 61



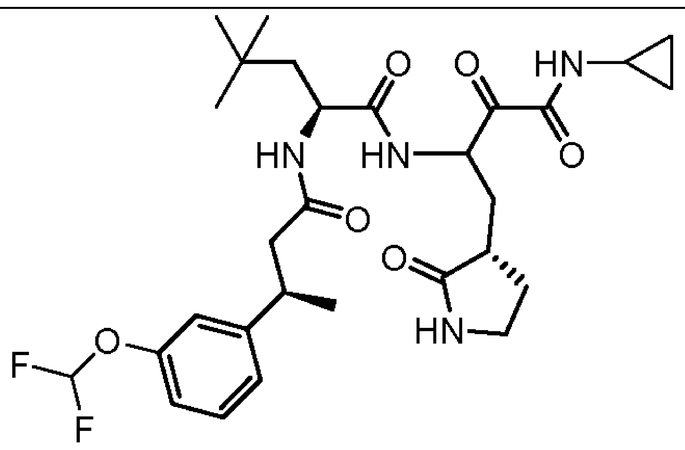
Example 62



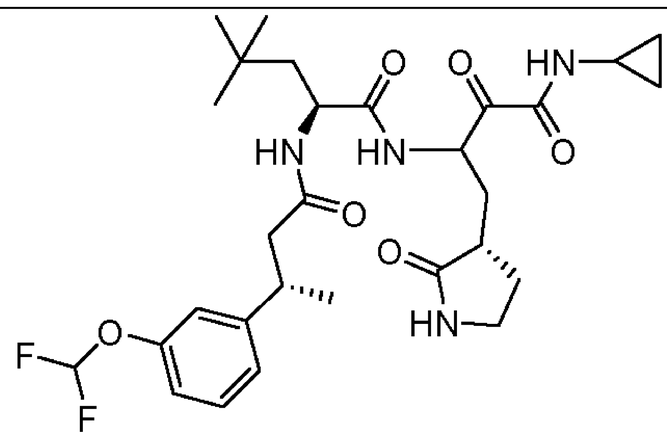
Example 63



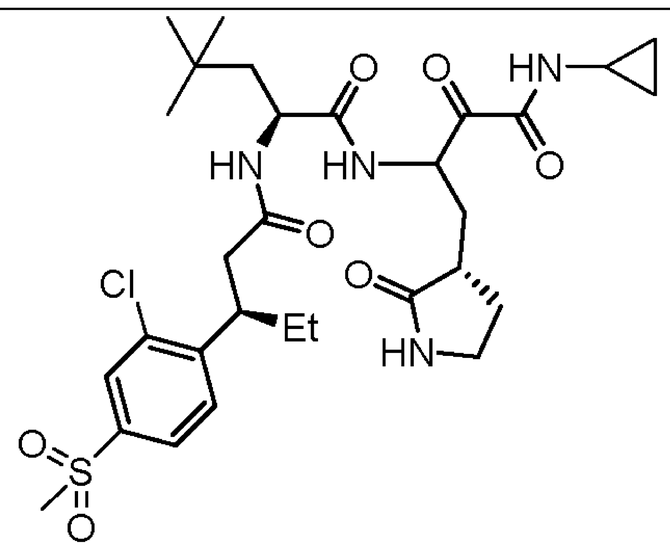
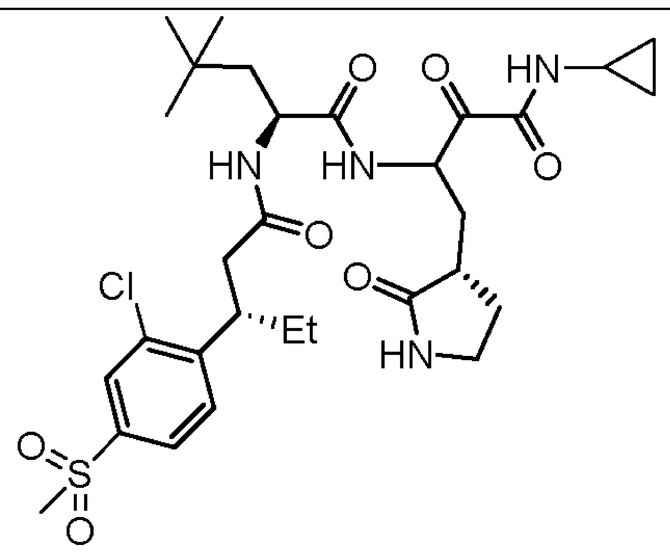
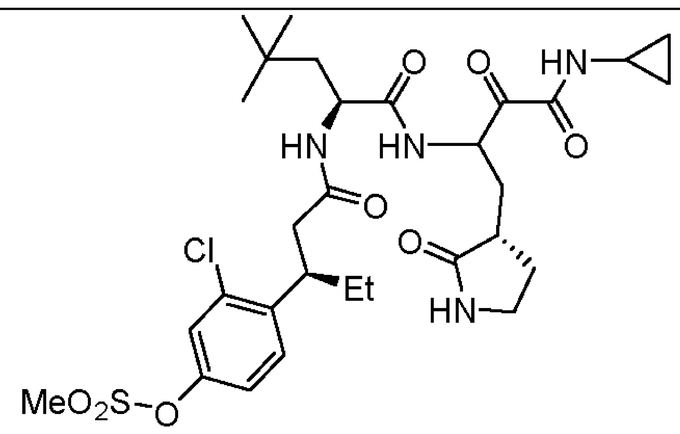
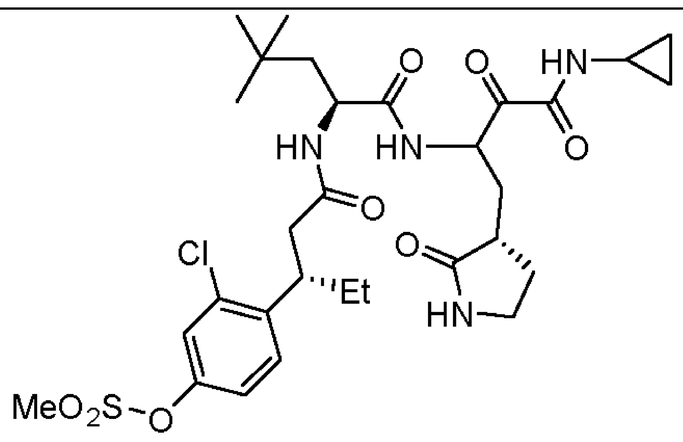
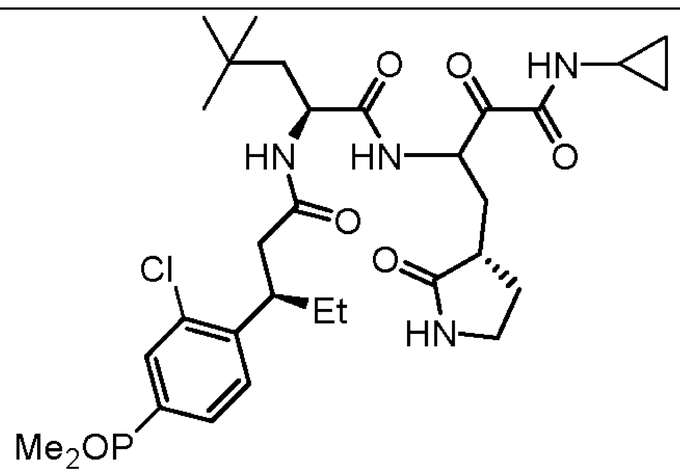
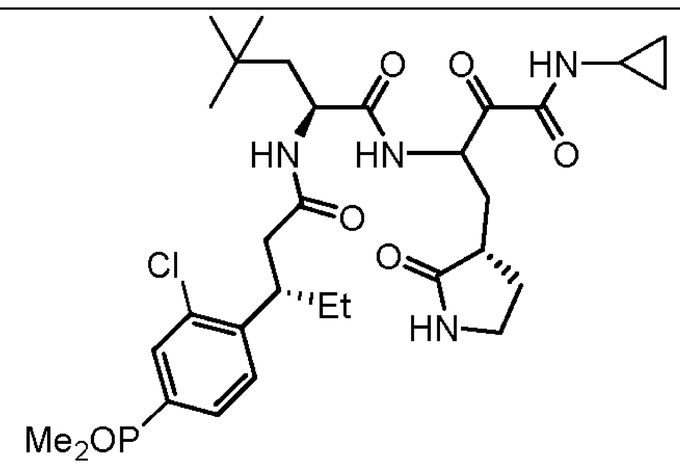
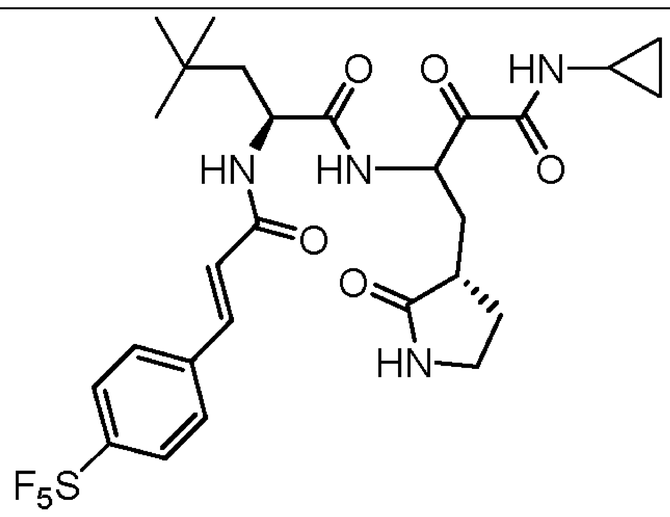
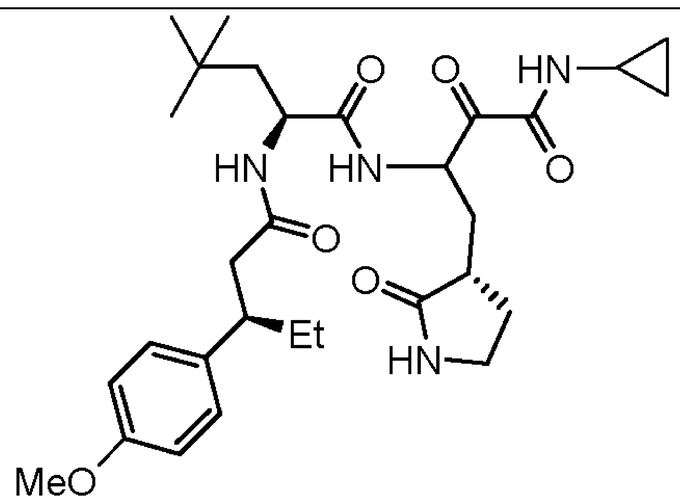
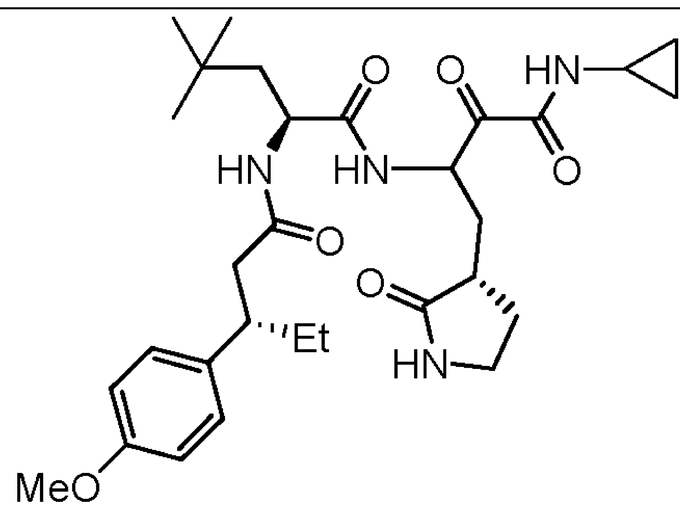
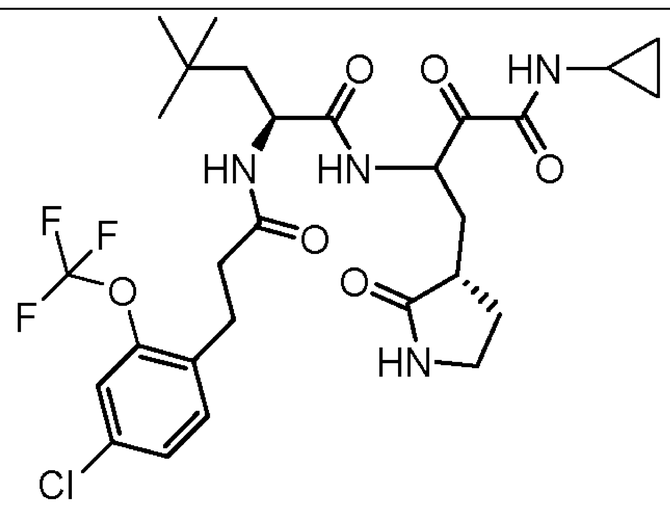
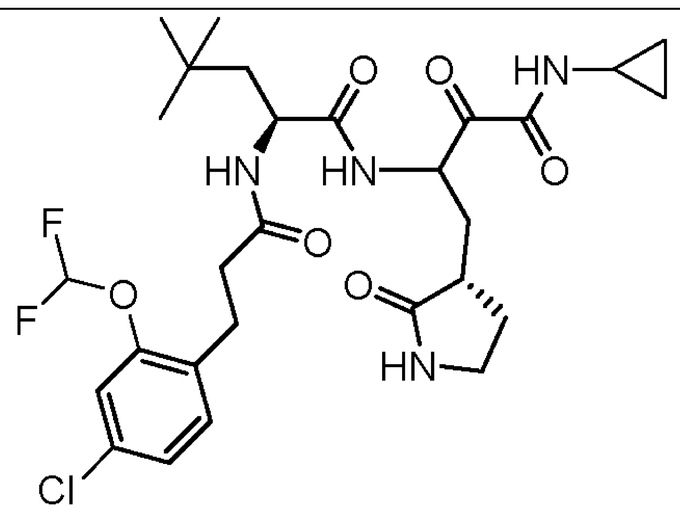
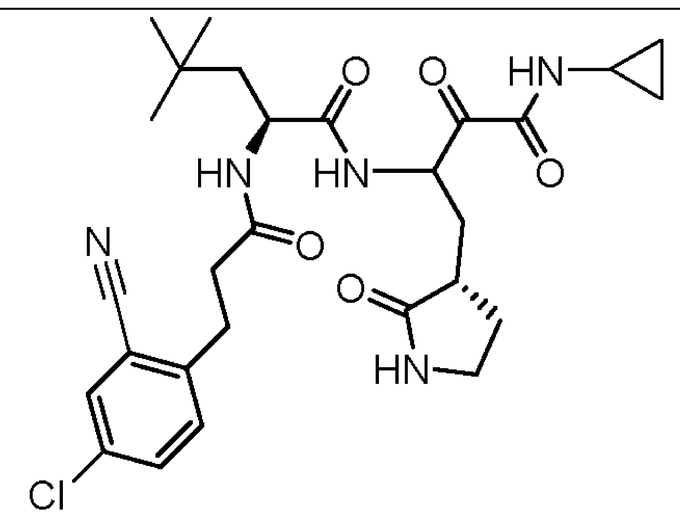
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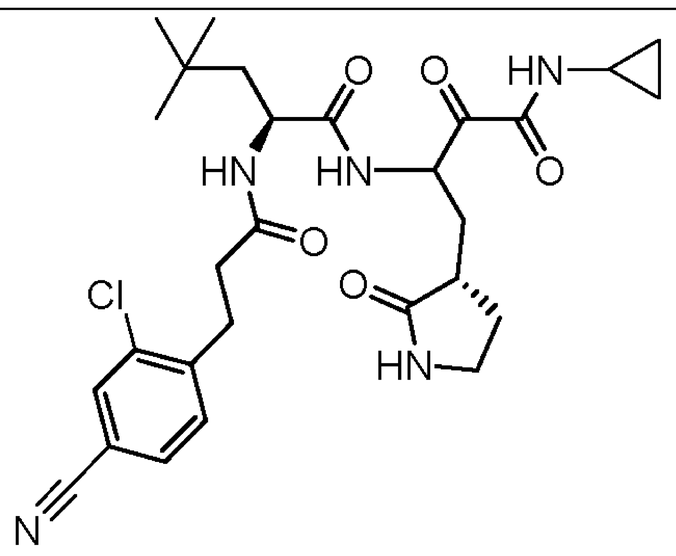


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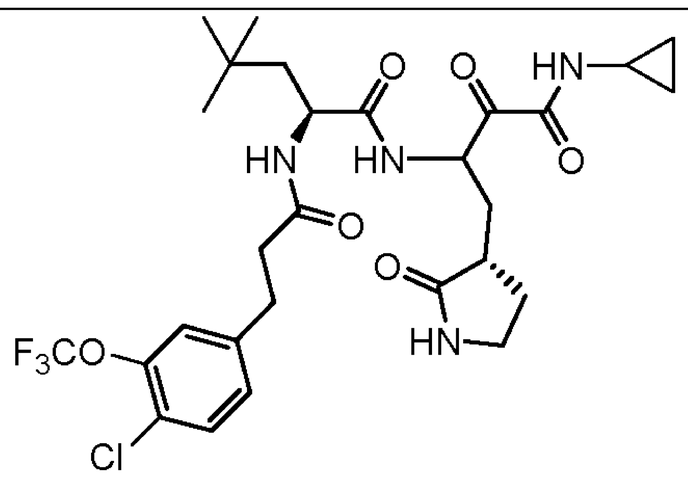


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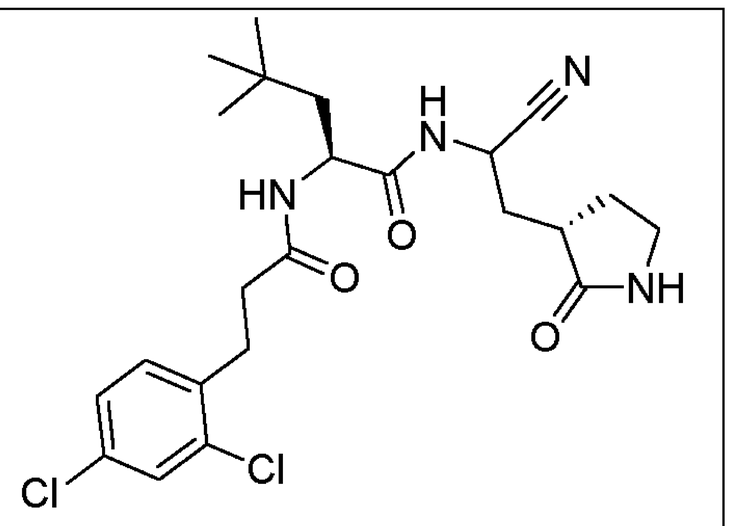
 Example 67	 Example 68	 Example 69
 Example 70	 Example 71	 Example 72
 Example 73	 Example 74	 Example 75
 Example 76	 Example 77	 Example 78



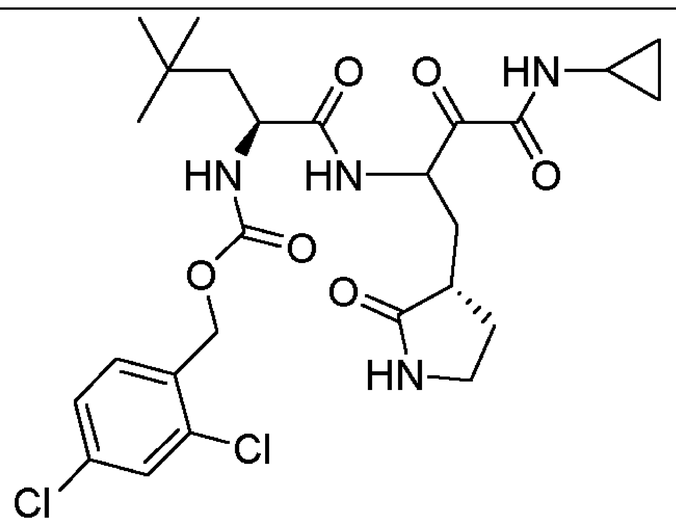
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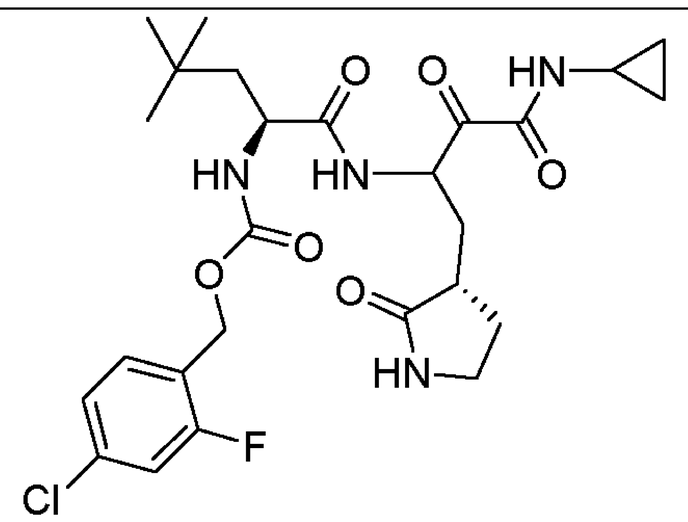
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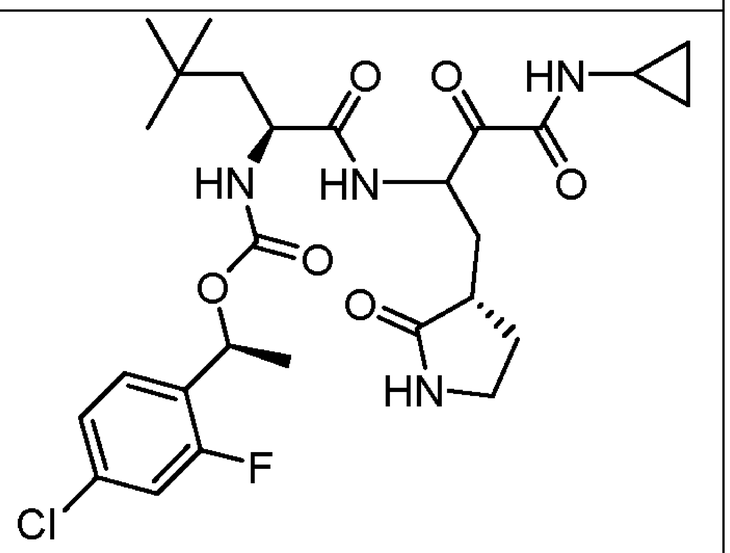
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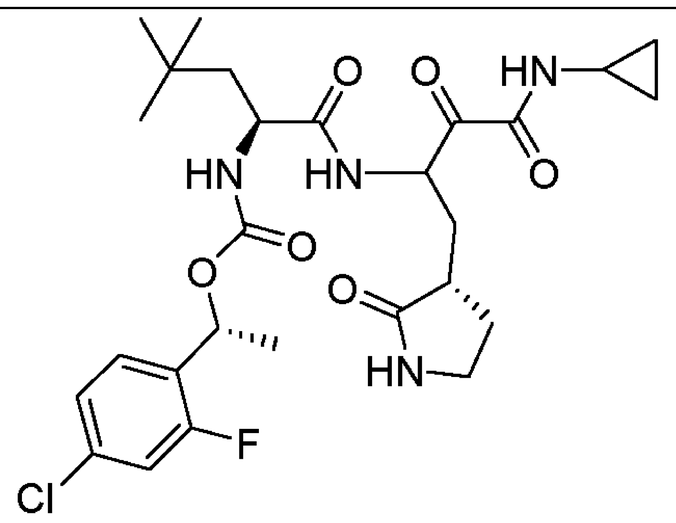
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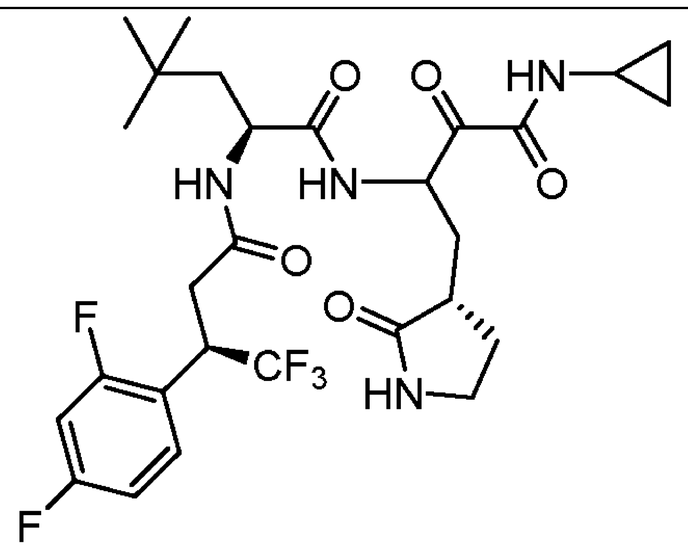
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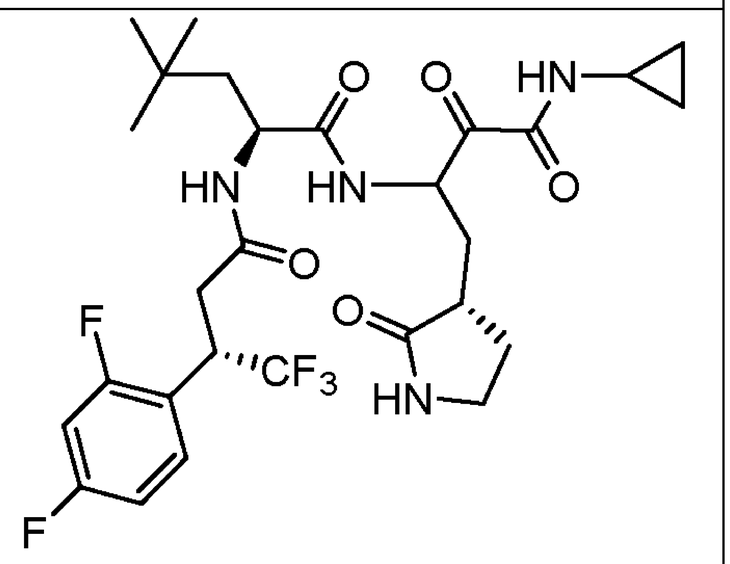
Example 84



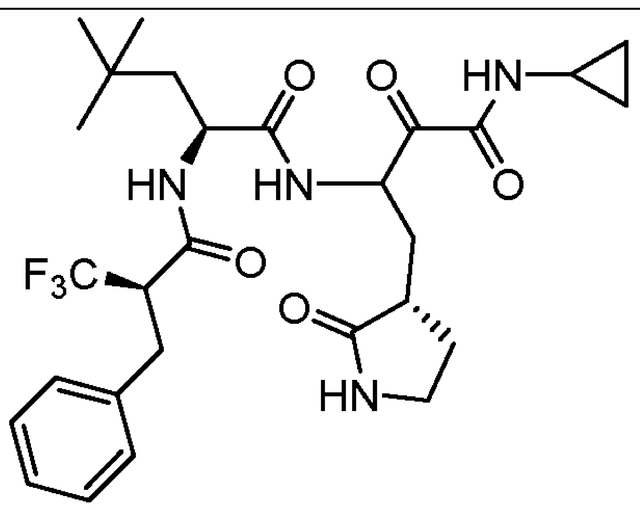
Example 85



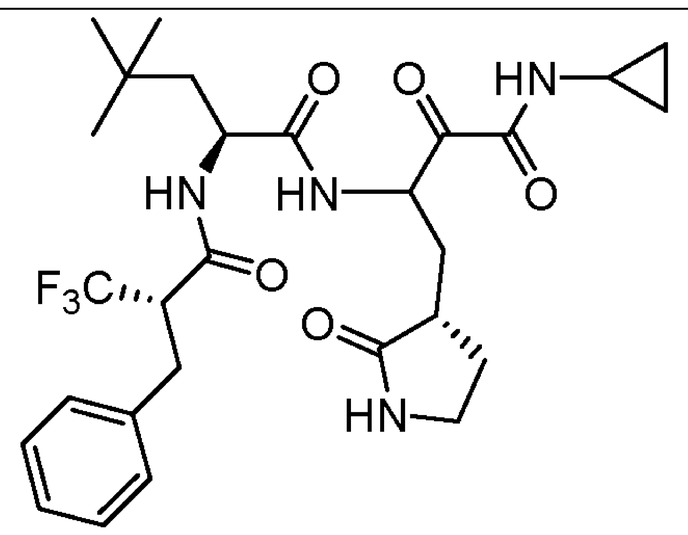
Example 86



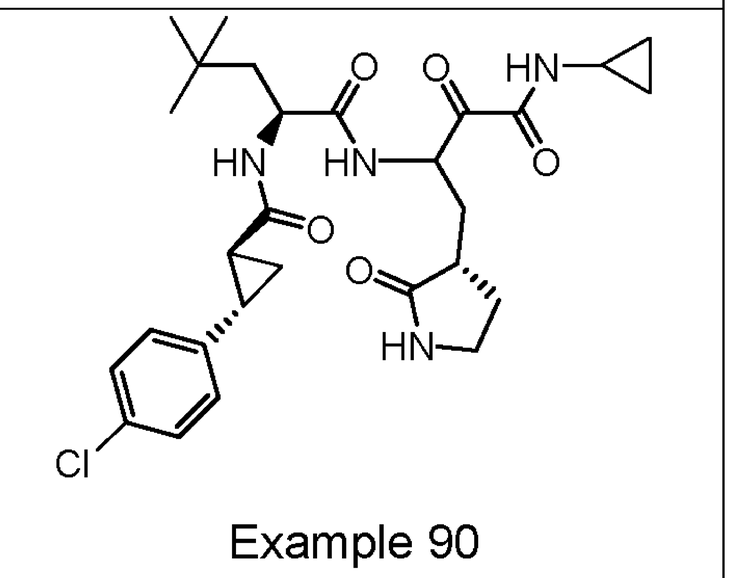
Example 87



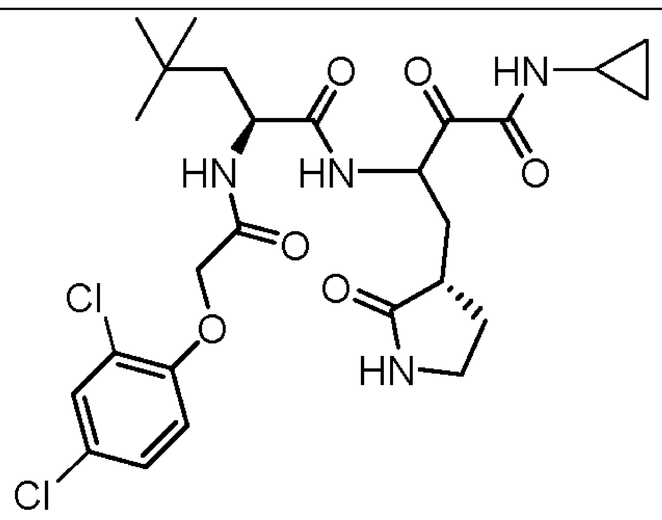
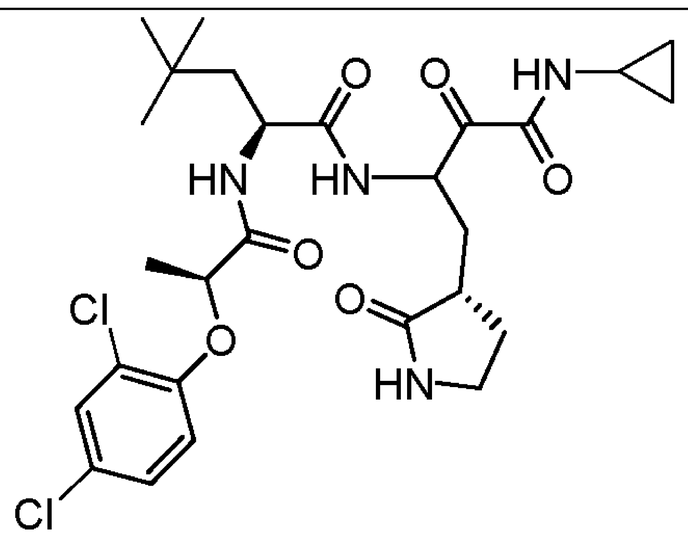
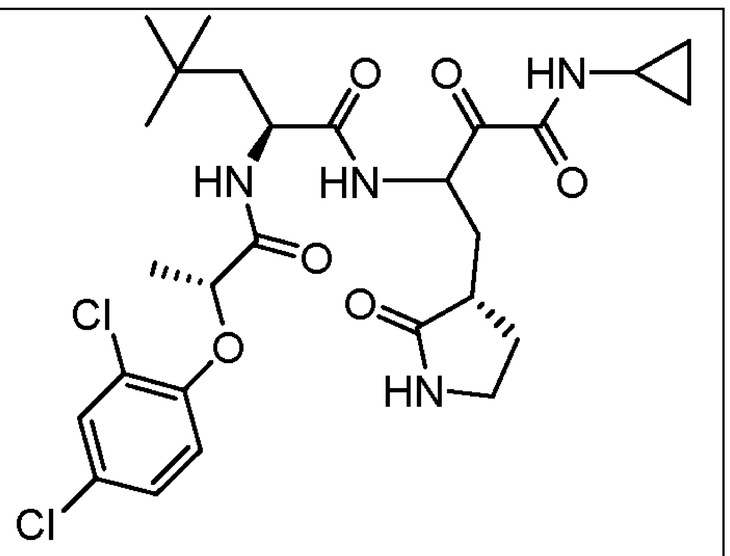
Example 88



Example 89



Example 90

 Example 91	 Example 92	 Example 93

PREPARATION OF THE COMPOUNDS OF THE INVENTION

Some compounds of the invention and derivatives or synthetic intermediates thereof can be prepared in accordance with synthetic methods known to the skilled person. In some embodiments, the invention provides a process for the preparation of a compound of the invention. Certain compounds of the invention may be prepared according to the methods described below.

PREPARATION OF THE COMPOUNDS OF THE INVENTION

Compounds of the invention may be prepared by routes including those in Figure 1. Details of many of the standard transformations such as those in the routes below and others which could be used to perform the same transformations can be found in standard reference textbooks such as "Organic Synthesis", M. B. Smith, McGraw-Hill (1994) or "Advanced Organic Chemistry", 4th edition, J. March, John Wiley & Sons (1992).

Ester derivatives of α-amino acids, for example methyl ester α-amino acid derivatives, are commercially available, or can be prepared by standard transformations which will be known to those skilled in the art, including transformations that are detailed in the following Synthesis of Intermediates and Synthesis of Examples sections. Ester derivatives of α-amino acids can be coupled with carboxylic acids to give the corresponding amide derivative (Route 1, step i). The amide coupling reaction conditions will typically use a coupling agent or agents, for example propylphosphonic anhydride (T3P) or HATU, with a suitable base such as DIPEA or Et_3N, in a solvent such as DCM or DMF, typically at room temperature. Alternatively, ester derivatives of α-amino acids can be coupled with carbamoyl chlorides, for example benzyl carbonochloridate, with a suitable base such as DIPEA, in a solvent such as DCM, typically at room temperature, to form a carbamate derivative. The ester functionality present in the product of the amide or carbamate formation can then be hydrolysed under acidic or basic conditions, for example using lithium hydroxide monohydrate in a solvent such as THF, MeOH,

1,4-dioxane or H_2O, or a mixture of these solvents, typically at room temperature (Route 1, step ii). The hydrolysis generates a carboxylic acid that can then be reacted with an ester derivative of an α-amino acid, under amide coupling conditions such as those above (Route 1, step iii). The ester functionality can be reduced to a primary alcohol using standard reduction conditions, for example the use of a reducing agent such as sodium borohydride, in a suitable solvent such as THF or MeOH and a combination of solvents, typically at room temperature (Route 1, step iv). Oxidation of the primary alcohol to an aldehyde can be performed using an oxidising agent such as Dess-Martin Periodinane (DMP) in a suitable solvent such as DCM, THF, or DMSO, or a mixture of these solvents, typically at room temperature (Route 1, step v). The aldehyde product can be reacted with acetone cyanohydrin, in the presence of a suitable base such as Et_3N, in a suitable solvent such as DCM, typically at room temperature to give a 1-cyano-1-hydroxy derivative (Route 1, step vi). The cyano group can be hydrolysed under standard conditions, such as using aqueous hydrogen peroxide in the presence of a base such as potassium carbonate, in a suitable solvent such as DMSO, typically at room temperature. A final oxidation step, using conditions such as those detailed above (Route 1, step v) can be used to synthesize compounds of the invention (Route 1, step viii).

Further compounds of the invention can be synthesised from other compounds of the invention. For example, the ketone group in the keto-amide functionality of compounds can be reacted with nucleophiles, for example hydroxylamine hydrochloride, in the presence of a suitable base such as potassium carbonate, in a suitable solvent such as ethanol, at an elevated temperature, for example 70 ºC (Route 2).

In a further route, compounds of the invention may be prepared from aldehyde intermediates resulting from Route 1, Steps i) to v) inclusive. The aldehyde may be reacted with an isocyanate, for example an alkyl isocyanate, in the presence of acetic acid, in a suitable solvent such as DCM, typically at room temperature (Route 2, step i). The acetate group of the 1-acetoxy-1-alkylamide product of this step can be hydrolysed under conditions such as those described above (Route 1, step ii) to yield a 1-hydroxy-1-alkylamide product (Route 3, step ii). A final oxidation step, using conditions such as those detailed above (Route 1, step v) can be used to synthesize compounds of the invention (Route 1, step viii).

In a further route, compounds of the invention may be prepared from aldehyde intermediates resulting from Route 1, Steps i) to v) inclusive. The aldehyde may be reacted with hydroxylamine hydrochloride, in the presence of a base such as potassium carbonate, in a suitable solvent such as ethanol, at an elevated temperature, for example 70 ºC (Route 4, step i). Dehydration of the resulting oxime, for example using a dehydrating agent such as methyl

N-(triethylammoniumsulfonyl)carbamate (Burgess reagent) can be used to synthesize compounds of the invention (Route 4, step ii).

General procedures

Where no preparative routes are included, the relevant intermediate is commercially available. Commercial reagents were utilized without further purification. Room temperature (rt) refers to approximately 20-27°C. ^{1}H NMR spectra were recorded at 300 or 400 MHz on Bruker instruments. Chemical shift values are expressed in parts per million (ppm), i.e. (δ)-values, relative to tetramethylsilane. The following abbreviations are used for the multiplicity of the NMR signals: s=singlet, br=broad, d=doublet, t=triplet, q=quartet, quin=quintet, h=heptet, dd=doublet of doublets, dt=double of triplets, m=multiplet. Coupling constants are listed as J values, measured in Hz. NMR and mass spectroscopy results were corrected to account for background peaks. TLC for monitoring reactions refers to TLC run using silica gel as a stationary phase.

LCMS experiments were carried out under the following conditions. Instruments: Agilent Technologies 1290 Infinity II Series LC / 6125 Quadrupole MSD SL (Methods A-E inclusive, H and K), ELSD detector (Polymer Laboratories PL-ELS 2100 ICE) used for UV inactive compounds in Method A; Columns: Waters XBridge C8 3.5µm, 4.6x50 mm (Method A), Atlantis dC18 5µm, 4.6x50mm (Method B), Zorbax XDB C18 5µm, 4.6x50mm (Method C), Zorbax extend C18 5µm, 4.6x50mm (Method D), XBridge C8 3.5µm, 4.6x50mm (Method E), Acquity BEH C18 1.7µm, 2.1x50mm (Method H), Xselect CSH C18 5µm, 4.6x50mm, CSH (Charged Surface Hybrid) (Method K); Gradient [time (min)/solvent B in A (%)]: 0.0/5, 2.5/95, 4.0/95, 4.5/5, 6.0/5 (Solvent A=0.1% TFA in H_2O:MeCN (95:5); Solvent B=0.1% TFA in MeCN (Method A)), 0.0/5, 2.5/95, 4.0/95, 4.5/5, 6.0/5 (Solvent A=0.1% HCO_2H in H_2O:MeCN (95:5); Solvent B=MeCN (Method B)), 0.0/5, 2.5/95, 4.0/95, 4.5/5, 6.0/5 (Solvent A=0.1% HCO_2H in H_2O:MeCN (95:5); Solvent B=MeCN (Method C)), 0.0/10, 4.0/95, 5.0/95, 5.0/10, 6.0/10 (Solvent A=770.1 mg of NH_4OAc in 1 L Milli-Q Water; Solvent B=MeCN (Method D)), 0.0/10, 4.0/95, 5.0/95, 5.5/10, 7.0/10 (Solvent A=790.1 mg of NH_4HCO_3 in 1 L Milli-Q Water; Solvent B=MeCN (Method E)), 0.0/5, 0.25/5, 2.5/100, 3.0/100, 3.1/5, 4.0/5 (Solvent A=770.1 mg of NH_4OAc in 1 L Milli-Q Water; Solvent B=MeCN (Method H)), 0.0/05, 2.5/95, 4.0/95, 4.5/05, 6.0/05 (Solvent A=0.1%v/v TFA in Milli-Q water; Solvent B=0.1% TFA in MeCN) (Method K)); Injection volume typically 1 µL; UV detection 210 to 400 nm (Methods A-E inclusive and H and K); column temperature 25°C; Flow rate 1.5 mL/min (Method A, B, C, K), 1.2 mL/min (Method D, E) or 0.8 mL/min (Method H). LCMS data in the experimental section are given in the format: Mass ion, retention time.

Analytical SFC experiments were carried out under the following conditions. Instrument: PIC-10 (Manufacturer PIC Solution Inc); Column: YMC Cellulose-SC 5µm, 4.5x250mm; Mobile phase: 60% CO_2/40% Co-solvent (0.5% Isopropyl Amine in Methanol); Injection Volume 15 µL; Flow Rate 4 mL/min; Column temperature 35ºC.

Mass directed preparative HPLC was carried out under the following conditions. Instrument: Agilent Technologies 1260 Infinity II Series LC. Method B: Column: X Bridge C8 (19 mm X 150mm), 5µm; Gradient [time (min)/solvent B in A (%)]: 0.0/10, 15/95, 18/95, 19/10, 21/10 (Solvent A=0.1% HCO_2H in H_2O; Solvent B=MeCN). Method F:Column: Xselect CSH C18 (19 mm X 150 mm), 5µm; Gradient [time (min)/solvent B in A (%)]: 0.0/10, 10/50, 12/100, 16/100, 18/10, 20/10 (Solvent A=0.1% HCO_2H in H_2O; Solvent B=MeCN).

Preparative HPLC was carried out under the following conditions. Method B: Instrument: Agilent Technologies 1260 Infinity II Series LC; Column: YMC Exrs C18, 5µm, 30x150mm; Gradient [time (min)/solvent B in A (%)]: 0.0/10, 20/95, 23/95, 24/10, 26/10 (Solvent A 0.1% HCO_2H in H_2O, Solvent B=MeCN).

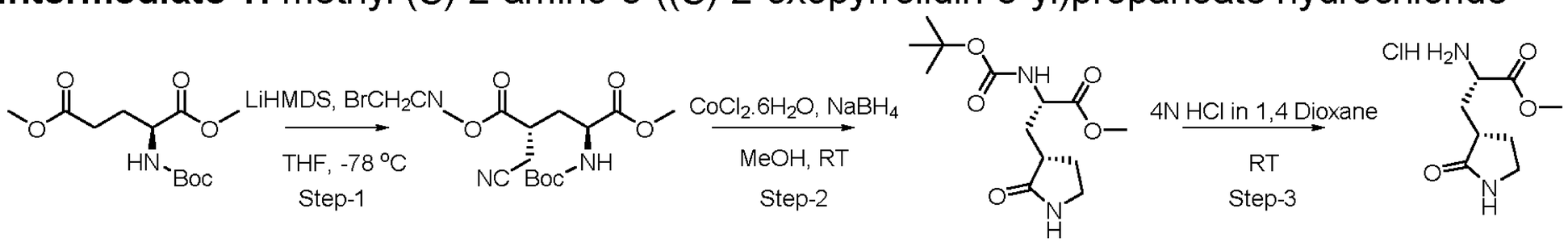
Abbreviations

DCM	=	dichloromethane
DMF	=	*N*,*N*-dimethylformamide
DMP	=	Dess-Martin Periodinane
DIPEA	=	*N*,*N*-diisopropylethylamine
DMSO	=	dimethylsulfoxide
EtOAc	=	ethyl acetate
h	=	hour(s)
HATU	=	1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HPLC	=	high performance liquid chromatography
L	=	litre
LC	=	liquid chromatography
LiHMDS	=	lithium bis(trimethylsilyl)amide
MeCN	=	acetonitrile
min	=	minute(s)
MS	=	mass spectrometry
NMR	=	nuclear magnetic resonance
Rt or RT	=	room temperature
SFC	=	supercritical fluid chromatography
T3P	=	propylphosphonic anhydride
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
UPLC	=	ultra performance liquid chromatography

Prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, *iso*, and tertiary.

SYNTHESIS OF INTERMEDIATES

Intermediate 1: methyl (*S*)-2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate hydrochloride



Intermediate 1

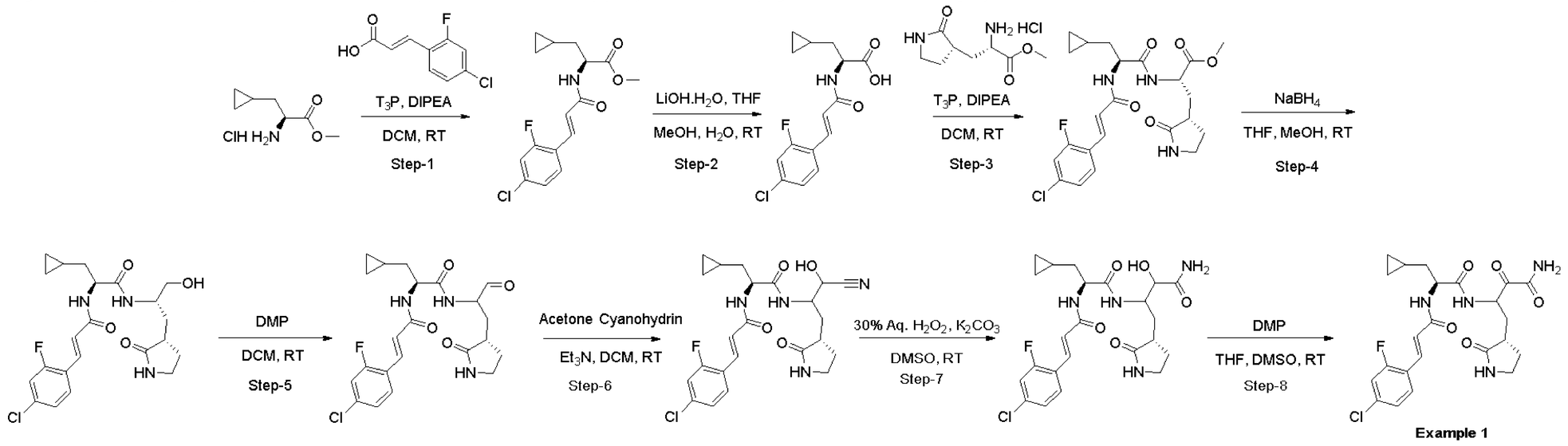
Step 1: To a suspension of dimethyl (*tert*-butoxycarbonyl)-*L*-glutamate (CAS No. 59279-60-6, 250 g, 0.908 mol) in THF (2500 mL) at -78 °C, LiHMDS (1M in THF, 1997 mL, 1.997 mol) was added dropwise and the resulting reaction mixture was stirred at -78 °C for 1 h followed by the addition of bromoacetonitrile (76.5 mL, 1.086 mol) at the same temperature. The resulting reaction mixture was stirred at -78 °C for 3 h; after the complete disappearance of the starting material as monitored by TLC, the reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (2 L) at -78 ℃ and then warmed to rt. The resulting mixture was extracted with EtOAc (2 x 2000 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography using silica gel (100-200 mesh), eluting with 0-20% EtOAc in petroleum-ether, yielded (2*S*,4*R*)-2-((*tert*-butoxycarbonyl)amino)-4-(cyanomethyl)pentanedioate as a pale-yellow gum (207 g, 0.65 mol). The reaction was performed in 5 batches on 50 g scale.
LCMS (Method C): m/z 337.1 (M+Na), at 1.93 min.
^{1}H NMR: (300 MHz, DMSO-d_6) δ 7.36 (d, J=8.1 Hz, 1H), 4.10-4.05 (m, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 2.87-2.73 (m, 3H), 2.05-1.99 (m, 2 H), 1.39 (s, 9H).

Step 2: To a stirred suspension of (2*S*,4*R*)-2-((*tert*-butoxycarbonyl)amino)-4-(cyanomethyl)pentanedioate (207 g, 0.659 mol) in MeOH (2 L) at 0 °C was added $CoCl_2.6H_2O$ (78.1 g, 0.329 mol) followed by the portion wise addition of $NaBH_4$ (149.6 g, 3.955 mol) during 30 min and the resulting reaction mixture was stirred at rt for 15 h. After completion of reaction as monitored by TLC, the reaction mixture was concentrated *in vacuo*, 20% MeOH in DCM (3 L) and H_2O (2 L) were added, and the mixture stirred for 10 min. The resulting suspension was filtered through celite and rinsed with 20% MeOH in DCM (2 L). The filtrate was transferred to a separating funnel, the organic layer was separated, washed with brine solution (2 L), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography using silica gel (100-200 mesh), eluting with 0-100% EtOAc in petroleum ether yielded methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate as a pale yellow solid (92 g, 0.32 mol).
LCMS (Method C): m/z 187.2 (M+H-100), at 1.34 min.
^{1}H NMR: (300 MHz, DMSO-d_6) δ 7.64 (s, 1H), 7.42 (d, J=7.8 Hz, 1H), 4.06-4.02 (m, 1H), 3.69 (s, 3H), 3.16-3.08 (m, 2H), 2.32-2.21 (m, 1H), 2.16-2.11 (m, 1H), 2.03-1.93 (m, 1H), 1.69-1.66 (m, 2 H), 1.33 (s, 9H).

Step 3: To a stirred solution of methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (10 g, 0.034 mol) in 1,4-dioxane (50 mL) at 0 °C was added 4 N HCl in dioxane (100 mL) and the resulting reaction mixture was stirred at rt for 3h. After completion of reaction as monitored by TLC, the supernatant layer was decanted from the reaction mixture and the gummy solid material remaining was dried *in vacuo* to yield methyl (*S*)-2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate hydrochloride (Intermediate 1, 8.5 g crude, 0.038 mol) as a yellow gum which was used without further purification.
LCMS (Method E): m/z 187.3 (M+H), at 0.82-1.19 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.67 (s, 3H), 7.98 (s, 1H), 4.19 (t, J=5.2 Hz, 1H), 3.76 (s, 3H), 3.21-3.18 (m, 2H), 2.53-2.51 (m, 1 H), 2.28-2.27 (m, 1H), 2.05-2.03 (m, 1H), 1.90-1.89 (m, 1 H), 1.70-1.65 (m, 1H).

SYNTHESIS OF EXAMPLES

Example 1: 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide



Step 1: To a stirred solution of methyl (*S*)-2-amino-3-cyclopropylpropanoate hydrochloride (CAS No. 206438-31-5, 17 g, 0.096 mol) and (*E*)-3-(4-chloro-2-fluorophenyl)acrylic acid (CAS No. 312693-55-3, 16 g, 0.08 mol) in DCM (10 mL), was added DIPEA (59 mL, 0.32 mol) followed by the addition of T3P in 50% EtOAc (101.7 mL, 0.16 mol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction as monitored by TLC, the reaction mass was partitioned between DCM (1 L) and 10% aqueous $NaHCO_3$ solution (1 L). The organic layer was separated, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-40% EtOAc in petroleum-ether yielded methyl (*S*,*E*)-2-(3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanoate as a white solid (18 g, 0.055 mol).

LCMS (Method D): m/z 326.1 (M+H), at 3.07 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.67 (d, J=7.2 Hz, 1H), 7.70 (t, J=8.4 Hz, 1H), 7.56-7.53 (m, 1H), 7.47 (d, J=16.0 Hz, 1H), 7.39-7.36 (m, 1H), 6.86 (d, J=15.6 Hz, 1H), 4.45-4.44 (m, 1H), 3.65 (s, 3H), 1.69-1.67 (m, 1H), 1.59-1.57 (m, 1H), 0.82-0.78 (m, 1H), 0.44-0.40 (m, 2H), 0.15-0.04 (m, 2H).

Step 2: To a stirred solution of methyl (*S*,*E*)-2-(3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanoate (18 g, 0.055 mol) in THF (200 mL), MeOH (20 mL) and H_2O (50 mL) at rt was added LiOH.H_2O (6.92 g, 0.165 mol). The resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated *in vacuo* and the residue obtained was dissolved in H_2O (300 mL), acidified to approximately pH 5 using 1.5 N HCl and then extracted with 10% MeOH in DCM (2 x 500 mL). The organic layers were separated, combined and dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield (*S*,*E*)-2-(3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanoic acid as an off-white solid (13 g, 0.044 mol).
LCMS (Method C): m/z 312.0 (M+H), at 2.06 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.83 (d, J=6.0 Hz, 1H), 7.77-7.73 (m, 1H), 7.51 (d, J=10.8 Hz, 1H), 7.41-7.34 (m, 2H), 7.03 (d, J=15.6 Hz, 1H), 4.04-4.00 (m, 1H), 1.65-1.52 (m, 2H), 0.82-0.78 (m, 1H), 0.30-0.29 (m, 2H), 0.04-0.01 (m, 2H).

Step 3: To a stirred solution of (*S*,*E*)-2-(3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanoic acid (10 g, 0.0365 mol) and methyl (*S*)-2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate hydrochloride (Intermediate 1, 8.5 g, 0.0365 mol) in DCM (150 mL), was added DIPEA (31.7 mL, 0.182 mol) followed by the addition of T3P (50% solution in EtOAc, 34.8 mL, 0.054 mol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction as monitored by TLC, the reaction mixture was partitioned between DCM (500 mL) and 10% aqueous $NaHCO_3$ solution (500 mL). The organic layer was separated, washed with 10% aqueous $NaHCO_3$ solution (500 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-90% EtOAc in petroleum-ether yielded methyl (*S*)-2-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate as an off-white solid (9.2 g, 0.019 mmol).
LCMS (Method C): m/z 480.2 (M+H), at 1.81 min.
^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.58 (d, J=7.8 Hz, 1H), 8.42 (d, J=7.8 Hz, 1H), 7.71-7.65 (m, 2H), 7.56-7.52 (m, 1H), 7.46-7.41 (m, 1H), 7.39-7.36 (m, 1H), 6.89 (d, J=15.9 Hz, 1H), 4.50-4.35 (m, 2H), 3.62 (s, 3H), 3.15-3.09 (m, 2H), 2.28-2.28 (m, 1H), 2.09-2.03 (m, 2H), 1.65-1.49 (m, 4H), 0.80-0.79 (m, 1H), 0.39-0.38 (m, 2H), 0.10-0.09 (m, 2H).

Step 4: To a stirred solution of methyl (*S*)-2-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (9.2 g, 0.019 mol) in THF (100 mL), was added MeOH (30 mL) followed by the addition of sodium borohydride (1.45 g, 0.038 mol) portion wise at 0 °C. The resulting reaction mixture was stirred at rt for 16 h. After the completion of reaction as monitored by TLC, the reaction mixture was partitioned between 20% MeOH in DCM (500 mL) and H_2O (500 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-6% MeOH in DCM yielded (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((*S*)-3-cyclopropyl-1-(((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopropan-2-yl)acrylamide as an off-white solid (6.4 g, 0.014 mol).
LCMS (Method C): m/z 452.2 (M+H), at 1.58 min.
^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.39 (d, J=8.1 Hz, 1H), 7.83 (d, J=8.7 Hz, 1H), 7.68-7.65 (m, 1H), 7.55-7.46 (m, 2H), 7.41-7.36 (m, 2H), 6.90 (d, J=15.9 Hz, 1H), 4.65 (t, J=5.7 Hz, 1H), 4.44-4.42 (m, 1H), 3.82-3.72 (m, 1H), 3.26-3.06 (m, 4H), 2.27-2.18 (m, 2H), 1.78 (t, J=11.7

Hz, 1H), 1.60-1.57 (m, 2H), 1.47-1.39 (m, 2H), 0.80-0.79 (m, 1H), 0.38-0.37 (m, 2H), 0.11-0.08 (m, 2H).

Step 5: To a stirred solution of (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((*S*)-3-cyclopropyl-1-(((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-1-oxopropan-2-yl)acrylamide (4.5 g, 9.95 mmol) in DCM (100 mL), was added Dess-Martin periodinane (6.34 g, 14.9 mmol) portion wise at rt. The resulting reaction mixture was stirred at rt for 1 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution (200 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-6% MeOH in DCM yielded (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((2*S*)-3-cyclopropyl-1-oxo-1-((1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)propan-2-yl)acrylamide as an off-white solid (4.4 g, 9.77 mmol) as a mixture of two diastereomers.

LCMS (Method E): m/z 450.0 (M+H), at 1.78-1.96 min.

Chiral SFC analysis (Method 2): 1.73 & 2.01 min (48.8% & 45.0%)

^{1}H NMR: (300 MHz, DMSO-d_6) δ 9.43 (s, 0.5H), 8.63 (d, J=7.6 Hz, 0.5H), 8.50 (d, J=7.6 Hz, 0.5H), 8.38 (d, J=7.6 Hz, 0.5H), 7.69-7.65 (m, 2H), 7.56-7.53 (m, 2H), 7.47-7.37 (m, 2H), 6.93-6.88 (m, 1H), 4.51-4.41 (m, 1H), 4.38-4.31 (m, 0.5H), 4.20-4.17 (m, 0.5H), 3.21-3.12 (m, 3H), 2.25-2.15 (m, 1.5H), 1.91-1.85 (m, 1.5H), 1.69-1.51 (m, 3H), 0.81-0.70 (m, 1H), 0.42-0.39 (m, 2H), 0.10-0.09 (m, 2H).

Step 6: To a stirred solution of (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((2*S*)-3-cyclopropyl-1-oxo-1-((1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)propan-2-yl)acrylamide (4.4 g, 9.7 mmol) in DCM (40 mL) at rt was added triethylamine (2.75 mL, 19.5 mmol) followed by acetone cyanohydrin (1.66 mL, 19.5 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 50 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM yielded (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((2*S*)-1-((1-cyano-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)acrylamide as an off-white solid (2.7 g, 5.66 mmol).

LCMS (Method E): m/z 450.1 (M-CN), at 1.79-1.96 min.

^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.37-8.07 (m, 2H), 7.60-7.24 (m, 5H), 6.82-6.74 (m, 1H), 6.64-6.55 (m, 1H), 4.46-4.22 (m, 2H), 3.91-3.85 (m, 1H), 3.15-2.93 (m, 2H), 2.33-2.23 (m, 1H), 2.02-1.71 (m, 2H), 1.52-1.31 (m, 4H), 0.71-0.54 (m, 1H), 0.29-0.27 (m, 2H), 0.15-0.09 (m, 2H).

Step 7: To a stirred solution of (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((2*S*)-1-((1-cyano-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)acrylamide (2.7 g, 5.6 mmol) in DMSO (30 mL) was added K_2CO_3 (2.34 g, 16.9 mmol) followed by the addition of 30% aqueous H_2O_2 solution (6.4 mL, 56.6 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction as monitored by TLC, the reaction mixture was partitioned between 10% MeOH in DCM (100 mL) and brine (100 mL). The aqueous layer was further extracted with 10% MeOH in DCM (3 x 200 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-10% MeOH in DCM yielded 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-hydroxy-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide as an off-white solid (960 mg, 1.93 mmol).

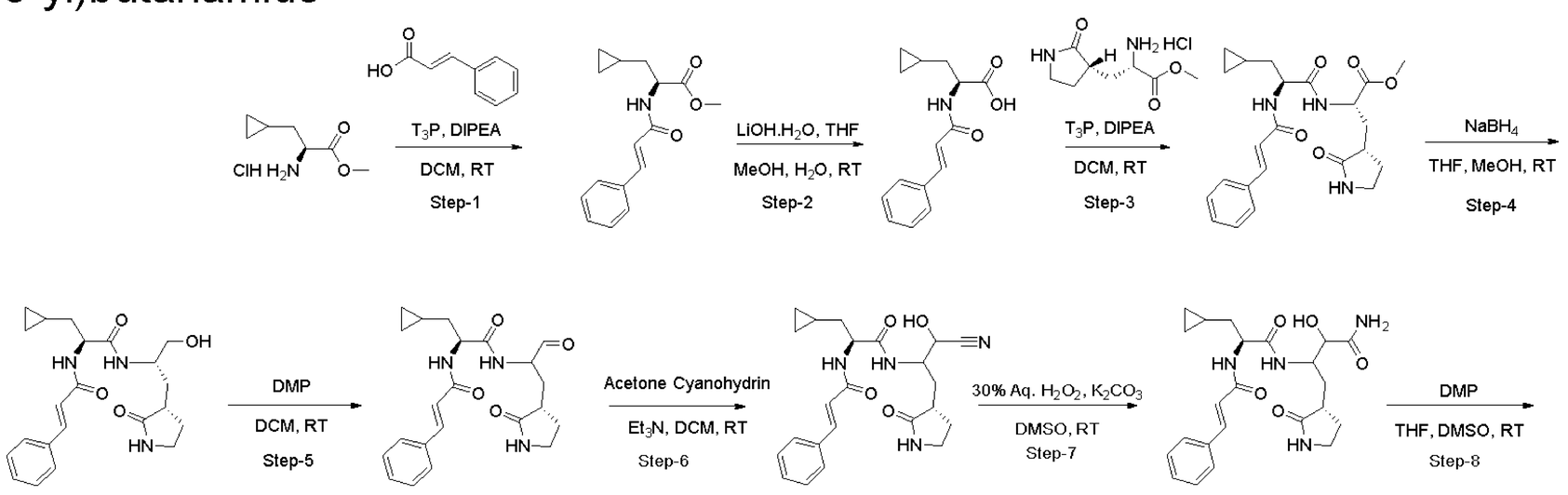
LCMS (Method E): m/z 495.0 (M+H), at 1.78 min.

^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.43 (d, J=7.6 Hz, 1H), 7.71-7.23 (m, 8H), 6.90 (d, J=21.2 Hz, 1H), 5.66 (d, J=7.6 Hz, 1H), 4.49-4.41 (m, 1H), 4.11-4.09 (m, 1H), 3.85-3.83 (m, 1H), 3.12-3.04 (m, 2H), 2.27-2.12 (m, 4H), 1.60-1.37 (m, 3H), 0.80-0.79 (m, 1H), 0.38-0.37 (m, 2H), 0.11-0.08 (m, 2H).

Step 8: To a stirred solution of 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-hydroxy-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide (960 mg, 1.93

mmol) in DCM (40 mL) and DMSO (10 mL) at rt was added Dess-Martin periodinane (1.22 g, 2.895 mmol). The resulting reaction mixture was stirred at rt for 1 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with 10% aqueous $NaHCO_3$ solution (200 mL) and extracted with EtOAc (200 mL). The organic layer was separated, washed with 10% aqueous $NaHCO_3$ solution (150 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 50 g silica SNAP cartridge (230-400 mesh), eluting with 0-10% MeOH in DCM yielded 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide as an off-white solid (Example 1, 400 mg, 0.811 mmol).
LCMS (Method C): m/z 493.1 (M+H), at 1.21-1.44 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.61 (d, J=7.6 Hz, 0.5H), 8.43-8.41 (m, 1H), 8.04-8.09 (m, 0.6H), 7.79-7.71 (m, 0.6H), 7.69-7.66 (m, 1.7H), 7.56-7.42 (m, 3.9H), 7.39-7.36 (m, 0.9H), 6.89 (d, J=16.0 Hz, 1H), 6.12 (d, J=40.8 Hz, 0.7H), 5.15-5.05 (m, 0.5H), 4.61-4.45 (m, 1H), 4.05-4.01 (m, 0.5H), 3.15-3.12 (m, 2H), 2.26-2.16 (m, 2H), 1.82-1.53 (m, 5H), 0.79-0.73 (m, 1H), 0.40-0.36 (m, 2H), 0.13-0.09 (m, 2H).

Example 2: 3-((*S*)-2-cinnamamido-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide



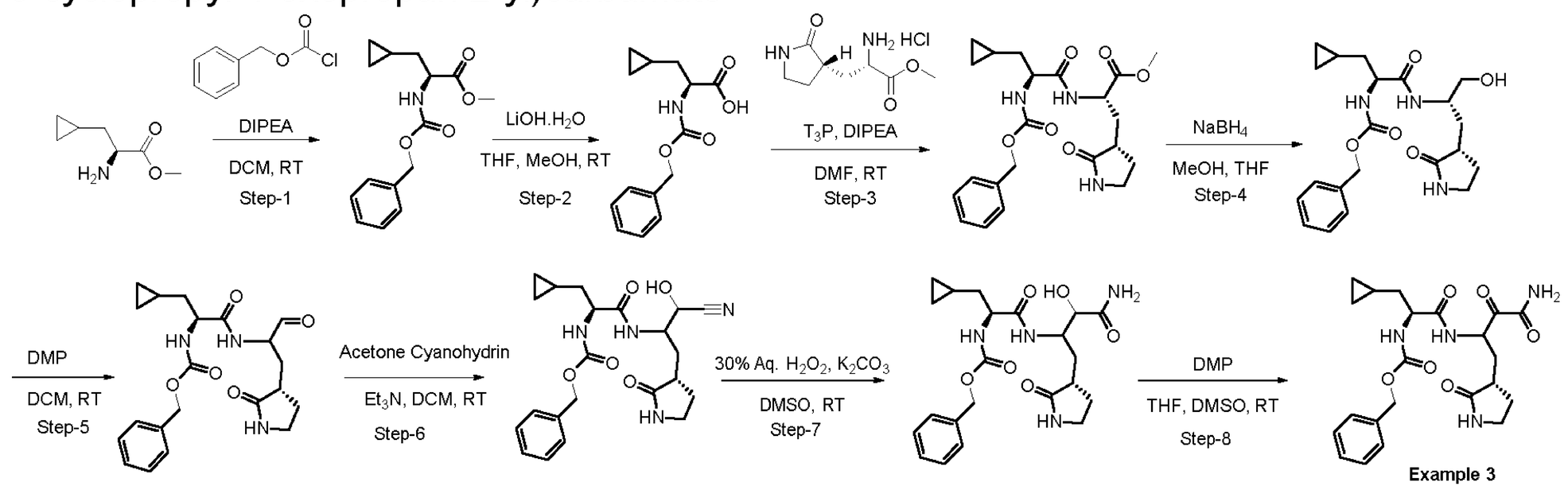
Example 2

Step 1: To a stirred solution of methyl (*S*)-2-amino-3-cyclopropylpropanoate hydrochloride (CAS No. 206438-31-5, 3.34 g, 18.57 mmol) and cinnamic acid (CAS No. 140-10-3, 2.75 g, 18.57 mmol) in DCM (40 mL), was added DIPEA (14 mL, 77.35 mmol) followed by the addition of T3P in 50% EtOAc (14.7 mL, 23.20 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction as monitored by TLC, the reaction mixture was partitioned between DCM (300 mL) and 10% aqueous $NaHCO_3$ solution (300 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-40% EtOAc in petroleum-ether yielded methyl (*S*)-2-cinnamamido-3-cyclopropylpropanoate as an off-white solid (4.40 g, 16.1 mmol).
LCMS (Method C): m/z 274.1 (M+H), at 2.10 min.
^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.52 (d, J=7.2 Hz, 1H), 7.58 (d, J=6.3 Hz, 2H), 7.48-7.39 (m, 4H), 6.75 (d, J=15.9 Hz, 1H), 4.42 (q, J=5.7 Hz, 1H), 3.64 (s, 3H), 1.71-1.54 (m, 2H), 0.82-0.77 (m, 1H), 0.43-0.41 (m, 2H), 0.16-0.03 (m, 2H).

Step 2: To a stirred solution of methyl (*S*)-2-cinnamamido-3-cyclopropylpropanoate (4.0 g, 14.63 mmol) in 1,4-Dioxane (50 mL), MeOH (10 mL) and H_2O (10 mL) at rt was added $LiOH.H_2O$ (1.23 g, 29.26 mmol). The resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction as monitored by TLC, the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in H_2O (100 mL), acidified to approximately pH 5 using 1.5 N HCl and then extracted with 20% MeOH in DCM (150 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield (*S*)-2-cinnamamido-3-cyclopropylpropanoic acid as an off-white solid (3.30 g, 12.7 mmol).
LCMS (Method B): m/z 260.0 (M+H), at 2.10 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 8.39 (d, J=8.0 Hz, 1H), 7.59-7.57 (m, 2H), 7.47-7.39 (m, 4H), 6.78 (d, J=15.6 Hz, 1H), 4.40 (t, J=2.8 Hz, 1H), 1.66-1.59 (m, 2H), 0.81-0.81 (m, 1H), 0.44-0.41 (m, 2H), 0.17-0.08 (m, 2H).

Steps 3-8: The title compound, Example 2, 3-((*S*)-2-cinnamamido-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide (25 mg, 0.079 mmol) was prepared from Step 2 product (3.30 g, 12.7 mmol) and Intermediate 1 (2.01 g, 10.7 mmol) over steps 3-8 using the procedures detailed for Example 1.
LCMS (Method K): m/z 441.2 (M+H), at 1.60-1.71 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.60 (d, J=7.2 Hz, 0.5H), 8.26-8.24 (m, 1H), 8.03 (s, 0.5H), 7.78 (s, 0.5H), 7.68-7.51 (m, 3H), 7.45-7.38 (m, 4H), 7.30-7.21 (m, 1H), 6.82-6.77 (m, 1H), 6.16-6.07 (m, 0.5H), 5.15-5.05 (m, 0.5H), 4.61-4.45 (m, 1H), 4.05-4.01 (m, 0.5H), 3.15-3.12 (m, 2H), 2.19-2.12 (m, 2H), 1.95-1.53 (m, 5H), 0.81-0.70 (m, 1H), 0.42-0.37 (m, 2H), 0.14-0.09 (m, 2H).

Example 3: benzyl ((2*S*)-1-((4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate



Step 1: To a stirred solution of methyl (*S*)-2-amino-3-cyclopropylpropanoate (CAS No. 732231-41-3, 1 g, 6.98 mmol) in DCM (15 mL), was added DIPEA (3.6 mL, 20.95 mmol) followed by the addition of benzyl carbonochloridate (1.42 g, 8.38 mmol) at 0 °C. The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction, as monitored by TLC, the reaction mass was partitioned between DCM (20 mL) and H_2O (50 mL). The organic layer was separated, washed with 10% aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-20% EtOAc in petroleum-ether yielded methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-cyclopropylpropanoate as an off-white solid (1.1 g, 3.96 mmol).
LCMS (Method A): m/z 278.2 (M+H), at 2.39 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.40-7.30 (m, 6H), 5.17 (s, 2H), 4.50-4.49 (m, 1H), 3.63 (s, 3H), 1.65-1.61 (m, 1H), 1.48-1.46 (m, 1H), 0.78 (s, 1H), 0.42-0.37 (m, 2H), 0.13-0.10 (m, 1H), 0.02-0.01 (m, 1H)

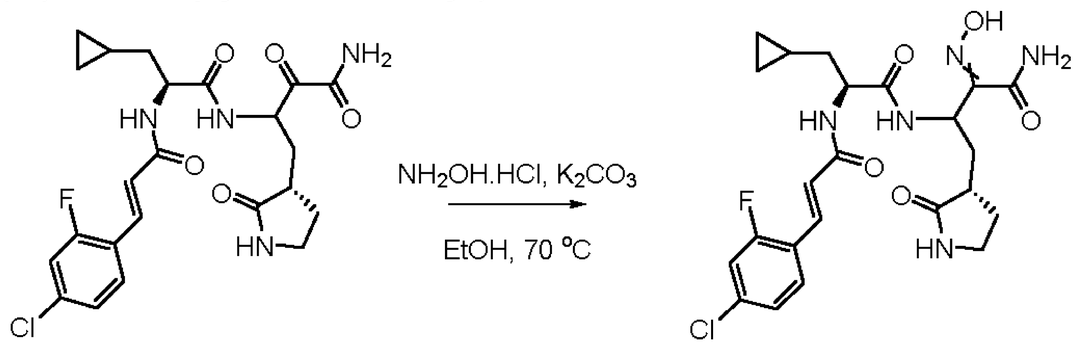
Step 2: To a stirred solution of methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-cyclopropylpropanoate (1.1 g, 3.96 mmol) in THF (10 mL) was added MeOH (2 mL) and H_2O (5 mL) followed by the addition of LiOH.H_2O (0.142 g, 5.94 mmol). The resulting reaction mixture was stirred at rt for 30 min. After completion of the reaction, as monitored by TLC, the reaction mixture was acidified to approximately pH 5 with 1.5 N HCl (5 mL) and partitioned between EtOAc (50 mL) and H_2O (50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM yielded methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-cyclopropylpropanoate as an off-white solid (1.0 g, 3.79 mmol).
LCMS (Method C): m/z 264.1 (M+H), at 1.77 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.58 (d, J=8.0 Hz, 1H), 7.40-7.22 (m, 6H), 5.13 (s, 2H), 4.03-3.97 (m, 1H), 1.63-1.59 (m, 1H), 1.50-1.47 (m, 1H), 0.79 (t, J=7.2 Hz, 1H), 0.42-0.36 (m, 2H), 0.16-0.01 (m, 2H)

Steps 3-8: The title compound, Example 3, benzyl ((2*S*)-1-((4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate (5 mg, 0.015 mmol) was prepared from Step 2 product (1.0 g, 3.79 mmol) and Intermediate 1 (0.84 g, 4.55 mmol) over steps 3-8 using the procedures detailed for Example 1.

LCMS (Method A): m/z 445.1 (M+H), at 1.95-2.09 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.43 (d, J=7.2 Hz, 0.5H), 8.01-7.96 (m, 1H), 7.77 (s, 0.5H), 7.65 (s, 0.5H), 7.59 (s, 0.5H), 7.49-7.47 (m, 1H), 7.37-7.31 (m, 5.5H), 7.04 (s, 0.5H), 5.08-5.03 (m, 2.5H), 4.31-4.28 (m, 0.5H), 4.15-4.05 (m, 1H), 3.15-3.05 (m, 2 H), 2.29-1.79 (m, 3H), 1.64-1.40 (m, 4H), 0.75-0.71 (m, 1H), 0.40-0.34 (m, 2H), 0.13-0.07 (m, 2H).

Example 4: 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-(hydroxyimino)-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide



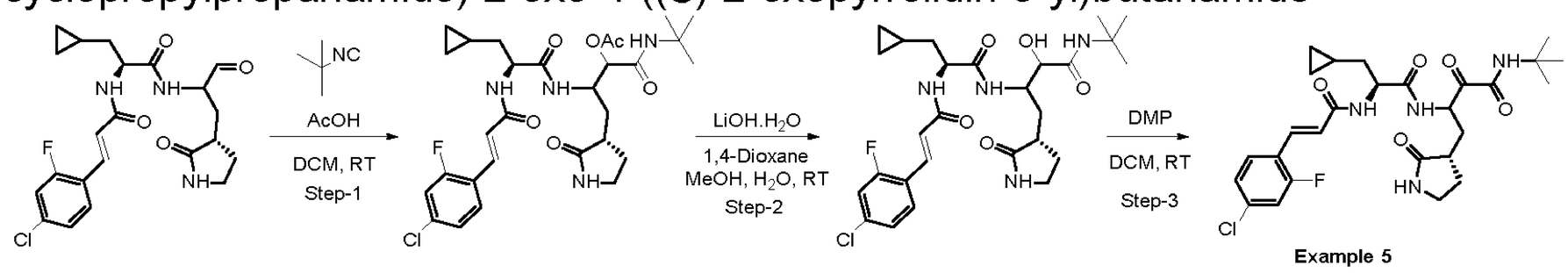
Example 1 **Example 4**

To a stirred solution of 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide (Example 1, 0.1 g, 0.20 mmol) in EtOH (10 mL), was added K_2CO_3 (55 mg, 0.4 mmol) and hydroxylamine hydrochloride (28 mg, 0.4 mmol) at rt. The resulting reaction mixture was stirred at 70 °C for 3 h. After completion of the reaction, as monitored by UPLC-MS, the reaction mixture was filtered and rinsed with EtOH (5 mL). The filtrate was concentrated *in vacuo* and purified by mass directed preparative HPLC (Method F) to yield the title compound, Example 4, 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-(hydroxyimino)-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide as a mixture of isomers (off-white solid, 10 mg, 0.019 mmol).

LCMS (Method C): m/z 508.0 (M+H), at 2.04 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.51-8.50 (m, 1H), 8.02-8.00 (m, 1H), 7.70-7.68 (m, 1H), 7.59-7.56 (m, 2H), 7.54-7.31 (m, 4H), 6.88 (d, J=16.0 Hz, 1H), 5.47-5.45 (m, 1H), 4.42-4.39 (m, 1H), 3.15-3.08 (m, 2H), 2.26-2.23 (m, 3H), 1.55-1.51 (m, 4H), 0.79-0.74 (m, 1H), 0.39-0.35 (m, 2H), 0.12-0.10 (m, 2H).

Example 5: *N*-(*tert*-butyl)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide



Example 1, Step 5 product **Example 5**

Step 1: To a stirred solution of (*E*)-3-(4-chloro-2-fluorophenyl)-*N*-((2*S*)-3-cyclopropyl-1-oxo-1-((1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)amino)propan-2-yl)acrylamide (Example 1, step 5 product, 430 mg, 0.955 mmol) in DCM (5 mL) at 0 °C was added AcOH (0.060 mL, 1.051 mmol) followed by *tert*-butylisocyanide (0.12 mL, 1.051 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction, as monitored by TLC, the reaction mass was concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM yielded 1-(*tert*-butylamino)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-1-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl acetate as an off-white solid (300 mg, 0.50 mmol).

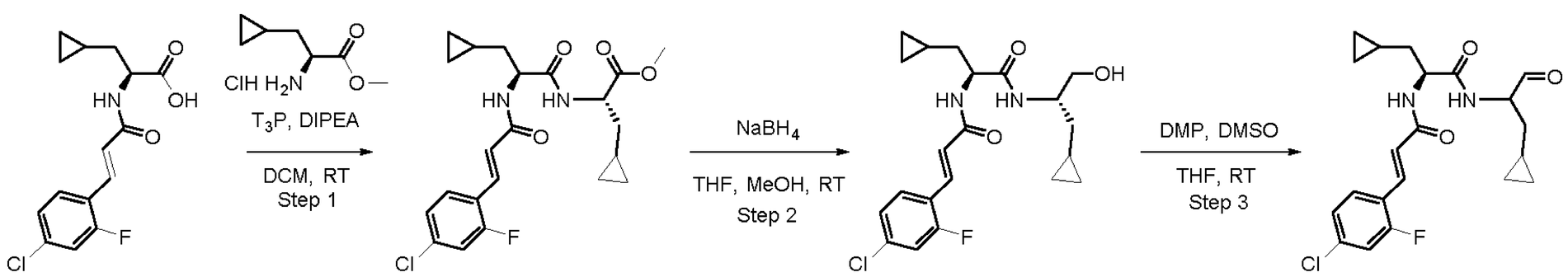
LCMS (Method C): m/z 593.2 (M+H), at 2.34 min.

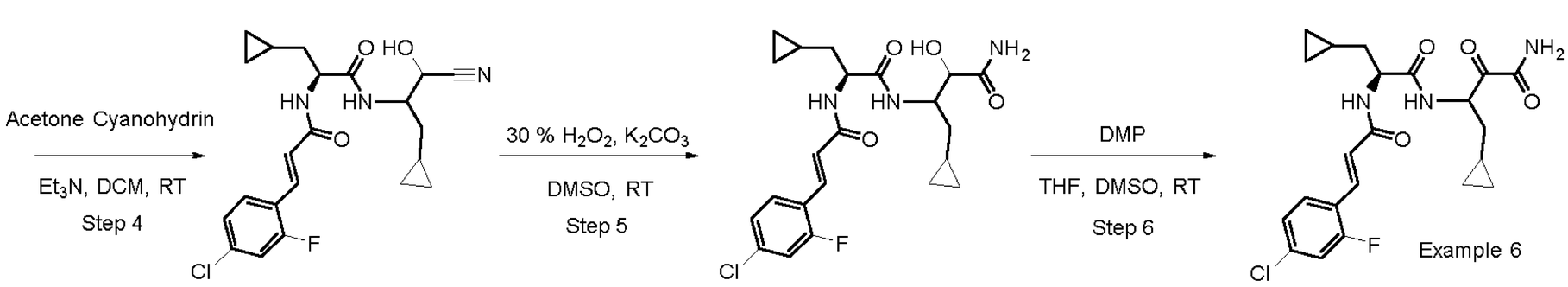
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.43-8.37 (m, 1H), 8.01-7.84 (m, 1H), 7.69-7.66 (m, 1H), 7.57-7.46 (m, 3H), 7.42-7.36 (m, 2H), 6.91-6.87 (m, 1H), 4.92-4.76 (m, 1H), 4.48-4.47 (m, 1H), 4.35-4.21 (m, 1H), 3.12-3.05 (m, 2H), 2.21-2.19 (m, 2H), 2.18-2.11 (m, 1H), 2.10-2.06 (m, 3H), 2.00-1.93 (m, 1H), 1.56-1.45 (m, 3H), 1.25-1.18 (m, 9H), 0.85-0.65 (m, 1H), 0.41-0.37 (m, 2H), 0.12-0.08 (m, 2H).

Step 2: To a stirred solution of 1-(*tert*-butylamino)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-1-oxo-4-((S)-2-oxopyrrolidin-3-yl)butan-2-yl acetate (300 mg, 0.629 mmol) in 1,4-Dioxane (3 mL), MeOH (1 mL) and H_2O (2 mL) was added LiOH.H_2O (52.2 mg, 1.25 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction, as monitored by TLC, the reaction mass was partitioned between EtOAc (25 mL) and H_2O (25 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM yielded *N*-(*tert*-butyl)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-hydroxy-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide as an off-white solid (200 mg, 0.36 mmol).
LCMS (Method A): m/z 551.2 (M+H), at 2.07 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.45-8.43 (m, 1H), 7.73-7.67 (m, 1H), 7.56-7.37 (m, 5H), 7.02 (s, 1H), 6.98-6.86 (m, 1H), 5.77-5.74 (m, 1H), 4.46-4.45 (m, 1H), 4.19-4.01 (m, 1H), 3.77-3.75 (m, 1H), 3.29-3.05 (m, 2H), 2.34-2.13 (m, 2H), 2.05-1.95 (m, 1H), 1.63-1.53 (m, 2H), 1.49-1.39 (m, 1H), 1.48-1.45 (m, 10H), 0.79-0.69 (m, 1H), 0.46-0.29 (m, 2H), 0.15 – 0.10 (m, 2H).

Step 3: To a stirred solution of *N*-(*tert*-butyl)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-hydroxy-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide (200 mg, 0.36 mmol) in DCM (10 mL) and DMSO (3 mL) was added Dess-Martin periodinane (230 mg, 0.54 mmol) portion wise at rt. The resulting reaction mixture was stirred at rt for 1 h. After the completion of the reaction, as monitored by TLC, 10% aqueous $NaHCO_3$ solution (50 mL) was added and the mixture extracted with DCM (2 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-6% MeOH in DCM yielded *N*-(*tert*-butyl)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide as an off-white solid (Example 5, 80 mg, 0.15 mmol).
LCMS (Method C): m/z 547.1 (M-H), at 2.19-2.62 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.58-8.56 (m, 1H), 8.42-8.40 (m, 1H), 7.92 (s, 1H), 7.70-7.66 (m, 2H), 7.56-7.53 (m, 1H), 7.46-7.42 (m, 1H), 7.39-7.36 (m, 1H), 6.91-6.87 (m, 1H), 5.01-5.10 (m, 1H), 4.54-4.52 (m, 1H), 3.18-3.12 (m, 2H), 2.35-2.49 (m, 1H), 2.37-2.34 (m, 1H), 2.08-1.92 (m, 1H), 1.72-1.61 (m, 1H), 1.61-1.50 (m, 3H), 1.39-1.20 (m, 9H), 0.85-0.70 (m, 1H), 0.42-0.37 (m, 2H), 0.14-0.09 (m, 2H).

Example 6: 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopropyl-2-oxobutanamide



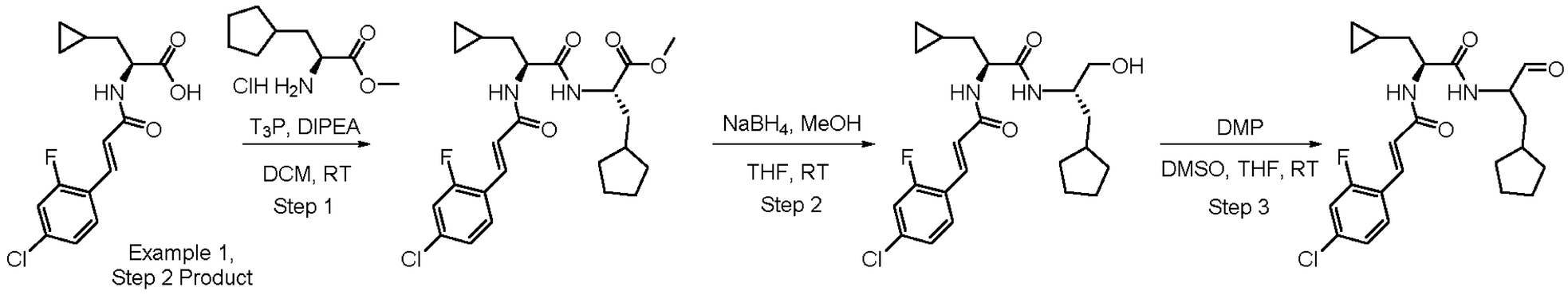


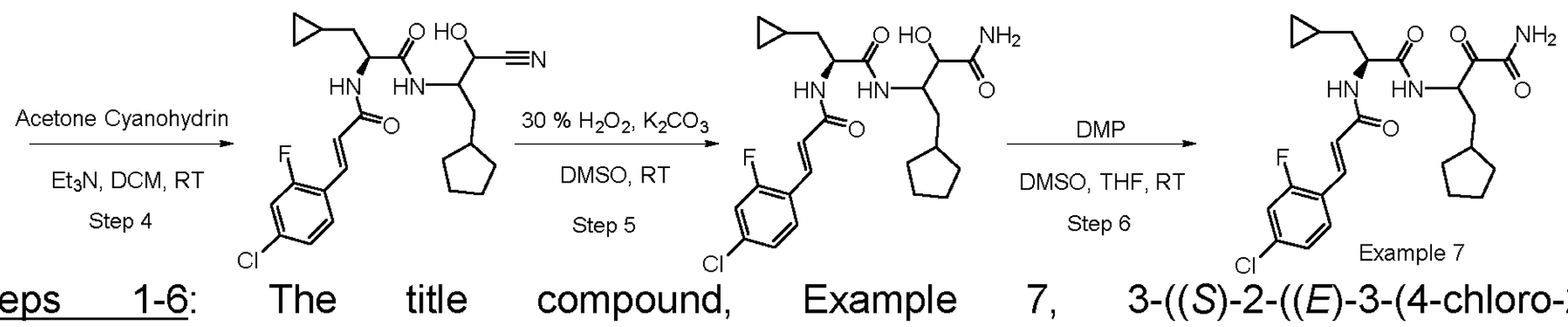
Steps 1-6: The title compound, Example 6, 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopropyl-2-oxobutanamide (25 mg, 0.05 mmol, white solid) was prepared from (*S*,*E*)-2-(3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanoic acid (Example 1, Step 2 product, 2.0 g, 6.41 mmol) and methyl (*S*)-2-amino-3-cyclopropylpropanoate hydrochloride (CAS No. 206438-31-5, 1.38 g, 7.69 mmol) over steps 1-6 using the procedures detailed for Example 1. Step 3 used THF/DMSO (2:1, 15 mL) as solvent.

LCMS (Method C): m/z 450.1 (M+H), at 1.79-2.06 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.50-8.39 (m, 2H), 8.01 (d, J=4.8 Hz, 1H), 7.74-7.66 (m, 2H), 7.56-7.53 (m, 1H), 7.48-7.43 (m, 1H), 7.39-7.36 (m, 1H), 6.94-6.88 (m, 1H), 5.15-5.10 (m, 1H), 4.66-4.58 (m, 1H), 1.67-1.47 (m, 4H), 0.84-0.74 (m, 2H), 0.42-0.35 (m, 4H), 0.13-0.02 (m, 4H).

Example 7: 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopentyl-2-oxobutanamide



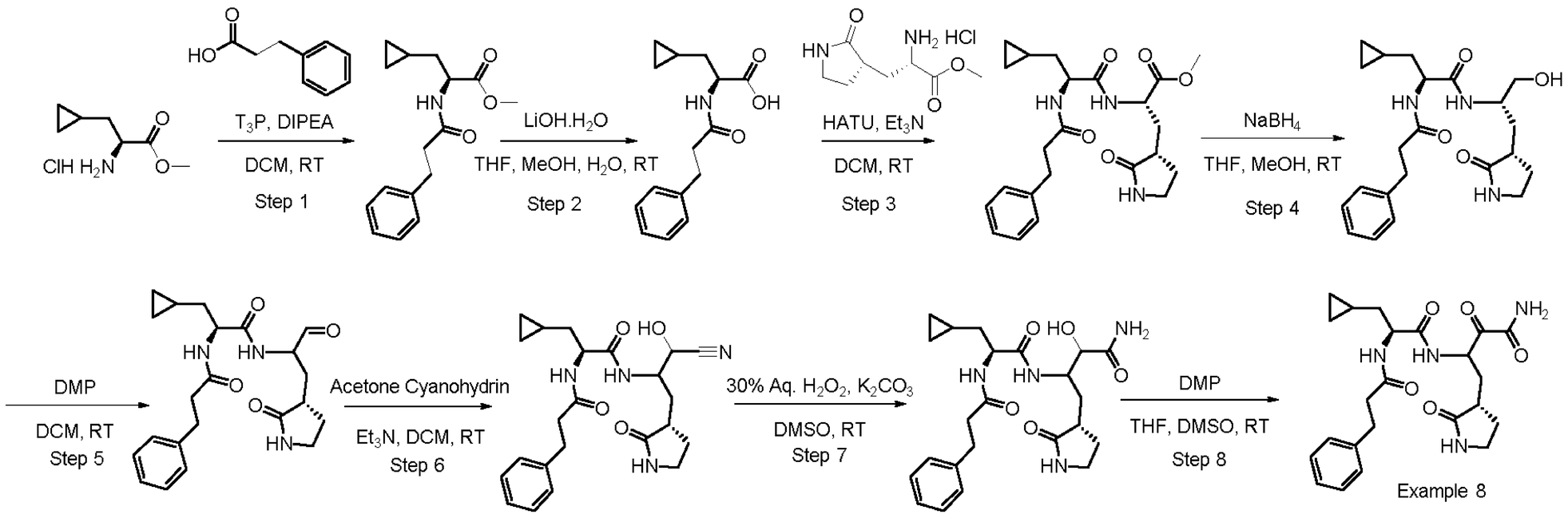


Steps 1-6: The title compound, Example 7, 3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopentyl-2-oxobutanamide (10 mg, 0.02 mmol, off-white solid) was prepared from (*S*,*E*)-2-(3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanoic acid (Example 1, Step 2 product, 1.0 g, 3.21 mmol) and methyl (*S*)-2-amino-3-cyclopentylpropanoate hydrochloride (CAS No. 1191996-99-2, 0.79 g, 3.85 mmol) over steps 1-6 using the procedures detailed for Example 1. Step 3 used THF/DMSO (10:1, 22 mL) as solvent.

LCMS (Method C): m/z 478.1 (M+H), at 2.00-2.28 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.48-8.34 (m, 2H), 8.02 (s, 1H), 7.76 (s, 1H), 7.70-7.65 (m, 1H), 7.56-7.53 (m, 1H), 7.45 (d, J=16.0 Hz, 1H), 7.39-7.36 (m, 1H), 6.93-6.88 (m, 1H), 5.05-5.05 (m, 1H), 4.60-4.51 (m, 1H), 1.90-1.44 (m, 11H), 1.15-1.09 (m, 2H), 0.87-0.76 (m, 1H), 0.42-0.36 (m, 2H), 0.12-0.07 (m, 2H).

Example 8: 3-((*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide



Step 1: To a stirred solution of methyl (*S*)-2-amino-3-cyclopropylpropanoate hydrochloride (CAS No. 206438-31-5, 2.38 g, 13.20 mmol) and 3-phenylpropanoic acid (2.01 g, 13.20 mmol) in DCM (30 mL) was added DIPEA (11.57 mL, 66.00 mmol) followed by T3P (50% in EtOAc, 12.68 mL, 19.90 mmol). The resulting reaction mixture was stirred at rt for 16 h. After completion of the reaction, as monitored by TLC, the reaction mixture was partitioned between DCM (100 mL) and 10% aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 100 g silica SNAP cartridge (230-400 mesh), eluting with 0-10% EtOAc in petroleum-ether yielded methyl (*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanoate as an off-white solid (2.12 g, 7.69 mmol). **LCMS (Method C):** m/z 276.1 (M+H), at 2.04 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.26-7.21 (m, 5H), 4.30-4.28 (m, 1H), 3.61 (s, 3H), 2.81-2.80 (m, 2H), 2.43-2.25 (m, 2H), 1.59-1.44 (m, 2H), 0.78-0.56 (m, 1H), 0.37-0.35 (m, 2H), 0.07-0.01 (m, 2H).

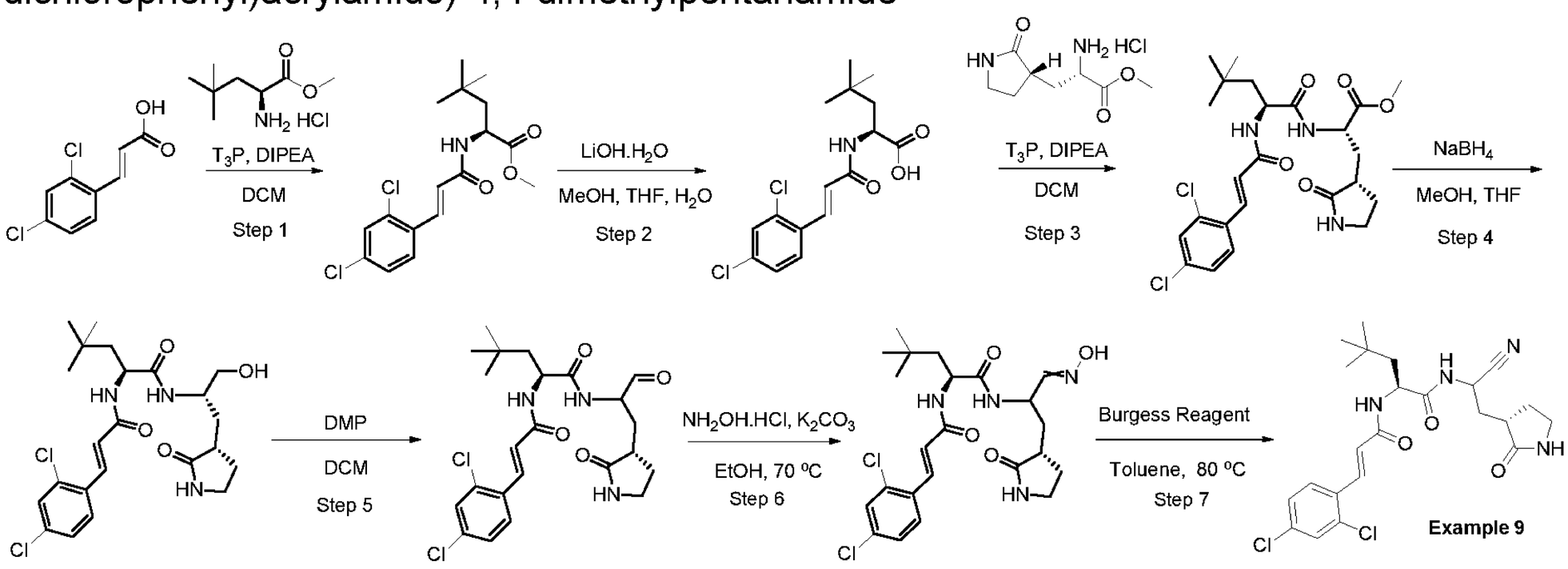
Step 2: To a stirred solution of methyl (*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanoate (2.12 g, 7.69 mmol) in 1,4-Dioxane (10 mL), MeOH (5 mL) and H_2O (5 mL) at rt was added $LiOH.H_2O$ (0.368 g, 15.3 mmol). The resulting reaction mixture was stirred at rt for 2 h. After completion of the reaction, as monitored by TLC, the reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in H_2O (100 mL), acidified with 1.5 N HCl to approximately pH 5 and extracted with 20% MeOH in DCM (150 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield (*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanoic acid as an off-white solid (1.90 g, 7.23 mmol) that was used without further purification.
LCMS (Method H): m/z 262.3 (M+H), at 1.50 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.50 (s, 1H), 8.13 (d, J=8.0 Hz, 1H), 7.28-7.17 (m, 5H), 4.25-4.24 (m, 1H), 2.84-2.70 (m, 2H), 2.56-2.31 (m, 2H), 1.56-1.46 (m, 2H), 0.81-0.65 (m, 1H), 0.52-0.35 (m, 2H), 0.15-0.09 (m, 2H).

Step 3: To a stirred solution of (*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanoic acid (1.90 g, 7.20 mmol) and methyl (*S*)-2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate hydrochloride (Intermediate 1, 1.35 g, 7.20 mmol) in DCM (10 mL) was added Et_3N (4.05 mL, 29.1 mmol) followed by HATU (4.14 g, 10.9 mmol). The resulting reaction mixture was stirred at rt for 16 h. After the completion of the reaction as monitored by TLC, the reaction mixture was partitioned between DCM (100 mL) and 10% aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, washed with saturated brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-2% MeOH

in DCM yielded methyl (*S*)-2-((*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate as an off-white solid (1.24 g, 2.88 mmol).
LCMS (Method A): m/z 430.3 (M+H), at 1.83 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.47-8.45 (m, 1H), 8.01-7.98 (m, 1H), 7.65 (s, 1H), 7.25-7.21 (m, 5H), 4.50-4.23 (m, 2H), 4.12-3.95 (m, 1H), 3.45-3.75 (m, 3H), 3.25-3.01 (m, 2H), 2.80-2.78 (m, 2H), 2.09-1.91 (m, 2H), 1.60-1.41 (m, 4H), 1.18 (t, J=9.2 Hz, 2H), 0.75-0.58 (m, 1H), 0.42-0.15 (m, 2H), 0.13-0.09 (m, 2H).

Steps 4-8: The title compound, Example 8, 3-((*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide (off-white solid, 20 mg, 0.045 mmol) was prepared from Step 3 product (1.24 g, 2.80 mmol) over steps 4-8 using the procedures detailed for Example 1. Example 8 was isolated after purification by preparative HPLC using Method B.
LCMS (Method C): m/z 443.1 (M+H), at 1.69-1.84 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.58-8.46 (m, 1H), 8.00-7.97 (m, 2H), 7.76 (s, 1H), 7.68 (s, 1H), 7.27-7.14 (m, 5H), 5.11-5.01 (m, 1H), 4.44-4.25 (m, 1H), 3.18-3.11 (m, 2H), 2.81 (t, J=8.0 Hz, 2H), 2.47-2.46 (m, 2H), 2.18-2.17 (m, 2H), 1.91-1.85 (m, 1H), 1.65-1.41 (m, 4H), 0.65-0.58 (m, 1H), 0.37-0.32 (m, 2H), 0.10-0.02 (m, 2H).

Example 9: (2*S*)-*N*-(1-Cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide



Step 1: To a stirred solution of (*E*)-3-(2,4-dichlorophenyl)acrylic acid (2.50 g, 11.5 mmol) and methyl (*S*)-2-amino-4,4-dimethylpentanoate hydrochloride (2.70 g, 13.8 mmol) in DCM (40 mL), was added DIPEA (6.00 mL, 34.6 mmol) followed by the addition of T3P (50% solution in EtOAc, 10.0 mL, 17.3 mmol). The reaction mixture was stirred at rt for 16 h, then partitioned between EtOAc (300 mL) and H_2O (200 mL). The phases were separated, the organic layer was washed with 10% aqueous $NaHCO_3$ solution (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 50 g silica SNAP cartridge (230-400 mesh), eluting with 0-8% EtOAc in Pet-ether gradient to afford methyl (*S*,*E*)-2-(3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanoate as a white solid (3.37 g, 9.40 mmol).
LCMS (Method C): m/z 357.8 (M+H), at 2.69 min.
^{1}H NMR: (300 MHz, DMSO-d_6) δ 8.66 (d, J=8.0 Hz, 1H), 7.75-7.66 (m, 3H), 7.53-7.50 (m, 1H), 6.76 (d, J=16.0 Hz, 1H), 4.50-4.45 (m, 1H), 3.65 (s, 3H), 1.76-1.57 (m, 2H), 0.92-0.90 (m, 9H).

Step 2: LiOH.H_2O (0.59 g, 14.1 mmol) was added to a solution of methyl (*S*,*E*)-2-(3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanoate (3.37 g, 9.40 mmol) in THF (40 mL), MeOH (5 mL) and H_2O (10 mL) and the mixture stirred at rt for 1 h. After concentration *in vacuo* the residue obtained was dissolved in H_2O (100 mL), acidified to approximately pH 5 using 1.5 N HCl and extracted with 20% MeOH in DCM (150 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield (*S*,*E*)-2-(3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanoic acid as a white solid (3.10 g, 9.00 mmol).

LCMS (Method C): m/z 344.0 (M+H), at 2.33 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 8.48 (d, J=8.4 Hz, 1H), 7.74-7.72 (m, 2H), 7.66 (d, J=15.6 Hz, 1H), 7.52-7.50 (m, 1H), 6.79 (d, J=15.6 Hz, 1H), 4.39-4.35 (m, 1H), 1.74-1.70 (m, 1H), 1.59-1.53 (m, 1H), 0.91 (s, 9H).

Step 3: To a stirred solution of (*S*,*E*)-2-(3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanoic acid (3.10 g, 9.00 mmol) and methyl (*S*)-2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate hydrochloride (Intermediate 1, 3.00 g, 13.5 mmol) in DCM (30 mL) was added DIPEA (4.70 mL, 27.2 mmol) followed by T3P (50% solution in EtOAc, 8.00 mL, 13.5 mmol) at 0°C. After stirring at rt for 16 h the reaction mixture was partitioned between EtOAc (150 mL) and H_2O (150 mL). and the organic layer was washed with 10% aqueous $NaHCO_3$ (100 mL) and saturated brine solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM yielded methyl (*S*)-2-((*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate as a pale yellow solid (1.50 g, 2.92mmol).
LCMS (Method C): m/z 511.7 (M+H), at 2.15 min.

Step 4: To a stirred solution of methyl (*S*)-2-((*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamido)-3-((*S*)-2-oxopyrrolidin-3-yl)propanoate (1.50 g, 2.92 mmol) in THF (20 mL) was added MeOH (2 mL) followed by $NaBH_4$ (166 mg, 4.39 mmol) portion wise at 0°C. After stirring at rt for 2 h the reaction mixture was quenched with brine solution (50 mL) and extracted with EtOAc (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain (*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-*N*-((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide as an off-white solid (1.2 g, 2.47 mmol).
LCMS (Method C): m/z 484.1 (M+H), at 1.68 min.

Step 5: Dess-Martin periodinane (1.57 g, 3.71 mmol) was added to a solution of (*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-*N*-((*S*)-1-hydroxy-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide (1.20 g, 2.47 mmol) in DCM (15 mL) added at 0°C. After stirring at rt for 1 h 10% aqueous $NaHCO_3$ solution (50 mL) and EtOAc (200 mL) were added and the phases were separated. The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-3% MeOH in DCM yielded (2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethyl-*N*-(1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)pentanamide as an off-white solid (0.75 g, 1.55 mmol).
LCMS (Method E): m/z 482.2 (M+H), at 1.90-2.10 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 9.41-9.38 (m, 1H), 8.65 (d, J=7.2 Hz, 1H), 8.51 (d, J=8.4 Hz, 1H), 7.79-7.63 (m, 3H), 7.53-7.50 (m, 2H), 6.83-6.78 (m, 1H), 4.51-4.50 (m, 1H), 4.48-4.30 (m, 1H), 3.21-3.09 (m, 2H), 2.50-2.41 (m, 1H), 2.34-2.26 (m, 1H), 2.13-2.12 (m, 3H), 1.72-1.49 (m, 2H), 0.93-0.91 (m, 9H).

Step 6: $NH_2OH.HCl$ (57 mg, 0.82 mmol) and K_2CO_3 (171 mg, 1.24 mmol) were added to a solution of (2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethyl-*N*-(1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)pentanamide (0.20 g, 0.41 mmol) in EtOH (10 mL). After stirring at 70°C for 16 h then reaction mixture was cooled to rt and partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM to yield (2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-*N*-(1-(hydroxyimino)-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide as an off-white solid 150 mg, 0.30 mmol).
LCMS (Method E): m/z 497.1 (M+H), at 2.09 min.

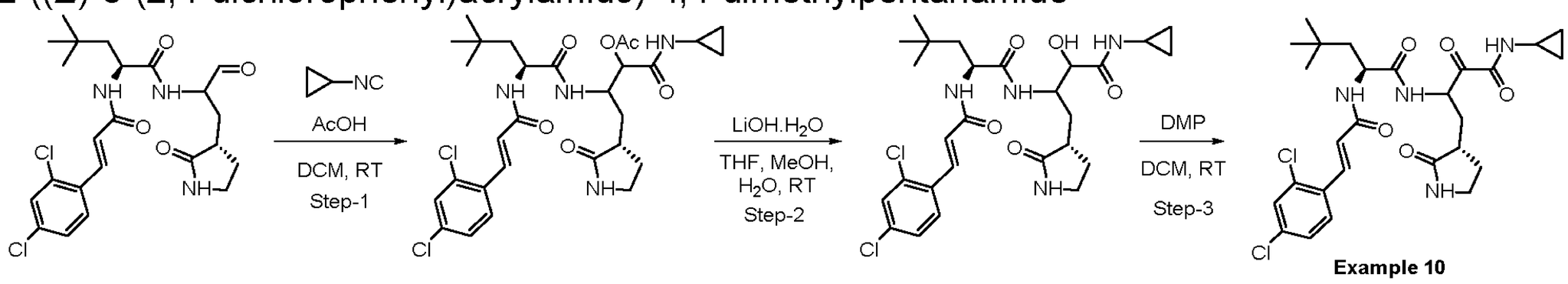
Step 7: Methyl *N*-(triethylammoniumsulfonyl)carbamate (0.071 g, 0.30 mmol) was added to a stirred solution of (2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-*N*-(1-(hydroxyimino)-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)-4,4-dimethylpentanamide (0.15 g, 0.30 mmol) in PhMe (50 mL) and the resulting reaction mixture was stirred at 80°C for 16 h. After partitioning between EtOAc (50 mL) and H_2O (50 mL) the organic phase was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude material was purified by gradient flash column chromatography (Biotage-Isolera) using a 10 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM, followed by mass directed preparative HPLC (Method B). Pure fractions were concentrated *in vacuo*, then partitioned between EtOAc (10 mL) and H_2O (10 mL). The organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo* and lyophilised to yield the title compound, Example 9, (2*S*)-*N*-(1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide as an off-white solid (10 mg, 0.02 mmol).

LCMS (Method C): m/z 479.1 (M+H), at 2.59 min.

Chiral SFC analysis (Method 2): 1.82 & 3.69 min (47.6% & 49.1%).

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.99 (d, J=8.0 Hz, 1H), 8.55 (d, J=8.4 Hz, 1H), 7.73-7.65 (m, 4H), 7.54-7.51 (m, 1H), 6.78 (d, J=15.6 Hz, 1H), 4.96-4.94 (m, 1H), 4.46-4.45 (m, 1H), 3.14-3.10 (m, 2H), 2.15-2.09 (m, 2H), 1.73-1.50 (m, 5H), 0.93 (s, 9H).

Example 10: (2*S*)-*N*-(4-(Cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide



Example 9, Step 5 product — Example 10

Step 1: AcOH (0.1 g, 1.65 mmol) followed by isocyanocyclopropane (55 mg, 0.82 mmol) were added to a stirred solution of (2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethyl-*N*-(1-oxo-3-((*S*)-2-oxopyrrolidin-3-yl)propan-2-yl)pentanamide (Example 9, Step 5 product, 0.40 g, 0.82 mmol) in DCM (15 mL). After stirring for 16 h at rt the reaction mixture was concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-5% MeOH in DCM yielded 1-(cyclopropylamino)-3-((*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamido)-1-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl acetate as an off-white solid (380 mg, 0.62 mmol).

LCMS (Method C): m/z 609.1 (M+H), at 1.91 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.40 (d, J=8.4 Hz, 1H), 8.08-8.03 (m, 2H), 7.89 (d, J=9.2 Hz, 1H), 7.72-7.63 (m, 3H), 7.57-7.50 (m, 1H), 6.81 (d, J=16.0 Hz, 1H), 5.76-5.66 (m, 1H), 4.76-4.74 (m, 1H), 4.74-4.68 (m, 1H), 3.27-3.12 (m, 2H), 2.12-2.05 (m, 4H), 2.00-1.92 (m, 3H), 1.54-1.49 (m, 4H), 0.92-0.89 (m, 9H), 0.63-0.57 (m, 2H), 0.44-0.42 (m, 2H).

Step 2: MeOH (3 mL) and H_2O (5 mL), followed by LiOH.H_2O (392 mg, 0.93 mmol) were added to a stirred solution of 1-(cyclopropylamino)-3-((*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamido)-1-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl acetate (380 mg, 0.62 mmol) in THF (5 mL) and the reaction mixture was stirred at rt for 1 h. EtOAc (50 mL) and H_2O (50 mL) were added, the phases were separated, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield (2*S*)-*N*-(4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide as an off-white solid (350 mg, 0.61 mmol).

LCMS (Method C): m/z 567.1 (M+H), at 1.75 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.47-8.44 (m, 1H), 7.78-7.64 (m, 3H), 7.58-7.50 (m, 2H), 7.46-7.43 (m, 1H), 7.34-7.33 (m, 1H), 6.88-6.77 (m, 1H), 5.82-5.63 (m, 2H), 4.06-4.03 (m, 1H),

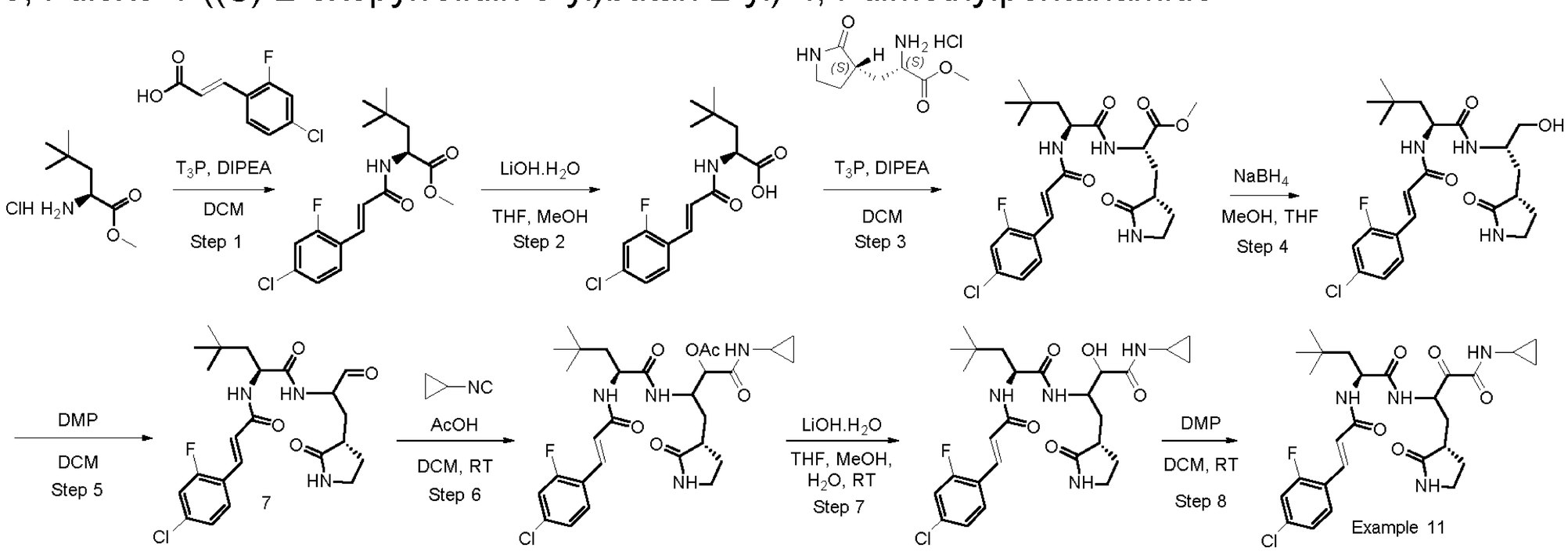
3.83-3.81 (m, 1H), 3.13-3.04 (m, 2H), 2.68-2.67 (m, 1H), 2.12-2.05 (m, 2H), 2.00-1.90 (m, 1H), 1.54-1.50 (m, 4H), 0.92-0.83 (m, 9H), 0.59-0.55 (m, 2H), 0.48-0.46 (m, 2H).

Step 3: Dess-Martin Periodinane (392 mg, 0.92 mmol) was added to a stirred solution of (2*S*)-*N*-(4-(cyclopropylamino)-3-hydroxy-4-oxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide (350 mg, 0.61 mmol) in DCM (10 mL) at 0°C. After stirring at rt for 1 h, 10% aqueous $NaHCO_3$ solution (20 mL) was added and the reaction mixture extracted with EtOAc (2 X 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. After purification by mass directed preparative HPLC (Method B), pure fractions were concentrated *in vacuo*, and partitioned between 10% aqueous $NaHCO_3$ solution (25 mL) and EtOAc (50 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield the title compound, Example 10, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide as a white solid (145 mg, 0.25 mmol).

LCMS (Method E): m/z 565.2 (M+H), at 2.05-2.23 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.73-8.66 (m, 2H), 8.41 (d, J=8.4 Hz, 1H), 7.72-7.64 (m, 3H), 7.56-7.50 (m, 1H), 7.34-7.33 (m, 1H), 6.81 (d, J=16.0 Hz, 1H), 4.98-4.90 (m, 1H), 4.56-4.55 (m, 1H), 3.18-3.12 (m, 2H), 2.91-2.86 (m, 1H), 2.74-2.73 (m, 2H), 2.53-2.50 (m, 2H), 2.22-2.17 (m, 1H), 1.70-1.63 (m, 2H), 0.92-0.83 (m, 9H), 0.67-0.63 (m, 2H), 0.59-0.57 (m, 2H).

Example 11: (2*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide

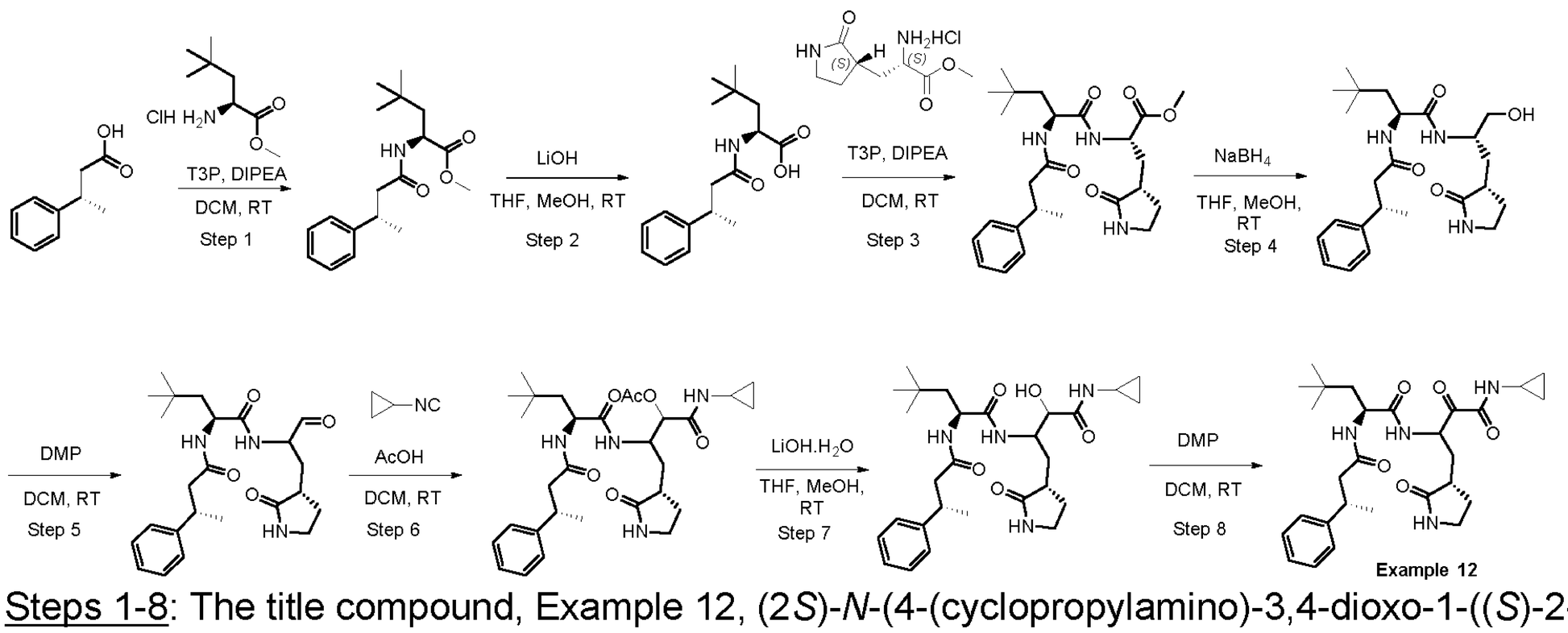


Steps 1-8: The title compound, Example 11, (2*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide was prepared as a white solid (17 mg, 0.03 mmol) using procedures similar to those detailed above.

LCMS (Method A): m/z 549.0 (M+H), at 1.87-2.04 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.73-8.62 (m, 1H), 8.46-8.40 (m, 1H), 7.75-7.65 (m, 2H), 7.55-7.52 (m, 1H), 7.49-7.42 (m, 1H), 7.38-7.33 (m, 1H), 6.86-6.80 (m, 1H), 6.25-6.14 (m, 1H), 5.10-5.00 (m, 1H), 4.61-4.59 (m, 1H), 3.18-3.11 (m, 2H), 2.74-2.67 (m, 1H), 2.18-2.15 (m, 2H), 1.67-1.50 (m, 3H), 0.97-0.91 (m, 2H), 0.86-0.82 (m, 9H), 0.66-0.51 (m, 4H).

Example 12: (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylbutanamido)pentanamide

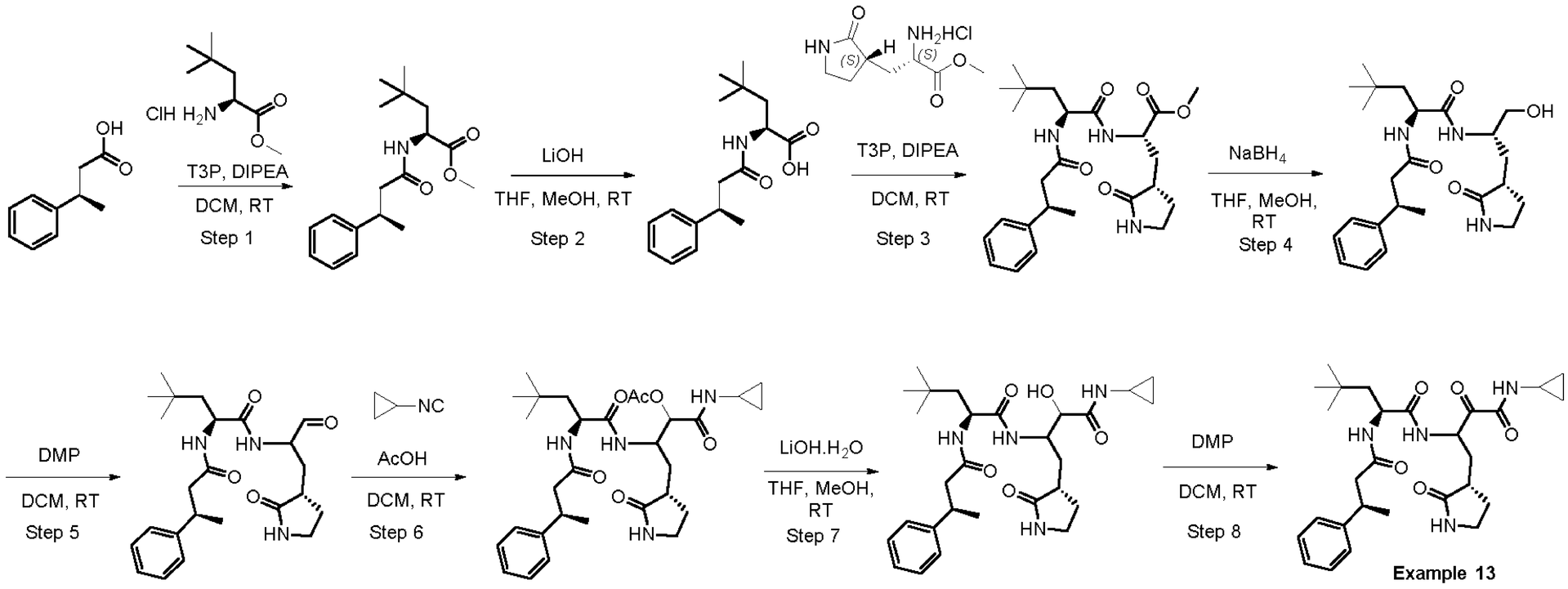


Steps 1-8: The title compound, Example 12, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylbutanamido)pentanamide was prepared as an off-white solid (9.9 mg, 0.02 mmol) using procedures similar to those detailed above.

LCMS (Method A): m/z 513.3 (M+H), at 1.74-1.92 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.73-8.71 (m, 1H), 8.48-8.46 (m, 1H), 8.03-8.01 (m, 1H), 7.72-7.69 (m, 1H), 7.29-7.15 (m, 5H), 4.95-4.90 (m, 1H), 4.37-4.36 (m, 1H), 3.18-3.15 (m, 4H), 2.68-2.67 (m, 1H), 2.40-2.36 (m, 2H), 2.30-2.10 (m, 1H), 1.90-1.88 (m, 1H), 1.68-1.56 (m, 3H), 1.46-1.40 (m, 1H), 1.17-1.14 (m, 3H), 0.90-0.85 (m, 9H), 0.66-0.57 (m, 4H).

Example 13: (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylbutanamido)pentanamide

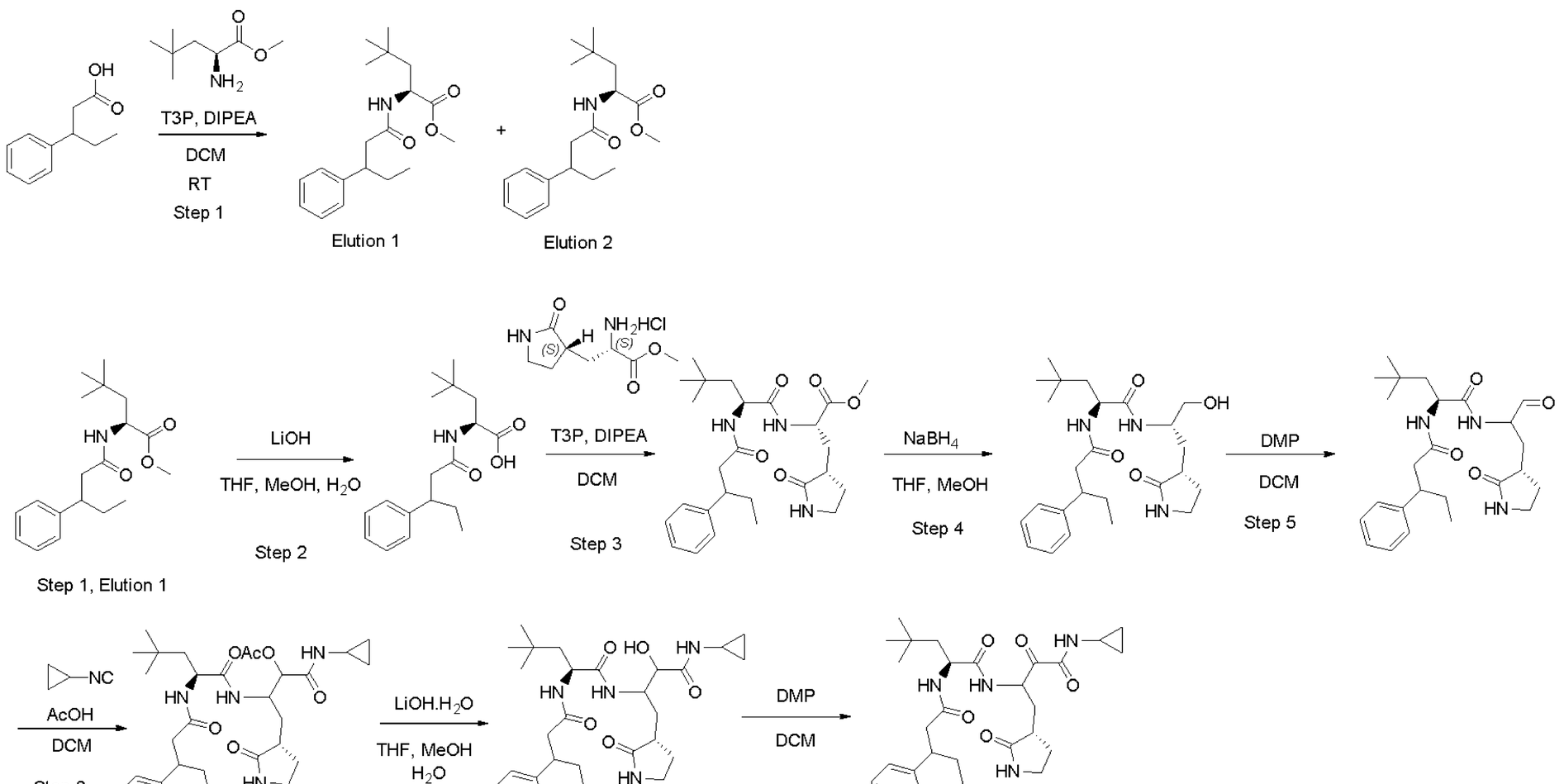


Steps 1-8: The title compound, Example 13, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylbutanamido)pentanamide was prepared as an off-white solid (10 mg, 0.02 mmol) using procedures similar to those detailed above.

LCMS (Method A): m/z 513.3 (M+H), at 1.78-1.96 min.

^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.74-8.71 (m, 1H), 8.58-8.48 (m, 1H), 8.06-7.97 (m, 1H), 7.72-7.70 (m, 1H), 7.30-7.15 (m, 5H), 5.05-5.01 (m, 1H), 4.31-4.29 (m, 1H), 3.20-3.20 (m, 3H), 2.74-2.73 (m, 1H), 2.39-2.34 (m, 2H), 2.19-2.14 (m, 1H), 1.91-1.86 (m, 1H), 1.76-1.50 (m, 3H), 1.36-1.32 (m, 2H), 1.28-1.25 (m, 3H), 0.89-0.80 (m, 9H), 0.67-0.64 (m, 2H), 0.59-0.58 (m, 2H).

Examples 14 and 15: (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylpentanamido)pentanamide and (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylpentanamido)pentanamide



Step 1: To a stirred solution of 3-phenylpentanoic acid (2.00 g, 11.2 mmol) and methyl (*S*)-2-amino-4,4-dimethylpentanoate hydrochloride (3.29 g, 16.8 mmol) in DCM (30 mL) was added DIPEA (5.80 mL, 33.7 mmol) followed by the dropwise addition of T3P (50% solution in EtOAc, 10.6 mL, 16.8 mmol) at 0 °C. After stirring at rt for 16 h the reaction mixture was partitioned between EtOAc (200 mL) and H_2O (200 mL) and the phases were separated. The organic phase was washed with 10% aqueous $NaHCO_3$ solution (200 mL) and Brine solution (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-14% EtOAc in petroleum ether, yielded methyl (2*S*)-4,4-dimethyl-2-(3-phenylpentanamido)pentanoate as an off-white solid, as a mixture of diastereomers.

The diastereomers were separated by preparative chiral SFC purification, using the below method. Instrument: PIC 100 (PIC Solution, Inc.); Column: Chiralcel OX-H (250*30) mm, 5µm; Mobile phase: CO_2:0.5% Isopropyl amine in MeOH (80:20); Flow rate: 70 g/min; Back pressure: 100 bar; Wavelength: 210 nm; Cycle time: 4.5 min.
The peak eluting first in the purification was named as Elution 1 and the second eluting peak was named as Elution 2. After separation the elutions were concentrated *in vacuo* to yield Step 1, Elution 1 product (1.0 g) and Step 1, Elution 2 product (0.8 g), which were used in the subsequent steps without determination of absolute stereochemistry.

Step 1, Elution 1:
LCMS (Method A): m/z 320.4 (M+H), at 2.41 min.

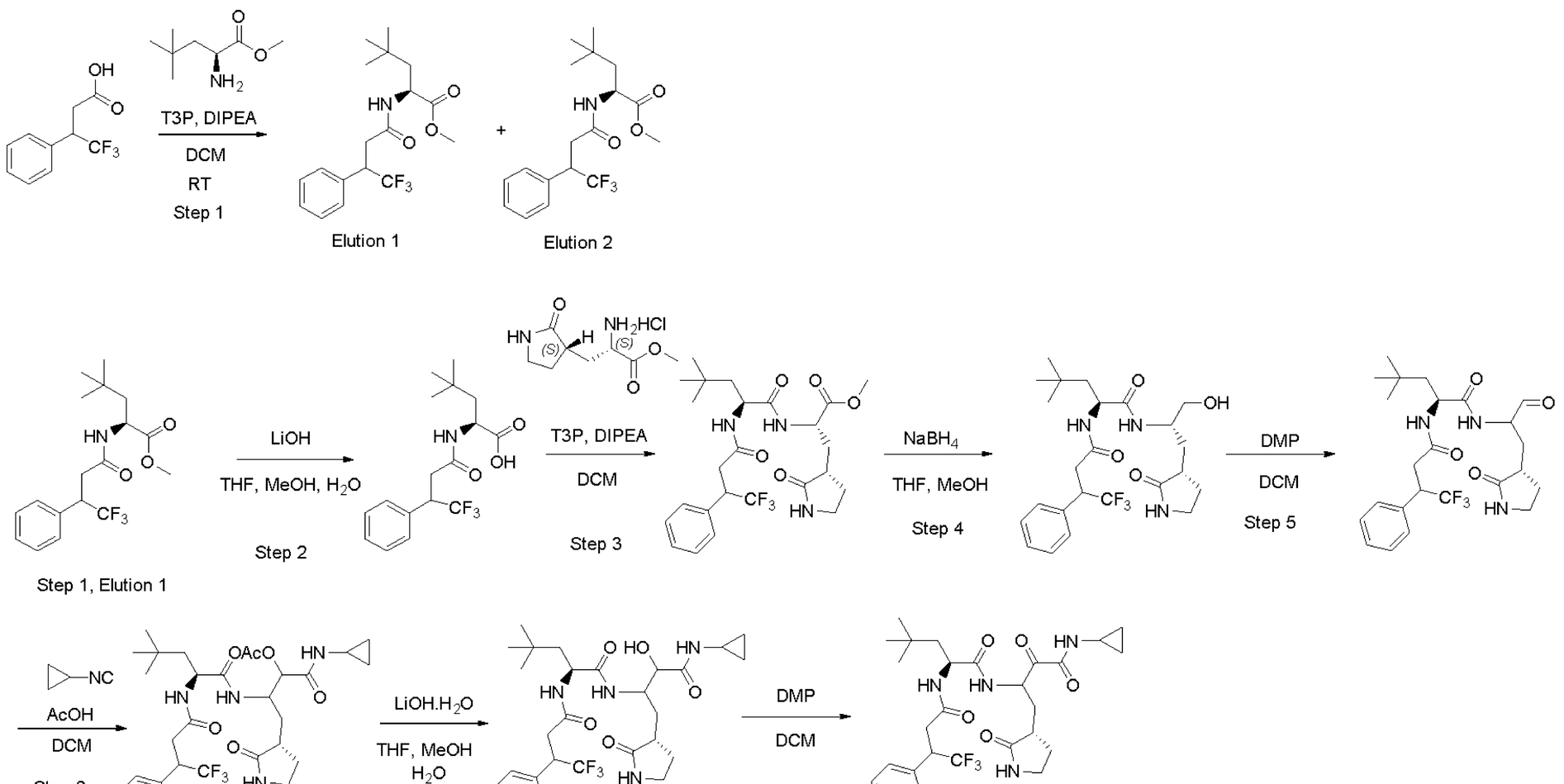
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.19 (d, J=7.6 Hz, 1H), 7.30-7.26 (m, 2H), 7.19-7.16 (m, 3H), 4.28-4.23 (m, 1H), 3.53 (s, 3H), 2.93 (d, J=4.8 Hz, 1H), 2.47-2.41 (m, 1H), 2.36-2.31 (m, 1H), 1.64-1.48 (m, 4H), 0.87-0.84 (m, 9H), 0.75-0.66 (m, 3H).

Step 1, Elution 2:
LCMS (Method A): m/z 320.3 (M+H), at 2.36 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.16 (d, J=7.6 Hz, 1H), 7.28-7.24 (m, 2H), 7.18-7.14 (m, 3H), 4.23-4.18 (m, 1H), 3.60 (s, 3H), 2.93-2.90 (m, 1H), 2.42-2.34 (m, 2H), 1.68-1.62 (m, 1H), 1.55-1.49 (m, 2H), 1.45-1.39 (m, 1H), 0.75-0.73 (m, 9H), 0.71-0.67 (m, 3H).

Steps 2 to 8, Example 14: The title compound, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylpentanamido)pentanamide or (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylpentanamido)pentanamide was prepared as an off-white solid (35 mg, 0.07 mmol) using procedures similar to those detailed above, from Step 1, Elution 1 product (1.4 g).
LCMS (Method A): m/z 527.4 (M+H), at 1.83-2.00 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.71 (d, J=4.8 Hz, 1H), 8.42 (d, J=6.8 Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 7.71-7.69 (m, 1H), 7.28-7.24 (m, 2H), 7.17-7.14 (m, 3H), 4.94-4.89 (m, 1H), 4.34-4.30 (m, 1H), 3.25-3.09 (m, 2H), 2.97-2.90 (m, 1H), 2.67-2.67 (m, 1H), 1.90-1.80 (m, 1H), 1.66-1.53 (m, 5H), 1.49-1.37 (m, 2H), 0.87 (s, 9H), 0.71-0.60 (m, 7H), 0.59-0.56 (m, 3H).

Steps 2 to 8, Example 15: The title compound, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylpentanamido)pentanamide or (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylpentanamido)pentanamide was prepared as an off-white solid (30 mg, 0.06 mmol) using procedures similar to those detailed above, from Step 1, Elution 2 product (1.0 g).
LCMS (Method A): m/z 527.4 (M+H), at 1.83-2.00 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.73-8.70 (m, 1H), 8.50-8.45 (m, 1H), 8.00-7.90 (m, 1H), 7.70 (d, J=5.6 Hz, 1H), 7.29-7.23 (m, 2H), 7.17-7.13 (m, 3H), 4.95-4.82 (m, 1H), 4.25-4.13 (m, 1H), 4.08-3.94 (m, 1H), 3.22-3.04 (m, 2H), 2.89-2.87 (m, 1H), 2.45-2.29 (m, 2H), 2.18-2.05 (m, 2H), 1.89-1.77 (m, 1H), 1.68-1.53 (m, 3H), 1.50-1.39 (m, 2H), 1.33-1.20 (m, 1H), 0.89-0.84 (m, 3H), 0.70-0.66 (m, 11H), 0.53-0.53 (m, 2H).

Examples 16 and 17: (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide and (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide



Step 1: To a stirred solution of 4,4,4-trifluoro-3-phenylbutanoic acid (2.0 g, 9.16 mmol) and methyl (*S*)-2-amino-4,4-dimethylpentanoate hydrochloride (2.18 g, 11.0 mmol) in DCM (30 mL) was added DIPEA (6.30 mL, 33.7 mmol) followed by the addition of T3P (50% solution in EtOAc, 8.60 mL, 13.8 mmol) at 0 °C. After stirring at rt for 16 h the reaction mixture was partitioned between EtOAc (200 mL) and H_2O (200 mL) and the phases were separated. The organic phase was washed with 10% aqueous $NaHCO_3$ solution (200 mL) and Brine solution (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by gradient flash column chromatography (Biotage-Isolera) using a 25 g silica SNAP cartridge (230-400 mesh), eluting with 0-14% EtOAc in petroleum ether, yielded methyl (*S*)-4,4-dimethyl-2-(4,4,4-trifluoro-3-phenylbutanamido)pentanoate as an off-white solid, as a mixture of diastereomers.

The diastereomers were separated by preparative chiral SFC purification, using the below method. Instrument: PIC 100 (PIC Solution, Inc.); Column: (*R*,*R*) Whelk 250*30mm, 5µm; Mobile phase: CO_2:MeOH (90:10); Flow rate: 70 g/min; Back pressure: 100 bar; Wavelength: 210 nm; Cycle time: 5.0 min.
The peak eluting first in the purification was named as Elution 1 and the second eluting peak was named as Elution 2. After separation the elutions were concentrated *in vacuo* to yield Step 1, Elution 1 product (1.0 g) and Step 1, Elution 2 product (0.8 g), which were used in the subsequent steps without determination of absolute stereochemistry.

Steps 2 to 8, Example 16: The title compound, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide or (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-

oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide was prepared as an off-white solid (5 mg, 0.01 mmol) using procedures similar to those detailed above, from Step 1, Elution 1 product (1.0 g).
LCMS (Method A): m/z 567.3 (M+H), at 1.88-2.07 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.71-8.70 (m, 1H), 8.55 (d, J=6.8 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H), 7.72 (d, J=5.6 Hz, 1H), 7.34-7.31 (m, 5H), 4.98-4.97 (m, 1H), 4.18-4.16 (m, 1H), 4.02-4.01 (m, 2H), 3.19-3.12 (m, 3H), 2.95-2.89 (m, 2H), 2.78-2.74 (m, 2H), 2.18-2.17 (m, 2H), 1.89-1.87 (m, 1H), 1.63-1.57 (m, 3H), 1.48-1.44 (m, 1H), 1.19-1.17 (m, 1H), 0.63-0.59 (m, 9H).

Steps 2 to 8, Example 17: The title compound, (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide or (2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide was prepared as an off-white solid (40 mg, 0.07 mmol) using procedures similar to those detailed above, from Step 1, Elution 2 product (0.8 g).
LCMS (Method A): m/z 567.3 (M+H), at 1.86-2.05 min.
^{1}H NMR: (400 MHz, DMSO-d_6) δ 8.71 (d, J=4.4 Hz, 1H), 8.47 (d, J=7.2 Hz, 1H), 8.24-8.18 (m, 1H), 7.74-7.69 (m, 1H), 7.34-7.31 (m, 5H), 4.89-4.85 (m, 1H), 4.32-4.31 (m, 1H), 4.04-4.02 (m, 1H), 3.16-3.11 (m, 2H), 2.85-2.67 (m, 3H), 2.17-2.16 (m, 1H), 2.05-2.02 (m, 1H), 1.84-1.81 (m, 1H), 1.65-1.54 (m, 2H), 1.40-1.24 (m, 1H), 1.22-1.19 (m, 1H), 0.71 (s, 7H), 0.59-0.56 (m, 6H).

Examples 18 to 33 were synthesized using procedures similar to those detailed above.

BIOLOGICAL ACTIVITY

Construct design of SARS-CoV-2 Mpro

The SARS CoV-2-Mpro (Main Protease/3C-like protease, UniProt ID: P0DTD1) protein sequence, up to and including its autocleavage boundaries, as well as the preceding N-terminal 5 amino acid residues, including the P1 glutamine residue, were codon optimised for *E. coli* expression and cloned into pET26b (Merck, #US169862-3) or pGEX6P1 (Fisher Scientific, #10350355) vectors using *Bam*HI and *Xho*I sites. The expression constructs thus featured a native viral N-terminal sequence, as well as a C-terminal modified 3C-protease cleavage site (LEVLFQGK), with an alternative lysine residue at the P2' position, followed by a polyhistidine (His-8) tag.

Protein expression and protein purification

Chemically competent BL21(DE3)-RIL *E. coli* (Agilent, #230240) cells were transformed with the relevant coronavirus Mpro construct and grown overnight at 37 °C on LB agar plates supplemented with the appropriate antibiotics. All culture steps were performed at 37 °C unless otherwise stated. A scraping of colonies was grown in 15 mL of antibiotic supplemented LB media, for a period of approximately 2 hours, taking care not to exceed an optical density (OD) density of 2.0 as measured in a spectrophotometer at 600 nm. This preculture was used to inoculate a 500 mL expression culture: either LB media for IPTG induced expression or autoinduction superbroth media (Formedium, #AIMSB0210). In LB media, expression was induced at an OD of 0.7-1.0 by the addition of IPTG to a final concentration of 0.5 mM. The culture was then grown at 18 °C overnight. In autoinduction expression, the temperature was dropped to 18 °C once an OD of 0.7-1.0 was observed then grown overnight. The cells were harvested by centrifugation and frozen until use.

Thawed cells were resuspended into resuspension buffer: 20 mM Tris-HCl pH 8.0, 150 mM NaCl, and DNase I (Merck #4716728001) and lysed by sonication. The lysate was clarified by centrifugation at 23,000 rcf for 15 mins at 4 °C. The supernatant was loaded onto 5 mL of NiNTA resin (Cytiva, #17-5248-02) at a flow-rate of 0.5 mL/min. The resin was washed with the same buffer as above containing 20 mM imidazole. Mpro protein was eluted using the same buffer containing 250 mM imidazole. The target protein was further purified using a Superdex S75 16/60 pg (GE, #GE28-9893-33) column in resuspension buffer. Protein purity was assessed by SDS-PAGE and identity confirmed by mass spectrometry. Purified protein was concentrated and frozen until later use.

SARS-CoV-2 Mpro enzyme assay

The activity of SARS-Cov-2 Mpro was determined in a Fluorescence Resonance Energy Transfer (FRET)-based enzymatic assay using FRET Substrate Dabcyl-KTSAVLQSGFRKM-E(Edans)-Amide. In brief, 5 µL of test compounds (concentrations ranging from 100 µM to 0.0017 µM) was preincubated with 5 µL of 20 nM (final concentration) Mpro enzyme for 30 min at 30 °C in an assay buffer containing 20 mM HEPES, 120 mM NaCl, 0.4 mM EDTA, and 4 mM DTT and 20% glycerol. Reaction was initiated by addition of 10 µL of 20 µM (final concentration) of FRET substrate (Dabcyl-KTSAVLQSGFRKM-E (Edans)-Amide). The reaction was incubated for 1 h and the resulting fluorescent intensity was measured at Ex=360 nm/Em=490 nm at 30 °C using a SPARK 20M plate reader (Tecan). Boceprevir was used a reference standard compound. pIC_{50} and pKi were determined using 4PL GraphPad Prism and data were represented as a mean n=2± SD.

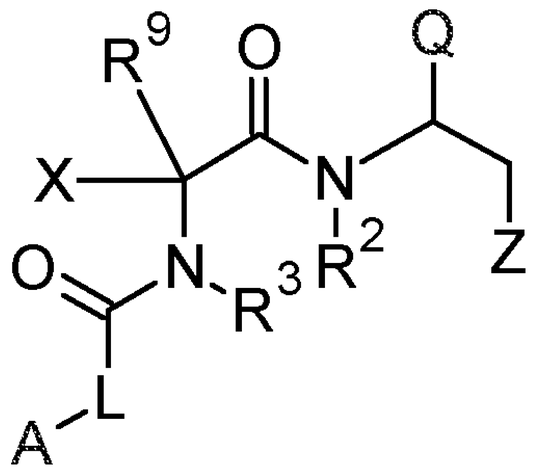
Table 2

Example No.	SARS-CoV-2 Mpro enzyme assay pKi
1	7.9
2	7.7
3	7.6
4	6.0
5	6.3
6	5.3
7	5.1
8	7.3
9	6.4
10	8.2
11	1
12	7.8
13	7.8
14	8.1
15	8.0
16	7.7
17	7.9
18	7.9
19	7.9
20	7.0

21	8.1
22	8.2
23	7.9
24	7.9
25	8.0
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31	7.6
32	7.9
33	7.6

CLAIMS

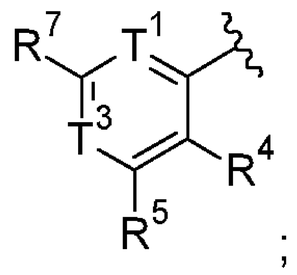
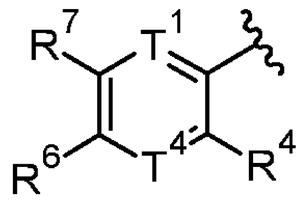
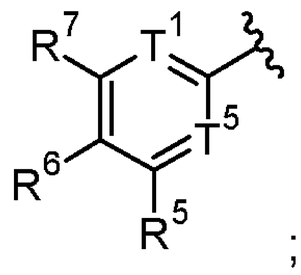
1. A compound of Formula (1'):

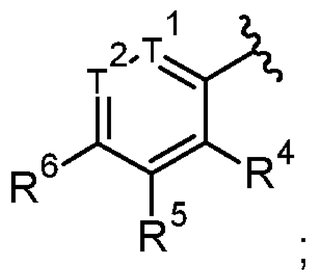
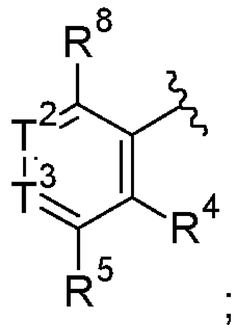
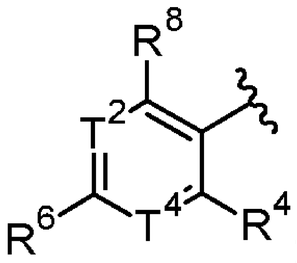


(1');

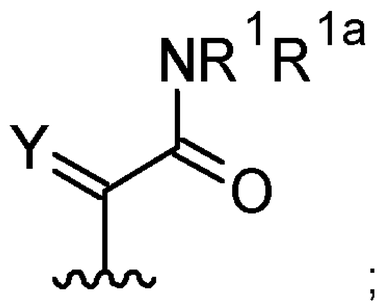
or a salt thereof, wherein;

A is selected from:


;

;

;


;

;

;

Q is CN or a group of formula:


;

X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

T^1 is CR^8 or N;

T^2 is CR^7 or N;

T^3 is CR^6 or N;

T^4 is CR^5 or N;

T^5 is CR^4 or N;

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is $-(CH_2)_pCONHR^{13}$, or Z is $-(CH_2)_pCO_2R^{13}$;

L is $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ or $-O-CHR^{11}-$;

R^1 and R^{1a} are independently H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CN, CO_2R^{14}, OR^{14}, SO_2R^{14}, $SONHR^{14}$, OSO_2R^{14}, $PO(R^{14})_2$, SF_5 or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms; or R^{11} and R^{12} are joined to form a cyclopropyl ring;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

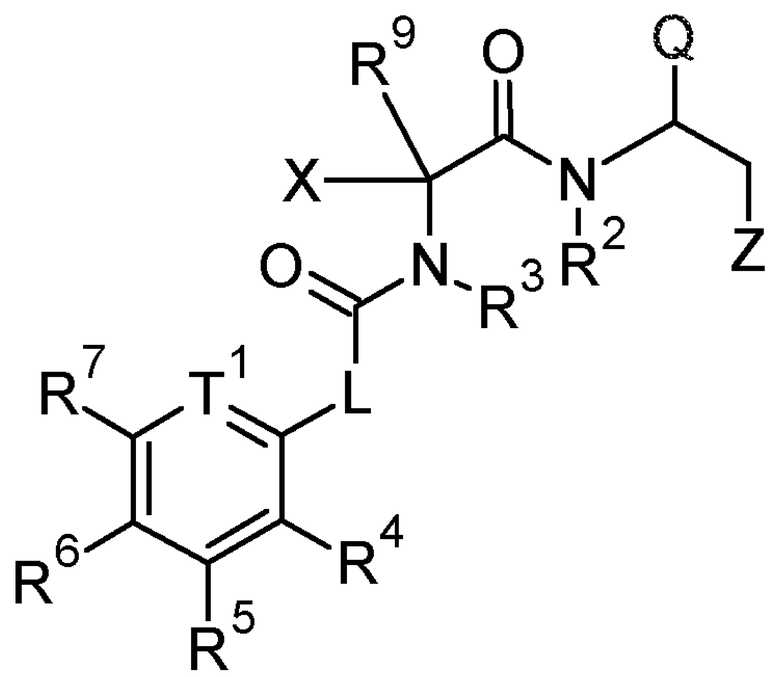
wherein when R^1 and R^{1a} are not both H, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

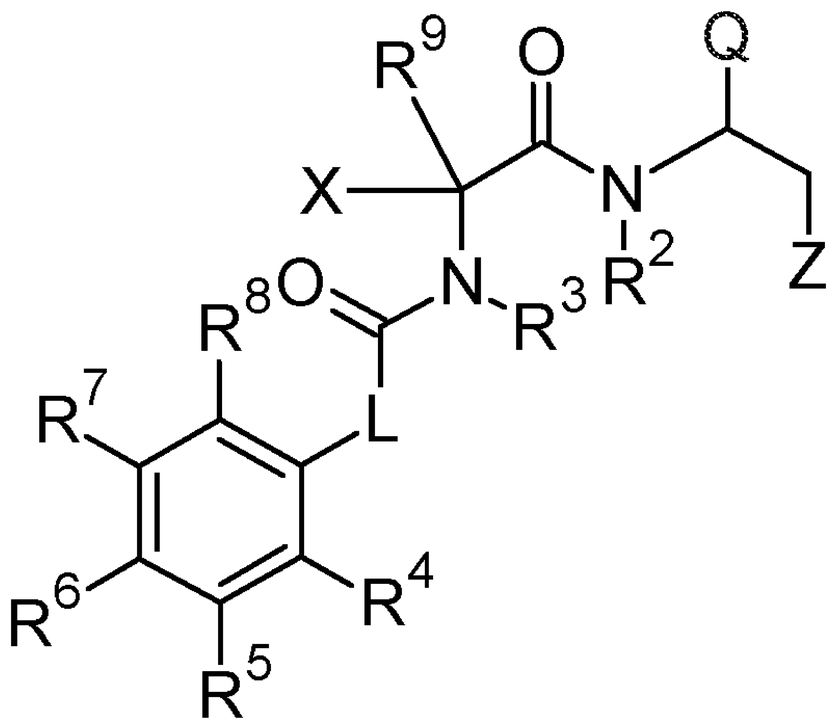
2. The compound according to claim 1, which is a compound of Formula (1c):



(1c);

or a salt thereof.

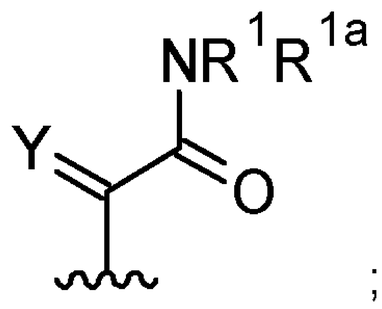
3. The compound according to claim 1, which is a compound of Formula (1b):



(1b);

or a salt thereof, wherein;

Q is CN or a group of formula:



;

X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is $-(CH_2)_pCONHR^{13}$, or Z is $-(CH_2)_pCO_2R^{13}$;

L is $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ or $-O-CHR^{11}-$;

R^1 and R^{1a} are independently H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CO_2R^{14} or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

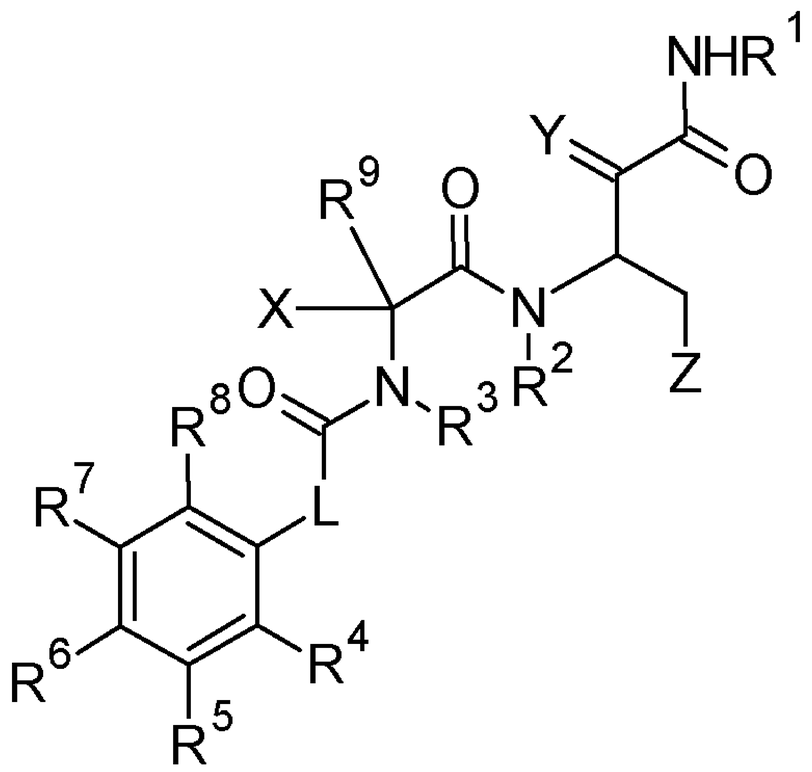
wherein when R^1 and R^{1a} are not both H, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

4. The compound according to claim 1, which is a compound of Formula (1):



(1);

or a salt thereof, wherein;

X is a C_{1-6} saturated or unsaturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms or X is joined with R^9 to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

Y is O or NOR^{16};

Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms, or Z is $-(CH_2)_pCONHR^{13}$, or Z is $-(CH_2)_pCO_2R^{13}$;

L is $-CR^{11}=CR^{12}-$, $-CHR^{11}-CHR^{12}-$ or $-O-CHR^{11}-$;

R^1 is H or a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms;

R^2 and R^3 are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^4, R^5, R^6, R^7 and R^8 are independently H, halo, CO_2R^{14} or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^9 is H or is joined with X to form a C_{3-6} cycloalkyl ring which is optionally substituted with 1 to 3 fluorine atoms or 1 to 3 C_{1-3} alkyl groups;

R^{11} and R^{12} are independently H, $-(CH_2)_mCO_2R^{15}$ or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{13}, R^{14} and R^{15} are independently H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

R^{16} is H or C_{1-3} alkyl optionally substituted with 1 to 6 fluorine atoms;

p and m are independently 0-3;

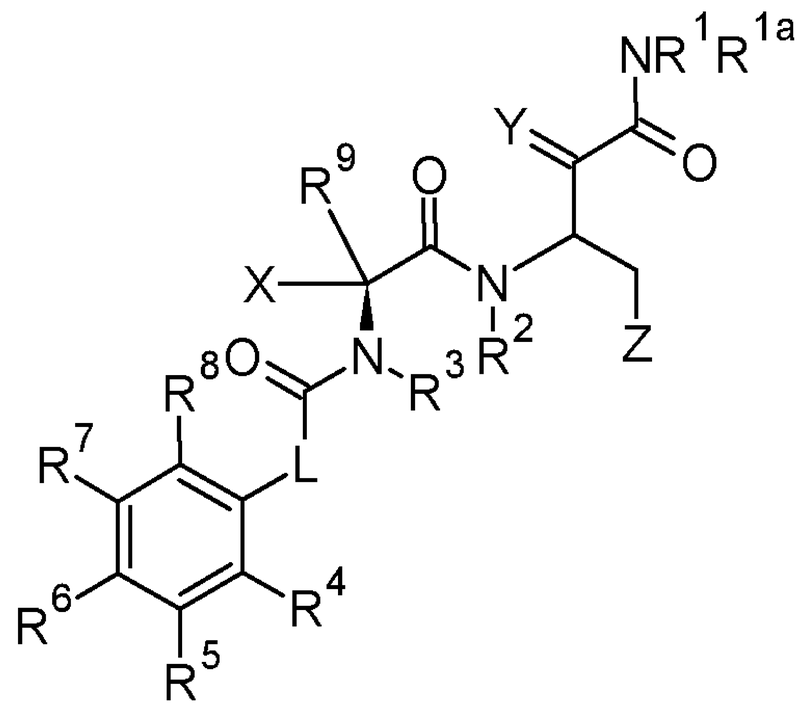
wherein when R^1 is a C_{1-6} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, L is:

$-CHR^{11}-CHR^{12}-$;

$-CR^{11}=CR^{12}-$ where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H;

or $-O-CHR^{11}-$ where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

5. The compound according to claim 1, which is a compound of Formula (1ai):

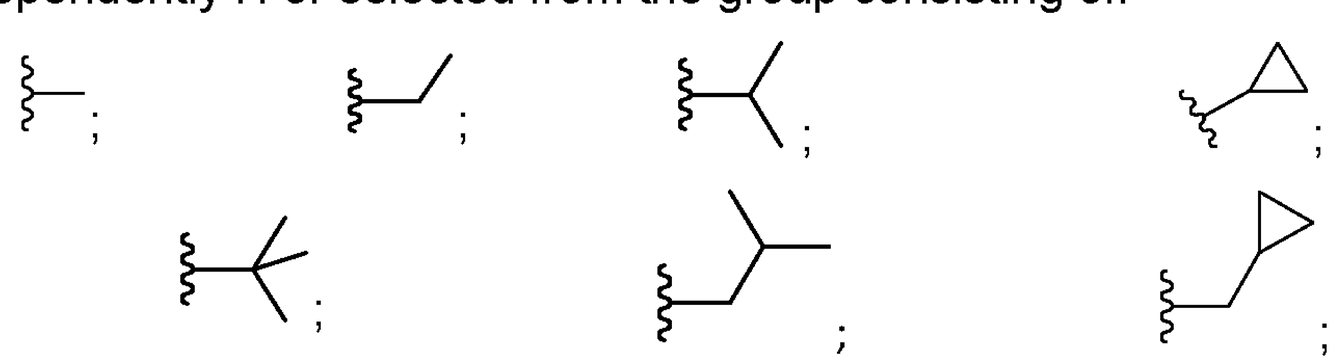


(1ai);

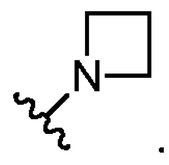
or a salt thereof.

6. The compound according to any one of claims 1 to 5, wherein Y is O.

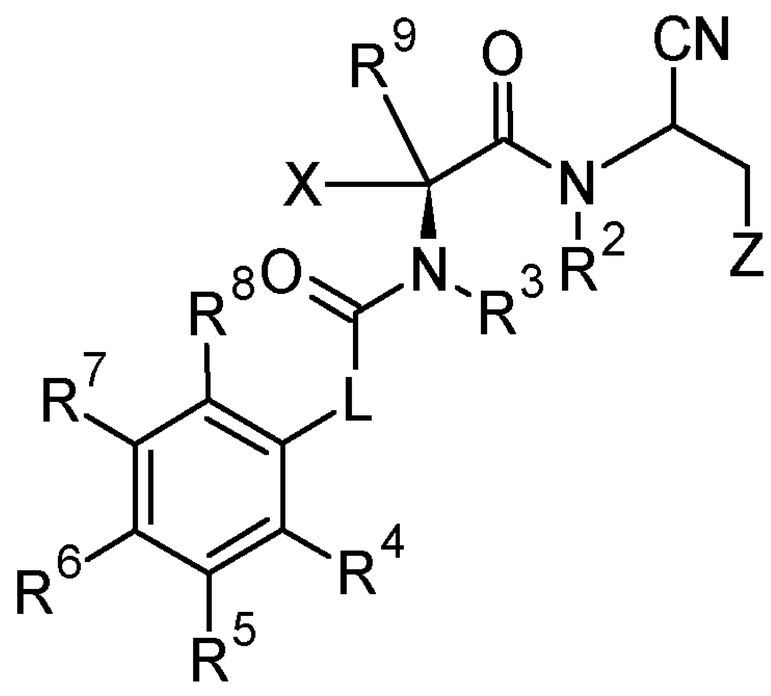
7. The compound according to any one of claims 1 to 3, wherein R^1 and R^{1a} are independently H or selected from the group consisting of:



or wherein R^1 and R^{1a} are joined to form a ring such that the group NR^1R^{1a} is:



8. The compound according to claim 1, which is a compound of Formula (1aii):

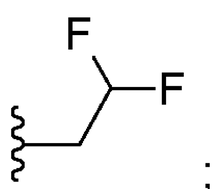
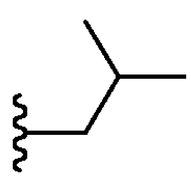
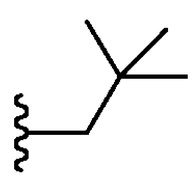
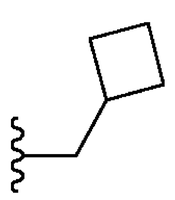
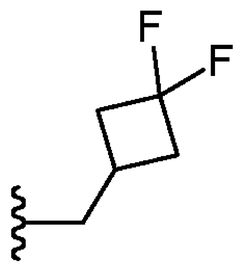
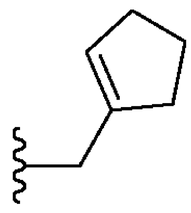
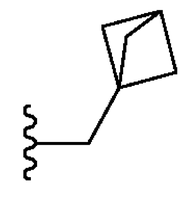
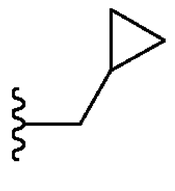
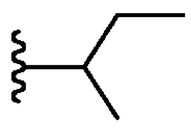
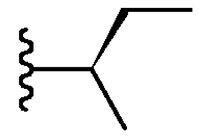
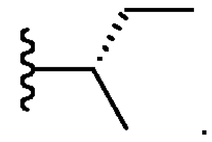


(1aii);

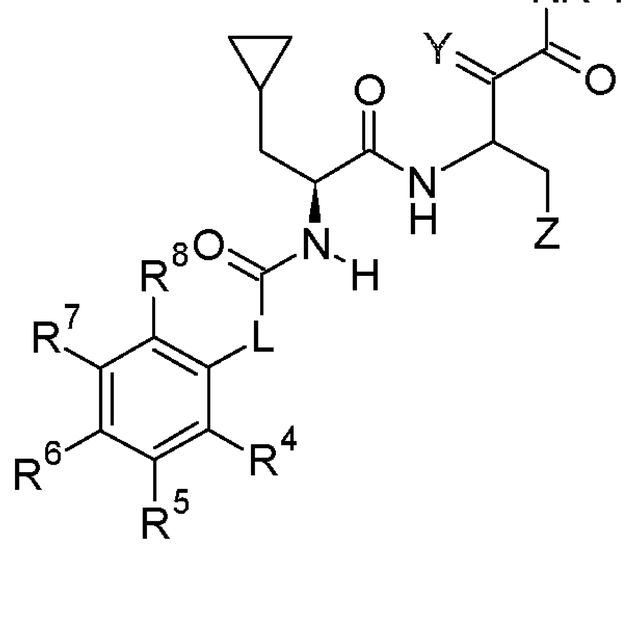
or a salt thereof.

9. The compound according to any one of claims 1 to 8, wherein R^2 is H.

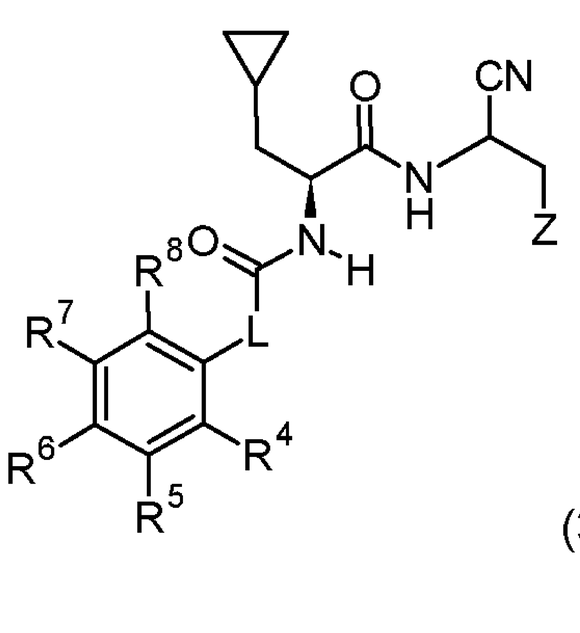
10. The compound according to any one of claims 1 to 9, wherein X is selected from the group consisting of:


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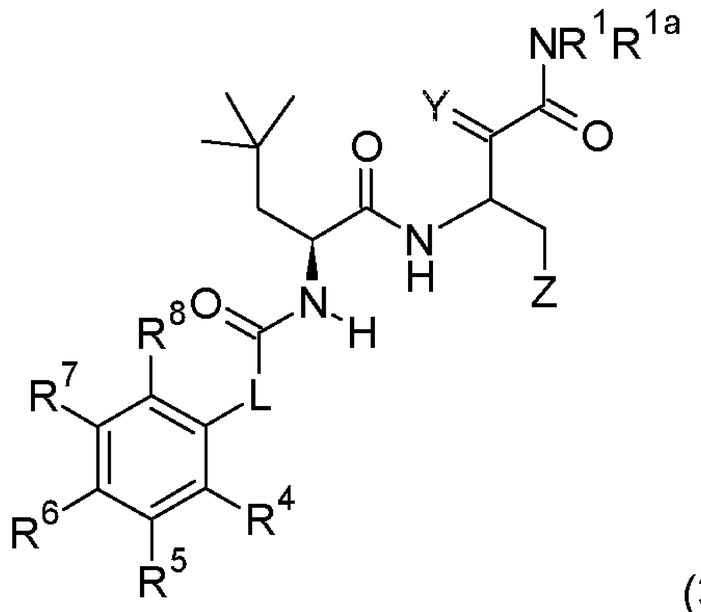
11. The compound according to claim 1, which is a compound of Formula (3bi), (3bii), (3ci) or (3cii):



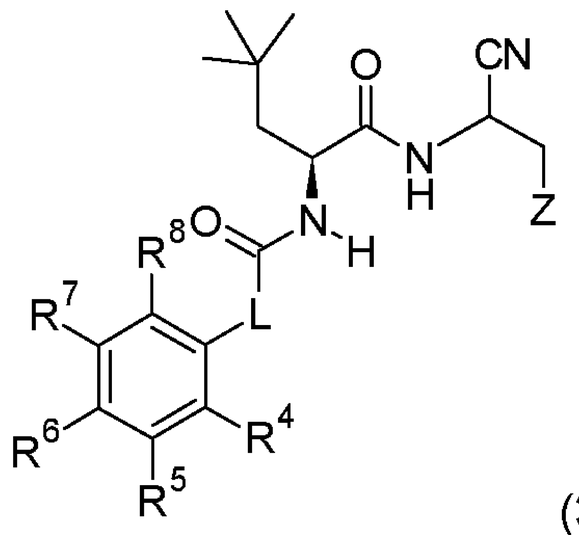
(3bi);



(3bii);



(3ci);



(3cii);

and salts thereof, wherein

Y is O or NOH;

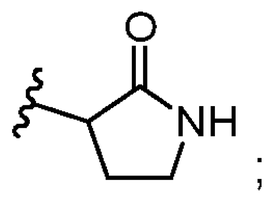
Z is a 5- or 6-membered heterocyclic ring optionally substituted with oxo or 1 to 6 fluorine atoms, or Z is C_{3-6} cycloalkyl optionally substituted with 1 to 6 fluorine atoms;

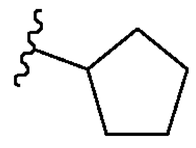
L is -CH=CH-, -CH_2-CH_2- or -O-CH_2-;

R^1 and R^{1a} are independently H or a C_{1-4} saturated hydrocarbon group optionally substituted with 1 to 6 fluorine atoms, or R^1 and R^{1a} are linked together to form a 3 to 6-membered saturated ring optionally containing an additional heteroatom;

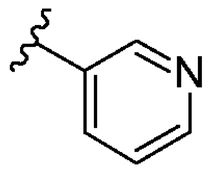
R^4, R^5, R^6, R^7 and R^8 are independently H or halo.

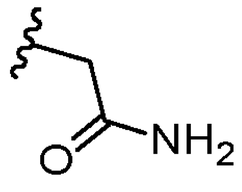
12. The compound according to any one of claims 1 to 11, wherein Z is selected from the group consisting of:

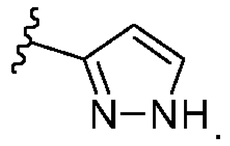

;


;

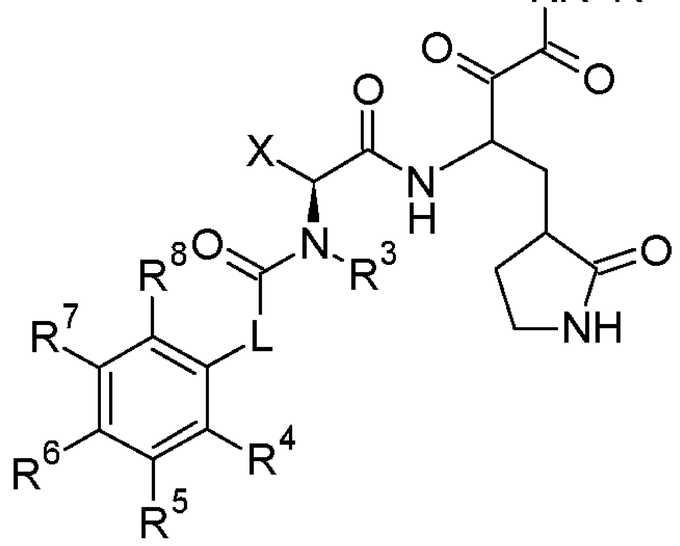

;


;

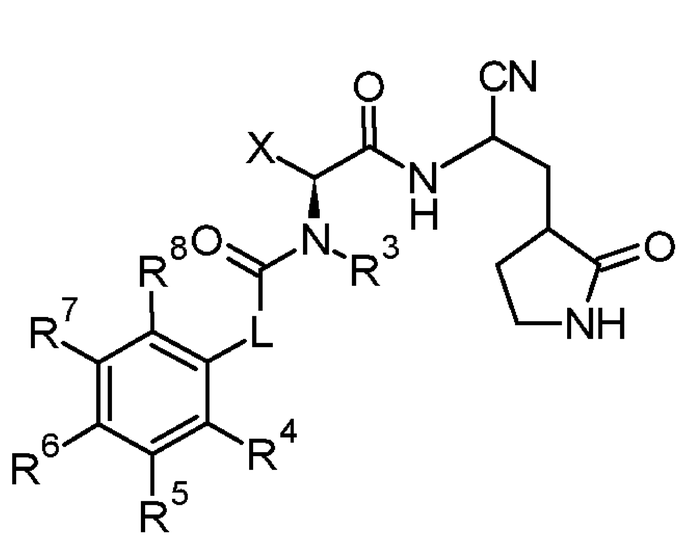

;


.

13. The compound according to claim 1, which is a compound of Formula (4ai) or (4aii):



(4ai);



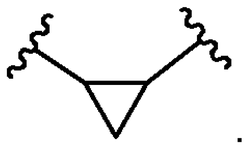
(4aii);

or a salt thereof.

14. The compound according to any one of claims 1 to 13, wherein L is -CHR^{11}-CHR^{12}-.

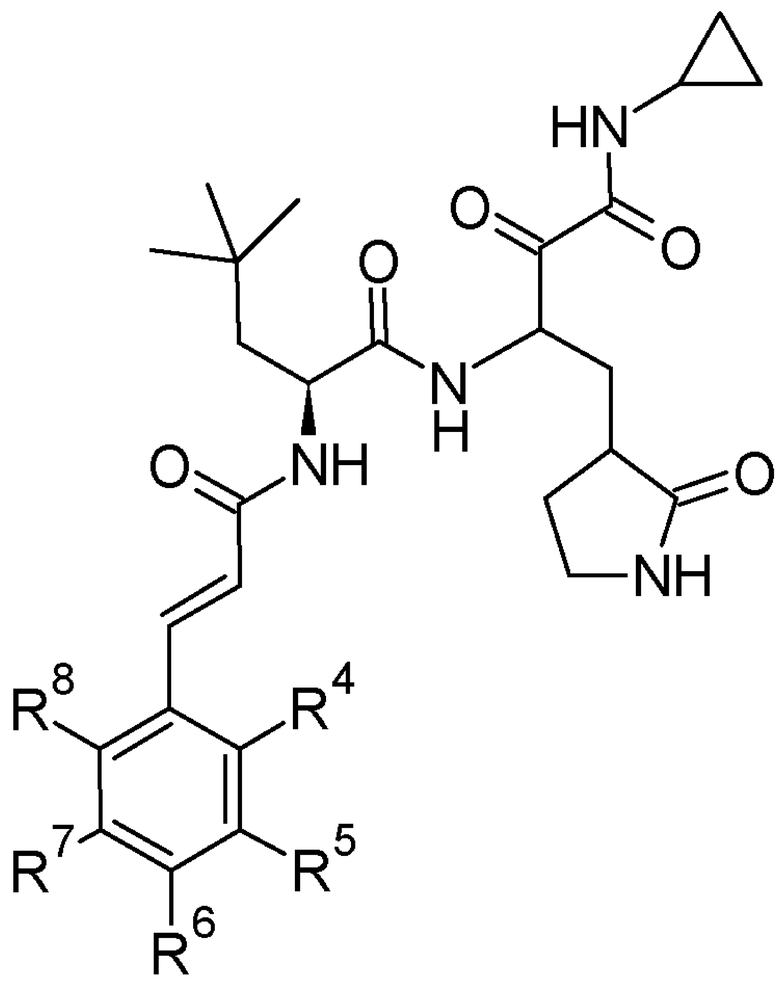
15. The compound according to claim 1, wherein R^1 and R^{1a} are both H and L is -CR^{11}=CR^{12}-, or wherein R^1 and R^{1a} are not both H and L is -CR^{11}=CR^{12}- where R^3, R^4, R^5, R^6, R^7 and R^8 are not all H.

16. The compound according to claim 1, wherein R^1 and R^{1a} are both H and L is -O-CHR^{11}-, or wherein R^1 and R^{1a} are not both H and L is -O-CHR^{11}- where R^3 is not H, or where two or more of R^4, R^5, R^6, R^7 and R^8 are not H.

17. The compound according to claim 1, wherein L is -CH=CH-, -CH_2CH_2-, -CH_2-$CH(CH_2CH_3)$-, -CH_2-$CH(CH_2CO_2H)$-, -OCH_2-, -CH_2-$CH(CH_3)$-, -CH_2-$CH(CF_3)$-, -$OCH(CH_3)$-, or .

18. The compound according to any one of claims 1 to 17, wherein R^3 is H, methyl or CH_2CF_3.

19. The compound according to claim 1, which is a compound of Formula (9b):



(9b);

or a salt thereof.

20. The compound according to any one of claims 1 to 19, wherein R^4, R^5, R^6, R^7, and R^8 are independently selected from H, CN, Cl, F, CF_2H, OCH_3, OCF_3, OCF_2H, SO_2CH_3, OSO_2CH_3, $PO(CH_3)_2$, SF_5 and CO_2H.

21. The compound according to claim 20, wherein R^4 is F, R^5 is H, R^6 is Cl and R^7 and R^8 are H.

22. The compound according to claim 1 which is selected from the group consisting of:
3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;
3-((*S*)-2-cinnamamido-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;
benzyl ((2*S*)-1-((4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate;
3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-(hydroxyimino)-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;
N-(*tert*-butyl)-3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;
3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopropyl-2-oxobutanamide;
3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-4-cyclopentyl-2-oxobutanamide;
3-((*S*)-3-cyclopropyl-2-(3-phenylpropanamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;
(2*S*)-*N*-(1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;
(2*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylbutanamido)pentanamide;
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylbutanamido)pentanamide;
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-phenylpentanamido)pentanamide;
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-phenylpentanamido)pentanamide;
(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-4,4,4-trifluoro-3-phenylbutanamido)pentanamide;

(2*S*)-*N*-(4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-4-methylpentanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-*N*-ethyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-3-cyclopropyl-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-*N*-cyclopropyl-2-oxo-4-((S)-2-oxopyrrolidin-3-yl)butanamide;

(2*S*)-*N*-(4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-*N*-(4-(ethylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

3-((*S*)-3-cyclopropyl-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)propanamido)-*N*-ethyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

N-cyclopropyl-3-((*S*)-3-cyclopropyl-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

(2*S*)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-*N*-(4-(ethylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-amino-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclopropylpropanamido)-*N*-cyclopropyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

benzyl ((2*S*)-3-cyclopropyl-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-1-oxopropan-2-yl)carbamate;

N-cyclopropyl-3-((*S*)-3-cyclopropyl-2-(3-(2,4-dichlorophenyl)propanamido)propanamido)-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

3-((*S*)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-3-cyclobutylpropanamido)-*N*-cyclopropyl-2-oxo-4-((*S*)-2-oxopyrrolidin-3-yl)butanamide;

(3*S*)-*N*-((2*S*)-3-cyclopropyl-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-1-oxopropan-2-yl)-3-phenylpentanamide;

(3*R*)-*N*-((2*S*)-3-cyclopropyl-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-1-oxopropan-2-yl)-3-phenylpentanamide;

(2*S*)-*N*-(4-(azetidin-1-yl)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-dichlorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(2,4-difluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chlorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(2-chloro-4-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-fluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-3-fluorophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(5-chloropyridin-2-yl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(5-fluoropyridin-2-yl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-(difluoromethyl)phenyl)acrylamido)-4,4-dimethylpentanamide;

(1*R*,2*R*)-*N*-((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-2-phenylcyclopropane-1-carboxamide;

(1*S*,2*S*)-*N*-((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-2-phenylcyclopropane-1-carboxamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2,4-difluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2,4-difluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2,4-dichlorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2,4-dichlorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(4-chloro-2-fluorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-3-(4-chloro-2-fluorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(4-chlorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-3-(4-chlorophenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(4-fluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(4-fluorophenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(azetidin-1-yl)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*E*)-3-(4-chloro-2-fluorophenyl)acrylamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-(2-(trifluoromethoxy)phenyl)pentanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-(2-(trifluoromethoxy)phenyl)pentanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2-(difluoromethoxy)phenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2-(difluoromethoxy)phenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-2-cyanophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(4-chloro-3-cyanophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*E*)-3-(2-chloro-4-cyanophenyl)acrylamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*R*)-3-(3-(trifluoromethoxy)phenyl)butanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*S*)-3-(3-(trifluoromethoxy)phenyl)butanamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(3-(difluoromethoxy)phenyl)butanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(3-(difluoromethoxy)phenyl)butanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-3-(2-chloro-4-(methylsulfonyl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(2-chloro-4-(methylsulfonyl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

3-chloro-4-((3*R*)-1-(((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-1-oxopentan-3-yl)phenyl methanesulfonate;

3-chloro-4-((3*S*)-1-(((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)amino)-1-oxopentan-3-yl)phenyl methanesulfonate;

(2*S*)-2-((*R*)-3-(2-chloro-4-(dimethylphosphoryl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-3-(2-chloro-4-(dimethylphosphoryl)phenyl)pentanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethyl-2-((*E*)-3-(4-(pentafluoro-l6-sulfaneyl)phenyl)acrylamido)pentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(4-methoxyphenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(4-methoxyphenyl)pentanamido)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-2-(trifluoromethoxy)phenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-2-(difluoromethoxy)phenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-2-cyanophenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(2-chloro-4-cyanophenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-(3-(4-chloro-3-(trifluoromethoxy)phenyl)propanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-*N*-(1-cyano-2-((*S*)-2-oxopyrrolidin-3-yl)ethyl)-2-(3-(2,4-dichlorophenyl)propanamido)-4,4-dimethylpentanamide;

2,4-dichlorobenzyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

4-chloro-2-fluorobenzyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

(*S*)-1-(4-chloro-2-fluorophenyl)ethyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

(*R*)-1-(4-chloro-2-fluorophenyl)ethyl ((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)carbamate;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-3-(2,4-difluorophenyl)-4,4,4-trifluorobutanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-3-(2,4-difluorophenyl)-4,4,4-trifluorobutanamido)-4,4-dimethylpentanamide;

(2*S*)-2-((*R*)-2-benzyl-3,3,3-trifluoropropanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(2*S*)-2-((*S*)-2-benzyl-3,3,3-trifluoropropanamido)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-4,4-dimethylpentanamide;

(1*S*,2*S*)-2-(4-chlorophenyl)-*N*-((2*S*)-1-((4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)amino)-4,4-dimethyl-1-oxopentan-2-yl)cyclopropane-1-carboxamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-(2-(2,4-dichlorophenoxy)acetamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*S*)-2-(2,4-dichlorophenoxy)propanamido)-4,4-dimethylpentanamide;

(2*S*)-*N*-(4-(cyclopropylamino)-3,4-dioxo-1-((*S*)-2-oxopyrrolidin-3-yl)butan-2-yl)-2-((*R*)-2-(2,4-dichlorophenoxy)propanamido)-4,4-dimethylpentanamide;

or a salt thereof.

23. The compound according to any one of claims 1 to 22 having SARS-CoV-2 Mpro inhibitor activity.

24. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 23 and a pharmaceutically acceptable excipient.

25. The compound or composition according to any one of claims 1 to 24 for use in the treatment of SARS-CoV-2 or in the treatment of disorders associated with SARS-CoV-2: Mpro.